

A Longitudinal Study of Neurodevelopmental Delay in HIV
Infected Children.

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ABSTRACT

Paediatric HIV remains one of the most significant challenges to face children, their families and their health care providers in South Africa. The prevalence rate of paediatric HIV infection in South Africa is set to remain high until such time as universal access to antiretrovirals for prevention of mother to child transmission is achieved, and the mother to child transmission rates of HIV start to come down.

HIV is neurotrophic and is known to invade the developing central nervous system and cause widespread damage. The result of this is a well described encephalopathy which has the potential to affect all facets of development.

Children in South Africa who are infected with HIV are vulnerable to a number of factors which may cause developmental delay. Poverty and malnutrition are likely to exacerbate the developmental delay caused by HIV encephalopathy. Physiotherapists in South Africa have not become involved in the long term management of children infected with HIV and paediatric HIV clinics do not routinely offer any rehabilitation services.

The prevalence and extent of developmental delay in HIV infected children in South Africa has not been established. Despite the fact that a number of studies have highlighted the prevalence of developmental delay in Western countries, no intervention studies addressing this problem could be found.

Caregivers of HIV infected children face numerous stressors. Poverty, stigma and their own health care needs make parenting an HIV positive child even more challenging. The needs of caregivers of HIV infected children have not been well researched in the context of developing countries.

The aim of this study was therefore to establish whether a basic home stimulation programme would have any impact on the neurodevelopmental status of young children infected with HIV, and on the parenting stress levels of their caregivers. Further

objectives of the study were to establish the prevalence and progression of developmental delay in HIV infected children; to monitor the effect of antiretrovirals on neurodevelopment; to determine who the caregivers of HIV infected children were and to determine what factors were predictive of neurodevelopmental status and parenting stress levels.

In order to meet these objectives a longitudinal randomized controlled trial was conducted. One hundred and twenty two HIV positive children, under two and a half years of age, were recruited for this study at Harriet Shezi Children's Clinic at Chris Hani Baragwanath Hospital in Soweto.

Children were randomly assigned to a control or an experimental group. The developmental status of all children was monitored over a year using the Bayley Scales of Infant Development II. Parenting stress was monitored with the Parenting Stress Index/Short Form. Children in the experimental group received a basic home stimulation programme, which was updated every three months when they came to visit the clinic, as well as all the usual clinic services. Children in the control group received all the usual services at the clinic but no stimulation programme.

Most of the children in the sample were cared for by their biological mothers. They came from poor homes with limited access to common household amenities. Most of the caregivers had not completed 12 years of schooling.

The children in the control and experimental groups were well matched for all their baseline measurements and demographic characteristics. At baseline the children were wasted and stunted and had very low CD4 counts. Only 16% of the children were on antiretrovirals at baseline assessment. The children were severely delayed with respect to both motor and cognitive development. The parenting stress levels of the caregivers were very high at baseline.

Over the period of one year the children in the experimental group showed a significantly greater improvement in cognitive ($p=0.01$) and motor ($p=0.02$) development

when compared to children in the control group. Although the children improved, they still had a degree of developmental delay at the end of the study period.

The parenting stress levels decreased significantly for caregivers in both the control and the experimental groups ($p < 0.001$), but there was no significant difference between the two groups ($p = 0.057$).

The groups were well matched at all time points for anthropometric measures and CD4 counts with no significant differences being found. There was also no difference in the number of children on antiretroviral therapy between the groups at any time.

Children who were antiretroviral naïve at the start of the study and then started highly active antiretroviral therapy showed a significant improvement in motor development ($p < 0.001$), but no improvement in cognitive development ($p = 0.77$).

A combination of a number of factors was predictive of developmental status. This included growth parameters, CD4 counts and the age of the child. Being in the experimental group and being older at baseline assessment were important predictors of improvement in MDI and PDI over time. Parenting stress was predicted by a number of factors, including educational level of the caregiver, type of housing and the number of children in the household. A decrease in parenting stress was most likely in caregivers who were better educated and who lived in households with fewer adults.

These results signify that a basic home programme can significantly improve both the cognitive and motor development of young children infected with HIV. This programme was simple and easily implemented and should become standard practice at paediatric HIV clinics in South Africa. The current protocol for administering antiretrovirals in South Africa allowed for motor, but not cognitive improvement in young children commencing treatment. Parenting stress was not affected by the addition of a basic home stimulation programme.

The psychosocial and developmental needs of South African children infected with HIV are complex and multifaceted. Further research is needed to establish the best possible interventions for these children and their families.

DECLARATION

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

Signed this day in Johannesburg

Signature

Date

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HIV: What do physical therapists need to know (Dept of Physical Therapy)

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ABBREVIATIONS USED.

AIDS: Acquired immunodeficiency syndrome

BSID: Bayley Scales of Infant Development

BSID II: Bayley Scales of Infant Development, second edition

CNS: Central Nervous System

CT scan: Computerised tomography scan

DDST: Denver Developmental Screening Tool

ELISA: Enzyme linked immunosorbant assay

HAART: Highly Active Antiretroviral Therapy

Haz: Height-for-age z-score

HI: Human Immunodeficiency

HIV: Human Immunodeficiency Virus

HSRC: Human Sciences Research Council

ICF: International Classification of Functioning, Disability and Health

MDI: Mental Developmental Index

PCR: Polymerase chain reaction

PDI: Psychomotor Developmental Index

PSI/SF: Parenting Stress Index/ Short Form

Waz: Weight-for-age z-score

WHO: World Health Organisation

Whz: Weight-for-height z-score

Chapter 1

INTRODUCTION

1.1 Paediatric HIV in South Africa

More than twenty years after it was first diagnosed, HIV remains a major global health problem. Sub-Saharan Africa is the region that has been most severely affected by HIV and continues to have the highest prevalence of HIV in the world (Lau and Muula, 2004). At present there are approximately one million children in Sub-Saharan Africa infected with HIV, this accounts for over 90% of the HIV infected children in the world (UNAIDS report, 2005). In Southern Africa HIV related illness has become the leading cause of death in children less than five years of age (Brown et al, 2000).

Despite being one of the better resourced countries in the region with a relatively well developed health care system, South Africa has not managed to escape the impact of HIV. The epidemic in South Africa shows no sign of relenting (UNAIDS, 2005). In South Africa young women between the ages of 25 and 35 years have the highest prevalence rates of HIV infection (UNAIDS, 2005). As more young women of child bearing age become infected with HIV, so the number of infants born with vertically transmitted HIV will continue to rise. The health care costs for these children are largely borne by the state as the majority are unable to afford private health care. At present the mother-to-child transmission of HIV in South Africa remains high, at approximately 30% (Meyers et al, 2000). Even though this figure is expected to come down as more women get access to antiretroviral therapy perinatally, there are still many thousands of HIV infected infants in our health care system.

Access to antiretroviral therapy in Sub-Saharan Africa remains an issue of grave concern. According to UNAIDS (2005), by mid 2005 only one in ten African people who need antiretrovirals were actually receiving them. Achieving universal access forms part of the long-term challenge of bringing HIV under control in Africa.

Until April 2004 most paediatric HIV clinics in South Africa only saw children over two years of age as these children had a better prognosis for long term survival. In April 2004 when antiretroviral treatment became available in the public sector, paediatric HIV services were extended to include infants. However there is still a general lack of experience among health care workers in managing young children infected with HIV and a need for treatment guidelines and protocols exists.

Neurological complications have been identified in children with HIV infection since the disease was first described in children in the early 1980s (Belman et al 1985; Epstein et al 1985). Several key international studies have identified the prevalence of neurological complication in HIV infected children to be 30-40% (Belman et al, 1996; Msellati et al, 1993; European Collaborative Study, 1990). Little research has been done in South Africa to describe the magnitude of the problem. One study done on infants under one year of age found that 40% of HIV infected infants in this age group presented with developmental delay (Potterton and Eales, 2001). As yet there have been no longitudinal studies done in South Africa to monitor the progression of developmental problems in HIV infected children.

Although numerous studies from developed countries have identified neurodevelopmental problems in HIV infected children, most of these studies have been prevalence studies and have not followed the children's progress over a period of time. A limited number of longitudinal studies have been done to monitor children's developmental progress, but these studies have all been done in developed countries where children have access to antiretroviral therapy (Llorente et al, 2003; Belman et al, 1996; Nozyce et al, 1994). No longitudinal studies done in South Africa could be found. The impact of antiretroviral therapy on childhood development has only been studied in well resourced countries and is still a contentious issue. There is therefore little information available on the natural progression of developmental problems in children infected with HIV. This makes it difficult to plan management programmes for these children and to monitor the effectiveness of programmes implemented.

South African physiotherapists have had little input into the long term management of children infected with HIV. Present staffing levels at provincial hospitals make it difficult to offer regular physiotherapy services to all HIV infected children in South Africa. To date no physiotherapy intervention studies have been done in the field of paediatric developmental delay due to HIV. There are no existing guidelines as to whether physiotherapy intervention would be of any benefit to these children in the South African setting. A study by Spiegel and Mayers (1991) found that a regular home-based physiotherapy programme provided a sense of purpose and competence for caregivers of HIV infected children. The study does not describe the physiotherapy programme, nor discuss its possible impact on the child. A few studies have been done on the role of physiotherapy in the management of patients infected with HIV, however all of them focus on the treatment of adults and do not mention the treatment of children (McLure, 1993). There is therefore very little information available to guide physiotherapists in determining whether or not to treat children infected with HIV, and what treatment would be most appropriate. As more children gain access to antiretrovirals and survive for longer so their rehabilitation needs are likely to increase (Nixon and Cott, 2000).

Recent research in paediatric physiotherapy has highlighted the need for a family-centered approach to the management of children with disabilities (O'Neil et al 2001, King et al 1999, Viscardis 1998). This approach requires that the needs of the disabled child must be met within the context of their individual family and that any rehabilitation programme given to the child must be designed specifically for the individual with input from the family. Goal setting must be done with the family. This therefore means that no two children will have exactly the same programme although similar principles of management will exist for children with similar conditions.

Paediatric HIV is a multigenerational disorder. The diagnosis of a child as HIV positive has far reaching social and financial implications for the family, over and above the immediate health concerns. Although the impact of chronic childhood illness and disability on family functioning and parenting stress has been previously studied (O'Neil et al, 2001; Button et al, 2001; Dyson, 1991), the situation of families in South Africa caring for children infected with HIV is a unique one which has not been studied in

depth. A number of studies conducted in the USA have highlighted high levels of parenting stress in caregivers of HIV infected and affected children (Goldstein et al, 2005; Linsk et al, 2004; Silver et al, 2003; Weiner et al, 2001).

1.2 Problem Statement

In their review article, Lwin and Melvin (2001) highlight the fact that very little research in the field of paediatric HIV has adopted a longitudinal, family focused approach. No studies have investigated the parenting stress in relation to the HIV infected child's developmental status. In developing countries such as South Africa, the emphasis is on providing basic health and social care to families affected by HIV and studies of psychosocial aspects, such as parenting stress, which affect quality of life have not been seen as a priority. Very little information is available on the developmental status of HIV positive children in South Africa. There is therefore a great need for studies that take both clinical and psychosocial markers into account.

1.3 Research Question

Does a basic home management programme impact on the neurodevelopmental status of HIV infected children and decrease the parenting stress of caregivers of HIV infected children who attend a busy paediatric outpatient clinic?

1.4 Aim

The aim of this study was to determine whether a basic home management programme had a positive impact on the parenting stress of caregivers of HIV infected children and the neurodevelopmental status of the children attending a busy paediatric outpatient clinic.

1.5 Objectives

The objectives of this study were as follows:

- to describe the extent and progression of neurodevelopmental delay in a population of HIV infected children
- to monitor the impact of a basic home management programme on the neurodevelopmental status of the child
- to determine what factors were predictive of neurodevelopmental status and parenting stress
- to determine whether a basic home management programme decreased the parenting stress experienced by the child's caregiver
- to monitor the neurodevelopmental progress of children who received antiretroviral therapy
- to determine what other factors impacted on the stress levels of caregivers of HIV infected children
- to determine who the main caregivers of HIV infected children attending HIV clinics were.

1.6 Significance of the Study

HIV continues to have adverse effects on the health and well being of children in South Africa. At present these children are not being offered any rehabilitation services at paediatric HIV clinics in South Africa, despite the fact that neurodevelopmental delay is a common complication of paediatric HIV. The results of this study will establish whether a home management programme, delivered in the context of a busy outpatient paediatric HIV clinic, can have a positive influence on the neurodevelopmental status of HIV positive children and reduce the parenting stress experienced by their caregivers. This knowledge can guide future practice and help to ensure that the needs of HIV positive children are met in a more holistic manner.

Chapter 2

LITERATURE REVIEW

2.1 Introduction

In this chapter the epidemiology of HIV in Sub-Saharan Africa will be discussed with particular reference to paediatric HIV. An overview of paediatric HIV will be given with a more detailed discussion on the neurological complications of this disease. The impact of paediatric HIV on the family will be discussed and various intervention strategies will be presented. The context in which South African children infected with HIV find themselves will be summarised. Literature relating to school going children and institutionalised children is not discussed in detail in this review.

Articles were sourced for this review using Pubmed, CINAHL, PSYCHInfo, Pedro and Cochrane Collaboration searches. A hand search was also conducted in the Health Sciences Library of the University of the Witwatersrand. Key words used in searches included; HIV, children, encephalopathy, developmental delay, neurodevelopment, parenting stress, psychosocial.

2.2 Epidemiology

Sub-Saharan Africa is home to only 10% of the world's population and yet 60% of all HIV positive people live in this region. An estimated 2.4 million adults and children died of AIDS in Sub-Saharan Africa in 2005 (UNAIDS, 2005). Although prevalence rates are coming down slowly in three African countries, Kenya, Uganda and Zimbabwe, HIV prevalence rates remain extremely high in other African countries and might not have reached their peaks in some countries (UNAIDS, 2005). Economic and social diversity between countries and even within countries mean that there is no one "African AIDS

epidemic". As prevalence rates vary enormously from country to country and even from one area to another within countries, generalisations must be made with caution.

South Africa has one of the fastest growing HIV epidemics in the world. Data collected over the last few years show that the epidemic has started to level off but this is probably due to natural saturation of the epidemic rather than the result of any particular intervention. The prevalence varies by age, gender and geographical area (Gouws and Karim, 2005). Recent data from the South African Department of Health, collected in ante-natal clinics, show that the prevalence in pregnant women has reached its highest yet at 29.5% (UNAIDS, 2005). Prevalence was highest in women between 25-34 years of age with more than one in three women in this age group being HIV positive. The prevalence was almost as high in women between 20-25 years of age. In KwaZulu-Natal, the province worst hit by HIV in South Africa, the prevalence reached 40% (UNAIDS, 2005)

Data on the prevalence of HIV in children is not easy to find, and is often extrapolated from antenatal studies. Mother-to-child transmission of HIV remains high in South Africa especially in areas where antiretrovirals are not available. According to Coovadia and Meyers (2001) mother to child transmission of HIV in South Africa is approximately 30%. In an extensive study commissioned by the Nelson Mandela Foundation and conducted in the Free State 47% of children with an HIV positive mother were infected as well (Shisana et al, 2005). In 2001 10% of all HIV infected individuals in South Africa were children under 14 years of age (Lau and Muula, 2004), and this translated to a quarter of a million children in 2003 (Saloojee and Pettifor, 2005). In the first nationwide study of HIV prevalence in children conducted in 2004, Brookes et al found that 5.4% of South African children were HIV positive. When they looked at younger children between two and nine years of age the prevalence was 6.2%. The authors of this report do caution that further studies should be done to confirm these prevalence rates which were higher than expected. As long as the prevalence rate of HIV in young women of child bearing age remains so high it can be anticipated that the number of paediatric infections will continue to increase, especially as universal access to HAART remains out of reach in most African countries.

The underlying reasons for Sub-Sahara's vulnerability to HIV are multifactorial and complex. Some of the reasons put forward as playing contributory roles include the following:

- Africa was exposed to HIV very early in the course of the disease's history, the epidemic has therefore had more time to affect African communities.
- HIV has spread very rapidly in Sub-Saharan Africa due to high rates of other sexually transmitted diseases and inadequate management to prevent transmission.
- Multiple sexual partners are common in Sub-Saharan Africa which facilitates the spread of HIV.
- Women hold a subordinate role in most African cultures and have little or no control over their sex lives, this places them at great risk of being infected. HIV is a taboo topic in many cultures which hinders discussion on the topic and makes prevention, diagnosis and treatment more complex.
- Poor nutritional status and poverty increases vulnerability to HIV and hunger may lead people to expose themselves to the risk of HIV through transactional sex. Chronic poverty means that large sectors of the country have reduced access to medical care.
- Political instability and violence inevitably leads to a decline in social services which makes initiation and maintenance of public health measures difficult.
- International funding agencies are reluctant to invest in programmes that may not be sustainable.
- Rape is common in conflict zones and basic health care and hygiene cease to be priorities, people are also less likely to change their behaviour when their futures are bleak.
- Urbanisation and migration of people in search for work or as refugees fuels the spread of HIV as people may have multiple sexual partners in different geographical areas. Urbanisation and the constant movement of people has also lead to the breakdown of traditional family structures and moral norms.

- Antiretroviral therapy is not universally accessible in Sub-Saharan Africa with rural communities being less likely to have access. Untreated individuals with high viral loads are more likely to spread HIV.
- Low levels of literacy and lack of understanding of a biomedical model have meant that the many education programmes started in Sub-Saharan Africa have had little impact.
- Leaders in Sub-Saharan Africa have been reluctant to recognise the potential impact of HIV and public health policies to address the issues have been slow to materialise (Lau and Muula, 2004).

This list is by no means exhaustive and may reflect certain biases on the part of the authors, the relative impact of each of these factors therefore warrants further investigation.

Thus far only three countries in Sub-Saharan Africa, Uganda, Kenya and Zimbabwe have been able to show a decrease in the spread of HIV. It would appear that prevention programmes initiated over the past decade are finally having an effect in these countries and more people are presenting themselves for testing and counselling as antiretrovirals become available (UNAIDS, 2005). In South Africa a multisectoral, sustained and coordinated effort is required to control the epidemic.

2.3 Paediatric HIV

2.3.1 Mother to child transmission of HIV.

Most HIV infection in infants is acquired through mother to child transmission although the possibility of transmission through sexual abuse or healthcare practices cannot be ignored (Brookes et al, 2004; American Academy of Pediatrics, 1999; Frederick et al, 1994). In the absence of antiretroviral treatment the vertical transmission of HIV is reported to be as high as 40% in Africa (Chakraborty, 2005; Wiznia et al, 1996). These very high rates in Africa may be attributed to breastfeeding, poor obstetric management

as well as limited access to antiretroviral therapy. The timing of transmission depends on a number of factors largely related to the mother's immune status (Tardieu, 1998)

Infection of the infant may take place in-utero and is thought to occur transplacentally. In-utero infection is associated with poor prognosis and increased risk of spontaneous abortion (Chakraborty, 2005; Wiznia et al, 1996). The HI virus has been isolated in 13-20 week aborted fetuses including in specimens of neural tissue (Falloon et al, 1989).

Intrapartum transmission of HIV which is thought to occur in two thirds of cases of mother-to-child transmission, can occur due to maternofetal transfusion of blood during labour or through contact of infant mucous membranes with maternal blood and other secretions during delivery. Risk factors for intrapartum transmission include prolonged rupture of membranes, invasive procedures, high maternal viral load at the time of delivery and vaginal delivery (Chakraborty, 2005; Wiznia et al, 1996). Severe maternal vitamin A deficiency has also been found to increase the risk of transmission (Brown and Lourie, 2000).

Post partum infection of infants through breast feeding is estimated to occur in 12-14% of cases. HIV has been detected in breast milk and colostrum. Infection is thought to occur due to prolonged exposure of the infant's oral and gastrointestinal tracts to infected breast milk. Infants are at greater risk of infection if the mother has cracked nipples or a breast abscess (Chakraborty, 2005) as well as if breastfeeding is interspersed with formula feeding. Mothers who choose to breast feed their infants should therefore be advised about exclusive breastfeeding (Coutsoudis et al, 2001).

2.3.2 Testing

The diagnosis of HIV infection in infants is evolving rapidly. In South Africa more sites are gaining access to polymerase chain reaction (PCR) testing which allows for accurate and early detection of HIV antigens, rather than having to wait until the child is 15 months old before performing an antibody test. In the absence of PCR testing serologic testing using enzyme-linked immunosorbant assay (ELISA) may be done. Although

much cheaper and more readily available, ELISA tests only detect the presence of HIV antibodies and are unable to distinguish whether these are maternal antibodies or not. The test may therefore yield false positive results in infants below 15-18 months who still have maternal antibodies in their bloodstreams (Falloon et al, 1989).

In their advocacy statement, the African Network for Care of Children Affected by HIV/AIDS (ANECCA) provide detailed guidelines for the accurate diagnosis of HIV in children in Sub-Saharan Africa taking possible clinical and financial constraints into account. Improved access to antiretrovirals, makes it imperative that infants are diagnosed as early as possible so that they can access treatment as soon as possible (ANECCA, 2005). Obstacles to early diagnosis such as limited laboratory facilities and expertise as well as the high cost of tests must be overcome (ANECCA, 2005).

2.3.3 Clinical Presentation and Progression

In their comprehensive overview of paediatric HIV infection Wiznia et al (1996) describe the natural history of children perinatally infected with HIV. *Rapid progressors* are described as children who present with AIDS by their first birthday. They usually present clinically very early in their lives, often before five months of age. These infants present with pneumocystis carinii pneumonia, failure to thrive, hepatitis, diarrhoea, neurodevelopmental delays and encephalopathy. *Slow progressors* on the other hand are relatively much healthier in infancy and have a better five year prognosis. This bimodal clinical presentation is also described by Chakraborty (2005) and by Bobat et al (1998) in their South African study as well as by Spira et al (1999) in their report on the natural history of HIV infection, in children in Rwanda.

HIV in children causes a broad spectrum of diseases which have been well described in the literature (Chakraborty, 2005; Cooper et al, 2004; Coovadia and Meyers, 2001; Spira et al 1999; Bobat et al, 1998; Wiznia et al 1996). Only the neurological complications of paediatric HIV will be discussed in detail in the following section of this literature review.

2.3.4 Antiretrovirals

Antiretroviral therapy has been used consistently in the management of HIV infected children in the developed world for well over a decade. The aims of antiretroviral therapy are to reduce the plasma viral load to undetectable levels and maintain good immunological status of the child in order to prevent disease progression and opportunistic infections. The combination of reverse transcriptase inhibitors and protease inhibitors has been pivotal in reducing HIV morbidity and mortality in Westernised countries (Chakraborty, 2005).

Reverse transcriptase inhibitors prevent HIV from transcribing itself from RNA to proviral DNA. This process is necessary for the virus to integrate into the host cell nucleus. A number of nucleoside, nucleotide and non-nucleoside reverse transcriptase inhibitors have been developed and are an integral part of HAART regimens. Protease inhibitors prevent the formation of mature competent virions which are capable of leaving the host cell after replication of the virus in the host nucleus has occurred. Protease inhibitors are extremely effective and their use has revolutionised antiretroviral therapy (Pratt, 2003).

Highly Active Antiretroviral Therapy (HAART) is a combination of three (or more) antiretroviral drugs, usually two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase inhibitor or a protease inhibitor. Although extremely effective these drugs are associated with a number of side effects which must be monitored by clinicians (Pratt, 2003).

Access to antiretroviral drugs and the potential of going on a highly active antiretroviral regime is only starting to be realised in South Africa and other African countries. The South African government began its antiretroviral roll-out programme in April 2004. This programme has been slower to gain momentum than planned and has been fraught with political controversy. The UNAIDS report of December 2005 estimates that fewer than 10% of people in Sub-Saharan Africa who need antiretrovirals are currently receiving them. Concerns have been raised that the widespread use of antiretrovirals in developing countries will result in resistance due to poor adherence. This would limit the

drug choices available in the future to these populations. Until recently the high cost of drugs was the main factor limiting access to antiretrovirals in sub-Saharan Africa, but now that drug prices have come down considerably, a lack of infrastructure and trained personnel are probably the major constraints. A number of models for distributing antiretrovirals in an effective and sustainable manner are currently being explored (Wood, 2005). In South Africa antiretrovirals are being phased in with tertiary hospitals gaining access first. As more personnel are trained and facilities are upgraded the programme is being expanded to include smaller hospitals and clinics.

The best age at which to initiate HAART in children has been a topic of some debate over the past few years. The decision to initiate HAART is a complex one and should only be taken in consultation with the child's caregivers (Wiznia et al, 1996). The Working Group on Antiretroviral Therapy suggests that HAART be started in the presence of moderate immunodeficiency as defined by age corrected CD4 counts. Chakraborty (2005) advocates "aggressive, multidrug therapy, as early in infection as possible" in order to suppress viral replication and prevent the emergence of resistant viral strains. Luzuriaga and Sullivan (2002) argue that antiretroviral therapy should be started within the first few months of life wherever possible. They base their argument on the premise that HIV can be accurately diagnosed in the first few weeks of life, that there is no way of determining which children will be rapid progressors, and finally that several antiretroviral regimes have been proven to be safe, effective and well tolerated in infants and young children. Current practice in most African countries, including South Africa is to start HAART only once the child's CD4 count has dropped to below 20% (Dept of Health, South Africa, 2005). South African children are thus facing significant immunocompromise before being able to start HAART. Newly revised World Health Organisation guidelines propose starting treatment of children earlier, at CD4<25%, in order to optimise long term outcomes (ANNECCA, 2005). A study conducted on adults in South Africa supports this proposal. Badri et al, 2006, found that delaying the initiation of HAART until the CD4 count was < 200 μ L resulted in increased morbidity and mortality. They suggest that criteria for commencing HAART, in resource poor settings, be amended.

The impact of HAART on the neurodevelopment of HIV positive infants will be discussed below.

2.4 HIV and the Developing Nervous System

Central nervous system involvement in HIV infected children was first described in the early 1980's, soon after AIDS had been identified (Epstein 1985). The neurological syndrome described, together with neuropathological findings, confirmed that HIV was a neurotrophic virus (Belman et al, 1992). Many questions about the natural progression and the pathogenic mechanisms of HIV related CNS disease in children remain unanswered (Rausch and Stover, 2001).

Neurological complications and resultant developmental delay are seen frequently in HIV positive children, especially in younger children who have been infected perinatally (Raskino et al, 1999; Nozyce et al, 1994; Belman, 1992). The stage of brain development at which HIV infection occurs varies between children and so the clinical presentation will differ too (Belman, 1990).

2.4.1 Neuropathology

The central nervous system (CNS) in HIV positive children may be affected by invasion by HIV directly or by opportunistic infections such as meningitis or by both (Fragoso et al, 1999; Davies et al, 1992). Children under the age of three years are more likely to show evidence of CNS involvement compared to children who have survived over six years of age (Blanche et al, 1990).

The CNS is a viral reservoir for HIV (Kolson, 2002). HIV is found in cerebrospinal fluid at the time or soon after seroconversion (Spector et al, 1993; Davies et al, 1992; Epstein et al, 1987; Goudsmit et al, 1986; Ho et al, 1985; Resnick et al, 1985). HIV has been isolated in the brains of HIV infected patients during autopsy (Boni et al 1993; Davies et al, 1992; Navia et al, 1986; Sharer et al, 1986) as well as in the CNS of aborted fetuses (Lyman et al, 1990). Increased levels of HIV DNA are found in brain tissue of patients who have encephalopathy (Sei et al, 1995).

HIV infected monocytes cross the immature blood brain barrier. The most frequently infected cells within the brain are the macrophages (Tardieu, 1998; Ensoli et al, 1997; Wiley et al, 1986). Macrophages in the white matter, the basal ganglia and around the blood vessels are the most vulnerable to infection. Monocytes, lymphocytes and astrocytes may also become infected but to a lesser degree (Tardieu, 1998; Wilfert et al, 1994; Tardieu, 1992).

Neuronal death, due to apoptosis, is thought to be due to the release of toxic products by infected macrophages. Infected macrophages secrete pro-inflammatory cytokines and other soluble factors such as HIV proteins which are toxic to nearby neurones (Kolson, 2002). Neurones and oligodendrocytes do not appear to be directly infected by the HI virus (Tardieu, 1998).

Calcification of the basal ganglia is a common finding in HIV infected children (Tardieu, 1998; Schmitt, 1991; Lenhart and Wiley, 1989; Belman, 1988; Belman, 1986). It may range from small vessel calcipherites to large calcific parenchymal deposits (Belman et al, 1988). Calcification of the white matter, especially in the frontal lobes has also been noted (Belman et al, 1988).

Neuroradiological findings show cerebral atrophy (Falloon et al, 1989; Belman et al, 1988) and enlargement of the ventricles and subarachnoid space (Tardieu, 1998) as well as the abovementioned calcification. Lateral as well as anterior corticospinal tract degeneration has been described (Belman et al 1988). Neuronal loss in the frontal cortex of patients with AIDS dementia has been described (Everall et al, 1991).

According to Falloon et al (1989) the encephalopathy that results may be due to the following:

- Release of toxins by infected macrophages leading to impaired neuronal function.
- Dysfunction of the blood-brain barrier due to HIV infection of the endothelial cells.
- Possible HIV infection of neuronal and glial cells leading to demyelination or neuronal damage (neuronal infection has not been conclusively documented).

- Blockage of binding of neuroleukin to neurones by the HIV envelope glycoprotein.
- Damage to neural tissues caused directly by the HIV envelope glycoprotein.

The discrepancy between the severity of the ensuing encephalopathy and the relatively small viral load in the CNS suggests that factors other than direct cellular damage may play a role in determining developmental outcome.

There has been some debate as to whether or not astrocytes are directly involved in HIV infection of the CNS. Tornatore et al (1994) postulate that astrocytes could serve as a reservoir for HIV in the developing CNS, thus facilitating infection of mononuclear and microglial cells. Alternatively the astrocytes may release cytokines capable of recruiting macrophages across the blood brain barrier or increasing replication in infected monocytes. Epstein et al (1993) suggest that infected macrophages initiate neurotoxicity which is amplified through interactions with astrocytes. They found that astrocyte-macrophage interaction produces cytokines which cause astroglial proliferation and neuronal death. These findings explain why relatively low numbers of infected macrophages can produce progressive and devastating neurological impairment. In an *in vitro* study, Ioannidis et al (1995) demonstrated that HIV-1 can productively infect infant microglia and that infection can be maintained for a long period of time. The release of cytokines, such as tumour necrosis factor, and neurotoxins by infected microglia and multinucleated giant cells was confirmed in this study. According to Schmidtmayerova et al (1996) HIV-1 infected monocytes are able to recruit uninfected T cells and monocytes to sites of active viral replication or inflammation, mainly the brain and lymph nodes, thus enhancing the spread of infection.

Wiley et al (1991) report neocortical damage in HIV positive adults with encephalitis. They demonstrated thinning of the neocortex with associated loss of large cortical neurones. The fact that they were unable to associate these changes with the presence of HIV antigens suggests that neocortical damage may be an indirect effect of HIV infection of the CNS.

De Carli et al (1993) found evidence of CT abnormalities in HIV infected children even prior to any clinical signs of encephalopathy. The most common finding was ventricular enlargement followed by cortical atrophy, leukoaraiosis and cerebral calcification. The degree of calcification seen on CT scans of young vertically infected children has been shown to correlate with the degree of cognitive dysfunction and aberrant behaviour in these children (Brouwers et al, 1995). The authors of the above two studies recommend the use of routine CT scans in HIV infected children to monitor presymptomatic brain disease and identify children at risk.

Tardieu et al (2000) found that encephalopathy was most prevalent in children under one year of age and equalled the prevalence in adults by the time the children were seven years of age. Infants who present with encephalopathy before one year tend to have signs of neurodevelopmental involvement at birth as well as decreased birth weight and head circumference. They hypothesise that early onset encephalopathy has different neuropathologic origins to later onset encephalopathy. Early encephalopathy may be related to pathologic events during late foetal life. This is very significant as the last few months of gestation are the period of fastest brain growth. McGrath et al (2006) found that the risk of neurodevelopmental delay was highest amongst infants who were already HIV infected at birth. Any attempt to reduce the onset of encephalopathy should therefore focus on the last months of pregnancy (Smith et al, 2000).

The current understanding of the neuropathology of paediatric HIV infection suggests that therapeutic intervention should be aimed at sustaining the immune activation of microglia, repairing the integrity of the blood-brain barrier and providing protection from neurotoxic agents to minimise neuronal damage (Epstein and Gelbard, 1999).

2.4.2 Clinical Manifestations of Neurological Involvement

A characteristic encephalopathy has been described in a number of studies related to infants and children infected with HIV (Chase et al, 1995; Spitaels, 1994; Pavlakis et al, 1994; Nozyce et al, 1994; Fowler, 1994; Blanche, 1990; European Collaborative Study, 1990; Diamond et al, 1990; Falloon et al, 1989; Ultman et al, 1986, 1987, 1996; Belman et al 1985, 1988, 1992, 1996; Epstein 1985, 1986;).

Encephalopathy may be one of the first clinical signs of HIV infection (Falloon, 1989). It initially presents with developmental delays, loss of milestones and deterioration in intellectual abilities. The developmental delay may progress to include pyramidal tract signs, ataxia, abnormal muscle tone and pseudobulbar palsy (Tardieu, 1998; Belman 1992; Falloon et al, 1989). Acquired microcephaly is common in infants (Falloon et al 1989). Ultimately the encephalopathy may result in spastic quadraparesis with dystonic posturing and regression of motor milestones (Tardieu, 1998). The development of severe encephalopathy in infancy has been correlated with serious systemic disease and an increased and early mortality (Llorente et al, 2003; Pearson et al, 2000; Belman, 1992). The presence of hepatosplenomegaly, splenomegaly and lymphadenopathy in the first three months of life increases the risk of HIV encephalopathy and death 28-fold (Laufer et al, 2000). Children who present with AIDS defining illnesses in the first two years of life are at risk of also having significant neurodevelopmental delays which may be attributed to HIV encephalopathy (Chase et al, 2000; Pearson et al, 2000; Belman et al, 1996; Nozyce et al, 1994).

A clinical description of the natural progression of the encephalopathy has been generally adopted with the following clinical pictures being described:

- *Subacute progressive*: where the child fails to attain new milestones and starts to lose previously attained milestones
- *Plateau*: no new milestones are attained, but there is no regression
- *Static*: the child continues to attain milestones but at a much slower rate than normal (Pizzo P and Wilfert C, 1994).

In her overview of CNS disorders related to paediatric HIV infection Belman (1992) notes that there are a number of other factors apart from encephalopathy that may result in neurodevelopmental delay in HIV infected children. These factors include:

- Metabolic and endocrinologic disturbances resulting from HIV infection
- Maternal illness, malnutrition and substance abuse during pregnancy
- Complications due to prematurity

- CNS complications due to underlying medical conditions
- Psychosocial stressors, including poverty, maternal illness, changing caretakers, chronic illness and frequent hospitalisations
- Iatrogenic problems due to toxic or metabolic complications of therapy (Belman, 1992).

Neuropsychological measures are good predictors of disease progression, even better than CD4 counts. Poor muscle tone is also significantly associated with poor outcome, as is poor strength and decreased muscle bulk (Pearson et al, 2000).

More recent studies by Smith et al (2000) and McGrath et al (2006b) have focussed on the impact of the timing of HIV infection on the neurodevelopment of HIV infected infants. Infants who are infected in utero present with clinical signs of neurodevelopmental delay earlier on and progress more rapidly. McGrath et al (2006) postulate that the difference in clinical presentation neurodevelopmentally could be explained by differences in the timing of infection with HIV when the developing central nervous system is at different stages of organisation. Early infection is more likely to result in motor delays as abnormal myelination could affect projection fibres as well as association and commissural connections. Later infection is more likely to result in cognitive delays as commissural connections and the connections with poles of cerebral lobes are more affected.

A lower CD4 count and a high viral load are associated with increased severity of disability, growth failure and slower attainment of milestones in perinatally infected infants and young children (Pearson et al, 2000; Belman et al, 1996; Pollack et al, 1996; Chase et al, 1995; Fowler, 1994).

2.5 Facets Of Development Affected

Not many studies have attempted to identify the facets of development most affected by HIV. More research is needed in this area to establish which areas of development are

most affected. The following section provides an overview of the lessons learnt from previous studies on neurodevelopment in HIV infected children.

2.5.1 Paediatric HIV and Cognitive Development

HIV infected infants have cognitive delay and deficits in neuropsychological functioning due to CNS impairments. Mental retardation and acquired microcephaly are common findings in children with HIV encephalopathy (McGrath et al, 2006a; Fragoso et al, 1999; Belman et al, 1996; Henry et al, 1996; Fowler, 1994; Belman et al, 1988; Epstein et al, 1986; Belman et al, 1985; Ulmann et al, 1985). Deficits in visual scanning, academic achievement and psychomotor speed have been found (Cohen et al, 1991). School-going children with AIDS have memory and visuopraxic impairments. However in the early stages of infection only minimal impairment of executive functions has been noted (Bisiacchi et al, 2000). Cognitive developmental skills such as comprehension and puzzle performance are less severely affected indicating that cognitive deficits increase with increasing age (Drotar et al, 1997). Children infected in utero appear to be the most severely affected (Brouwers et al, 1995; De Carli et al, 1993).

The cognitive deficits described in HIV positive children exist independently of environmental and social risk factors (McGrath et al, 2006; Chase et al, 2000; Knight et al, 2000; Henry et al, 1996).

2.5.2 Paediatric HIV and Motor Development

Motor development is compromised from an early stage in HIV positive infants and children may start presenting with motor impairments in the first few months of life (Potterton and Eales, 2001; Chase et al, 1995; Nozyce et al, 1994). Children's motor development, coordination, muscle tone and muscle strength are consistently affected by HIV infection (Pearson et al, 2000; Drotar et al, 1997; Chase et al, 1995). Dystonia, ataxia and tremor indicate extrapyramidal and cerebellar involvement (Chase et al, 1995; Belman et al, 1988). Diaparesis with mild spasticity and progressive long tract signs may be seen (Fragoso et al, 1999; Belman et al, 1996; Belman, 1992; Belman et

al, 1988; Belman et al, 1985). Children with encephalopathy often present initially with low tone which progresses to increased tone with hyperreflexia (Mitchell, 2001).

Children who present with motor delays early on are at greater risk of disease progression (Pearson et al, 2000). Muscle strength is decreased in children infected with HIV (Blanchette et al, 2001; Pearson et al, 2000), which may be a factor contributing to the fact that gross motor development is often more affected than fine motor development (Baillieu, 2005; Potterton and Eales, 2001; Parks and Danoff, 1999)

2.5.3 Paediatric HIV and Speech and Language Development

The neuropathology of language deficits in HIV infected children is not well understood (Wolters et al, 1995). Language is affected later in life than gross motor development and is thought to be a reflection of both the chronicity of the disease as well as direct CNS involvement (Bisiacchi et al, 2000; Msellati et al, 1993). Chronic otitis media is extremely common in children who are HIV positive and while this may explain language delay due to impaired hearing to some extent it cannot account for all the deficits in speech and language experienced by these children (Layton and Scott, 2000).

HIV infected children have been found to have both receptive and expressive language delay, with expressive language being affected earlier and to a far greater extent (McClowry, 2000; Coplan et al, 1998; Tardieu et al, 1995; Wolters et al, 1995; 1997; Pressman, 1992; Pizzo et al, 1988; Epstein et al, 1986). The clinical impairments progress from mild expressive dysfunction in non-encephalopathic children, to severe expressive and receptive dysfunction in encephalopathic children. Both verbal and non-verbal language are affected (Wolters et al, 1997). Verbal language skills are strongly related to motor function and therefore any motor deficits including those in motor planning, and muscle coordination may impact on oro-motor skills and lead to feeding problems as well as articulation and speech difficulties (Wolters et al, 1997).

All aspects of development are adversely affected by paediatric HIV infection. Expressive language and gross motor development appear to be the most severely

impaired. Further studies on the relative severity of developmental impairment are needed, particularly in developing countries.

Evolving knowledge on the pathology of CNS involvement in children infected with HIV has underpinned a number of clinical studies over the last two decades. Clinical studies on the impact of HIV on the development of young children will be discussed in the following section.

2.6 Clinical Studies

Clinical studies relating to paediatric HIV and neurodevelopmental delay will be discussed. The studies will be grouped together in terms of when they were conducted as this makes it easier to see the evolution of knowledge on the topic over time. The studies done in Africa will be discussed separately as they raise issues of particular relevance to this study that need to be highlighted.

2.6.1 Clinical studies from the developed world

The first studies of HIV infected children and neurodevelopment emerged from three study sites, the University of Medicine and Dentistry in New Jersey, Albert Einstein College of Medicine in New York and the State University of New York. Two distinct groups of researchers co-authored nine of the first published articles produced on this topic between 1985 and 1988 (see table 2.1). The above factors must be borne in mind before attempting to extrapolate the findings of these studies to other parts of the world.

These preliminary studies were mainly descriptive in nature and none of them compared HIV positive children to a control group. Most had very small sample sizes ranging between four to 18 children (Epstein et al, 1986, 1988, Ultmann et al 1985, Belman et al, 1985, 1986). Epstein et al (1986) included 36 children in their study and Belman et al (1988) had a sample size of 68 children, making the findings of these studies more credible, although none of the authors discussed the power of their studies. The abovementioned studies also covered a very broad age range from six weeks to 13 years which makes it difficult to compare the findings of various studies. There is also

little consistency in the assessment tools used in the different studies. The Denver Developmental Scale in conjunction with the Bayley Scales of Infant Development (BSID) was used by Ulmann et al (1985, 1987) and by Belman et al (1985). Belman et al (1988) relied on hospital records and parents for developmental histories and did not specify how they assessed motor development. Epstein et al (1986) considered evaluation of milestones sufficient in infants less than 15 months of age and used the BSID for children over 15 months. Epstein et al (1985) report on four case studies but do not specify whether or not standardised assessments were used. The lack of consistency in the method of assessment makes it difficult to draw meaningful conclusions from the above findings.

All of the early studies reviewed highlighted the presence of neurological complications in children who are HIV positive. Epstein et al (1985) concluded that a progressive encephalopathy was an early feature of AIDS in children. Ulmann et al (1985) noted that developmental delays were worse in children with AIDS than in children with Aids Related Complex (ARC). They propose that these developmental abnormalities could be due to neurological, social or medical factors. Belman et al (1985) documented neurological involvement in all the children in their study (n=18). The severity of involvement varied but the most frequent manifestations included acquired microcephaly, encephalopathies and pyramidal tract signs. In 1986, Belman et al showed a 61% incidence of calcification of the basal ganglia in children who had AIDS. The study by Epstein et al (1986) confirmed his earlier findings (Epstein et al, 1985) and those of Belman et al (1985). It also showed a correlation between pathologic findings and clinical presentation and postulated that the encephalopathy described in children could be due to the direct effects of HIV on the developing nervous system. Ulmann et al (1987) described similar neurodevelopmental findings to previous studies and identified the need for sensitive standardised tests to be used in future studies. They also highlighted the fact that many other factors may influence developmental progress in HIV positive children. Ulmann et al (1987) advocated that all children with AIDS should have regular developmental assessments. In 1988, Belman et al published the largest longitudinal study to date (n=68) which delineated the clinical characteristics of CNS involvement in children with symptomatic HIV infection.

By the end of the 1980s the clinical presentation of HIV related encephalopathy had been well documented and described. The studies however represented a limited sample in terms of culture, socioeconomic status and geographical setting. These factors may themselves influence childhood development and therefore the results of these studies can not be extrapolated to different parts of the world. The emphasis of research now shifted to establish the prevalence of neurological involvement, the time of onset of clinical symptoms as well as the natural progression of neurological impairments. Although most of the studies were still based in the United States, more centres became involved and some European studies were also undertaken.

The age range of the studies done in the 1990's was narrower with most researchers focussing on the first two years of life with some extending to four years (Belman et al, 1996; Chase et al, 1995; Gay et al, 1995; Nozyce et al, 1994; Blanche et al, 1990; The European Collaborative Study, 1990). The fact that these studies focussed on children of similar ages makes it easier to compare their findings and draw conclusions.

With more studies focussing on younger children the issue of early accurate diagnosis became more pertinent. Blanche et al (1990) tested for HIV antibodies to confirm their diagnosis. In children younger than 15 months clinical diagnostic criteria used by the CDC were used to make a diagnosis, thus no asymptomatic children under 15 months of age were included in the study which could have led to possible bias. The sample was likely to under-represent the children who were slow progressors and still clinically well. The European Collaborative Study followed children born to HIV positive mothers. They were tested for HIV at 18 months and those who had antibodies were considered HIV positive and compared to those who had seroreverted. This meant that the assessors were, in theory, blind to the HIV status of the children until they were 18 months old. The reality is that the clinical signs of HIV infection are often very obvious, and therefore true blinding is difficult to achieve. This methodology was also used by Nozyce et al (1994) and Belman et al (1996) who tested for HIV antibodies at 15 and 18 months. Schmitt et al (1991) do not specify how diagnosis of HIV was made despite the

fact that all their subjects were under a year old. Lobato et al (1995) also do not discuss the diagnostic measures used in the six centres involved in their study.

A trend began to emerge with more researchers using standardised developmental assessment tools with the majority of studies making use of the Bayley Scales of Infant Development (Belman et al, 1996; Pollack et al, 1996; Henry et al, 1996; Chase et al, 1995, Gay et al, 1995; Nozyce et al, 1994). Unfortunately some studies still made use of non standardised tests and questions of validity and reliability were seldom raised (Schmitt et al, 1991; Blanche et al, 1990; The European Collaborative study, 1990).

Despite some methodological differences between the studies the findings relating to neurological complications and HIV infection were fairly consistent. In their longitudinal follow-up study Blanche et al (1990) identified encephalopathy in one third of their HIV positive sample in the first year of life. The European Collaborative Study had similar results with 31% of the HIV positive children in their sample presenting with neurological complications. Lobato et al (1995) conducted a large cross-sectional multicentre surveillance study and diagnosed HIV encephalopathy in 10% of their HIV infected children and in 23% of children with AIDS. Chase et al (1995) compared a group of HIV infected children to a group of HIV exposed but uninfected children under 30 months of age, and identified developmental delay in 50% of HIV infected children compared to 18% of seroreverter children. Nozyce et al (1994) and Belman et al (1996) both found severe encephalopathy in almost all children with symptomatic AIDS. Both these studies compared HIV positive children to HIV negative children and followed children up from birth to two years of age. The severity of neurological involvement appeared to be associated with the severity of clinical disease. Gay et al (1995) found that HIV positive infants under two years of age were developmentally delayed compared to their HIV negative controls even when the effects of HIV were not confounded by prenatal maternal drug use. Belman et al (1996) concluded that exposure to HIV in utero did not negatively impact on the developing CNS if the child did not become infected with HIV.

Pollack et al (1996) conducted a longitudinal follow up study of HIV positive infants, HIV exposed infants and HIV negative infants under the age of two years. They established

a correlation between HIV viral load and both neurodevelopment and linear growth. They found that infants with more pronounced growth failure had the most marked cognitive and motor delay. The sample size of infected children in this study was small and the authors acknowledge that maternal drug use and nutrition were possible confounding factors. In their study Henry et al (1996) controlled for the effects of psychosocial and environmental risk factors and still found that HIV positive children were significantly developmentally delayed compared to an HIV negative control group. They confirmed that the degree of cognitive delay was related to the level of immune system function (CD4 count). The age range in this study was very broad (one to nine years) and the sample size was relatively small with no power calculation given, the results should therefore be interpreted with caution. A number of other authors began to do comparative studies on neurodevelopment that also controlled for factors which may negatively impact on development (maternal education, prenatal drug exposure, minority status, birth conditions) and found that HIV positive infants still demonstrated early and marked cognitive and motor delay which may be early indicators of HIV disease progression (Chase et al, 2000; Knight et al, 2000).

The quality of these studies was considerably better than those done in the 1980's with use of control groups, larger sample sizes and standardised assessments. The results of these more recent studies are therefore more credible and can be generalised to other populations of HIV infected children.

Emphasis now shifted to establishing the effect of the timing of infection on the neurological development of the child. Early infection with HIV, while still in utero, was found to be related to more severe neurodevelopmental delay with more rapid progression (McGrath et al, 2006; Smith et al, 2000). The reasons for these findings have been discussed in section 2.4.1 on neuropathology.

Neuropsychological functioning was found to be an independent risk factor for death in HIV infected adults (Ellis et al, 1997). Pearson et al (2000) found that neuropsychological and motor function (especially reduced muscle mass) were useful indicators of disease progression in infants, children and adolescents and could be used

to predict long term outcomes, including longevity. Missmer et al (2000) found that growth parameters, immune status as well as social factors were important predictors of functional status in HIV infected children. Llorente et al (2003) found that BSID scores in the lower quartile were independent predictors of mortality after adjusting for treatment, clinical category, gestational age, viral load and CD4 percentage.

As children infected with HIV are gaining access to better treatment options they are surviving beyond early childhood and even into adolescence (Sullivan and Luzuriaga, 2001). This has meant that the focus of research in developed countries has shifted from the very young child to include children of school going age. More studies are now being done on the cognitive and behavioural problems experienced by these children in school. Receptive and expressive language impairments are also being more fully investigated in this group of older, verbal children (McClowry, 2000).

McClowry (2000) presented an overview of the literature and described the language and cognitive disorders found in school age children and confirmed that expressive language is more affected than receptive. This study highlighted issues of relevance for speech and language pathologists. Mellins et al (2003) suggested that the high rate of behavioural problems, particularly Attention Deficit Hyperactivity Disorder, experienced by HIV infected children, older than three years, are not as a result of HIV infection. They concluded that other biological and social factors such as poverty, family disruption, trauma, parental drug use and mental illness are likely to contribute to behavioural issues. Smith et al (2006) conducted cognitive assessments on HIV positive and HIV exposed children in a large, multicentre, longitudinal study. They found that children who had an AIDS defining illness early on in childhood were at risk for static encephalopathy and cognitive delay in pre-school and early school years.

Nozyce et al (2006) investigated behavioural and cognitive function of 274 clinically and immunologically stable antiretroviral-experienced HIV infected children. The age range in this study was broad (2-17 years) which necessitated the use of a number of different assessment tools. Children enrolled in this study were found to be four times more likely to present with behavioural problems and were at risk for cognitive and developmental

delay. There was no control group in this study and scores were compared to established childhood norms.

The findings of these studies highlight the fact that developmental issues are going to be a lifelong concern for children infected with HIV and that cognisance needs to be taken of this, especially with respect to planning educational services for these children. Developing countries have yet to experience the full impact of HIV positive children in school but can anticipate challenges in the future as more children gain access to HAART and survive to school going age.

Very little research has emerged from developing countries other than Africa during this time period. One study from Brazil (Fragoso, 1999) aimed to identify neurologic involvement in a cohort of HIV infected adolescents and children. Unfortunately this was a retrospective study and no formal neurodevelopmental assessment tools were used. The very low rate of neurological involvement identified (less than 10%) should therefore be viewed with some circumspection. The studies conducted in Africa will be discussed in section 2.6.2.

A summary of the most important studies done on the impact of HIV on the development of children in the developed world is presented in table 2.1.

Table 2.1 Summary of Neurodevelopmental studies in the developed world.

Authors	Country	Sample (n)	Age range	Measures	Main Findings
Belman et al 1985	USA	6	6m-5yrs	DDST BSID I Stanford Binet	All children had developmental or neurological involvement.
Ullmann et al 1985	USA	16	10m-6yrs	DDST BSID I Stanford Binet	All children delayed, especially in language and cognitive abilities
Epstein et al 1985	USA	4	10m-11yrs	CT scan Neurological examination	All 4 children had neurological deterioration
Epstein et al 1986	USA	36	2m-11yrs	BSID I Stanford Binet	Progressive encephalopathy due to primary infection of brain with HIV
Ullmann et al 1987	USA	16	6m-6yrs	DDST BSID I	Variable Neurodevelopmental courses
Belman et al 1988	USA	68	6wks-13yrs	BSID I Stanford-Binet Preschool language scale Kaufman Assessment Battery for Children	90% of children had evidence of CNS dysfunction. Severity of dysfunction and neurologic course was variable.
Blanche et al 1990	France	94	1m-9yrs	Neurological examination	One third of patients had severe immuno-suppression and encephalopathy early on, the majority had less clinical symptoms.
European collaborative study 1990	8 European centres	39 HIV + 164 HIV -	Birth-4yrs	Neurological examination	Lower prevalence of developmental delay than previously reported (31%)
Nozyce et al 1994	USA	21 HIV+ 65 sero-reverted 95 HIV-	Birth-2 yrs	BSID	HIV symptomatic children at greater risk for developmental impairments. HIV exposed, uninfected children not at risk for developmental delay.
Chase et al 1995	USA	24 HIV + 27 sero-reverted	4m-30m	BSID	Early and persistent delay is common in HIV + children. Exposed, uninfected children are not at risk.
Lobato et al 1995	USA Multi-centre	1811	Birth-13 yrs	Record review	HIV encephalopathy is common and associated with increased morbidity and mortality
Gay et al 1995	USA	126	Birth-2yrs	BSID	Rate of development in first 24 months slower in HIV infected children.
Belman et al 1996	USA	32 HIV + 99 sero-reverters 116 HIV-	Birth-2yrs	Neurological examination	Neurological deterioration associated with severe clinical disease. HIV exposed, uninfected children not at risk.

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Pollack et al 1996	USA	22HIV+ 42 Sero-reverters 27HIV-	Birth-2yrs	BSID	Developmental delay associated with decreased linear growth in HIV infected children. Growth and development associated with HIV viral load.
Chase et al 2000	USA	114HIV + 481 HIV-	4m-30m	BSID II	Cognitive and motor delays and declines in HIV infected children are important markers of disease progression, independent of other risk factors.
Smith et al 2000	USA	114	Birth-30m	BSID II	Early infected children are at greater risk for developmental impairment than those infected later.
Pearson et al 2000	USA	831	Birth-16yrs	BSID II McCarthy scales of children's abilities. Wechsler intelligence scale. Wechsler adult intelligence scale.	Neuropsychological and motor outcomes can predict long term outcomes (eg longevity) in HIV infected children.
Missmer et al 2000	USA	65	Mean 5.5yrs	Functional Status II	Growth parameters, immune status and social factors are important predictors of functional status.
Blanchette et al 2000	USA	25 HIV+ 25HIV -	Mean 24.7m Mean 18.5m	BSID II CT scan	CT abnormalities were associated with developmental delay
Macmillan et al 2001	USA	147HIV+ 383 drug exposed	Birth-30m	BSID II	HIV infection associated with slow neurodevelopment and decreased head growth.
Llorente et al 2003	USA	157	4m-30m	BSID II	BSID scores at 4m independently predict mortality.
Smith et al 2006	USA	117 HIV+ 422 HIV-	3yrs-7yrs	McCarthy scales of children's abilities	An early AIDS defining illness increased the risk of static encephalopathy during pre-school and early school age years.
Nozyce et al 2006	USA	274	2yrs-17yrs	Conner's Parent Rating scale. Wechsler – intelligence scale for children III Wechsler Pre-school and primary scales of intelligence.	Stable HIV + children had more behavioural problems and lower developmental and cognitive scores than established norms.

2.6.2 Clinical studies from Africa.

Despite the fact that Sub-Saharan Africa has the highest prevalence of paediatric HIV infection in the world (UNAIDS, 2005), very little research into the neurological complications of HIV in children has been done in Africa.

In the 1990's a small number of studies relating to neurodevelopmental delay in African children infected with HIV was published. Spitaels (1994) documented two case studies, Vetter et al (1996) and Emodi and Okafor (1998) reported on general clinical manifestations of HIV in children and Msellati et al (1993) conducted a prospective cohort study which assessed neurological development in HIV positive children. Boivin et al (1995) compared HIV positive children to their negative counterparts and followed a small group of HIV positive children up for a two year period, Drotar et al (1997) compared HIV infected infants to uninfected and sero-reverter infants in a prospective study of 18 months.

The ages of the children included in these four studies varied widely. Emodi and Okafor (1998) and Vetter et al (1996) included children from birth to 16 years of age in their studies. Spitaels (1994) presented two case studies one of a 10 month old and one of a two and a half year old. Msellati et al (1993), Boivin et al (1995) and Drotar et al (1997) followed children up from birth to 18 months or two years of age. The fact that these studies included children of such different ages makes it difficult to compare their findings.

A second problem arising from the research in Africa is that few of the studies explain how the diagnosis of HIV in children younger than 15 months was made. All authors appear to have relied, to some extent on clinical diagnosis which means that the findings for children under 15 months should be interpreted with caution as false positive and negative diagnoses are possible.

Most of the authors did not use standardised developmental assessments although Msellati et al (1993) did draw up their own tool based on existing tools. Unfortunately

they do not specify whether or not this was validated prior to commencing the study. Boivin et al (1995) used the Denver Developmental Screening Test and Drotar et al (1997) used the Bayley Scales of Infant Development. The differences in assessment methods mean that significant comparisons between studies cannot easily be made.

The two children assessed by Spitaels (1994) both presented with delayed milestones and changes in tone and neither had focal neurological signs. Vetter et al (1996) did not assess patients for neurological signs specifically, they did however note that meningitis with neurological sequelae was very common among HIV infected children. Emodi and Okafor (1998) identified neurological complications in only 9.5% of their patients. This figure could be low relative to other studies because this was a retrospective study which relied on clinical notes. Neurodevelopment was not routinely assessed and therefore may often have been missed by the examining doctors. The age range of this study (birth to 16years) was also much wider than other studies which detected a higher prevalence of neurological involvement (Nozyce et al, 1994; Msellati et al' 1993; Belman, 1992)

The large prospective cohort study conducted by Msellati et al (1993) identified 31% of infants in their study as being developmentally delayed at 12 months of age, and by the time the children were 18 months of age this had risen to 40%. These findings are similar to the findings of the European Collaborative Study (1990) which found 31% of infants infected with HIV had neurological complications. Msellati et al (1993) recognise that factors related to disease chronicity as well as direct neurological involvement may contribute to the developmental delay seen in these children. Boivin et al (1995) assessed 14 asymptomatic HIV positive children using the Denver Developmental Screening test and concluded that HIV affects the CNS of infected children even before the children become symptomatic. Drotar et al (1997) compared HIV positive children to seroreverted children and uninfected children and concluded that HIV infection results in early motor and cognitive delay that is not attributable to environmental and biological risk factors.

A study done in South Africa comparing HIV positive to HIV negative children (Potterton and Eales, 2001) found that 40% of HIV positive children under 12 months of age presented with developmental delays. This study made use of the Neurodevelopmental Assessment Score (Goodman et al, 1985), which although valid and reliable and designed for use on South African children, is a screening tool and did not provide much insight into the extent of delay experienced.

The most comprehensive studies of neurodevelopment and paediatric HIV to emerge from Africa have been done in Tanzania by one group of authors. McGrath et al (2006b) studied the timing of mother to child transmission of HIV and the neurodevelopment of a large sample of Tanzanian children in a longitudinal follow-up study from birth to 18 months. They found that HIV positive children performed worse on tests of neurodevelopment than HIV negative children and were more likely to be developmentally delayed by 18 months of age. Children who were already infected at birth were at greater risk of developmental delay. This study made use of the Bayley Scales of Infant Development II. The authors of this study stress that regular developmental assessments of all HIV infected children should be carried out in order to plan for medical, rehabilitative, educational and psychological interventions. In their secondary analysis of the same cohort, McGrath et al (2006a) investigated the impact of double blinded, placebo controlled, multi-vitamin supplementation trials on the neurodevelopment of children born to HIV positive mothers. Multivitamin supplementation was not associated with better mental scores, but did improve motor scores between six and 18 months of age. The authors of this study caution that vitamin supplementation is not an alternative to antiretroviral therapy and should be used in combination with usual HAART regimes.

Only one study relating to HIV and school going children in Africa could be found (Bagenda, 2006). This study examined the neurologic and neuropsychologic functioning of long-surviving, antiretroviral-naïve children in Uganda. The children were between six and 12 years of age and were assessed using the Kaufman Assessment Battery and the Wide Range Achievement- third edition. HIV infected children did not differ significantly in neurologic and cognitive assessments when compared to age and gender matched

controls. This study highlights the fact that there is a subgroup of HIV infected children of school going age who do well, despite not being on HAART and that their needs should not be neglected. The sample size of HIV infected children in this study was relatively small (n=28) and further studies are required to confirm these findings.

There remains a huge need for studies on the neurodevelopmental complications of HIV in developing countries and especially in Sub-Saharan Africa where the prevalence of paediatric HIV remains very high and where antiretrovirals are not yet universally accessible. Intervention studies are urgently needed to establish the best way to manage these children in the long term.

A summary of the studies on neurodevelopmental delay in HIV positive children conducted in Africa is presented in table 2.2.

Table 2.2 Neurodevelopmental studies conducted in Africa.

Authors	Country	Sample (n)	Age	Measures	Main Findings
Msellati et al, 1993	Rwanda	50 HIV+ 136 HIV- 32 HIV unknown	6m-24m	Neurological examination	HIV + children more likely to be developmentally delayed than HIV- children. Delay is related to stage of HIV infection.
Boivin et al, 1995	Zaire	14 HIV+ 36 HIV-	Birth-24m	DDST	HIV infects the developing CNS, even in asymptomatic children.
Drotar et al, 1997	Uganda	79 HIV+ 241 Sero-reverters 116 HIV-	6m-24m	BSID	HIV results in motor and cognitive delay that is not attributable to environmental risk factors.
Emodi and Okafor, 1998	Nigeria	63	Birth - 16yrs	File review	Less than 10% of children presented with neurological signs.
Potterton and Eales, 2001	South Africa	30 HIV + 30HIV -	Birth-12m	Neurodevelopmental assessment score	Developmental delay is common and presents early in HIV infected infants
McGrath et al, 2006	Tanzania	327	6m-18m	BSID II	Developmental delay is highest amongst children already infected with HIV at birth
McGrath et al, 2006	Tanzania	327	6m-18m	BSID II	Maternal multivitamin supplementation can reduce the risk of developmental delay
Bagenda et al, 2006	Uganda	28 HIV+ 42 Sero-	6-12yrs	Kaufman Assessment Battery	Antiretroviral naïve HIV infected children, did not differ significantly in neurologic and cognitive

		reverters 37 HIV-		for Children Wide Range Achievement III	functioning when compared to a control group.
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2.7 Paediatric HIV and Growth

Malnutrition is common in children infected with HIV. This can be as a result of reduced calorie intake due to poverty or poor feeding practices, or can be due to the effect of the virus on the gastrointestinal system which results in malabsorption. Chronic diarrhoea, vomiting and oral candidiasis are also contributory factors. Malnutrition affects the growth of HIV positive children. Children with growth failure may have decreased weight for height (wasting) and decreased height for age (stunting). Malnutrition initially causes wasting, while stunting is associated with prolonged malnutrition (Wiznia et al, 1996; Chantry and Moye, 2005).

Wasting may result from failure to gain weight or from loss of weight and indicates that there is decreased fat or tissue mass relative to what is expected for a child of that height or length. Wasting can have a very rapid onset, but can also recover very quickly under favourable circumstances (WHO, 1986). Stunting is an indication of slow skeletal growth and is often associated with poor socio-economic conditions, chronic or repeated infections as well as inadequate nutrition. Stunting takes a long time to correct once adverse circumstances have been corrected as skeletal growth is a slower process than growth in body mass. Head circumference and arm circumference measurements are usually considered as proxies for height and weight and are therefore frequently omitted in studies on growth in children (WHO, 1986).

Until recently growth was routinely recorded on growth charts from the NCHS (National Centre for Health Statistics in the United States). Although the NCHS growth charts represent children in the USA the World Health Organisation has endorsed their use around the world based on evidence that growth patterns of pre-school children from different ethnic backgrounds are in fact very similar (Chantry and Moye, 2005). WHO growth charts for breast fed infants are now available for height and weight and should be used in future studies (WHO Bulletin August 2006). Anthropometric measures may

be expressed as z-scores which signify the distance in standard deviation scores above or below the reference median z-score of 0.0 which is the 50th percentile for a specified age and sex (Chantry and Moye, 2005).

In HIV infected children weight, height and head circumference may all be affected within the first six months of life. The association between HIV and malnutrition is bi-directional. Malnutrition can cause more rapid progression of HIV disease, and HIV causes worsening malnutrition through its direct impact on the gastrointestinal system. Certain antiretroviral drugs can contribute to malnutrition by causing diarrhoea and vomiting. Regular monitoring of weight, height and head circumference is recommended in all HIV infected children (Chantry and Moye, 2005; Nachman et al, 2002; Coovadia and Meyers, 2001; Bobat et al, 1998). In a child who is not meeting his growth milestones, vitamin and micronutrient deficiencies should be considered as well (Mintz, 1999).

Growth delay is a direct effect of paediatric HIV infection. Growth hormone levels in HIV infected children are usually normal. Causes for poor growth in HIV infected children may be due to decreased sensitivity to circulating growth hormone, decreased sensitivity to insulin-like growth factors or to the fact that the release of cytokines as a result of HIV infection may lead to ineffective action of growth hormone (Newell et al, 2003; Lepage et al, 1991; Laue et al, 1990).

A number of studies have investigated growth deficiencies in children infected with HIV. Nathan et al (2003) reported stunting, but not wasting in a sample of institutionalised HIV positive African children. Spira et al (1999) found that failure to thrive in the first few months of life was associated with increased risk of death or progression to AIDS in HIV infected infants in Rwanda. Bobat et al (2001) investigated the growth of HIV infected children born in Durban, South Africa. They found that HIV positive infants exhibited early and sustained low mean length-for-age and weight-for-age z scores but weight-for-length was within normal limits. The authors of this study concluded that HIV infected children have early and sustained stunting, but not wasting. Children with rapidly progressing disease are stunted and wasted and have a poor prognosis.

There is an association between growth and neurodevelopmental delay in HIV positive children especially in children with advanced stages of the disease (Pollack et al, 1996). Infants with the most severe growth delay had significant cognitive and motor delay even if this only became apparent later (Pollack et al, 1996). Wiznia et al (1996) report a strong correlation between poor weight for age and decreased cognitive function and a low CD4 count. Missmer et al (2000) found that a decreased height for age z-score was a strong predictor of decreased functional status, suggesting that height may be used as an indicator of disease severity.

Acquired microcephaly has been noted by a number of authors and is usually due to impaired brain growth and cerebral atrophy secondary to encephalopathy (Mitchell, 2001; Macmillan, 2001; Mintz, 1999). Cortical atrophy is associated with disease progression and neurodevelopmental delay (Llorente et al, 2003; Pearson et al, 2000).

Growth parameters are important markers of disease progression in HIV infected children and may be predictive of neurodevelopmental status. Height and weight should be routinely monitored in children infected with HIV.

2.8 Effect of HAART on Neurodevelopment.

As new treatment options become available and children in developed countries have easier access to HAART, concerns have been raised about the long term effects of these drug regimens on the development of children (Brady et al, 1996). These issues are important for Sub-Saharan Africa and other developing countries where more children are slowly gaining access to antiretroviral medication.

The first study to be done on the effect of antiretrovirals on neurodevelopment was conducted by Pizzo et al (1988). They found that continuous infusion of zidovudine in children with symptomatic HIV infection resulted in a marked improvement in neurodevelopmental function in children who were encephalopathic prior to treatment. Despite the small sample size and concerns about long term toxicity, especially

myelosuppression, this study raised great hopes for the future management and possible reversal of encephalopathy.

Wolters et al (1997) conducted a follow up study on children with symptomatic HIV disease who were initially antiretroviral naive. They found that cognitive scores remained stable at six and 24 months after starting antiretroviral therapy but that both expressive and receptive language scores deteriorated at six and 24 months despite antiretroviral therapy. Raskino et al (1999) investigated the effect of different nucleoside antiretroviral regimes on neurologic, neurocognitive and brain growth outcomes in children. They concluded that combination therapy (zidovudine and didanosine) was superior to monotherapy for most CNS outcomes evaluated. In their retrospective study Sanchez-Ramon et al (2003) claim that antiretroviral therapy was responsible for reversing neurologic changes in some patients and delayed onset of progressive encephalopathy if commenced prior to onset of neurologic symptoms. In 2005, Jeremy et al investigated whether the addition of a protease inhibitor would improve neuropsychological functioning in antiretroviral therapy experienced children. They found no significant improvements except for a slight improvement in vocabulary scores. This study did not investigate the effects on motor function.

Resino et al (2006) conducted a retrospective study of 113 children who had six years of follow up after commencing antiretroviral therapy. All children had received mono- or dual-nucleoside therapy prior to starting HAART. They concluded that long-term HAART was able to restore CD4 counts and control viral loads in HIV infected children as long as it was started before the onset of severe immuno-suppression. Children who commenced HAART with CD4 counts of greater than 25% achieved counts of over 30% quickly and were able to maintain them.

The studies reviewed present a case for cautious optimism on the protective and restorative effects of antiretrovirals on the CNS. Future studies need to be done on narrower age ranges and need to monitor functional as well as clinical outcomes.

2.9 Paediatric HIV and the Family

Paediatric HIV is a multigenerational disease. The diagnosis of a child as HIV positive almost always means that at least the mother, and possibly the father, is infected as well. This makes HIV very different from other chronic childhood diseases. Families affected by HIV are also more likely to be poor and are often inhibited from accessing the services and support which they require due to the stigmatisation of HIV. They may also have limited access to health care (Deacon et al, 2005; Sher, 2005). Families affected by HIV also experience multiple losses which add to the psychosocial burden and emotional distress experienced by the family (Orner, 2006; Katapa, 2004; Lewis et al, 1996; Lewis et al, 1994; Sherwen and Boland, 1994; Reidy et al, 1991).

Many studies have identified stigma as one of the main concerns facing HIV infected mothers and their children (Silver et al, 2003; Antle et al, 2001; Hackl et al, 1997). The stigma attached to HIV makes it difficult for HIV positive mothers to form meaningful relationships with people outside the immediate family. Many mothers reported being lonely and having no friends (Antle et al, 2001). Stigma exists not only at a social level but also within the health care system and mothers reported feeling humiliated and ostracised when trying to access health and social care. Silver et al (2003) reported that mothers who perceived themselves to be stigmatised were more likely to be depressed and to report lower levels of parenting self-efficacy.

Two studies conducted in Africa identified a number of concerns expressed by caregivers of HIV infected adults. Some of the issues identified by the caregivers of adults infected with HIV as being problematic were; stigma, lack of/cost of transport to clinics, lack of training, poverty, loneliness and lack of acknowledgement of themselves as caregivers by health care workers and non-governmental organisations (Orner, 2006; Katapa, 2004). Care-giving also impacted negatively on employment and social life. Caregivers expressed the problem of the cost of transport to clinics for on going medical care. Katapa (2004) makes the point that “home-care” in developing countries is different to that in developed countries as it merely means that the patient is being sent home to be cared for by their family and does not imply the provision of continued

professional medical care within the home. Within this context the need for training and empowerment of caregivers becomes imperative. These studies are of importance as they were conducted in developing countries.

In their extensive review Richter et al (2004) highlight the fact that adult caregivers of HIV infected and affected children have needs of their own which must be addressed in an attempt to prolong the length of time that they are able to care for the children as well as to improve their ability to care for children. They advocate programmes that provide psychosocial and emotional support to help families and children deal with the multiple stresses and losses that they face.

Reidy et al (1991) highlighted the fact that children who are HIV positive require nurturing as well as care necessitated by their illness. This places an increased burden on the primary caregiver of the child, who may themselves be HIV positive. HIV is a progressive chronic illness which requires long term family involvement and commitment. As the disease progresses the child will present with severe acute signs and symptoms which require frequent and intensive medical intervention. Caring for a child with HIV is a time consuming and burdensome activity. Caregivers are beset with constant concerns over the child's health and worries about what the future may hold, they often feel inadequate as they are unable to meet the child's needs and lack confidence in their own parenting abilities (Adler, 2000; Weiner et al, 1994; Reidy, 1991). Linsk and Mason (2004) investigated the stresses on grandparents and other relatives caring for children affected by HIV, and found that the caregivers infected with HIV themselves, experienced the most stress.

2.9.1 Parenting Stress

Being the parent of any child is inherently stressful to a certain degree (Deater-Deckard and Scarr, 1996; Abidin, 1992). Some level of parenting stress is normal. Abidin (1992) argued that there is no linear relationship between parenting stress and good parenting and that some parents may disengage from their children completely and experience very little parenting stress. A number of studies investigating the factors that may influence the levels of stress experienced by caregivers have been conducted.

Ostburg and Hagekull (2000) investigated the predictors of parenting stress in a population of 1081 Swedish mothers of healthy children. They found that high work load, low social support, perception of the child as 'difficult', negative life events, child caretaking hassles, more children in the family and high maternal age were directly related to increased levels of parenting stress. No buffering effects of social support were found. This study is valuable in that it was well carried out and very comprehensive. However the sample of mothers was well educated and from a highly developed country with extraordinary social "safety nets" and care should therefore be taken before applying these findings to other socioeconomic and cultural contexts. Quittner et al (1990) also found no moderating effects for social support in their study on chronic parenting stress.

Schor (2003) favours the family stress model developed by Conger in 2000. According to this model children's outcomes are strongly influenced by how well their families function. Stresses within the family, including stress brought about by ill health, can disrupt parenting and can lead to short term and long term poor outcomes. The development of effective interventions to improve family functioning may lead to significant benefits for children and their families. Cadman et al (1991) conducted a large epidemiologic study in Canada and found that families of children who had chronic health problems are not necessarily dysfunctional compared to families with healthy children, although they may experience moderately elevated psychosocial problems. They urge clinicians not to assume that a family will have increased levels of psychosocial problems simply because they have a child with a chronic health problem. However, having a child with a disability or a chronic health condition has repeatedly been shown to increase parenting stress (Esdaile and Greenwood, 2003; Ultmann et al, 2002; Dyson, 2001; Button et al, 2001; Ong et al 1998; Bithony et al, 1995). Dyson (2001) examined parental stress and family functioning in families with children with handicaps. She found that parental stress was independent of economic and social constraints and that levels of stress did not affect family functioning. She suggests that to lessen stress, intervention should focus on increasing child competencies, caretaking of the child and changing parental perception of the child as it was these areas which

contributed most to parental stress. Abidin and Wilfong (1989) found that parents of young children seek appropriate health care for their children regardless of their parenting stress levels. Stanton (1999) conducted a comprehensive review of family functioning and outcomes in children with neurological disorders. She concluded that family functioning does influence outcome in certain cases but that more research needs to be done in this area.

Esdaile and Greenwood (2003) found that having a child with a disability led to elevated stress scores in both mothers and fathers and that there was no gender difference in levels of stress. The impact of having a disabled child on the father is not often considered and they suggest that programmes should address the needs of both mothers and fathers. Deater-Deckard and Scarr (1996) also found very similar levels of stress between mothers and fathers in their sample of non-referred parents of healthy children.

A number of studies have been done to try and determine what factors have the most effect on parenting stress. Button et al (2001) found that the level of impairment in disabled children was a significant predictor of stress in mothers of children with cerebral palsy, however the amount of partner support the mother received did not influence parenting stress levels. These findings are in contrast to those of McKinney and Peterson (1987) who found that mothers with less spousal support had higher levels of parenting stress. Silver et al (1998) concur with Button et al (2001) in finding that parents of children with greater functional limitations experience higher levels of parental distress. A study conducted in Malaysia by Ong et al (1991) found that mothers of children with cerebral palsy who had greater care-giving demands and required more frequent hospitalisation were more stressed. Mothers with lower levels of education also experienced more parenting stress in their study. It would appear that there are a number of factors which influence parenting stress and that there is no clear consensus on which are the most important. Individual family assessment therefore remains important and generalisations should be avoided.

In response to the complexity of caregiver burden, Raina et al (2004) have developed a complex multidimensional model to explain this concept. The concept of caregiver burden is broader than that of parenting stress and encompasses aspects of formal and informal caregiving within a comprehensive model. The five constructs included in the proposed model are:

- Background and context. This includes socioeconomic status of the family which can be determined using measures of parental education, occupation and income. The authors of the proposed model hypothesise that higher socio-economic status will be associated with fewer child behaviour problems, less caregiving demands and better psychosocial and physical health;
- Child characteristics. Behaviour problems and level of disability will be assessed. Better scores in these areas are expected to be associated with improved caregiver self-perception and better physical and psychological health;
- Caregiver strain. Factors considered under this construct are care giving demands and perception of formal care. Fewer caregiving demands are expected to be associated with higher scores on measures of self perception. Caregivers who report formal care as being more family centered are anticipated to have better psychological and physical health;
- Intrapsychic factors. Factors such as mastery and self esteem are expected to be associated with higher perceived levels of social support, better family functioning and higher use of stress management strategies.
- Coping/ supportive factors and health outcomes. These factors will measure informal support derived from family and friends as well as stress management. The authors hypothesize that higher scores will be associated with better psychological and physical health of the caregivers (Raina et al, 2004).

This multidimensional model will allow researchers to investigate the direct relationships between constructs and outcomes as well as the indirect effects through intervening constructs. This will help to determine the most relevant factors impacting on caregiver health and well being and possibly assist in planning family centred services (Raina et

al, 2004). This model is still being tested and will provide valuable insights into caregiver burden and the factors which influence it.

Parenting stress has traditionally been investigated with the mother as the primary caregiver. As society goes through rapid transformation one can not assume that the biological mother will always be the primary caregiver (Schor, 2003). The following sections will explore the parenting stress of mothers, grandmothers and fathers caring for children infected or affected by HIV.

2.9.2 Mothers

It is important to note that many of the HIV positive mothers included in the following studies have children who are not necessarily HIV positive (Goldstein et al, 2005; Silver et al, 2003; Marcenko and Samost, 1999; Hackl et al, 1997; Faithfull, 1997; Black et al, 1994b). The issues raised in these studies are similar to those expressed by HIV positive mothers with HIV positive children, however they have the additional concern for their child's health and well being (Shambley-Ebron, 2006).

Goldstein et al (2005) investigated psychological distress and substance abuse among a large sample of parents living with HIV. They found that custodial parents who were HIV positive themselves were significantly more likely to be emotionally distressed, this being even more significant in mothers. HIV positive mothers were overburdened and often unable to meet their own health care needs. Greater perceived parental distress was associated with medical non-adherence and more missed clinic appointments. Parental distress was not associated with increased number of children in the household which is in contrast to the hypothesis originally put forward by the authors. Mothers who are HIV positive face the dual challenge of being a patient and a caregiver (Hackl et al, 1997).

DeMarco et al (2002) found that mothers who were HIV positive themselves tended to "silence" their own needs and attend to the needs of their children and others first. This included physical and health needs as well as psychological needs. This practice of "silencing self" ultimately placed an increased burden on the mothers and meant that

they did not readily seek the help they need even when it is available. Mothers who experienced difficulty in caring for their children due to ill health experienced high levels of psychological disturbance (Silver et al, 2003). These findings are corroborated by Shambly-Ebron (2006) who conducted an in depth qualitative study on self-care and mothering in HIV positive African American women. She also found that mothers would put the needs of their children and others in their care above their own. The mothers in this study valued their role as mothers very highly and found that it helped to create a “life of meaning”. Black et al (1994) found that mothers who were HIV positive were more receptive to an intervention programme aimed at optimising their child’s developmental progress than HIV negative mothers.

Young mothers with HIV appear to enjoy their children in infancy but find their increased levels of activity as their motor development improves more challenging. Mothers described their toddlers as “bad” or “mean” rather than typical or normal (Abdalian and Wright, 2000).

Varga et al (2005) conducted a study in Johannesburg where they investigated the psychosocial consequences of mothers receiving their babies HIV diagnosis at four months rather than waiting until twelve months. Most mothers preferred the early diagnosis as it meant they did not have to deal with the uncertainty and fear of an unknown diagnosis. However in the case of sero-discordant couples, the early diagnosis placed enormous stress on the mother who was still dealing with the birth of her child and now had to face issues of disclosure and stigma as well. Careful counselling and support are advocated in the event of early diagnosis of HIV in infants.

Mothers of HIV infected children experience chronic sorrow, from the time of their child’s diagnosis and for the rest of the child’s life as she faces the challenges and illnesses which paediatric HIV inevitably brings (Antle et al, 2001). A need exists for support groups which address the needs of HIV positive mothers within the context of their family (Hansell et al, 1998). Mothers who are HIV positive also express the need for a “one-stop” clinic where all the health needs of themselves and their children can be met (Marcenko and Samost, 1999; Hackl et al, 1997).

Very few studies were found in which both the mothers and their children were HIV positive. The needs of this group require further investigation, particularly in the context of developing countries where paediatric HIV is still so common.

2.9.3 Grandmothers

As the biological mothers of HIV infected children become incapacitated or die due to their own infection the care of the children is often transferred to the grandmothers. This is particularly common in Africa where institutions for care of orphans are few and far between and where traditionally care of orphans falls on surviving relatives (Richter et al, 2004). This situation, although preferable to institutionalisation, places additional stresses on aging caregivers and raises a new set of concerns. The stigmatisation and isolation experienced by HIV affected families may compound the problems and stresses experienced by grandmother caregivers (American Academy of Pediatrics, 1999; Joslin and Harrison, 1998; Caliandro and Hughes, 1998). Grandmothers' own health problems may complicate the problems inherent in parenting. Grandparents tend to neglect their own health as they prioritise the health care and nurturing needs of their grandchildren. The health of elderly caretakers is at risk of being compromised as they assume a caretaking role, which involves multiple tasks, at a time of their lives when their own health needs are increasing (Linsk and Mason, 2004; Schor et al, 2003). The parenting role assumed by grandmothers often occurs in the context of grieving for multiple family members including grandchildren, sons and daughters (Joslin and Harrison, 1998)

Musil (1998) investigated the parenting stress of grandmothers caring for their grandchildren. She found that grandmothers who were the primary caregivers had significantly high parenting stress levels on the PSI-SF compared to grandmothers who did not have primary care of their grandchildren. She suggests that additional research into the psychosocial health of grandmother caregivers will provide valuable insight and provide direction for developing programmes to support grandmother caregivers in meaningful ways. This study provides some fuel for thought in a country where more and more children are being cared for by their grandmothers.

2.9.4 Fathers

Not many studies have investigated the impact of having an HIV positive child on fathers and male caregivers. Strug and Burr (2003) investigated the service needs of male caretakers of HIV infected and affected children. Not many HIV services cater specifically for the needs of male caretakers. They found that men requested help with accessing finance, housing and transport as priorities, and then parenting and emotional support. Forty three percent of services surveyed offered parenting skills training, but these seldom employed male staff or made an effort to address the concerns of male caretakers specifically. Men requested support groups for men caring for HIV infected children. In their study on parenting stress and psychosocial adjustment of fathers caring for HIV positive children Weiner et al (2001) reported high levels of parenting stress and psychological distress. Fathers in this study also requested gender-specific support groups as well as parenting skills and assistance with disease management and planning for the future. Antle et al (2001) urge that the parenting preparation of fathers be considered in programmes for families affected by HIV.

The needs of fathers and other male caregivers caring for children infected with HIV have not been well explored and further studies need to be conducted in order to gain better insight into the challenges faced by this small, but growing, group.

Parenting stress is a complex issue which is confounded by many psychosocial factors. Caregivers of HIV positive children are at risk of increased levels of parenting stress. The parenting stress of caregivers of HIV positive children in developing countries has not been fully explored.

The following section will briefly discuss the context of paediatric HIV in South Africa.

2.10 Socioeconomic Context of Paediatric HIV in South Africa

Decades of apartheid left the health system in South Africa plagued by racial disparity and inequality. Addressing these issues posed an immense challenge to the new democratic government in 1994 (Saloojee and Pettifor, 2005). A number of social and

economic reforms aimed at alleviating the worst consequences of apartheid and hopefully leading to improved child health and well-being were initiated soon after the ANC came into power (Cameron, 2003). These measures included providing free access to health care for all children under six years of age and pregnant women, increasing access to social grants and providing primary health care that was both accessible and affordable to all (Saloojee and Pettifor, 2005). Despite these efforts the divide between rich and poor continues to increase and the health and well-being of the majority of children in South Africa remains sub-optimal (Romani and Anderson, 2002). HIV has played a large contributing role to this unfortunate state of affairs and has placed an enormous burden on existing health care facilities. Saloojee and Pettifor (2005) report that more than 40% of deaths of children under five are due to AIDS and that in-hospital mortality rates have more than doubled in the last ten years.

Cameron (2003) found that a large cohort of infants born in South Africa in 1990 failed to gain weight as rapidly as expected in the first year of life and that differences between white and black children persisted into childhood and early adolescence. These findings again highlight the worrying disparity between the well-being of black and white South African children and the fact that the economic and social changes made since the end of apartheid have not been sufficient to overcome these. Richter et al (2004) and Williamson (2000), also acknowledge that nutrition, as well as access to health care, are factors that need to be addressed in the bid to meet the needs of vulnerable children in South Africa, including those infected with HIV.

The number of children orphaned by HIV/AIDS in South Africa is expected to continue to rise for a number of years, as is the number of child-headed households (Skinner et al, 2004). At present 10% of children in South Africa have lost at least one parent by the time they are nine years old (Brookes et al, 2004). Orphaning in the context of HIV is often preceded by a period of time where children become the caregivers for their dying parents and younger siblings. This is often a time of immense emotional and financial stress for children and parents alike (Loening-Voysey, 2002). In Sub-Saharan Africa the burden of caring for children orphaned by HIV has largely been met by the extended family, this may place financial burdens on the family and lead to exploitation and abuse

of orphans (Lau and Muula, 2004). The stresses of grandmothers assuming care for their orphaned grandchildren has been previously discussed in this review.

Poverty in South Africa remains a serious and complex challenge which is inextricably linked to the spread of HIV (Loening-Voysey, 2002; Barbarin and Richter, 2001; Barbarin and Khomo, 1997). Barbarin and Khomo (1997) in their extensive study on economic status and social capital in South African townships found that the poorest families in Soweto were those headed by single mothers who did not attend high school, living in households of six people or more, and who were unemployed. They also found that the presence of a grandmother in these households was more of a mediating factor for hunger than the presence of a male partner. They attribute this to the fact that grandmothers may bring a small but important income to the family if they receive a pension.

2.10.1 Poverty and child development

Poverty has the potential to impact negatively on early childhood development (Lima et al, 2004; Schor et al, 2003; Linver et al, 2002; Catherwood, 1999). Emerson (2004) noted that even in developed countries, poverty was associated with poor parental health and well-being and consequently poorer parenting practices and that the experience of poverty is often associated with poor child health and well-being. Duncan et al (1994) state that the length of time a child is exposed to poverty is an important factor to take cognisance of, while Burgess et al (2004) argue that the timing of exposure to poverty is also important with children born into a poor household being at greater risk than those exposed to poverty at a later stage of their childhood. A number of studies have investigated ways in which to possibly mediate the effects of poverty on the development of young children. These studies have mainly been conducted on poor people living in wealthy countries, we should therefore take care not to assume automatically that their findings will apply to our context in South Africa where people's experiences of poverty may be very different.

Schor et al (2003) report that parents are central to paediatric care. The health and well-being of children are inextricably linked to their parents' physical, emotional and social health as well as their social circumstances and child rearing practices. There is enormous diversity among families and this impacts on child rearing practices and the way in which families and individual parents respond to stress. Child health is strongly related to family income. The findings of this study are of relevance in South Africa where unemployment remains unacceptably high with the potential to impact seriously on child health and development.

In a large prospective study done in northeast Brazil, Lima et al (2004) found that poor performance in the first year of life on the BSID was related to environmental conditions associated with poverty. Children who had more stimulating homes performed better especially in the mental developmental indices of the BSID. Poor motor development was associated with extreme poverty for example mud floors that mothers were not happy to put their infants on. Biological factors did not influence development as much and only accounted for 6% and 5% of the variance in mental and motor development respectively. This study is of relevance to South Africa due to the similarities in socio-economic status of this study cohort and the majority of South Africans. Lima et al (2004) conclude by stating that health professionals should advocate for policy aimed at reducing poverty and for programmes that strengthen social capital and provide low cost sustainable interventions that promote psychosocial development. This approach supports the findings of Dunst et al (1986) who found that supportive social networks were associated with better personal well-being, more positive attitudes and positive parent-child play opportunities and child behaviour and development in families with a disabled or developmentally at-risk child.

Linver et al (2002) aimed to identify ways to mediate the effect of low income on the development of young children. They found that providing stimulating activities in the home mediated the impact of poverty on child development and that decreasing parental distress and improving parenting practices mediated the relationship between income and children's behavioural problems. Huston et al (1994) report that high quality day care has a mediating effect on the intellectual development and early school

performance of children from very poor families. Richter et al (2004) propose that the expansion and improvement of early childhood care and education centres at a national level could potentially benefit a large number of vulnerable children.

Poverty remains a serious concern in South Africa with the potential to impact negatively on the development of South African children. Around the world HIV is a disease exacerbated by poverty. The most vulnerable members of a community are hit hardest by this disease (Adler, 2000; Foster and Williamson, 2000; Dutra et al, 2000). Children in South Africa are therefore extremely vulnerable as they face exposure to both poverty and HIV.

2.11 Rehabilitation and HIV

2.11.1 A Role for Physiotherapy?

As the life expectancy of people living with HIV has increased due to the availability of HAART so the rehabilitation needs of this population has increased (Nixon and Cott, 2000). Many of the conditions to which HIV infected individuals are vulnerable result in impairments and disabilities which may benefit from rehabilitation. Despite this, very little research has been done into the role of physiotherapists in the long term management of people living with HIV. What research has been done has focussed mainly on the adult population and very little has been done on children.

Some of the first reports to emerge on the rehabilitation needs of adults living with HIV came from the Departments of Physical Medicine and Rehabilitation at The Graduate Hospital, Philadelphia. O'Dell et al (1991) described the types and degree of disability in 37 HIV positive people on discharge from acute hospitalisation. A significant number of subjects required assistance with ambulation, stair climbing, feeding and bathing. They concluded that significant physical disability exists in persons with AIDS discharged from hospital and advocate that rehabilitation professionals be consulted as rehabilitation may be of benefit. O'Connell and Levinson (1991) described the rehabilitation services utilised by 51 HIV positive patients. These services included therapeutic exercise, gait

aids, pain management, vocational assessment and counselling. Unfortunately they did not comment on how patients responded to these interventions. O'Dell and Dillon (1992) reviewed HIV-related disease, impairment, disability, and handicap pertinent to rehabilitation. They again conclude that current rehabilitation knowledge and practice could be applied to HIV-related disability in an attempt to improve quality of life. Despite this early recognition of the potential role for rehabilitation in the management of HIV infected individuals very few intervention studies have ever been done.

The only areas where significant research has been done in the field of rehabilitation and HIV are in the fields of aerobic exercise and strength training in adults who are HIV positive. Both aerobic exercise and graded strength training have been shown to have significant positive effects on aerobic fitness and muscle strength respectively, as well as on overall quality of life (Nixon and Cott, 2000).

Paediatric rehabilitation specialists world wide have been very slow to take up the challenge of paediatric HIV in any meaningful way. HIV has been known to cause neurodevelopmental delay for the last 20 years and yet not one intervention study examining the rehabilitation of these children could be found. Various authors have given anecdotal evidence for the need for rehabilitation for HIV infected children with neurodevelopmental delay (Mintz, 1999; McDougall, 1998; Cohen, 1991; Harris-Copp, 1988) however none of them support their claims with any evidence-based literature. The clinical rationale that these authors use for motivating for rehabilitation of HIV positive children with neurodevelopmental delay are sound and they do highlight the need for further research and intervention studies in this area.

Other areas of paediatric HIV that may benefit from rehabilitation have also not been thoroughly investigated.

2.11.2 Intervention Frameworks

The framework in which the rehabilitation of adults and children with HIV could be placed is well presented by Nixon and Cott (2000) in their article on reconceptualising HIV within a rehabilitation framework. They discuss how HIV can be viewed within the

context of the World Health Organisation's International Classification of Impairment, Disability and Handicap (now the International Classification of Functioning, Disability and Health (ICF)). Their comprehensive overview of impairments suffered by HIV positive individuals and consequent disabilities and handicaps is well presented and the implications for practice, education and research are of importance for physiotherapists around the world. Unfortunately they do not pay much specific attention to paediatric HIV. Hwang and Nochajski (2003) also discuss HIV within the framework of the ICF, again more attention is paid to adult HIV. This study focuses more on the technical aspects of the ICF and pays less attention to the clinical aspects of HIV disease. Mitchell and Linsk (2004) stress that HIV should be viewed as a chronic, long term illness which warrants a multidimensional approach.

The ICF recognises that health extends beyond the concept of disease. The main components of the ICF are body functions and structures, activities and participation. Impairments refer to any loss of body structure or function and may be temporary or permanent. An individual's impairments may limit their activities and their ability to participate fully within their community (WHO, 2001). The ICF allows researchers and clinicians to identify the components of health rather than the consequences of disease and is broad enough to be used in a number of different clinical settings (WHO, 2001).

Helders et al (2003) discussed the changes that have occurred in paediatric rehabilitation over the years from an impairment oriented model, through a functional approach and finally to a family-centred approach, and argue that paediatric rehabilitation has evolved into a dynamic discipline in its own right. They advocate careful standardised assessment and a system of rehabilitation for disabled children that is functionally based and family orientated. A number of studies have highlighted the need for a family-centred approach to the rehabilitation of children with chronic disabilities (O'Neil et al, 2001; King et al, 1999; Viscardis, 1998) This approach requires that the needs of the child are met within the context of their individual family and that any rehabilitation programme given, is designed for the individual child with input from the family. Programmes are designed to build on families' strengths and support families in their natural caregiving and decision making roles. Parents and professionals are

seen as equals in a partnership to optimise care of the child. Interpersonal aspects of care are emphasised in this approach. Programmes designed in this way are more likely to be sensitive to the individual and cultural differences in families and to meet the needs of the child and the caregivers. Adherence to programmes that have been designed together is thought to be better than that in programmes imposed on the family by the practitioner (O'Neil et al, 2001; Coleman, 2001).

Although HIV is not mentioned in these articles, the general approach advocated has definite relevance for the rehabilitation of HIV positive children with neurodevelopmental delay. Both the ICF and the concept of family centred intervention, stress the importance of looking at the child within their family and social context and designing interventions that look beyond the impairment level.

2.11.3 Service Delivery

Possible methods of service delivery to children with developmental delays will now be discussed as well as some of the services which have been developed for children who do have neurodevelopmental delay as a consequence of HIV infection.

A number of studies have been done to evaluate the best way of delivering developmental services to children with neurodevelopmental delay. Some controversy exists on the most effective way of providing developmental services and no single approach is suitable for all situations. Awareness of child development is increasing in developing countries and early intervention is advocated for children with low birth weight, developmental delays and children from disadvantaged backgrounds (Engle et al, 2007).

Early child development programmes are directed towards improving growth and development of young children as well as to ameliorate the negative effects of risk factors. The most effective early intervention programmes provide learning opportunities for the children and their families, are targeted towards younger and more disadvantaged children, are of longer duration and are integrated into other child and family health services (Engle et al, 2007).

Shannon (2004) investigated the barriers to family centred services, he concluded by urging professionals to evaluate each family's needs individually and not to assume that early intervention is a priority for all families. Brinker et al (1994) found that attending early intervention programmes could increase levels of parenting stress and that high levels of parenting stress were in turn related to poor cognitive outcomes.

Wasik et al (1990) and Loeb et al (2004) both found that high quality day care improved young children's cognitive abilities. Both studies were done on children from poor communities in well resourced countries. Wasik et al (1990) compared children in day care to children who received home stimulation programmes while Loeb et al (2004) compared children in day care to children in family care. The possible reasons for the advantages of day care include the fact that at day care the child's activities are the primary focus whereas at home the caregiver has a lot of other tasks and responsibilities and structured play activities with the child are not often a priority. The results of these two studies need to be interpreted with care as the stimulation and facilities at all day care centres are not equal.

Black et al (1994), Powell et al (1998) and Eickmann et al (2003) investigated the use of home stimulation programmes for children with developmental delay. All three studies used the Bayley Scales of Infant Development as their developmental outcome measure. Black et al (1994) found no difference in cognitive or psychomotor development between children in a control and an intervention group despite biweekly home visits from birth to 18 months of age. The children in this study all had drug abusing mothers, half of whom were HIV positive. The study was conducted in a poor inner city area. In contrast Powell et al (1989) and Eickmann et al (2003) found that development improved with increasing frequency of home visits. The aim of both the interventions in both these studies was to provide skills and knowledge to mothers to promote their children's development within the limited resources of the family. Both of these studies were done in developing countries, namely Jamaica and Brazil. Eickmann et al (2003) acknowledge that the once weekly visits that they provided are not sustainable in the long run, they do however urge that more projects that include

mothers and that can be carried out by community workers supervised by health care professionals, be initiated. They also stress that poverty alleviation be a part of any project aimed at promoting child development and that the most vulnerable children are selected out for intervention.

Although no individual intervention studies could be found on the management of developmental problems in HIV infected children, a number of authors call for the establishment of holistic family centred services that address complex psychosocial aspects as well as developmental components (New et al, 2006; Barnard and Muller, 2004; Strug and Burr, 2003; Barnet and Whiteside, 2002; DeMatteo et al, 2002; Prado et al, 2002; Kmita et al, 2002;; Coscia et al, 2001; Boland, 2000; Salisbury, 2000; Himid et al, 1998; Woodruff, 1994; Cohen, 1991; Hopkins et al, 1989; Crocker, 1989). Strug and Burr (2003) and DeMatteo et al (2002) emphasise that these services should include specific support for fathers and other males who find themselves in the role of primary caregivers. Hopkins et al (1989) and Coscia et al (2001) stress that parenting workshops and training should be included in the programme. Coscia et al (2001) argue that these interventions may mediate the environmental risk factors such as poverty.

Hansell et al (1998) warn that improving social support does not necessarily improve coping and stress management in caregivers of HIV positive children. Prado et al (2002) confirm that participation in psychosocial interventions is often low. They found that HIV positive mothers were more likely to engage in these programmes if they perceived a need for the intervention, they had high stress levels and low social support and if they established a “therapeutic alliance” with the service provider from the outset. The therapeutic alliance was the strongest independent predictor of engagement. They therefore encourage interventionists to prioritise the establishment of rapport with patients early on in the intervention process. Cost effectiveness, equity and cultural sensitivity should be considered when planning a new service (Scott et al, 2005; Desmond et al, 2002; Farmer et al, 2001).

A number of authors have identified the need for comprehensive, holistic services for children infected with HIV, which should include developmental services. Paediatric

rehabilitation specialists have not been optimally involved in the long term management of children with HIV and neurodevelopmental delay, especially in developing countries. A need exists for studies that evaluate intervention programmes aimed at HIV positive children with neurodevelopmental delay.

2.12 Conclusions

Paediatric HIV remains a serious health challenge in South Africa where the epidemic has not yet reached its peak.

HIV is known to be neurotrophic and to cause neurological damage through a number of pathological mechanisms. This results in a well described encephalopathy which causes developmental complications early on in childhood. All facets of development are negatively affected by paediatric HIV independent from other environmental and biological risk factors. This has been demonstrated in studies from around the world, including a limited number from Africa.

Paediatric HIV is a multigenerational disorder and impacts heavily on the entire family. Increased stresses are placed on the primary caregiver and parenting stress is high.

The role of physiotherapy as an intervention for children with developmental delay as a result of HIV infection has never been investigated. Any intervention which occurs should address the needs of the child within the context of the family and recognise cultural and social differences. The family should be partners in service planning and delivery.

Children infected with HIV in South Africa generally live in poor socio-economic circumstances which impact negatively on all facets of development, but especially cognitive development. Interventions should aim to address these issues and policies are needed to improve conditions and developmental outcomes for all vulnerable children in South Africa, not only those infected with HIV.

Taking cognisance of these factors the main aim of this study was to determine whether a basic home stimulation programme had an impact on the neurodevelopmental status of HIV infected children.

Chapter 3

MEASURING INSTRUMENTS and PILOT STUDIES

In this chapter the measuring instruments used in this study will be discussed. Issues of suitability, reliability and validity are highlighted. The pilot studies done to ensure suitability of each measure are described.

3.1 Bayley Scales of Infant Development II

The Bayley Scales of Infant Development were first published in 1969 and have long been considered the gold standard in developmental assessments (Harris et al, 2005; Tieman et al, 2005). In 1993, the second edition of the Bayley scales (BSID II) was introduced in an attempt to address some of the concerns that were raised about the original version. The aims of the revision of the Bayley scales were to update the normative data, extend the age range, improve content coverage, update test materials and address gender and cultural biases that may exist, conduct reliability and validity studies and improve the clinical utility while preserving the basic qualities of the BSID (Bayley, 1993).

The BSID II is an individually administered test that assesses current developmental status. The primary objective of the BSID II is to identify children who have developmental delay and to plan intervention strategies. The BSID II consists of three scales, the mental scale, the motor scale and the behavior rating scale. The mental scale assesses cognitive, language and personal-social aspects of development and includes items to evaluate memory, habituation, problem solving, early number concepts, generalisation, classification, vocalization, language and social skills. The motor scale assesses gross and fine motor development and includes assessment of movements associated with rolling, creeping and crawling, sitting, standing, walking, running jumping and climbing, as well as grasp and fine motor coordination. The behavior rating scales assess the child's behavior during the testing situation. Raw scores obtained in the mental and motor assessments are converted to standard scores which are age adjusted. These are the Mental Developmental Index and the

Psychomotor Developmental Index which have a mean of 100 and a standard deviation of 15 (Black and Matula, 2000).

The mental and motor scales of the BSID II have been shown to have excellent reliability coefficients (an average of .88 and .84 respectively) as calculated using coefficient alpha (Bayley, 1993) and suggest that the BSID II is a highly reliable tool. Test-retest stability showed a high degree of stability over time and across age groups for mental and motor development (ranging from .77 to .91) (Bayley, 1993). Interscorer agreement was established by having an examiner and an observer score each child (n=51). Interscorer agreement was calculated by correlating the MDI score of the examiner with that of the observer. The same process was applied to the PDI. Interscorer reliabilities were .96 for the MDI and .77 for the motor scale. It was felt that the observer was at a disadvantage when scoring the motor scale as some items involve physical manipulation of the child to determine their abilities and the observer would not have experienced this directly (Bayley, 1993). The author provides evidence that the MDI and PDI scales of the BSID II have content, construct, predictive and discriminant validity.

The Behavior Rating Scale has not stood up to rigorous psychometric testing to the same level as the MDI and PDI. It is therefore not included in any of the clinical studies discussed previously and was not included in this study.

The norms for the BSID II were derived from a national, stratified random sample representing American infants between one and 42 months of age. One thousand seven hundred children were assessed, 100 in each of the 17 age groups between one and 42 months. Gender, race, geographical region and parental education level were proportionally represented based on the figures from the 1988 US census (Bayley, 1993).

The BSID II was tested by the research team on a sample of 35 HIV positive children. In relation to the normative sample, these children had a mean MDI of 79.6 and a mean PDI of 81.1, approximately 1.3 standard deviations below the normative sample. The

standard deviations observed with these children showed far greater variance than the normative sample, the motor scale had a standard deviation of 27.2 and the mental scale had a standard deviation of 19.8. Bayley warns that not all HIV positive children will necessarily perform in a similar manner due to the presence of different developmental risk factors (Bayley, 1993).

Despite its wide use in research and clinical practice some concerns about the BSID have been raised over the years. One of the issues raised is the concern that final scores on the BSID can vary considerably depending on where in the test the examiner chooses to start administering items. Mayes (1997) found that scores were inflated if testing began at the child's chronological age (as recommended in the testing manual) and were skewed in the opposite direction if testing started at the lowest item set. Mayes (1997) proposes that examiners test upward until the child fails all items and downward until the child passes all items and not to follow the basal and ceiling guidelines in the manual. Administering the test in this way would increase the administration time. Gauthier et al (1999) also addressed the issue of where to start with administering the test. They agree that small variances in testing procedure can influence a child's end score significantly. They recommend that testing of all full term infants be started at the child's chronological age and that the examiner should not use clinical discretion in determining the starting point. Following this simple directive ensures that results obtained are meaningful and comparable.

A number of authors have identified concerns over the stability of the BSID in assessing high risk infants. Niccols and Latchman (2002) found that the BSID was sensitive to changes in development in high risk infants during the first two years of life. The findings of their study support the clinical validity of the BSID. They do however warn that BSID scores obtained in the first year of life should not be used in an attempt to predict future performance later in life, especially in infants with non-typical development. This cautionary note is reiterated by Harris et al (2005) who found that the BSID demonstrated only modest stability over time when administered to a group of high risk infants.

The BSID was normed on a sample of typical American children. Raw scores obtained on the mental and motor scales are converted to age adjusted standard scores, the mental developmental index and the psychomotor developmental index. The scoring manual for the BSID only allows for MDI and PDI scores from 50 to 150. It is therefore not possible to assign a developmental index score for a child with a very low raw score. As the BSID is often used with children with developmental delay a need for describing scores below 50 was identified. Robinson and Mervis (1996) used statistical modeling to extrapolate MDI and PDI scores between 30 and 50. They recommend that any child who scores below 30 be assigned a score of 29. These scores can be used to monitor children's progress and assess the impact of intervention but examiners must remember that MDI and PDI scores below 50 are estimated and not based on actual data (Black and Matula, 2000).

Richter et al (1992) recognized the need to identify developmental assessment tools which were appropriate and valid assessments of developmental progress in South African children. The first version of the Bayley Scales of Infant Development (BSID I) was administered to a large group (n=722) of South African children from both urban and rural areas (Richter et al, 1992). The local sample was modeled on the American standardization sample. The South African children performed consistently well on the BSID I and in fact in many instances better than their American counterparts. This was particularly evident in the younger children under 12 months of age, where South African children achieved significantly higher scores than the American standardization sample in both mental and motor scores. Rural South African children tended to score lower than urban children in both motor and mental development. Richter et al (1992) found the original materials in the BSID to be appropriate for use with South African children and suggest that they can be used without modification.

African children have previously been described as having precocious gross motor development (Capute et al, 1985). The pattern of precocious developmental performance in the first year found by Richter et al (1992) was also found by Aina and Morakinyo in 2005 when they normed the BSID on 128 Nigerian children. Unfortunately they do not state whether they use the BSID I or the BSID II. In this study children in all

age groups performed better in psychomotor assessments than in the mental assessments. The highest mean MDI was in the 16 week age group and the lowest was in the 30 month age group. The highest PDI mean score was in the eight week age group and the 10 month age group had the lowest mean PDI. All age groups had mean MDI and PDI scores which were well above the minimal normal developmental index score as stipulated by the author of the test (Aina and Morakinyo, 2005). The sample size of 128 used by Aina and Morakinyo (2005) is too small to draw conclusive, generalisable results for the rest of Africa.

The BSID II has not been normed on South African children although it has been used for research purposes in South Africa as well as other African countries and other developing countries (Aina and Morakinyo, 2005; Cooper and Sandler, 1997). Results from the BSID I have been shown to correlate strongly with results from BSID II (Bayley, 1993). Due to these factors and because of the study design in this study it was decided that re-norming the BSID II on South African children would not be necessary. However it must also be acknowledged that many social and political changes have occurred in South Africa since the BSID I was normed. Changes in the socio-political environment could have influenced child development so it was decided to conduct a pilot study in order to identify whether the BSID II was still a valid and appropriate developmental assessment tool for urban black South African children.

3.1.1 Training and pilot study

No specific qualification is required prior to using the BSID. However it is recommended that testers are experienced in the field of paediatrics and should have experience in administering and scoring paediatric developmental assessments. The researcher and research assistant for this study attended a one week training workshop on the BSID II conducted by a clinical psychologist from Baylor University, USA, who had extensive experience using the BSID clinically and as an outcome measure in a number of different research projects.

Each item of the BSID was discussed and possible problems in administration were highlighted. The BSID was administered to a number of normal (n=3) and at risk (n=5)

children in order to practice and to assess the suitability of the tool in the South African context. The children all responded well to the test items and all the healthy children scored within the normal range of the test for mental and motor development.

Once the training week was completed and the researcher and research assistant were confident with the administration and scoring of the BSID II, it was decided to undertake a further pilot study to confirm that the BSID II was indeed a suitable tool for use on high risk, urban, black South African children. Twelve children (10% of sample size of main study) were assessed using the BSID II. The researcher performed all assessments while the research assistant observed the testing and scored the children independently. A sample of convenience was used. Children were drawn from the paediatric follow up clinic at CH Baragwanath hospital. They thus came from similar socioeconomic and cultural backgrounds to the children who were included in the main study.

The following inclusion criteria were used:

- Children who had had a hospital admission for an upper respiratory tract infection.
- Children who had tested HIV negative on Elisa or PCR (depending on age) during admission.
- Children who were now declared healthy and free of impairments by the assessing doctor.
- Children who were less than 42 months of age.

Children were assessed seated on their mother's laps or at a small table on a child sized chair. The guidelines for administering the BSID II were followed. The mental scale was administered before the motor scale. Testing commenced at the child's chronological age.

Results

The children all appeared to enjoy the testing and responded well to most of the testing equipment. The scores obtained by the children can be seen in table 3.1

The mean MDI for this group of children was 96.2 ($\pm$ 12.7) with a range of 83-120. The mean PDI was 101.2 ($\pm$ 14.88) with a range of 80-132.

Table 3.1 Age, MDI and PDI of children in Pilot Study

Age (months)	MDI	PDI
3	101	103
5	97	109
6	120	132
8	88	117
11	83	87
12	93	97
15	85	85
17	90	94
21	106	108
24	84	80
30	118	110
37	89	93

All of the children except one achieved mental and motor scores within the normal range for the BSID II. One child had scores in the accelerated development category for mental and motor development, one for motor development only and one for mental development only.

The scores of the researcher and the research assistant were very close, having a 98% agreement for MDI and 96% for PDI. Although the researcher conducted all the assessments in the main study it was necessary for the research assistant to have a thorough understanding of how the BSID II was scored and how to interpret the results in order to be able to plan the intervention programme.

Based on the findings of this pilot study and on the work of Richter et al (1992) it was concluded that the BSID II remained an appropriate tool for assessing development in South African children.

3.2 Parenting Stress Index- Short Form

Conceptualisation and measurement of parenting stress present a formidable challenge and many research models have viewed stress differently. These factors make research in this area complex and challenging (Reitman et al, 2002).

The Parenting Stress Index was developed by Abidin in 1978 as a screening and diagnostic assessment tool. It is a 120 item self-administered Likert scale which yields information about the magnitude of stress in the parent-child dyad. The PSI has proven reliability and validity but is considered time consuming for use in research or as a screening tool (Reitman et al, 2002; Pearson and Chan, 1993)

The Parenting Stress Index/Short form (PSI/SF) is a direct derivative of the original Parenting Stress Index, with all items being contained in the original version with identical wording. It is a 36 item, self administered questionnaire. Parents score each item presented on a five point Likert scale ranging from “strongly agree” to “strongly disagree”. Values of one to five are allocated for each response and added to give a total stress score and three sub-scale scores, higher scores indicate higher levels of stress (Abidin,1995).

The PSI/SF was developed in response to clinicians and researchers identifying the need for a concise, easy to administer version of the PSI which could be administered in a limited amount of time. A number of researchers who analysed the PSI indicated that a three way factor analysis would be the best way to describe the data (Abidin, 1995). Based on their suggestions a short version which consisted of a total score and three sub-scales was developed. The three sub-scales were labeled Parental Distress, Parent-Child Dysfunctional Interaction and Difficult Child (Abidin, 1995). The process of factor analysis is described in detail in the test manual.

The Total Stress score gives an indication of the overall level of parenting stress that the individual is experiencing. The total stress score is a reflection of stress experienced within the role of being a parent and does not reflect other life stresses. Parents who

experience a Total Stress score of greater than or equal to 90 are experiencing clinically significant levels of stress and should be referred for counseling (Abidin, 1995).

The Parental Distress score indicates the level of stress a parent is experiencing in his or her role as a parent, as a function of a number of personal factors inherent to parenting. The component factors associated with the Parental Distress subscale include, impaired sense of parenting competence, stresses associated with restrictions in other life roles, conflict with partner, lack of social support and the presence of depression. When the Parental Distress subscale scores above the 90th centile therapeutic intervention that aims at improving parent's self esteem and sense of competence as a parent may be the most beneficial to both the parent and the child (Abidin, 1995).

The Parent-Child Dysfunctional Interaction (P-CDI) subscale focuses on the parent's perception of whether or not their child meets their expectations and whether their interactions with their child affirm them as a parent. Parents who score high in this subsection feel alienated and rejected by their children. A risk of child abuse exists for parents who score above the 95th centile in this subscale and immediate referral is recommended (Abidin, 1995).

The Difficult Child subscale probes some of the behavioral issues children may have which make them easier or more difficult to handle. These may be inherent characteristics of the child or may be learnt oppositional and non-compliant behavior. Children over two years of age are more likely to exhibit behavioral problems that are learnt rather than younger children whose behavior is more likely to be due to temperament or physiological disturbances such as colic. Regardless of the cause parents who produce high scores in this subscale require professional assistance (Abidin, 1995).

Test-retest reliability was established on a sample of 270 parents over a six month period. The total stress score was .84 with the subscale scores of .85, .68, and .78 for

PD, P-CDI and DC respectively. In order to test validity of the scale the author correlated the PSI/SF to the full length PSI and found a high correlation of .94 (Abidin, 1995).

Reitman et al (2002) evaluated the PSI/SF in a low socio-economic, primarily African American population. They found that the PSI/SF had very good to excellent internal consistency and that the three factor model was marginally better than a single factor model. A series of multiple regression analyses examined the relationship of various psychosocial and demographic factors with the PSI/SF. The Difficult Child subscale was associated with a measure of child oppositionality, the Parental Distress subscale was associated with self reported psychological symptoms and low income and the Parent-Child Dysfunctional Interaction subscale was associated with self reported psychological symptoms as well as low income and education. The findings of this study support the generalisability of a three factor measurement of parenting stress (Reitman et al, 2002).

The PSI/SF has been used in a number of studies, conducted around the world, and authors have found it to be clinically useful as well as psychometrically sound (Feldman et al, 2004; O'Neil et al, 2001; Button et al, 2001; Musil et al, 1998; Deater-Deckard et al, 1996). Studies using the PSI/SF could not be found from African countries.

3.2.1 Translation and Pilot Study

In order to ensure that the PSI-SF could be self administered by the majority of caregivers in the study sample it was decided to translate it into Zulu and Southern Sotho. These are the two most commonly spoken languages in Soweto where the study was conducted (Barbarin and Khomo, 1997).

Permission was obtained from the original author of the PSI/SF to translate the scale. The author stipulated what procedure should be followed and this is outlined below.

The questionnaire was translated by professional, home language translators into Zulu and Southern Sotho.

These translations were then back-translated into English by two individuals whose mother tongue was Zulu and Southern Sotho respectively.

This back translation was then sent to the original author and he checked them for accuracy and to ensure that the concepts being tested remained stable during translation.

Comments were sent back to the researcher. The Southern Sotho translation was accepted by the author, however a few changes were requested for the Zulu translation. The researcher met with the translators and discussed possible alternatives.

A second Zulu translation was produced with minor changes.

The second version was then back-translated again and the back-translation resubmitted.

This version was approved and both the Zulu and Southern Sotho translations of the PSI/SF were adopted by the original author and Psychological Assessment Resources as official versions. (See appendix V for PSI/SF and translations).

Testing

The translated versions of the PSI-SF were tested in a pilot study to ensure test-retest reliability and to determine whether they were easily understood by caregivers of children living in Soweto.

The testing took place at Chris Hani Baragwanath hospital where the study was to be conducted. A sample of convenience was used.

The PSI/SF was handed out by a physiotherapist to caregivers of young children whom she was treating. A physiotherapy assistant who spoke both Zulu and Southern Sotho fluently was available to translate any questions the caregivers had and the instructions if necessary.

The questionnaire was given to 10 Zulu and 10 Southern Sotho speaking caregivers of children admitted to the medical wards. Caregivers completed the questionnaire in the ward and then returned it to the physiotherapist.

The PSI/SF was re-administered to the same group of caregivers five days later.

The total scores can be seen in table 3.2.

Table 3.2 Test re-test scores for Zulu and Southern Sotho translations

Southern Sotho PSI/SF Total		Zulu PSI/SF Total	
Test	Re-test	Test	Re-test
51	50	87	87
92	90	63	62
85	85	146	146
119	111	49	46
62	61	46	42
140	140	51	42
109	104	52	51
48	45	110	105
113	108	118	110
86	91	91	89

Results

The Zulu and Southern Sotho translations of the PSI-SF showed very high test-retest reliability over a five day period for the Total Stress scores (Zulu $r = .995$, S Sotho $r = .993$).

The means and standard deviations for the total PSI/SF scores obtained in this pilot study are found in table 3.3

Table 3.3 Means and Standard Deviations for Test Retest scores of translated PSI/SF

Southern Sotho PSI/SF		Zulu PSI/SF	
Test	Re-test	Test	Re-test
90.5(± 30.4)	88.5 (±29.7)	81.3 (± 34.8)	78.0 (± 35.2)

Discussion

None of the caregivers required assistance with completing the PSI-SF and only occasional questions were asked. Caregivers reported that the questionnaire was easy to understand and that most of the questions were relevant to their situations as parents.

Some of the issues raised included queries about question six “I am unhappy with the last purchase of clothing I made for myself”. Two mothers in the pilot study could not remember when they had last bought new clothing for themselves as they relied on handouts from family members or charity. This problem was not encountered in the main study. A few mothers also asked about question 33 “Think carefully and count the number of things that your child does to bother you”. The choices for this question start with the option of “1-3” things, some caregivers asked what they must choose if their child did nothing that bothered them. It was explained that they should choose the option “1-3”.

Questions with a different format were somewhat confusing (Q22, Q32 and Q33). Questions 22 and 32 require that the respondent select one of five statements that best describes them. The layout of these two questions is different from the rest. It was decided that these two questions as well as question 33, described above, should be explained individually to all caregivers prior to commencing the test.

Most caregivers took between 20 and 30 minutes to complete the questionnaire.

The very high Total Stress scores obtained by this group of caregivers was of concern, although one would expect high levels of parenting stress in caregivers of hospitalized children. A small unpublished pilot study done on the parenting stress of parents of typically developing South African children compared to children with cerebral palsy found that the parenting stress levels of South African parents with healthy children was within normal limits, mean= 69.4 (Haniff et al, 2005).

Conclusion

Based on the findings of this pilot study and on the literature reviewed, it was decided that the PSI/SF was an appropriate outcome measure to use to assess the parenting stress of caregivers of children in Soweto, South Africa.

3.3 Household Economic and Social Status Index (HESSI)

The Household Economic and Social Status Index (HESSI) was used to collect demographic information in this study. The HESSI was developed and standardized in Soweto, South Africa and has been used to collect demographic data for the longitudinal “Birth to Twenty” study (Barbarin and Khomo, 1997). It is therefore ideal to use to collect data from caregivers of children living in Soweto. No pilot study was considered necessary prior to using this questionnaire. Barbarin and Khomo (1997) recognized that financial resources alone are not an accurate measure of poverty in developing countries. They developed the HESSI to include measures of food adequacy, shelter, utilities, durable consumer goods, accumulated assets, social status, education, occupation and family structure in order to provide a more holistic picture of the socio-economic conditions in which people live. This questionnaire may lack economic specificity but it does highlight factors which have a direct bearing on child development and is sensitive to socio-economic variations at the lower end of the economic scale. This is important in developing countries where poverty is widespread and decisions need to be made about how best to allocate limited resources (Barbarin and Khomo, 1997).

3.4 Conclusion

Based on the literature reviewed and the pilot studies conducted it was decided that the BSID II was the most appropriate developmental assessment tool for use in this study.

The PSI/SF was translated into Zulu and Southern Sotho and proved to have good test-retest reliability. It was decided to use this tool to measure parenting stress even though it has not been used extensively in developing countries as yet.

The HESSI was considered to be an appropriate tool for assessing socio- economic status in the study population as it was developed in Soweto, South Africa and focuses on socio economic factors which may impact on child development.

Chapter 4

METHODS

In this chapter the methodology for this study is presented. The study design and subject recruitment is described and the study procedure will be discussed.

It should be noted that when this study was designed antiretroviral therapy was not available in government hospitals in South Africa. Four months after data collection commenced the South African government made antiretrovirals available in a limited number of sites, including at Harriet Shezi clinic where this study was conducted. This introduced a confounding variable to this study but did present the opportunity to investigate the interaction between HAART and the intervention provided in this study, as well as the impact of HAART on the neurodevelopmental status of the children in the study.

4.1 Location

This study was conducted at the Harriet Shezi Children's Clinic at Chris Hani Baragwanath Hospital in Soweto, South Africa. This is an outpatient clinic which provides follow up care for HIV positive children. The clinic is staffed with doctors, nurses and counselors. A social worker and a dietician visit the clinic on a regular basis.

4.2 Ethical Considerations

Ethical clearance for this study was obtained from the Committee for Research on Human Subjects at the University of the Witwatersrand. (Clearance certificate M03-05-68) See Appendix I.

Permission to conduct the study was obtained from the relevant authorities at Chris Hani Baragwanath Hospital. Informed, written consent, for themselves and the child was

obtained from the primary caregiver of each child prior to him/her being enrolled in the study.

According to the guidelines of the Committee for Research on Human Subjects at the University of the Witwatersrand, a contribution to transport costs was made to the caregivers at each visit to the clinic. Although the children in the control group did not receive any intervention they continued to receive all the services usually available at the clinic. There were no rehabilitation services offered at the clinic. At the end of the study period all children were given a home management programme, regardless of which group they were in, and were referred for further rehabilitation if this was considered necessary. All children were given a small book at the end of the study to thank them for their participation.

4.3 Study Design

The design for this study was a randomized, controlled clinical trial. The study was pragmatic in nature.

4.4 Subjects

Subjects were drawn from a paediatric HIV clinic (Harriet Shezi clinic) at Chris Hani Baragwanath hospital. The caregivers of all children who met the inclusion criteria were asked to participate in the study.

Inclusion criteria:

- children with vertically transmitted HIV
- children under 2 and a half years old on entry to the study
- children who attend the paediatric HIV clinic with their primary caregiver

Exclusion criteria:

- children with clinically evident congenital abnormalities
- prematurity (< 37 weeks)

- children resident in an institution
- children already receiving physiotherapy

During the course of the study children were excluded from developmental assessment if they presented with an oxygen saturation of less than 85%, cyanosis or a temperature of over 38 degrees Celsius. These were criteria set by the clinic to screen children who needed to be fast tracked through the system and see a doctor as soon as possible. An appointment to do the developmental assessment was then given for the following week.

4.5 Materials and Measurements

Bayley Scales of Infant Development II

The BSID II is the most widely used developmental assessment tool in paediatric research (Long and Cintas, 1995). Scores are obtained in three areas, cognitive, motor, and behavioral. The raw scores obtained in the motor and cognitive areas are then converted to standard scores. Validity and reliability have been well established on a number of study samples, including on children infected with HIV (Black and Matula, 2000).

Parenting Stress Index- Short Form

The Parenting Stress Index (PSI/SF) contains 36 items across 3 subscales that are reported to have good reliability (Abidin 1995). The 3 subscales are “Parental Distress”, “Parent-Child Dysfunctional Interaction” and “Difficult Child”. Items are rated on a 5 point scale from “strongly agree to “strongly disagree,” with higher scores indicating higher levels of stress. The PSI/SF provides a total stress score as well as 3 sub-scale stress scores. Evidence for test-retest reliability (Pearson correlations of .84 for the total stress scores and .68 to .85 for subscale scores) is given in the test manual (O’Neil et al 2001).

The PSI-SF was translated into Zulu and Sotho and these translations have been accepted by the original author as official versions as previously discussed.

The BSID II and the PSI/SF have been discussed in more detail in chapter three.

CD4 Counts

CD4 counts are routinely used to quantify the immune status of a patient. Children who attend Harriet Shezi clinic have their CD4 count taken as part of their baseline work-up when they first register with the clinic. Thereafter CD4 counts are done at 6 monthly intervals unless the child's clinical condition deteriorates rapidly and further investigation is warranted. CD4 counts are used to determine eligibility for HAART and to monitor response to medication.

Anthropometric Measurements

Height/length and weight were measured routinely by the clinic nurses prior to the children seeing a doctor. Measurements were recorded in the child's file.

Children who could stand independently had their height measured using a wall mounted scale (Hottain Ltd, Crymych, Dyfed). The children stood against the measure, bare foot or in socks, with their heels against the wall, and had the horizontal plate lowered until it rested on top of their heads. Height was recorded in centimeters.

Infants, and children who could not stand, had their length measured in supine on a "Morena Baby Measuring Mat". Their heads were placed against the vertical board and the measurement was taken at the heel. Every attempt was made to keep the children well aligned on the mat until measurement was complete. Length was recorded in centimeters.

Children who could stand had their weight measured on a Standing Digital Scale (Seca). Infants were weighed on a Tanita 1584 Baby Scale. Weight was recorded in kilograms to two decimal places.

Head circumference was measured using the tape measure in the BSID II kit. The researcher measured the head circumference all the children as this was not routinely measured at the clinic. The tape was placed around the head at the broadest part of the occiput. Three measurements were taken and the mean was calculated and recorded in centimeters. In the case where children had braids in their hair every effort was made to pass the tape measure under the braids and as close to the scalp as possible. Mean head circumference z-scores were calculated at each visit. This was done using NCHS growth tables and using the formula: observed head circumference minus mean population head circumference divided by the standard deviation of the population. Software for calculating head circumference z-scores and standard deviations was not available at the Medical Research Council of South Africa at the time this study was done.

Oxygen saturation was measured using a Datex Ohmeda Saturation Monitor. This reading was not recorded but was noted to determine whether the children were well enough to be assessed developmentally.

4.6 Home Management Programme

A home management programme was given to each child in the experimental group. The main aim of the home programme was to optimise the child's functional potential and to encourage age appropriate behaviour in normal movement patterns. The home programme was taught by a qualified physiotherapist. It was not possible to design a standardized programme for all the children as their needs and levels of function varied greatly. A broad outline of the aspects to be addressed was drawn up in consultation with clinical experts who have many years of experience working with children with neurodevelopmental delay (See appendix II). Principles of Neurodevelopmental Therapy were followed when drawing up each programme and activities were chosen according to the child's age and developmental level. This was done within the context of the needs and concerns expressed by the caregiver. The home programme given to each child was recorded in their file.

The intervention was structured around activities of daily living and developmentally appropriate play which could be incorporated into the family's daily routine. It incorporated aspects identified as concerns by both the caregiver and the research assistant. Care was taken to ensure that the programme complied with the principles of Family Centred Intervention. Caregivers were encouraged to let their children play and interact with other children as much as possible and to use older siblings and other family members to reinforce the home programme.

As speech and language are commonly affected in HIV positive children all children were given a small picture book to take home. Caregivers were encouraged to read to them every day or at least to tell them stories related to the pictures in the book. For the older children books were selected that could be used to reinforce emerging concepts of shape, number, colour and size. The children could return their book and exchange it for a new one at each visit.

All caregivers of perambulatory children were asked not to use walking rings (baby walkers) as these are very popular despite their negative influence on the development of walking (Seigal and Burton, 1999).

4.7 Procedure

Most children attending Harriet Shezi Clinic are followed up at three monthly intervals. Children who are healthy and have CD4 counts of over 25% may only be seen every six months. Children who are ill, or who are starting HAART may be seen more regularly.

The researcher did not want to put an extra burden on the caregivers so this study was designed to fit in with the clinic schedule. This was convenient for the majority of caregivers as they were not required to make extra visits to the clinic only to see the researcher. This also ensured that the intervention was sustainable beyond the duration of the study.

Pilot Studies

Prior to commencement of the study, a pilot study was conducted using the PSI-SF. The research assistant and the researcher were trained in the administration of the BSID II by a child psychologist from Baylor University in the USA. The pilot studies have been described in detail in chapter three.

Baseline data collection

The files of all children booked to attend the clinic that day were screened by the researcher and research assistant. The caregivers of all children attending the HIV clinic who met the inclusion criteria were asked to participate in the study. If caregivers were interested in participating they were given the information sheet to read, which was available in Zulu, Sotho and English. Written informed consent was obtained from the caregivers for themselves and the children prior to any testing being done (See appendix III). Caregivers were asked to complete the biographical questionnaire in any of the abovementioned languages (See appendix IV). Children were assigned consecutive numbers as they joined the study and were then randomly allocated to either the control or experimental group using a computer generated random number table. The research assistant kept a record of which group each child was in, the researcher remained blinded to the group allocation of each child.

Study procedure

Session 1 (baseline)

Height/length and weight as measured by the clinic sisters were recorded for all children.

Head circumference was measured by the researcher.

The child's file was checked for their latest CD4 count and to determine whether the child was on antiretroviral therapy or not.

Caregivers were asked to complete the Parenting Stress Index-Short Form (See appendix V). This self administered questionnaire was available in English, Southern Sotho and Zulu. If the caregiver could not read but spoke English the research assistant read the items to them and allowed them to circle their response. A counsellor read the items to caregivers who could not read Zulu or Sotho and who did not understand English.

All caregivers were asked to complete the Household Economic and Social Status Index (HESSI) (See appendix VI). As with the PSI-SF a counsellor helped if the caregiver could not understand English.

The BSID was administered by the researcher who was blinded as to whether the child was in the control or experimental group. The BSID was administered with the child seated on the caregiver's lap at a table or seated at a child sized table on a small chair if the child was older. Testing was conducted in an area of the clinic away from the main waiting room in order to try and minimize distractions. The Mental Scale was administered before the Motor Scale as recommended in the testing manual. Testing was started at the child's chronological age for both the Mental and the Motor Scales.

Children in both groups were referred to the social worker or dietician if appropriate. Any questions which the caregivers asked about their child's developmental status were answered.

Children in the experimental group were given individual home programmes by the research assistant. Each home programme was based on the concerns and priorities expressed by the caregivers as well as the child's performance on the BSID II. The reasons for potential developmental delay were explained to the caregivers with a very basic explanation that HIV itself can affect the baby's brain and therefore their developmental progress. The impact of repeated illness, hospitalization and malnutrition on normal development was also explained.

The research assistant asked the caregivers if they were happy with the child's development and whether there was anything in particular which they thought their child should be able to do which they could not yet do. The child's performance on the test items was then discussed with the caregivers and areas of strength and weakness were highlighted.

These assessments and intervention took place at routine clinic visits and there was therefore no extra cost to the caregiver.

Session 2 (3 months)

Children in the control and experimental group had their height/length, weight and head circumference measurements taken. The most recent CD4 count was recorded from the children's files.

Children in the experimental group also had their home programmes updated by the research assistant. This was based on progress made since their last assessment as reported by their caregiver as well as clinical observation on the part of the research assistant. Children were given a new picture book.

Session 3 (6 months)

Growth (height/length, weight and head circumference) parameters were recorded for all children in both the control and experimental group.

The most recent CD4 count was recorded from the children's files.

All caregivers completed the PSI/SF again.

The researcher assessed all children using the BSID II according to the procedure previously outlined.

The research assistant updated the home programmes of the children in the experimental group. This was again done in consultation with the child's caregiver and based on the results of their BSID II assessment. Any additional concerns raised by the caregivers were addressed.

Session 4 (9 months)

Growth parameters for all children in both the experimental and control groups were recorded.

The most recent CD4 count was recorded from each child's file.

The experimental group had their home programme updated by the research assistant in consultation with the caregiver.

Session 5 (12 months)

Growth parameters were recorded for all children in both the experimental and control groups.

The most recent CD4 count was recorded from the children's files.

All the caregivers completed the PSI/SF again.

The researcher reassessed all children using the BSID II.

The research assistant updated the home programmes of the children in the experimental group in consultation with the caregivers.

As this was the last visit all caregivers were given a home management programme for their children. Children who presented with neurological signs were referred to the physiotherapy department at Chris Hani Baragwanath hospital for further management. All children were given an age appropriate story book to thank them for participating in the study.

Measures to reduce attrition

Harriet Shezi clinic serves the communities of Soweto, Eldorado Park, Lenasia and Orange Farm. These communities are poor and most people rely exclusively on public transport which is costly. Attendance at out patient clinics is often sporadic and regular attendance is rare.

In order to try and ensure that patients do not miss appointments the clinic has the following system in place: If a patient misses an appointment the caregiver is phoned the same afternoon and asked why they did not come. They are given a new appointment for the following week. If the caregiver does not have finances for transport

a counselor will do a home visit and provide money for a trip to the clinic, where the patient will also be seen by a social worker who will try to assist with finances. If the counselors are unable to contact the caregiver by phone an attempt is made to organize a home visit to ascertain if there are any problems preventing return for follow up. Home visits were not possible for families who did not live in Soweto due to time and financial constraints.

The researcher benefitted from this system in that most patients were traced by the counselors, however if a subject continued not to come for follow up the research assistant would phone them and request them to come in. Messages could not be left for caregivers as confidentiality and privacy had to be maintained at all costs.

4.8 Statistical Analysis

Statistical analysis was performed in consultation with the Medical Research Council of South Africa using STATA, Release 8.0, for Windows. Attendance at the clinic was monitored and the primary analysis of data was done using intention to treat analysis. Intention to treat analysis is considered to be the primary analysis of choice for randomised controlled trials, especially when the study is pragmatic in nature such as this one was (Herbert et al, 2005; Wright and Sim, 2003; Kruse et al, 2002; Fergusson et al, 2002; Hollis and Campbell, 1999; Newell D, 1992, Consort Agreement, 2001). Intention to treat analysis has the advantage of maintaining randomisation and minimising type 1 errors (Fergusson et al, 2002; Newell, 1992), however where there is a large loss to follow up some controversy exists on how best to deal with the missing data (Raghunathan, 2004). In this study all available data was analysed at each time point.

The loss to follow-up in this study was high (24.5%) so a secondary per protocol analysis of the primary outcomes was performed in order to verify the results. The per protocol analysis only considers the data of those children for whom complete data sets are available, subjects who have missing data or who dropped out of the study are excluded from analysis. Per protocol analysis is usually favoured in explanatory trials

(Herbert, et al 2005). (The results of the per protocol analysis are presented at the end of chapter five).

A sample size of 49 children in each of the two groups had 90% power to detect a 10 percentage point change in BSID scores, between the control and experimental groups, using a standard deviation of 15 (Bayley, 1993). A sample size of 50 children in each of the two groups (control and experimental) had 90% power to detect a decrease of 10.5 percentage points in the PSI/SF scores of caregivers. A standard deviation of 15.9 was assumed and was calculated as a pooled standard deviation from 3 studies (O'Neil et al 2001; Ong et al 1998; Bithoney et al 1995). A factor of 0.3 was used to make the statistics from the three studies comparable, that is to be able to compare statistics from the Parenting Stress Index to those from the Parenting Stress Index/Short Form. Fifty children were therefore needed per group. A further twenty two children were recruited to allow for a 20% drop-out during the year of follow up. A total of 122 children were therefore assessed. Testing was done at the 0.05 level of significance.

The data were summarised using means and standard deviations as descriptive statistics. Baseline data for the control and experimental group were compared using a two-sample t test with equal variance.

With respect to the BSID II, PSI-SF, CD4 counts and growth parameters, the control and experimental groups were compared over time in an appropriate analysis of variance (ANOVA) for repeated measures.

Stepwise regression analysis was conducted to determine which demographic and anthropometric variables were the best predictors of MDI, PDI and PSI/SF scores at each visit, as well as which factors were predictive of change in these scores over time. In order to get a comprehensive fit, a step-up model was used with automatic elimination procedures (Petrie, 1987). Of importance here was to derive good predictive equations and therefore the aim was to ensure that the coefficient of determination was as big as possible. Hence the p value for entry into the regression was set at 0.25.

The results of this study are presented in chapter five.

Chapter 5

RESULTS

In this chapter the results of this study will be presented and briefly commented on. The loss to follow up that occurred during the study will be presented and reasons for drop out will be explained. The baseline data will then be presented, thereafter the results for each outcome assessed over time will be presented. The factors which influenced developmental status and parenting stress at each visit will be described as well as the factors which influenced the amount of change that occurred over time. In chapter six the implications of all the results will be discussed in more detail.

5.1 Loss to Follow-up

One hundred and twenty two children and their caregivers were enrolled in this study. Only two caregivers approached, refused to participate in the study. Due to the nature of HIV disease in children a large drop-out of children was anticipated due to death and socio-economic factors. The following diagram represents the loss to follow up that occurred over the course of the study.

// Figure 5.1 follows on next page.

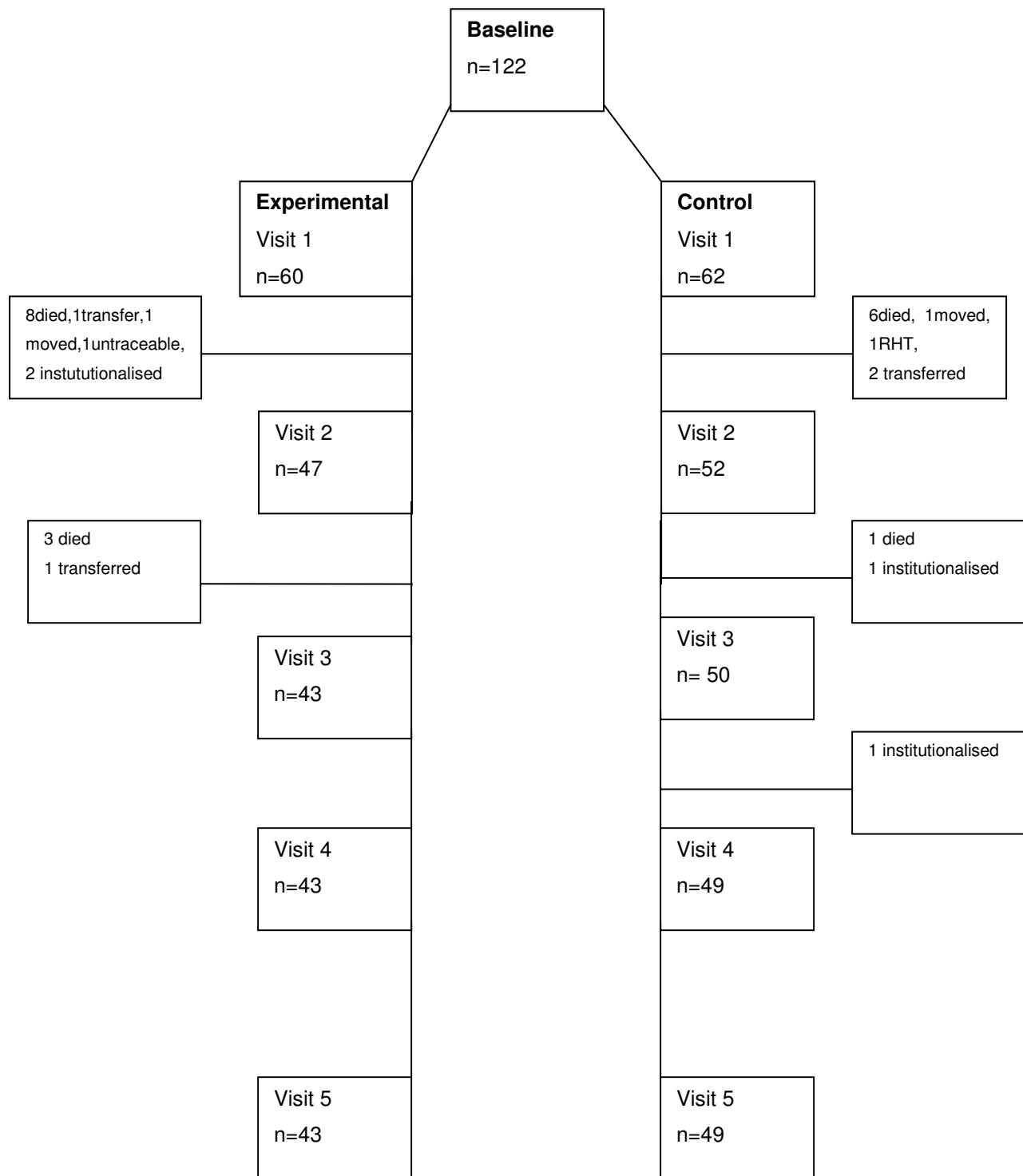


Figure 5.1 Loss to follow-up.

The methods to prevent loss to follow up at Harriet Shezi clinic were described in chapter three. Thirty children were lost to follow-up during the course of this study, this equates to 24.6% of the initial sample size, which although high is to be expected in a study of this nature.

Death of children.

The main cause of loss to follow up in this study was due to death of the children (60% of children lost to follow-up). When the study commenced in February 2004 antiretroviral therapy was not available at government hospitals in South Africa and the mortality rate of HIV infected children was therefore high. All of the children who died did so after their first or second visit to the clinic, usually before or just after they were able to get on to HAART. More children in the experimental group died than in the control group.

Transferred to other clinics.

After April 2004 as HAART became available in South Africa more outlying hospitals and clinics gradually gained access to the medication. This meant that children who initially attended Harriet Shezi clinic because it was one of the first sites to dispense HAART, were gradually referred back to their closest hospital or clinic once they could receive their medication there. When children were thus referred, the caregiver was asked whether they were still prepared to come to Harriet Shezi to continue to participate in this study, however they would no longer be able to receive the other services at the clinic. Understandably, few caregivers were willing to do this. This accounted for the five children lost to follow up during the study due to being transferred elsewhere.

Institutionalisation of children.

Three children were placed in institutions during the course of the study. These children could no longer be part of the study because they no longer had a primary caregiver to do the home programme with them and fill in the PSI/SF. Although no longer part of the study, these children were followed-up and developmental advice was given to the caregivers from the orphanage who brought them to their clinic visits.

Change of caregiver

One child had to be excluded from the study after her initial visit as she changed primary caregivers twice in six months. Her mother died and she was sent to her grandmother who died three months later. She was then sent to live with her aunt.

Family moved out of area.

Three children moved out of Gauteng during the study and no longer attended Harriet Shezi clinic. Two of the children moved with their mothers, the third child was sent to live with his grandmother in the Free State after his mother died.

Untraceable.

One child did not return to the clinic after his first visit. There was no contact number in the child's file and when a counsellor from Harriet Shezi went to the address given in the file to find the family, she was unable to trace the child or the caregiver.

Refused hospital treatment.

One child did not return after the first visit as the mother decided to take her to a traditional healer and not to return to the hospital.

5.2 Baseline Data

5.2.1 Demographic information

The demographic information for the experimental and the control groups at the start of the study is presented in table 5.1. Relevant information was extracted from the demographic questionnaire and the HESSI. The HESSI was not scored and analysed separately as many of the caregivers were not able to provide all the information requested, especially for items relating to the amount of rent paid and the cost of services for the household. Means and standard deviations or percentages were used to summarise the data. The demographic data of the control and experimental groups were compared using a two sample t test with equal variance.

Table 5.1 Demographic information for experimental and control groups.

	Experimental group n=60	Control group n=62	p value
Age(months)	18.0 (±8.1)	19.0(±8.2)	p=0.76
Gender			
Male	30 (50.0%)	32 (51.6%)	p=1
Female	30 (50.0%)	30 (48.4%)	
Primary caregiver			
Mother	49 (81.7%)	55 (88.7%)	p=0.54
Father	1 (1.7%)	1 (1.6%)	
Grandmother	7(11.7%)	4 (6.5%)	
Aunt	2 (3.3%)	0 (0%)	
Other	1 (1.7%)	2 (3.3%)	
Age of caregiver	31.7 (±10.5)	29.8 (±8.4)	p=0.27
Educational level caregiver			p=0.87
< Gr 5	1 (1.7%)	2 (3.2%)	
Gr 5-6	0 (0%)	2 (3.2%)	
Gr 7-9	9 (15.0%)	9 (14.5%)	
Gr 10-11	32 (53.3%)	30 (48.4%)	
Gr 12	16 (26.7%)	16 (25.8%)	
Tertiary	2 (3.3%)	3 (4.8%)	
Number of adults in household	3.2 (±2.0) Median= 3	3.2 (±1.9) Median= 2	p=0.99
Number of children in household	4.1 (±7.6) Median= 3	3.0 (±1.9) Median= 2	p=0.59
Monthly income	R1435 (±5098.88)	R939,16 (±1893.83)	p=0.52
Housing			
-Shack	13 (21.7%)	13 (21.0%)	p=0.30
-Room	9 (15.0%)	7 (11.3%)	
-Flat	4 (6.7%)	0 (0%)	
-Shared house	10 (16.7%)	14 (22.6%)	
-Own house	24 (40.0%)	28 (45.2%)	
Amenities in home			
-Fridge	46 (76.7%)	44 (71.0%)	p=0.54
-TV	48 (80.0%)	44 (71.0%)	p=0.30
-Telephone/cell phone	41 (68.3%)	37 (59.7%)	p=0.35
-Car	5 (8.3%)	2 (3.3%)	p=0.27
-VCR	13 (21.7%)	10 (16.1%)	p=0.49
-Washing machine	5 (8.3%)	9 (14.5%)	p=0.40
-Microwave	11 (18.3%)	11 (17.7%)	p=1

(Values presented are means and standard deviations unless otherwise indicated)

The two groups were well matched for all demographic variables measured, with no significant differences found between the two groups. The study population was relatively young and the vast majority of children were still being cared for by their biological mothers, the majority of whom were in their twenties and thirties. The families in which the children lived were poor with little access to common household amenities. One third of families lived in their own houses which they did not share with other families. Only one third of caregivers had completed school (12 years). The reported income varied widely due to the fact that a few wealthier families chose to bring their children to this clinic despite having medical aid. This accounts for the very wide standard deviation observed for income levels. The number of children per household was also skewed due to one mother caring for 60 abandoned and orphaned children in her home, without being registered as an orphanage or having any state support. She and her mother were the only adults in the household and the child she brought to the clinic was her own biological child.

5.2.2 Growth parameters

The baseline anthropometric data for children in the experimental and control groups is presented in table 5.2. The data for the control and experimental groups is compared using a two sample student's t test with equal variance.

Table 5.2 Baseline anthropometric data for children in experimental and control groups

	Experimental group n=60	Control group n=62	p value
Head circumference z-score	-2.54 ($\pm$ 1.3)	-2.35 ($\pm$ 1.3)	p=0.42
Height for age z-score	-3.01 ($\pm$ 2.1)	-2.71 ($\pm$ 1.6)	p=0.37
Weight-for-age z-score	-2.61 ($\pm$ 1.4)	-2.17 ($\pm$ 1. 6)	p=0.10
Weight-for-height z-score	-0.74 ($\pm$ 2.1)	-0.57 ($\pm$ 1.2)	p=0.59

(Values are means and standard deviations)

The children in the control and experimental groups were well matched for head circumference, weight and height. Malnutrition and stunting were present in both groups of children with stunting being more apparent than wasting. Weight for height z-scores were within normal limits due to the fact that both variables were decreased. These baseline anthropometric measurements indicate that the children in this study, as a group, were malnourished and that all their growth parameters were suboptimal.

5.2.3 CD4 counts and HAART

The number of children receiving HAART at their initial visit is depicted in table 5.3. The data for the control and experimental groups was compared using a two sample student's t test.

Table 5.3 Number of children in experimental and control groups receiving HAART

	Experimental group n=60	Control group n=62	p value
CD4%	14.2 ($\pm$ 8.3)	14.5 ($\pm$ 9.4)	p=0.86
HAART			
No	n=52 (86.7%)	n=52 (83.9%)	p=0.8
Yes	n=8 (13.3%)	n=10 (16.1%)	

(Values are means and standard deviations unless otherwise stated)

The mean CD4% counts for both groups of children were very low, indicating that many of these children had severe immuno-suppression and would be eligible for starting HAART. The majority of the children were not receiving HAART at the start of this study as it was not yet available in South African hospitals. Those children who were on HAART were paying for it privately or were enrolled in drug trial studies. There was no difference in the number of children on HAART between the two groups at the start of the study (p= 0.8).

5.2.4 Developmental status

The developmental status of the children in the experimental and control groups at baseline is presented in table 5.4. Developmental status is presented as age corrected developmental indices, the Mental Developmental Index (MDI) and the Psychomotor

Developmental Index (PDI). The data for the control and experimental groups was compared using a two sample student's t test with equal variance.

Table 5.4 MDI and PDI for children in the experimental and control groups at baseline.

	Experimental group n= 60	Control group n=62	p value
MDI	62.6 ($\pm$ 21.5)	68.5 ($\pm$ 22.1)	p=0.14
PDI	49.8 ($\pm$ 22.3)	57.4 ($\pm$ 24.8)	p=0.08

(Values are means and standard deviations unless otherwise stated)

The children in both the experimental and control groups were extremely delayed in both mental and motor development at their initial assessments. Motor development was particularly severely affected with scores being extremely low. The PDI scores of the experimental group were lower than those of the control group, but not significantly so.

The BSID allows for classification of children as having accelerated development, being within normal limits, having mild delay or severe delay. The breakdown for this sample at baseline is presented in table 5.5.

Table 5.5 Developmental status of groups according to BSID classification at visit one.

	MDI			PDI		
	Experimental n=60	Control n=62	Total n=122	Experimental n=60	Control n=62	Total n=122
Accelerated (>115)	0%	0%	0%	0%	1.6%	1%
Normal (85-115)	21.7%	25.8%	22%	8.5%	17.7%	12%
Mild delay (70-84)	16.7%	32.2%	26%	18.5%	13%	15%
Severe delay (<70)	61.6%	42%	52%	73%	67.7%	72%

It is of concern to note that half the children had severely delayed mental development and almost three quarters had severely delayed motor development. Less than 25% of the children had normal mental development scores and only 12% fell into the normal category for motor development. The experimental group had more children in the severely delayed category for both mental and motor development than the control group.

5.2.5 Parenting stress

The means and standard deviations of parenting stress levels for caregivers of children in the experimental and control groups as measured by the PSI/SF are presented in table 5.6. The data for the two groups was compared using a two sample student's t test with equal variance.

Table 5.6 Parenting stress of caregivers of children in experimental and control groups at baseline.

	Experimental group n=60	Control group n=62	p value
PSI/SF Total	104.1 (± 20.0)	103.7 (± 19.2)	p=0.92
PD	37.5 (± 9.3)	36.9 (± 7.5)	p=0.72
P-CDI	33.2 (± 8.6)	32.2 (± 9.0)	p=0.55
DC	33.3 (± 7.1)	34.6 (± 7.4)	p=0.31

(Values are means and standard deviations unless otherwise stated)

The parenting stress levels of both groups of caregivers were extremely high. Values of over 90 for total stress indicate clinically significant levels of stress. There was no difference between the two groups in terms of total stress scores, or any of the three subscale scores. All three of the sub-scales were elevated, indicating that parents experienced high levels of stress in all of the domains measured. The parental dysfunction (PD) subscale score was slightly higher than the rest. This could be attributed to the fact that most of the caregivers were the child's biological mother and HIV positive themselves which could affect their own health related quality of life and emotional well being.

5.3 Outcomes Over Time as Measured by Intention to Treat Analysis.

This section presents the changes that occurred in each of the outcomes that were measured over the study period will be presented. CD4 counts and anthropometric measures (height, weight and head circumference) were performed every three months at each visit. Whether or not the child was on HAART was also documented at all five visits. MDI, PDI and PSI were measured at baseline, six months and twelve months.

Change in anthropometric scores as well as in MDI, PDI and PSI was assessed using repeated measures analysis of variance.

5.3.1 HAART over time

At each visit it was recorded whether or not the child was on HAART. The percentage of children receiving HAART at each visit is shown in table 5.7. The data for the two groups was compared using Fisher's exact test.

Table 5.7 Percentage of children in each group receiving HAART at each visit.

	Experimental group	Control group	p value
Visit 1.	13.3%	16.1%	p=0.80
Visit 2.	46.8%	34.6%	p=0.23
Visit 3.	65.1%	64.0%	p=1
Visit 4.	79.1%	77.6%	p=1
Visit 5.	86.1%	85.7%	p=1

The number of children receiving HAART increased steadily throughout the duration of the study. At no point was there a significant difference between the two groups in the number of children receiving HAART. The increase in number of children receiving HAART is a measure of the success of the rollout of antiretroviral therapy at Harriet Shezi clinic.

5.3.2 Anthropometric outcomes over time.

The height, weight and head circumference of each child were measured at every visit.

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Head Circumference

In table 5.8 the head circumferences of the children in the experimental and control groups at each visit are shown.

Table 5.8 Change in head circumference over time

	Experimental group	Control group	Total
Visit 1	n=60 45.13($\pm$ 3.12)	n=62 45.45 ($\pm$ 2.91)	n=122 45.29($\pm$ 3.01)
Visit 3	n=43 46.68($\pm$ 2.85)	n=50 46.85($\pm$ 2.41)	n=93 46.77($\pm$ 2.61)
Visit 5	n=43 47.91($\pm$ 2.34)	n=49 48.07($\pm$ 2.05)	n=92 47.99($\pm$ 2.18)
Total	n=146 46.41($\pm$ 3.04)	n=161 46.68($\pm$ 2.73)	n=307 46.55($\pm$ 2.88)

The absolute values for head circumferences of the two groups were very similar, with no significant differences found between groups over time ($p=0.42$). The head circumference of both groups of children increased significantly over time from baseline to 12 months follow up ($p=0.00$).

The mean z-scores for the control and experimental groups are presented in table 5.9.

Table 5.9 Mean head circumference z-scores over visits by group.

	Experimental group	Control group
Visit 1	-2.54	-2.35
Visit 2	-2.23	-2.12
Visit 3	-2.02	-1.88
Visit 4	-1.82	-1.73
Visit 5	-1.53	-1.48

Although they improved over the course of the study the head circumference z-scores for both the control and the experimental groups remained well below the international norm at the end of the study period (-1.53 and -1.48 respectively).

Height

The height-for-age- z-scores for the experimental and control groups at each visit are presented in table 5.10

Table 5.10 Change in height- for-age z-score over visits by group

	Experimental group	Control group	Total
Visit 1	n=60 -3.01($\pm$ 2.06)	n=62 -2.71($\pm$ 1.60)	n=122 -2.86($\pm$ 1.83)
Visit 2	n=47 -2.87($\pm$ 1.54)	n=52 -2.61($\pm$ 1.57)	n=99 -2.73($\pm$ 1.56)
Visit 3	n=43 -2.76($\pm$ 1.33)	n=50 -2.49($\pm$ 1.25)	n=93 -2.62($\pm$ 1.28)
Visit 4	n=43 -2.70($\pm$ 1.36)	n=49 -2.27($\pm$ 1.08)	n=92 -2.47($\pm$ 1.24)
Visit 5	n=43 -2.40($\pm$ 1.46)	n=49 -2.13($\pm$ 1.06)	n=92 -2.25($\pm$ 1.26)
Total	n=236 -2.77($\pm$ 1.61)	n=262 -2.46($\pm$ 1.36)	n=498 -2.61($\pm$ 1.49)

The two groups had similar height-for-age z-scores which increased significantly for both groups combined over the year ($p < 0.001$). The children were stunted, with mean z-scores of -2.86 for the combined group at the start of the study. Although the improvement over the year was significant the children remained stunted with mean z-scores of -2.25 at the end of the follow-up period. There was no significant difference between the groups ($p=0.22$).

Weight

The weight-for-age z-scores for each group over time are presented in table 5.11.

Table 5.11/

Table 5.11 Change in weight-for-age over visits by group.

	Experimental group	Control group	Total
Visit 1	n=60 -2.61(±1.37)	n=62 -2.17(±1.56)	n=122 -2.39(±1.48)
Visit 2	n=47 -2.42(±1.51)	n=52 -2.10(±1.50)	n=99 -2.25(±1.50)
Visit 3	n=43 -2.05(±1.35)	n=50 -1.67(±1.22)	n=93 -1.84(±1.29)
Visit 4	n=43 -1.87(±1.28)	n=49 -1.46(±1.13)	n=92 -1.65(±1.21)
Visit 5	n=43 -1.55(±1.13)	n=49 -1.26(±1.12)	n=92 -1.39(±1.13)
Total	n=236 -2.14(±1.38)	n=262 -1.76(±1.37)	n=498 -1.94(±1.39)

Weight-for-age was below normal in both groups with a mean combined z-score for the two groups of -2.39. The children did gain weight during the study period with the final mean weight-for-age z-score approaching normal at -1.39. There was a significant change in weight-for-age z-scores over the study period for the two groups combined ($p<0.001$). There was no significant difference between the two groups in terms of weight-for-age ($p=0.08$).

The weight-for-height z-scores for the experimental and control groups at each visit are presented in table 5.12.

Table 5.12 Change in weight-for-height z-score over visits by group

	Experimental group	Control group	Total
Visit 1	n=60 -0.74(±2.06))	n=62 -0.57(±1.22)	n=122 -0.66(±1.68)
Visit 2	n=47 -0.83(±1.32)	n=52 -0.62(±1.38)	n=99 -0.72(±1.35)
Visit 3	n=43 -0.51(±1.07)	n=50 -0.27(±1.19)	n=93 -0.38(±1.14)
Visit 4	n=43 -0.31(±1.15)	n=49 -0.15(±1.08)	n=92 -0.22(±1.11)
Visit 5	n=43 -0.17(±1.14)	n=49 0.02(±1.07)	n=92 -0.07(±1.10)
Total	n=236 -0.53(±1.46)	n=262 -0.33(±1.21)	n=498 -0.43(±1.34)

The weight for height of both groups of children was within normal limits and was close to normal by the end of the study period. The weight-for-height z-score for the groups combined was -0.43 at the end of the study period which is 98% of the median. This reflects that the weight gain exceeded the growth in length of the children during this time period. There was a significant improvement in weight-for-height z-scores for the two groups combined ($p < 0.001$) and there was no significant difference between the two groups ($p = 0.24$).

5.3.3 CD4% counts over time

Each child's most recent CD4% was noted at every visit. The change in CD4% for each group over the year is depicted in table 5.13.

Table 5.13 Change in CD4% over visits by group

	Experimental group	Control group	Total
Visit 1	n=60 14.25(±8.32)	n=62 14.53(±9.36)	n=122 14.39(±8.83)
Visit 2	n=47 15.01(±8.38)	n=52 15.24(±9.88)	n=99 15.13(±9.15)
Visit 3	n=43 18.75(±11.57)	n=50 15.77(±8.44)	n=93 17.15(±10.06)
Visit 4	n=43 20.62(±11.13)	n=49 17.08(±7.82)	n=92 18.73(±9.63)
Visit 5	n=43 21.91(±10.21)	n=49 19.65(±7.59)	n=92 20.72(±8.95)
Total	n=236 17.78(±10.26)	n=262 16.33(±8.83)	n=498 17.02(±9.56)

The two groups were well matched in terms of their CD4% throughout the study period ($p=0.64$). The CD4% for both groups increased significantly over the one year follow-up period ($p<0.001$). The initial CD4% for both the experimental and control group was very low (14.25% and 14.53% respectively), as previously mentioned very few children were on HAART when enrolled onto the study. The CD4% at the end of the study was significantly improved for both groups (21.91% and 19.65% respectively). Many more children were on HAART by the end of the study period as seen in table 5.7.

5.3.4 Developmental status over time

Children were assessed with the BSID at visit 1 (baseline), visit 3 (six months) and visit 5 (12 months). The changes in the mental developmental index (MDI) and the psychomotor developmental index (PDI) over time for each group of children can be seen in figures 5.14 and 5.15.

MDI

The change in MDI for each group over time is represented in table 5.14.

Table 5.14 Change in MDI over visits by group

	Experimental group	Control group	Total
Visit 1	n=60 62.60(±21.51)	n=62 68.53 (±22.10)	n=122 65.61(±21.93)
Visit 3	n=43 61.63(±20.45)	n=50 69.38(±22.33)	n=93 65.80(±21.72)
Visit 5	n=43 69.30(±19.84)	n=49 64.31(±17.43)	n=92 66.64(±18.66)
Total	n=146 64.29(±20.83)	n=161 67.51(±20.85)	n=307 65.98(±20.87)

The MDI for both groups of children was extremely low initially. There was no significant difference between the two groups, with respect to MDI ($p=0.27$). The MDI also did not change significantly for the two groups combined over the period of one year ($p=0.86$). However the amount of change in the experimental group over the year (MDI=62.6 to MDI=69.3) was significantly greater ($p=0.01$) than the change seen in the control group (MDI=68.5 to MDI=64.3). In fact the control group deteriorated slightly over the year while the experimental group improved. Despite the fact that the children in the experimental group improved during the course of the study the mean MDI scores at the end of the study period indicate that the children still had significant delay in their mental development.

PDI

The change in PDI for each group over time is presented in table 5.15.

Table 5.15/

Table 5.15 Change in PDI over visits by group

	Experimental group	Control group	Total
Visit 1	n=60 49.78(±22.25)	n=62 57.44 (±24.76)	n=122 53.67(±23.77)
Visit 3	n=43 59.26(±25.08)	n=50 63.20(±24.75)	n=93 61.38(±24.85)
Visit 5	n=43 70.49(±25.05)	n=49 65.86(±24.47)	n=92 68.02(±24.72)
Total	n=146 58.67(±25.29)	n=161 61.79(±24.78)	n=307 60.31(±25.03)

There was no significant difference between the two groups, with respect to PDI ($p=0.57$). The PDI scores of the two groups combined improved significantly over the one year period ($p=0.00$), however the amount of improvement over time in the experimental group (PDI=49.8 to PDI=70.5) was significantly more than in the control group (PDI=57.4 to PDI=65.9) ($p=0.02$). Although both groups showed some improvement in PDI scores over the study period, the mean PDI scores for both groups remained low, indicating that the children still had with significant motor delay at the end of the study period.

The classification of the developmental status of the children according to the BSID II at visit five is presented in table 5.16.

Table 5.16 Classification of groups according to BSID II scores at visit five.

	MDI			PDI		
	Experimental n=43	Control n=49	Total n=92	Experimental n=43	Control n=49	Total n=92
Accelerated	2.3%	0%	1%	0%	0%	0%
Normal	11.6%	12.2%	12%	34.8%	26.5%	30.4%
Mild delay	48.8%	28.6%	38%	23.3%	18.4%	20.6%
Severe delay	37.2%	59.2%	49%	41.9%	55.1%	48.9%

The proportion of children with severe delay according to their MDI scores was very similar to those seen at baseline (See table 5.5). Although nearly half the children were still classified as severely delayed in terms of their PDI scores this is an improvement on the 72% of children who fell into this category at visit one. Children in the experimental group were less likely to be severely delayed at visit five than children in the control group. A greater proportion of children scored within normal limits for PDI at the end of the study than at visit one, 30.4% as opposed to 12%. This improvement in motor function for the two groups combined could probably be attributed to the availability of HAART for all children who qualified for it by the end of the study period.

5.3.5 Parenting Stress

The PSI/SF was administered to the caregivers of the children at visit 1 (baseline), visit 3 (6months) and visit 5 (12 months). Table 5.17 depicts the changes in total stress scores for each group over the study period.

Table 5.17 Change in parenting stress over visits by group.

	Experimental group	Control group	Total
Visit 1	n=60 104.13(±20.00)	n=62 103.77 (±19.18)	n=122 103.95(±19.51)
Visit 3	n=43 100.86(±24.96)	n=50 96.08(±21.19)	n=93 98.29(±23.00)
Visit 5	n=43 97.35(±24.12)	n=49 96.06(±21.49)	n=92 96.66(±22.64)
Total	n=146 101.17(±22.80)	n=161 99.04(±20.75)	n=307 100.05(±21.74)

The PSI total scores were well matched for the two groups ($p=0.62$). The PSI scores came down significantly during the course of the study with the scores at visit five being significantly lower than those at visit one ($p<0.001$). There was no difference in the amount of change that occurred in parenting stress between the two groups ($p=0.57$). Closer analysis revealed that of the three subscales of the PSI/SF there was a

significant decreases in Parental Dysfunction over time ($p<0.001$) as well as in Parent-Child Dysfunctional Interaction ($p<0.001$) but no significant change in the Difficult Child subscale ($p=0.08$). The two groups were well matched for each of the three subscale scores over time with no significant differences between groups being noted.

5.4 Variables that Predicted Outcomes.

As a result of a step-wise regression analysis the variables that were predictors of each outcome were determined. As a result of the lenient p value set for entry into the regression ($p=0.25$), a number of variables entered each regression analysis. The three most important variables, as determined by the order in which they enter the regression, are highlighted in the discussion that follows each table.

The factors that predicted MDI at visit one are shown in table 5.18a and 5.18b.

Table 5.18a Order and significance of variables entering regression analysis for MDI at visit one (n=122).

Begin with empty model	p value
Adding weight-for-age z-score	P=0.0001
Adding age	p=0.0000
Adding On HAART	p=0.0080
Adding gender	p=0.0534
Adding group	p=0.1707

Table 5.18b Variables predicting MDI at visit one (n=122).

MDI	Coefficient	Std Error	t	P> t	95%confidence interval	
Waz	6.65	1.15	5.76	0.00	4.36	8.93
Age	-1.22	0.21	-5.91	0.00	-1.62	-0.81
On HAART	-13.12	4.59	-2.85	0.01	-22.21	-4.02
Female	-6.22	3.27	-1.90	0.06	-12.71	0.27
Control group	4.50	3.23	1.38	0.17	-1.97	10.97
Cons	116.90	16.74	6.98	0.00	83.69	150.12

Many variables were predictive of MDI at visit one. The most important of these factors are seen in table 5.18b and accounted for 37.0% of the variance seen. The three most

important factors predicting MDI at this visit were weight for age z-scores, the age of the children and whether the children were on HAART. Children were more likely to have higher MDI scores if they had better weight-for-age z-scores, were younger and not on antiretrovirals.

Table 5.19a and 5.19b shows the variables predictive of MDI at visit three.

Table 5.19a Order and significance of variables entering regression analysis for MDI at visit three (n=93).

Begin with empty model	p value
Adding weight-for-age z-score	p=0.0000
Adding age	p=0.1041
Adding height-for-age z-score	p=0.1788
Adding weight-for-height z-score	p=0.0463
Adding number of children	p=0.1144
Adding group	p=0.1726
Adding education level	p=0.1847
Adding housing	p=0.1500
Adding CD4 count	p=0.1825

Table 5.19b/

Table 5.19b Variables predicting MDI at visit three (n=93).

MDI	Coefficient	Std. Error	t	P> t	95% Confidence Interval
Waz	-24.37	-10.65	-2.29	0.02	-45.57 -3.16
Age	-0.17	0.27	-0.62	0.54	-0.70 0.37
Haz	20.22	6.44	3.14	0.00	7.40 33.04
Whz	22.17	7.77	2.85	0.01	6.70 37.64
No. children	-0.55	0.34	-1.65	0.10	-1.22 0.12
Control group	9.23	4.00	2.31	0.02	1.26 17.21
<i>Education caregiver</i>					
Grade 5-6	7.23	23.03	0.31	0.75	-38.64 53.11
Grade 7-9	30.16	19.12	1.58	0.12	-7.94 68.25
Grade 10-11	35.45	18.74	1.89	0.06	-1.87 72.78
Grade 12	33.71	18.94	1.78	0.07	-4.02 71.43
Tertiary	38.96	21.35	1.82	0.07	-3.57 81.49
<i>Housing</i>					
Room	-2.05	6.71	-0.31	0.76	-15.41 11.30
Flat	12.75	13.93	0.92	0.36	-14.99 40.48
Shared house	5.40	6.28	0.86	0.39	-7.11 17.91
Own house	-8.25	5.20	-1.59	0.11	-18.60 2.11
CD4%	0.28	0.21	1.35	0.18	-0.13 0.68
Cons	48.18	22.63	2.13	0.04	3.12 93.25

At visit three a large number of variables were again predictive of MDI and together explained 44.4% of the variance seen. The three most important variables predicting MDI were weight-for-age z-score, age of the child and height-for-age z-score. Low weight-for-age was predictive of better MDI scores, this is in contrast to the finding at visit one where children with greater weight-for-age z-scores performed better. Younger children performed better and children with a greater height-for-age z-score also did better.

The variables predicting MDI scores at visit five are shown in tables 5.20a and 5.20b.

Tables 5.20a and 5.20b /

Table 5.20a Order and significance of variables entering regression analysis for MDI at visit five (n=92).

Begin with empty model	p value
Adding weight-for-age z-score	p=0.0000
Adding CD4 count	p=0.0058
Adding group	p=0.0640
Adding on HAART	p=0.0662
Adding number of children	p=0.1626
Adding gender	p=0.1888

Table 5.20b Variables predicting MDI at visit five (n=92).

MDI	Coefficient	Std Error	t	P> t	95% confidence interval	
Waz	7.29	1.49	4.90	0.00	4.33	10.25
CD4%	0.33	0.20	1.66	0.10	-0.06	0.71
Control group	-7.35	3.36	-2.19	0.03	-14.04	-0.66
On HAART	-9.30	4.86	-1.92	0.06	-18.96	0.35
No. children	-0.41	0.27	-1.54	0.13	-0.94	0.12
Female	-4.38	3.01	-1.32	0.19	-10.96	2.19
Cons	85.54	7.95	10.76	0.00	69.72	101.36

At visit five higher weight-for-age z-scores, higher CD4% counts and being in the experimental group were the three most important predictors of better MDI scores. A number of other factors as seen in table 5.20b contributed to predicting MDI scores at this visit. These factors accounted for 35.71% of the variance seen in MDI scores.

The variables influencing PDI at visit one are presented in tables 5.21a and 5.21b.

Tables 5.21a and 5.21b /

Table 5.21a Order and significance of variables entering the regression analysis for PDI at visit one (n=122).

Begin with empty model	p value
Adding weight-for-age z-score	p=0.0000
Adding age	p=0.0000
Adding on HAART	p=0.0107
Adding gender	p=0.0548
Adding group	p=0.1451
Adding CD% count	p=0.1392
Adding income	p=0.1705

Table 5.21b Variables predicting PDI at visit one (n=122).

PDI	Coefficient	Std Error	t	P> t	95% confidence interval	
Waz	8.73	1.25	6.98	0.00	6.25	11.21
Age	-1.04	0.21	-4.89	0.00	-1.46	-0.62
On HAART	-12.07	4.73	-2.55	0.01	-21.43	-2.70
Female	-6.35	3.33	-1.91	0.05	-12.95	0.25
Control group	5.31	3.31	1.60	0.11	-1.26	11.88
CD4%	0.29	0.20	1.43	0.16	-0.11	0.69
Income	0.00	0.00	1.38	0.17	-0.00	0.00
Cons	91.03	7.76	11.73	0.00	75.65	106.41

The three most important predictors of PDI at visit one were weight-for-age z-score, age of the child and whether they were on HAART or not. Children who were not on HAART, were younger and had higher weight-for-age z-scores were more likely to have better PDI scores. A number of other factors contributed towards predicting PDI. Together they accounted for 45.94% of the variance seen.

Variables predicting PDI at visit three are shown in table 5.22a and 5.22b.

Table 5.22a Order and significance of variables entering the regression analysis for PDI at visit three (n=93).

Begin with empty model	p value
Adding weight-for-age z-score	p=0.0000
Adding HAART	p=0.0541
Adding CD4 count	p=0.0918
Adding gender	p=0.2238

Table 5.22b Factors predicting PDI at visit three (n=93).

PDI	Coefficient	Std Error	t	P> t	95% confidence interval	
Waz	9.57	1.70	5.63	0.00	6.19	12.94
On HAART	-9.62	4.71	-2.04	0.04	-18.98	-0.27
CD4%	0.29	0.23	1.27	0.21	-0.16	0.75
Female	-5.62	4.58	-1.23	0.22	-14.73	3.49
cons	83.16	8.01	10.39	0.00	67.25	99.07

A combination of a number of variables was predictive of PDI scores at visit three. The three most important variables were weight for age z-score, whether or not the child was on HAART and their CD4 count. Children with a higher weight-for-age z-score, with a higher CD4 count and not on HAART achieved better PDI scores. The combination of factors shown in table 5.22b accounted for 36.11% of the variance in PDI scores at this visit.

The variables predictive of PDI at visit five are shown in table 5.23a and 5.23b.

Table 5.23a and 5.23b /

Table 5.23a Order and significance of variables entering the regression analysis for PDI at visit five (n=92).

Begin with empty model	p value
Adding height-for-age z-score	p=0.0001
Adding CD4 count	p=0.0003
Adding on HAART	p=0.0194
Adding weight-for-age z-score	p=0.0647
Adding weight-for-height z-score	p=0.0759
Adding income	p=0.1504
Adding gender	p=0.2347
Adding group	p=0.2340

Table 5.23b Variables predicting PDI at visit five (n=92).

PDI	Coefficient	Std Error	t	P> t	95% confidence interval	
Haz	-9.94	9.07	-1.10	0.27	-27.98	8.09
CD4%	0.70	0.25	2.82	0.01	0.21	1.20
On HAART	-15.51	6.28	-2.47	0.02	-27.98	-3.02
Waz	28.67	15.48	1.85	0.07	-2.13	59.47
Whz	-18.32	11.94	-1.53	0.13	-42.07	5.42
Income	-0.00	0.00	-1.50	0.14	-0.00	0.00
Female	-5.33	4.31	-1.24	0.22	-13.92	3.25
Control group	-5.15	4.30	-1.20	0.23	-13.70	3.40
Cons	90.27	10.26	8.80	0.00	69.86	110.68

The three most important predictors of PDI at visit five were height-for-age, CD4% count and whether or not the child was on HAART. Children were more likely to have higher PDI scores if they had a greater height-for-age z-scores, higher CD4% counts and were not on HAART. These variables in combination with those in table 5.23b explained 41.07% of the variance seen in PDI scores at this visit.

In general children who were not yet eligible for HAART (ie. had higher CD4 counts) and with better growth parameters appeared to do better in terms of motor performance at each of the three time points.

Table 5.24a and table 5.24b show the variables that predicted parenting stress of caregivers at visit one.

Table 5.24a Order and significance of variables entering the regression analysis for PSI at visit one (n=122).

Begin with empty model	p value
Adding weight-for-age z-score	p=0.0070
Adding education level	p=0.0168
Adding number of children	p=0.0419
Adding number of adults	p=0.0551
Adding age of caregiver	p=0.2282

Table 5.24b Variables predicting PSI of caregivers at visit one (n=122).

PSI	Coefficient	Std Error	t	P> t	95% Confidence interval	
Waz	-2.69	1.15	-2.34	0.02	-4.96	-0.41
Education caregiver						
Grade 5-6	15.87	16.29	0.97	0.33	-16.41	48.16
Grade 7-9	7.92	11.15	0.71	0.48	-14.17	30.00
Grade 10-11	19.94	10.58	1.88	0.06	-1.04	40.92
Grade 12	7.87	10.86	0.72	0.47	-13.64	29.38
Tertiary	3.07	13.05	0.28	0.77	-22.15	29.56
No. children	0.90	0.34	2.67	0.01	0.23	1.57
No. adults	-0.58	0.97	-1.63	0.11	-3.51	0.34
Age caregiver	0.23	0.19	1.21	0.23	-0.14	0.59
Cons	78.72	13.47	5.84	0.00	52.03	105.42

Weight-for-age, educational level of the caregiver and the number of children in the household were the most important predictors of parenting stress at this visit. Caregivers of children with higher weight-for-age z-scores had lower stress levels, while those with

higher levels of education experienced more stress. Caregivers were more likely to have increased parenting stress if there were more children in the household. The combination of factors seen in table 5.24b accounted for 23.03% of the variance seen in PSI/SF scores at this visit.

Variables predicting parenting stress scores at visit three are shown in table 5.25a and table 5.25b.

Table 5.25a Order and significance of variables entering the regression analysis for PSI at visit three (n=93).

Begin with empty model	p value
Adding weight-for-age z-score	p=0.0062
Adding housing	p=0.0153
Adding education level	p=0.0465
Adding gender	p=0.0458
Adding number of children	p=0.2168

Table 5.25b Variables predicting PSI/SF scores at visit three (n=93).

PSI/SF	Coefficient	Std Error	t	P> t	95% Confidence interval	
Waz	-5.09	1.74	-2.93	0.00	-8.54	-1.63
Housing						
Room	-2.63	7.39	-0.36	0.72	-17.34	12.08
Flat	-8.44	15.20	-0.56	0.58	-38.70	21.82
Shared house	19.53	7.07	2.76	0.01	5.46	33.59
Own house	-2.80	5.61	0.50	0.62	-13.97	8.37
Education						
caregiver						
Grade 5-6	-37.35	24.97	-1.50	0.14	-87.03	12.34
Grade 7-9	-12.62	21.14	-0.60	0.55	-54.68	29.44
Grade 10-11	-14.25	20.42	-0.70	0.49	-54.89	26.40
Grade 12	-29.09	20.59	-1.41	0.16	-70.08	11.88
Tertiary	-24.02	23.26	-1.03	0.31	-70.31	22.26
Female	9.00	4.32	2.08	0.04	0.40	17.60
No. children	0.44	0.36	1.24	0.22	-0.27	1.16
Cons	100.04	21.69	4.61	0.00	56.88	143.20

At this visit weight-for-age, housing and educational level were the most important predictors of parenting stress. Decreased weight-for-age z-scores were associated with increased parenting stress at this visit. Caregivers who shared a house with others were more likely to have high parenting stress levels and a higher level of education was associated with lower levels of parenting stress. The combination of factors shown in table 5.25b accounted for 34.69% of the variance seen at this visit.

The variables that predicted parenting stress scores at visit five are shown in table 5.26a and 5.26b.

Table 5.26a Order and significance of variables entering the regression analysis for PSI at visit five (n=92).

Begin with empty model	p value
Adding number of children	p=0.0019
Adding education level	p=0.0267
Adding CD4 count	p=0.0680
Adding housing	p=0.1903
Adding on HAART	p=0.2384

Table 5.26b /

Table 5.26b Variables predicting PSI/SF scores at visit five (n= 92).

PSI/SF	Coefficient	Std Error	t	P> t	95% Confidence interval	
Children	1.03	0.36	286	0.01	0.31	1.76
<i>Education caregiver</i>						
Grade 5-6	-27.13	29.81	-0.91	0.37	-86.47	32.12
Grade 7-9	-48.46	22.15	-2.19	0.03	-92.55	-4.37
Grade 10-11	-49.46	21.39	-2.31	0.02	-92.04	-6.88
Grade 12	-62.99	21.45	-2.94	0.00	-105.70	-20.28
Tertiary	-53.53	24.04	-2.23	0.03	-101.40	-5.66
CD4%	-0.27	0.26	-1.00	0.32	-0.79	0.26
<i>Housing</i>						
Room	10.87	7.45	1.46	0.15	-3.97	25.71
Flat	1.93	15.11	0.13	0.89	-28.14	32.00
Shared house	9.21	7.27	1.27	0.21	-5.26	23.68
Own house	-3.47	5.86	-0.59	0.55	-15.14	8.19
On HAART	7.75	6.52	1.19	0.24	-5.24	20.74
Cons	142.90	21.17	6.75	0.00	100.75	185.05

The number of children in the household, the educational level of the caregiver as well as the CD4% count of the child were the three most important predictors of parenting stress at this visit. Caregivers who lived in households with more children had higher stress levels. Those with higher levels of education had lower stress levels. The higher the child's CD4% count, the lower the caregivers parenting stress was. The factors shown in table 5.26b accounted for 32.45% of the variance in parenting stress scores seen at this visit.

A number of factors influenced the amount of parenting stress experienced by caregivers. Housing, educational level as well as the number of children in the household all played a role as did anthropometric measures and CD4% counts of the child to a lesser degree.

A further analysis was done to see which factors predicted a change in the children's developmental status and the caregiver's parenting stress levels from visit one to visit

five. Table 5.27a and table 5.27b show which factors predicted an improvement in MDI over time.

Table 5.27a Order and significance of variables entering the regression analysis for change in MDI (n=92).

Begin with empty model	p value
Adding age	p=0.0021
Adding group	p=0.0460
Adding income	p=0.0437
Adding on HAART	p=0.1381

Table 5.27b Variables predicting a change in MDI over time (n=92).

Change in MDI	Coefficient	Std Error	t	P> t	95%Confidence interval	
Age	0.98	0.27	3.63	0.00	0.44	1.51
Control group	-10.10	4.34	-2.33	0.02	-18.73	-1.47
Income	0.00	0.00	1.55	0.12	-0.00	0.01
On HAART	8.94	5.96	1.50	0.14	-2.93	20.82
Cons	-16.31	6.20	-2.63	0.01	-28.63	-3.98

The children who were most likely to improve with respect to their mental development were those who were older, in the experimental group and came from households with a higher monthly income. A number of other factors contributed towards predicting an improvement in MDI scores over the study period, but accounted for only 19.98% of the variance seen.

Variables predicting a change in PDI over time are presented in table 5.28a and 5.28b.

Table 5.28a and 5.28b /

Table 5.28a Order and significance of variables entering the regression analysis for change in PDI (n=92).

Begin with empty model	p value
Adding age	p=0.0004
Adding group	p=0.0060
Adding on HAART	p=0.0257
Adding weight-for-height z-score	p=0.0390
Adding gender	p=0.1802
Adding education level	p=0.1724
Adding weight-for-age z-score	p=0.1951
Adding height-for-age z-score	p=0.0056
Adding housing	p=0.2312
Adding number of adults	p=0.1496
Adding number of children	p=0.2021

Table 5.28b Variables predicting change in PDI over time (n=92).

Change in PDI	Coefficient	Std Error	t	P> t	95% Confidence interval	
Age	1.66	0.34	4.90	0.00	0.98	2.33
Control group	-12.76	4.04	-3.16	0.00	-20.81	-4.72
On HAART	10.72	5.46	1.96	0.05	-0.16	21.59
Whz	17.63	7.14	2.47	0.02	3.41	31.86
Female	-11.06	4.22	-2.62	0.01	-19.46	-2.66
<i>Educational level</i>						
Grade5-6	5.87	26.77	0.22	0.83	-47.48	59.21
Grade 7-9	-15.58	19.66	-0.79	0.43	-54.76	23.59
Grade10-11	-1.25	19.05	-0.07	0.95	-39.21	36.71
Grade 12	-6.89	19.34	-0.36	0.72	-45.45	31.66
Tertiary	-37.13	22.18	-1.67	0.09	-81.34	7.07
Waz	-31.63	9.87	-3.20	0.00	-51.30	-11.95
Haz	19.63	6.62	2.978	0.00	6.44	32.82
<i>Housing</i>						
Room	8.65	6.99	1.24	0.22	-5.27	22.57
Flat	-22.27	14.57	-1.53	0.13	-51.31	6.77
Shared house	-8.56	7.43	-1.15	0.25	-23.38	6.26
Own house	-0.56	5.28	-0.11	0.92	-11.07	9.96
No. adults	2.42	1.29	1.87	0.07	-0.16	5.00
No. children	-0.48	0.38	-1.29	0.20	-1.23	0.27
Cons	-12.23	22.84	-0.54	0.59	-57.75	33.28

The children who were most likely to show an improvement in their psychomotor developmental index scores were children who were older at baseline assessment, in the experimental group and already on HAART at their initial assessment. The factors presented in table 5.28b accounted for 49.82% of the variance seen.

The most important factors that were common to both MDI and PDI improvement are children who were older at baseline assessment and in the experimental group.

The variables that were predictive of a change in parenting stress over the study period are presented in table 5.29a and 5.29b.

Table 5.29a Order and significance of variables entering the regression analysis for change in PSI over time (n=92).

Begin with empty model	p value
Adding education level	p=0.0464
Adding number of adults	p=0.0561

Table 5.29b Variables predicting change in PSI over time (n=92).

Change in PSI	Coefficient	Std Error	t	P> t	95% Confidence interval	
<i>Educational level</i>						
Grade5-6	40.91	27.10	1.51	0.13	-12.96	94.79
Grade7-9	50.99	19.94	2.55	0.01	11.25	90.55
Grade10-11	58.72	19.34	3.04	0.00	20.28	97.17
Grade 12	59.48	19.53	3.05	0.00	20.65	98.31
Tertiary	58.28	22.12	2.63	0.01	14.30	102.25
No. adults	-2.09	1.08	-1.94	0.05	-4.23	0.06
Cons	-41.74	19.41	-2.15	0.03	-80.34	-3.14

A decrease in parenting stress levels over the study period was predicted by the educational level of the caregiver and the number of adults in the household. Caregivers with higher levels of education were more likely to experience a decrease in stress

levels. The more adults there were living in the household the less likely parenting stress levels were to decrease. The factors in table 5.29b accounted for only 15.80% of variance seen.

5.5 The Impact of HAART on Development.

In order to determine the impact of HAART on the development of children in this study a sub-analysis of data was done. The MDI and PDI scores of all children who were not on HAART at visit one, but were on HAART by visit three were analysed separately. The results of the analysis of variance for MDI and PDI can be seen in tables 5.22 and 5.23 respectively.

Table 5.30 Changes in MDI over time for children starting HAART.

	MDI Experimental group n=23	MDI Control group n=22	MDI Total n=45
Visit 1 (no HAART)	64.22 ($\pm$ 19.76)	68.77 ($\pm$ 20.38)	66.44 ($\pm$ 19.97)
Visit 3 (on HAART)	59.43 ($\pm$ 19.57)	69.32 ($\pm$ 23.49)	64.27 ($\pm$ 21.90)
Visit 5 (on HAART)	70.57 ($\pm$ 19.94)	60.50 ($\pm$ 16.85)	65.64 ($\pm$ 18.98)

There was no significant improvement in MDI scores for the two groups combined over time ($p= 0.77$). The group of children who were receiving HAART as well as the intervention programme improved over the study period (MDI=64.22 to MDI= 70.57) while the children in the control group who received HAART showed a decline in MDI scores over time (MDI=68.77 to MDI=60.50). The difference in the amount of change between the two groups was significant ($p=0.003$). These findings suggest that HAART did not have a positive impact on cognitive development in this short follow up period.

Table 5.31 /

Table 5.31 Change in PDI over time for children starting HAART.

	PDI Experimental group n=23	PDI Control group n=22	PDI Total n=45
Visit 1 (no HAART)	46.65 (± 19.60)	52.86 (± 23.57)	49.69 (± 21.62)
Visit 3 (on HAART)	57.87 (± 24.34)	58.36 (± 23.63)	58.11 (± 23.72)
Visit 5 (on HAART)	71.74 (± 22.92)	55.18 (± 21.60)	63.64 (± 23.57)

There was a significant improvement in PDI scores for the two groups combined over time, after starting HAART ($p < 0.001$) with both the experimental and control groups showing an improvement. The amount of improvement seen in the experimental group was however significantly more than that seen in the control group ($p < 0.001$). These findings suggest that HAART does have a positive impact on motor development and that this effect was enhanced by the addition of a developmental stimulation programme.

Only 13 children enrolled on this study never received HAART during the study period. Due to the very small number of children in this sub-group statistical analysis of their developmental scores is inappropriate. For the sake of completeness their MDI and PDI scores at visit one and visit five are summarised in table 5.32.

Table 5.32 MDI and PDI scores of children never on HAART.

	Experimental group n=6	Control group n=7
MDI visit 1	75.0 (± 24.4)	67.8 (± 21.0)
MDI visit 5	80.0 (± 21.7)	77.7 (± 14.4)
PDI visit 1	71.7 (± 22.5)	65.1 (± 19.8)
PDI visit 5	86.2 (± 17.6)	91.7 (± 17.4)

(Values represented are means and standard deviations unless otherwise indicated)

The children in both the experimental and control groups, who never received HAART, showed an improvement in MDI and PDI scores over time. There were no apparent differences between the two groups. PDI scores for both groups were within normal

limits at the end of the study period. The CD4% counts for this group of children were higher than those of the children who were eligible for HAART. At visit five the mean CD4 count for the children not on HAART in the experimental group was 24.3% (± 9.2) and 28.4% (± 8.8) for children not on HAART in the control group.

5.6 Per Protocol Analysis of Primary Outcomes.

The loss to follow-up over the study period was high at 24.5%. It was therefore decided to do a secondary per protocol analysis of the primary outcome measures namely the Bayley Scales of Infant Development (MDI and PDI) and the Parenting Stress Index (Short Form) in order to ascertain whether the loss to follow-up impacted significantly on the results of the study.

The per protocol analysis was done using only the data for the 92 subjects who completed the study and had complete data sets. The baseline values for these three outcomes for the 92 subjects were compared to those of the 122 subjects recruited into the study using a two sample students t test. Repeated measures analysis of variance was used to analyse the changes in MDI, PDI and PSI(SF) over time.

Table 5.33 Comparison of baseline data for per protocol and intention to treat analyses.

	Baseline n=92	Baseline n=122	p value
MDI	66.33 (± 21.1)	65.64 (± 21.8)	0.81
PDI	53.58(± 23.5)	53.71(± 23.7)	0.97
PSI	105.60(± 18.3)	103.95(± 19.51)	0.88

There was no significant difference between the baseline data of the total sample (n=122) and the sample of children with complete data sets (n=92). The children who were lost to follow up were therefore representative of the sample as a whole.

5.6.1 Outcomes over time.

The changes that occurred in each of the primary outcomes that were measured over the study period will be presented. MDI, PDI and PSI were measured at baseline, six months and twelve months. Repeated measures analysis of variance was used to analyse changes over time.

5.6.2 Developmental status over time

Children were assessed with the BSID at visit 1 (baseline), visit 3 (six months) and visit 5 (12 months). The changes in mental developmental index (MDI) and the psychomotor developmental index (PDI) over time for each group of children can be seen in tables 5.34 and 5.35.

MDI

The change in MDI for each group over time as measured by the repeated measures ANOVA is represented in table 5.34.

Table 5.34 Change in MDI over visits by group.

	Experimental n=43	Control n=49	Total n=92
Visit 1	64.4(±20.8)	68.3 (±21.3)	66.4(± 21.0)
Visit 3	61.6(± 20.5)	69.9 (±22.2)	66.1(±21.7)
Visit 5	69.3(±19.8)	64.3(±17.4)	66.64(±18.7)
Total	65.1(±20.4)	67.5(±20.4)	66.4(±20.4)

The MDI for both groups of children was extremely low initially. There was no significant difference between the two groups with respect to MDI ($p=0.48$). The MDI also did not change significantly for the two groups combined over the period of one year ($p=0.90$). However the amount of change in the experimental group over the year (MDI=64.4 to MDI=69.3) was significantly greater ($p=0.01$) than the change seen in the control group (MDI=68.3 to MDI=64.3). In fact the control group deteriorated slightly over the year while the experimental group improved. Despite the fact that the children in the

experimental group improved during the course of the study the mean MDI scores at the end of the study period indicate that the children still have significant delay in their mental development.

PDI

The change in PDI for each group over time is presented in table 5.35.

Table 5.35 Change in PDI over visits by group.

	Experimental n=43	Control n=49	Total n=92
Visit 1	49.6($\pm$ 22.0)	57.1($\pm$ 24.4)	53.6($\pm$ 23.5)
Visit 3	59.3($\pm$ 25.1)	63.8($\pm$ 24.6)	61.7($\pm$ 24.8)
Visit 5	70.5($\pm$ 25.1)	65.9($\pm$ 24.5)	68.0($\pm$ 24.7)
Total	59.8($\pm$ 25.5)	62.3($\pm$ 24.6)	61.1($\pm$ 25.0)

There was no significant difference between the two groups with respect to PDI ($p=0.57$). The PDI scores of the two groups combined improved significantly over the one year period ($p=0.00$), however the amount of improvement over time in the experimental group (PDI=49.6 to PDI=70.5) was significantly more than in the control group (PDI=57.1 to PDI=65.9) ($p=0.02$). Although both groups showed some improvement in PDI scores over the study period, the mean PDI scores for both groups remained low, indicating that the children still presented with significant developmental delay at the end of the study period.

5.6.3 Parenting Stress

The PSI/SF was administered to the caregivers of the children at visit 1 (baseline), visit 3 (6months) and visit 5 (12 months). Figure 5.36 depicts the changes in total stress scores for each group over the study period as analysed by repeated measures analysis of variance.

Table 5.36 Change in Parenting Stress over visits by group.

	Experimental n=43	Control n=49	Total n=92
Visit 1	105.9(±19.6)	105.3(±17.1)	105.6(±18.2)
Visit 3	100.9(±25.0)	96.0(±21.4)	98.3(±23.1)
Visit 5	97.4(±24.1)	96.1(±21.5)	96.7(±22.6)
Total	101.4(±23.1)	99.1(±20.4)	100.2(±21.7)

The PSI total scores were well matched for the two groups ($p=0.55$). The PSI scores came down significantly during the course of the study with the scores at visit five being significantly lower than those at visit one ($p<0.001$). There was no difference in the amount of change that occurred in parenting stress between the two groups ($p=0.55$). Closer analysis revealed that of the three subscales of the PSI/SF there was a significant decreases in Parental Dysfunction over time($p<0.001$) as well as in Parent-Child Dysfunctional Interaction ($p<0.001$) but no significant change in the Difficult Child subscale ($p=0.08$). The two groups were well matched for each of the three subscale scores over time with no significant differences being noted.

5.6.4 Comparison of intention to treat analysis and per protocol analysis of results.

As can be seen in table 5.37 the results for the analysis of variance for the primary outcomes did not differ whether the intention to treat or the per protocol approach was used. The fact that the results do not change depending on the method of analysis used indicate that the findings of this study can be interpreted with confidence (Wright and Sim, 2003).

Table 5.37 /

Table 5.37 Comparison of primary outcomes using intention to treat and per protocol analyses.

	Intention to treat	Per protocol
Mental Developmental Index		
Within group	$p=0.8558$	$p=0.8965$
Between groups	$p=0.2674$	$p=0.4845$
Change over time by group	$p=0.0108^*$	$p=0.0091^*$
Psychomotor Developmental Index		
Within group	$p=0.0000^*$	$p=0.0000^*$
Between groups	$p=0.5714$	$p=0.5707$
Change over time by group	$p=0.0185^*$	$p=0.0191^*$
Parenting Stress Index		
Within group	$p=0.0001^*$	$p=0.0001^*$
Between groups	$p=0.6202$	$p=0.5516$
Change over time by group	$p=0.5709$	$p=0.5502$

The ANOVA results for the anthropometric measures were also very similar whether the data were analysed using the intention to treat or the per protocol method.

5.7 Recalculation of sample size

The loss to follow up in this study was higher than anticipated; the standard deviations for the MDI and PDI scores were also higher than expected. This means that the initial sample size calculation did not yield the anticipated power. Taking the actual loss to follow up and standard deviations obtained into account, the power yielded by the sample size of 60 subjects per group is in fact only 65% and not 90% as initially calculated.

Conclusion

The findings of this study confirm that children who are HIV positive are at risk for developmental delay from an early age. The children in this study had severe developmental delay as measured by the Bayley Scales of Infant Development II. The

anthropometric indices for the children in this study were also decreased at baseline. The children were at risk for wasting and stunting and had decreased head circumference z-scores.

Caregivers of children infected with HIV tended to be poor and many had not completed 12 years of schooling. They had very high levels of parenting stress. Parenting stress was influenced by housing and educational level as well as the number of children in the household. Parenting stress levels came down in both the control and experimental groups during the course of the study but remained high.

The children in the experimental group showed a significantly greater improvement in both MDI and PDI scores than the children in the control group. The children who improved the most were those who were older at their baseline assessment and in the experimental group. Although the children in the treatment group did improve in terms of motor and cognitive development they remained very delayed at the end of the study.

Children who went onto HAART during the course of the study showed a significant improvement in motor development but not in cognitive development. These findings suggest that HAART may have a greater influence on motor development than on cognitive development, at least in the short term.

The results for the primary outcomes used in this study, namely the BSID II and the PSI/SF were very similar whether the results were analysed using an intention to treat analysis or a per protocol analysis.

The implications of these findings will be discussed in more detail in chapter six.

Chapter 6

DISCUSSION

The results of this study will be discussed in more detail in this chapter. Each of the main outcomes assessed will be discussed as well as possible reasons for the changes that were seen. The demographic information of the sample will be discussed as well as the challenges that were encountered doing this research. A number of suggestions for future research and clinical management will be put forward.

6.1 Prevalence and Extent of Developmental Delay.

The baseline developmental scores of the children in this study were extremely low with 78% of children having delayed cognitive development and 87% of children presenting with delayed motor development. This high level of developmental delay, is in keeping with findings from studies conducted in other parts of the world where prevalence rates of 50% or higher have been documented (Pollack et al, 1996; Chase et al, 1995; Belman et al, 1986; Epstein et al, 1986).

The prevalence of developmental delay in this study is double that of the only other South African study conducted. The study by Potterton and Eales (2001) reported a 40% prevalence in developmental delay. However the children in their study were all under 12 months of age and the assessment tool used was a screening tool only and possibly not as sensitive as the BSID II used in this study. Msellati et al (1993) and Gay et al (1995) reported an increase in prevalence of developmental delay with increasing age in the first 18 months of life, it is therefore possible that the prevalence reported by Potterton and Eales (2001) would have been greater had older children been included in their study.

The mean values for MDI and PDI were extremely low at baseline for both the control and the experimental group. The mean MDI for the two groups combined was 65.61 (± 21.93). This value is considerably lower than the mean MDI obtained by Bayley (1993) when she tested 35 HIV positive children in the process of validating the BSID II (79.6

± 19.8). The difference can be explained in part by the fact that the children in the validation sample in the USA all had access to antiretrovirals whereas only 14.5% of the children in this study were on HAART at baseline. The standard deviations for the study sample and Bayley's validation sample are very similar and reflect the range of abilities present in children infected with HIV. The mean MDI for this study at baseline reflects that the majority of children could be classified as having severe cognitive delay ($\text{MDI} < 70$). The mean PDI for the two groups combined at baseline, was 53.67 (± 23.77). This value is extremely low and is again much lower than the mean PDI value obtained by Bayley in her validation sample (81.1 ± 27.2). Differences in access to medication again probably account for these discrepancies, as well as possible socio-economic differences. The standard deviation for motor development is high, indicating large variability in motor performance in children who are HIV positive.

Various other studies have not identified such low developmental scores. Chase et al. (2000) documented mean MDI scores between 81.9 and 96.8 in HIV infected children between four and 30 months of age who had access to antiretrovirals. Mean PDI scores in Chase's study were between 78.2 and 97.7. Knight et al (2000) reported mean MDI scores of 76.1 and mean PDI scores of 79.8 in their small sample of HIV infected children, the data for this study being collected prior to the use of HAART.

According to Chase et al (2000) MDI or PDI scores of two standard deviations below the mean (ie < 70) are important early markers of severe HIV-related CNS disease and are diagnostic of encephalopathy. Similarly a drop in MDI and PDI over time of 2 standard deviations indicates early CNS involvement and encephalopathy. Taking these findings into account implies that the children in this study are at risk of severe central nervous system involvement. The changes that occurred in MDI and PDI scores over the course of the study will be discussed later.

Clinical implications.

- Children infected with HIV are at risk of significant developmental delay. Developmental screening should be an integral part of services offered to children

who are HIV positive. Caregivers should be made aware of the fact that developmental delay is a common finding in children who are HIV positive and should be asked about their child's developmental progress at every clinic visit.

- Developmental screening and intervention should be an integral part of services offered to children who are HIV positive. This could happen across all sections of health care delivery, primary, secondary and tertiary.

Research implications.

- Future studies could design and test a developmental screening tool that is efficient and reliable in detecting developmental delay in HIV positive children within the context of busy clinics in developing countries.
- The third edition of the Bayley Scales of Infant Development which is now available should be tested on a large sample of South African children to establish whether it is still a reliable assessment tool in the South African context.

6.2 Factors Predicting Developmental Delay

As discussed in chapter two there are a number of factors which may contribute to developmental delay. Step-wise regression analysis was performed to determine what variables were predictive of MDI and PDI at each of the three assessment visits. A number of variables were significant at different time points. The relationship between variables and their relative importance changed over time as the children's clinical picture changed. The regression analyses were characterised by very wide confidence intervals and were unable to account for more than 50% of the variance seen. Factors other than those assessed must therefore also have contributed to predicting the developmental status of children in this study. The factors that were most important in predicting developmental status will be discussed in more detail.

6.2.1 Growth parameters

Malnutrition as evidenced by wasting and stunting has previously been associated with poor neurodevelopmental scores in studies on children with HIV. Pollack et al (1996) found that children with the most marked growth delay had the lowest cognitive and

motor development scores. Wiznia et al (1996) reported a strong correlation between low weight-for-age and decreased cognitive function. However the children in this study were malnourished and stunted, but not wasted. Weight-for-age was found to be significantly related to MDI at each of the three assessments, those children with better weight-for-age z-scores obtained higher MDI scores. Weight-for-height and height-for-age were related to MDI scores but were not as important as weight for age. These results confirm the link between growth parameters and MDI especially as reported by Wiznia et al in 1996.

Weight-for-age z-scores were also strongly predictive of PDI scores at all three visits. Weight-for-height and height-for-age were not as consistently predictive of PDI as weight for age was.

Growth parameters have previously been identified as being markers of disease progression (Bobat et al, 2001) as has developmental delay (Mintz, 1999). It is therefore not surprising that anthropometric status should be predictive of developmental status in HIV infected children.

Head circumference was not a predictor of developmental status at any of the visits. This was surprising considering that head circumference has previously been linked to the extent of developmental delay by a number of authors (Mitchell, 2001; MacMillan 2001; Mintz, 1999). This is discussed further in section 6.6. Head-circumference-for-age z-scores improved equally for both groups of children in this study over the study period.

Muscle weakness was not tested in this study but it was noticed anecdotally during administration of the BSID II that performance in activities that require strength against gravity was particularly delayed, for example standing, walking, climbing stairs and jumping. Muscle weakness has been associated with poor motor function in children infected with HIV (Pearson et al, 2000; Blanchette et al, 2002) and could be a result of muscle atrophy secondary to malnutrition. Pearson et al (2000) found that decreased muscle bulk was an independent predictor of disease progression in HIV infected infants.

Clinical implications.

- The nutritional status and weight gain of children infected with HIV should be carefully monitored and supplements should be given early on to try and prevent the wasting and stunting that was evident in this study sample. Children with decreased weight-for-age should be referred for developmental screening in order to pick up early delays and monitor CNS involvement. According to the South African Department of Health guidelines once encephalopathy is suspected children may be started on HAART regardless of their CD4 count. This may lead to decreased prevalence of the delays of cognitive function observed in this sample.

Research implications.

- The link between wasting, muscle strength and functional outcomes in children infected with HIV needs to be established through further research.

6.2.2 Age

Younger children achieved significantly better MDI scores at visit one and three, but not at visit five. Younger age was predictive of better PDI scores at visit one only. This finding is in keeping with those of Msellati et al (1993), Gay et al (1995) and Blanchette et al (2002) who reported that developmental delay in children infected with HIV became progressively worse in the first 18 months of life. This is explained by the disease progression witnessed in children infected with HIV and the associated encephalopathy. The influence of age on developmental status over time in this study is confounded by the addition of the intervention programme and HAART.

The items on the BSID in the early months require little strength against gravity and do not assess learned cognitive concepts such as shapes and colours. Typically developing African children in South Africa and Nigeria performed at a level superior to their American counterparts when tested with the BSID I before 12 months of age (Aina and Morakinyo, 2005; Richter et al, 1992). This early precocious development in African children has been well documented and could, in part, contribute to the fact that the children in this study performed better when they were younger. The items on the BSID

It may be less culturally specific in the younger item sets and this may explain why younger children in Africa score better in the younger age groups.

Clinical implications.

- Younger children should be very carefully monitored so that any changes in developmental status can be detected as early as possible and the appropriate referrals made timeously.

Research implications

- Further research needs to be done in South Africa to determine the age of onset of developmental delay and which children are at the greatest risk of becoming delayed.

6.2.3 Socioeconomic factors

Family income was not a strong predictor of the cognitive developmental status of children in this study. It did however form part of the set of predictors at every visit. This could be due to the fact that most families had very similar levels of income and all experienced equivalent levels of hardship. Fifty percent of caregivers in this sample reported a monthly family income of R700 ($\pm$ \$100) or less which is well below the breadline in South Africa. The mean income for the group was R1183 which is only slightly above the breadline. Poverty has been shown to impact negatively on cognitive development and to a lesser degree on motor development as well (Lima et al, 2004; Schor et al, 2003; Linver et al, 2002). Despite the very high levels of poverty in South Africa which have persisted for many decades, young South African children have generally performed well on standardized developmental testing in the past (Richter et al, 1992).

The educational level of the caregiver was part of the set of factors predicting MDI at each visit, although it was never one of the most important factors. Having a caregiver with a higher level of education was predictive of better MDI scores. The majority of caregivers in this study had been to school until at least grade ten. Caregivers with a

better level of education were probably better able to respond appropriately to the counseling and informal education provided at Harriet Shezi clinic. An education level of grade ten implies a reasonably high level of literacy and proficiency in English. However without a matriculation certificate (grade 12) these caregivers would find it difficult to enter the formal labour market, and thus their earning potential is limited. Chase et al (2000) found that HIV infected children whose mothers had less than nine years of formal education were more likely to get MDI scores of below 69.

Housing was included in the set of factors predicting MDI and PDI at most time points. Improved housing was associated with better MDI and PDI scores, but interestingly having a house that was not shared with others did not always add additional predictive value over a shared house. An increased number of children in the household made a small negative contribution to MDI and PDI scores as did an increase in the number of adults in the household.

Clinical implications.

- Health care providers need to be more aware of the educational levels of the people in their care and make sure that they are giving information at an appropriate level.

Research implications

- Further research needs to be done to investigate the impact of socioeconomic factors on the ability of families affected by HIV to cope with the burden of disease they face.

6.2.4 CD4 counts and HAART

CD4% was consistently predictive of better MDI and PDI scores. This is in keeping with the findings of other studies where low CD4% counts have been associated with more severe developmental delay, especially in the cognitive domain (Henry et al, 1996). If the children had been monitored for longer an even greater impact may have been noted as their CD4 counts continued to improve.

The frequency of hospitalization was not assessed in this study. The very low mean CD4% counts at the beginning of the study period (14.39%) do however mean that the children were severely immunocompromised at this point and that they would have been prone to frequent illness and possibly periods of hospitalization. This general ill health could be a contributing factor to the low mean MDI and PDI scores obtained at visit one (MDI=65.61, PDI=53.67). Frequent hospitalization has been shown to impact negatively on developmental progress (Cooper et al, 2004; Fiser et al, 2000; Ulmann et al, 1985).

It is evident from previous research that children assessed in the pre-HAART era (Knight et al, 2000) scored worse on the BSID than those who had access to HAART from an early age (Chase et al, 2000). As previously discussed the children in this study did not have access to HAART when the study started, only 14.5% of children being on HAART at their baseline assessment. Children in South Africa also only have access to HAART once their CD4 counts are below 20% of normal. Most authors suggest starting HAART in children before they become symptomatic (Chakraborty, 2005; Luzuriaga and Sullivan 2002). This implies that children in South Africa are at considerable risk for severe CNS involvement before they are able to start on an appropriate treatment regime. This damage may be irreversible even if HAART is started at a later stage and may lead to lifelong cognitive and motor impairment. Being on HAART was frequently predictive of lower MDI and PDI scores in this study, indicating that developmental delay is occurring prior to starting HAART and that those children who qualify for HAART may already have significant impairments.

Research implications.

- As more children in South Africa gain access to HAART, studies should be conducted to monitor the long term effects of HAART on developmental outcomes of children who are HIV positive.
- The impact of starting HAART at different stages of the disease process could also be investigated in order to establish a protocol that allows for the best long term outcomes.

Clinical implications

- All healthcare professionals in South Africa should be aware of the criteria for initiating HAART in children, and should refer children infected with HIV to specialist clinics where they can be managed holistically and appropriately.

The changes that occurred in developmental status over time will be discussed in section 6.3.

6.3 Changes in Development Over Time.

The children in the experimental group of this study showed a significantly greater improvement in both MDI and PDI scores over the study period when compared to the control group. These results indicate that a basic home management programme does have a positive effect on the neurodevelopmental status of children who are HIV positive.

Although both the MDI and PDI improved significantly in the treatment group the scores reached at the end of the study were still well below the normal ranges (MDI 66.64; PDI 68.02). This indicates that although the children improved they remained severely delayed and need further follow up and intervention.

The children in the control group deteriorated in their MDI scores although their PDI scores improved over time. Many studies have shown that children infected with HIV show a gradual decline in cognitive and motor development over time, especially in the first 18 months of life (Blanchette et al, 2002; Gay et al, 1995; Msellati et al, 1993). The fact that the children in the control group also showed an improvement in their motor development could be due to a number of different factors. Only 16 % of the children in the control group were on HAART when they started the study, this had risen to 85. % by the time they completed the study. A number of studies have been done on the impact of HAART on neurodevelopment and although the results of all the studies are not conclusive and not all of them considered motor development, there does seem to be a positive effect of HAART on developmental status (Resino et al, 2006; Sanchez-Ramon et al, 2003; Raskino et al, 1999; Pizzo et al, 1988). Children in the control group

also showed slight improvements in their weight-for-age, height-for-age, and weight-for-height over the study period. These improvements in weight and growth could also contribute to the improved motor function observed at the end of the study. An increase in weight may mean that muscle bulk and muscle strength increased as well and contributed to the improved motor performance. Many of the children received nutritional support from the dieticians at Harriet Shezi clinic in the form of food supplements as well as education and dietary advice. Although the abovementioned factors may have contributed to the improvements in motor development seen in the control group they were not sufficient to prevent the deterioration in cognitive development seen in this group of children.

6.3.1 Factors predicting change in neurodevelopmental status.

The children who showed the greatest amount of improvement in their MDI scores over time were those who were in the experimental group and were older at baseline. They came from families with higher monthly incomes and were more likely to be on HAART at baseline. The fact that older children did better could be due to the fact that these children were more likely to be *slow progressors* as described by Wiznia et al (1996). These children would have had a healthier infancy and be less likely to develop neurodevelopmental complications, they may also be better able to respond appropriately to intervention programmes. Families with higher income levels may be better placed to access health care services for their children and provide a more stimulating home environment. A higher level of caregiver education was also part of the set of factors predicting improvement in MDI. The fact that children who were already on HAART did better supports the international trend to start children on HAART as soon as possible.

The children who showed the greatest improvement in their PDI scores were in the experimental group, were older at baseline assessment and on HAART at the onset of the study (see table 5.28b). They were less likely to be wasted but more likely to be malnourished at baseline. The fact that they were malnourished at baseline may indicate that they were more likely to gain weight once they could utilize the services offered by the clinic, and that this could lead to increased muscle bulk, improved muscle strength

and better motor performance. The children who had already been on HAART from the time they entered the study had a longer period in which to improve their immune status, general health and wellbeing than the children who only went on HAART during the course of the study. This relative health is reflected in the improvement in motor developmental status in these children. A higher level of caregiver education was not always associated with improved PDI scores.

Many factors contributed to predicting improvement in developmental status and were able to account for less than 50% of the variance seen. Further investigation to determine the relative importance of each of these factors is needed.

Being in the experimental group was predictive of improved MDI and PDI scores over the study period. The intervention programme will now be discussed in more detail.

6.3.2 Intervention programme

In designing the intervention programme the researcher was cognisant of the time and cost constraints facing both health care providers and users in South Africa. An intervention that was sustainable beyond the boundaries of the study was envisaged. The intervention was planned with these time and cost constraints in mind.

Mothers infected with HIV have expressed the need for one point of call for all services (Marcenko and Samost, 1999; Hackl et al, 1997). The intervention was therefore administered at the clinic on the same day as the mother had an appointment to see the doctor. While this approach saved transport money and meant that there was not the stress of an extra appointment day which could mean time off work for the mother and a very early start and long day, it did present some challenges. The drawbacks of this approach are that the caregiver had input from a number of different people within a relatively short period of time. Some caregivers would see a doctor, a counselor, a dietician and the social worker as well as participate in the study all in one morning. Mothers may have been more receptive to the intervention programme if it was given in a calmer atmosphere and on a day where there was less competing information given.

The fact that the assessments and intervention were done at the clinic on the same day as the doctor's appointment may also have lent the study credibility as it was seen as an integral part of the clinic services. The doctor's support and interest also helped reinforce the messages that were given by the research assistant and the importance of the programme. Prado et al (2002) found that mothers were more likely to participate in a psychosocial intervention if they perceived a need for the intervention, had low social support, high stress levels and most importantly if they established a therapeutic alliance with the health care provider from an early stage in the intervention. Caregivers who participated in this study certainly seemed aware of their child's developmental difficulties and expressed concern over their delay. Black et al (1994) noted that HIV positive mothers in her study were more receptive to the home programme given than HIV negative mothers, they also found that mother's valued their parenting role highly and used the phrase "positive parenting" to describe the mothers' involvement in their children's lives. Perhaps the realisation that they may not have a lot of time with their children encourages HIV positive mothers to do the best for their children while they can. The research assistant who administered the intervention took time to address each caregiver's concerns and to affirm them as parents. Although these factors were not formally measured the fact that many of the caregivers wished to continue with the programme once the study period was completed suggests that they saw the value of the programme and enjoyed their interactions with the research assistant.

A non structured approach was used and the research assistant followed the leads given by the caregivers as to what aspects of development were delayed as well as her own assessment of the child's strengths and weaknesses and the results of the most recent BSID II assessment. While this approach worked in this situation it does rely heavily on the clinical expertise and the critical thinking and decision making of the person administering the intervention. A more structured set of guidelines may be necessary to guide clinicians or community workers with less experience and expertise. The possibility of counsellors and home based caregivers administering a stimulation programme makes a lot of sense as more people could be reached more effectively. A set of guidelines and a developmental screening form are being developed and need testing.

A number of authors have recommended that any intervention programme should aim at increasing the child's competence and functional abilities and should highlight the child's strengths (Ong et al, 1998; Dyson, 1991). The intervention programme therefore focused mainly on activities of daily living that were age appropriate for each individual child. Caregivers were shown how to encourage play in positions that required use of antigravity muscles and games and activities that required increasing levels of physical activity were emphasised. Activities and handling skills that would facilitate and reinforce emerging motor skills were taught to the caregivers. Activities where the caregiver would be involved with the child anyway were used as learning opportunities, for example reinforcing colours when dressing, counting toes when washing them, leaning body parts when washing. Play activities were also strongly encouraged using common household appliances for example banging a pot with a spoon, pouring water from one cup to another, using a pair of rolled socks as a ball.

The home programme could have influenced cognitive development through a number of different routes. By improving children's mobility they would have a greater potential for enhanced sensorimotor experiences which has been shown to correlate to improved cognitive performance. Advice on positioning the children in positions that allowed for better communication and interaction could also contribute to providing more opportunities for cognitive stimulation. The home programme emphasised functional activities within the child's natural environment. This allows the child to practice emerging skills in a meaningful way (McEwan and Hansen, 2006).

The research assistant recorded comments made by the caregivers in this study in relation to the intervention programme and their child's progress. A selection of these comments will be presented.

Mothers expressed appreciation at having the underlying reasons for their child's developmental delay explained to them.

- *“I thought she was just lazy, now I don’t shout at her when she is slow to do things the other children can do.”* Mother of a twenty month old child.
- *“I knew HIV made his chest bad but I never knew it could get in his brain. My poor baby.”* Mother of a 6 month old child.

There is very little information available in the form of pamphlets or booklets that addresses the impact of HIV infection on children in particular. Non governmental organisations and aid agencies tend to focus their education campaigns on young adults and have sorely neglected this aspect of the pandemic.

Many caregivers felt that the programme gave them an opportunity to have a positive contribution to their child’s well being. They felt they were empowered by being able to play a role in their child’s management. This was a benefit of home programmes identified by Spiegel and Mayers (1991) in their review of psychosocial issues facing families affected by paediatric HIV.

- *“I feel powerful when we are playing your teaching games, my baby loves the attention and I feel I am doing something right for her.”* Mother of a 9 month old child.
- *“The medicine (HAART) makes her better, but she hates it and I hate fighting with her, but we continue because we must. The things we do with you are more fun and I feel proud that I can be the one to help my baby at home.”* Mother of a 36 month old child.

Not all caregivers were convinced of the value of the programme and did not always see it as a priority. This was not an unexpected finding considering the multiple stressors experienced by the caregivers in this study. Similar attitudes were expressed by Shannon (2004) in his study on barriers to family centered intervention. These feelings need to be respected and the priorities of the caregiver need to be addressed as well. These often include concerns about financial stability.

- *“She likes it when I do games with her, but it does not make her better and I am too tired and too sad to keep trying.”* Grandmother of a 24 month encephalopathic child.
- *“It is medicine that will help my child, not games, the government must give us medicine.”* Mother of a 16 month old child prior to HAART being available.

As children began to improve caregivers became more excited:

- *“She can read, she can read! When I ask her where the flower is she points to it”* Grandmother of a three year old on returning her book.
- *“I never believed you when you said she would walk one day, I had no hope. Now I hold her hand and she takes her baby steps and we will go forward together.”* Mother of a 22 month old girl who had just started walking.
- *“He is better and running and climbing, but ‘eish’ now he makes me tired!”* Grandmother of a 30 month old boy.
- *“I stopped going to church when she was so sick and could do nothing. What would the people say? They would know she is positive. Now she can sit and she is gaining weight. I spend my spare money on beautiful outfits for her and I take my baby wherever I go, also to church. This clinic has given me my baby and my life back, thank you.”* Mother of a 15 month old girl.
- *“I didn’t know such a small boy could be clever, he knows his body parts now and he knows red and blue.”* Uncle of a 40 month old boy.

All in all the intervention was perceived as positive by the caregivers who participated.

Most children and their caregivers who participated in this study were recruited on their first or second visit to the clinic. Antiretrovirals became available at Harriet Shezi clinic in April 2004. This meant that from this point on many young infants were referred to the clinic. Before this time Harriet Shezi, like many other paediatric HIV clinics in South Africa, limited its services to children over two years who had a better chance of long term survival in the absence of antiretrovirals. The fact that caregivers began the intervention programme at the same time as accessing all the other services at the clinic

may have helped to establish the developmental programme as an integral part of their child's management. The doctors, nurses and counsellors at Harriet Shezi clinic were also very supportive of this study and would enquire about the children's progress and remind the mothers to see the research team as well. The commitment of the entire team at Harriet Shezi to addressing the developmental needs of the children in their care made the implementation of this programme possible.

Clinical implications

- Paediatric clinicians working with children infected with HIV need to take cognisance of the developmental and psychosocial needs of the children in their care.
- A basic home stimulation programme should be available to all children infected with HIV and their caregivers. More attention needs to be paid to the education of caregivers on the possible effects of HIV on their child's development and the role they can play in managing developmental delay.
- The impact of HIV on the development of children needs to be better publicized in both lay and professional literature. All health care professionals need to be made aware of these issues and need to start addressing them.
- Policies regarding service delivery to children who are HIV positive should include developmental assessments and management.

Research implications

- Alternative ways of delivering developmental programmes need to be explored and the most effective mode of service delivery should be established. This could include home visits and the training of community care workers in basic child development and stimulation.
- Caregiver's perceptions of the effectiveness and value of intervention programmes need to be established.
- The role of other rehabilitation interventions for children who are HIV positive needs to be established. These should include, muscle strengthening, aerobic fitness, cognitive , perceptual , as well as speech and language issues.

- The functional problems facing older children have not been investigated in developing countries at all. This is an area that needs urgent research as more HIV positive children gain access to HAART and survive for longer.

6.4 The Effect of HAART on Development

The results of a sub-group of children ($n=45$), who were not on HAART at visit one but were on HAART by visit three, were analysed separately. This was done in an attempt to monitor the impact of going on HAART on children's developmental status.

There was no significant change in MDI scores for this group of children between visit one and visit five ($p=0.77$). The children in this group who received the stimulation programme did show an improvement in MDI while those in the control group deteriorated.

The PDI scores for this group of children did improve significantly after going onto HAART ($p<0.001$). Children in both the control and the experimental groups improved, however the amount of improvement by children in the experimental group was significantly greater than that of children in the control group ($p<0.001$).

The findings relating to the impact of HAART on cognitive development in this study are similar to those of Wolters et al (1997) who found that cognitive scores remained stable at six and 24 months after starting HAART. Sanchez-Ramon (2003) found that antiretroviral therapy was able to reverse neurologic deterioration in some patients and to prevent the onset of encephalopathy if commenced prior to the onset of symptoms. Studies that have investigated the effect of HAART on the cognitive development of children have often had a very broad age range of children in their samples (Raskino, et al, 1999). The natural maturation and stage of development of the CNS should be considered and children of similar ages should be compared. Very few studies make any mention of the effect of HAART on the motor development of young children.

The fact that the motor development showed an improvement after the initiation of HAART and cognitive development showed no improvement warrants further investigation with a longer follow up period. A possible reason for the changes seen in this study is that children may have become stronger as their health improved on HAART and may have gained muscle bulk. This increased muscle strength would contribute to improved motor performance. The fact that children in South Africa only start HAART once their CD4 count has dropped to below 20% may explain, in part why their cognitive scores did not improve after initiating treatment. By the time the CD4 count has dropped to 20% irreversible brain damage may already have occurred due to the onset of HIV encephalopathy. Resino et al (2006) found that children who started HAART before their CD4 count was below 25% had the best chance of remaining asymptomatic and achieving and maintaining a CD4 count of over 30%. The WHO is also advocating that HAART be started when a child's CD4 count is 25% in an attempt to prevent the long term, irreversible organ damage that may occur in children with CD4 counts below 20% (ANECCA, 2005). The children who received HAART as well as the stimulation programme did show some improvement in MDI scores. This suggests that there is potential for some cognitive improvement in the right circumstances due to neural plasticity. This does not mean that the damage can be totally reversed and clinicians should be cautious in predicting complete reversal of cognitive deficits after starting HAART.

Only 13 of the children enrolled on this study did not start HAART during the course of the study period. This makes it difficult to gauge the impact of the home programme on developmental status without the confounding influence of HAART. Descriptive analysis of this very small sub-group did not reveal any obvious benefit of the intervention programme. This finding should be interpreted with caution due to the very small sample size.

Clinical implications

- Initiation of HAART may have beneficial effects on motor development, but not always on cognitive development. Clinicians should continue to monitor both motor and cognitive development after commencing HAART.
- Where possible HAART should be started as soon as possible in infants and before a child's CD4 count drops below 25% as this may minimise permanent brain damage and long term cognitive deficits.

Research implications

- Further studies should monitor the long term effects of children on HAART and should compare children in the same age ranges and include cognitive and motor assessments.
- CT scans should be used in conjunction with developmental assessments to monitor the impact of HAART on the developing CNS.
- Further studies on muscle strength and motor development in young children with HIV need to be conducted.
- The impact on neurodevelopment of starting HAART when the CD4 count is 25% needs to be established in the context of a developing country.
- The neurodevelopmental status of children not eligible for HAART, and the impact of developmental stimulation in this group, warrants further investigation.

The parenting stress levels experienced by the caregivers and how they changed over time will be discussed in section 6.5.

6.5 Parenting Stress Levels.

The parenting stress levels in the caregivers who participated in this study were extremely high at the baseline assessment (103 ± 19.51). These very high parenting stress levels are of concern as any score over 90 is considered to be clinically significant and to warrant referral for further investigation (Abidin, 1995). All three sub-scales were equally elevated and there were no differences between the two groups in terms of sub-scale scores.

Other studies that have used the PSI/SF with caregivers of disabled children have not documented scores as high as these even though their scores were also elevated (O'Neil et al, 2001; Button et al, 2001; Musil, 1998). It is important to remember that these studies were conducted on caregivers of children who were disabled, but not HIV positive, and direct comparisons can therefore not be made. Studies that have investigated the stress levels of caregivers of HIV positive children have not made use of the PSI/SF, this makes it difficult to compare levels of parenting stress measured in this study to those found in other studies.

6.5.1 Predictors of parenting stress.

The results of the stepwise regression analysis carried out revealed a number of factors which were predictive of high parenting stress at each of the visits at which it was assessed. Regression analyses were again characterised by wide confidence intervals and were not able to explain more than 50% of the variance seen despite having a very lenient p value for entry into the regression (0.9). Variables other than those assessed in this study must also have contributed to the levels of parenting stress experienced by the caregivers.

The number of children in the household was an important predictor of parenting stress at visit one and visit five. The more children a caregiver had in their home, the higher their parenting stress levels were. This finding is in keeping with the findings of Ostburg and Hagekull (2000) but in contrast to the findings of Goldstein et al (2005). Neither of the above mentioned studies involved children who were HIV positive or needed any other special medical care. This fact makes it difficult to draw meaningful comparisons between the findings of this study and those of Ostburg and Hagekull (2000) and Goldstein et al (2005). A further factor that was predictive of parenting stress was the number of adults in the household. The more adults there were in the household the lower the parenting stress levels of the caregivers. The role of other adults in the household and their potential to reduce stress needs further investigation. Other female adults may provide valuable caregiving assistance while other adults may contribute

financially to the household. Interestingly, “sharing a house with others” was a predictor of higher parenting stress at visit three and five. This may indicate that the presence of adults who are not family members causes increased parenting stress, possibly due to the lack of privacy and stigma. Many caregivers spoke about the stress of keeping their diagnosis secret from friends and even other family members.

Higher CD4% counts contributed to lower parenting stress levels. Higher CD4 counts have been shown to be predictive of higher MDI and PDI scores. Although having a child with a disability has been shown to cause increased levels of parenting stress (Esdaile et al, 2003; Button et al, 2001; Ong et al, 1998; Dyson, 1991) the degree of disability does not consistently influence the amount of stress experienced (Button et al, 2001; Silver et al, 1998; Dyson, 1991). It must also be remembered that although the children in the experimental group improved over the study period both groups of children were still significantly delayed developmentally at the end of the study period.

The education level of the caregiver at visit five was an important factor in predicting parenting stress. Caregivers with higher levels of education had lower levels of parenting stress. These findings are in keeping with those of Ong et al (1998), who found that mothers of children with cerebral palsy experienced less parenting stress if they had a higher educational level. Higher levels of education may mean that the caregivers are more empowered and better able to access the services they need and get the most benefit out of them.

The fact that over 80% of the children were still being cared for by their biological mothers is remarkable. Although this is the most desirable situation it does explain the very high parenting stress scores. Linsk and Mason (2004) investigated the stress levels of caregivers of children affected by HIV and found that caregivers who were HIV positive themselves experienced the highest levels of stress. In this study all the biological mothers as well as all their children were HIV positive giving dual reason for elevated stress levels. The mothers in this study were coping with their own ill health and meeting their own health care needs as well as worrying about the health and needs of their infected children. Many mothers had older children who were not infected

or more than one infected child. These factors were not explored in this study and warrant further investigation.

Many studies have shown that having a child with a chronic illness leads to increased levels of parenting stress (Deater-Deckard and Scarr, 1996). It is not at all surprising that caregivers of children infected with HIV experience such high parenting stress levels. The levels in this study may be particularly high due to the feelings of helplessness that caregivers must experience when they are not able to access optimal care for their children. As access to HAART improves and the overall health status of children infected with HIV hopefully improves as well, it would be interesting to see whether the parenting stress levels of these caregivers begins to come down to more clinically acceptable levels.

The multigenerational aspect of HIV sets it apart from most other chronic childhood disabilities. The fact that the mothers in this sample are dealing with their own diagnoses, that of their child, as well as possibly their partner may contribute to their extraordinarily high parenting stress levels. Social support has been shown to be a mediating factor for parenting stress in some (Raina et al, 2004; Ostburg and Hagekull, 2000; McKinney and Peterson 1987) but not all studies done on parenting children with disabilities (Button et al, 2001; Hansell et al, 1998). The fact that the caregivers in this study had to deal with the stigma and isolation often associated with HIV diagnosis may have made it more difficult for them to access social support (Orner, 2006; Antle et al, 2001, Hackl et al, 1997).

The results of the parenting stress of grandparents were not isolated from the overall group due to the fact that the number of caregivers who were not mothers was so small. The needs of grandparents caring for their HIV positive grandchildren must not be overlooked. Grandparents are in many cases having to assume financial responsibility for their grandchildren as well as becoming their primary caregiver. The physical challenges of caring for a young child again at a time of their lives when their own health care needs are increasing could be placing the health related quality of life of these grandparents in jeopardy. Numerous studies have found that grandparents, like

mothers, will place the needs of their children and grandchildren first and are at risk of neglecting their own health (Linsk and Mason, 2004; Musil, 1998; Joslin and Harrison, 1998). The health and psychosocial needs of grandmother caregivers should be given particular attention.

6.5.2 Change in parenting stress levels.

Both the experimental and the control group showed a decrease in parenting stress over the study period. There was no significant difference in the amount of improvement seen in the two groups. Of the three sub-scales, the Parental Dysfunction and Parent Child Dysfunctional Interaction scores came down significantly over the study period, however there was no significant improvement in the Difficult Child sub-scale scores over time. The parent's perception of their child as being 'difficult' has been shown to be a predictor of increased levels of parenting stress (Ostburg and Hagekull, 2000).

The addition of the intervention programme in the experimental group did not influence the parenting stress levels even though these children showed significant improvement in motor and mental development. It is important to remember that even though the children in the experimental group showed significant improvement they remained developmentally delayed at the end of the study period.

The three factors which were the most important predictors of a decrease in parenting stress levels were, the educational level of the caregiver, the number of adults in the household and the type of house the family lived in. A higher level of education was predictive of a decrease in parenting stress. These caregivers may be better able to access the support and information offered to them at Harriet Shezi clinic. The more adults there were in the household the less likely the parenting stress levels were to come down. The stress of secrecy and stigma may have contributed to this. Living in a flat or their own house was predictive of decreasing parenting stress, however staying in a room or a shared house was predictive of increasing stress levels. The lack of privacy associated with living in a confined space or with other families are possible explanations for this.

Clinical implications

- Caregivers of children who are HIV positive are experiencing clinically significant levels of parenting stress. Additional psychosocial support and possibly formal counseling and psychological services should be made available to these caregivers.

Research implications.

- The levels of parenting stress were extremely high in this group of caregivers. Although the PSI/SF scores did come down significantly over the study period they remained clinically significant. Further research is needed to explore in more detail the factors that contribute to such high parenting stress levels and to start to investigate how best to address this problem in this population of caregivers.
- Qualitative research may help elucidate the problems experienced by different groups of caregivers and the particular needs of mothers, grandmothers and fathers.
- The impact of the mother's own health status on her levels of parenting stress should be established.

6.6 Growth Parameters

There were no significant differences between the two groups in terms of their growth parameters at baseline or at any point during the study period. This was to be expected as the groups were randomly assigned and the subsequent care that the children received was the same for both groups apart from the intervention programme which was not expected to influence growth in any significant way.

The head circumferences of both groups of children was below normal at baseline but increased steadily throughout the study. By the end of the study period the head circumference-for-age z-scores were still below the internationally acceptable means at -1.53 for the experimental group and -1.48 for the control group. Most studies on growth in HIV positive children have focused on height and weight and not on head-circumference. According to the World Health Organisation (1986) head circumference

can be considered a proxy for height and weight and is therefore not an essential measurement in studies of growth. Z-scores for head circumference are not readily available and could not be found for children over 36 months. The mean head circumference z-score for each group at each visit was therefore calculated. Measuring head circumference in this study was not always easy as many of the children had braids in their hair which made it difficult to get an accurate measurement. The head circumference measurements should therefore be interpreted with some caution.

The two groups of children combined had decreased height-for-age at baseline with a z-score of -2.86. Although the height-for-age increased throughout the study period the gains made were small. The children remained stunted with a final z-score of -2.61. Stunting is associated with poor socio-economic conditions and repeated or chronic infections as well as inadequate nutrition (WHO, 1986). It is therefore not surprising that stunting was observed in this group of children.

Weight-for-age was decreased at the beginning of the study period (-2.39). Although there was a general improvement over the course of the study the children remained underweight with final weight-for-age z-scores of -1.94.

Weight-for-height was slightly decreased at the start of the study period (-0.66) but compared favourably to international norms by the end of the study period (-0.43) indicating that the children were not wasted. This slight improvement would suggest that although the children gained weight during the study period their growth in length was less significant. The fact that the children were stunted but not wasted is similar to the findings of Bobat et al (2001) in their large cohort of black South African children in Durban. The widespread poverty still present in South Africa as well as the impact of repeated infections due to HIV infection are likely to account for the poor growth seen in HIV positive children in South Africa. The impact of HIV on the efficacy of circulating growth hormone must also be taken into account (Lepage et al, 1991; Laue et al, 1990).

These anthropometric scores are of concern as they indicate that although the children had access to a dietician at the clinic and were able to get food supplements free of

charge there was very little improvement in their growth scores over the study period of one year. Wasting responds more quickly to improved nutritional circumstances while stunting takes longer to resolve as skeletal growth is a naturally slower process (WHO, 1986).

The growth parameters as measured in this study are lower than those reported by Bobat et al (2001) in a study which investigated early childhood growth in HIV-exposed and infected infants in Durban, South Africa. The children assessed by Bobat et al (2001) were only followed up until 18 months of age and were tending to show decreasing weight-for-age and height-for-age as they got older. This increasingly significant growth delay with increasing age was confirmed by Newell et al (2003) in their large, prospective European study. Further investigation into the growth of African children infected with HIV is needed.

Clinical implications

- All HIV infected children should have their height and weight monitored at regular intervals, even if they are asymptomatic. Nutritional support and dietary advice should be available to all HIV infected children as soon as their diagnosis is known.

Research implications

- The growth status of children infected with HIV in developing countries needs further investigation. Long term follow up studies with growth as the primary outcome measure need to be undertaken.
- The best ways of providing scientifically sound nutritional support, in conjunction with appropriate medical management, to HIV infected children need to be investigated.
- Growth deficits were very common in this group of children and require further follow-up and intervention.

6.7 Demographic Information

The demographic information presented was collected using the form drawn up by the researcher as well as the Household Economic and Social Status Index (Barbarin and Khomo, 1997). The HESSI was not scored due to the fact that many of the caregivers were not able to provide all the information required, for example, educational level of child's father and cost of electricity. It was therefore decided to extract the most relevant and complete sets of information for further analysis.

6.7.1 Age of children

The two groups were very well matched at baseline in terms of all their demographic information. The average age of the children at baseline was 18.5 months. There were not that many very young infants in the study. This is a reflection of the time taken to diagnose children as being HIV positive. Many of these children are not being diagnosed soon after birth and are only diagnosed once a level of clinical suspicion has warranted further investigation. This is often only after the child has had at least one hospitalisation for pneumonia or gastroenteritis. The children who are slow progressors are often not diagnosed at a very young age as they are relatively well in infancy. The exceptions to this are the children born to mothers known to be HIV positive. These children are tested for HIV infection within the first few weeks after birth if their mothers are in agreement. This state of affairs explains why young infants are often not being seen at HIV clinics and also suggests that the results of this study may be somewhat biased as relatively healthy children may not be adequately represented in the sample. Young infants diagnosed with HIV in the Prevention of Mother to Child Transmission clinics or in the neonatal wards should be referred to their closest paediatric HIV clinic before they become symptomatic so that follow up and treatment can be initiated as soon as possible.

6.7.2 Caregivers

As has been previously mentioned, the majority of caregivers in this study were the biological mothers of the children (85.25%). This high proportion of children being cared for by their own mothers is obviously the desired situation. However the children are still very young and many may lose their mothers in time to come.

The next biggest group of caregivers were grandmothers. Almost 10% of children in this study were being cared for by their grandmothers. The needs of grandmothers caring for their HIV infected grandchildren have been explored (Linsk and Mason, 2004; Schor et al, 2003; Joslin and Harrison,1998). However, very little has been done in the context of developing countries. A huge need exists for further investigation in this area. Grandmothers often expressed their fatigue especially when caring for active toddlers as well as their concern for what would become of their grandchildren should they die.

Only two children in this study were being cared for by their fathers. The role of fathers in child care in this group seemed insignificant with many of the mothers stating that the father was “not around” and not providing any emotional or financial support to her or the child. One cannot assume that if the mother dies the father will step forward to assume responsibility for his children. Jones et al (2005) identified lack of paternal support as one of the factors affecting lack of compliance with follow up of HIV infected children in their study conducted in Johannesburg, South Africa.

Approximately 4% of children were being cared for by “others”. This included aunts, an uncle and a foster mother who subsequently adopted the child. The needs of this small group of caregivers should not be overlooked. Taking a child into one’s home is likely to bring many new concerns and stresses, especially if the child is infected with HIV (Brookes et al, 2004; Loening-Voysey, 2002). These families should be referred to a social worker or psychologist for counseling, support and monitoring.

The mean age of the caregivers in this study was 30.7 years. The majority of the mothers were between the ages of 24 and 34 years. This is the age of young women most vulnerable to HIV infection (UNAIDS, 2005). A need exists for measures to help these young women protect themselves and their future children from infection.

Only one quarter of caregivers had completed school and matriculated. The majority of caregivers had at least a grade nine level of education. While this would ensure basic numeracy and literacy, finding stable employment with less than a grade 12 level of

education is very difficult (Barbarin and Khomo, 1997). This means that many of these caregivers would be unemployed or be doing poorly paid menial work. Many caregivers reported that they sold sweets or vegetables on the side of the road to generate income for their families.

The average household composition was 3.2 adults and 3.5 children. The mean monthly income was R1183 ($\pm$ \$170). The families in this study were therefore extremely poor with many similarities to the group studied by Barbarin and Khomo in Soweto in 1997. Reported income is not always accurate, some families may under-report their income in the hope that they will qualify for some form of financial aid while others may inflate their income out of embarrassment. Income may also be spent in very different ways in different households and therefore is not always indicative of material welfare or food security. Income should not be interpreted in isolation when determining family wellbeing (Barbarin and Richter, 2001).

The impact of poverty on the lives of families affected by HIV cannot be underestimated. Jones et al (2005) identified poverty as a key factor influencing loss to follow up in a group of HIV infected mothers and their children attending a Prevention of Mother to Child Transmission clinic (PMTCT clinic) in Johannesburg, South Africa. Poverty was also identified as a key concern of caregivers of HIV positive individuals in South Africa by Orner (2006) and in Tanzania by Katapa (2004).

While 42.6% of caregivers in this study lived in a brick house not shared with other families, 21.3% lived in shacks. The remaining families lived in shared brick homes or rented rooms. Those who lived in shacks shared outside toilet facilities with other families and did not have running water in the home. Very few shacks had an electricity supply. The increased burden of caring for a chronically ill child under such difficult circumstances is hard to imagine. In these situations it is easy to see why a developmental stimulation programme would not always be seen as a priority when basic shelter and food security are not being realized. Missed clinical appointments are also understandable in these circumstances where money for transport is not always available (Orner, 2006; Jones et al, 2005; Katapa, 2004).

Most caregivers included in this study had access to a refrigerator, a television and a cellular phone in the household (73.7%, 75.4% and 63.9%). Other household amenities were less commonly available. The fact that over 25% of caregivers of children infected with HIV did not have a refrigerator in their homes is of concern. Many medications, including some antiretrovirals require refrigeration. At Harriet Shezi clinic prior to prescribing HAART, doctors enquire about whether the family has access to a refrigerator, this determines which medications may be prescribed and in what form. Caregivers may be required to break open capsules which do not need to be refrigerated and mix the powder with water and then give it to the child. This is not ideal as the powder is bitter and unpalatable to the child.

Only 5.7% of caregivers had access to a private car. The rest all relied on public transport to get to clinic appointments or to the hospital when the child is ill. This is an expensive, time consuming and unreliable form of transport and makes adherence with appointments difficult at times. Despite this and in contrast to the findings of Orner (2006) who identified lack of transport as one of the main reasons for missed clinical appointments in a group of HIV positive adults in Cape Town, South Africa, no caregivers in this study dropped out due to transport problems unless they were transferred to another clinic.

Clinical implications.

- More effort must be made to identify HIV infected children from a younger age and get them into clinics where they can receive comprehensive follow up from before they become symptomatic. This can be done through voluntary counseling and testing programmes which are already in operation.
- Mothers should have access to counseling to plan for the care of their children after their own death.
- Grandmothers need support in their parenting roles and ways of meeting their unique needs need to be investigated.
- The diversity of families caring for children infected with HIV needs to be recognized and individual family centered programmes need to be applied.

- Poverty alleviation should be a national priority in South Africa and healthcare workers should advocate for programmes that can improve the wellbeing of the patients in their care.

Research implications

- Family structure and support mechanisms need to be explored.
- The concept of resilience, not explored in this study, needs to be investigated in relation to families affected by HIV and caring for HIV infected children

6.8 Challenges

There are many challenges associated with conducting clinical research in a multi-cultural, developing country such as South Africa. The challenges experienced during this study will be presented and their possible impact on the results will be discussed.

6.8.1 Loss to Follow Up

A large loss to follow up was anticipated in this study and a 20% dropout was built into the original sample size calculation. Loss to follow up was expected due to the nature of the disease and its high mortality rate, the fact that HAART was not yet available at the start of the study and that the anticipated rollout would influence which facilities would be used as referral centres. The fact that poverty is widespread and public transport is expensive and somewhat unreliable also influences people's ability to adhere to clinic appointments. The multiple stresses that people experience in their daily lives mean that keeping appointments is not always possible or a priority. Thirty children were lost to follow-up in this study which equates to 24.6% of the initial sample size. The unexpectedly high loss to follow-up meant that the final power of the study was not as high as anticipated.

The main reasons for loss to follow up have been described in chapter five. Death of the child was the most common cause of loss to follow up (60%). The mean CD4 count of the children was very low at the beginning of the study placing the children at risk of death. Children were usually enrolled onto this study at their first or second visit to the

clinic. Getting on to HAART is a process which takes four to six weeks at Harriet Shezi clinic. Suitability of the child and the family has to be established and all the necessary pre-HAART counseling and education has to be completed. The children who died during the course of this study usually did so after their first or second visit to the clinic, usually before or soon after starting HAART.

The next most common cause of loss to follow up was that the children were transferred to another hospital or clinic. As HAART became more widely available children were referred to the health care facility closest to their homes which was able to provide them with all the services and medication they required. This was done to reduce the pressure on the tertiary care facilities which initially saw the majority of children infected with HIV in their area. The caregivers of these children were not always willing or able to bring the children back to participate in this study. Many studies have identified the cost and inconvenience of finding transport to clinics as a major reason for loss to follow up in populations affected by HIV (Orner, 2006; Jones et al, 2005; Katapa, 2004; Hackl et al, 1997).

If the primary caregiver of the child died the child was either institutionalized or changed caregivers which sometimes meant moving out of the area. If the primary caregiver died the child was excluded from the study as the Parenting Stress Index had to be filled in by the same person every time and continuity in the home programme was required.

Three children were institutionalized during the study, one due to poor socio-economic conditions at home and one because the mother was imprisoned. The third child went to live in a hospice facility with her dying mother as no one in the family could care for them. Institutionalisation of children is not common practice in South Africa and usually only occurs in cases of dire poverty or occasionally if no-one else in the family is willing to take the child (Richter et al, 2004). This was the case for the child whose mother was imprisoned as their family had rejected the mother and her child when they found out that they were HIV positive, they did however take in the two older uninfected siblings.

6.8.2 Assessment tools

Very few standardised assessment tools have been normed on South African populations. Researchers run the risk of drawing conclusions that are invalid if the assessment tool is not appropriate for use in a culture different from the one for which it was designed. The process to establish suitability of the assessment tools used in this study were described in chapter three. Some challenges were still faced despite the efforts of the researcher to eliminate these prior to commencing the study. Each of the assessment tools will be discussed.

Bayley Scales of Infant Development

As previously mentioned the BSID II has not been normed on South African children although the BSID I has been. Researchers should consider testing the BSID III which is now available on a large group of South African children to ensure its continued validity.

The children all responded well to the test items and enjoyed participating in the activities. Many did not want to relinquish the test items when they went home, especially the car and the crayons. The doll was the only item which the children did not like and some coaxing was often required before they would interact with it.

The researcher was not fluent in Zulu and Southern Sotho and use had to be made of the mothers as interpreters. The instructions given to the children were therefore not always exactly the same. This is the procedure used by Richter and Griesel (1988) when they tested the BSID I on a large group of South African children and it did not appear to affect their results. In a country with eleven official languages it is often difficult to communicate with research subjects. The researcher and the research assistant did however have many years of experience working in paediatric units in government hospitals in South Africa. They were therefore well equipped to adapt to the situation.

Many of the children in this study obtained index scores below 50. Extrapolated scores were therefore used for index scores of 30 to 49 and a score of 29 was assigned for all children with scores below 30. The measure of the extent of delay at the lower end of the scale is therefore not as reliable.

Parenting Stress Index/ Short form

No problems over and above those identified in chapter three were experienced during administration of the parenting stress form. Caregivers took longer than anticipated to complete the form (up to 30 minutes), but appeared to understand and relate to the questions well.

Household Economic and Social Status Index

Unfortunately not all the caregivers were able to complete all the items on the questionnaire. This was particularly the case for young, unmarried women living with their parents. They often did not know the educational level of their child's father, did not know how much rent was paid or how much electricity cost. Because of these gaps the HESSI was not scored as described by the authors and only the most relevant information was extracted from the questionnaire and analysed descriptively.

6.8.3 Language and culture.

Care was taken when giving the home programme to get as much input from the caregiver as possible in an attempt to understand and respect cultural differences in child rearing. The research assistant has many years of experience working with families of different cultures. Nurses and counselors at Harriet Shezi clinic were always willing to act as translators when this was required.

6.8.4 Conclusion

The children in this study had severe developmental delay which improved significantly after a home programme intervention. Although the children in the experimental group did improve, they remained delayed and require further follow-up and investigation.

There are many factors which influence developmental status and parenting stress in HIV infected children in South Africa. Further research is needed to investigate the relative importance of these factors and to test intervention programmes.

The conclusions drawn from this study will be presented in chapter seven.

Chapter 7

CONCLUSIONS

The main conclusions drawn from this study can now be summarised.

- Children infected with HIV, living in South Africa are at great risk of having severe developmental delay. This delay affects both cognitive and motor development.
- Children who received a basic home stimulation programme showed improvements in both cognitive and motor development when compared to children in the control group. This home programme is an easy and relatively cost effective intervention to administer. Although the children improved they remained delayed and require long-term follow up and management.
- Children in the control group who started HAART showed an improvement in motor but not cognitive development after initiation of treatment. Improved muscle strength due to improved general health may be responsible for the improvement in motor development seen in these children. Irreversible brain damage may have already occurred thus limiting the potential for cognitive improvement after starting HAART. Additional support in the form of a developmental stimulation programme is recommended. Further studies are urgently required in this area.
- A number of different factors were found to be predictive of developmental scores at each visit. The most important predictors of cognitive development include weight for age, the age of the child and whether they were on HAART. The important predictors of motor development were weight for age, the CD4% count and whether or not the child was on HAART. Being older at baseline assessment and in the experimental group were the most important factors predictive of improvement in cognitive and motor development over time.

- The children included in this study came from poor socioeconomic backgrounds. The majority of them were cared for by their biological mothers. The parenting stress levels of caregivers of these children were extremely high and was a cause of grave concern. Parenting stress decreased in both the control and experimental groups over the study period but remained clinically significant throughout.
- A number of factors were found to be predictive of high parenting stress levels. The most important of these being the educational level of the caregiver, the type of housing and the number of children in the household. Higher educational level of the caregiver, the type of housing and the number of adults in the household were the factors that emerged as being the most important predictors of a decrease in parenting stress over time.
- The psychosocial and developmental needs of young children infected with HIV in South Africa are not currently being met. Developmental assessment and a basic home stimulation programme should be available for all children infected with HIV. More attention needs to be paid to the concerns and stresses of caregivers of HIV positive children. A family centered approach to the assessment and management of children infected with HIV and their caregivers should be implemented at all paediatric HIV clinics in South Africa.

"The true revelation of a society's soul is the way in which it treats its children"

Nelson Mandela

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Appendix I

Ethical clearance certificate.

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. Machane 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
Works2\lain0015\HumEth97.wdb\IM 03-05-68

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 II

Outline of home programme.

HOME PROGRAMME.

Advice to the caregiver will be given in the following areas. Activities suggested must take into account the child's age and developmental status. The main aim is to optimize the child's functional potential and to encourage age appropriate behavior in normal movement patterns.

Sleeping Positions

Avoid supine

Encourage alternate side lying.

Prone for naps during the day.

Dressing

Encourage participation from the child

Talk about the clothes as you put them on, including colour or describing pictures on the clothes.

Encourage body awareness eg I am putting your shoe on your foot.

Give the child an element of choice eg "Do you want to wear your red shirt or your blue shirt?"

Feeding

Encourage a symmetrical posture while eating.

If the child is held during feeding it must be in an upright, well aligned position.

If the child can sit independently they should sit at a table with their feet supported.

Independent feeding should be encouraged. (Feeding utensils should be encouraged if culturally appropriate)

Bathing

Use this time to encourage body awareness. Name body parts as you wash them.

Encourage the child to do as much as possible for themselves.

If the child bathes in a tub play pouring games with different sized containers.

Carrying

Give alternatives to carrying the child on the caregivers back.

Examples include:

Against the chest, looking forward, one leg flexed

Cradled, with both arms forward and shoulders protracted

Prone over the caregivers arm

If the child is very disabled and has a poor prognosis for independent walking a McLaran pushchair will be ordered for them.

Play Activities

Depending on the child's functional level appropriate activities will be suggested. These will include games and activities that encourage fine and gross motor coordination.

Interaction with other children will be encouraged.

Games that include songs and rhymes will also be included.

Speech and Language

Verbal interaction with the child will be encouraged, picture books will be used to facilitate this.

If appropriate, positions to optimize communication will be shown.

If a child has significant feeding problems they will be referred to a speech therapist.

Caregiver's Concerns

Any additional aspects of the child's development that the caregiver identifies as being problematic will be addressed.

Appendix III

Informed consent letter.

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 for one year. 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.....

Appendix IV

Biographical questionnaire.

DEMOGRAPHIC QUESTIONNAIRE.

Caregivers name:.....
Age:.....
Relationship to child:.....
Level of education:.....
Number of people in household Adults..... Children.....
Ages of people in household.....
Address.....
.....
Telephone number.....
Occupation.....
Home language.....
Approximate monthly income for household.....
Do you belong to a support group?.....
If Yes, how often do you meet?.....

Child's name.....
Date of birth.....
Random number.....

Appendix V

Parenting Stress Index/Short form.

	SA = Strongly Agree	A = Agree	NS = Not Sure	D = Disagree	SD = Strongly Disagree
1. I often have the feeling that I cannot handle things very well.	SA	A	NS	D	SD
2. I find myself giving up more of my life to meet my children's needs than I ever expected.	SA	A	NS	D	SD
3. I feel trapped by my responsibilities as a parent.	SA	A	NS	D	SD
4. Since having this child, I have been unable to do new and different things.	SA	A	NS	D	SD
5. Since having a child, I feel that I am almost never able to do things that I like to do.	SA	A	NS	D	SD
6. I am unhappy with the last purchase of clothing I made for myself.	SA	A	NS	D	SD
7. There are quite a few things that bother me about my life.	SA	A	NS	D	SD
8. Having a child has caused more problems than I expected in my relationship with my spouse (or male/female friend).	SA	A	NS	D	SD
9. I feel alone and without friends.	SA	A	NS	D	SD
10. When I go to a party, I usually expect not to enjoy myself.	SA	A	NS	D	SD
11. I am not as interested in people as I used to be.	SA	A	NS	D	SD
12. I don't enjoy things as I used to.	SA	A	NS	D	SD
13. My child rarely does things for me that make me feel good.	SA	A	NS	D	SD
14. Sometimes I feel my child doesn't like me and doesn't want to be close to me.	SA	A	NS	D	SD
15. My child smiles at me much less than I expected.	SA	A	NS	D	SD
16. When I do things for my child, I get the feeling that my efforts are not appreciated very much.	SA	A	NS	D	SD
17. When playing, my child doesn't often giggle or laugh.	SA	A	NS	D	SD
18. My child doesn't seem to learn as quickly as most children.	SA	A	NS	D	SD
19. My child doesn't seem to smile as much as most children.	SA	A	NS	D	SD
20. My child is not able to do as much as I expected.	SA	A	NS	D	SD
21. It takes a long time and it is very hard for my child to get used to new things.	SA	A	NS	D	SD
For the next statement, choose your response from the choices "1" to "5" below.					
22. I feel that I am:	1	2	3	4	5
1. not very good at being a parent					
2. a person who has some trouble being a parent					
3. an average parent					
4. a better than average parent					
5. a very good parent					
23. I expected to have closer and warmer feelings for my child than I do and this bothers me.	SA	A	NS	D	SD
24. Sometimes my child does things that bother me just to be mean.	SA	A	NS	D	SD
25. My child seems to cry or fuss more often than most children.	SA	A	NS	D	SD
26. My child generally wakes up in a bad mood.	SA	A	NS	D	SD
27. I feel that my child is very moody and easily upset.	SA	A	NS	D	SD
28. My child does a few things which bother me a great deal.	SA	A	NS	D	SD
29. My child reacts very strongly when something happens that my child doesn't like.	SA	A	NS	D	SD
30. My child gets upset easily over the smallest thing.	SA	A	NS	D	SD
31. My child's sleeping or eating schedule was much harder to establish than I expected.	SA	A	NS	D	SD
For the next statement, choose your response from the choices "1" to "5" below.					
32. I have found that getting my child to do something or stop doing something is:	1	2	3	4	5
1. much harder than I expected					
2. somewhat harder than I expected					
3. about as hard as I expected					
4. somewhat easier than I expected					
5. much easier than I expected					
For the next statement, choose your response from the choices "10+" to "1-3."					
33. Think carefully and count the number of things which your child does that bother you. For example: dawdles, refuses to listen, overactive, cries, interrupts, fights, whines, etc.	10+	8-9	6-7	4-5	1-3
34. There are some things my child does that really bother me a lot.	SA	A	NS	D	SD
35. My child turned out to be more of a problem than I had expected.	SA	A	NS	D	SD
36. My child makes more demands on me than most children.	SA	A	NS	D	SD

Appendix VI

Household Economic and Social Status Index.

Household Economic and Social Status Index (HESSI)

(Barbarin, et al, 1995)

Who provided the information below _____)

I. Family Structure/Household Composition(Score 1-10)

Ia. Marital Status of Mother

1. Never married, not now living with a partner
2. Married, but not living now with a partner(e.g. divorced, separated)
3. Widowed
4. Never married, but now living with partner
8. Married and currently living with partner

Ib. Household Membership. How many people currently reside in the household? _____

Number 18 and older _____

Number 6-18 yrs old _____

Number under 6 yrs old _____

Ic. Are there adult relative now residing in the household? 0. No 2. Yes.

If yes who are they in relationship to the child? _____

II. Social Status- (Education, Occupation,[2-18])

A. Mother's Education: What is the highest level of education attained by mother?

1. Less than Standard 3
2. Primary School (Standard 3-4)
3. Junior Secondary (Standard 5-7)
4. Senior Secondary (Standard 8-9)
5. Matric/High School graduate/vocational training diploma
6. 1-2 yr College, Technikon
7. 3-4 yrs of University
8. Ph.D., M.D., J.D., D.D.S., or other doctoral degree

B. Education of Mother's Partner: What is the highest level of education attained?

1. Less than Standard 3
2. Primary School (Standard 3-4)
3. Junior Secondary (Standard 5-7)
4. Senior Secondary (Standard 8-9)
5. Matric/High School graduate/vocational training diploma
6. 1-2yr College, Technikon
7. 3-4 yrs of University
8. Ph.D., M.D., J.D., D.D.S., or other doctoral degree

What are the names, occupation and industry of the primary wage earners in the house?

Name	Occupation	Industry
1. _____	_____	_____
2. _____	_____	_____
3. _____	_____	_____

Access to Finances Who in the family earns money? Check all that apply.

- ___ BTT mother
- ___ Partner
- ___ Parent
- ___ Parent Pension
- ___ Sibling/Aunt/Uncle

III. Housing Accommodation. In what type of housing do you live?

- 0. None, homeless
- 1. Shack
- 2. Hostel
- 3. Room, garage
- 4. Flat, cottage
- 5. Home shared with other family(ies).
- 6. Home that is not shared with other families.

B. Does your home have

- 1) A Separate Kitchen? 0. No 1. Yes
- 2) A Separate Bathroom? 0. No 1. Yes

a) In your home how many separate rooms are there just for sleeping?
(circle one number) 0 1 2 3 4 or more.

b) What type of toilet facilities does your home have:

- 0. None
- 1. Pit or Bucket
- 2. Outside flush toilet
- 3. Inside flush

c) Do you own or rent a home.

- 0. Neither
- 1. Rent
- 2. Purchasing on Bond
- 3. Own

d) How much do you pay monthly for rent or bond? R_____.
For Service Charges R_____

e) For Electricity:
(highest in the last year) R_____
(the lowest) R_____

Does the place you live in have a . . . ?

- a) Refrigerator 0. No 1. Yes
- b) Television 0. No 1. Yes
- c) Telephone 0. No 1. Yes
- d) Car 0. No 1. Yes
- e) Video recorder 0. No 1. Yes
- f) Washing machine 0. No 1. Yes
- g) Microwave oven 0. No 1. Yes

h) In the past, have your children gone hungry because you did not have food?:

- 3. No, never
- 2. Rarely
- 1. Often
- 0. All the time

Factor VI. Savings: (Score 0-3)

- a) Do you have savings or participate in a savings plan? 0. No 1. Yes
- b) Do you have life insurance (version 1/25/96) 0. No 1. Yes

Maternal Well-being

Do you have any problems you might like to talk over with a doctor?

- 0. No
- 1. Yes (specify)

During the past 3 months have you had any physical or emotional condition for which you have been receiving treatment or taking medication?

- 0. No
- 1. Yes (specify)

During the past 3 months Have you been anxious, worried or upset?

- Extremely so—to the point of being sick or almost sick
- Very much so
- Quite a bit
- Some—enough to bother me
- A little bit
- at all

During the past 3 months, have you felt so sad, discouraged, hopeless or had so many problems that you wondered if anything was worthwhile?

Extremely so—to the point that I have just about given up

Very much so

Quite a bit

Some—enough to bother me

A little bit

Not at all

In any one year have you had at least 12 drinks of any kind of alcoholic beverage? Yes No

Have you ever had any serious physical handicap? 0. No 1. Yes

Have you ever been a patient (or outpatient) at a mental hospital, mental health ward of a hospital, or a mental health clinic for any personal emotional, behavior, or mental problem?

Yes, during the past year

Yes, more than a year ago

No

Neighborhood Safety

A. In general how safe is the area in which you live?

1. Extremely dangerous

2. Dangerous

3. Safe

4. Extremely Safe

B. How much do you worry about your child getting hurt when s/he is outside of your home?

1. Never

2. Sometimes

3. Often

4. All the time

Satisfaction with Family Life (Support)

My family has a lot of problems:

1. Not True 2. Sometimes True 3. Often True 4. Always True

My family is always there for me when I need them.

1. Not True 2. Sometimes True 3. Often True 4. Always True