THE MOTOR AND COGNITIVE DEVELOPMENT OF CHILDREN, UNDER THE AGE OF 42 MONTHS, WHO ARE INFECTED WITH HIV

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Abstract

Background: Antiretroviral therapy has ensured that children who are infected with the human immunodeficiency virus (HIV) survive for longer periods. However, despite improvements in mortality rates, large numbers of children living with HIV continue to exhibit abnormal developmental performance associated with HIV infection of the central nervous system (CNS). Although these problems have been well documented, the impact of the virus on the motor and cognitive performance of South African children is less well known. **Aim:** The main aim of this study was to document the prevalence and severity of motor and mental delay in a sample of HIV infected children. A secondary aim was to document their motor and mental performance at three monthly intervals for a period of six months. **Objectives:** The specific objectives of the study were: (i) to document the demographic and medical characteristics of a sample of HIV infected children, (ii) to document the socioeconomic status of their caregivers, (iii) to compare the prevalence and severity of motor and mental delay of the HIV infected sample at the initiation of the study, to the performance of an age-matched sample, who have been established to have similar demographic characteristics, using the Bayley Scales of Infant Development Second Edition (BSID II), (iv) To compare the characteristics of a subgroup within the HIV infected sample who *were not on HAART* at the initiation of the study to a subgroup within the HIV infected sample who *were on HAART* at the initiation of the study, (v) to compare the motor and mental performance of the subgroup who *were not on HAART* at the initiation of the study to the performance of participants who *were on HAART for less than six months* and to those who *were on HAART for more than six*

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months, vi) to document the motor and mental performance of the HIV infected sample at three monthly intervals for a period of six months. **Study Design:** A cross sectional descriptive, correlational study design was used to describe the sample and to document the prevalence and severity of motor and mental delay. A longitudinal, repeated measures design was incorporated to monitor the performance of the sample over six months. **Participants:** 51 HIV infected children, attending the Infectious Diseases Clinic (IDC) at The Red Cross War Memorial Children's Hospital (Red Cross Hospital) in Cape Town and 35 age-matched children receiving services at outpatient community clinics in Langa, Vanguard and Khayelitsha participated in this study. Among the HIV infected sample, 34 children were already receiving HAART at the initiation of the study, and 17 were deemed not eligible according to the criteria for initiation of HAART used at Red Cross Hospital. **Instrumentation:** The BSID II was used to measure the motor and mental performance of all participants. A questionnaire, developed by the researcher, was administered via an interpreter, to record demographic and medical information from the participants. **Methods:** Informed consent was taken prior to the enrolment of each subject. The BSID II was then administered to each participant in the HIV infected sample at the initiation of the study and then three monthly intervals over a period of six months. Each participant in the age-matched sample was assessed once and their scores were compared to the scores of the HIV infected sample at baseline. **Data analysis:** All data was analysed using the STATISTICA software programme. A significance level of $p \leq 0.05$ was used throughout. Extrapolated scores were calculated for participants who achieved a raw score that could not be converted into an index score. Normal distribution of all data was checked using the Shapiro-Wilks test. Frequency tables and means were

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used to describe the characteristics of the sample and their caregivers. Chi squared tests were used to establish if there was an association between characteristics of the sample and group membership. Either the t-tests or the Mann Whitney U test was used to compare the performance of the HIV infected sample with the age-matched sample, depending on whether the data was normally distributed. The Friedman's ANOVA was used to determine if there was any difference in the ranking of the motor and mental scores over time and the Wilcoxan matched pairs test was used to determine where the difference occurred. **Results:** The HIV infected sample and the age-matched sample were comparable with regards to mean age ($p=0.58$), caregiver level of education ($p=0.42$), caregiver employment status ($p=0.35$), receiving child support grants ($p=0.43$) and caregiver income ($p=0.28$). However, the HIV infected sample had significantly more hospital admissions ($p<0.01$), their caregivers were mostly single ($p=0.04$) and most lived in brick houses ($p<0.01$). The prevalence of significant motor delay was 66.7% in the HIV infected sample compared to 5.7% in the age-matched sample. The motor performance of the HIV infected sample (mean PDI = 63.0) was significantly poorer ($p<0.001$) than the performance of the age-matched sample who scored a mean PDI of 92.3. The prevalence of significant mental delay was 52.9% in comparison to 11.4% in the age-matched sample and the mean MDI scores were significantly different ($p<0.01$). The HAART and non-HAART groups were demographically comparable however, participants in the HAART group reported more hospitalisations ($p=0.01$) and reported less exposure to PMTCT prophylaxis ($p=0.03$). There were no significant differences in the motor ($p=0.11$) and mental performance ($p=0.36$) when comparing the HIV infected sample who not on HAART, those were on HAART for six months or less

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and those who were on HAART for more than six months. Thirty-four participants completed the longitudinal assessment. Examination of the longitudinal performance of the sample who completed the study, showed no significant change in both motor ($p=0.15$) and mental performance ($p=0.87$) over the course of the study. No significant change in both motor ($p=0.24$) and mental ($p=0.82$) scores was found on examination of the longitudinal performance of those who were on HAART from the initiation of the study. **Discussion and Conclusions:** As expected, the performance of the HIV infected sample was significantly poorer compared to the age-matched sample. However, the extent of the delay is a cause of concern as so many children presented with significant motor and mental delay. The reasons for their poor performance could be attributed to a variety of reasons including their ill health and social circumstances. It was expected that the children not receiving HAART might perform better as they were not deemed ill enough to start HAART. Despite the fact that HAART was available to the children, there was no sign of motor or cognitive improvement. However, considering that the condition is progressive in nature, there was no evidence of decreased motor and cognitive performance over time, and HAART may prevent further developmental deterioration. The fact that children who were not yet eligible for HAART performed as poorly as the children receiving HAART, would indicate that the HIV itself may contribute to a large extent to the delay, over and above the contribution of opportunistic infections. Unexpectedly, a significant number of healthy children also displayed delayed performance. The reasons for their poor performance are not clear. The socio-economic situation of their caregivers was poor; there were a large number of unemployed, single mothers who lived in informal housing, with little or no space for their children to play

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physically active games. The fact that this group also performed poorly suggests that the prevalence of delay in the HIV infected sample may be over-represented. It is recommended that the continuing effect of HAART be monitored over a longer period to determine whether the developmental delay can be reduced with treatment. In the interim, there is a need to provide stimulation and treatment to the large number of children who are developmentally delayed including those uninfected children in the community who are at risk due to their socio-economic status.

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University of Cape Town

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University of Cape Town

Table of Contents

Abstract ii

Acknowledgements vii

Table of Contents ix

List of Tables xiii

List of Figures xiv

List of Abbreviations xv

List of Appendices xvi

1 Introduction 1

1.1 Background *1*

1.2 Effect of HIV on development *2*

1.3 Instrumentation *4*

1.4 Justification for the study in South Africa *7*

1.5 Significance of the study *9*

1.6 Research setting *10*

1.7 Aims and objectives *12*

1.7.1 Aims 12
1.7.2 Objectives: 12

2 Literature review 14

2.1 Paediatric HIV infection *14*

2.1.1 Epidemiology 14
2.1.2 Biology 16
2.1.3 Transmission 16
2.1.4 Prevention of vertical transmission 19
2.1.5 Diagnosis 20
2.1.6 Disease progression 21

University of Cape Town

2.1.7 Disease classification 21

2.2 Manifestations of HIV infection in children *22*

2.2.1 Immunocompromise 22

2.2.2 Opportunistic infections of the CNS 23

2.2.3 HIV infection of the CNS 24

2.2.4 HIV and developmental delay 27

2.3 Treatment and rehabilitation *31*

2.3.1 Prophylactic regimens 32

2.3.2 Antiretroviral therapy 32

2.3.3 The role of physiotherapy 36

2.4 Additional risk factors for developmental delay in HIV infected children *39*

2.4.1 Biological risk factors 40

2.4.2 Psycho-social risk factors 45

2.4.3 Socio-economic risk factors 47

2.4.4 Assessing socio-economic status 49

2.5 Assessing development *51*

2.5.1 Developmental assessment tools 51

2.5.2 The Bayley Scales of Infant Development Second Edition 53

2.6 Development of children with HIV – methodological issues *59*

2.6.1 Subject recruitment 59

2.6.2 Effects of repeated evaluations 60

2.6.3 Scheduling testing 60

2.6.4 Impaired test taking ability 60

2.7 Conclusion *61*

3 Methodology **64**

3.1 Research design *64*

3.2 Participants *65*

3.2.1 The HIV infected sample 65

3.2.2 The age-matched sample 67

3.3 Procedure *70*

3.3.1 Pilot study 70

3.3.2 Reliability testing 70

3.3.3 Ethical approval 71

3.3.4 Funding 72

University of Cape Town

3.4 Instrumentation *72*

3.4.1 Demographic Questionnaire 72

3.4.2 Administration of the demographic questionnaire 72

3.4.3 The Bayley Scales of Infant Development 72

3.4.4 Administration and scoring of the BSID II 73

3.5 Data collection *74*

3.5.1 Red Cross Hospital: The HIV infected sample 74

3.5.2 Community heath centres: The age-matched sample 77

3.6 Data analysis *78*

3.7 Ethical considerations *79*

3.7.1 Informed consent 79

3.7.2 Autonomy 80

3.7.3 Convenience of testing for caregivers 80

3.7.4 Risk 81

3.7.5 Beneficence 81

3.7.6 Confidentiality 81

4 Results 82

4.1 Demographic and medical characteristics of the sample *82*

4.2 Socio-economic characteristics of the caregivers *85*

4.3 Prevalence and severity of developmental delay *87*

4.3.1 The age-matched sample 88

4.3.2 Motor performance 90

4.3.3 Mental Performance 92

4.4 Influence of HAART on motor and mental performance *94*

4.4.1 Characteristics of the subgroups 94

4.4.2 Motor and Mental Performance 96

4.5 Longitudinal performance of the HIV infected sample *97*

4.5.1 Attrition 97

4.5.2 The longitudinal sample 100

4.5.3 Motor Performance 101

4.5.4 Mental Performance 102

5 Discussion 104

5.1 Summary of Main Findings *104*

University of Cape Town

5.2 The sample ... *105*
5.2.1 The HIV infected sample ... 105
5.2.2 The age-matched sample ... 108
5.3 Prevalence and severity of motor and mental delay ... *110*
5.3.1 Performance of the HIV Infected sample ... 110
5.3.2 Performance of the age-matched sample ... 116
5.4 Influence of antiretroviral therapy ... *121*
5.4.1 Influence of PMTCT prophylaxis ... 122
5.4.2 Influence of HAART on developmental performance ... 123
5.5 Longitudinal performance of HIV infected sample ... *125*
5.6 Methodological issues ... *127*
5.6.1 Research design ... 127
5.6.2 Use of the BSID II ... 128
5.7 Limitations and Recommendations ... *130*
5.7.1 The HIV infected sample ... 130
5.7.2 The age-matched sample ... 131
5.7.3 Attrition rate ... 131
6 Conclusions and recommendations ... **133**
6.1 Performance of the HIV group ... *134*
6.2 Effects of HAART ... *134*
6.3 Longitudinal performance ... *135*
6.4 Demographic characteristics ... *136*
6.5 Performance of the age-matched sample ... *136*
6.6 Final conclusions ... *137*
7 References ... **138**
8 Appendices ... **151**

University of Cape Town

List of Tables

Table 1: Illnesses diagnosed on each hospital admission in the HIV infected sample (n= 48 participants admitted to hospital) 85
Table 2: Socio-economic profile of caregivers of the HIV infected sample (n=51) and caregivers of the age-matched sample (n=35) 86
Table 3: Differences in relationship status between caregivers of HIV infected sample (n=51) and caregivers of the age-matched sample (n=32) 89
Table 4: Differences in housing type occupied by caregivers of the HIV infected sample (n=51) and caregivers of the age-matched sample (n=33) 90
Table 5: Comparison between the HIV infected sample (n=51) and the age-matched sample (n=35) based on Motor Classification 92
Table 6: Results of the t- test to compare the MDI scores of HIV sample (n=51) and the age-matched sample (n=35) 93
Table 7: Comparison between the HIV infected sample (n=51) and the age-matched sample (n=35) based on Mental Classification 94
Table 8: Comparison of between sample receiving HAART (n=34) and those not receiving HAART (n=17) in terms of exposure to antiretroviral prophylaxis 95
Table 9: Comparison of sample receiving HAART (n=34) and those not receiving HAART (n=17) in terms of hospital admissions 95
Table 10: Comparison of mean PDI and MDI scores of participants who were not on HAART, receiving HAART for less than six months and receiving HAART for more than 6 months96
Table 11: Number of participants who withdrew and each stage of the study, reasons for attrition and previous classifications of performance 100
Table 12: Period between assessments for the longitudinal sample (n=34) 101
Table 13: Mean PDI scores of participants who completed the study (n=34) 102
Table 14: Mean MDI scores of participants who completed the study (n=34) 103

University of Cape Town

List of Figures

Figure 1: Histogram of PDI scores of the HIV (n=51) and the age-matched sample (n=35) 91
Figure 2: Histogram of MDI scores of the HIV (n=51) and the age-matched sample (n=35) 93
Figure 3: PDI and MDI of the children not on HAART (n=17), receiving HAART for less than 6 months (n=17) and receiving HAART for more than 6 months (n=17) 97
Figure 4: The median PDI score at each of the three periods (n=34)..102
Figure 5: The median MDI score at the three periods (n=34)...103

University of Cape Town

List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
BRS	Behaviour Rating Scale
BSID II	Bayley Scales of Infant Development Second Edition
CHC	Community Health Centre
CNS	Central Nervous System
DQ	Developmental Quotient
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus Type 1
IDC	Infectious Diseases Clinic
MDI	Mental Development Index
PDI	Psychomotor Development Index
PMTCT	Prevention of Maternal To Child Transmission (*of HIV*)

University of Cape Town

List of Appendices

Appendix I Demographic Questionnaire

Appendix II Informed consent forms

Appendix III Red Cross Children's Hospital Antiretroviral Treatment Guidelines

University of Cape Town

1 Introduction

1.1 Background

The first case of paediatric Acquired Immune Deficiency Syndrome (AIDS) was reported in the United States of America (USA) in the 1980's (Centres for Disease Control and Prevention, 1982). Ever since, health care providers around the world have become burdened with managing a rapidly growing population of chronically ill and dying children (Saloojee and Violari, 2001).

The effects of the HIV epidemic have been most evident in developing countries. The sub-Saharan Africa region reportedly has the highest prevalence of HIV infection in the world, containing more than 60% of all HIV infected individuals worldwide (www.avert.org, 2001). At the end of 2005, approximately 5.5 million individuals in South Africa were infected with HIV, including approximately 240 000 children under the age of 15 years (UNAIDS/WHO, 2006). The majority of these children had acquired the infection by vertical transmission (Saloojee and Violari, 2001).

Much of the focus in paediatric AIDS in the past has been on the tragically rapid progression to death of many infected infants and children because the disease was viewed as progressive and there was limited knowledge of effective treatment strategies (Nozyce, Hittleman, Muenz, Durako, Fischer and Willoughby, 1994). However, since the advent of antiretroviral medication and the advancement of medical research in HIV treatment, significant changes have occurred in the management of HIV in children. The

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introduction of prophylactic and antiretroviral therapies has been associated with a decline in mortality and has lessened the severity of several illnesses associated with HIV infection (Gisslen and Hagberg, 2001, Saloojee and Violari, 2001, Sharland, Castelli Gattinara di Zub, Ramos, Blanche and Gibb, 2002). Since the life expectancy of HIV-infected children, who have access to these regimens, has started to increase, attention must be directed to the morbidities associated with HIV infection, such as chronic lung disease, oncological problems and neurological impairments (Nozyce *et al.*, 1994). It has now become increasingly important for clinicians involved in the management of children with HIV to consider the impact of HIV infection in relation to quality of life. In addition, rehabilitation professionals should be aware of their role in maximising the potential of these children.

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1.2 Effect of HIV on development

HIV was originally thought to affect only the immune system. However, it has been documented that the human immunodeficiency virus also directly infects the brain (Wolters and Brouwers, 1998), especially in children (Byers, 1989) who may be exposed to the virus at various stages of development. Reports on varying degrees of impairment ranging from mild developmental delay to severe progressive encephalopathy have been documented in numerous paediatric cohorts (Ungvarski and Trzcianowska, 2000, Wolters and Brouwers, 1998) indicating the effect of the virus on the CNS. The majority of early studies investigated the neurodevelopment of children who were naïve to antiretroviral therapy (Wolters and Brouwers, 1998). Although international studies have documented the performance of children receiving treatment (Smith R, Malee, Charurat, Magder,

Mellins, MacMillan, Hittleman, Lasky and Moye, 2000) to the author's knowledge, very little research on the neurodevelopmental performance of HIV infected South African children has been documented.

According to Wolters and Brouwers (1998), the presence of HIV in the CNS is a necessary, but not sufficient condition for CNS compromise (Wolters and Brouwers, 1998). They have suggested that increased replication of the virus probably results in greater interference with CNS processes. Therefore, the periods of the child's life during which the disease process is most active may result in different patterns and degrees of abnormalities. In addition, it appears that the timing of entry of the virus into CNS structures may also affect outcome (Smith R *et al.*, 2000, Wolters and Brouwers, 1998).

The effects of the virus on paediatric neurodevelopment have been documented in international studies (Angelini, Zibordi, Triulzi, Cinque, Giudici, Pinzani and Plebani, 2000, Bruck, Tahan, da Cruz, Martins, Antoniuk, Rodrigues, de Souza and de Bruyn, 2001, Ungvarski and Trzcianowska, 2000) and in North African studies (Drotar, Olness, Wiznitzer, Guay, Marum, Svilar, Hom, Fagan, Ndugwa and Kiziri-Mayengo, 1997, Msellati, Lepage, Hitimana, van Goethem, van de Perre and Dabis, 1993). The prevalence of developmental delays and neurological disorders in children infected with HIV has been estimated to range between 25% and 90% of children with HIV infection (Layton and Davis-McFarland, 2000). In a recent South African study, the prevalence of neurodevelopmental delay among HIV infected children in Johannesburg was reported to be 40% (Potterton and Eales, 2001).

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The course of development among HIV infected children is highly variable. Two disease profiles have been reported in HIV infected children. There are those who begin to manifest mental and motor deficits as early as three months of age (Gay, Armstrong, Cohen, Lai, Hardy, Swales, Morrow and Scott, 1995) and others who tend to progress slowly and show signs of infection when they get older (Mitchell W, 2001). In addition, children infected with HIV can be separated into three broad neurological profiles: those with encephalopathy, those who exhibit mild neurological signs that does not affect their functioning and those whose mental, motor and behavioural skills are within the normal range of functioning (Wolters and Brouwers, 1998).

Physiotherapists have been recognised as having a positive role to play in the management of adults with HIV (Coates, 1990, McClure, 1993, Smith K, 1993). However, in the absence of a comprehensive understanding of the neurological deficits exhibited by children with HIV, it is difficult for physiotherapists to plan treatment and intervention strategies. An understanding of the neurological complications seen in HIV infection is especially important in order to plan effective rehabilitation programmes (Amosun, Gatsi and Mawere, 1995).

1.3 Instrumentation

Cross-cultural studies suggest that development varies among children growing up in different regions of the world (Abbot and Bartlett, 1999). These differences can be attributed to variations in socio-economic status of the population, differences in child and maternal health status and care as well as cultural differences. Lower socio-economic

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status or poverty in childhood has been linked to a number of adverse developmental outcomes such as substandard educational attainment, behavioural problems and poor health (Brunner, 1997, Duncan, Brookes-Gunn and Klebanov, 1994). Since many children in South Africa experience levels of poverty that are well below the levels of living in developed nations such as the United States (Dieden and Gustafsson, 2003) it is expected that their performance may not be equivalent to those children living in developed countries. Superior maternal and paediatric health care in developed nations may also collectively contribute to better developmental outcomes for children growing up in these regions.

Many studies on the development of children with HIV have used developmental instruments that have been normed and standardised in developed nations (Chase C , Ware, Hittelman, Blasini, Smith, Llorente, Anisfield, Diaz, Fowler, Moye and Kaligh, 2000, Coplan, Contello, Cunningham, Weiner, Dye, Roberge, Wojtowycz and Kirkwood, 1998, Gay *et al.*, 1995). One particular test, the Bayley Scales of Infant Development is widely used in studies related to development of children infected with HIV (Bayley, 1993). This test, although developed and normed in the United States of America, has been used to assess the development of HIV positive children in Haiti (Gay *et al.*, 1995), Uganda (Drotar *et al.*, 1997) and Brazil (Bruck *et al.*, 2001).

Apart from unpublished manuscripts reflecting the performance of South African children on the Griffiths Developmental Scales (Alan, 1992, Bhamjee, 1991)and unpublished norms reflecting the performance of children in the Western Cape on AIMS

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scale (Matyida and Jelsma, 2004), current developmental norms for South African children are not easily accessible. The Bayley Scales of Infant Development first edition was normed on a Black South African population in 1986 (Richter and Griesel, 1988). As this test was normed twenty years ago, the norms represented in these studies may not be applicable to the population being examined today due to the socio-economic and political changes that have occurred in South Africa since 1986. Poverty, crime and violence are just some of the challenges facing children growing up in a post-apartheid democratic South Africa, all of which impact of the development of children (Dieden and Gustafsson, 2003).

In an attempt to ensure that the norms of scales developed elsewhere are valid for South African children, there have been pilot studies which have tested the Bayley Scales of Infant Development Second Edition (BSID-II) (Matyida and Jelsma, 2004) and the Alberta Infant Motors Scale (AIMS) on typically developing isiXhosa speaking children in resource poor areas of Cape Town (Jelsma, Peters, van Bekenbergen and Feys, 2004). The results of these studies indicated that children with no evidence of immune suppression were performing below the norms predicted by both tests. In the one study using a sample of 25 typically developing children as a control sample, the motor developmental quotient (DQ) was found to be 93.3 (SD=18.2) on the Bayley Scales of Infant Development (BSID) (Matyida and Jelsma, 2004). In another similar study, the DQ of 74 typically developing children in the control group was found to be 91.71 (SD=16.78) using the Alberta Infant Motor Scale (Jelsma *et al.*, 2004). In both cases, as the motor quotient is defined as the developmental age divided by the chronological age

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multiplied by 100, the mean DQ should be 100. Although these studies are unpublished and may be flawed, they do challenge the assumption that the published norms can be accepted without further investigation. If typically developing children who live in townships in Cape Town are developing more slowly than their counterparts elsewhere are, delay noted in children with HIV may in part be due to the instrument rather than to the impact of HIV.

In the absence of current normative data on the mental and motor performance of typically developing children living in Cape Town, children was recruited from various Community Health Centres (CHC's) in Cape Town and evaluated using a standardised developmental assessment battery, i.e. The BSID II. This sample of children was recruited to represent the performance of isiXhosa speaking children growing up in a resource poor area of Cape Town. Unfortunately, it was not possible to test these children for HIV. Therefore, multiple episodes of ill health with hospitalisation were chosen as a crude measure of immunodeficiency to limit the inclusion of children with HIV infection.

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1.4 Justification for the study in South Africa

To the author's knowledge, the long-term impact of the virus on the motor performance of South African children has not been described in detail in available publications. This indicates that further research is required to monitor the development of children with HIV in South Africa and to document the effects of HIV infection that are unique to our setting. According to Drotar et al (1997), the neurological disorders described in studies conducted in developed countries cannot be extrapolated to the African context because

the use of antiretroviral therapy in developed countries has probably lessened the severity of mental and motor deficits seen in HIV infected children (Drotar *et al.*, 1997). In addition, reports have identified maternal intravenous drug use as the most common risk factor for transmission of HIV among HIV infected pregnant women in the United States whereas heterosexual transmission of HIV is more common in developing countries (Lachman, 1998). The development of children with HIV in South Africa where maternal drug addiction is less likely to have an influence would therefore need to be investigated.

Children infected with HIV come from different environmental and social backgrounds and some, like the general population, may have co-existing medical conditions commonly seen in children that are unrelated to HIV infection, such as asthma for example. Determination of the extent to which HIV itself influences development therefore remains complex due to the number of confounding factors that may mask the effects of HIV on the CNS. Although HIV infection of the CNS is the most common reason for neurological impairment in HIV infected infants, other aetiologies must be excluded and the impact of other developmental risk factors should be evaluated. Many children born to mothers from high-risk groups may suffer from social neglect or malnutrition that can have an impact on development (Byers, 1989, Mueller and Pizzo, 1998). In a developing country such as South Africa, the impact of poverty and consequent poor health cannot be ignored as a significant risk factor for poor motor and mental performance.

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1.5 Significance of the study

Although many children with HIV succumb to the effects of opportunistic infections or oncological processes early in life, a number of children may thrive for many years before showing signs of illness. Some children lead long lives with the assistance of antiretroviral therapy and yet presently HIV remains an incurable disease with a progressive course. The effect of having a progressive illness in childhood has serious implications for development. Parallels can be drawn when considering the impact of childhood cancers (Copeland, deMoor, Moore and Ater, 1999, Mitchell W G, Brumm, Azen, Patterson, Aller and Rodriguez, 2005) or illnesses such as chronic lung disease (Bohm and Katz-Salamon, 2003) on developmental progress. These studies have reported on the adverse effects of chronic illness on childhood development in relation to the physical impairment caused by the illness and in relation to the effects of psychosocial variables.

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Based on the prevalence of paediatric HIV infection in the South African population, it can be concluded that a large number of children with HIV are at risk of developmental delay. In order to provide effective services it is important to document the developmental history of these children. While it has been established that the use of Highly Active Antiretroviral Therapy (HAART) has a neuroprotective effect (Sanchez-Ramon, Resino, Bellon Cano, Ramos, Gurbindo and Munoz-Fernandez, 2003), the extent to which it influences developmental outcome needs to be documented. Continuous monitoring of the development of HIV infected children is essential to address their medical and educational needs. If therapists are able to detect the presence of delays early

on, they may limit the deterioration of motor skills and improve outcomes through direct intervention strategies and by training caregivers to provide developmental stimulation.

1.6 Research setting

The research was conducted at three sites: The Red Cross War Memorial Children's Hospital (Red Cross Hospital), the Nolungile Community Health Centre (Nolungile CHC) in Khayelitsha and the Vanguard Community Health Centre (Vanguard CHC). Additional participants were identified and recruited at the Langa Community Health Centre (Langa CHC).

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Red Cross Hospital is a tertiary level academic hospital situated in Cape Town, South Africa. The hospital provides specialist paediatric services to children under the age of 12 years through various medical, surgical, allied health and social services departments. The Infectious Diseases Clinic (IDC) is an outpatient service run by the hospital. Children who are diagnosed with HIV in the wards of Red Cross Hospital are referred to the IDC after discharge where their condition is monitored until they are ready to start antiretroviral therapy. In addition, HIV infected children may also be referred to the IDC from primary and secondary health institutes around the country. Once the decision is made to start antiretroviral therapy, the child is given monthly appointments to attend the IDC in order to monitor their health and their adherence to the antiretroviral regimen. The eligibility criteria for commencement of antiretroviral medication at Red Cross Hospital are provided in Appendix III. Children receiving services at the IDC, who met the eligibility criteria for this study, formed a sample of convenience.

Specific CHC's were chosen while recruiting patients attending the IDC at Red Cross Hospital. The majority of children attending the IDC were identified as isiXhosa speakers who were living in areas such as Langa, Khayelitsha, Gugulethu and other smaller informal settlements. The Nolungile CHC in Khayelitsha, Vanguard CHC in Bonteheuwel and Langa CHC in Langa were therefore chosen since the majority of attendees at these CHC's were isiXhosa speakers. The aforementioned CHC's are primary level health care institutions situated in resource poor, peri-urban residential areas in Cape Town. These centres provide medical and social services to adults and children via a system of clinics and departments. The "well-baby clinics", located within these CHC's provide immunization, growth-monitoring services, nutritional support, and other health related services to children living in the areas they serve. In addition to these services, the Vanguard CHC offers a family planning clinic and attendees share the well share a common waiting room with the well baby clinic. Children attending the community health centre were predominantly there for vaccinations or accompanying family members who were seeking medical attention, and all the children tested were healthy.

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1.7 *Aims and objectives*

1.7.1 Aims

The main aim of this study was to document the prevalence and severity of motor and mental delay in a sample of HIV infected children using the Bayley Scales of Infant Development Second Edition (BSID II). A secondary aim was to document the prevalence and severity of motor and mental delay of the abovementioned sample at three monthly intervals for a period of six months using the BSID II.

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1.7.2 Objectives:

The specific objectives of the study were:

1. To document the demographic (defined by: sex and mean age) and medical characteristics (defined by: HIV status, exposure to antiretroviral prophylaxis, antiretroviral status, number of hospitalisations since birth and the reasons for hospital admissions) of a sample of children infected with HIV attending Red Cross Hospital.

2. To document the socio-economic status (defined by: marital status, level of education, employment status, receiving a grant, income and housing status) of the caregivers of the sample of children infected with HIV.

3. To compare the prevalence and severity of motor and mental delay of the HIV infected sample at the initiation of the study using the BSID II with the performance of an age- matched sample, who have been established to have similar demographic characteristics.

4. To compare the characteristics of the HIV infected subgroup who was not on HAART at the initiation of the study to the subgroup who were on HAART at the time.

5. To compare the motor and mental performance of the subgroup who *were not on HAART* at the initiation of the study to the performance of participants who *were on HAART for less than six months* and to those who *were on HAART for more than six months*.

6. To document the motor and mental performance of the HIV infected sample at approximately three monthly intervals for a period of six months.

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2 Literature review

In this review, the relationship between HIV infection and its effects on childhood development will be explored. The following areas will be examined: a brief introduction to paediatric HIV infection will be provided reflecting on the epidemiology of HIV infection in children, the biology and pathogenesis of HIV infection, vertical transmission of the virus, prevention of vertical transmission and diagnosing HIV infection in children. The neurological manifestations of HIV infection will be described in detail with special emphasis on HIV-related developmental delays. The effect of antiretroviral and other therapies on childhood development will also be explored. The impact of other determinants of delay in children infected with HIV will be presented, including factors that are specifically related to their caregivers. Finally, methodological issues relating to longitudinal developmental assessment of children will be discussed with emphasis on instruments used to evaluate developmental delay.

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2.1 *Paediatric HIV infection*

2.1.1 Epidemiology

The first case of paediatric HIV infection was reported in the United States in 1982/3 (Dobosz and Marczynska, 2004). Cases of Paediatric AIDS or as it was then called, PAIDS, were commonly reported among children born to drug addicted mothers who were also prostitutes (Hopp and Rogers, 1989). The scope of the epidemic started gaining

momentum in the mid 1980's and since then, rates of paediatric HIV infection have rapidly increased throughout the world. HIV can now be found on every continent and AIDS is the leading cause of death in many resource-poor countries (Spiegel and Bonwit, 2002).

The highest prevalence of HIV in the world occurs in sub-Saharan Africa (www.avert.org, 2001). It is estimated that 29.5 million people are infected with HIV in this region including an estimated 2 million children under the age of 15 years (UNAIDS/WHO, 2004). According to reports by UNAIDS (2004), the epidemic in southern Africa is due to a variety of reasons, including poverty, family instability, migrant labour systems, high levels of sexually transmitted infections, sexual violence and poor response from governments to address these problems (UNAIDS/WHO, 2004).

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According The South African National Department of Health annual HIV antenatal surveys, HIV infection rates among pregnant women attending South African antenatal clinics have increased from less than one percent to approximately 25 percent over the past 10 years (Department of Health, 2003). The high prevalence of HIV amongst antenatal clinic attendees suggests that unless antiretroviral therapy is available for all HIV positive pregnant women, paediatric HIV infection threatens to become a major public health burden. This is most evident in reports by UNAIDS, suggesting that approximately 5.5 million South Africans were infected with HIV at the end of 2005, including 240 000 children (www.avert.org, 2006).

2.1.2 Biology

The aetiological agent of AIDS is a retrovirus known as the human immunodeficiency virus (Hopp and Rogers, 1989). HIV belongs to a family of viruses known as lentiviruses, which are known to cause chronic disease and immune suppression in infected patients (Layton and Davis-McFarland, 2000). The HI virus targets specific cells viz. T-lymphocytes, macrophages, and CNS cells. CD4, situated on these cells, act as receptors for the HI virus. The virus enters the cell and replicates inside eventually causing depletion of the host cell. This weakens the host's immune system, damages the CNS and facilitates the development of neoplasms (Layton and Davis-McFarland, 2000).

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2.1.3 Transmission

Evidence suggests that a mother can transmit HIV to her child by three possible routes: in utero (via the placenta), during the birthing process (through exposure to maternal blood or other fluids) or postpartum (through breastfeeding) (Bobat, Coovadia, Coutsoudis and Moodley, 1996).

The rate of vertical transmission of HIV from mother to child in South Africa is estimated to be between 26-42% (Bobat *et al.*, 1996). Viral, immunological and clinical factors in both the mother and the infant all play a role in the process of vertical transmission (Cohan, 2003). The risk of transmission is significantly increased if the mother has advanced HIV disease, increased levels of HIV in her bloodstream, or a lower CD4 count (Ioannidis, Tatsioni, Abrams, Bulterys, Coombs, Goedert, Korber, Mayaux,

Mofenson, Moye, Newell, Shapiro, Teglas, Thompson and Wiener, 2004, Smith R *et al.*, 2000).

Transmission in utero is established when infants test positive for HIV in the first 48 hours of life. Although the exact timing of in utero infection is unknown, most evidence points to transmission in the latter stages of gestation in the majority of live born infants (Brouwers, Moss, Wolters and Schmitt, 1994). However, transmission has been documented in the first trimester of gestation based on finding the HI virus in aborted foetuses (Lachman, 1998).

Transmission of HIV during the birthing process is defined by a negative culture and polymerase chain reaction (PCR) assay in infants within the first 48 hours of life and then a positive culture and PCR assay after 48 hours and up to 90 days after birth. Factors associated with transmission of the virus during the birthing process include maternal viral load in both the bloodstream and in vaginal secretions (Ioannidis *et al.*, 2004), mode of delivery, trauma, the duration of ruptured membranes and placental factors such as abruption or co-infections (Cohan, 2003).

HIV can also be transmitted from infected mothers to their infants through breastfeeding. However, although breast milk contains the HI virus, transmission and subsequent infant infection is not absolute dependent on a number of criteria. According to Coutsoudis (2005), strong evidence has been noted that women with a higher viral load, those who exhibit severe disease, those who are newly infected, those with breast pathology and

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those who have breastfed their infants for more than 6 months have a greater potential to transmit the virus to their infants via breastfeeding (Coutsoudis, 2005). Although it is recommended that women with HIV should not breastfeed their infants and should use alternative meal replacements, the WHO acknowledges that this recommendation may not be possible or applicable for all women (Newell, 2004). This would be especially true for women living in resource poor countries, who may not have access or be able to afford meal replacements. In addition, it has been noted that breastfeeding is especially important to the survival and development of children in developing nations as a greater number infants die annually due to malnutrition than the number of children who become infected with HIV each year (Coutsoudis, 2005). Therefore, international guidelines suggest that women who are faced with situations where it would be unaffordable, unsustainable and unsafe to use replacement feeding, should resort to exclusive breastfeeding for a maximum of 6 months (Newell, 2004).

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Some studies suggest that the timing of HIV transmission affects the rate of neurodevelopment. A study by Smith et al (2000) suggested that those infected in the early stages of development (defined as: diagnosed with HIV in the first 48 hours of life) displayed increasingly and significantly lower scores than those infected late (defined as having a negative HIV result in the first 48 hours of life and then a positive result thereafter). However, the authors acknowledged that their results should interpreted with caution since the majority of the early infected group were exposed to antiretroviral prophylaxis which had failed to prevent transmission and their subsequent poor

developmental performance was possibly a sequela to prophylaxis failure (Smith R *et al.*, 2000).

Similar findings were also reported by McGrath et al (2006) who reported that infants who tested positive in the first 21 days of life had poorer developmental performance scores than those who were diagnosed as being HIV positive later in life due to breastfeeding. The authors reiterated the conclusions made by Smith et al (2000) who suggested that early interference in the development of the CNS results in greater abnormalities (McGrath, Fawzi, Bellinger, Robins, Msamanga, Manji and Tronick, 2006).

It would appear that exposure to the HI virus during gestation does not affects the clinical course of the disease in the infant (Brouwers *et al.*, 1994). Studies on the neurodevelopment of uninfected children born to HIV infected mothers show that the performance of children exposed to HIV in utero is comparable to children born to uninfected women (Belman, Muenz, Marcus, Goedert, Landesman, Rubinstein, Goodwin, Durakot and Willoughby, 1996, Msellati *et al.*, 1993)

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2.1.4 Prevention of vertical transmission

It can be said that the epidemiology of HIV in children is essentially the epidemiology of HIV infection among childbearing women (Brown and Lourie, 2000). As the number of HIV infected women has increased, consequently so has the problem of paediatric AIDS.

The use of antiretroviral therapy in pregnancy has reduced the number of vertically infected children in developed nations (Cohan, 2003, Lachman, 1998, Peters, Liu, Dominguez, Frederick, Melville, Hsu, Ortiz, Rakusan, Gill and Thomas, 2003, Spiegel and Bonwit, 2002). In addition, the institution of voluntary counselling and testing for HIV has led to better detection of children who may be infected with HIV. The use of Caesarean-section mode of delivery and antiretroviral therapy has led to an overall reduction of the number of infected children in many developed countries (Spiegel and Bonwit, 2002). Reports suggest that Nevirapine (an antiretroviral drug), administered at the time of delivery to the mother and one dose given to the baby within 72 hours of birth results in a 47% reduction in viral transmission (Saloojee and Violari, 2001).

Efforts to reduce transmission of HIV from mothers to their infants have been put in place in a number of centres in the South Africa. Over time, these strategies will reduce the number of perinatally infected children in this country. Presently, many sectors of society still do not have access to these regimens due to resource constraints within the national department of health (www.usaid.gov, 2003).

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2.1.5 Diagnosis

Early diagnosis is extremely important in the management of infants and children infected with HIV. By identifying children who are infected, it is possible to institute early prophylactic and antiretroviral regimens and thus reduce morbidity and mortality associated with HIV infection.

At the start of the epidemic, diagnosis was hampered by the presence of maternal antibodies in infant blood. This meant that a period of uncertainty regarding HIV status lasting up to two years would sometimes follow the birth of a child (Sherr, 1999). Recently, the use of sophisticated techniques such as polymerase chain reaction tests (PCR) allows for more rapid and definitive diagnosis of HIV in newborns. Using this technique, nearly 50% of all infected infants can be diagnosed in the first few days of life, 90% by 3 months and nearly 100% by 6 months of age.

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2.1.6 Disease progression

The latency period between infection and the first signs of HIV disease in vertically infected children varies among HIV infected children. Children who are infected by vertical transmission seem to fall into two broad categories in terms of illness progression. The first group includes those who are symptomatic at birth and become ill with opportunistic infections early in life, generally before the first year (Gay *et al.*, 1995). The second group of children are those who remain relatively well, only showing symptoms later (Mitchell W, 2001, Sherr, 1999). According to Brouwers et al (1994), the age at which symptoms occur is an important prognostic factor for mortality and may predict the occurrence of neurological deficits (Brouwers *et al.*, 1994).

2.1.7 Disease classification

There are two systems available that classify the stages of HIV infection in children viz. the Centre for Disease Control (CDC) and the World Health Organisation (WHO)

systems. The CDC based in the United States developed a classification system to categorise children with HIV infection based on immunological status and clinical status. Immunological categories (numbered 1 to 3) reflect age specific CD4 cell count levels and clinical categories (labelled N, A, B or C) are based on signs, symptoms or diagnoses associated with HIV infection (Bankaitis, 1998).

The WHO clinical case definition of AIDS in children is based on both clinical and epidemiological information. Children are classified into one of three stages (I, II or III). Problems with the WHO definition are that many conditions are not clearly defined and some common conditions are not considered (Eley, 2004). As a result, the South African National Department of Health has adopted a modified version of the WHO clinical staging system that addresses these issues.

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2.2 Manifestations of HIV Infection in children

2.2.1 Immunocompromise

HIV causes a wide spectrum of illnesses in children ranging from those who present with no symptoms to those with severe illness depending on the degree of immune system dysfunction. AIDS represents the most severe stage of HIV infection. Without antiretroviral medication, the patients' immune system is not able to suppress or eliminate the replication of HIV. The continuous production of HIV eventually overwhelms the patients' immune system leading to progressive immunodeficiency and

eventually AIDS. Infants have an immature immune system and thus have much higher viral loads during the acute infection period than adults which leads to the destruction and depletion of CD4 cells (Spiegel and Bonwit, 2002).

Immunocompromised children are subject to a variety of opportunistic infections including viral and bacterial infections. A South African study investigating infectious episodes in children found a high incidence of bacterial infections in HIV infected children, particularly Streptococcus Pneumoniae which was the predominate pathogen isolated on blood culture (Westwood, Eley, Gilbert and Hanslo, 2000).

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2.2.2 Opportunistic infections of the CNS

Non-congenital opportunistic infections of the CNS are rare in infants and young children. However, these infections should be considered in individuals with severe immune suppression as a potential cause of abnormal neurological presentations (Wolters and Brouwers, 1998). According to Mintz (1998), fungal infections, parasitic lesions and viral infections usually present with signs such as chronic headache, malaise, behavioural problems and neurological decline or focal neurological signs depending on its location within the CNS (Mintz, 1998).

A definitive diagnosis is usually required prior to starting treatment for opportunistic infections of the CNS. These include reviewing radiological and computerised images of the CNS, CSF microbiologic analysis and in some instances, brain biopsy (Mintz, 1998).

2.2.3 HIV infection of the CNS

The pathological changes that take place in HIV infected children are widespread. Evidence suggests that not only does HIV directly infect the brain, but also affects the spinal cord and peripheral nerves resulting in developmental dysfunction. This evidence is based upon the findings of a number of authors who isolated the virus in the brains; cerebrospinal fluid and spinal cords of HIV infected children with neurological symptoms (Wolters and Brouwers, 1998). In addition, Computerised Tomography (CT) scans and Magnetic Resonance Imaging (MRI) of the brain has shown variable degrees of abnormalities ranging from cerebral atrophy to ventricular enlargement, widened sulci and bilateral symmetrical calcification of the basal ganglia and frontal white matter in children infected with HIV (Mintz, 1998, Wolters and Brouwers, 1998). Other findings, such as autopsy reports and brain biopsies of children infected with HIV have revealed that neurological deficits could be due to mineralisation of blood vessels in the brain, calcific deposits; diffuse white matter astrocytosis and the presence of inflammatory exudates. In addition, motor deficits have been be attributed to corticospinal degeneration and vacuolar myelopathy (Wolters and Brouwers, 1998). Neurological deficits were previously thought to be caused by a process similar to white matter degeneration, however, recent studies indicate that neuronal injury is becoming increasingly recognised as the mechanism responsible for encephalopathy (Mintz, 1998).

Several studies have related the severity of neurological abnormalities in HIV infected infants with disease stage (Belman *et al.*, 1996, Drotar *et al.*, 1997, Msellati *et al.*, 1993). Belman et al (1996) reported that children with AIDS defining diagnoses experienced

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more severe and persistent neurological abnormalities than those without AIDS defining clinical conditions (Belman *et al.*, 1996). This suggests a two-fold effect of HIV infection on development, viz., the adverse impact of chronic illness and the effects of increased viral replication within the CNS.

In addition, it appears that timing of the insult is equally important. Neurological insults affecting the CNS of foetuses at the early stages of development are likely to cause severe problems. In HIV infected children, poorer developmental outcome has been reported in infants who were infected early in gestation compared to those infected later (Smith R *et al.*, 2000).

Damage to the CNS gives rise to secondary changes. Since HIV infection results in such widespread damage to the CNS, it may bear close resemblance to the commonly described impairments seen in children with cerebral palsy. Recent studies suggest that muscle weakness has been identified as a major problem which may be a cause of dysfunction in children with cerebral palsy (Damiano and Abel, 1998, Dodd, Taylor and Graham, 2003). A number of studies have described the musculoskeletal problems in children with cerebral palsy (Cusick and Stuberg, 1992, Damiano and Abel, 1998) and minimisation of these problems have formed a major basis of physiotherapeutic interventions.

The Paediatric Neurology/Psychology Working Group, a subsidiary of the Paediatric AIDS Clinical Trials Group (PACTG), established a list of criteria needed to establish the

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diagnosis of HIV associated encephalopathy (Mintz, 1998). Children who are neurologically normal at baseline are required to meet one criterion and children with neurological dysfunction at baseline are required to fulfil two criteria within the following domains:

- Impaired brain growth, as determined by two successive serial head circumference measures in the absence of other aetiologies
- Decline in cognitive functioning, which is defined as a drop of two Standard Deviations (SD) on a standardised developmental assessment for children 0 to 3 years of age and a drop of one or more SD on a standardised intelligence test for children older than three.
- A loss of previously attained cognitive or language milestones, confirmed by standardised testing, are also considered.
- Progressive motor milestone loss or deterioration of previously attained motor skills.

In addition, if any two of the following signs are present, the child may also be considered to have HIV- associated encephalopathy:

- Diffuse or symmetrical loss of strength
- Diffuse or symmetrical abnormalities of tone and
- Diffuse, symmetric and pathologically increased deep tendon reflexes

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2.2.4 HIV and developmental delay

One of the most common outcomes of brain involvement in HIV infected children is the marked delay of developmental milestones or the actual loss of milestones previously acquired by the infant or child (Byers, 1989).

2.2.4.1 Prevalence

Varying prevalence rates have been reported for developmental delays in children with HIV infection. Estimates suggest that between 25 to 90% of children with HIV infection exhibit development delays or disorders (Layton and Davis-McFarland, 2000). The prevalence of developmental delays in a recent South African study was reported to be 40% (Potterton and Eales, 2001).

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2.2.4.2 Cognitive delay

A number of studies have documented the effect of HIV infection on neurodevelopment by comparing HIV infected children to uninfected children and to children who were exposed to the HI virus in utero but later tested negative.

Studies conducted by Aylward et al (1992) and Nozyce et al (1994) and Chase et al (2000) found that HIV infected children scored significantly lower mental development index scores, as measured by the BSID, compared to HIV negative and HIV exposed children (Aylward, Butz, Hutton, Joyner and Vogelhut, 1992, Chase C *et al.*, 2000, Nozyce *et al.*, 1994). Similar findings were reported by Levenson et al (1992) who

detected "below average" cognitive functioning in a sample of HIV infected children using the McCarthy Scales of Children's Abilities (Levenson, Mellins, Zawadzki, Kairam and Stein, 1992). In addition, Levenson et al (1992) also reported that children with added neurological impairments performed significantly worse (Levenson *et al.*, 1992). Cognitive performance was unrelated to gender, ethnicity and drug exposure thus supporting the suggestion that developmental delays are attributed to effects of the virus on the CNS.

Nozyce et al (1994) reported that HIV positive children without a CDC defined diagnosis of AIDS showed similar developmental outcomes to uninfected children exposed to the virus in utero, and HIV negative children of comparable social backgrounds (Nozyce *et al.*, 1994). These findings were also reported by Chase et al (1995) who confirmed comparable mental development in the HIV infected and uninfected children exposed to HIV in utero. However their findings indicated that HIV infected infants performed worse as they got older (Chase C, Vibbert, Pelton, Coulter and Cabral, 1995).

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An African perspective is given by Drotar et al (1997) who were able to assess the neurodevelopment of children un-confounded by the risk factor of maternal drug addiction (Drotar *et al.*, 1997). They concluded that even though HIV infected infants exhibited an earlier onset of mental impairment than uninfected infants did, their cognitive skills were less powerfully affected than their motor performance. In addition, their visual recognition memory, as measured by the Fagan test of infant intelligence, was

not adversely affected suggesting that information-processing abilities are spared from HIV related deficits (Drotar *et al.*, 1997).

2.2.4.3 Motor delay

Impaired motor function is a frequent manifestation of paediatric HIV disease (Wolters and Brouwers, 1998). HIV infected children have been reported to have lower motor developmental scores on standardised tests in a number of studies (Bruck *et al.*, 2001, Chase C *et al.*, 2000, Nozyce *et al.*, 1994). Children with HIV infection of the CNS may display varying degrees of impairments in the following motor areas: fine motor skills, gross motor skills and gait. In addition, neurological signs like hypotonia, hypertonia and spasticity may also occur either globally or unilaterally as a result of mass lesions or infarcts resulting in hemiplegia (Mintz, 1998).

Msellati et al (1993) examined a group of HIV infected infants from Rwanda and compared them to 136 uninfected infants using a self-developed neurodevelopmental assessment test (Msellati *et al.*, 1993). In this and in other studies, HIV infected infants scored persistently lower than children born to HIV negative mothers and to uninfected children who had been exposed to HIV in utero (Gay *et al.*, 1995, Msellati *et al.*, 1993, Nozyce *et al.*, 1994). An important finding from this study was the fact that neurodevelopmental delay in this sample of HIV infected children was directly attributable to gross motor delay.

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Smith et al (2000) compared infants who had been infected with HIV during early gestation with those who had been infected later in gestation. On examination of their motor performance, the authors concluded that the group of children, who had been infected early, demonstrated a notable decline in motor functioning over time (Smith R *et al.*, 2000).

2.2.4.4 Language delay

The prevalence of language delay in HIV infected children has been reported in a number of studies (Bruck *et al.*, 2001, Copeland *et al.*, 1999, Wolters, Brouwers, Moss and Pizzo, 1995). In these studies, HIV infected children consistently exhibited worse performance than HIV negative children did. Those with severe abnormalities noted on CT brain scans were shown to have poorer overall language function which suggests that HIV infection of the CNS is related to abnormal language outcomes (Wolters *et al.*, 1995). In addition, Wolters et al (1995) reported that HIV infection affects expressive language development to a greater extent than receptive language skills (Wolters *et al.*, 1995).

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Coplan et al (1998) compared the language development of young HIV infected children to a group of uninfected infants using the Early Language Milestone Scale Second Edition (ELM-2) (Coplan *et al.*, 1998). In this study, most participants exhibited deterioration in language development over time. However, three participants exhibited improved language outcomes after initiation of antiretroviral therapy suggesting that developmental language delay may be reduced by the early introduction of antiretroviral medication.

2.2.4.5 *Behavioural deficits*

HIV infection may affect the behavioural functioning of children directly and indirectly. Direct behavioural effects are associated with the impact of HIV and opportunistic infection on the CNS and indirect effects refer to the psychosocial issues that goes along with living with the disease (Mintz, 1998, Wolters and Brouwers, 1998). Other factors such as drug toxicities, electrolyte disturbances, genetic predisposition to behavioural problems and cortical carcinomas with increased intracranial pressure also need to be considered (Mintz, 1998). Some HIV infected children may experience symptoms of attention deficit disorder (Brown and Lourie, 2000, Layton and Davis-McFarland, 2000). Again, other aetiological factors need to be considered. Attention deficit disorders with hyperactivity are quite prevalent in children with progressive encephalopathy but hyperactivity is often replaced with apathy and lack of energy in the end stages of disease (Mintz, 1998).

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2.3 *Treatment and rehabilitation*

Despite the increasing use of antiretroviral therapy, prophylactic regimens remain an important adjunct in the care of children infected with HIV (Bernadi, Thorne, Newell, Giaquinto, Tovo and Rossi, 2000). In addition, the medical profession has advocated for a multidisciplinary approach to the care and management of HIV infected children.

2.3.1 Prophylactic regimens

Prophylactic drugs are administered to immunocompromised children to decrease the incidence and severity of opportunistic infections. As a result, the child may avoid the adverse effects of prolonged or recurrent hospital admissions. Furthermore, symptom alleviation may also be associated with an improvement in psychological and developmental outcome (Sherr, 1999). Common prophylactic regimens administered to children infected with HIV include drugs that protect against Pneumocystis Carinii Pneumonia (PCP) (Bernadi *et al.*, 2000) and prophylaxis for fungal and bacterial infections.

The effect of multivitamin and micronutrient supplementation in children infected with HIV has also been debated. Micronutrients play an important role in immune function and thus play a vital role in children infected with HIV (Garg and Miller, 1999). Support for the use of vitamin supplementation in these children has demonstrated that vitamin A supplementation was beneficial in reducing the severity of diarrhoeal episodes amongst HIV infected children in South Africa (Coutsoudis, Bobat, Coovadia, Kuhn, Tsai and Stein, 1995). A reduction in disease severity has several positive outcomes, including decreasing episodes of immobility and thus enhancing opportunities for development.

2.3.2 Antiretroviral therapy

Antiretroviral drugs inhibit the progression of HIV by suppressing the replication of the virus, thereby reducing morbidity and mortality in children infected with HIV (Mueller and Pizzo, 1998). Five main classes of antiretroviral agents have been identified; these

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include nucleoside reverse transcriptase inhibitors (NRTI's) and non-nucleoside reverse transcriptase inhibitors (NNRTI's). Both target the reverse transcriptase enzyme. The third class, protease inhibitors (PI), target the viral protease enzyme (Mueller and Pizzo, 1998, Saloojee and Violari, 2001, Spiegel and Bonwit, 2002). The other two classes include fusion inhibitors and integrase inhibitors. Current treatment regimens usually include NRTI's in combination with a PI and/or a NNRTI (Gisslen and Hagberg, 2001).

It is recommended that all infants under 12 months of age, infected with HIV, be treated with antiretroviral agents regardless of clinical, immunological or virological status (Spiegel and Bonwit, 2002). However, in most settings, the decision to start HAART is based on clinical disease stage, viral load and CD4 percentage data (Sharland, Gibb and Giaquinto, 2000). The age of a child is very important when considering starting therapy based on viral load or CD4 percentage. For children over one year of age, it is arbitrary to take any cut-off as a recommendation to start therapy as both viral load and CD4 percentage represents a spectrum of risk and the positive predictive value of either marker for mortality are low. However, according to Sharland et al (2000), a CD4 percentage of less than 15% and a viral load of more than 100 000 represents a very significant mortality risk (Sharland *et al.*, 2000).

In asymptomatic infants, current markers are not specific enough to predict who may remain asymptomatic and who will develop more rapid progressive disease (Sharland *et al.*, 2002). Infants have a substantial risk of developing AIDS even with high CD4 values. The limited experience of treatment initiated in the first months of life leading to

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undetectable viral loads and apparently normal immune function supports the idea of treating infants as early as possible (Sharland *et al.*, 2002).

The Western Cape Department of Health has developed modified guidelines in accordance with the World Health Organisation (WHO) guidelines to assist clinicians with the decision of starting HAART in children. The criteria for starting antiretroviral therapy in children are:

- Classification as WHO stage II or III, or
- a CD4 percentage of less than 20% if under 18 months of age, or less than 15% if older than 18 months of age (irrespective of disease stage).

Support for the early initiation of antiretroviral treatment are confirmed by reports that suggest that it delays the progression of HIV infections to AIDS, improves growth, reconstitutes the immune system and reduces HIV replication (Sharland *et al.*, 2002). Early initiation of HAART has been shown to suppress viral activity to such an extent that all clinical and immunological manifestations of infection are avoided (Hainaut, Peltier, Gerard, Marissens, Zissis and Levy, 2000). However, immune function may not always be associated with markers such as CD4 count or viral load in patients at different stages of highly active antiretroviral therapy. Clerici et al (2002) demonstrated that CD4 and CD8 cell counts remained unchanged in naïve and long term HAART patients over a two year periodic and CD4 cell counts increased and viral loads diminished in short term HAART patients (Clerici, Seminari, Maggiolo, Pan, Migliorino, Trabattoni, Castelli, Suter, Fusi, Minoli, Carosi and Maserati, 2002).

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Findings of a retrospective study on 58 HIV infected children who developed Progressive Encephalopathy (PE), concluded that initiating antiretroviral therapy before the onset of neurological symptoms delayed the presentation of PE. In addition, 72% of children who had developed PE experienced neurological improvement soon after the initiation of HAART (Sanchez-Ramon *et al.*, 2003).

In a review of the effects of antiretroviral therapy effects on CNS HIV infection, Gisslen and Hagberg (2001) concluded that HAART regimens are responsible for improved cognitive outcomes and lowered viral loads in adults who are infected with HIV (Gisslen and Hagberg, 2001). Mueller and Pizzo (1998) also conducted a review of current antiretroviral agents used in paediatric HIV infection (Mueller and Pizzo, 1998). The authors acknowledge the efficacy of using Zidovudine (ZDV) in treating encephalopathy as it is well established that ZDV penetrates the blood brain barrier more effectively than other agents do. This is supported by a study in which significant improvements in cognitive functioning, gait, coordination and language were noted in children with and without encephalopathy when using continuous infusion ZDV (Pizzo, Falloon, Balis, Murphy, Moss, Wolters, Brouwers, Jorosinski and Rubin, 1988). Studies indicate that Didanosine (ddI), when used alone or in combination with ZDV, also results in a marked and sustained increases in CD4 counts, decreased p24 antigen levels, improved weight gain in children and marked improvement in psychometric tests (Mueller and Pizzo, 1998). Agents such as Lamivudine (3TC), Stavudine (d4T), NNRTI's and some PI's although, having a positive effect in reducing viral load, have not been proven to have

University of Cape Town

any efficacy in treating encephalopathy as they do not penetrate the blood brain barrier effectively (Mueller and Pizzo, 1998).

It is important to monitor the health status of children on HAART to assess the child's response to antiretrovirals, to identify adverse events and to identify problems with adherence. Antiretroviral treatment has several limitations, including viral breakthrough, resistance and treatment failure (Saloojee and Violari, 2001). Strict adherence is essential for achieving and maintaining undetectable viral load in the blood and avoiding the incidence of drug resistance and viral mutations (Spiegel and Bonwit, 2002). Poor social circumstances, unpalatable paediatric formulations and side effects of the medication all compound adherence issues. Children are dependent on their caregivers to administer medication and psychosocial factors or illness within the family may affect adherence.

University of Cape Town

2.3.3 The role of physiotherapy

Children who are infected with HIV are at risk for neurodevelopmental problems due to the direct effect of the virus on the CNS (Wolters and Brouwers, 1998). The clinical presentation of HIV infection varies according to the stage of the disease process (Nozyce *et al.*, 1994). Deficits such as delayed milestones or severe neurological abnormalities such as spasticity may or may not occur in the presence of opportunistic infections. Severe neurological dysfunction has been associated with high mortality rates (Llorente, Brouwers, Charurat, Magder, Malee, Mellins, Ware, Hittelman, Mofenson, Velez-Borras and Adeniyi-Jones, 2003). Therefore, monitoring the progression of neurological abnormalities is important in the management of children infected with HIV.

In fact, it has been suggested that physiotherapists, because of their specific knowledge, play an active role in monitoring the neurodevelopmental outcome of this high-risk population by conducting standardised developmental tests (Wolters and Brouwers, 1998).

In many developed nations, the multidisciplinary approach to the management of HIV infected children is advocated. A number of studies have identified the role of physiotherapists in the treatment of children infected with HIV. There is evidence supporting the use of chest physiotherapy techniques in HIV infected children who have chest infections (Plebani, Pinzani, Startari, Brusa and Padoan, 1997). There have also been studies documenting the effects of physiotherapy based techniques such as massage (Shor-Posner, Hernandez-Reif, Miguez MJ, Quintero, Baez, Perez-Then, Soto, Mendoza, Castillo and Zhang, 2006), aerobic exercises prescription (Nixon, O'Brien, Glazier and Tynan, 2005) and progressive resisted exercises (Robinson F P, Quinn and Rimmer, 2007) in HIV infected individuals.

It has been suggested that a major cause of disability or impairment in HIV infected individuals can be addressed by physical activity and exercise (O'Brien, Nixon, Glazier and Tynan, 2004). Results from a systematic review on the effects of aerobic exercise in HIV infected adults showed positive outcomes for cardiopulmonary fitness (Nixon *et al.*, 2005). Another report showed that a performing progressive resisted exercise or a combination of progressive resisted and aerobic exercise was safe and could lead to improvement in cardiopulmonary fitness, body weight and body composition in

University of Cape Town

medically stable adults with HIV (Robinson F P *et al.*, 2007). However, results of this review have limited generalisability for women and children since most of the studies reviewed were conducted with adult, male participants. Studies on strengthening in children with disabilities have however shown positive outcomes in other populations, uninfected with HIV. Strength training has been show to improve upper limb strength in children with cystic fibrosis (Orenstein, Hovell, Mulvihill, Keating, Hofstetter, Kelsey, Morris and Nixon, 2004) and has improved functional outcomes in children with cerebral palsy (Damiano and Abel, 1998, Liao, Liu, Liu and Lin, 2007). Based on the aforementioned studies, it can be concluded that strength training for children with HIV may also be beneficial, however further studies should be conducted considering the limited evidence.

Although physiotherapists, occupational therapists and other rehabilitation professionals have long been on the forefront in providing services to children with neurological problems, such as cerebral palsy, minimal attention has been given to identifying the role of therapists in the rehabilitation of children with CNS dysfunction caused by HIV (Sherr, 1999).

Children with evidence of delayed motor milestones and/or neurological symptoms are often referred to physiotherapists for treatment. Physiotherapy for the child with neurological impairment often follows a neurodevelopmental (NDT) approach. The principles underlying this approach include the inhibition of abnormal tone and facilitation of functional motor patterns and automatic reactions (Hinds-Harris, 1991). However, the role of NDT in the treatment of children with deficits due to HIV infection

University of Cape Town

has not been established. It is therefore important that research is conducted to establish the role and efficacy of paediatric physiotherapy in the long term management of children with HIV (Potterton and Van Aswegen 2006). Knowledge of factors associated with HIV infection of the CNS in children may assist physiotherapists in planning treatment programmes, setting goals and organising other appropriate services. Physiotherapy can be used to teach parents skills regarding appropriate handling, feeding and developmental motor activities.

2.4 *Additional risk factors for developmental delay in HIV infected children*

Unless one does a prospective case-control study and thereby controls for all other variables, poor performance can be attributable to other factors apart from HIV infection of the CNS. The influence of biological, psychosocial and environmental variables on the development of children with HIV cannot be ignored.

Development is a complex interactive process that is influenced by maturation of body systems as well as the interaction of the child with his environment (Burns and Higgins, 1996). Contemporary theories suggest that development of motor skills is based on the resultant interaction of many systems that contribute to control motor behaviour (Horak, 1991). These systems include the interaction of both the internal and external environments to produce and refine movement. The neuronal group selection theory suggests that development results from processes of selection and variation. Early development is characterised by primary variability of motor behaviour facilitating the

University of Cape Town

development of neuronal circuitries, which enables selection. Secondary variability occurs on exposure to various experiences enabling adaptation of motor control (Hadders-Algra, 2000). Neurological insults occurring in the pre-, peri- and post-natal periods of childhood may result in the disruption of normal development, leading to variable patterns of childhood disability.

2.4.1 Biological risk factors

The developing CNS of the foetus is vulnerable to damage by factors present in the uterine environment. Prenatal factors such as maternal substance abuse (Messinger, Bauer, Das, Seifer, Lester, Lagasse, Wright, Shankaran, Bada, Smeriglio, Langer, Beeghly and Poole, 2004, Stewart, Richardson and Olson, 1996) and infections during pregnancy (Benedetto, Tibaldi, Marozio, Marini, Masuelli, Pelissetto and Sozzani, 2004, Munro, Trincado, Hall and Rawlinson, 2005) have all been associated with variable health and developmental outcomes in children. In addition, factors relating to the perinatal period such as premature delivery and birth asphyxia (Bartlett and Fanning, 2003, Carli, Reiger and Evans, 2004, Goyen and Lui, 2002) have also been reported to result in poor developmental functioning. Postnatal risk factors for developmental delay include the impact of infections, malnutrition and traumatic head injury.

2.4.1.1 Maternal substance abuse

Intravenous drug use has been described as a major risk factor for maternal HIV infection in the United States (Brown and Lourie, 2000, Drotar *et al.*, 1997). Maternal drug use has

University of Cape Town

also been cited as a possible reason for poor developmental outcome in children born to HIV infected drug using mothers (Drotar *et al.*, 1997). This is assumed to be due to the direct effect of the drug on the developing CNS as well as the potential adverse effects on child-caregiver interaction and the child's environment (Stewart *et al.*, 1996).

Examination of the literature regarding the effects of prenatal drug exposure on infant development, suggests variable developmental outcomes depending on the drug of choice (Stewart *et al.*, 1996). Frank et al (2002) concluded that variables such as low birth weight, gender and being in the care of someone other than biological parents increased the risk for poor developmental outcomes in cocaine-exposed infants (Frank, Jacobs, Beeghly, Augustyn, Bellinger, Cabral and Heeren, 2002).

Although intravenous drug use is not an associated risk factor for HIV infection in South African women, alcohol abuse during pregnancy is reported to be responsible for many of the adverse developmental outcomes in high-risk populations in South Africa (Adnams, Lavies, Kodituwakku, Kitching, Viljoen and May, 2004). Excessive alcohol consumption during pregnancy may result in a condition known as Foetal Alcohol Syndrome (FAS). Manifestations of FAS include cognitive delay and central nervous system defects (Stewart *et al.*, 1996). Therapists involved in evaluating the neurodevelopmental status of children with HIV need to be aware that poor performance on cognitive tests may be attributed to maternal abuse of alcohol during pregnancy.

2.4.1.2 Maternal malnutrition

Varying degrees of malnutrition are common amongst population groups living in extreme poverty. When one considers the epidemiology of HIV infection in South Africa,

University of Cape Town

it is evident that HIV prevalence is higher amongst individuals who originate from lower socio-economic backgrounds. In addition, mothers with advanced disease may experience conditions such as severe wasting syndrome and chronic diarrhoea, which contribute to inadequate nourishment for the developing foetus. As a result, maternal malnutrition may be a contributing factor for adverse neonatal outcomes. Moderate malnutrition may result in small size for gestational age and small brain size whereas severe malnutrition may result in infant death. Malnutrition during pregnancy has also been correlated with lower IQ scores and behavioural deficits in children of school-going age (Mawn and Kammerer, 1999).

2.4.1.3 Prematurity and low birth weight

Prematurity and low birth weight has been associated with poor cognitive and motor outcomes in children. Furthermore, long-term studies indicate that the incidence of disabilities is higher in this group of infants (Goyen and Lui, 2002). According to Facchinetti and Ottolini (2004), high levels of stress experienced during pregnancy have been associated with premature delivery (Facchinetti and Ottolini, 2004). One can assume that HIV infected pregnant women may experience high levels of anxiety especially when a positive diagnosis for HIV infection is established during pregnancy. Recent studies have demonstrated that increased stress and anxiety during pregnancy is associated with lower developmental scores in infants at 8 months (Huizink, Robles de Medina, Mulder, Visser and Buitelaar, 2003). Compared to uninfected women, HIV infected pregnant women are at higher risk for adverse outcomes during pregnancy including low birth weight and prematurity (Fawzi and Msamanga, 2004). This is

University of Cape Town

supported in a study by Mwanyumba et al (2001) who reported that HIV infected women in Kenya were more likely to have low birth weight babies (Mwanyumba, Claeys, Gaillard, Verhofstede, Chohan, Mandaliya, Ndinya-achola, Bwayo and Temmerman, 2001).

Mothers who smoked during pregnancy or were undernourished are more likely to give birth to an infant of lower birth weight (Papalia, Olds, Feldman and Gross, 2001). As discussed previously, a strong association has been established between severe HIV associated diarrhoeal disease and malnutrition. Studies have shown that children who weigh less than 2500g at birth are at risk for cognitive and motor delay (Hediger, Overpeck, Ruan and Troendle, 2002). A child's prospects for overcoming the disadvantage of being born at a lower than normal birth weight depends on several interacting factors. Family income, mothers educational level, older maternal age and marital status all seem to play a major role in whether or not a child who was born with a lower than average birth weight will be developmentally challenged (Hediger *et al.*, 2002).

University of Cape Town

2.4.1.4 Birth trauma

Birth asphyxia is major cause of disability in children and these infants are likely to develop cerebral palsy (Couper, 2000). The range of disability may vary from mild to severe dysfunction. Clinical signs and symptoms commonly used to define birth asphyxia include low APGAR scores and low cord pH (Wu, Backstrand, Zhao, Fullerton and Johnston, 2004). Examining these factors is important when considering the

developmental status of all children including those infected with HIV. Wu et al (2004) reported a higher incidence of birth asphyxia amongst lower socio-economic and black ethnic groups in the United States (Wu *et al.*, 2004). One can therefore conclude that children born to HIV positive mothers may be at additional risk for adverse developmental outcome associated with oxygen deprivation during labour due to the high prevalence of complicated labour in the general population.

2.4.1.5 Impact of malnutrition

Proper nutrition is essential for CNS development and functioning. Studies have shown that moderate to severe protein-energy malnutrition during early infancy is related to significantly lower cognitive, social and behavioural skills (Mawn and Kammerer, 1999). The majority of children infected with HIV in this country are from poor socio-economic backgrounds. In addition, mothers are discouraged from breastfeeding their infants as this practise facilitates transmission of the virus. These factors put HIV infected children at risk for experiencing malnutrition early in life, a factor that is associated with worse clinical outcomes.

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2.4.1.6 Impact of chronic illnesses

Children infected with HIV are susceptible to multiple and recurrent episodes of infections due to their weakened immune systems. Chronic illness experienced during infancy has been reported to compromises gross motor and language development in children. Illness such as heart disease (Feldman, Dollaghan, Campbell, Colborn, Janosky, Kurs-Lasky, Rockette, Dale and Paradise, 2003, Wray and Radley-Smith, 2004); chronic

otitis media (Campbell, Dollaghan, Rockette, Paradise, Feldman, Shriberg and Sabo, 2003) and severe forms of chronic lung disease (Bohm and Katz-Salamon, 2003) have been implicated in predicting poor developmental outcomes.

The ability of a child to interact with his environment is an important determinant of development. Wray and Radley Smith (2004) suggest that impaired physical abilities associated with children who have heart disease results in poor developmental performance (Wray and Radley-Smith, 2004). However, Campbell et al (2003) have suggested that the impact of chronic illness extends beyond the scope of the biological limitations imposed by a specific disease (Campbell *et al.*, 2003). While otitis media may cause hearing loss and consequently delayed language development, the study by Campbell et al (2003) also implicated the collective effect of confounding variables including maternal education.

University of Cape Town

2.4.2 Psycho-social risk factors

Different social environments can act as either a rate-limiting factor to inhibit infant development or as a factor to promote advancement (Abbot and Bartlett, 1999). Evidence of this is seen in studies that examined the impact of cultural influence on aspects of development (Irwin-Carruthers, 1987, Kolobe, 2004). Factors that may place an infant at risk for developmental delay include prolonged hospitalisation and poor caregiver-child relationships.

2.4.2.1 *Cultural practices*

The notion of the emergence of universal milestones within a specified time frame is a Western idea of development (Cintas, 1988). Cultural influences have been associated with variable developmental outcomes in families from diverse ethnicities (Middlemiss, 2003, Nelson, Yu, Wong, Wong and Yim, 2004). Studies have demonstrated that parental expectations and cultural care-giving practices have an important influence on motor development(Abbot and Bartlett, 1999). Although motor development seems to follow a virtually universal sequence, the rate at which it progresses is affected by environmental factors. The use of special handling routines such as bouncing and stepping exercises to strengthen babies' muscles in many African and West Indian cultures has been implicated as a factor resulting in the variation in age of motor milestone acquisition (Papalia *et al.*, 2001).

University of Cape Town

2.4.2.2 *Impact of hospitalisation*

Children infected with HIV often experience chronic illnesses that require frequent hospitalisation. Separation from the family and isolation may exacerbate developmental problems and places young children at risk for both short term and long term negative outcomes (Byers, 1989, Melnyk, 2000). The adverse effects of frequent and prolonged hospitalisation have been reported in a number of studies (Bonn, 1994, Melnyk, 2000, Shields, 2001). Admission to hospital can be at traumatic experience for a child due to factors within the physical environment, separation anxiety and stresses associated with the illness and medical procedures. Parental anxiety and separation during a child's

hospitalisation may indirectly affect development by limiting opportunities for quality interaction (Shields, 2001).

2.4.3 Socio-economic risk factors

Therapists involved in the care of children with HIV should be aware of the impact of environmental risk factors on the dynamics of child development (Stewart *et al.*, 1996). These include factors within the home environment and community setting.

2.4.3.1 Poverty and socioeconomic status

Children born into poverty are at greater risk for acquiring developmental problems than children born to middle or high socio-economic environments (Abbot and Bartlett, 1999). Many studies have shown that poverty places children at risk for negative health and social outcomes (Brunner, 1997, Duncan *et al.*, 1994, Petterson and Albers, 2001). This has been attributed to the co-occurrence of poverty and teen parenting, single parenting, marital distress, family dysfunction, and parental psychopathology that are all are associated with negative outcomes for children (Papalia *et al.*, 2001). In addition, the associated negative aspects of poverty such as increased stress have led to the conclusion that negative parenting is common amongst those from impoverished backgrounds (Middlemiss, 2003).

Many research studies have concluded that lower socio-economic status have a negative effect on childhood development (Barbarin and Khomo, 1997). Poverty and social stress

University of Cape Town

in infancy that continues into adulthood have been demonstrated to have biological effects that influence the development of degenerative diseases and poorer health outcomes (Brunner, 1997). Richter and Grieve (1991) demonstrated that, amongst other factors, a child's socio-economic environment is a significant predictor of his cognitive development toward the end of their first year of life (Richter and Grieve, 1991). Specific indictors, making up the profile of socio-economic status, such as lower education levels were associated with the unfavourable development of chronic diseases in adults from lower socio-economic status (van der Meer and Mackenbach, 1998). Amongst children, low socio-economic status has been linked to high rates of behavioural problems, low school achievement, community violence and substance abuse (Barbarin and Khomo, 1997).

The American Academy of Paediatrics published a paper in which it acknowledges that race, ethnicity, gender and socio-economic status can influence a child's health and development recommends that child health studies include critical social variables to enhance understanding (Committee on Pediatric Research, 2000).

University of Cape Town

2.4.3.2 The effects of the home environment

The physical and social aspects of the home environment are important factors influencing infant development (Abbot and Bartlett, 1999). Physiotherapists often conduct home visits as part of the evaluation process. This is done in recognition of the fact that factors within the home environment may influence outcomes related to independence and developmental progression. The evaluation of an infant's home

environment is mainly concerned with aspects such as quality of family interaction, safety and organisation of the physical environment and availability of resources and opportunities for stimulation (Case-Smith, 1998).

A safe home environment is thought to encourage motor and cognitive development by allowing the infant to explore his environment. Children living in areas that are considered to be unsafe or unhygienic may be prohibited from playing outside or on the floor (Lima, Eickmann, Lima, Guerra, Lira, Huttly and Ashworth, 2004). Children who are raised in areas that are regularly affected by crime are also less likely to spend time outdoors as mothers fear for their safety. As a result, certain cognitive and social skills development may be inhibited.

2.4.4 Assessing socio-economic status

The interaction between social and environmental factors may serve to either inhibit or facilitate childhood development. Social scientists have identified socio-economic factors that are considered to place children at risk for developmental dysfunction in the early years of life.

Socio-economic status is a term that is often used in social science research to describe the social and economic status of individuals or groups. Indicators such as social class, income, and material possessions are often used to derive indices of socio-economic status. Rao (1975) suggests that because social phenomena often have economic implications, social statistics may be regarded as socio-economic (Rao, 1975). The

University of Cape Town

indictors that contribute to defining socio-economic status vary amongst authors. They may include aspects such as inequalities in income distribution within society (Kennedy, Kawachi, Glass and Prothrow-Stith, 1998), level of education (van der Meer and Mackenbach, 1998), employment and unemployment (Rao, 1975), occupation, age and gender (Committee on Pediatric Research, 2000).

Policy makers, economists and social science researchers are all interested in measuring socio-economic status. However, because their objectives and interests in these measures are different, varied arrays of indictors are used to represent socioeconomic status. Health professionals are also interested in conducting research into this area because they realise that there is a link between child development and welfare (Barbarin and Khomo, 1997).

A variety of tools is available for use to measure socio-economic status. Most of these instruments are targeted for use among economists, which contain variables of interest for that particular profession. In South Africa, measures of poverty include the Poverty Datum Line, Minimum Living Level (developed by the Bureau for Market Research, UNISA) and the Supplementary Living Level (Developed by Statistics South Africa, 2000).

The lack of a quick, easy, valid and reliable tool for use in health research prompted the development of an instrument, which considers indicators of SES specifically applicable to childhood development and relevant to the situation of families in developing economies (Barbarin and Khomo, 1997). This instrument assesses the material well-being

University of Cape Town

and social resources of families using a set of observable indicators that are inversely related to poverty.

For the purpose of this study, the researcher constructed a questionnaire to document aspects reflecting socio-economic status. This was done because it was considered that an extensive battery of testing and questionnaires would be time consuming for participants and may cause fatigue. Since an objective of this study was to document the socio-economic status of the caregivers and in so doing, gain insight into the impact of SES variables on childhood development, a self-constructed questionnaire was considered adequate.

University of Cape Town

2.5 Assessing development

2.5.1 Developmental assessment tools

Physiotherapists are increasingly becoming involved in the assessment of infants at risk for developmental delay (Piper and Darrah, 1994). Therapists' knowledge of the normal progression of motor milestones is often used to identify children with delayed development. Although physiotherapists have traditionally assessed motor development, they have not relied on standardized assessment (Palisano, 1993).

Infant assessments may be subdivided into two categories, viz. criterion referenced tests and norm-referenced tests. Criterion referenced tests examines the quality of a child's

performance against a set of predetermined criteria (Burns and Higgins, 1996). Scores are interpreted on the basis of absolute criteria rather than on how others performed (Derstine, 1989). An example of a criterion-referenced test is the Gross Motor Function Measure (Russell, Rosenbaum, Gowland and Hardy, 1989).

Norm-referenced tests allows one to compare a child's test score to a score obtained from an assessment of a large representative reference group of other children of the same chronological age (Burns and Higgins, 1996). A reference group could be either a group of children without a disability or a group of children with a similar condition to the child being tested, for which norms have been obtained (Burns and Higgins, 1996).

Norm referenced tests may be further divided into two broad categories: functional assessments and general developmental scales. Functional assessments monitor specific areas of development e.g. motor development, language development and cognitive development. Examples include the Alberta Infant Motor Scale (Piper and Darrah, 1994), the Pre-School Language Scale-3 (Zimmerman, Steiner and Pond, 1992) and the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 1989). General developmental tests usually contain items of gross and fine motor performance, language, self-help, cognitive and personal-social development (Derstine, 1989). Examples include, the Bayley Scales of Infant Development, the Gesell Developmental Schedules, the Griffiths Developmental Scale and the Batelle Developmental Inventory.

University of Cape Town

2.5.2 The Bayley Scales of Infant Development Second Edition

In choosing an instrument to measure the neurodevelopment of children in South Africa, two tests were considered; The Griffiths Scale of Mental Development (Griffiths, 1970), and the Bayley Scales of Infant Development Second Edition (BSID II) (Bayley, 1993). The Griffiths was considered because it is widely used by developmental paediatricians in South Africa and has been proven by a number of authors to be a valid measure of performance among South African children (Alan, 1992, Bhamjee, 1991, Luiz, Foxcroft and Tukulu, 2004). However, The Griffiths is only available for use by psychologists and medical doctors who have undergone intensive training (Luiz *et al.*, 2004). The BSID II was therefore chosen because it is the assessment of choice in a number of studies investigating the development of children with HIV (Aylward *et al.*, 1992, Chase C *et al.*, 1995, Gay *et al.*, 1995, Mellins, Levenson, Zawadzki, Kairam and Weston, 1994). The second edition of the BSID II were developed by Bayley (1993) and normed on a population of normal, healthy American children between the ages of one and 42 months (Bayley, 1993). The scales are used to assess and chart the developmental level of infants and to assist in planning intervention strategies for children with developmental delay. It is also used a research tool in a variety of clinical settings (Bayley, 1993).

The BSID II consists of three scales, a motor scale, a mental scale and the behaviour rating scale. For the purposes of this study, only the motor and mental scales were used. The mental scale assesses aspects relating to memory, habituation, problem solving, numeracy, language and social skills. The motor scale assesses, gross movements such as crawling, rolling and walking and fine motor control.

University of Cape Town

Each scale consists of a set of items/tasks that are administered to the child by an examiner. Strict directions for administration of each item/task are given in the manual. Testing usually commences at the child's chronological age, and the child is taken through a list of items/tasks known as an item set. However, the manual allows the examiner to begin testing at level above or below the child's chronological age (Bayley, 1993) based on the child's level of performance. Basal and ceiling rules apply so that the examiner may know where to commence and when to stop the assessment. A child needs to achieve a "basal" minimum score in an item set in order to continue testing in an item set. If this does not occur, testing should commence at the preceding item set. The examiner is allowed to terminate testing once a child reaches a "ceiling" i.e. achieves no credit for a set number of items on the motor and mental scale.

A raw score is derived from the number of items credited in the item set, which is added to, credits for all items below the basal item. This raw score can be converted into a developmental quotient based on the child's chronological age i.e. a Psychomotor Development Index (PDI) or Mental Development Index (MDI) using specially constructed tables in the manual. These index scores may be converted into classification scores, signifying accelerated development, normal development, mildly delayed development and significantly delayed development.

Reliability and validity

Reliability refers to the ability of a test to yield consistent results when the same test is given to the same individual more than once (Derstine, 1989). The average reliability

University of Cape Town

coefficients obtained for the mental (.88) and motor scales (.84) shows that the BSID II is a highly reliable instrument. These results indicate that there is a high level of agreement between two raters observing a child's performance on the BSID II (Bayley, 1993).

Test-Retest Reliability refers to the degree of similarity of the information obtained when the measurement is repeated on the same subject (Katzenellenbogen, Joubert and Yach, 1991). When this measure is high, it is likely that the test is reflecting actual abilities of the testee. Test-retest reliability of the BSID II was also established during the re-norming of the scales. The results of this sub-study revealed that the BSID II demonstrates a high degree of stability over time and across age groups. However, the stability of scores over a longer period in high-risk populations in a situation where some intervention may occur remains to be determined (Bayley, 1993).

University of Cape Town

Validity refers to the extent to which an assessment actually measures what it is meant to measure and how well it does that (Katzenellenbogen *et al.*, 1991).The content validity of the BSID II mental and motor scales was established by asking a set of experts to identify those ability domains relevant to developmental assessment. Once these domains were identified, the same experts reviewed each of the items on the BSID to ensure that adequate content coverage existed (Bayley, 1993).

Concurrent Validity represents the relationship between a test and a concurrent criterion variable (Stengel, 1991). Concurrent validity was established between the MDI of the BSID II and the General Cognitive Index (GCI) of the McCarthy Scales of Children's

Abilities (Bayley, 1993). In addition, good correlation of age equivalent scores for the BSID II motor scale was established with the Peabody Gross Motor Scale (r=0.83) and Peabody Fine Motor Scale (r=0.87) (Provost, Crowe and McClain, 2000). However, standard scores showed poor correlation between the BSID II and the Peabody Scales.

Limitations

Although the scales can be stratified into domains such as cognitive, language, social and self-help, the BSID II was not designed to provide reliable and valid scores in these domains (Bayley, 1993). The manual cautions against the use of the test to diagnose deficiencies in specific skills e.g. language, perception etc.

The goal of the research study is to provide a basis of support for further investigation into the aspects of development that require further attention in children with HIV. If a child fails most items in a particular facet, the researcher may refer the child to an appropriate therapist (speech therapy, audiology, occupational therapy or physiotherapy) for further investigation.

Children with HIV display a range of motor dysfunction ranging from no evidence of delay to severe motor and intellectual dysfunction (Layton and Davis-McFarland, 2000). The performance pattern of any individual child may not be the same as that of the group. Therefore, caution should be heeded when interpreting BSID II results in clinical populations. The BSID II was intended to be used to assess children with developmental delays, but was it was standardised on "normal" children and no validation studies have

University of Cape Town

been conducted on out-of norm children (Mayes, 1997). The authors suggest that the test be administered to children who have a disability in the prescribed manner and to note the extent to which the disability affects performance. This permits one to compare the child to his norm-referenced peers and allows one to assess the degree to which the deficits affect his performance. The BSID manual (Bayley, 1993) does however state that adaptations to the testing procedure may be made to " minimize the impact of the child's disability on his or her performance." However, the authors caution that by using this approach, one automatically "...void(s) the basis for comparing the child's performance to the reference group..." (Bayley, 1993).

Therapists have often asserted that norm-referenced assessments are inappropriate for children with moderate to severe motor dysfunction, as quality of movement is not emphasised. This is justified but one should not exclude the use of a norm-referenced test/s as they may be used appropriately to monitor the development of infants for research and clinical purposes (Palisano, 1993).

Another cause for concern arises when assessing infants with fine motor dysfunction. Many items on the mental scale require fine motor manipulation of pellets, cubes, pegs, form board pieces and a crayon. Consequently the Mental Scale may not provide a valid indication of cognitive development for an infant with limited fine motor control and should not be used to assess the mental ability of a child with cerebral palsy or other physical handicaps (Mayes, 1997, Palisano, 1993). The Bayley manual acknowledges this

University of Cape Town

limitation by stating "it is inappropriate to obtain a norm-referenced score for a severely sensory or physically impaired child" (Bayley, 1993).

The BSID II test manual suggests that infants should be tested on an item set, which is concurrent with their chronological or corrected age. However, it also allows for the use of clinical impressions based on prior information regarding developmental progress to determine the item set with which to begin testing. This however leads to problems where researchers have noted that a child's abilities are underestimated when testing begins at a lower level instead of at the child's chronological age (Gauthier, Bauer, Messinger and Closius, 1999, Mayes, 1997). The authors recommend standardised use of the test to minimise variability in test scores by starting the test at the child's chronological age (Gauthier *et al.*, 1999).

A further limitation of the BSID II is that if a child attains a raw score that cannot be converted to an index score, they receive an index equivalent of "<50" (Robinson BF and Mervis, 1996). This limits the use of index scores when conducting statistical research. For this reason other studies have relied on the use of raw scores (Drotar *et al.*, 1997, Nozyce *et al.*, 1994) or have chosen an arbitrary score below the cut-off point (Smith R *et al.*, 2000).

In recognition of this limitation, Robinson and Mervis (1996) extrapolated scores from the BSID II and generated estimated index scores for children who scored below 50 (Robinson BF and Mervis, 1996). This was done by calculating a regression equation

University of Cape Town

based on the relationship between the raw score and index scores between 51 and 84. However, the use of extrapolated scores has inherent limitations as well. They are acknowledged to be only estimates, and very little is known about the distribution of scores in populations who score below 50 (Black and Matula, 2000, Robinson BF and Mervis, 1996). In addition, the extrapolated scores do not have confidence intervals or error measures since they are not based on actual data (Robinson BF and Mervis, 1996). The use of extrapolated scores is thus not recommended for clinical evaluation, but to facilitate parametric analysis for research purposes (Black and Matula, 2000).

2.6 Development of children with HIV – methodological issues

When conducting longitudinal assessments of children who are infected with HIV, careful consideration should be given to the following factors:

2.6.1 Subject recruitment

Numerous studies investigating the development of children with HIV infection have included a sample of uninfected infants born to infected mothers (Chase C *et al.*, 2000, Nozyce *et al.*, 1994). These children are often included to control for the potential confounding impact that a dying, ill or absent mother may have on a child's development (Sherr, 1999).

University of Cape Town

2.6.2 Effects of repeated evaluations

According to Wolters and Brouwers (1998), when conducting serial assessments, one must remember that when the rate of progression of the disease under study is rapid or the effect of treatment is immediate, shorter intervals will be required to assess the change in performance. The possibility of practice effects due to repeated administrations of the same test also imposes a significant limitation. The authors have concluded that the magnitude of practise effects is associated with the child's rate of development, comparative level of functioning, health status and potential for latent learning.

2.6.3 Scheduling testing

One should avoid testing children when they are acutely ill, febrile or upset as these factors make it difficult to obtain reliable and valid data. Therefore assessments must be arranged when the child is active, alert and the environment should be conducive to active social engagement and participation. If these criteria are not met, this will greatly impact on the quality of data collected and assessments may differ over time due to the effects of confounding factors such as a child's temperament at the time of testing (Wolters and Brouwers, 1998).

2.6.4 Impaired test taking ability

Children with HIV may exhibit a wide range of cognitive and motor impairments that will impair their test taking abilities. Problems such as sensory impairments, deficits in auditory, tactile or visual modalities and diminished expressive language due to HIV infection, opportunistic infections or other non-HIV related causes might severely limit

University of Cape Town

their ability to perform test items correctly (Wolters and Brouwers, 1998). These problems often necessitate the modification of assessment procedures. However, the manufacturers of certain assessments such as the Bayley scales of infant development caution against adapting the assessment procedures. In addition, these children often exhibit behavioural problems (uncontrolled activity levels, short attention spans, and uncooperative and resistant behaviours) that make the assessment procedure difficult and may influence results (Wolters and Brouwers, 1998).

2.6.4.1 Attrition

Subject attrition in studies relating to childhood HIV infection may occur based on medical grounds such disease progression, medication toxicities or immune reconstitution disease (for those on antiretroviral medication). Careful consideration of other potential reasons for defaulting appointments must also be determined and reasons for default must be included where possible. This is important to establish whether those who drop out of the study represent a subgroup that differs from those who do not drop out (Katzenellenbogen *et al.*, 1991).

2.7 Conclusion

HIV is a huge public health burden in South Africa as it affects thousands of adults and children. In the absence of widespread provision of antiretroviral therapy to infected pregnant women, the prevalence of paediatric HIV will continue to rise.

University of Cape Town

Manifestations of HIV infection include immunocompromise and CNS damage. The prevalence and severity of these symptoms varies considerably in different groups of children with HIV depending on the timing of infection, age of onset of illness, severity of immunocompromise and severity of neurological damage. One of the most common manifestations of HIV infection in children is the marked delay of developmental milestones directly caused by infection of the CNS and indirectly due to the impact of chronic illness.

Antiretroviral therapy has been shown to have positive outcomes for HIV infected individuals. Since the advent of antiretroviral therapy, the nature of HIV disease has changed from an acute, relentlessly progressive illness to a chronic condition that can be managed. Considering that populations infected with HIV, who are using antiretroviral therapy, are living for longer periods, it is important that we direct our attention to issues addressing the disabilities caused by HIV infection and improving their quality of life.

The role of physiotherapists in the rehabilitation of adults with HIV has been described in a number of studies. However, very little is known about the role of physiotherapy interventions in the rehabilitation of children with HIV. The efficacy of physiotherapy interventions in the treatment of conditions associated with HIV, such as lung diseases and developmental delay have been established in other populations. It can therefore be concluded that while physiotherapists and other rehabilitation professionals possess the skills and knowledge to treat these conditions, there is a need to conduct research into the

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safety and efficacy of these intervention strategies in the management of HIV infected children

Developmental delay in children with HIV may be attributed to any one, all or a combination of the following factors: the effect of the virus on the CNS, the impairment caused by of opportunistic infections during critical periods of development and the effect of the child's social environment.

It is important that researchers and clinicians investigating the developmental performance of HIV infected children are aware of additional risk factors associated with development. Certain risk factors such as the impact of poverty, culture and malnutrition are especially important when assessing the developmental status of HIV infected children in South Africa as the majority of infected infants are born to poor African women who mainly reside in resource poor areas.

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3 Methodology

The following chapter describes the processes involved in collecting and preparing the data obtained from the participants. Firstly, the research design is discussed, followed by a description of how participants were identified and recruited. Secondly, the instruments used to collect the data are briefly described. Thirdly, the data collection procedure is discussed. Finally, the statistical tests used to analyse the data are presented followed by a discussion on the ethical considerations of this study.

3.1 Research design

A cross-sectional, descriptive correlational study design was used to record the developmental performance of a sample of children with HIV. According to Katzenellenbogen et al (1991), longitudinal designs are best suited to measure the natural history of a disease within a population (Katzenellenbogen *et al.*, 1991). Therefore, a longitudinal, repeated measure, study design was incorporated to document the performance of the group over time. The use of longitudinal serial assessments to document the neurodevelopment of children with HIV was recommended by Wolters and Brouwers (1998) and a number of other studies have used similar designs in neurodevelopmental research (Bruck *et al.*, 2001, Msellati *et al.*, 1993, Nozyce *et al.*, 1994).

University of Cape Town

3.2 Participants

Samples of convenience were selected at each research setting. Convenience sampling was chosen due to the accessibility of suitable groups of children receiving services at Red Cross Hospital and the community clinics. The methods used to identify and recruit participants at each setting are described below:

3.2.1 The HIV infected sample

New participants were identified and recruited between April and November 2004. Children infected with HIV were recruited from attendees at the IDC at Red Cross Hospital. The IDC appointment diary was reviewed weekly to identify potential participants. This diary contained information regarding the child's name, gender and date of birth. All children receiving services at this clinic on that particular day were infected with HIV. This information enabled the production of a list of participants who met the age and HIV status criteria. Screening interviews were then conducted with the caregivers of those participants whose names were on the list to determine the eligibility criteria.

University of Cape Town

3.2.1.1 Inclusion criteria:

IsiXhosa speaking children whose HIV status had been confirmed by a PCR test, who were between the ages of one and 33 months at the time of recruitment and whose parent/guardian consented to participate were included.

3.2.1.2 Exclusion criteria:

- Acute illness, pain or irritability at the time of recruitment as assessed by the researcher.
- Diagnosis of cerebral palsy as recorded by the child's paediatrician in his or her medical folder described as quadriplegic, hemiplegic, diplegic or athetoid.
- Diagnosis of hypoxic ischemic encephalopathy acquired perinatally or any acquired post-natal brain damage recorded in the child's medical file.
- Prematurity, defined as less than 36 weeks gestational age at birth
- Low birth weight, defined as weighing less than 2000g at birth
- Diagnosis of a profound hearing loss or visual impairment recorded by the paediatrician in the child's medical folder.
- Children previously treated with antiretroviral medications who were no longer receiving the treatment.
- Children with recorded diagnoses of congenital abnormalities and/or Down's syndrome.

University of Cape Town

The sample size required was calculated using the hypothesis that there would be no difference in the developmental quotient between children infected with HIV and the age-matched sample. According to Currier (1990), knowledge of the standard deviation from a previously reported study can be used to estimate the sample size (Currier, 1990). Therefore, an undergraduate study, investigating the neurodevelopment of HIV positive infants using the BSID II (Matyida and Jelsma, 2004) was used to calculate the sample size required to disprove the above hypothesis. The results from this study (SD= 13.30)

were entered into a statistical calculator, viz. the Harvard sample size calculator (http://hedwig.mgh.harvard.edu). Accordingly, it was established that 39 participants were needed to enter this parallel-design study in order to detect a ten-point difference between the two groups at a two-sided 5.00% significance level. However, to allow for attrition, additional patients were recruited.

3.2.2 The age-matched sample

University of Cape Town

A sample of children, whose status was either unknown or negative, was recruited from two community clinics. Participants were recruited and tested between February and March 2004 and between September and October 2004 at the Nolungile clinic in Khayelitsha. Data collection resumed in January 2005 at the Vanguard Community health centre and concluded in March 2005. Two different recruitment strategies were used at each research setting. At the Nolungile clinic in Khayelitsha, nurses were given a list containing the eligibility requirements and were asked to send suitable participants for assessment. On arrival, eligibility criteria were checked again and informed consent was taken. At the Vanguard clinic, the research assistant was placed in the "check- in" area of the well baby clinic. All children who intended to see a doctor or nurse for whatever reason pass through this area so that the nurses on duty can complete an assessment of weight, height and temperature. All IsiXhosa speaking caregivers were asked to inform us of their child's age. If the child's age was appropriate, the research assistant briefly explained the nature of the research and asked the caregivers if they were interested in participating. If they agreed, screening interviews were conducted and their clinic files were examined for eligibility.

3.2.2.1 Inclusion criteria:

IsiXhosa-speaking children between the ages of 1 and 33 month, whose parent or legal guardian consented to participate in this study, were included.

3.2.2.2 Exclusion criteria:

- Acute illness, pain or irritability at the time of recruitment as assessed by the researcher, and confirmed by nursing staff.
- Diagnosis of cerebral palsy as recorded by the child's paediatrician in his or her medical folder
- Diagnosis of hypoxic ischemic encephalopathy acquired perinatally or any acquired post-natal brain damage recorded in the child's medical file
- Prematurity, defined as less than 36 weeks gestational age at birth
- Low birth weight, defined as weighing less than 2000g at birth
- Diagnosis of a profound hearing loss or visual impairment as recorded by the paediatrician in the child's medical file
- A positive diagnosis of HIV infection by PCR or ELISA testing
- A record of three or more hospital admissions since birth for infectious diseases as reported by the caregiver or recorded in the child's medical file.
- A record or report of any of the following diseases: encephalopathy, oral candidiasis, meningitis, tuberculosis
- A recorded diagnosis of congenital abnormalities or Down's Syndrome

Caregivers were asked to bring their child's clinic folder and Road- to- Health clinic card to the assessment area. In some cases, the Road- to- Health clinic cards of children

University of Cape Town

attending the community clinics also contained information regarding the HIV status of the mothers. All the clinics have voluntary HIV counselling and testing facilities. Some mothers in this study had voluntarily been tested for HIV during pregnancy. If their test results were positive for HIV infection, these mothers then joined the PMTCT programme. The children born to mothers belonging to this programme had the letters "PMTCT" printed on their road to health cards, indicating that the mothers were infected with HIV. It was then possible to determine the status of those children by examining the PMTCT register where PCR test results were recorded.

In order to minimise the possibility of including HIV infected children in this sample, specific exclusion criteria were formulated based on the assumption that children who had experienced three or more hospital admissions for infectious illnesses could likely be infected with HIV. Although this was a crude way of assessing a child's HIV status, access to larger numbers of known HIV negative children was limited to those who were by chance attending the clinic during the data collection period.

In order to construct an age-matched sample, age categories were defined based on the age categories used in presenting data on the BSID II norming sample (Bayley, 1993). Frequency tables representing the ages of the HIV infected sample and the reference sample at baseline were then calculated. Children in the reference sample were matched with children in the HIV sample based on age categories. Because data collection at the community clinics occurred concurrently with data collection at Red Cross Hospital, it was not known how many children were needed in each category. As a result, the number

University of Cape Town

of children (i.e. reference sample) in each category was either equal to or less than the number of children in the HIV sample. In cases where there were more children in the reference sample, children were randomly selected using a random number generator in Excel and excluded from the final sample.

3.3 Procedure

Data collection took place between March 2004 and November 2005. Data from the HIV infected children and their caregivers were collected at approximately three monthly intervals, while healthy children attending community clinics were assessed once. Permission was granted from the relevant institutions and a place for testing was identified in each site.

3.3.1 Pilot study

A pilot study was conducted in March 2004. The BSID II mental scales were applied to a group of children recruited at Red Cross during the initial phases of the research. During the pilot study, translation of the BSID II instructions was standardised.

3.3.2 Reliability testing

During the course of the study, inter-rater reliability testing of the BSID II was conducted to determine whether two scorers would achieve comparable results using the BSID II.

University of Cape Town

Ten HIV infected participants, consisting of five males and five females, who had been newly recruited into the main study, formed a sample of convenience. After signing a consent form to participate in the main research study, additional consent forms were signed that allowed an external observer to witness and score the assessment. All participants were assessed by the researcher while an observer sat behind her and scored the performance of the children. Since the motor scales required physically handling the child, reliability testing was conducted only on the mental component of the BSID II in order to limit the exposure of the child to someone other than the researcher. At the end of the assessment, the researcher and observer independently calculated the BSID II scores. The researcher and observer then met to discuss discrepancy in test scores, which were recorded. Raw scores were entered into Microsoft Excel and later transferred into the STATISTICA program for analysis.

Inter-scorer agreement was calculated using the raw scores calculated by the researcher vs. the observer. The reliability score was 0.99 which was higher than the reliability score reported in the BSID II manual (r=0.96) (Bayley, 1993). The reliability coefficient indicates a high level of agreement suggesting that the researcher administered the BSID II appropriately and objectively and thus, the results can be interpreted with confidence.

3.3.3 Ethical approval

Ethical approval was granted by the University of Cape Town Medical Research Ethics Committee, Reference Number: 029/2003.

University of Cape Town

3.3.4 Funding

Funding for this study was granted by the NIH and Medical Research Council. Funds were used to purchase the BSID II kit and to provide the caregivers with money for transport and lunch (R40 or $6 per subject/assessment).

3.4 Instrumentation

3.4.1 Demographic Questionnaire

A questionaire was constructed by the researcher to document demographic, socio-economic and medical information of the sample and their caregivers. See Appendix I.

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3.4.2 Administration of the demographic questionnaire

The questionnaire was printed in English and verbally translated into isiXhosa by the research assistant and administered by the assistant in a structured interview format in each case. Each participant was questioned in the same manner to ensure reliability. The section regarding medical information was completed by the researcher, who transcribed the necessary information from the participants' medical folders.

3.4.3 The Bayley Scales of Infant Development

The BSID II was used to assess the motor and cognitive development of all participants.

3.4.4 Administration and scoring of the BSID II

The researcher, who had received training in the use of the instrument, administered the BSID II in every case, assisted by an isiXhosa-speaking research assistant. In most cases, the mental scales were administered before the motor scales depending on the demeanour and energy levels of the child. The test was administered in the same manner to all clients. The children were allowed to sit on their caregivers lap or at a child size table while the researcher sat across from them. Explanations were given to the caregivers regarding their expected level of assistance with the testing procedures. Instructions were first given in English and then translated into isiXhosa by the assistant. Caregivers were allowed to repeat the instructions in isiXhosa as demonstrated by the assistant. A second period of free play was introduced prior to starting the motor assessment and items requiring observation could then be scored. Testing was conducted in a quiet room, and stair climbing and running was assessed in the corridor outside this room.

University of Cape Town

In recognition of the recommendations made by Gauthier et al (1999) and Mayes (1997), children were assessed at their chronological age (Gauthier *et al.*, 1999, Mayes, 1997) and scored according to the criteria recorded in the BSID II manual (Bayley, 1993). One credit/point was awarded for each item correctly performed. These points were added to determine the raw score and then converted into developmental quotients by referring to the tables in the BSID II manual. Classifications of delay were also recorded to describe the developmental performance of the participants.

Those whose raw scores could not be converted into index scores were identified and extrapolated scores were calculated using the tables and formulas presented in Robinson and Mervis (1996). Tables of extrapolated scores (Robinson BF and Mervis, 1996)were used where possible to convert raw scores. However, in cases where this was not possible (i.e. the tables do not contain all the scores that could be achieved), the regression equations developed by Robinson and Mervis (1996), were use to calculate an index score (Robinson BF and Mervis, 1996). In some cases, this regression equation yielded a negative index value. By convention, all individuals who scored a "negative" index score were awarded "0" by the researcher to facilitate analysis. Analysis of PDI and MDI scores were thus based on extrapolated scores.

3.5 Data collection

The methods for collecting data differed slightly at each research site.

3.5.1 Red Cross Hospital: The HIV infected sample

Data Collection took place on two mornings per week at Red Cross Hospital. Each HIV infected child in the sample was assessed at baseline and two follow up appointments were planned at three monthly intervals.

At the baseline assessment, caregivers and their children were escorted to a private room where the informed consent forms were completed. All children were allowed time to

University of Cape Town

play freely and interact with the researcher while the research assistant administered the demographic questionnaire to the caregiver.

Once the demographic questionnaire had been completed, the researcher administered the BSID II as described previously.

Caregivers were given feedback regarding the performance of their child after the assessments were concluded. They were then asked to return to see the researcher for an assessment at the clinic in three months. Cards indicating the researchers' contact details and the appointment date and time were given to each caregiver along with transport money in a sealed envelope.

Follow up appointments were scheduled for the day when the children had clinic appointments as caregivers rarely missed these appointments. However, this system was problematic as many caregivers and their children were tired after their clinic appointments and refused to attend the follow up assessments.

When caregivers missed a follow up assessment, telephone calls were made to determine the reason for not attending. The reasons varied: either the child or his/her caregiver was ill, or they had simply forgotten. When asked to return in a week, caregivers admitted that they had spent the money provided to them for transport and had no funds to return to the clinic. In many cases, telephone numbers provided were either no longer in service, which made tracking the caregivers difficult. In a few cases, assessments had to be

University of Cape Town

rescheduled, as the child's demeanour on the day of testing was not conducive to testing. It was not uncommon for participants to have temper tantrums while being tested.

At the first follow up appointment, motor and mental assessments were conducted in the same manner as before. At this stage, patients who had been identified by the BSID II as having a significant motor delay were referred to the physiotherapy department at Red Cross Hospital for further evaluation. However, after consultation with senior therapists in the clinic, it was decided that only children who were significantly delayed (as identified by the BSID II) *and* who were severely functionally delayed would be referred to the physiotherapy department, as the caseload at the clinic was quite high. The researcher then undertook to provide caregivers whose children were significantly delayed with limited advice on stimulating development. If caregivers wished to receive additional therapy, they were advised to contact the physiotherapy department themselves. Similarly, those who performed poorly on the mental scales were referred to either the speech or occupational therapy departments at Red Cross Hospital. It is acknowledged that the intervention might have influenced subsequent results but it was deemed ethically unacceptable to deny children some form of treatment.

The second follow up assessments were scheduled for three months later and the BSID II was administered in the same standardised manner as before.

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All data collected was kept in individual files for each child identified by their initials, hospital folder number and research subject number. The researcher and the assistant regularly reviewed these files to ensure accuracy. Once all assessment forms had been completed, demographic and medical records were cross-referenced with information obtained from records held at the clinic. Data was then entered into Microsoft Excel and imported into the Statistica programme for analysis. Regular analyses were conducted at various stages of the data collection process to identify and correct errors.

3.5.2 Community health centres: The age-matched sample

Data collection took place on two mornings per week at the Nolungile community health centre in Khayelitsha and later at the Vanguard community health centre. All eligible, participants were escorted into a quiet room where informed consent was taken and the demographic questionnaire was administered. While the questionnaires were being completed, the researcher allowed the child to play freely. The BSID II assessments were then conducted with the assistance of the assistant and the caregiver. All assessments were administered according to guidelines provided in the manual. Caregivers were given money to buy lunch as a token of appreciation as the assessment procedure took longer because all tests and questionnaires had to be completed on the same day. Children who were identified as having a significant motor delay were referred to the resident physiotherapist at the particular community health centre for further investigation.

University of Cape Town

All data collected from the participants were filed and identified by subject number to maintain confidentiality. After the data collection period, the medical records of participants attending the Nolungile health centre were requested and cross-referenced with data obtained from the questionnaires to ensure accuracy. Although reliability testing was not conducted on this group of children, a paediatrician trained in the administration of the BSID II accompanied the researcher to the clinic for a period of one week during the course of the study to ensure that the tests were being administered correctly.

3.6 Data analysis

All data was analysed using the STATISTICA software programme. A significance level of $p \leq 0.05$ was used throughout.

Frequency tables and descriptive statistics

Frequency tables and descriptive statistics such as the mean (with standard deviation and range) were used to analyse and present the following demographic, medical and socio-economic variables related to the children and caregivers in both samples. Frequency tables were also used to describe the classification distribution of motor and mental delay of the two samples.

T-tests

T-tests were used to compare data that were normally distributed. Normal distribution was tested using the Shapiro Wilks test.

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Mann Whitney U

The Mann Whitney U was used as the alternative to the t-test to compare data that was not normally distributed.

Chi squared

The Chi-squared test was used to establish if there was an association between the ordinal and nominal variables and group membership.

Friedman's ANOVA and the Wilcoxan matched pairs sign test

The Friedman's ANOVA test was used to determine if there was any difference in the ranking of the motor and mental scores over time. The Sign matched pairs test was then conducted to determine where the difference occurred.

University of Cape Town

3.7 Ethical considerations

3.7.1 Informed consent

Each caregiver signed a consent form before participating in the study. The consent form (see Appendix I) contained information relating to the nature of the study, an explanation of the test procedure, the risks and benefits of participating in the study and a statement assuring confidentiality. For the purpose of this study, caregivers were defined as either a parent or legal guardian. Caregivers who were receiving grants on behalf of the child in their caregiver were also included. The research assistant, fluent in English and isiXhosa,

was present on most occasions to ensure that isiXhosa speaking participants understood all aspects of the research process.

3.7.2 Autonomy

Despite efforts to retain participants in this study, caregivers were allowed to withdraw from the study without prejudice or consequence if they wished to do so. As the research was separate from the clinic in which these participants received treatment, withdrawal from the study had no influence on the treatment received by the participants. Caregivers also reserved the right to refuse if they were unhappy with any part of the assessment.

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3.7.3 Convenience

Caregivers attending the IDC chose which day they preferred to attend. Caregivers were given the option of either attending before or after their clinic appointment or returning on another date. A transport fund was available for those who chose to attend another day. It is important to note that transport funds were not used to solicit participants. .Caregivers and children attending the community health centres would usually arrive early in the morning and often waited in long queues to be examined. As the assessments took place either before or after their clinic appointment, a lunch fund was given to all participants in appreciation for remaining behind. Caregivers who wished to be part of the study could also chose to return to the clinic on another day if it was more convenient.

3.7.4 Risk

A major ethical concern was that the testing should not harm or tire the child. The researcher, a registered professional physiotherapist administered all the tests. Although, testing took up to 90 minutes in some cases, regular breaks were scheduled to ensure the child did not tire. The wellbeing of the children was considered at all times and when children became distressed and irritable, testing was stopped. Safety precautions were put in place to ensure the research testing area was free from any hazards.

3.7.5 Beneficence

Children with severe development delay were referred for physiotherapy treatment at each research setting. Where significant evidence of developmental delay was found, the researcher in her capacity as a trained physiotherapist advised the caregivers on how to stimulate development.

3.7.6 Confidentiality

Information gained from the participants was kept confidential. Steps taken to preserve confidentiality included identifying participants using initials, subject numbers and hospital folder numbers. All discussions with medical staff about the subject were done with the caregivers consent. It was agreed that the isiXhosa-speaking research assistant would handle the gathering of demographic and socio-economic data. Certain questions were culturally sensitive and it was deemed more appropriate for the assistant to ask these questions.

University of Cape Town

4 Results

The results are presented as set out in the objectives: Firstly, the demographic and medical characteristics of the HIV infected children and their caregivers are presented. Next, the motor and mental performance of the HIV infected children are compared with the performance of the age-matched sample at baseline. This is followed by a presentation on the performance of children who were receiving HAART, compared to those who were not eligible. The performance of children on HAART for longer than six months is then compared with those on HAART for less than six months. Finally, the longitudinal performance of the HIV infected sample is presented.

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4.1 Demographic and medical characteristics of the sample

Fifty-eight children met the inclusion criteria. Of these, seven were excluded from the final sample because they had the following exclusion criteria: One child had been diagnosed with Down's syndrome, another was diagnosed with a hearing impairment, three were premature and two were born at a low birth weight.

Thus, the effective sample consisted of 51 HIV infected children including 26 females (51.0%) and 25 males (49.0%) All children in this sample were of Black African descent and isiXhosa was the primary home language of all the participants. The mean age of the sample at baseline was 15.8 months (SD= 7.5, Range= 6.2 to 31.7 months).

The gestational age of the child could not be determined in one case. This child lived with his grandmother who was not in possession of his Road to Health Card. Medical staff at the HIV clinic was also unaware of this information. This child was included nonetheless since he met the inclusion criteria and had no other exclusion criteria. Similarly, on examination of the birth weights of the participants, the birth weights could not be determined in eight cases. In these cases, the caregivers were either not in possession of the Road to Health Card or the birth weights had not been recorded on the cards for unknown reasons. These children were still included in the final sample.

Twenty children (39.2%) had been exposed to antiretroviral prophylaxis in utero. Despite this, all the children in this sample tested positive for HIV infection. Information on four children (7.69%) could not be determined since there was no record of whether or not they had been exposed to antiretroviral prophylaxis. These four children were not in the care of their biological mothers (who would have been able to share this information) and both their caregivers and doctors were unaware of this information.

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A large percentage (94.1%) of the sample reported having had at least one hospital admissions for serious illness. Three participants (5.9%) had never been admitted to hospital. Of those who were admitted to hospital (n=48), 23 participants had been admitted more than three times (47.9%) and sixteen (33.3%) were admitted to the pediatric intensive care unit (ICU), indicating the severity of their illness. The duration of stay in hospital varied among participants ranging from one day to 90 days (median: 25 days). The range of illnesses diagnosed on admission to hospital for these participants is shown in Table 1 below. Other illnesses (less than 10 cases) reported included dermatitis (n=3), parotitis (n=1), gastro-oesophageal reflux disease (n=1), anaemia (n=1), septic arthritis (n=1) and chicken pox (n=1).

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Thirty-four participants (66.6%) were on antiretroviral therapy (HAART) at the start of this study and 17 (33.3%) were not yet eligible according to the hospital criteria for initiation of HAART. Of those who were receiving HAART, 17 (50.0%) had been on HAART for less than six months and 17 (50.0%) were on HAART for more than six months.

Table 1: Illnesses diagnosed on each hospital admission in the HIV infected sample (n= 48 participants admitted to hospital)

Diagnosis	Count (n)	% of participants with this diagnosis
URTI	36	70.6
Diarrhoea or gastro –enteritis	35	68.6
Pneumonia	33	64.7
FTT, Marasmus and/or Kwashiorkor	15	29.4
Septicaemia and/or septic shock	14	27.5
Tuberculosis	14	27.5
Meningitis, encephalopathy and/or seizures	13	25.5
Oral Thrush	9	17.6

Note: Each subject could have had more than one diagnosis.

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4.2 Socio-economic characteristics of the caregivers

Five children (9.8%) were cared for by someone other than their biological mother. Three participants were in the care of their maternal grandmothers, as the mothers were ill. One was accompanied by this great-grandmother because his biological mother had died and another was in the care of his maternal aunt because his mother had also died.

The socio-economic status of the caregivers is presented in Table 2 below. Three questionnaires were incomplete for highest level of schooling for unknown reasons, and there were 14 cases in which the caregivers were either unaware of the monthly household income or did not feel comfortable answering the question.

Table 2: Socio-economic profile of caregivers of the HIV infected sample (n=51) and caregivers of the age-matched sample (n=35)

		HIV infected sample N=51			Age-matched sample N=35			p
Variable	*Category*	*n*	*% of valid cases*	*% of all cases*	*n*	*% of valid cases*	*% of all cases*	
Relationship status	Single	37	75.5	75.5	16	50	45.7	**0.04**
	Partner/ married	14	27.5	27.5	16	50	45.7	
	Missing/ undisclosed	0	0	0	3		8.6	
	Total	51	100	100	35	100	100	
Educational level	Grade 3-7	4	8.3	7.8	2	6.3	5.7	0.42
	Grade 8-11	21	43.8	41.2	18	56.3	51.4	
	Grade 12	20	41.7	39.2	12	37.5	34.3	
	Tertiary	3	6.3	5.9	0	0	0	
	Missing/ undisclosed	3		5.9	3	9.4	8.6	
	Total	51	100	100	35	100	100	
Employment status	Employed	8	15.7	15.7	3	8.8	8.6	0.35
	Unemployed	43	84.3	84.3	31	91.2	88.6	
	Missing/ undisclosed	0	0	0	1		2.9	
	Total	51	100	100	35	100	100	

University of Cape Town

Child support grant	Yes	35	68.6	68.6	26	76.5	74.3	0.43
	No	16	31.4	31.4	8	23.5	22.9	
	Missing/ undisclosed	0	0	0	1		2.9	
	Total	51	100	100	35	100	100	
Own monthly income	R0-R300	20	54.1	39.2	15	53.6	42.9	0.28
	R301- R999	14	37.8	27.5	13	46.4	37.1	
	>R1000	3	8.1	5.9	0	0	0	
	Missing/ undisclosed	14	37.8	27.5	7	25	20	
	Total	51	100	100	35	100	100	
Housing type	Formal/brick structure	27	52.9	52.9	4	12.1	11.4	**<0.01**
	Informal structure	24	47.1	47.1	29	87.9	82.9	
	Missing/ undisclosed	0	0	0	2	6.1	5.7	
	Total	51	100	100	35	100	100	

University of Cape Town

4.3 Prevalence and severity of developmental delay

The performance of the HIV infected sample is presented below in comparison to the performance of an age-matched group of children.

4.3.1 The age-matched sample

The age-matched sample was selected to match the HIV infected sample in terms of age and home language. Fifty-nine children met the inclusion criteria but 19 were excluded in order to facilitate age matching, three were excluded based on prematurity and two were excluded for being low birth weight. Thus, the sample consisted of 35 age-matched isiXhosa speaking children (mean age: 14.6 months, SD=6.61, Range= 14.6 to 31.0 months). The ages of the two samples were not normally distributed and the Mann-Whitney U test confirmed that the two samples were comparable with regard to mean age (p=0.58).

On examination of the clinic records, it was established that five participants (14.3%) in the age-matched sample were born to mothers who were infected with HIV. This information was recorded in the child's clinic file because their mothers had participated in the PMTCT programme. All these children tested negative for HIV infection by means of the PCR test. Of those who were born to HIV infected mothers, two (5.7%) had been exposed to antiretroviral prophylaxis. The HIV status of the remaining 30 participants (85.7%) in the age-matched sample remained unknown.

Children in the age-matched sample had significantly fewer hospital admissions than the HIV infected sample (p<0.01). This was because only those with fewer than three hospital admissions were included in the age-matched sample. Eleven participants (31.4%) had been admitted to hospital once since birth. Eight participants (22.9%) had previously been diagnosed with chest infections. Nine (25.7%) cases of either diarrhoea or gastro-enteritis were also reported. Twelve participants had a record of multiple (two

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or more) episodes of a particular illness. Other illnesses reported by the caregivers or recorded in the clinic files included: episodes of intestinal worm infestation, skin or nappy rash, earache, superficial burns and colds or flu.

Since the age-matched sample were recruited at clinics in areas that isiXhosa speaking populations were likely to be found, it was expected that the caregivers would have the same socio-economic status however, there were some discrepancies.

When comparing the socioeconomic status of the caregivers of the age-matched sample and the HIV infected sample (See Table 2), there was no difference in caregiver education levels (p=0.42), caregiver employment status (p=0.35), receiving grants (p=0.43) and monthly income (p=0.28). The main differences was that more caregivers in the age-matched sample were married or living with a partner (p=0.04) than in the HIV infected sample. In addition, more caregivers of the HIV infected sample lived in brick houses (p<0.01) compared to the age-matched sample. See Tables 3 and 4.

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Table 3: Differences in relationship status between caregivers of HIV infected sample (n=51) and caregivers of the age-matched sample (n=32)

Group	Single	Partners	Row
HIV infected sample	37	14	51
	72.5%	27.5%	
Age-matched sample	16	16	32
	50.0%	50.0%	
Totals	53	30	83

Note: Pearson Chi-square=4.33 p= 0.04

Missing data on relationship status n=3 in age-matched sample, see Table 2

Table 4: Differences in housing type occupied by caregivers of the HIV infected sample (n=51) and caregivers of the age-matched sample (n=33)

Group	Informal housing	Formal housing	Row total
HIV infected sample	24	27	51
	47.1%	52.9%	
Age-matched sample	29	4	33
	87.8%	12.1%	
Totals	**53**	**31**	**84**

Note: Pearson Chi-square=14.34 p< 0.01

Missing data on housing status n=2 in the age-matched sample, see Table 2

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4.3.2 Motor performance

4.3.2.1 Psychomotor Development Index (PDI)

Eleven participants in the HIV infected sample achieved raw scores on the motor assessment that could not be converted into index scores because they were so low, indicating very poor performance. In these cases, extrapolated scores were used to convert their raw scores into PDI scores. The PDI scores should thus be interpreted with caution as the extrapolated scores are merely estimates (Black and Matula, 2000).

The mean PDI scores for the HIV infected sample was thus 63.0 (SD=20.2, Range= 17 to 109) and the age-matched sample scored a mean of 92.3 (SD=15.3, Range= 60 to 110). Histograms of the PDI scores are depicted in Figure 1 below. The PDI scores for the HIV infected sample were normally distributed (Shapiro- Wilks W= 0.98, p= 0.59) whereas the scores for the age-matched sample were not normally distributed (Shapiro Wilks W= 0.87, p=0.01). Therefore, non-parametric statistics, i.e. the Mann Whitney U test was

used to detect if there was a significant difference between samples. This difference was significant ($p < 0.01$).

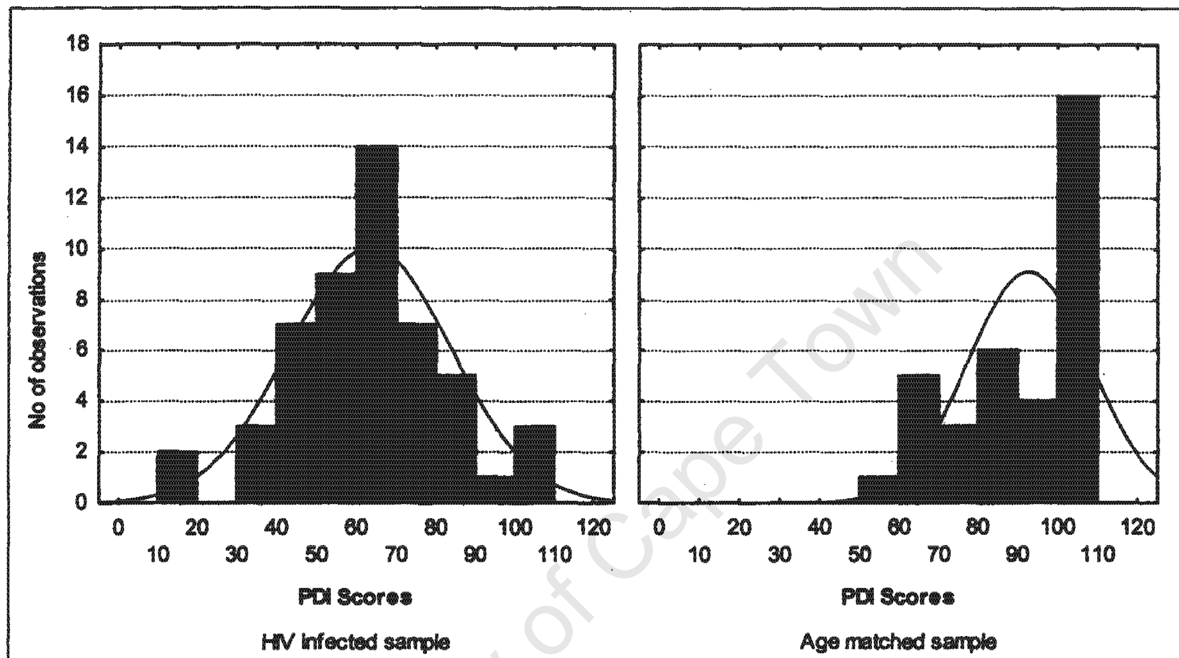

Figure 1: Histogram of PDI scores of the HIV (n=51) and the age-matched sample (n=35)

4.3.2.2 Motor Classification

None of the children in both samples achieved accelerated development. Two thirds of the HIV infected sample (66.7%) displayed significant delays in motor performance. A greater percentage of HIV infected children were significantly delayed compared to the age-matched sample and the overall performance of the two groups were significantly different (Pearson Chi-square= 38.55; $p<0.001$). The extent of delay in motor performance is shown in Table 5 below.

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Table 5: Comparison between the HIV infected sample (n=51) and the age-matched sample (n=35) based on Motor Classification.

Motor Classification	HIV infected sample		Age-matched sample	
	Count (n)	*Percent (%)*	*Count (n)*	*Percent %*
Accelerated performance	0	0.0	0	0.0
Within normal limits	5	9.8	23	65.7
Mildly delayed	12	23.5	10	28.6
Significantly delayed	34	66.7	2	5.7
Total	51	100	35	100

4.3.3 Mental Performance

4.3.3.1 Mental Development Index (MDI)

As with the motor assessment, six participants achieved raw scores on the mental scale that could not be converted into index scores. Extrapolated scores were used in these cases as well. The mean MDI score for the HIV infected sample was 69.9 (SD=16.1, Range= 28 to 103). The age-matched sample scored a mean of 84.3 (SD=11.8, Range= 56 to 108). The scores of both groups were normally distributed. (Shapiro Wilks W= 0.98, p=0.89 and W= 0.98, p= 0.68 respectively). Histograms of the MDI scores are depicted in Figure 2 below. Consequently a t-test was used to determine if there was a significant difference in the mean scores and the means were significantly different (t= -4.52, p< 0.01) See Table 6 below.

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Table 6: Results of the t- test to compare the MDI scores of HIV sample (n=51) and the age-matched sample (n=35)

Group	N	Mean MDI	Min	Max	SD
HIV infected sample	51	69.92	28	103	16.12
Age-matched sample	35	84.31	56	108	11.77

Note: T= -4.52 p<0.01

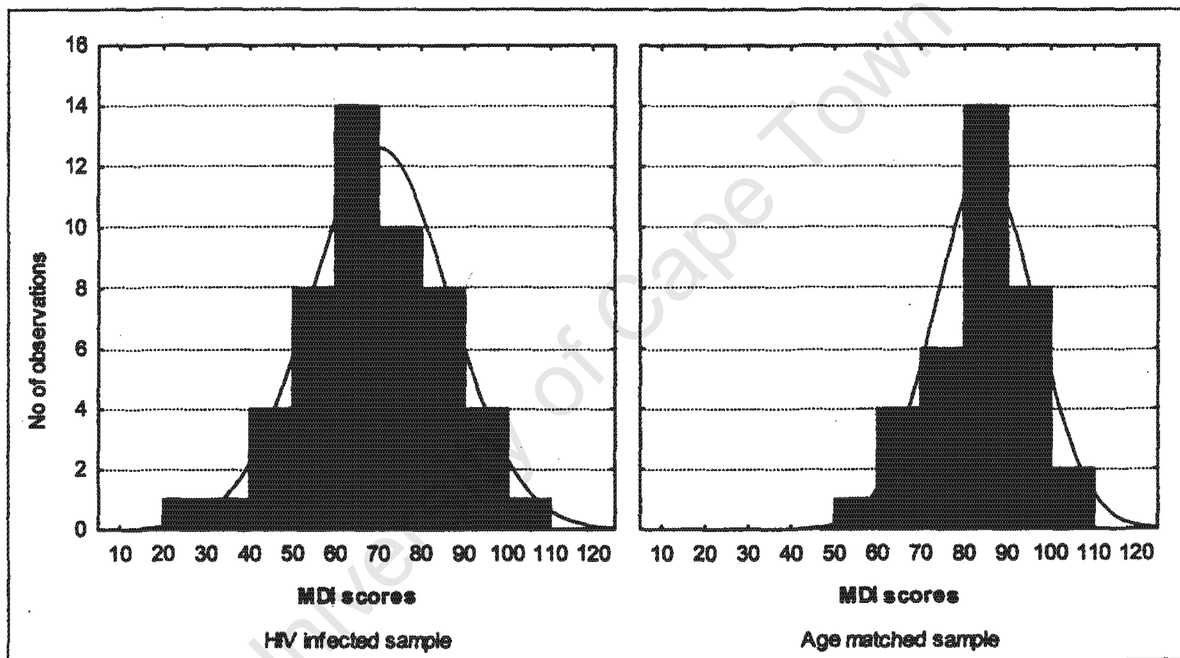

Figure 2: Histogram of MDI scores of the HIV (n=51) and the age-matched sample (n=35)

4.3.3.2 Mental classification

The extent of mental delay in the two samples is presented in Table 8 below. The overall performance of the two samples were significantly different (Pearson Chi square= 16.62; p<0.001). See Table 7 below.

A greater percentage of children in the HIV infected sample scored within normal range on the mental scales (17.6%) than on the motor scales (9.8%).

Table 7: Comparison between the HIV infected sample (n=51) and the age-matched sample (n=35) based on Mental Classification

Mental Classification	HIV infected sample		Age-matched sample	
	Count (n)	*Percent (%)*	*Count*	*Percent (%)*
Accelerated performance	0	0.0	0	0.0
Within normal limits	9	17.6	16	45.7
Mildly delayed	15	29.4	15	42.9
Significantly delayed	27	52.9	4	11.4
Total	51	100	35	100

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4.4 Influence of HAART on motor and mental performance

Two subgroups were identified within the HIV infected sample, those who were receiving HAART at the initiation of the study and those who were not eligible according to the criteria at Red Cross Hospital at the time. These two subgroups were identified as the HAART group and the non-HAART group

4.4.1 Characteristics of the subgroups

Thirty-four participants were receiving HAART at baseline and 17 were not eligible. The two subgroups were comparable concerning mean age (p=0.83). However, there were differences with regard to exposure to antiretroviral prophylaxis and hospital admissions.

Firstly, a greater number of children who were exposed to antiretroviral prophylaxis in utero were not yet eligible for HAART. Secondly, the HAART group had a greater number of children who had been admitted to hospital. See Table 8 and Table 9 below.

Table 8: Comparison of between sample receiving HAART (n=34) and those not receiving HAART (n=17) in terms of exposure to antiretroviral prophylaxis

Exposure to antiretroviral prophylaxis	HAART	Non HAART	Row total
Yes	9	11	20
	26.5%	64.7%	
No	22	5	27
	64.7%	29.4%	
Unknown	3	1	4
	8.8%	5.9%	
Totals	34	17	51

Note: Pearson Chi Square: 7.02 p= 0.03

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Table 9: Comparison of sample receiving HAART (n=34) and those not receiving HAART (n=17) in terms of hospital admissions

Admitted to Hospital	HAART	Non HAART	Row total
Yes	34	14	48
	100.0%	82.4%	
No	0	3	3
	0.0%	17.6%	
Total	34	17	51

Note: Pearson Chi Square: 6.37 p=0.01

The HAART sample was then further stratified into two groups i.e. those who were on HAART for less than six months (HAART<6months) and those who were HAART for more than six months (HAART>6 months). These groups were compared to those not receiving HAART in terms of their motor and mental performance.

4.4.2 Motor and Mental Performance

Although it appeared that the mean PDI score was lowest in the group receiving HAART for less than six months, no significant differences in PDI scores were found between the three groups (p=0.11). Similarly, the group not receiving HAART achieved the highest mean MDI, however there was no significant difference in mean the MDI between the three groups (p=0.36). See Table 10 and Figure 3 below.

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Table 10: Comparison of mean PDI and MDI scores of participants who were not on HAART, receiving HAART for less than six months and receiving HAART for more than 6 months

HAART Groups	N	PDI		MDI	
		Mean	*SD*	*Mean*	*SD*
Not receiving	17	65.5	4.78	74.5	16.1
Less than 6 months	17	54.9	4.78	67.2	11.9
More than 6 months	17	68.8	4.78	68.1	18.5

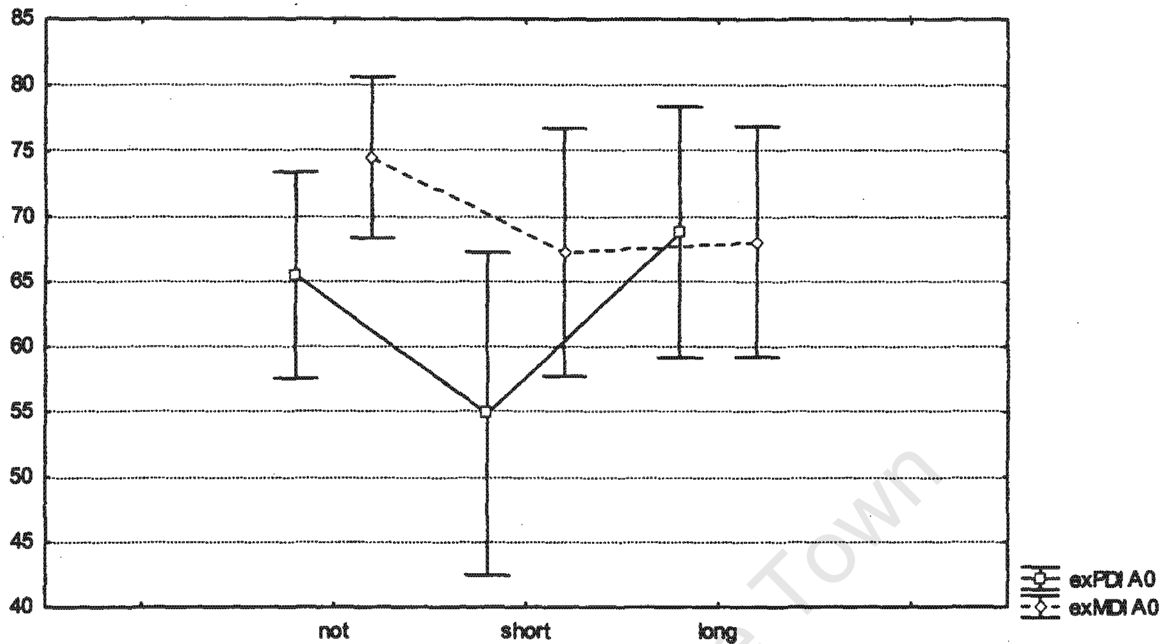

Figure 3: PDI and MDI of the children not on HAART (n=17), receiving HAART for less than 6 months (n=17) and receiving HAART for more than 6 months (n=17)

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4.5 Longitudinal performance of the HIV infected sample.

4.5.1 Attrition

The number of participants enrolled in this study decreased from 51 participants tested at baseline (A0) to 34 participants tested at the final assessment (A2).

After the baseline assessment, nine participants had been lost to follow up, leaving 43 participants in the sample at A1.

In four cases, the caregivers did not return for re-assessment despite the availability of a transport fund. These caregivers were contacted telephonically and each one gave their assurance that they would return, but did not arrive on the day scheduled for re-assessment for unknown reasons. After numerous attempts to re-schedule appointments had failed, the decision was taken to discontinue follow up with those children.

One subject had died due to complications related to septicaemia following a prolonged period of hospitalisation and another had moved to the Eastern Cape. In another case, the subject's mother had died and the child was institutionalised.

One of the caregivers started a new job after the first assessment and indicated that she would have to return to work immediately after the doctor's appointments, and therefore could no longer participate in the research project.

Another subject, although tested at baseline refused to co-operate with the both the researcher and the research assistant at the next assessment. Steps to facilitate co-operation, such as such as free play, observing the child from a distance and allowing the mother to lead the interaction, were taken but all attempts were unsuccessful. As a result, the child's scores could not be used. The caregiver was then asked to return on another day but the child again refused to co-operate. Since the BSID II had strict administration criteria, it was felt that the integrity of the results would be compromised if too many adjustments were made. The decision was then taken to exclude this child from further testing.

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After the first follow-up assessment (A1), eight more participants were lost to follow-up, leaving 34 participants at A2.

Of the eight participants who dropped out, three participants were acutely ill at the time of their scheduled re-assessment and remained ill for the duration of the study. Another subject was not assessed at assessment two because he was irritable and uncooperative. The caregiver was asked to bring the child in on another day but did not keep her appointments. Four caregivers did not return for re-assessment despite attempts to arrange convenient appointments. The reasons for not attending varied among the caregivers, ranging from having spent the transport money, being tired and wanting to go home, having other appointments to attend, etc.

The attrition rate of 33.3% is reflected in Table 11 below.

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Table 11: Number of participants who withdrew and each stage of the study, reasons for attrition and previous classifications of performance

Withdrawal stage	Count (n)	Reason	% (n=51)	Motor A0	Mental A0	Motor A1	Mental A1
After A0	4	Miscellaneous	7.8	SD	MD	N/A	N/A
				SD	SD	N/A	N/A
				MD	WNL	N/A	N/A
				SD	WNL	N/A	N/A
After A0	1	Uncooperative	2.0	WNL	WNL	N/A	N/A
After A0	1	Moved	2.0	SD	SD	N/A	N/A
After A0	1	Caregiver working	2.0	MD	SD	N/A	N/A
After A0	1	Subject died	2.0	MD	WNL	N/A	N/A
After A0	1	Caregiver died	2.0	SD	SD	N/A	N/A
After A1	4	Miscellaneous	7.8	SD	SD	SD	SD
				SD	MD	SD	MD
				SD	SD	SD	SD
				SD	SD	SD	SD
After A2	3	Sick	6.0	SD	WNL	SD	MD
				SD	MD	SD	SD
				SD	SD	SD	SD
After A3	1	Irritable	2.0	MD	MD	SD	MD
Total	**17**		**33.3**				

NB: SD=significant Delay, MD= Mild Delay, WNL= Within Normal Limits, N/A=Not applicable

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4.5.2 The longitudinal sample

Tests were not done to compare the scores of all the participants at each assessment as there may have been bias due to differential drop-out of healthier participants (unknown drop-outs) or participants who died or were admitted to hospital (See Table 11 above). For the purpose of this presentation, only the scores of those who attended all the follow-up assessments were analysed.

The effective sample analysed in the longitudinal study thus consisted of 34 children of which 44.1% were male. All but two children in the longitudinal sample had been admitted to hospital (94.1%). Of those who were admitted, 53.1% were admitted fewer than three times. Thirteen participants had been exposed to antiretroviral prophylaxis in utero, 19 had not and there were two cases where this information was unknown. The caregivers of the longitudinal sample, were mainly single (70.6%), unemployed (82.4%), relied on a childcare grant (79.4%) and earned very little money (48.6% earned less than R300/month). Seventeen participants in the longitudinal sample lived in informal housing.

The period between each assessment for those who completed the study is illustrated in Table 12 below.

Table 12: Period between assessments for the longitudinal sample (n=34)

Period	Mean (months)	Minimum	Maximum	Std. Dev.
Time A0-A1	3.1	2.0	6.9	0.9
Time A1-A2	3.9	2.7	7.6	1.5
Time A0- A2	7.0	4.6	11.3	1.8

Note: A0=baseline assessment.

4.5.3 Motor Performance

The mean PDI scores of the 34 participants who completed the study are reflected in Table 14 and in Figure 4 below.

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Table 13: Mean PDI scores of participants who completed the study (n=34)

PDI	Mean	Minimum	Maximum	SD
A0	65.4	17.6	108	18.7
A1	65.2	0.0	108	26.6
A2	70.0	9.0	104	22.7

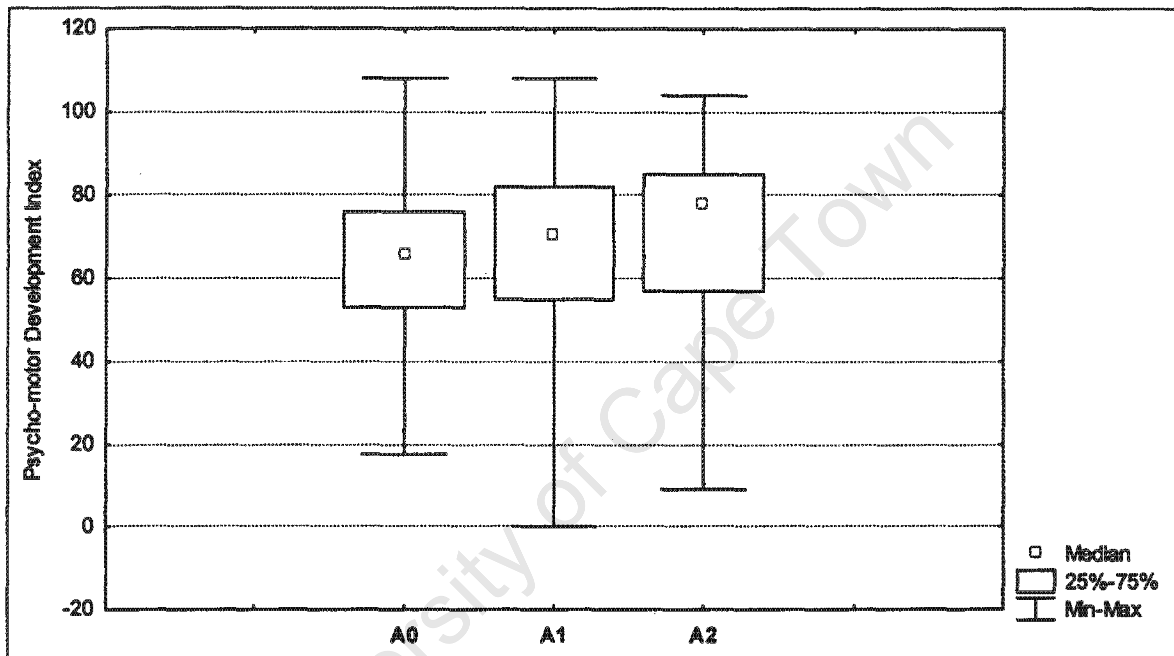

Figure 4: The median PDI score at each of the three periods (n=34)

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Analysis of the motor performance of the longitudinal sample over the course of the study revealed that there was no significant difference in the mean ranks of the PDI over time (Friedman ANOVA Chi Squared = 3.80, p = 0.15).

4.5.4 Mental Performance

The mean MDI scores of the sample are presented in Table 15 and Figure 5 below:

Table 14: Mean MDI scores of participants who completed the study (n=34)

MDI	Mean	Minimum	Maximum	SD
A0	68.9	28.0	103	16.5
A1	73.4	40.0	108	14.8
A2	71.7	36.0	101	16.5

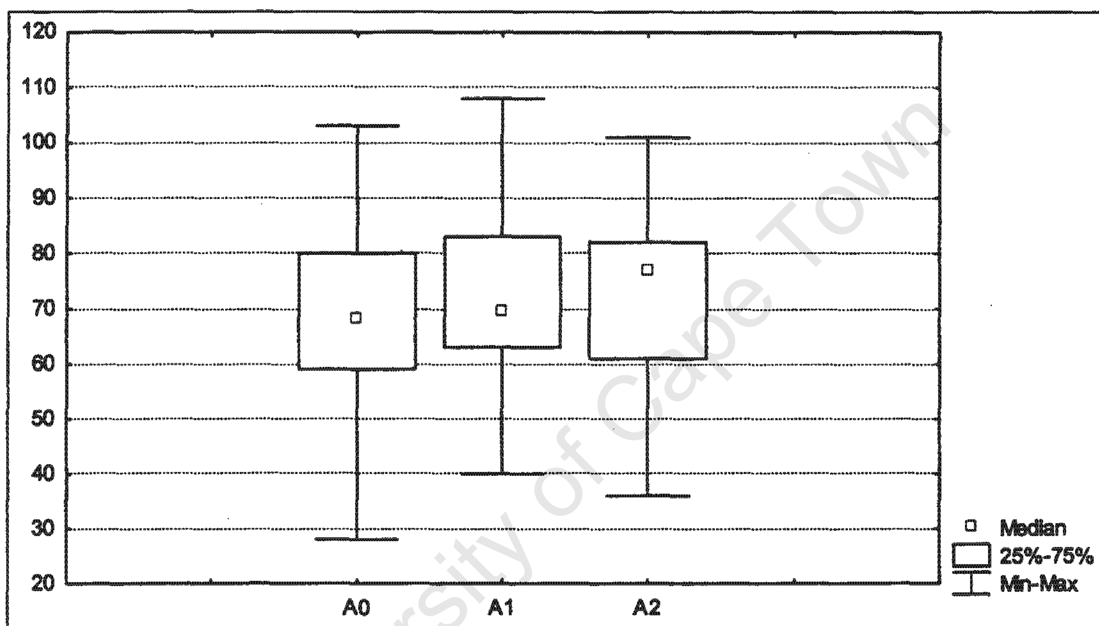

Figure 5: The median MDI score at the three periods (n=34)

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The rank ordering of the performance on the MDI did not change over time (Friedman ANOVA Chi Squared = 0.28, p =0.87)

Analysis of the longitudinal performance of those who were receiving HAART at baseline (n=22) using Friedman's ANOVA, indicated that there was no significant change in the rankings of their motor (Chi-sq=2.89, p=0.24) or mental performance (Chi-sq=0.16. p= 0.9).

5 Discussion

The following discussion focuses on the prevalence and severity of developmental delay in the HIV infected sample assessed in this study. Firstly, the representativeness of the sample is presented in relation to the characteristics of other HIV infected samples. This is followed by a discussion of the characteristics of the age-matched sample. The prevalence of motor and mental delay is then considered in relation to the age-matched sample, to local samples and to samples of children from international studies. Hypotheses regarding the reasons for delay in the HIV infected sample are also presented. This is followed by a discussion on the effects of HAART on development. The longitudinal performance of the HIV infected sample is then reviewed followed by a presentation of the methodological issues associated with this study. Finally, the limitations of this study are examined and recommendations are made.

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5.1 Summary of main findings

The HIV infected sample displayed a high prevalence of motor and mental delay (mild and significant delay). However, a number of children in the age-matched sample also showed delay in motor and mental performance. It is therefore suggested that the prevalence of delay in the HIV infected sample may be over-representative. Thus, for the purpose of this discussion, only children who presented with *significant* delay will be considered to be delayed.

The longitudinal performance of the sample on the motor and mental scales is a cause of concern because the sample of children who completed the study did not improve over the course of the study. However, it can be argued that while there was no improvement in performance, there was also no indication that the sample was deteriorating. Of those who completed the study, 64.7 % were receiving HAART since the initiation of the study. However, the results indicated that those on HAART were performing at the same level as those who were not on HAART. In addition, there was no difference in the performance of those who were on HAART for a longer period compared to those who were on HAART for a shorter period.

5.2 The sample

5.2.1 The HIV infected sample

The HIV infected sample in this study displayed variable health status as reflected by the variation in number of hospital admissions and duration of stay at the hospital. Further variation in their health status was evident by the number of severe/AIDS-defining conditions reported by the sample and by the fact that a third had been admitted to the intensive care unit during their stay in hospital. Another indication of the health status of the sample was that, at the initiation of the study, 66.6% were deemed ill enough to be on HAART.

It is documented that children infected with HIV display a variety of symptoms, ranging from no symptoms, to mild and severe illness (Centers for Disease Control and

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Prevention, 1994). The variation in health status of the sample assessed in this study reflects the phenomenon that within a sample of HIV infected children; some may be in worse state of health than others. Since the children attending the Infectious Diseases Clinic at Red Cross Hospital were primarily identified as being HIV infected when they were admitted to the hospital, it is likely that the sample selected in this study was biased toward children who had experienced serious ill health, requiring hospitalization, in the past. Similar findings were reported by Potterton and Eales (2001) who also concluded that the sample assessed in their study were biased toward those who had been admitted to hospital in the past (Potterton and Eales, 2001).

At the time of this study, twelve sites in the Western Cape had enrolled children onto antiretroviral therapy programme (The Children's Institute and University of Cape Town, 2004). The majority of children receiving these services were enrolled at one of the three tertiary hospitals in the Western Cape. These centres were able to provide treatment to HIV infected children primarily through donor funding (The Children's Institute and University of Cape Town, 2004). Since the study took place at Red Cross Hospital, it is possible that the sample identified in this study were more likely to have access to antiretroviral therapy than other groups of HIV infected children receiving services at other sites.

From a socio-economic perspective, the sample consisted of isiXhosa speaking children who resided in resource poor informal urban settlements (townships) in Cape Town. Their caregivers were mainly single, unemployed women who earned very little money.

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Although the majority lived in formal, brick houses, the quality of the home environments may not have been of a high standard and resources within the home may have been limited considering that these women were not earning much money.

The South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey of 2005 reported that people living in townships have a higher prevalence of HIV than those living in formal urban or formal rural areas (Shisana, Rehle, Simbayi, Parker, Zuma, Bhana, Connolly, Jooste and Pillay, 2005). This same study suggested that that residents of informal settlements were most at risk of contracting HIV as a result of poverty and the breakdown of the normal supportive family structures (Shisana *et al.*, 2005). In addition, it is reported that African women represent a particular high-risk group for HIV infection (Shisana *et al.*, 2005). These studies have cited reasons such as gender dynamics, poverty and the influence of migrant labour systems for the higher prevalence of HIV among African women (Department of Health, 2006, Dunkle, Jewkes, Brown, Gray, McIntryre and Harlow, 2004, Shisana *et al.*, 2005).

Since the majority of the children in this study sample lived in informal townships and their mothers were poor, single African women, it can be concluded that the sample was representative of the sample identified in the South African National HIV Prevalence, HIV Incidence, Behaviour and Communication Survey, 2005. However, the sample may be considered as biased, since it is well known that HIV occurs in all population groups, regardless of race, income and area of residence. Thus, the results of this study should be interpreted with caution and inferences should be limited to this specific group.

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5.2.2 The age-matched sample

This group was constructed to match the HIV infected sample in terms of language, age and because they showed no signs of immune supression or apparent ill health. In addition, their medical records indicated that these children were hospitalized less than three times since birth. However, there were children within this sample who had had recurrent episodes of ill health such gastroenteritis and chest infections whose symptoms were not severe enough to warrant an admission to hospital. Their caregivers were mainly poor, unemployed women, the majority of who lived in shacks. A greater percentage of the caregivers of the age-matched sample were married or living with a partner compared to the HIV infected sample.

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Information on the living conditions of children in the Western Cape suggests that 35% of children live in poverty, 6% have inadequate access to sanitation, 28% live in overcrowded dwellings, 8.3% are underweight and 0.9% are severely underweight (Jacobs, Shung-King and Smith, 2005). Cummins (2002) has suggested that children living in township areas of the Western Cape, are particularly at risk to conditions such as tuberculosis, gastric and other chest infections because of environmental influences (Cummins, 2002). Clearly, the number of children in our study who had a history of illnesses commonly associated with unsanitary environments, overcrowding and malnutrition can be interpreted as being representative of poor children living in townships in Cape Town.

Analysis of a report from the Western Cape Metropolitan Council showed that the age-matched sample in this sample represented a disproportional amount of people who lived in informal housing. The Cape Metropolitan council reported that 19% of the population in the Western Cape lived in informal housing (Cape Metropolitan Council, 2001). The disproportionate number of shack dwellers in the age-matched sample could be explained by the assumption that the area from which the age-matched sample were drawn, consisted of a large proportion of recent migrants to the Western Cape who were living in shacks because they were unable to access decent housing and employment opportunities. In addition, since the majority of the age-matched sample reported earning less than R1000 per months, it is likely that they could not afford adequate formal housing.

In conclusion, the HIV infected sample may not have accurately reflected the situation of all HIV infected children in Cape Town, since a large proportion were symptomatic and receiving HAART. Thus, the sample of children in this study may not be representative of the general population of HIV infected children in Cape Town, as this sample recruited in this study may have been at the severe end of the disease spectrum.

Participants in the age-matched sample shared many health and social characteristics with the majority of township dwelling children in Cape Town thus contributing to the external validity of this study. However, the representivity of this sample is limited to children who reside in resource poor areas of Cape Town. Comparison between the Cape Town sample of age-matched children and children resident in other parts of South

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Africa should be made with caution, as there may be socio-economic, environmental and cultural differences between children in the different cities and provinces.

5.3 Prevalence and severity of motor and mental delay

5.3.1 Performance of the HIV infected sample

The prevalence of significant motor delay was 66.7% and the prevalence of significant mental delay was 52.9% among the HIV infected sample. While it was expected that many children within the HIV infected sample would be delayed, a cause of concern was that so many children presented with significant delay. The extent of the delay in some children is emphasised further by the fact that extrapolated scores were calculated for eleven participants on the motor scale and for six participants on the mental scale because they achieved deficient raw scores.

Neurodevelopmental studies of children with HIV suggest that the prevalence of developmental delay varies considerably in HIV infected populations. Spiegel and Bonwit (2002) suggested that the prevalence of developmental delay in HIV infected children ranges between 25-90% (Spiegel and Bonwit, 2002). Variations in prevalence of delay can be attributed to a variety of reasons, including the characteristics of the samples assessed as well the instruments used to measure the presence of delay.

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The motor delay reported among the HIV infected infants at the initiation of this study was quite high (66.7%) in comparison to prevalence of motor delay (i.e. 40%) reported by Potterton and Eales (2001). Differences in the prevalence rates reported in this study compared to Potterton and Eales study (Potterton and Eales, 2001) can be attributed to two main features, viz., the different characteristics of the samples and the difference in the instrument used to assess motor delay.

The population of HIV infected children studied by Potterton and Eales (2001) included 30 HIV infected children under the age of 12 months who had previously been hospitalised for HIV related illness (Potterton and Eales, 2001). The motor performance of this sample was assessed using the Neurodevelopmental Assessment Score. The authors of this study, attributed the poor performance of their sample to evidence that suggests children who develop clinical signs and symptoms early in life usually have poorer developmental outcomes (Potterton and Eales, 2001).

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In comparison, the mean age of the participants in this sample at the initiation of the study, was older (i.e. 15.8 months) than the Potterton and Eales sample (i.e. 7.5 months) (Potterton and Eales, 2001). Since HIV is progressive, it can be hypothesised that the increased prevalence of motor delay in this study was attributed to the older children in the sample due to progressive viral replication in the CNS over time or the effect of multiple or chronic opportunistic infections. This hypothesis is confirmed on examination of a study by Msellati et al (1993), who found that the proportion of infected children with delayed performance was highest at 12 and 18 months (Msellati *et al.*, 1993).

None of the children in the Potterton sample belonged to a group who had been receiving HAART (Potterton and Eales, 2001). Although it is unclear from their study whether the resources were available to commence treatment, it is possible to assume that these children were not ill enough to commence HAART. In contrast, 66.6% of the participants in this study were considered ill enough to commence HAART. The sample in this study could thus be viewed as being in a poorer state of health, thus contributing to the higher prevalence of delay.

Another reason for the increased prevalence found in study compared to the Potterton and Eales (2001) study could be attributed to the different instruments used. Potterton and Eales (2001) used the Neurodevelopment Assessment (NDA) tool to establish the presence developmental delay. While this tool is appropriate for use in a busy clinic environment as it is quick and easy to administer, the authors acknowledged that it may not have been as sensitive as a more comprehensive test, such as the BSID II (Potterton and Eales, 2001). The NDA and BSID II have not been formally compared in terms of concurrent validity; therefore, it is difficult to compare the scores. However, both tools are able to detect the presence of delay. It is likely that the BSID II was able to detect more cases of developmental delay than the NDA thus resulting in a greater number of children with delay.

The prevalence of delay in this sample was also compared to the prevalence of delay in other African samples. These studies were chosen for comparison, because it is well

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known that the epidemiology of HIV infection in developed countries is not comparable to the epidemiology of HIV infection in Africa (Drotar *et al.*, 1997).

According to a study conducted in Rwanda, the prevalence of motor and mental delay varied at different ages and with disease stage (Msellati *et al.*, 1993). In the Rwandan study, 31% of HIV infected children displayed developmental delay and at 18 months, this figure had risen to 40% (Msellati *et al.*, 1993). Although the prevalence detected in Rwandan sample was lower (31-40%) than the prevalence found in our study, the prevalence of delay was higher among those with severe illness. Amongst those who were diagnosed with AIDS, 87% of children aged 12 months and 70% of those aged 18 months were classified as being neurodevelopmentally delayed. It can be concluded from the Rwandan study that the prevalence of developmental delay increases with age and disease severity. Therefore, it is likely that the older, more severely ill children in this sample contributed to the high prevalence of delay. However, the variation in prevalence of motor and mental delay between the Rwandan study and this study may be also be attributed to fact that Msellati et al (1993) used a self- constructed developmental instrument and not the BSID II.

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In a Ugandan study by Drotar et al (1993), the prevalence of delay, among HIV infected infants was assessed using the BSID. Therefore the results may be more comparable, although the BSID I was used and not the BSID II. Their study, like the previously discussed study by Msellati et al (1993), showed that prevalence of motor delay increased with age (Drotar *et al.*, 1997). Their results showed that the greatest percentage of

children with abnormal BSID scores occurred at 24 months, with 23% showing abnormal motor performance. The highest prevalence of mental delay occurred at 18 months of age, where 18% of those assessed demonstrated abnormal scores (Drotar *et al.*, 1997). In comparison to this study, the study by Drotar et al (1997) showed a lower prevalence of motor and mental delay. Although the authors also used the BSID, different methods were used to record the results obtained in their sample. Drotar et al (1997), measured the raw scores of the HIV infected sample in their study against the mean raw scores of a sample of uninfected infants and then classified the results as either normal or abnormal (Drotar *et al.*, 1997). Since the scores of the HIV infected sample in their study were compared to the scores of their peers and not to the norm referenced scores published in the BSID II manual, it can be concluded that the prevalence of delay would be different.

The high prevalence of delay in the HIV infected sample in this study can also be considered in terms of their socio-economic characteristics. According to studies, children living in impoverished conditions are more likely to develop frequent episodes of illness (Duncan *et al.*, 1994, Kvalsvig and Connolly, 1994), are more likely to be in poorer state of health (Bradley and Corwyn, 2002) and are likely to be malnourished (Armstrong J, Dorosty A, Reilly J, Emmet P, Child Health information Team; 2003).

Although relatively equal numbers of children in the HIV infected sample lived in either informal dwellings (47.1%) or formal dwellings (52.9%), it can be inferred from the abovementioned studies that those who lived in informal dwellings contributed to the prevalence of delay in the sample. However, since many caregivers of the HIV infected

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sample were poor, it is suspected that among those who lived in formal brick houses, their home environments may have been limited in terms of provision of developmental stimulation resources.

5.3.1.1 Performance on motor scale versus mental scale

The HIV infected sample in this study, performed slightly better on the mental scales than on the motor scales. Comparisons relating to the performance of this sample cannot be made with the Potterton and Eales (2001) sample since mental/cognitive aspects of development are not assessed by the NDA (Potterton and Eales, 2001). However, Potterton and Eales noted that the infants in their study were most delayed in motor activities requiring core/central muscle strength and co-ordination (Potterton and Eales, 2001). The authors suggested that these deficits are likely attributed to a combination of weakness caused by de-conditioning and ill health as well as poor coordination of muscle activation caused by CNS damage (Potterton and Eales, 2001). This would explain the finding that the HIV infected sample in this study performed worse on the motor scale since those who had been admitted to hospital might have experienced deconditioning related to muscle strength and cardiovascular endurance.

The finding from our study regarding mental performance is consistent with findings reported by Msellati et al (1993) and Drotar et al (1997), who found language, social and mental development to be less severely affected compared to motor performance of HIV infected participants (Drotar *et al.*, 1997, Msellati *et al.*, 1993).

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The reasons for better performance on the mental scale in comparison to the motor scale can be attributed to various reasons. It has been suggested that cognitive tests that require significant motor input may affect the results obtained (Bayley, 1993, Mayes, 1997, Palisano, 1993). In recognition of this, Drotar et al (1997), included an additional measure of cognitive performance, "infant visual recognition memory", and found that this skill was not affected by HIV infection suggesting that cognitive skills may be spared in children with HIV infection (Drotar *et al.*, 1997).

Similar findings were also reported in a study of HIV infected children living in Canada (Blanchette, Smith, Fernandes-Penney, King and Read, 2001). The authors documented that mental performance was less severely affected compared to motor performance. They attributed this to the fact that HIV infection of the CNS causes disruption of the myelination process in the frontal and parietal regions of the developing brain. Damage to these areas early in life may not be recognizable at a young age, and is therefore expressed as spared cognitive function, but leads to delays in higher level functions later in life (Blanchette *et al.*, 2001).

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Thus, it can be concluded that the poorer performance on the motor scales is likely to be attributed to the effects of chronic illness, resultant muscle weakness and CNS damage.

5.3.2 Performance of the age-matched sample

As expected, the age-matched sample performed better than the HIV infected sample in both motor and mental tests. However, the age-matched sample performed worse than the

South African norming sample (Richter and Griesel, 1988) and worse than children tested in the American norming sample (Bayley, 1993).

5.3.2.1 Comparison to the HIV infected sample

A number of studies have documented that the neurodevelopmental performance of HIV infected children was significantly poorer than the performance of uninfected infants (Bruck *et al.*, 2001, Drotar *et al.*, 1997, Gay *et al.*, 1995, Msellati *et al.*, 1993, Wolters *et al.*, 1995). In order to control for the influence of additional risk factors for developmental delay, these authors chose to compare the performance of HIV infected children to various types of control groups. The majority of these studies used samples of uninfected infants born to HIV infected women as control groups (Bruck *et al.*, 2001, Drotar *et al.*, 1997, Gay *et al.*, 1995, Msellati *et al.*, 1993).

Although the performance of the HIV infected sample was significantly poorer than the performance of the age-matched sample, the purpose of the age-matched sample was not to serve as a control group. Comparison of the performance of the two samples should therefore be interpreted with caution, as not all children in the age-matched sample were identified as HIV negative. However, this undiagnosed age-matched sample, was considered to suitable for use as a reference sample from which the performance of the HIV infected sample could be evaluated in the absence of current BSID II norms for isiXhosa children.

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5.3.2.2 Comparison of the age-matched sample to the SA BSID norms (1988)

The age-matched sample in this study displayed poorer motor (mean PDI= 92.3, SD=15.3) and mental performance (mean MDI= 84.3, SD=11.8) than the norming sample established by Richter and Griesel (1988). Richter and Griesel (1988) reported that Black South African infants were in advance of their North American counterparts between 2 to 10 months of age on the motor scale and between 4 to 15 months of age on the mental scale (Richter and Griesel, 1988). After the first year, the performance of the two samples was reported to be comparable. South African infants also passed certain items on the motor and mental scale at a younger age compared to the USA sample (Richter and Griesel, 1988).

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According to Richter and Griesel (1988), a major motivation for establishing a local set of norms was to contribute to the debate on African infant precocity (Richter, Griesel and Rose, 1992). Irwin Carruthers (1987) had previously conducted a norming study among infants in the Western Cape, using the Denver Developmental Screening Test (Irwin-Carruthers, 1987) .and concluded that Black South African infants were in advance of their American peers in gross and fine motor activities (Irwin-Carruthers, 1987). The findings by Richter and Griesel (1988) thus contributed to the concept suggesting that African infants displayed advanced performance.

A review on African infant precocity, conducted by Warren (1975), concluded that the phenomenon could not be empirically proven and that variation in development was attributed to social or cultural variations (Warren, 1972). The concept of African infant precocity was further challenged by Super (1976), Cintas (1988) and Kolobe (2004) who

suggested that differences in child rearing regimes and other cultural practices influenced development and resulted in variation in acquisition of milestones among different groups (Cintas, 1988, Kolobe, 2004, Super, 1976).

In contrast to the studies by Richter and Griesel (1988) and Irwin-Carruthers (1987), two unpublished studies reporting on the performance of Black African children were considered. These studies, one of which used the BSID-II (Matyida and Jelsma, 2004) and the other which used the Alberta Infant Motor Scale (AIMS) scale (Jelsma *et al.*, 2004) were conducted on samples of healthy isiXhosa children with no evidence of immunosupression , who resided in resource poor townships,. Both studies reported a developmental lag between the isiXhosa samples and the norming samples as found in this study.

In addition, the comparison between the classification of performance of the age-matched sample and the current USA norming sample tells a similar story. In both groups of typically developing children, over 30% of the South African sample demonstrated delayed performance, compared to 15% of the American norming sample (Bayley, 1993).

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A possible reason for the increased number of children with poor developmental performance over the past twenty years could be attributed to the differences in scoring requirements of the BSID II in comparison to the BSID I. Studies undertaken by the contributors responsible for formulating the BSID II have concluded that children need a higher raw score on the BSID II to achieve the same index score on the BSID I because children are now performing better than when the standardisation data for the original BSID were collected (Bayley, 1993). This would imply that the South African sample is not performing at a lower level than the 1988 sample, but that their performance has not increased at the same rate as their peers in North America.

It is difficult to know exactly what factors are responsible for the increased prevalence of delay as none could be identified through this study. The poor performance could be because of the living conditions that might have deteriorated over the past 20 years. The majority of caregivers in the age-matched sample were living in shacks. The housing in informal settlements is cramped and there is little space in which children can engage in physical play, which limits their ability to explore and learn and develop motor skills.

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The impact of poor quality housing was described by Lima et al (2004) who reported that caregivers living in the most deprived areas of northeast Brazil; avoided putting their infants on the (mud) floor to play as "...mud attracted ants" and "the rough surface grazed the child's legs when crawling..." (Lima *et al.*, 2004). Cummins (2002), noted that residents of informal settlements in the Western Cape are particularly at risk to the adverse weather conditions experienced during winter (Cummins, 2002). Personal communication over the course of this study with caregivers who resided in townships revealed that they too avoided placing infants on the floor to avoid exposure to cold, wet floors, which could lead to illnesses. In addition, Richter and Grieve (1991) established that the home environment affects child development. In their study, it was noted that quality of the home environment significantly contributes to mental performance (Richter and Grieve, 1991).

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Despite the clear commitment by the City of Cape Town to upgrade services and facilities to the informal settlement areas, and the freely available child support grant, which must aid in the alleviation of poverty to a certain extent, the situation of many of the mothers appears dire. As Abbot and Bartlett state "the effects of deprivation, parental expectations and poverty have a contributing influence on infant motor development" (Abbot and Bartlett, 1999) and the decrease in motor performance could be reflection of the poor socio-economic status of the mothers.

5.4 Influence of antiretroviral therapy

Two important findings relating to the effect of antiretroviral therapy were noted in this

study. Firstly, it appeared that the use of PMTCT prophylaxis delayed the onset of severe illness and thus the need for initiation of HAART. Secondly, developmental performance was not influenced by being on HAART for any length of time.

5.4.1 Influence of PMTCT prophylaxis

In this study, the large numbers of children who were diagnosed with HIV infection subsequent to exposure to antiretroviral prophylaxis would point to the limited efficacy of this regime to prevent transmission. While the primary aim of providing PMTCT prophylaxis is to prevent the transmission HIV from mother to child, the use of antiretroviral prophylaxis also appears to be associated with a later onset of illness (Ioannidis *et al.*, 2004). Therefore, even if PMTCT prophylaxis should fail to prevent infection, Ioannidis et al (2004) have suggested that disease progression in HIV infected infants may be delayed if maternal viral loads are kept low during pregnancy through the provision of antiretroviral prophylaxis (Ioannidis *et al.*, 2004). In this study, a significant association between being exposed to antiretroviral prophylaxis and not yet requiring HAART was established.

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5.4.2 Influence of HAART on developmental performance

No difference in scores on the BSID II was detected between those who had been receiving antiretroviral therapy (HAART) and those who had not. This finding was not expected as studies have shown that HAART improves neurological outcome (Pizzo *et al.*, 1988, Sanchez-Ramon *et al.*, 2003). The hypothesis made at the initiation of the study was that children who were not eligible for HAART would in a better state of health than those who were on HAART since those not on HAART were deemed to be well enough not warrant treatment. Thus, it was also expected that those not receiving HAART would exhibit better developmental scores. The results from this study confirmed this assumption because the HAART subgroup reported more hospital admissions, indicating the criteria for placing children on HAART are correct.

However, it seems that HAART did not influence developmental performance. In the absence of neurological imaging and health status markers such as viral loads and CD4 counts, it is difficult to determine the exact reasons for the equivalent performance. When considering hospital admissions alone as an indicator of health status, it is possible to assume that the delay seen in this sample was less likely influenced by health status and was probably due to CNS damage caused by HIV.

A study on the prevalence of encephalopathy in HIV infected children showed a marked decrease in the rate of Progressive HIV Encephalopathy (PHE) following the introduction of antiretroviral therapy (Chiriboga, Fleishman, Champion, Gaye-Robinson and Abrams, 2005). However, this study also showed that children who had had PHE continued to display residual neurological and cognitive impairment compared to those

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who never had PHE despite receiving antiretrovirals (Chiriboga *et al.*, 2005). It can therefore be concluded that the delay caused by HIV infection may be persistent despite HAART, and therefore no difference in the performance of the two groups was detected.

Another surprising finding was there was no difference in the performance of those who had been on HAART for a longer time (i.e. six months or longer) compared to those who had been on HAART for a shorter time (i.e. less than six months). The assumption was that those who had been on HAART for a longer time would display higher developmental scores. This assumption was based on evidence that suggests that children who commence HAART may take some time to show improvement in immune status markers and that some infants may actually exhibit deterioration in health status as they reconstitute their immune systems (Lindsey, Malee, Brouwers and Hughes, 2007). The fact that children, who were on HAART for longer periods were comparable to those who were on HAART for shorter periods. This could possibly be attributed to the evidence presented by Lindsey et al (2007), who examined the effect of HAART on neurodevelopment and concluded that although the introduction of HAART results in positive outcomes in terms of immunological status and mortality, the effect of HAART on neurodevelopment in the first three years of life is limited (Lindsey *et al.*, 2007).
In conclusion, limited inferences can be drawn from the findings related to HAART and interpretations should be limited to the sample assessed in this study. It is difficult to predict the reasons for the comparable performance of the samples and it is recommended that further longitudinal research be conducted to investigate the impact of HAART on neurodevelopment.

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5.5 Longitudinal performance of HIV infected sample

The lack of improvement in motor and mental development over the course of the study is cause for concern. Although these results are to be interpreted with caution due to the rate of attrition, neither the introduction of HAART nor the sustained status of good health, which precluded recruitment into the HAART regime, resulted in improved performance.

Nozyce et al (1994) and Belman et al (1996) confirmed that persistent developmental delays predominate in children who develop AIDS-defining conditions within the first two years of life. In contrast, children who did not develop an AIDS defining condition were comparable to uninfected infants (Belman *et al.*, 1996, Nozyce *et al.*, 1994). Nozyce et al (1994) attributed the poor performance of the AIDS group to the effects of illness since all participants in this group had had multiple hospital admissions. However, the same group also had abnormal serial head circumference measures and abnormal neurological examinations which indicated that they also had significant CNS involvement which contributed to poor performance (Nozyce *et al.*, 1994).

The reasons for this lack of improvement in this study could be attributed to a number of reasons. Firstly, the plateau could be explained by the influence of differential attrition. It is possible that children who responded best to the treatment were less likely to return to the clinic than those who remained the same or deteriorated.

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Secondly, the damage to the CNS is primary and takes place independently of the amount of illness or hospitalization that the child undergoes. This conclusion is borne out by the comparable performance between children who were receiving HAART and those who were not eligible. The health status of the participants over the course of the study varied considerably. Some children had been hospitalized during assessment intervals and others had been seriously ill. As is the nature of HIV infection, children were prone to periods of ill health. Although, they were excused from assessment when they were ill, it is possible that the effects of illness may have lingered even after their temperatures had returned to normal. As assessments were scheduled at three monthly intervals, it was not always possible to accurately assess the impact of illnesses experienced in that period.

Nozyce et al (1994) used raw scores instead of index scores to assess a cohort of infants from New York, between the ages of 3 and 24 months. Approximately 50% of their mothers had used drugs during pregnancy. Nozyce et al (1994) picked up a modest decrement in motor and mental performance of the HIV infected children over the course of the study, a result that was not found in our study, as our study reported no change over time.

The lack of improvement is of serious concern as, if the results are applied to the general population; the advent of HAART is still not going to prevent large numbers of children with developmental delay being admitted to a school system that may be unprepared to provide special support.

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5.6 *Methodological issues*

5.6.1 Research design

Several authors have used case-control designs when investigating the development of children with HIV to minimize the effects of confounding variables (Aylward *et al.*, 1992, Bruck *et al.*, 2001, Fishkin, Armstrong, Routh, Harris, Thompson, Miloslavich, Levy, Johnson, Morrow, Bandstra, Mason and Scott, 2000). Although a case-control design was not followed in this study, attempts were made to ensure that the age-matched sample matched the HIV infected sample in terms of gender and language. It was assumed that since many participants in the HIV infected sample resided in the same areas and received state sponsored health care, that their socio-economic status would be comparable. Although factors such as income, employment status and educational level of the caregivers were not significantly different, other factors such as housing status and relationship status of the caregiver were different.

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Despite problems relating to attrition, longitudinal study designs are an appropriate choice to investigate the development of children with HIV. Several authors have used longitudinal study designs and have been able to follow up infants from birth, thereby documenting their natural history (Drotar *et al.*, 1997, Llorente *et al.*, 2003, Msellati *et al.*, 1993). Bayley (1993) supports the use of repeated measures especially when children have medical or social risk factors that would cause developmental deviations from the normal path (Bayley, 1993).

Ideally, the developmental trends of the age-matched sample should be followed along with the development of the HIV infected infants to determine the onset of developmental problems and to allow for comparison at each stage. It is recommended that future studies incorporated longitudinal analysis of "normal" healthy children since so many children in the age-matched sample were delayed.

5.6.2 Use of the BSID II

One of the major problems associated with the use of the BSID II outside of the USA, is that the test equipment and questions contain items that are not commonly seen by children living in poor social settings.

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Since the majority of the children in this study lived in poverty, it can be assumed that failure to hold a pencil correctly or to place puzzle pieces together was partly because these children had not been exposed to these types of toys at home. Many items used in the test were unfamiliar to the children (e.g. beads, blocks and puzzles) and the doll supplied with the test kit had distressed quite a number of children who refused to interact with it. Another problematic item included the naming of colors. Personal communication with isiXhosa speaking mothers revealed that colours are often taught to the children in English. Since English is not spoken within the home, this concept appears to develop later once the children start crèche or school. While their apprehension or unfamiliarity with the test items may have had an obvious effect on their performance in the mental test, it seems less likely that the test items would affect motor performance, since assessment of gross motor skills did not require much interaction with unfamiliar toys.

In addition to problems relating to test equipment, the BSID II has not been formally translated into isiXhosa. While it appeared that participants and caregivers understood what was expected from each test item, there was a possibility that certain test items may have been misunderstood despite the presence of a translator.

The length of time for required for testing might have resulted in somewhat lower performances if children became tired during the assessment. It would have been ideal to separate the administration of the mental and psychomotor scales but this would have entailed a further visit to the clinic for the participants.

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In the absence of appropriate standardized developmental assessment tools developed for use among African infants, the BSID II seems to perform well in measuring the developmental status of children infected with HIV. While it seems that the validity of the motor scale items was less affected by the aforementioned limitations, the high prevalence rate of developmental disability as detected by the BSID II among both the HIV infected sample and the age-matched sample warrants further research.

5.7 Limitations and Recommendations

The cross-sectional study resulted in an adequate sample size and the results based on the section of the study relating to the prevalence of delay are likely to be externally valid to children who have been diagnosed with HIV and have been hospitalized. However, the external validity of the longitudinal study is limited due to the rate of attrition.

5.7.1 The HIV infected sample

The HIV infected sample consisted primarily of children who had been identified as being HIV positive because they showed signs of HIV. Thus, the sample recruited from Red Cross Children's Hospital could represent a sample of HIV children biased towards the more severe end of the disease spectrum. However, within this limitation it was a suitable sample for this study. An ideal study, however, would be to follow a cohort of children identified through PMTC clinics and to monitor the development of both the HIV infected and uninfected children from birth over a period.

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5.7.2 The age-matched sample

As with the original norming samples of the BSID II, a more diverse and appropriate reference group could be identified at other sites where children are present. However, there is the possibility that samples would be biased by the location from which they were recruited. The performance of children attending playgroups or crèches could be influenced by the receiving additional stimulation whereas children attending health care institutes may represent a disproportionate population of children who are ill. It is conceded that there may have been children with HIV in the age-matched sample that was undiagnosed despite all efforts to exclude children on clinical grounds. Ideally, a sample of children who have been tested for HIV infection would have been a more appropriate choice.

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5.7.3 Attrition rate

The sample remaining at the end of the study was smaller than anticipated even though efforts were put in place to ensure participants attended all follow up sessions. Money to pay for transport from home to the clinic was given to all participants so that they could attend the clinic. Telephone numbers were recorded and contact details were checked and updated frequently. The high attrition rate is a cause of concern because the cause of the attrition was unknown in many cases.

While many caregivers were eager to join the study, very few attended the follow up appointments consistently. Personal communication from clinicians at Red Cross Hospital suggest that while many caregivers may recognize the importance of monitoring

children's motor and language milestones, the health and nutritional status of their children are often regarded as more important. Kolobe (2004) has commented on the influence of culture on the developmental expectations of Mexican-American mothers in the United States. Her conclusion that Mexican –American parents place greater emphasis on the development of other aspects such as demeanour than on the attainment of other developmental milestones supports the suggestion that culture defines to a certain extent, the importance attached to aspects of development (Kolobe, 2004). The caregivers in this study, who shared similar cultural backgrounds, may have been more concerned with other aspects of their children's development, e.g. weight gain, rather than monitoring gross motor milestones.

A number of longitudinal studies investigating the development of children infected with HIV have showed good retention of participants (Drotar *et al.*, 1997, Msellati *et al.*, 1993). Drotar et al (1997) reported a drop out rate of only 7% and Msellati et al (1993) reported a default rate of 10% for reasons other than mortality suggesting that attrition occurs even under careful investigation. These studies had the advantage of being conducted in collaboration with large research teams at centres where mothers were tested for HIV during pregnancy and their children followed up. In addition, follow up appointments were arranged in dedicated outpatient clinics that were convenient for the caregivers. In some cases, children were even hospitalised and treated free of charge in order to assess their neurological status.

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A longitudinal study by Smith et al (2000) experienced high default rates at follow -up assessments for reasons other than mortality. Although all their participants had been assessed at baseline, only 54% attended all follow up appointments and 32 had been followed up for less than 2 years. Of those who were followed up for less than two years, 43% had discontinued participation or missed visits for undisclosed reasons (Smith R *et al.*, 2000).

The ability to retain children in a study of this nature is dependent upon the collaboration of a dedicated team of people. Unfortunately, resource and time constraints limited the ability to control attrition in this study and the sample of children who completed every stage of the assessment was small. Coplan et al (1998) have acknowledged that it is often difficult to control attrition in large sample sizes and managed their small sample (n=9) quite well with a 100% follow up rate (Coplan *et al.*, 1998).

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6 Conclusions and recommendations

This study set out to document different aspects of the development of children with HIV. The most important findings relating to the objectives are summarised below:

6.1 Performance of the HIV group

Both motor and mental delays were expected, but the extent of the delay, was greater than anticipated. The finding that development was not influenced by treatment on HAART or by the number of hospital admissions indicates that the delay is primary and takes place before the child is ill enough to warrant receiving anti-retroviral medication.

It is recommended that developmental delay be investigated as a criterion for admission onto the HAART regime and that the impact of early medical and rehabilitation intervention be investigated.

6.2 Effects of HAART

On the basis of the above study, it would appear that the criteria for admission to HAART and the treatment itself do not mitigate the effects of the virus on development. As the impact on the school system of having to provide support for large numbers of children with mental and psycho-motor delay is likely to be considerable, it is recommended that a large longitudinal study, embedded within the service for treatment provision and monitored by a larger medical team is necessary in order to address the important issue of lack of motor improvement over time.

The study provided support for the role of PMTC prophylaxis in delaying the onset of immunocompromise since only 34% of those whose mothers received prophylaxis were on HAART at baseline, compared to 67% of those who had not been exposed to PMTC prophylaxis.

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Criteria for HAART are correct in terms of medical outcome, as there were more hospitalizations in the HAART group however there was no difference in the extent of delay between the two groups. It is recommended that the criteria for commencing HAART include the presence of a severe developmental delay, even in the absence of HIV defining illnesses.

One of the primary challenges in the care of children with HIV should be the early and accurate identification of developmental delays, with the aim of initiating early antiretroviral treatment before permanent lasting motor problems and referral for intervention.

6.3 Longitudinal performance

The sample size was small and these findings should be treated with caution. The findings of this study is limited to the sample assessed and cannot be applied to other groups of HIV infected infants who do not share the same characteristics. No improvement in motor performance was detected from baseline to the final assessment. Although this is a cause of concern, it should be borne in mind that evidence of change was limited by the fact that the sample was not followed up for a longer period. However, if there was little evidence of improvement, there was no evidence of progression of developmental delay which may be viewed as a positive finding for this group of infants.

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6.4 Demographic characteristics

The demographic characteristics of the age-matched sample and the HIV infected group were similar in many respects. However, the mothers with HIV were more likely to be single parents, although more likely to live in brick housing. Both groups live in poor socio-economic conditions and this fact might have contributed to the poor performance in the BSID of both groups.

It is recommended that apart from the child support grants, continued socio-economic support needs to be made available to this group of mothers who are, in the main, single parents without any income apart from government grants.

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6.5 Performance of the age-matched sample

The age-matched sample were performing at a lower level than their peers, and at a lower level than a sample tested 20 years previously, although the majority of the children are still performing within normal limits. The first, most obvious conclusion to be drawn is that, if the BSID-II are to be used to monitor the development of any group of children suspected of having delayed development, the normed values should be treated with caution and possibly 90 should be taken as the mean score (rather than 100, with a SD of 15). If this is not taken into consideration, children with, for example HIV/AIDS may be reported as being more delayed than is in fact the case. The second implication is that the poor performance of the age-matched sample is likely to be symptomatic of the dire socio-economic situations of the mothers.

6.6 Final conclusions

The extent of developmental delay in children with HIV is considerable and there is an urgent need to investigate how best this delay should be managed. Despite the fact that HAART was available to the children, there was no sign of motor or cognitive improvement. However, considering that the condition is progressive in nature, there was no evidence of decreased motor and cognitive performance over time, and HAART may prevent further developmental deterioration. Severe delay and lack of improvement implies that school system will need to meet the needs of children with gross motor problems, and problems with learning and cognition. A longitudinal study, embedded within the treatment provision and monitored by a larger medical team is necessary in order to address the important issue of lack of motor improvement over time. Accurate longitudinal data need to be collected to assist in planning of both rehabilitation and educational intervention. Therapists need to become part of management teams which provide comprehensive services and which monitor the outcome of therapies over time.

A famous statement by Gabriela Mistral, as cited by Morley and Lovel (1986) could not be truer for all the HIV infected children who are suffering from an epidemic and illness not of their making:

"We owe it to them to develop the best possible management and support structures for both themselves and their mothers. Many of the things we need can wait. The child cannot. Right now is the time his bones are being formed, his blood is being made and his senses are being developed. To him we cannot answer Tomorrow. His name is Today".

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8 Appendices

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Questionnaire

Research Area ____________________

Date ____________________

Child's Details

Name ______________________________

Surname ______________________________

Hospital Folder Number ______________________________

DOB ______________________________

Gender Male ______________ Female ______

Gestational Age ______________________ weeks

Birth weight ______________________ grams

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Child's Medical Information

Exposed to PMTCT ______________________________

If Y, what ______________________________

PCR/ELISA ______________________________

PCR date ______________________________

HAART Yes ______________________ No ______

Date started ______________________________

Indication for starting Rx ______________________________

Lab test results

CD4 count HAART Start	
CD4 percent HAART Start	
VL HAART Start	
VL log HAART Start	
Stage HAART Start	

Hospital admissions record

No	Admitted	Diagnosis	Discharged	Duration	ICU	ICU days
1						
2						
3						
4						
5						
6						
7						
8						

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Any of the following illnesses since birth (tick all that apply)

Thrush	
TB	
Encephalopathy	
Meningitis	

Caregiver Details

Name ______________________

DOB ______________________

Contact number ______________________

Where do you live? ______________________ (area)

What is your relationship to this child? ______________________

If not the mom, why? ______________________

Are you the legal guardian? ______________________

Do you receive a grant? ______________________

Married/single/divorced/
widowed/living with partner ______________________

Highest level of Education Grade ______________________

Are you employed? ______________________

Own monthly income
R0-300 ______
R300-600 ______
R600- 1000 ______
More than R1000 ______

Type of house Informal formal

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School of Health and Rehabilitation Sciences
University of Cape Town
Division of Physiotherapy
Consent Form

Title of study: An investigation into the development of children using the BSID II

Researcher: Gillian Ferguson
Contact: 0829743924

Supervisor: Assoc Prof Jennifer Jelsma
Contact: 021 406 6401

I, *(name)*______________________________ (parent/legal guardian), hereby give permission for my son/daughter *(name)*________________________ to participate in a research project under the direction of the abovementioned researcher investigating the development of children attending this Clinic. I understand that this research will be used to describe and understand the motor and mental development of children living in the Western Cape using the Bayley Scales of Infant development Second Edition (BSID II). The purpose of this study is to compare the development of children in the Western Cape with the normative sample used in the construction of the BSID II. This study form part of a broader study investigating the development of children who are infected with the HI virus. The results obtained from children attending this clinic will be compared to the results obtained from children who are infected with the HI virus

I understand that I will not be given anything extra for participating in this study and that participating will not have any other benefit to my child or me. If my child is diagnosed with a developmental problem, the researcher may refer my child to the therapist at this clinic for assessment. I understand that there will be no physical risk to my child during the assessment process. Neither my child nor I will be harmed in any way. In agreeing to participate in this study, I understand that the researcher will spend about 45 minutes assessing my child's development using the BSID II. This involves the administration of a set of motor and cognitive tasks that my child is expected to complete. I understand that participation in the study is voluntary and I know that I can stop the test at any time I want to. I have the right to withdraw at any stage during and/or after the assessment. I authorise the researcher to keep, use and dispose of the results of this study with the provision that my name will not be associated with any of the results. I understand that only the researcher will know what the results of the test are and that the information requested from me will remain confidential. I have the right to consent or refuse that information be shared with my doctor. If I refuse to participate in this study it will not affect the services my child is receiving at this clinic.

I have read the content of this form, and I AGREE TO PARTICPATE in this study

Signed ________________________ Date______________

I have explained and defined in detail the research process to which the subject has consented in his/her home language.

Researcher ________________________ Date______________

Translator (witness) ________________________ Date______________

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University of Cape Town
School of Health and Rehabilitation Sciences
Division of Physiotherapy

Consent form

Title of Study:	Assessment of the motor and cognitive development of infants with HIV	
Investigator:	Gillian Ferguson	BSc Physiotherapy
	Contact:	082 974 3924
Supervisor:	Dr Jennifer Jelsma	PhD Physiotherapy
	Contact:	021 406 6404

- ☐ I have been asked to give permission for my child to participate because he/she attends the Red Cross IDC clinic
- ☐ This research is to help healthcare workers to understand the development of children who have HIV
- ☐ I understand that I will not be given anything extra for participating in this study
- ☐ If my child is diagnosed with a developmental problem, the researcher may refer my child for further investigation if appropriate
- ☐ Participation in this study will not have any other benefit to me
- ☐ Neither my child nor I will be harmed in any way.
- ☐ The researcher will spend about 40 minutes with us every three months for a period of one year to assess my child's development
- ☐ They have explained that if I do not attend on my given appointment day, they will contact me to attend the clinic.
- ☐ The researchers may contact me at home to arrange to assess my child in his home environment during the course of the study
- ☐ I know that my child does not have to take part in these tests and that I can stop the test at any time and withdraw from the study
- ☐ I understand that only the researcher will know what the results of the test are and that all information requested from me will remain confidential.
- ☐ I have the right to refuse that information be shared with my doctor
- ☐ If I refuse to participate in this study it will not affect the treatment and medication given to me by the doctors

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I acknowledge that I am the child's legal guardian. I hereby give consent for him/her to participate in this study

Signed ____________________ Date______________

Interviewer ____________________ Date____________________

Witness/Translator ________________ Date____________________

RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL ANTIRETROVIRAL TREATMENT GUIDELINES Version 2.3, Valid from June 2004

VISION

The Children's Hospital is dedicated to serving the best interests of the child, and accordingly is committed to the goal of antiretroviral therapy for all children who may benefit from it, and for their families. This commitment includes facilitating the development of management guidelines that are feasible outside of tertiary institutions.

OBSTACLES

The overwhelming magnitude of the number of children affected, the cost of medicines and monitoring their efficacy, and the scarcity of drugs, of manpower, and of physical resources stand in the way of achieving our goal. The situation with regard to all these factors is fluid and this makes us hopeful that our goal will ultimately be achieved.

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WAY FORWARD

Given the obstacles it is necessary to tackle the problem piece by piece, group by patient group, in an orderly, consistent and fair manner, guided by objective criteria.

Between June 2003 and December 2003 antiretroviral therapy was offered to all HIV-infected children whose discharge was held up by persistent medical problems and those with multiple admissions.

Henceforth, all children with modified WHO category III disease and / or severe immune suppression will also be considered for antiretroviral therapy.

As more staff members at Red Cross Children's Hospital become experienced at treating children and as resources improve, so the indications for treatment will be further liberalised to include all children with modified WHO clinical stage II disease.

PATIENT SELECTION

Who qualifies?

Antiretroviral therapy is henceforth approved for all children who are certified by an infectious diseases service consultant to meet the criteria for antiretroviral therapy specified below:

Criteria for commencing antiretroviral therapy in children

Children being considered for antiretroviral therapy will need to meet both medical and social criteria before starting therapy.

Medical criteria

- Recurrent hospitalisations (> 2 admissions per year) for HIV-related disease, or prolonged hospitalisation (> 2 weeks) OR
- Modified WHO stage 3 disease OR
- CD4 percentage < 20% in a child under 18 months old, irrespective of disease stage, OR
- CD4 percentage < 15% in a child over 18 months old, irrespective of disease stage.

(See Appendix A for Modified WHO Staging.)

Social criteria

Mandatory

- An identifiable adult who is able to administer medication.
- Demonstrated reliability in adult caregiver i.e. has attended three or more scheduled visits to an HIV clinic. Immunization record of child is up-to-date.

Desirable

- Previous record of adherence to nutritional supplements or other chronic care regimens such as TB drugs may help to identify children who are at risk of poor adherence.
- Able to attend the antiretroviral centre on a regular basis (transport may need to be arranged for patients in rural areas or for those remote from the treatment site).
- Disclosure: it is recommended that clients have disclosed their HIV status to at least one friend or family member or have joined a support group

PROCEDURE FOR REGISTRATION ON THE PROGRAMME

Decisions about initiating antiretroviral therapy are NEVER URGENT. Please ensure that children meet the selection criteria. Where necessary, consult with the Infectious Diseases team.

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Inpatients

Treatment decisions are finalised at the weekly antiretroviral patient round on Monday afternoon between 13h30 and 16h00.

1. Ward registrar should identify children who qualify for treatment, inform the parents about antiretroviral therapy and counsel the caregiver, and obtain parental agreement to proceed.
2. Caregivers should be counselled on at least two separate occasions by the ward registrar and / or a Wola Nani counsellor (Appendix B). The social record should be completed on each patient (Appendix C).
3. The caregiver is provided with an educational pamphlet
4. Screening questionnaire and initial CD4 count (Appendix D) to be done.
5. Patients should be presented at the weekly antiretroviral patient round by the registrar. Completed screening questionairres and social reports must be available at the time of discussion.
6. If it is decided to treat a child, an Infectious Diseases Consultant will authorise treatment.
7. Ward registrar to inform parents about the decision.
8. The ward registrar to oversee the completion of baseline investigations (CXR, Viral load, ALT, FBC and differential count, fasting cholesterol, fasting glucose)
9. Antiretroviral therapy commenced as soon as possible. The signature of an Infectious Diseases Consultant against the initial prescription for antiretroviral drugs authorises their use. Subsequent prescriptions to be signed by the attending doctor.

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Ambulatory patients

1. Attending doctor identifies children who meet qualification criteria. If necessary, a CD4 count (percentage) is included in the screening assessment.
2. At the initial visit, the attending doctor discusses antiretroviral therapy with the caregiver, provides the caregiver with an educational pamphlet and completes the screening questionnaire ± CD4 count (Appendix D).
3. Caregiver attends a educational session with one of the Wola Nani counsellors.
4. The social report should be completed (Appendix C).
5. All documents are appraised by the treatment team and a decision about antiretroviral treatment taken.
6. At the next visit the caregiver is informed about the outcome of the process.
7. If it is decided to treat a child, an Infectious Diseases Consultant will authorise treatment.
8. The attending doctor to oversee the completion of the flow sheet and baseline investigations (CXR, Viral load, ALT, FBC and differential count, fasting cholesterol, fasting glucose)
9. Antiretroviral therapy commenced as soon as possible. The signature of an Infectious Diseases Consultant against the initial prescription for

antiretroviral drugs authorises their use. Subsequent prescriptions to be signed by the attending doctor.

DRUG THERAPY

First line therapy

Unless contraindicated, all children will commence therapy on:

Children < 6 months of age

If fridge available:
1. Stavudine (d4T), with
2. Lamivudine (3TC), and
3. Ritonavir

If no fridge available:
1. Zidovudine (AZT), with
2. Lamivudine (3TC), and
3. Ritonavir

Children > 6 months of age

If fridge available:
1. Stavudine (d4T), with
2. Lamivudine (3TC), and
3. Lopinavir / ritonavir OR Efavirenz

If no fridge available:
1. Zidovudine (AZT), with
2. Lamivudine (3TC), and
3. Lopinavir / ritonavir OR Efavirenz

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- Switch to tablets or capsules from syrups or solutions as soon as possible
- Children may occasionally need to change a drug from the first-line regimen to one from the second-line regimen, because of intolerance or a serious adverse reaction. Swapping limits the patient's second-line treatment options. The decision to swap must be made by a doctor with antiretroviral experience.
- If intolerance develops to ritonavir or lopinavir / ritonavir, switch to nelfinavir.
- Lopinavir / ritonavir needs to be kept cool (< 25 degrees Celsius)
- Remember to recalculate doses according to body weight or body surface

Concomitant tuberculosis
Tuberculosis is a common co-morbid illness with HIV. There are two scenarios to consider:

1. Child presents with tuberculosis before commencing antiretroviral therapy

- Complete TB therapy if possible before commencing ART OR delay ART for at least 2 months.
- If the child has failed the nevirapine vertical transmission programme or is less than 3 years old or weighs less than 10 kg, use ritonavir as the third drug.
- If the child was not on the nevirapine vertical transmission programme and is more than 3 years old and weighs more than 10 kg, use efavirenz as the third drug. Monitor ALT monthly.

2. Child develops tuberculosis while on antiretroviral therapy

- If the child is on lopinavir / ritonavir or nelfinavir, then switch to ritonavir.
- If the child is on nevirapine, and is less than 3 years old or weighs less than 10 kg, switch to ritonavir.
- If the child is on nevirapine and is more than 3 years old and weighs more than 10 kg, switch to efavirenz.
- If the child is unable to tolerate the large number of drugs, antiretroviral therapy may have to be interrupted until TB therapy has been completed. Discuss all cases with a paediatrician with antiretroviral experience, before interrupting therapy.
- Monitor ALT monthly.

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Prescribing information

STAVUDINE (D4T)
Dosage
Paediatric dose: 1 mg per kg body weight every 12 hours (up to 30 kg)

Adolescent / adult dose: body weight 30 - 60 kg: 30 mg twice daily;
body weight ≥ 60 kg: 40 mg twice daily
Major toxicities
More common: headache, gastrointestinal disturbances, skin rashes
Less common: peripheral neuropathy and pancreatitis. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.
Rare: increased liver enzymes

Drug interactions
Should not be administered in combination with AZT

Special instructions
Can be administered with food
Oral solution must be kept refrigerated

LAMIVUDINE (3TC)

Dosage

Paediatric dose: 4 mg per kg body weight twice daily

Adolescent / adult dose: body weight < 50 kg: 2 mg per kg twice daily; body weight ≥ 50 kg: 150 mg twice daily;

Major toxicities

More common: headache, fatigue, nausea, diarrhoea, skin rash, abdominal pain

Less common: pancreatitis, peripheral neuropathy, decreased neutrophil count, increased liver enzymes. Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases have been reported.

Special instructions

Can be administered with food

Oral solutions may be stored at room temperature

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ZIDOVUDINE (AZT)

Dosage

Neonatal / infant (< 90 days of age): 2 mg per Kg four times per day (reduce the dose in preterm infants)

Paediatric dose: 180 mg/m^2 every 12 hours

Adolescent / adult dose: 300 mg twice daily

Major toxicities

More common: haematological toxicity including granulocytopaenia and anaemia, and headache

Less common: myopathy, myositis, and liver toxicity

Unusual (severe: Lactic acidosis, severe hepatomegaly with steatosis, including fatal cases

Special instructions

Can be administered with food

Oral solutions may be stored at room temperature

Decrease dose in patients with renal failure.

Reduced dosage may be indicated in patients with substantial hepatic dysfunction

RITONAVIR (RTV)

Dosage

Paediatric dose: 400 – 450 mg/m^2 every 12 hours. To minimise nausea and vomiting, commence therapy at 250 mg/m2 every 12 hours and increase stepwise to full dose over 5 days as tolerated.

Adolescent / adult dose: 600 mg twice daily. To minimise nausea and vomiting, commence at 300 mg twice daily and increase stepwise to full dose over 5 days as tolerated.

Major toxicities
More common: nausea, vomiting, diarrhoea, headache, abdominal pain, anorexia
Less common: circumoral parathesis, increased liver enzymes
Rare: spontaneous bleeding in haemophiliacs, pancreatitis, increased levels of triglycerides and cholesterol, hyperglycaemia, ketoacidosis, diabetes, and hepatitis

Special instructions
Administration with food increases absorption
Oral solution should be refrigerated
To improve tolerance: mix oral solution with milk, chocolate milk, or vanilla or chocolate pudding or ice cream. Coat the mouth with peanut butter before administration.

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LOPINAVIR (LPV) / RITONAVIR (RTV)
Dosage
Paediatric dose: 230mg LPV / 57.5mg RTV twice daily to a maximum of 400mg / 100mg twice daily, with food
Adult dose: 400mg / 100mg twice daily, with food

Co-administration with Efavirenz or nevirapine: increase the dose to 300mg LPV / 75mg RTV twice daily to a maximum of 533mg / 133mg twice daily. In treatment experienced patients where reduced susceptibility to lopinavir is suspected, the higher dosage is recommended.

Formulations
Paediatric solution: 1ml = 80mg LPV / 20mg RTV
Capsule: 133.3mg LPV / 33.3mg RTV per capsule

LVP/RTV is registered for use in children from the age of 6 months onwards..

Major toxicities
More common: diarrhoea, headache, asthenia, nausea and vomiting, and rash
Less common (more severe): fat redistribution, lipid abnormalities
Rare: spontaneous bleeding episodes in haemophiliacs, pancreatitis, hyperglycaemia, ketoacidosis, diabetes, hepatitis

Special instructions
Administer with food. High fat meal increases absorption
Oral solution and capsules should be refrigerated. Can be kept at room temperature up to 25°C if used within 2 months

EFAVIRENZ (EFV)

Dosage

Paediatric dose: Administered once daily - body weight 10 – 15 kg: 200 mg; 15 – 20 kg: 250 mg; 20 – 25 kg: 300 mg; 25 – 32.5 kg: 350 mg; 32.5 – 40 kg: 400 mg; > 40 kg: 600 mg
Adolescent / adult dose: 600 mg once daily

Major toxicities

More common: skin rash, CNS problems primarily in adults (somnolence, insomnia, abnormal dreams, confusion, impaired concentration, agitation. Hallucinations, euphoria), increased liver enzymes

Special instructions

Efavirenz can be taken with or without food
Bedtime dosing is recommended
Capsules may be opened but the granules have peppery taste

Calculating body surface area (m^2)

$$\sqrt{\frac{\text{Mass (kg) X Length (cm)}}{3600}}$$

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FOLLOW-UP AND MONITORING ARRANGEMENTS

Refer Appendices E and F

MANAGING OF ADVERSE EVENTS

General principles

- Try to establish whether the adverse event is due to antiretroviral agents, or other medication.
- If there is a need to discontinue antiretroviral therapy, it is advisable to discontinue all antiretrovirals rather than continuing with one or two agents alone.

Severe or Life-threatening events e.g. pancreatitis, hepatic failure, severe rashes including Stevens-Johnson syndrome

- Discontinue the most suspect medication
- May need to discontinue all antiretroviral medication temporarily.

Low-grade events

- Continue treatment at effective doses
- Increased and more frequent observation, monitoring and evaluation

CLINICAL SIGNS OF RESPONSE

- Increased awareness in surroundings, people
- Decreased frequency of infections (bacterial infections, thrush, and / or other opportunistic infections)
- Resolution of organ-specific complications e.g. discontinuation of supplemental oxygen in children with chronic lung disease, increasing platelet count in children with thrombocytopaenia
- Improved growth in children who previously failed to grow
- Improvement in neurological signs or neurodevelopment

INDICATIONS FOR CHANGING ANTIRETROVIRAL THERAPY

Clinical

Any one of the following:

- Progressive cognitive and / or developmental deterioration or development of encephalopathy.
- Lack of growth among children who show an initial response to treatment, or decline in growth among children who show an initial growth response to therapy
- Occurrence of new opportunistic infection or malignancy signifying clinical disease progression
- Recurrence of prior opportunistic infections, such as oral candidiasis that is refractory to treatment.

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Immunological

Either one of the following:

- A return of CD4 percentage (or for children > 6 years of age, absolute CD4 cell count) to or below pre-therapy baseline, in the absence of other concurrent infection to explain transient CD4 decrease (consideration should be given to performing a confirmatory CD4 count if resources permit)
- ≥ 50% fall from peak level on therapy of CD4 percentage (or for children > 6 years of age, absolute CD4 cell count), in absence of other concurrent infection to explain transient CD4 decrease

Virological

- less than tenfold (1.0 $\log_{10}$) decrease from the baseline viral load after 24 weeks of treatment

- persistent increase in viral load after beginning treatment i.e. greater than fivefold (0.7 $\log_{10}$) increase in children < 2 years and greater than threefold (0.5 $\log_{10}$) increase in children ≥ 2 years
- Rebound of viral load to baseline
- a detectable viral load in children who initially responded to antiretroviral therapy with undetectable levels

Note: Viral load should not be measured during intercurrent infection, but preferably one month after resolution.

SECOND LINE THERAPY

Consult infectious Diseases staff if a change of therapy is needed.

When changing therapy:

- Determine whether poor adherence has possibly caused failure
- If it is not possible to improve adherence, attempt directly observed therapy (DOT) with a health care worker, family member or friend.
- If the patient is adherent assume that failure is due to resistance and change to 3 new antiretroviral agents.
- Review all other medication for possible drug interactions
- Consider the patient's quality of life

CONTACT DETAILS

Dr Brian Eley Tel:6585321 or bleep: 4173
Dr James Nuttall Tel: 6585518 or bleep: 4521

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APPENDIX A: MODIFIED WHO PAEDIATRIC STAGING FOR HIV INFECTION

Stage One
- Asymptomatic
- Generalized lymphadenopathy
- Hepatomegaly
- Splenomegaly
- Hepatosplenomegaly
- Parotomegaly

Stage Two
- Unexplained chronic diarrhoea (≥ 2 weeks)
- Failure to thrive
  - 60 - 80% expected body weight
  - Not responding to nutritional rehabilitation or anti-TB therapy (if clinically indicated). Other correctable causes excluded
- Recurrent or severe bacterial infection (≥ 2 episodes pneumonia or 1 episode of meningitis)
- Oral candidiasis beyond neonatal period
  - Severe persistent or recurrent, not responding to topical therapy
- Persistent fever (≥ 2 weeks)
- Haematological
  - Thrombocytopenia (platelet count < 40 000 X 109/l) not responding to prednisone 2 mg/kg/day after 2 weeks
  - Neutropenia (neutrophil count < 500 X 109/l) not responding to switch from cotrimoxazole to dapsone
- Severe lymphoid interstitial pneumonitis with clubbing
- 2 episodes Zoster or severe herpetic disease
- Otorrhoea > 6 weeks
- Single episode of proven or probable tuberculosis

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Stage Three
- AIDS opportunistic infection
- Severe failure to thrive
  - < 60 % expected body weight
  - Not responding to nutritional rehabilitation or TB therapy if clinically indicated
- Progressive encephalopathy
- Recurrent septicaemia (□□2 episodes)
- Bronchiectasis (clubbing and persistent nocturnal cough)
- Cardiomyopathy
- Progressive nephropathy
- Candidiasis (oesophageal or pulmonary).
- Disseminated fungal infection (Coccidioidomycosis, Cryptococcosis, Histoplasmosis)
- Disseminated mycobacterial infection (M. tuberculosis, BCG, avium-intracellulare, Kansasii)
- Recurrent, culture-positive tuberculosis

- CMV disease with onset at age > 1 month (at site other than lymph nodes, spleen, liver).
- HSV causing mucocutaneous ulcer persisting > 1 month, or bronchitis, oesophagitis, pneumonitis, oesophagitis in a child older > 1 month.
- *Pneumocystis carinii* pneumonia (PCP)
- Progressive multifocal leukoencephalopathy.
- Recurrent pulmonary tuberculosis
- Salmonella (non-typhoid) septicaemia, recurrent
- HIV-related malignancy

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APPENDIX B: PRE-ANTIRETROVIRAL THERAPY COUNSELLING GUIDELINES FOR ATTENDING DOCTORS, NURSES AND COUNSELLORS

- Review knowledge and understanding of HIV infection & AIDS
- Discuss acceptance of diagnosis of HIV infection in the child
- Provide an understanding that the HIV infection has progressed to the point where the child would benefit from antiretroviral therapy
- Discuss the aims of antiretroviral therapy: Antiretroviral therapy is not a cure. Long-term suppression of HIV in the body will allow the child to grow and develop, and experience fewer infections and hospital admissions
- Help to identify individual(s) who will be responsible for giving medication to the child, after careful instruction by medical staff
- Initiation of antiretroviral therapy is a lifelong commitment. A minimum of three medications is given every day. Regular follow-up visits to clinic with monitoring blood tests are absolutely necessary to ensure that the child remains healthy
- Strict adherence to medication is essential to long-term successful treatment and preventing HIV becoming resistant to the medication
- Concerns, fears, expectations and problems that the caregiver anticipates in relation to antiretroviral therapy for the child should be discussed
- Potential short and long-term side effects of antiretroviral medication, including potential failure of all medications to prevent progression to AIDS
- Treatment may be stopped by medical staff if there is poor adherence or follow up
- Assess family and social support, and whether there has been, or is a commitment to disclosure of HIV status
- Assurance of ongoing counselling support and medical follow-up by clinic staff

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