

Chapter 2

Literature review

2.1 Introduction

This literature review describes the prevalence of HIV/AIDS in adults and children in developed and developing countries. The incidence and outcome of HIV/AIDS in Sub-Saharan Africa is highlighted, as well as the additional compounding factors of limited basic resources, poverty and malnutrition. With the increase in the number of orphans as a result of the disease, comparisons are made between those cared for within the community and in institutions. This literature review mainly covers the neurological aspects of the HIV infection in infants and children and how their neurodevelopment is affected, as well the influence the virus has on their anthropometric measurements.

Literature dating from 1978 was assessed via Pubmed, Cochrane and Pedro search engines. Personal searches were conducted in the Health Sciences Library at the University of the Witwatersrand.

2.2 Prevalence of HIV/AIDS in adults

In developing countries the mortality rates from HIV/AIDS are twenty times greater than in developed countries (UNAIDS 2004). It was also stated that people in their twenties and thirties are most susceptible to HIV/AIDS. The estimated life expectancy of a South African will be reduced to 43 years by the year 2010 (see figure 2.1). Lee et al. (1996)

projected that, by the same year, 28 to 52% of all deaths in Soweto, South Africa will be related to HIV/AIDS.

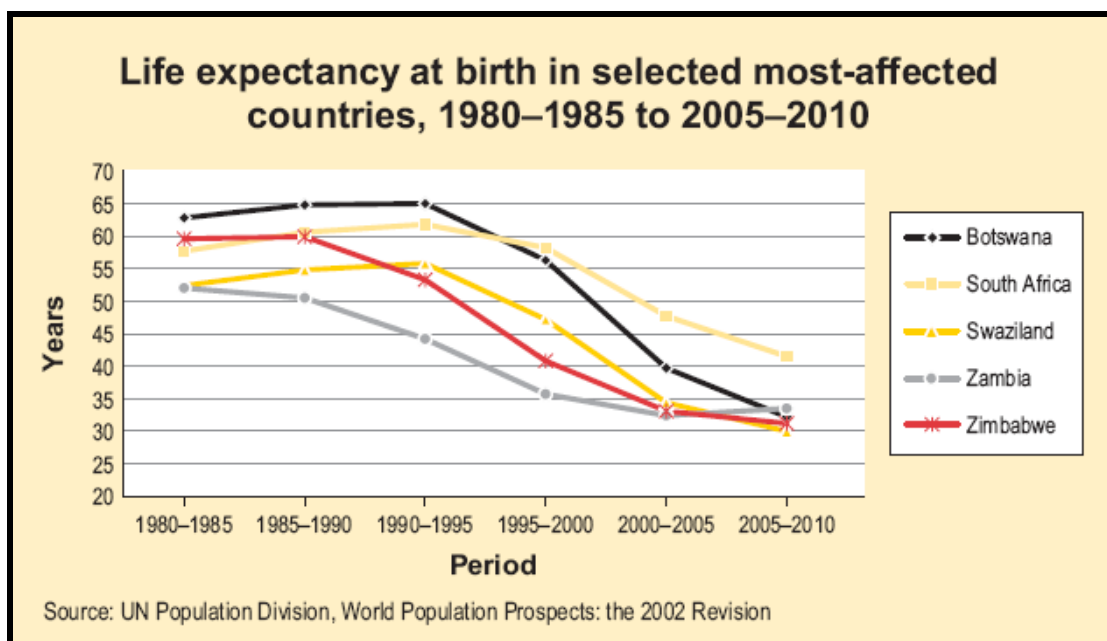


Figure 2.1

**Life expectancy at birth in selected most-affected countries,
1980 - 1985 to 2005 - 2010**

A greater number of women are infected by HIV/AIDS than men. The age of infection of women is younger and their mortality is higher (UNAIDS 2004) (see figure 2.2).

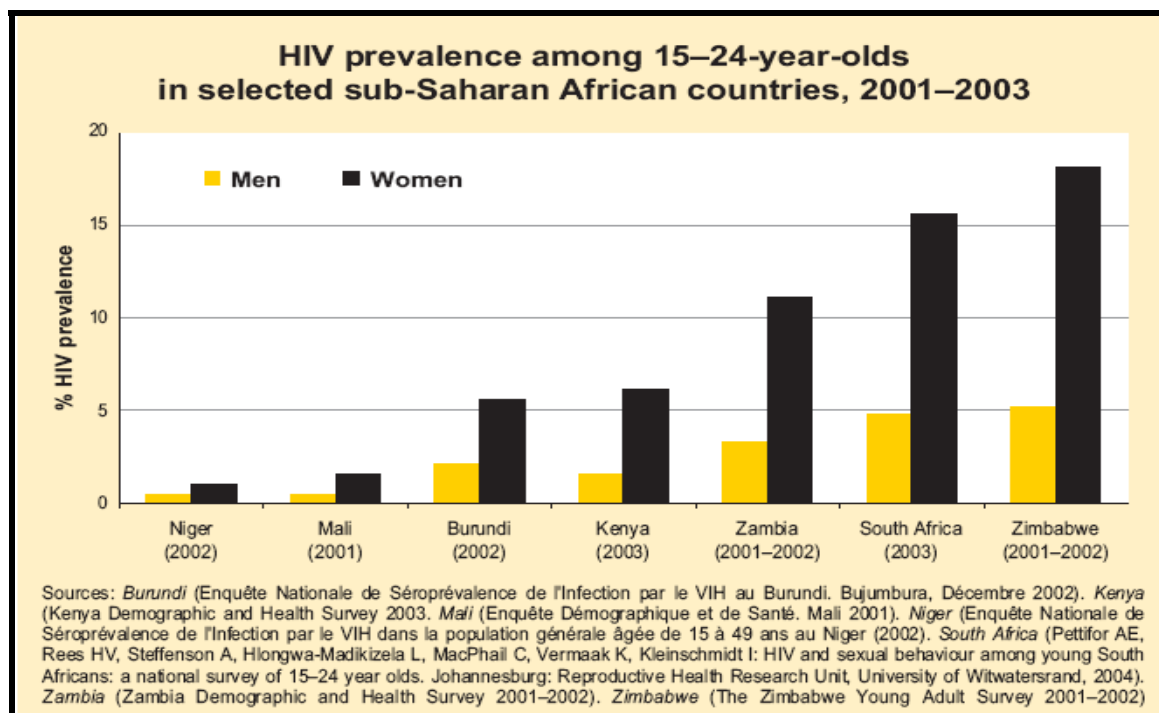


Figure 2.2

HIV prevalence among 15-24 year olds in selected Sub-Saharan African countries, 2001-2003

2.3 Vertically infected children

The methods of HIV infection in children are well known and understood.

The European Collaborative study (1994) states that 15% of infants born to HIV infected and untreated mothers, will become infected. Tardieu (1998) states that 20% of children are infected from their mothers and Quinn et al. (1994) gave rates of between 14-40%.

Transplacental and intrapartum transmission are the most common cause of infections from mother to child. Mother to child transmission accounts for over 90% of children infected with HIV (Luzuriaga and Sullivan 2002). Quinn et al. (1994) claim a slightly lower percentage of

85% of children being vertically infected. Infants can be infected during pregnancy, at birth and from breast feeding. Tardieu (1998) shows that 80% of the infections occurred at birth, whereas Wilfert and McKinney (1998) state that 66% of HIV infected children contract the virus a few days before and during birth. In contrast to this, in a study of HIV infected children in Nigeria, 30% were vertically infected and 68% were infected by another means, namely by blood transfusions (Emodi and Okafor 1998).

Vertical infection has stabilised in the USA and Western Europe because of perinatal screening and the treatment of HIV infected pregnant women which limit transmission to the infant. However, in Africa and Asia it remains the major cause of children infected with HIV (Miller 2000). The preventative treatment of HIV infected mothers can reduce the incidence of virus transmission to their infants from twenty six to eight percent (Tardieu 1998, Wilfert and McKinney 1998).

2.4 Prevalence of HIV/AIDS in children.

There are 2,1 million HIV infected children in the world, and 1,9 million of these children are in Sub-Saharan Africa (UNAIDS 2004). This equates to 90% of paediatric infections which occur in this region in contrast to the 76% of all HIV infected people (UNAIDS 2004). In South Africa, the prevalence of paediatric infections is 230 000 and is expected to rise rapidly due to an increasing number of adult infections. In 2000, Meyers

et al. had already reported that in Soweto, South Africa, almost a third of paediatric admissions into hospital were HIV related.

In developed countries the number of children with HIV infection is declining due to improved medical management by means of antiretroviral treatment, immune system maintenance and early treatment of opportunistic infections. The HIV infected children now have a better quality of life and survive longer (Laufer and Scott 2000). However, this is not the case in developing countries for a variety of reasons, one of which is the limited availability of antiretroviral treatment (Laufer and Scott 2000). Malnutrition and HIV/AIDS is the leading cause of death in children in these areas (Mars 2004, Laufer and Scott 2000). HIV related deaths of children under five years of age account for 20% of all mortalities in Sub-Saharan Africa (Luzuriaga et al. 2002). In Malawi, Africa, the probability of survival to five years of age is 56%, compared to 75% in the United States of America (Nathan et al. 2003).

2.5 Pathophysiology of central nervous system invasion

The human immunodeficiency virus is a retrovirus, belonging to the lentivirus subfamily. A lentivirus has a long incubation period and targets specific organs. The human immunodeficiency virus targets the immune system (lymotrophic) and central nervous system (neurotrophic) (Belman 1992).

2.5.1 Methods of invasion

The pathogenesis of HIV resulting in CNS impairment is not yet fully understood, but there seems to be a direct and indirect mechanism of invasion of the CNS. The direct mechanism is via infected cells into the brain where they can replicate themselves, and the indirect mechanism is as a result of the release of toxic inflammatory factors by infected and uninfected cells (Belman 1992, Rausch and Stover 2001).

a) Direct mechanism

The direct infection of the brain is mainly via macrophages and microglial cells. Neurons themselves are not infected by the HIV. Monocytes, lymphocytes, endothelial cells and astrocytes can also be infected, but to a lesser degree (Tardieu 1998, Epstein and Gelbard 1999, Laufer and Scott 2000, Rausch and Stover 2001). Foetal astrocytes are more susceptible to the virus than mature astrocytes (Tardieu 1998). Resident microglial cells in the brain can be directly infected as they have viral receptors. They comprise 10-20% of the glial population, are said to have a low turn-over rate and harbor the virus in a latent state for many years. Tardieu (1998) states that these resident microglial cells are commonly found in the basal ganglia and white matter of the CNS. They are dormant cells that probably resist the virus, but are activated by cytokines to become brain macrophages which are susceptible to the virus. Brain macrophages are the most frequently affected cells within the CNS. Activated brain macrophages secrete chemokines which attract more leucocytes

from the blood. The HIV virus therefore has the ability to infect and replicate itself within the brain, as seen on post mortem studies (Tardieu 1998).

Astrocytes and endothelial cells form the blood brain barrier. Their infection and resulting dysfunction allows further entry of toxic viral or cellular products, as well as HIV infected cells, into the CNS (Epstein and Gelbard 1999, Rausch and Stover 2001).

b) Indirect mechanism

The indirect mechanism is that of neurotoxicity from the secretion of inflammatory cytokines and HIV proteins from activated macrophages, microglial cells and astrocytes, both infected and uninfected. Over time, and in high concentrations, these are toxic to nearby neurons. (Tardieu 1998, Epstein and Gelbard 1999, Rausch and Stover 2001). The neuronal death may trigger neurotoxicity themselves by direct interaction with neurons or by the activation of microglial and macrophages. Tardieu et al. (1995) postulate that the decreased immunodeficiency is dependent on increased viral load within the brain and associated increased activation of brain macrophages which induces a neurotoxic effect. Neuronal death results in a variety of neuropathology, one of which is a decreased head circumference.

2.5.2 Clinical picture

The most common clinical features of encephalopathy in children are diminished brain volume, with an associated reduced head circumference, white matter changes and basal ganglia calcification. The white matter lesions have variable degrees of cerebral atrophy. Due to the accumulation of macrophages in the basal ganglia, neuronal loss, tissue necrosis and calcification of the basal ganglia are caused. There are vascular and perivascular changes indicating chronic inflammation. Enlarged subarachnoid spaces and ventricles are also present. (Sharer et al. 1986, Belman et al. 1988, Epstein et al. 1988, Belman 1992, Spitaels 1994, Tardieu 1998, Rausch and Stover 2001).

2.6 HIV related encephalopathy

Encephalopathy is a significant, common complication of HIV in children that occurs more frequently, earlier and with greater variety in children than in adults (Rausch and Stover 2001, European Collaborative Study 1990). The human immunodeficiency virus invades the CNS from the onset of infection. But, the time from infection to the development of encephalopathy is uncertain, the type of clinical symptoms is diverse and the degree of involvement varies from none to severe neurological dysfunction (Epstein et al. 1986, Belman et al. 1985, Belman 1992, Chase et al. 1995). There are no predictive characteristics that will determine which child will develop encephalopathy and who will not (Tardieu 1998, Spitaels 1994). Other factors that can affect the

progression of the disease are that the HIV may have different clones that have different affinities for brain cells, however, this is poorly understood (Tardieu 1998). Also, within the general population, 10% of people have a genetic characteristic that resists the disease progression because they have modified receptors (Tardieu 1998, Persaud et al. 1992). Encephalopathy is a major concern, because the incidence of mortality is greater when comparing HIV individuals with neurological impairment to those without neurological impairments (Rausch and Stover 2001).

2.6.1 Definition of encephalopathy

The Working Group of the American Academy of Neurology AIDS task Force (1991) diagnoses encephalopathy when one of the following findings present in an HIV infected child, for at least two months and without other identifiable causes:

- Failure to attain or loss of developmental milestones, or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests.
- Impaired brain growth or acquired microcephaly, demonstrated by head circumference measurements, or brain atrophy, demonstrated by computerized tomography or magnetic resonance, with serial imaging required in children less than two years of age.
- Acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia or gait disturbance.

2.6.2 Static and progressive encephalopathy

In the earlier stages of the HIV epidemic it was considered that HIV encephalopathy could be divided into two groups; progressive and static encephalopathy (Ultrmann et al. 1985, Blanche et al. 1990). The incubation period, from initial onset of HIV infection to the onset of encephalopathy, in both static and progressive groups, ranges from two months to five years (Spitaels 1994, Epstein et al. 1986).

The first, smaller group, classified as progressive encephalopathy, showed early signs of immunodeficiency and the onset of opportunistic infections, increased viral load with rapid deterioration and subsequent death within three to fourteen months (Blanche et al. 1990, Belman 1992, Belman et al. 1996, European Collaborative Study 1990). The second, larger group, classified as static encephalopathy, showed a slower progression of the disease and longer survival (Blanche et al. 1990, Belman 1992).

a) Progressive encephalopathy

Progressive encephalopathy is characterized by deterioration in neurodevelopment, impaired brain growth and mortality (Belman et al. 1986, Epstein et al. 1985, Epstein et al. 1987). It is a persistent infection of the brain and can be divided into;

- progressive encephalopathy with deterioration,
- progressive encephalopathy with plateau,

- progressive encephalopathy with plateau followed by deterioration,
- progressive encephalopathy with plateau followed by improvement.

Children with progressive encephalopathy are often severely immunodeficient with an increased number of hospitalizations; survival time is limited and mortality high (Belman 1992). Epstein et al. (1986) found that there was a significant correlation between progressive encephalopathy and death. Encephalopathy was more common in the advanced stages of the disease and thus increases the risk of death 28 fold (Laufer and Scott 2000).

b) Static encephalopathy

Children with static encephalopathy achieved new skills and milestones, but at a slower rate than expected for their age. They continued to progress along their own development growth curve without further declines (Epstein et al. 1988, Spitaels 1994, Chase et al. 1995). They had a delay in cognitive and motor development but there was no loss of milestones or a progression of neurological deficits. This was also the finding in the study done by Emodi and Okafor (1998) in Nigeria, Africa, where the commonest form of neurological involvement in HIV infected children was a delay in attaining developmental milestones. They found no evidence of loss of previously attained milestones.

2.6.3 Earlier and recent studies

Earlier studies focused on more severe CNS involvement in the HIV infected child. With greater knowledge and advances in treatment advances, children are living longer and there is now more emphasis on the milder forms of neurological impairment and the early identification and progression of these more subtle neurological signs (Belman 1992, Rausch and Stover 2001). The more recent studies analyse the association between HIV and neurodevelopmental delays in symptomatic and asymptomatic children (Chase et al. 1995, Rausch and Stover 2001, Tardieu et al. 1995).

2.6.4 Prevalence of encephalopathy

The reported prevalence of encephalopathy varies, but is commonly estimated to be 13-23% of HIV infected children (Wolters et al. 1995, Lobato et al. 1995, Chase et al. 2000, Macmillan et al. 2001). Other researchers show higher rates of up to 31% (European Collaborative Study 1990). Tardieu et al. (1995) found that 44% of HIV infected children had difficulties in cognition and fell within the “mentally retarded” range. Earlier studies of Belman et al. (1986) showed that 50% showed progressive encephalopathy, and two years later (Belman et al. 1988) stated that 90% of HIV infected symptomatic children have delays in development, deficits in language, motor and cognitive functioning.

Prevalence of encephalopathy varies, depending on the age of the child. Msellati et al. (1993) showed a 12,5% prevalence at 6 months, 16% at 12 months, 20% at 18 months and 9% at 24 months. The delays were mainly in gross motor abilities.

2.6.5 Mortality

Encephalopathy is known to progress more rapidly in infants and children than in adults. Children are therefore more likely to die sooner (Rausch and Stover 2001).

In the early studies of HIV and morbidity in the United States, it was noted that the main cause of death from HIV was from encephalopathy. In Durban, South Africa, the common cause of death of HIV infected infants is diarrhoea and respiratory infection. Eighty three percent of the deaths occur before the age of ten months. Many children fail to thrive and 50% show neurological complications. (Bobat et al. 1999). Meyers et al. (2000) reported that 77% of the HIV related deaths in hospital in Soweto, South Africa, were between the ages of one to six months. These deaths were from causes other than encephalopathy; 65% of the children died from pneumonia. This pattern was also reported in the study in Nairobi, Kenya where children with a rapid progression of HIV died most commonly from lung infections and meningitis. (Nathan et al. 2003). Differences in mortality rates may also indicate differing availabilities of health care (European Collaborative Study 1994). A study in Kigali, Rwanda, showed a lower than expected mortality rate of 19%,

probably because these children had regular and improved medical care (Lepage et al. 1996).

2.6.6 Encephalopathy with and without immunodeficiency

HIV invades the CNS early in the course of the infection, suggesting that CNS impairments are the consequence of the viral load (Belman 1992, Epstein et al. 1987). In general, there is a correlation between immunodeficiency, opportunistic infections and encephalopathy (Blanche et al. 1990). A child's prognosis, as a result of encephalopathy, is worsened if there is an associated increase in viral load and immunodeficiency (Blanche et al. 1990, Belman et al. 1996). Nozyce et al. (1994) showed that there is a relationship between severe neurodevelopmental delays and other HIV related clinical symptoms as well as between average neurodevelopmental abilities and no clinical symptoms.

It is, however, not uncommon to have low viral loads in the cerebral spinal fluid but to display early severe neurological symptoms. Only 10% of children with severe immunodeficiency show encephalopathy, indicating early CNS involvement (Tardieu 1998). There is an association between neurodevelopmental functioning in HIV infected children who are symptomatic and asymptomatic (Belman 1992). Although many HIV infected children are asymptomatic, there are subtle cognitive and language delays indicating CNS involvement. Neurological and developmental signs are often early indicators of HIV disease in infants,

and these may precede other signs of immunodeficiency (Epstein et al. 1988, Tardieu 1998). This is likely to be due to the early invasion of the virus into the CNS, without other system infections. This CNS infection is probably what causes the developmental delays of infants and children, indicating that there is probably irreversible brain involvement before birth (Tardieu 1998). In school-aged children there is a significant correlation between the immunodeficiency in the child's early years of life and their later cognitive abilities. This indicates that there was an early invasion of the central nervous system (Belman 1992).

Belman 1992 summarized a "trimodal" evolution of symptoms in children

a) First group

These are the children with severe opportunistic symptoms, usually, but not always, with progressive encephalopathy. Mortality is increased in this group which only has a life expectancy measured in months to a few years. The causes of death are varied.

b) Second group

It would appear that children who survive to four and five years have a greater chance of not having CNS symptoms. The exact number of children who are asymptomatic or mildly symptomatic is unknown (Belman 1992). HIV infected children commonly develop symptoms of the disease during the first two years, of these, 10-20% are likely to die by the age of four years (American Academy of Pediatrics 1999). Deaths of children under five years accounted for 20% - 35% of all mortalities

(Blanche et al. 1990, European Collaborative Study 1994, Luzuriaga and Sullivan 2002).

Lobato et al. (1995) and Tardieu (1998) identified children with encephalopathy before three years of age. These children usually die before the age of five to six years, after periods of plateaus over two to four years, during which time they can show some progress. After three years the child usually has a clear cognitive impairment, with small head circumference and spastic quadriplegia. This was associated with an immunodeficiency and high viral load present from the first weeks of life. (Tardieu et al. 1995, Tardieu 1998). The European Collaborative Study (1994) found that 40% of infected children had encephalopathy and opportunistic infections by the age of four years. Blanche et al. (1990) found that the probability of survival in a child's third year was three percent whereas Wilfert and McKinney (1998) reported that 16% of the infected infants died before the age of four years.

c) Third group

The third group comprise those in late childhood and adolescence. Tardieu et al. (1995) showed that two thirds (67%) of HIV infected children perform adequately at primary school. This percentage is similar to that of Epstein et al. (1986) who showed that 60% of HIV infected children will be alive and pursuing a normal school career at ten years of age. Later, in 1998, Tardieu stated that 80% of children are asymptomatic and are coping at school, except for deficits in visual-

spatial and temporal orientation abilities. These are similar to the percentages of the American Academy of Pediatrics (1999) of 80% to 90% of HIV infected children living beyond their ninth year. Many of these children will attend school and reach adolescence and some will reach adulthood.

The European Collaborative Study (1994) found that opportunistic infections were less frequent with the increasing age of the HIV infected child. HIV infected children who exhibit a relatively normal course of development until this stage, were presumed to be asymptomatic of neurological involvement. However, these children may still develop signs of CNS involvement before, or with, other symptoms.

It would seem that there are subtle signs of encephalopathy in school-going children. An increasing number of children with HIV encephalopathy will reach school-going age but will have expressive language, perceptual motor deficits and attention difficulties (Lobato et al. 1995, Tardieu et al. 1995). Receptive language or cognitive delays are present to a lesser degree. Deficits in language are commonly reported in research, and language skills are strongly related to academic performance (Epstein et al. 1986, Lobato et al. 1995). As the disease progresses the children may show loss of interest in school work, declining academic progress, social withdrawal, be emotionally labile and display further attention deficit disorders, possibly together with conduct disorders (Pearson et al. 2000, Spitaels 1984). Tardieu et al. (1995)

reported a correlation between immunodeficiency and poor academic achievement.

2.7 Relationship between neurodevelopment and HIV

The extent of the neurological involvement in vertically infected children is postulated to be influenced by the following factors (Tardieu 1998, Persaud et al. 1992, Luzuriaga and Sullivan 2002);

- the severity of maternal viral load at the time of transmission to the child,
- the timing of the transmission – in utero, at delivery or through breast feeding,
- the general health and nutritional status of the mother,
- the time of penetration of the virus into the CNS of the infant, because the different stages of CNS involvement, are partly dependent on the stage of development when infection occurs (Belman 1992).

The HIV virus is known to enter the CNS soon after systemic infection (Davis et al. 1992, Blanche et al. 1990). The virus has been found in foetal brain tissue (Rausch and Stover 2001, Lobato et al. 1995, Epstein et al. 1986, Tardieu 1998), and in the CNS (Belman et al. 1986). Encephalopathy can be the first signs of HIV infection in infants, especially if children are infected early in their development.

This indicates that the earlier the child is infected, the more rapidly the disease progresses. The European Collaborative Study (1994) however,

mentioned that there is little evidence to support the idea that a child who shows early an onset of encephalopathy and opportunistic infections is infected in utero. But Smith et al. (2000) showed that the earlier the child was infected, the poorer the neurological functioning. This is also the finding of Macmillan et al. (2001) namely, that infants who were infected in utero had a less favourable neurological outcome when compared to infants infected intrapartum at two years of age.

The speculated reasons why the earlier infected infants have a more severe neurological impairment are (Smith et al. 2000);

- the brain is infected at an earlier stage in its development and has therefore been infected for a longer period of time,
- CNS development and organization is disrupted,
- viral replication occurs when the immune system is immature,
- the longer the period of infection the greater the probability of viral mutation which infects brain cells,
- the HIV affects the developing immune system, which in turn may have an effect on the developing CNS, and the effects of the virus on the CNS may also have an effect on the immune system (Belman 1992).

An infant's brain experiences rapid myelination of the nervous system within the first two years of life. This myelination coincides with the attainment of significant motor and cognitive milestones. An interruption

of this process by HIV invasion can be expected to produce neurodevelopmental delays (Gay et al. 1994).

Neurological and developmental signs are often early indicators of HIV disease in infants and may precede other signs of immunodeficiency (Epstein et al. 1988, Pearson et al. 2000). HIV infected children with normal neurological signs were within two standard deviations below the mean on neurodevelopmental evaluations, whereas children with abnormal neurological signs were three standard deviations below the mean (Knight et al. 2000). Chase et al. (2000) concurred, and also stated that an indicator of neurological involvement in HIV infected children was a neurodevelopmental score which was two standard deviations below the mean. However, other factors like prematurity, drug exposure, poverty and environmental stresses can impact on these measurements.

Since myelination of the nervous system in a child is not complete by two years of age, it is expected that further developmental delays are to be expected over time. In particular, the frontal and parietal regions continue to develop through childhood. This will affect the higher cortical functions such as language, sequencing and integration of multi-stimuli. Visual motor processing, attention, verbal memory, processing speed and sequential processing are the more advanced developmental skills which develop after two years. Impairment in these specific areas of brain function are indicators of CNS involvement (Blanchette et al. 2002).

Numerous studies have concluded that HIV affects a child's cognitive and motor development (Belman 1988, Msellati et al. 1993, Nozyce et al. 1994, Chase et al. 1995, Chase et al. 2000, Gay et al. 2000, Knight et al. 2000, Potterton and Eales 2001, Macmillan et al. 2001, Blanchette et al. 2002). The delays are mainly in the gross motor abilities (Msellati et al. 1993, Chase et al. 1995, Drotar et al. 1997, Knight et al. 2000). The onset of cognitive deficits occur later than motor deficits (Msellati et al. 1993) and with less severity. Chase et al. (1995) showed that 21% of HIV infected children had a severe motor delay at 30 months, whereas at the same age 17% showed severe cognitive delays. Motor skills were lower in the HIV infected group from four to six months of age, regressing to severe motor delays of 18% at 18 months and 23% at 24 months (Drotar et al. 1997, Chase et al. 1995). The only neurodevelopmental study on South African infants, Potterton and Eales (2001) confirmed other research findings, namely that HIV infected children under 12 months of age were delayed with regards to their motor development.

A Rwandan study in Africa, by Msellati et al. (1993) showed that in comparing two large groups of HIV infected and uninfected children in their first two years of life, the HIV infected groups were more frequently developmentally delayed, with 15-40% having neurological impairments. The HIV uninfected children had fewer developmental delays, with less than 15% being neurologically impaired. This was confirmed in South Africa by Potterton and Eales (2001) who found that 40% of HIV infected

children under 12 months of age showed a developmental delay, compared to 13% of HIV uninfected children.

Infected children, with lower neurodevelopmental functioning as a result of HIV, are at higher risk of disease progression (Pearson et al. 2000). This is also the finding of Llorente et al. (2003) namely, that HIV infected children with lower neurodevelopmental scores at four months are a higher mortality risk. This is confirmed by other researchers who found that poor performance on neurodevelopmental measures is associated with developing encephalopathy and mortality (Nozyce et al. 1994, Chase et al. 2000). Pearson et al. (2000) added that children with motor dysfunction, namely muscle bulk, muscle tone and strength, are also at a greater risk of the disease progressing.

Early identification of developmental delays may therefore assist with treatment decisions. Continued neurodevelopmental assessments of children with HIV assist in determining declines in functioning and survival rates (Llorente et al. 2003). The monitoring of neurodevelopment growth is an important factor in the early diagnosis of neurological impairment. Neurodevelopmental scores of below two standard deviations are an indication of severe HIV neurological involvement, and early treatment needs to be initiated (Chase et al. 2000)

2.8 Head circumference

Epstein and Epstein (1978) showed that there is a relationship between head circumference and brain weight. A reduced head circumference is interpreted as impaired brain growth and is associated with developmental delays (Dolk 1991). In contrast to this, Chase et al. (1995), were unable to correlate the relationship between head size and neurodevelopment. They stated that the broad range of normality with respect to head circumference makes any relationship difficult to establish. Abnormal brain growth and neurodevelopmental progress is not fully understood (Dolk 1991, Chase et al. 1995).

HIV associated encephalopathy causes neural injury with associated impaired brain growth, which results in reduced head circumference and regression or delayed development and death (Nozyce et al. 1994, Epstein and Gelbard 1999, Macmillan et al. 2001). A deceleration in head circumference growth has a detrimental impact on neurodevelopment (Smith et al. 2000).

Since HIV affects the CNS early in the course of the disease (Davis et al. 1992), it can be expected that newborn infants with HIV associated encephalopathy will have reduced head circumferences (Tardieu et al. 1998, Epstein and Gelbard 1999). A characteristic feature of encephalopathy is a reduced head circumference. The onset being between two and four months of age (Epstein and Gelbard 1999). Tardieu et al. (1998) stated that when the onset of encephalopathy

occurred before the age of 12 months, there is a reduced head circumference as compared to cases where the onset of encephalopathy occurred after 12 months. Acquired microcephaly makes a diagnosis of encephalopathy probable, especially if the head circumference falls below the second percentile (Belman 1992). Epstein et al. (1986) showed that 19 out of 20 children with progressive encephalopathy had impaired brain growth. This was indicated by head circumference measurements or by cerebral atrophy on CT (computerized tomography) scans.

2.9 Other factors influencing development

It is difficult to dissociate environmental, psychological and nutritional factors as possible causes or contributors of neurodevelopment delays in HIV infected children (Spitaels 1994, Spiegel and Mayers 1991, Belman 1992). Subtle neurological deficits in HIV infected children may be due to encephalopathy, but poverty and poor environmental circumstance also influence their neurodevelopment (Epstein et al. 1988, Brown and Lourie 2000). Chase et al. (1995) commented on the frequent separations from the primary caregiver, family stress as a result of poverty and/or caring for an ill child, as having an effect on the child's development. Pearson et al. (2000) agreed that there are many factors which can influence a child's development and these include muscle bulk, muscle tone and strength. The impact, during pregnancy, of maternal illness and inadequate care on the developing nervous system of a foetus is not known (Epstein et al. 1988, Belman 1992).

A study by Coscia et al. (2001) investigated the association between socio-economic status, home environment and cognitive function in HIV infected children. They stated that HIV infected children living in deprived homes are less stimulated and that their level of cognitive functioning is negatively affected. However, Drotar et al. (1997) could not attribute neurodevelopmental deficits with the quality of home environment.

2.10 Basic needs

Nathan et al. (2003) showed that the accelerated progression of HIV/AIDS in African children may be a reflection of their poverty and of the lack of their basic needs being met with respect to adequate nutrition, clean water and access to medical care. Malnutrition and HIV/AIDS is the leading cause of death in children in these areas (Mars 2004, Laufer and Scott 2000).

Prior to the HIV/AIDS epidemic, the living standards of disadvantaged people in many African countries were already declining (UNAIDS 2004). The impact of HIV/AIDS has worsened their already fragile state. The people who are most vulnerable to HIV/AIDS are those living in low- and middle-class developing countries. In these countries there is poverty, a poor infrastructure, limited basic resources and high incidences of other fatal diseases (American Academy of Pediatrics 1999). Sub-Saharan Africa has 11% of the world's population and 24% of the world's undernourished people (UNAIDS 2004). Although South Africa is one of

the most developed countries in Africa, fewer than half of the households have running water and only one quarter of rural households have adequate toilet facilities (UNICEF 2002). A study in Nigeria by Emodi and Okafor (1998) showed that 51% of HIV infected children under the age of 16 years were malnourished. Meyers et al.'s study (2000) of HIV infected children in South Africa showed that 65.8% were malnourished compared to 33.1% of HIV uninfected children. The study in Abidjan, West Africa (Vetter et al. 1996) showed that respiratory tract infections and malnutrition were the dominant diseases in the HIV-positive children, especially after 15 months of age. Malnutrition is also found amongst uninfected children, but to a lesser degree (Vetter et al. 1996). Children in developing countries tend to die from common childhood diseases before they are able to develop the clinical symptoms of HIV/AIDS (Brown and Lourie 2000).

2.11 Nutrition and growth

It is commonly accepted that HIV infected infants and children have growth delays. Even children who show no other symptoms of HIV can still be growth retarded (Wilfert and McKinney 1998)

“Stunting” is defined as a reduced height-for-age. “Undernourished” is a reduced weight-for-age.” Wasting” is a reduced weight-for-height. Chase et al. (1995) used “nutritional status” as measurements of height and weight.

Lepage et al. (1996) reported on stunting, but not wasting, within the first two years of an HIV infected child's life. Nathan et al. (2003) speculated that there is a breakdown in proteins that occurs during severe and persistent infections, and that this results in a negative nitrogen balance which affects a child's linear growth.

Delays in growth are said to be one of the first signs of HIV infection. Decreased linear growth (stunting) often precedes progressive encephalopathy (Laufer and Scott 2000).

Miller (2000) stated that HIV infected infants have a similar birth weight and length when compared to uninfected children. Moye et al. (1996) found that the HIV infected child's weight and length declined through to 18 months. However, an infant's low birth weight may also be due to poor maternal health status (European Collaborative Study 1994, Moye et al. 1996). Lepage et al. (1996) showed that weight was reduced markedly at 12 and 36 months and that height was significantly delayed from nine months of age. This researcher claimed that low weight-for-age and height-for-age occurred with children with opportunistic infections, suggesting that infections were an important cause of poor growth with HIV infected children. Low height-for-age can be as a result of poor nutrition, frequent infections, or both, whereas low weight-for-height is associated with acute infection, malnutrition, diarrhoea and starvation (Moye et al. 1996).

Growth is compromised in children with HIV infections even where there is adequate and appropriate nutrition (Nathan et al. 2003). In a developed country like the USA, where there are good nutritional resources, there are still 30% - 50% of HIV infected children who show evidence of protein energy malnutrition (Miller 2000). This is in contrast to the study by Chase et al. (1995) who found no difference in height and weight between HIV infected children with normal or very low neurodevelopmental scores. This result was probably due to an aggressive treatment plan that was implemented for children with poor weight gain.

The consumption of adequate energy needs should match the child's metabolic needs because metabolism and energy utilization are related. An HIV infected child has a higher resting energy expenditure than uninfected children and they are therefore in need of more calories (Miller 2000, Laufer and Scott 2000). More calories are also needed by any child who has a raised temperature, acute diarrhea and/or sepsis. In addition, when a child is malnourished, bradycardia results and this also increases the energy expenditure (Miller 2000). If there is an imbalance between energy intake, absorption and the metabolic needs of the child, wasting and stunting are likely to occur.

A lack of nutritious food allows HIV to progress quicker in a person with HIV/AIDS. Improved nutrition has been shown to have a positive influence on health in other chronic conditions (Miller 2000). The

nutritional status of HIV infected children is dependent on the availability of nutritional food and the ability of the child to meet its energy needs. Besides the reduced oral intake, due to oral infections and nausea, a common concern is gastrointestinal malabsorption (Miller 2000).

Gastrointestinal malabsorption can result from both malnutrition and HIV. Severe malnutrition causes intestinal inflammation and atrophy with resultant malabsorption. HIV infected children are at risk of intestinal malabsorption due to small intestinal overgrowth. Pancreatic and hepatobiliary insufficiency in HIV infected children also causes malabsorption (Miller 2000).

Malnutrition and HIV affect the immune system in a similar way. Therefore, a child who has malnutrition and HIV infection has a worse outcome regarding their immunity than what a child would have with either condition alone (Miller 2000).

Another similarity between malnutrition and HIV is the pulmonary infection 'pneumocystic carinii'. It is also a common opportunistic infection associated with HIV and malnutrition. It is the major cause of mortality in paediatric HIV in Africa (Vetter et al. 1996).

2.12 Management of HIV disease in children

Since the start of the HIV epidemic there have been significant advances made in the medical management and pathophysiological knowledge of the HIV disease. In developed countries children are managed medically

with antiretroviral therapy, their immune system is monitored and maintained, and opportunistic infections are prevented. Newly developed antiretroviral treatment regimes are available together with treatment for opportunistic infections. These advances have resulted in a dramatically improved quality of life and the prolonged survival of HIV infected children. In developed countries the disease is now classified as chronic rather than sub-acute (Laufer and Scott 2000, Rausch and Stover 2001).

Antiretroviral therapy is reported to improve the neurological involvement of children with progressive encephalopathy or late occurring encephalopathy (Schmitt et al. 1991, Smith et al. 2000), especially if the antiretroviral is one of those that penetrate the blood-brain barrier. This was also noted on improved CT findings (Spitaels 1994). Schmitt et al. (1991) found that early treatment reduces the neurological deterioration and partly reduces the symptoms. Belman (1992) showed an improvement in expressive language and adaptive behaviour in HIV infected children on antiretroviral therapy.

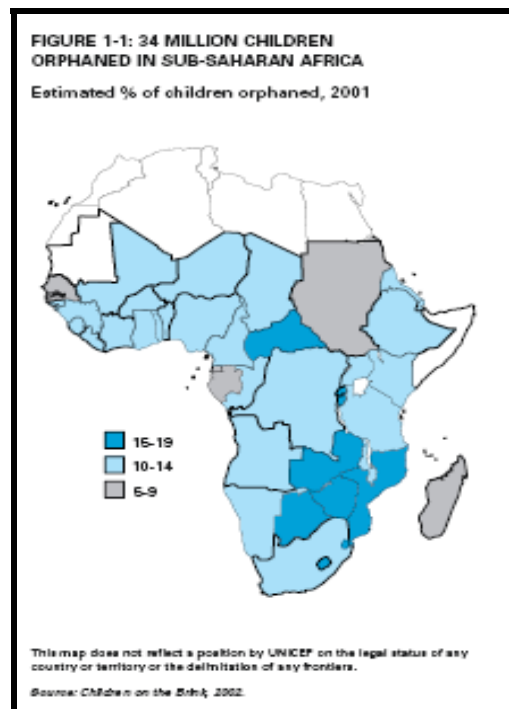
Another reported benefit of antiretroviral therapy was that growth rates normalized (Wilfert and McKinney 1998). There was an improvement in weight, in weight-for-height and there was a borderline effect on height (Miller 2000).

With the improved rate of survival of HIV infected children on treatment, there is a need to determine the impact of antiretroviral therapy on the

incidence and prevalence of milder neurological impairments (Rausch and Stover 2001). These milder impairments are likely to increase because the treatment affects their outcome, and the children survive longer (Rausch and Stover 2001). There is a need to establish whether antiretroviral intervention delays clinical and developmental problems (Nozyce et al. 1994). HIV infected children therefore need regular neurological and developmental evaluations as well as early educational and therapeutic interventions (Spitaels 1994, Lobato et al. 1995, Smith et al. 2000).

2.13 Prevalence of orphans in Africa

Almost every country in the world has children who are orphaned, but the percentage of orphans due to HIV/AIDS is increasing and far outnumbers those orphaned by other causes. Some countries have a few thousand orphans, but in Sub-Saharan Africa there are millions of orphaned children (see figure 2.3).



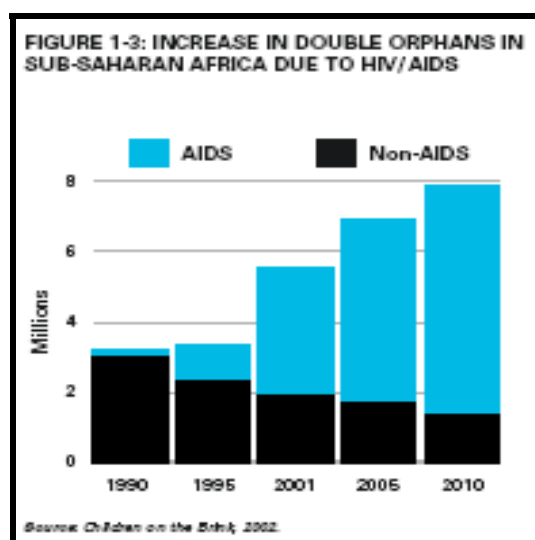
Source: Children on the Brink 2002

Figure 2.3

24 million children orphaned in Sub-Saharan Africa

An orphan is viewed differently by different people (Foster 1997). The UNAIDS (2004) classified an orphan as a child younger than 18 years of age, who has lost at least one parent ; an orphan can be a maternal orphan - a child whose mother has died, a paternal orphan - a child whose father has died, or a double orphan - a child who has lost both parents. Due to the nature of the infection, HIV/AIDS usually affects both parents making double orphans a characteristic feature of the HIV/AIDS epidemic (see figure 2.4). Therefore, countries that have a high HIV/AIDS population will have a proportionally higher number of double orphans. In 2003 Sub-Saharan Africa had 7.7 million single orphans and four million double orphans. This is almost as many of the total number of orphans in Asia; notwithstanding the fact that Asia has four times as

many children. It is estimated that by 2010 there will be almost eight million double orphans in Sub-Saharan Africa (UNICEFT 2003). There is also a higher rate of infection and mortality in women which results in maternal orphans outnumbering paternal orphans. South Africa has 60% maternal orphans compared to 40% in Asia, Latin America and the Caribbean (UNICEFT 2003). UNAIDS/UNICEF/USAIDS (2004) stated that 12% of orphans are below the age of six years and 55% of orphaned children are above the age of 12 years.



Source: Children on the Brink 2002

Figure 2.4

Increase in double orphans in Sub-Saharan Africa due to HIV/AIDS.

Human Right's Focus (UNAIDS 2004) states that, the phrase "AIDS orphan" should be avoided because of a stigma which is associated with the term. This description violates a child's rights. However, for the purpose of research the use of the phrase "HIV/AIDS orphan" is used to describe children who are orphaned directly as a result of HIV/AIDS.

2.14 Woman-headed households

Three quarters of rural households in South Africa have women as the primary care-giver, provider and guardian of the family (UNAIDS 2004). They raise and nurture their own children and often the children of others. Women are more likely than men to care for their own children and they are also more willing to take in orphans. On average, a female-headed household is prepared to accommodate two double orphans from other families whilst a male-headed household averaged one double orphan (UNAIDS 2004). Therefore, the impact of the HIV/AIDS epidemic is particularly severe if the infected person is the woman. Women in their 20's and 30's are particularly vulnerable to HIV/AIDS and this is their child-bearing and child-rearing age. Once ill or terminal, the task of caring, providing and nurturing becomes the responsibility of others in the family; usually the surviving generations - the older women and younger girls. They shoulder the burden of the orphaned children from their own family and from the extended families. They are forced, out of necessity; to become the main care-givers, providers and guardians of the household (UNAIDS 2004).

2.15 Community support of orphans

Prior to the HIV/AIDS epidemic, many children were already growing up in the absence of one or both parents. Although this phenomenon is not unique in Sub-Saharan Africa, the numbers of such children needing care is increasing because of HIV/AIDS. A UNICEF (2003) analysis showed that, in South Africa, extended families have assumed the responsibility for 90% of orphaned children. One of the consequences of the HIV/AIDS epidemic is the inability of the extended family to cope with the care of another child. Family life is the best option for orphaned children, but there is a need to strengthen the family's capacity to care for and to protect these children. It would be in the child's best interests for the adults to be kept healthy so that they are able to care for their own children (UNAIDS/UNICEF 2004).

Orphaned children need social and medical intervention as well as a stable, consistent environment that provides love and nurturing (American Academy of Pediatrics 1999). An institution could fulfill this role, but internationally there is a preference to keep children within their communities (Foster 1997). The number of children in need of care should not, and logistically cannot, be institutionalised. Formal institutions provide a last resort for a limited number of orphaned children. Many countries do not have, nor do they enforce, registration and regulation of institutions (UNAIDS/UNICEF 2004). Institutions are an appealing alternative because they provide food, clothing, security and education. However, UNAIDS/UNICEF/USAIDS (2004) and International Save the

Child Alliance (2004) estimated that financially, institutionalization is up to 12 - 14 times more expensive per capita than the cost of community-based care.

Institutionalisation conflicts with the child's fundamental right to grow up in a family and community environment. Children lose their independence and autonomy because institutions promote dependency (UNICEF 2002). UNAIDS/UNICEF (2004) states that institutionalization does not meet the child's developmental, emotional or psychological needs. Most institutions have too few care-givers and therefore cannot provide children with the affection and attention they need. The children are deprived of the social connections with their families and communities and they have difficulty in re-integrating into society (UNAIDS/ UNICEF 2004). Where institutionalised care is offered, programs need to be developed to integrate these children back into their communities at the earliest opportunity (UNICEF 2002).

The stigma that is associated with HIV/AIDS in the community is also very prevalent (American Academy of Pediatrics 1999). In South Africa, one third of HIV infected people who revealed their status received a supportive response from their community. One in ten reported that they were subject to rejection and outright hostility (UNAIDS 2004). Without a protective home and community environment, orphaned children face the risk of exploitation, abuse, violence and ill treatment. Orphaned children

living with foster families are more likely to be malnourished and short in stature in comparison to non-orphans (UNAIDS 2004).

UNAIDS 2004; with respect to orphans: 'These children could still have a safe, healthy and productive childhood if immediate, sustained and coordinated efforts are made that give high priority to children and to the preserving of the family unit.' This is also the opinion of the International Save the Children Alliance (2004), which recommends that family-based care and support for these children is needed in order to maintain the links with their community and family environment. The United Nations Convention on the Rights of the Child, Article 3 (1990) states that all actions concerning the child shall be in the 'best interests of the child', and Article 6 states that 'all children have a right to a safe, secure and nurturing family and the right to participate as a member of that family'. Children's villages and adoptive placements can therefore be viewed as an inappropriate alternative (Foster 1997, Foster and Williamson 2000, UNAIDS/UNICEF 2004, UNAIDS/UNICEF/USAIDS 2004). It would be advantageous to support families or guardians in order to enable them to have the capacity to nurture and mature their children in a family unit, within a community. In rural communities, traditional values are better preserved, and extended families play a greater role in the care of orphans than is the case in urbanised extended families. However, in either situation, those children who are not cared for are at risk of becoming street children, working children and the heads of child-headed households (UNAIDS/UNICEF/USAIDS 2004).

2.16 Benefits of institutionalisation

In South Africa, it is estimated that only a small percentage of orphaned children are able to be accommodated in institutions; reliable statistics are however, not available (UNICEF 2002). According to Munoz-Hoyos et al. (2001) institutionalisation does not, in itself, have a negative influence on the development of a child. Nathan et al. (2003) found that the survival of HIV infected children in institutions was 70% in comparison to 11% of children attending outpatient clinics. It would thus seem that in poorly resourced settings the development of similar institutions could be an option. Nathan et al. (2003) attributed the reason for the better survival rates in an institution to be adequate nutrition as well as appropriate and timely clinical care. Nogueira-de-Almeida et al. (2001) found that with institutionalised children in Brazil the HIV infected children's growth was normal although they did have anemia. There was, however, a general improvement in their quality of life. An institutional approach could therefore be a way of assisting the vulnerable and needy HIV children in Sub-Saharan Africa (Nathan et al. 2003).

2.17 Bayley scale of infant development II

The Bayley scale of infant development (BSID) is an individually administered evaluation tool used to assess the neurodevelopmental functioning of an infant or child from birth to 36 months. The BSID was revised in 1993 (Bayley 1993) and referred to as the BSID second edition

or BSID II. The age range of the BSID II was extended to assess children up to, and including, the age of 42 months. There is a correlation coefficient of 0.62 between the BSID and BSID II. Given this relationship, the validity of BSID II is supported (Black and Matula 2000). BSID II possesses content, constructive and discriminatory validity. It has been widely used and is a highly regarded developmental assessment tool for clinical and research purposes. It is a detailed and appropriate measure of a child's mental and psychomotor development (Macmillan et al. 2001).

The BSID II consists of three scales namely; the mental scale, the psychomotor scale and the behaviour rating scale. The behavioural rating scale does not have standardised norms. It is used to give additional information when interpreting results (Bayley 1993).

The mental scale assesses overall cognitive development. This includes test items to evaluate the child's memory, habituation, problem solving, generalisation, classification, social skills, the early acquisition of number concepts and linguistic skills.

The psychomotor scale is used to assess overall motor development. This scale includes test items to evaluate the child's gross movements relating to body control and the co-ordination of muscles and fine motor abilities, which include prehension, the use of writing instruments, hand movements and manipulation skills.

Tables in the BSID II manual provide an easy method of converting raw scores to standardised, age-related index scores. The mental scores are referred to as the 'mental development index' (MDI) and motor scores are referred to as the 'psychomotor developmental index' (PDI) (Black and Matula 2000).

Index scores are restricted to a range of 50-150. It is therefore not possible to obtain an index score below 50 unless extrapolated scores are used. Using statistical methods, Robinson and Mervis (1996) extrapolated the index score from 50 down to 30. Index scores below 30 were allocated a score of 29 (Macmillan et al. 2001, Smith et al. 2000).

Concerns have been raised regarding the different scores obtained on the BSID II if testing is not commenced at the child's chronological age. Mayes (1997) and Gauthier et al. (1999) demonstrated that testing a child on an age item that does not correspond to their chronological age affected the child's score. To ensure test validity, all infants must begin being tested at the 'item set' that corresponds to their chronological age; as recommended in the BSID II manual (Mayes 1997, Gauthier et al. 1999).

BSID II was standardised on a sample of American infants and children. They were full-term children with no significant medical or developmental concerns. BSID II has been used for research purposes in developing

populations, but it is recommended that studies that are normed on the population being studied be used, rather than the American norms (Black and Matula 2000). Norms for the BSID using the South Africa population were established by Richter and Griesel (1988). A group of children from urban and peri-urban population in Kwa-Zulu Natal and Gauteng comprised the population sample. These norms were statistically not different from the American BSID norms, except in the early months. Statistical differences occurred between four and fifteen months on the mental scale and between two and ten months on the motor scale. These differences were, however, higher in the South Africa norms than in the American norms. It is therefore acceptable that the BSID is valid as a tool to be used with South African children. Since there is a high correlation between the BSID and BSID II, the score obtained from BSID II can be justified as the appropriate norm for use in the South African context.

Niccols and Latchman (2002) validated the BSID II on children with special needs and these would include high risk infants. Children with HIV are considered high risk infants and children. BSID II discriminates between infants at risk and those developing normally. The test showed sensitivity to changes in development in these children (Niccols and Latchman 2002). They did emphasise that high risk children's results should be interpreted with caution. The BSID II should not be used as a predictive measure in high risk infants (Gauthier et al. 1999, Niccols and Latchman 2002).

BSID-II adequately assesses quantitative aspects of mental and motor dysfunction affected by HIV (Chase et al. 1995). However, the same researcher commented that the BSID and BSID II do not adequately assess subtle qualitative aspects of neurological impairment like attention, memory and quality of movement. Lower BSID scores early in life are associated with greater mortality (Nozyce et al. 1994, Chase et al. 2000, Pearson et al. 2000, Llorente et al. 2003). Developmental signs can occur without high viral loads in children with HIV; therefore the BSID is a good measure of the neurodevelopmental state of these children. The BSID is a prompt and reliable indicator of early HIV related central nervous system impairments. It therefore makes it possible for an aggressive and appropriate treatment plan to be initiated to prevent the effects of HIV on the developing brain (Chase et al. 2000). Measurements of neurodevelopment and motor function using the BSID are better predictors of the progression of HIV than the immunostatus (Pearson et al. 2000). Lower cognitive and motor scores at four months predict early mortality in infants with HIV (Llorente et al. 2003). The infant's information processing abilities are a more robust predictor of a child's cognitive development at school age, than measures of sensory motor development. (Drotar et al.1997). In HIV infected children there is a variety of speech, language and communication difficulties. Delays in this area may indicate the CNS involvement as a result of the HIV (Layton and Scott 2000). Since the BSID II has more language based items after the age of 18 months, the HIV infected children have difficulty

in carrying out verbal instructions without the associated physical demonstration, as well as having difficulty with verbal responses (Gay et al. 1995).

2.18 Conclusion

The prevalence of HIV and the increasing incidence of adults and children with HIV in Sub-Saharan Africa is a matter of grave concern. There is a difference in the incidence and outcome of children with HIV infection in developed versus developing countries. Important factors that compound the problem in developing countries are their limited basic resources, high levels of poverty and malnutrition, as well as the prevalence of other fatal diseases. As a result of the epidemic, there are an increasing number of orphans. These orphans are better cared for within the community, but an institutionalised environment does provide certain benefits. The research on neurodevelopmental and growth impairments of the HIV infected children in Sub-Saharan Africa is limited and additional studies of the South African population group would be invaluable in order to add to the accumulated base of knowledge of HIV/AIDS in this area. The outcome of children's growth and neurodevelopment on ART and not on ART is vital in establishing the effectiveness of therapy. It is important to address these children's needs with appropriate and adequate, social and medical interventions to enable them to live longer and to enjoy a better quality of life.