Psychomotor functioning of HIV positive adolescents on antiretroviral treatment in Johannesburg, South Africa

Stephanie MacIlwaine (693205)

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Supervisor: Professor Marilyn Lucas

I declare that this research report is my own, unaided work. It has not been submitted before for any other degree or examination at this or any other university.

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Abstract

In 2009 an estimated 33 million people were living with the Human Immunodeficiency Virus (HIV). Of this global population, 35% live in South Africa. Furthermore, sub-Saharan Africa is home to 80% of the world's population of HIV-1 positive children and adolescents. The most prominent form of transmission of HIV in children in South Africa is from mother to child. Until 2004, South Africans had limited access to ARV treatment at and after birth due to the government legislation. As a consequence, treatment of HIV in children may only have been initiated after clinical presentation of immune deficiency. Therefore, currently, HIV-1 positive adolescents born during the period of restricted ARV-access may have experienced physical and developmental symptoms associated with the virus including neurological deficits, prior to initiating treatment. This study investigated the current psychomotor functioning, such as psychomotor speed, manual dexterity, graphomotor and visual-motor coordination of a group of low socio-economic HIV-1 positive adolescents in Johannesburg, South Africa, who are now on a managed antiretroviral programme and how this compared to a HIV negative contrast group. A Mann-Whitney U Test indicated a significant difference in mean non-dominant hand performance in the Grooved Pegboard Test between the two groups (U = 738, $p < .05$), with the HIV positive group performing slower than the HIV negative group. An independent samples t-test indicated a significant difference between groups in the Block Design subtest of the WISC-R [$t(88) = -2.93$, $p < .01$] where the HIV positive group performed significantly worse than the HIV negative group. Additionally, a Mann-Whitney U Test revealed a significant difference in number of errors made in the WISC-R Mazes subtest between groups (U = 736.50, $p < .05$), where the HIV negative group made more errors. Another Mann-Whitney U Test revealed a significant difference between groups in the ROCFT Copy score (U = 534.50, $p < .01$) where the HIV positive group achieved a significantly lower score than the HIV negative group. Lastly, a Mann-Whitney U Test

demonstrated significant differences between the groups in the Trail Making Test A time (U = 445.00, $p < .01$), Trail Making Test B time (U = 509.00, $p < .01$), the number of errors made on the Trail Making Test B (U = 729.00, $p < .05$) and the difference between Trail Making Test B – A time (U = 769.50, $p < .05$) with the HIV positive group performing slower and making more errors in Part B than the contrast group. The findings of the current study imply that HIV-1 vertically-infected adolescents in Johannesburg, South Africa, on a delayed HAART programme appear to have persisting difficulties in complex psychomotor skills where an integration of functions is required. Furthermore, these results indicate an overall poor psychomotor performance in comparison to international normative data, supporting previous findings. Developmental, remedial and therapeutic recommendations were made.

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2.1 Introduction

In 2009, approximately 33 million people worldwide were estimated to be living with the Human immunodeficiency virus (HIV) (UNAIDS, 2010). Sub-Saharan Africa was home to two thirds of the global HIV positive population with 72% of Autoimmune Deficiency Syndrome (AIDS)-related deaths in 2009. Furthermore, 87% of HIV-infected children under the age of 15 are found in sub-Saharan Africa (Wachsler-Felder & Golden, 2002). Women and children are the most at risk for infection (Wachsler-Felder & Golden, 2002) with vertical mother to child transmission being the predominant mode of transmission in children in South Africa (Shisana et al., 2005). The exact incidence of vertical HIV infection in South Africa is currently not known due to poor information systems but, in 2007, an estimated 280 000 children were born with HIV (Technau, 2009).

It has been well-documented that HIV infection causes significant cognitive deterioration in adult (Lawler et al., 2010; Singh et al., 2010; Toborek, M., et al., 2005) and paediatric populations (Govender, Eley, Walker, Petersen & Wilmshurst, 2011; Koekkoek, de Sonneville, Wolfs, Licht & Geelan, 2008; Sherr, Mueller & Varrall, 2009). However, little is known about the cognitive functioning of those who survive childhood; vertically-infected HIV positive adolescents. In addition, the majority of studies on neurodevelopment in HIV positive children have emerged from the USA and Europe (Koekkoek, et al., 2008; Martin, Wolters, Toledo-Tamula, Zeichner, Hazra & Civitello, 2006; Wachsler-Felder & Golden, 2002) where the predominant strain of HIV-1 is different to that found in South Africa.

Up until 2004, the availability of antiretroviral (ARV) treatment in the public health sector was limited in South Africa. Therefore, the incidence of vertical child infection was high and

those children were not initiated on pre- or post-natal ARV treatment, as is the normal protocol now. The current study hypothesised that those children may have been subject to the neuropathological effects of HIV. Some of those children, however, have survived through early childhood and are now entering, or are in, adolescence. Very little is known about the effects of HIV on the adolescent brain and particularly an adolescent brain on delayed ARV treatment.

As the ability to move and explore one's environment is one of the earliest functions to develop, the impact on later functions may be detrimental as intact psychomotor skills are an integral part of everyday human functioning. It is well-documented that HIV negatively affects the fronto-striatal motor pathways in the brain and has detrimental consequences on the motor development of infants as well as on previously developed motor skills in adults (Melrose, Tinaz, Castelo, Courtney & Stern, 2008; Wachsler-Felder & Golden, 2002). There is a paucity of literature regarding the effects of vertically-acquired HIV infection on the psychomotor functioning of seropositive adolescents, however.

This study formed part of a larger cohort investigating the neuropsychological profile of vertically-infected HIV positive adolescents, who, although currently on a managed highly active antiretroviral treatment (HAART) programme, received delayed initiation of treatment due to the South African government's restrictions on ARV rollout. The aim of this specific study presented here was to investigate the presence of possible ongoing motor deficits in these adolescents with delayed ARV treatment. Secondary objectives included the aim to stimulate further research on the topic and to better advise appropriate interventions to address the neuropsychological needs of HIV positive adolescents on antiretroviral treatment.

The following literature review will discuss HIV as a virus and its effects on the developing brain. It will then describe the different HIV subtypes in support of the need for South African-specific HIV research before discussing the methods of ARV treatment and the history of ARVs in South Africa. Then it will focus specifically on HIV-1 infection and psychomotor functioning, going into more detail regarding the development of motor functions and how this and specific brain areas are affected by HIV. It will also discuss the available research that demonstrates the motor deficits in children, adolescents as well as the effect of ARV treatment on such deficits. This will provide the foundation for and lead onto a description of the rationale of the current study.

2.2 The Human Immunodeficiency Virus

The human immunodeficiency virus (HIV) epidemic is a global public health issue. It predominantly affects the body's immune system but this research will focus on its effects in the brain. HIV affects the central nervous system (CNS) in two ways: indirectly via opportunistic infections, tumours and systemic disease processes; and directly via specific HIV-induced neuropathology (Gray & Keohane, 2003). It doesn't however affect the neuron directly, but rather its surrounding, supportive structures. HIV-induced neuronal damage is thought to involve glutamate toxicity, oxidative stress and apoptosis (Gray & Keohane, 2003).

HIV is a retrovirus, belonging to the family of lentiviruses, which leads to acquired immunodeficiency syndrome (AIDS). Immune deficiency in HIV manifests once the virus has entered through bodily fluids, infecting the $CD4^+$ lymphocytes (T-cells) and monocytes of the immune system (Ellis, Calero & Stockin, 2009). The virus overrides the programming of these host cells and causes the manufacture of reverse transcriptase to convert the viral

RNA into DNA (Ellis et al., 2009). In so doing, the viral RNA is able to invade the host cell's genetic material. HIV infection gradually causes the $CD4^+$ T-cells to die. $CD4^+$ T-cells function to initiate the body's immune responses to infection therefore loss of these cells results in critical compromise of the immune system and risk of life-threatening opportunistic infections. A $CD4^+$ count of less than 200 indicates significant risk of infections.

Monocytes, on the other hand, remain infected and transport the virus through the blood brain barrier into the brain. HIV invades the CNS early in infection through these infected monocytes (Tardieu, 1998). Once inside the brain, the infected monocytes differentiate into specific CNS types such as perivascular macrophages, perivascular microglia and microglia, and further replication occurs. In the CNS, HIV indirectly affects neurons though viral factors (neurotoxic proteins produced by the HIV genome), host factors and co-factors (factors related to the infected individual) (Civitello, 2003; Ellis et al., 2009).

Viral factors, such as Gp120, are located on the surface of the virus allowing it to bind to the target or host cells. In addition to the effect on the host cell's DNA, this results in an immune response causing alteration of the glutamate pathway resulting in the stimulation and production of cytokines, causing synaptodendritic damage in the neurons leading to a break down in efficient cognitive functioning (Ellis et al., 2009). Several proteins are also encoded by the virus' RNA, including the transcriptional transactivator (Tat) protein which is specifically associated with mitochondrial dysfunction, dendritic loss and neuronal cell death (Ellis et al., 2009). Therefore, although the virus does not directly affect the neuronal bodies themselves, it affects the scaffolding structures around them.

A secondary effect of HIV infection in the CNS occurs as the infected microglia and macrophages stimulate a further immune response and the release of pro-inflammatory cytokines and chemokines (Ellis et al., 2009). The activation of their receptors, which is found in microglia, astrocytes, oligodendrocytes and neurons, results in structural and functional neuronal changes and apoptosis is facilitated (Ellis et al., 2009; Koekkoek et al., 2008; Toborek et al., 2005). Lipton (1998) argues that injury or damage sustained to the neural networks may not inevitably result in death, but rather in reversible dysfunction, suggesting opportunity for treatment. Therefore, HIV infection is characterised by immune deficiency as well as a prolonged immune, and excitotoxic, response.

2.3 HIV in the Developing Brain

The neuropathology of HIV-1 infection in adults and children is relatively similar (Dickson, Llena, Nelson & Weidenheim, 1993) however the effect of neurological insult in a developing brain compared to a mature brain is quite different. In the former case, the acquisition of developmental abilities is disrupted whereas in the latter case, the result is a breakdown in functions and skills that have already developed (Zillmer, Spiers & Culbertson, 2008).

Autopsies and neuropathological studies of HIV infected infants have demonstrated irregularities such as abnormally small head growth, cortical atrophy, enlarged ventricles, diffuse gliosis (particularly affecting the grey and white matter), calcification of the basal ganglia and cerebral white matter, reduction of white matter, cortical spinal tract degeneration and HIV encephalitis, suggesting significant neurodevelopmental disruption (Armstrong, Seidel & Swales, 1993; Belman et al., 1985; Belman et al., 1986; Civitello, 2003; Dickson et al., 1993; Epstein, Berman, Sharer, Khademi & Desposito, 1987; Lyman, Kress, Kure,

Rashbaum, Rubinstein & Soerio, 1990). In contrast, autopsies on adults with AIDS have revealed lymphomas, bacterial infections, cryptococcosis, tuberculous meningitis with brain abscesses, HIV encephalitis, tumours (e.g. Kaposi's sarcoma), toxoplasmosis and intracerebral haemorrhage (Kibayashi et al., 1999; Reichert, O'Leary, Levens, Simrell & Macher, 1983; Silva et al., 2012). In both infant and adult brains, the devastating effect the virus has on the cerebral integrity is evident.

It has been suggested that the progression of the disease is faster in children due to its harmful effects on the developing immune and nervous systems (Belman, 1997). Furthermore, it has been documented in the literature that the clinical presentation and progression in HIV-infected children varies considerably and is influenced by several factors including the timing of infection, the viral load in the mother's blood, the genetic characteristics of the child and the genetic characteristics of the virus. However, HIV infection can significantly affect a child's cognitive, physiological, emotional, behavioural and psychological development (Wachsler-Felder & Golden, 2002). Clinical symptoms of paediatric HIV encephalopathy include "cognitive impairment, poor brain growth, abnormalities of motor function and tone, movement disorders, cerebella signs and mood and behavioural problems" (Wachsler-Felder & Golden, 2002, p.444). CNS abnormalities can appear within the first few months of life (Chase et al., 2000) or several years later. Although some children do not demonstrate major neuropathological signs (Armstrong et al., 1993), there are two main types of HIV encephalopathy: severe progressive encephalopathy and progressive encephalopathy.

Approximately 25% of HIV-1 infected children will have a progressive encephalopathy in its severe infantile form which is characterised by significantly delayed cognitive functioning,

neuromotor deficits and opportunistic infections beginning in the first three years after birth (Armstrong et al., 1993; Tardieu, 1998). Radiological abnormalities seen in such children include enlargement of the subarachnoid space and ventricles, basal ganglia calcifications and reduction of the white matter (Tardieu, 1998). With damage like this, one would expect significant deficits and abnormalities; children with HIV-related severe progressive encephalopathy do not usually survive beyond five years of age.

Progressive encephalopathy is more slowly progressive and is most prevalent in HIV-1 infected children (Armstrong et al., 1993; Tardieu, 1998). Subacute progressive encephalopathy is characterised by patterns of cognitive deterioration interspersed with periods of stability. Children with plateau progressive encephalopathy, on the other hand, may remain asymptomatic for several years. The neurologic effects are less severe and may include "hypotonia, marked delays in attainment of motor milestones, delayed mental development with concomitant language deficiencies, mild atrophy with or without basal ganglia calcification and poor brain growth" (Wachsler-Felder & Golden, 2002, p.445). Some vertically-infected children do not fall prey to opportunistic infections or encephalopathy and thus their disease progression, like this, is slow (Blanchette, Smith, King, Fernandes-Penney & Read, 2002). Therefore, there are a number of seropositive children who progress normally through the early developmental stages into school-age. The reason for this, however, is unknown and thought to be due to a multitude of factors.

There are limited and conflicting research findings regarding the effects of vertical HIV-1 infection in school-age children. In their review of the literature, Wachsler-Felder and Golden (2002) indicated cognitive deterioration, language difficulties, reduced attention, reduced psychomotor speed, poor fine motor skills, social withdrawal and emotional lability.

However, in a study of vertically-infected school-age children, normal neurodevelopment and only subtle motor difficulties were found (Blanchette et al., 2002) reiterating the variability of infection effects. There seems to be a lack of conclusive and consistent results for this age group.

There is therefore a considerable dearth of research concerning the effects of vertical HIV-1 infection in adolescents. Whilst children with slow-progressing infection may be able to cope with pre- and primary school demands, the academic and social expectations of the child increase considerably when they enter adolescence. However, little is known about the neuropathological as well as neuropsychological effects of vertical HIV-1 infection in this age group. Whilst the majority of grey matter has matured prior to adolescence and declines during this period, increases in white matter and cortical maturation, particularly in the prefrontal cortex, continue to develop into adulthood (De Luca & Leventer, 2008). As HIV-1 infection affects the development of white matter, it is thought that it may have a negative effect during this period of neurodevelopment. However, this is yet to be explored.

2.4 Different HIV Subtypes

There are three classes of HIV-1: M (major), which accounts for more than 90% of reported HIV infections; O (outlying); and N (new) (Spira, Wainberg, Loemba, Turner & Brenner, 2003). Class M can be further classified according to the nine different subtypes, or clades. HIV-1 clade C accounts for more than 50% of all new infections worldwide and is the predominant subtype in South Africa (Koh et al., 2010). In Europe and the Americas, where the majority of HIV research has been conducted, the most common subtype is HIV-1 clade B (Ellis et al., 2009). Sherr et al. (2009) reported that 63% of the available literature on HIV

and child development is from North America and therefore regarding HIV-1 clade B infection.

Clinical symptomologies vary between clades and affect the brain differently (Rao, et al., 2008). The incidence and severity of problems such as HIV-associated dementia (HAD), for instance, revealed that HAD severity and morbidity rates were more severe in North American HIV-1 clade B infection when compared to parts of Asia and sub-Saharan Africa. Even where HAD was suspected in clade C-affected individuals, the clinical cases were milder than in clade B-affected individuals revealing clade-specific neuropathogenicity (Rao et al, 2008). Several studies have shown that specific glycoproteins of clade C are different to those of clade B and that the development of cognitive impairment related to HIV in clade C may be quite low (Gandhi, Saiyed, Thangavel, Rodriguez & Nair, 2009). On the other hand, a study of HIV positive adults in South India, where clade C is prevalent, found mild to moderate cognitive deficits which were attested to be similar to that reported in ARV-naïve individuals infected with the clade B virus (Gupta et al., 2007). Thus, there appears to be contradicting evidence regarding neurotoxicity of different HIV clades. Nevertheless, literature on HIV-1 clade C vertically-infected adolescents is scarce to none.

2.5 Antiretroviral Treatment

The aim of antiretroviral (ARV) treatment is to suppress replication of the HIV-1 virus in order to delay normal progression of the disease (Wood et al., 2000). There are currently seven types of antiretroviral agents in use, each targeting a different stage of the viral cycle: nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), integrase inhibitors (IIs), fusion inhibitors (FIs) and chemokine receptor

antagonists (CRAs). Prior to 1995, the prognosis of an HIV diagnosis was dismal with disease progression rapidly leading to death. However, with the advent of combination antiretroviral treatment (CART), also referred to as highly active antiretroviral treatment (HAART), the suppression of the virus and improvement of the body's immune system has meant that the effects of opportunistic infections are reduced as is the inflammatory response in the CNS (Gray & Keohane, 2003). Thus, HIV-1 patients are surviving longer.

Nevertheless, like any drug, ARVs do cause physical side-effects such as nausea, vomiting, diarrhoea, fever and rash initially (van Rossum, Fraaij & de Groot, 2002; Wamalwa et al., 2007). Longer term effects include drowsiness and lethargy (Koekkoek et al., 2006). Whilst neuropsychological functioning is thought to improve with HAART, this response is variable (Smurzynski et al., 2011). This is thought to be due to several factors, including the variation in penetration of ARVs across the blood-brain barrier. In order to determine the efficacy of ARVs for the blood-brain barrier penetration, the CHARTER Group has produced the Antiretroviral CNS Penetration Effectiveness (CPE) ranking that provides information regarding ARV drug regime penetrance (Letendre et al., 2008). The CPE score for each ARV drug is based on "pharmacokinetic data, results of clinical studies, and drug properties"; the higher the score, the better the CNS penetration, suggesting the better the improvement in immune system and neuropsychological functioning (Garvey et al., 2011, p.693). In their large population study, Smurzynski et al. (2011) concluded that treatment with three or more ARVs, with better overall CPE scores, results in better neuropsychological improvement compared to treatment with less than three ARVs. Therefore it is important to be selective in choosing which ARVs to use to treat patients.

2.5.1 Antiretroviral treatment in South Africa.

Current South African guidelines for the initiation of HAART in children suggest Abacavir (ABC), Lamivudine (3TC) and Efavirenz (EFV) as first line treatment for children older than three years of age (Department of Health, 2010). Previously, Stavudine (d4T) was recommended instead of ABC and, if experiencing no adverse side-effects, some children may still be on this regimen. According to the CPE rankings, the current first line regimen for children has an overall CPE score of eight (Levin, 2011), suggesting good blood-brain barrier penetration. Currently, in South Africa, children are eligible to initiate HAART if: they are less than one year old; they are between the ages of one and five with a clinical WHO stage III or IV or a $CD4^+$ count $\leq 25\%$ or an absolute $CD4^+$ count < 750 cells/µl; they are between five and 15 years with a clinical WHO stage III or IV or $CD4^+$ count ≤ 350 cells/µl (Department of Health, 2010). If a child has a clinical WHO stage IV or has multi-drug resistant or extreme drug resistant Tuberculosis they are also eligible for HAART initiation. The following table describes the different WHO stages of HIV/AIDS for infants and children (WHO, 2005, p.11):

Table 1

Revised WHO clinical staging of HIV/AIDS for infants and children

Clinical Stage	Description
1	Asymptomatic; persistent generalised lymphadenopathy.
2	Hepatosplenomegaly; popular pruritic eruptions; seborrhoeic dermatitis; extensive human papilloma virus infection; extensive molluscum contagiosum; fungal nail infections; recurrent oral ulcerations; lineal gingival erythema; angular cheilitis; parotid enlargement; herpes zoster; recurrent or chronic respiratory tract infections.

3	Moderate unexplained malnutrition not adequately responding to standard therapy; unexplained persistent diarrhoea (≥ 14 days); unexplained persistent fever (intermittent or constant, for longer than one month); oral candidiasis (outside neonatal period); oral hairy leukoplakia; acute necrotising ulcerative gingivitis/periodontitis; pulmonary tuberculosis; severe recurrent presumed bacterial pneumonia; chronic HIV-associated lung disease including bronchiectasis; lymphoid interstitial pneumonitis; unexplained anaemia, and or neutropenia and or thrombocytopenia for more than one month.
4	Unexplained severe wasting or severe malnutrition not adequately responding to standard therapy; pneumocystis pneumonia; recurrent severe presumed bacterial infections; chronic herpes simplex infection; extrapulmonary tuberculosis; Kaposi's sarcoma; oesophageal candidiasis; CNS toxoplasmosis (outside the neonatal period); HIV encephalopathy; cytomegalovirus infection; extrapulmonary cryptococcosis including meningitis; any disseminated endemic mycosis; cryptosporidiosis; isosporiasis; disseminated non-tuberculous mycobacteria infection; candida of trachea, bronchi or lungs; visceral herpes simplex infection; acquired HIV associated rectal fistula; cerebral or B cell non-Hodgkin lymphoma; progressive multifocal leukoencephalopathy; HIV-associated cardiomyopathy or HIV-associated nephropathy.

In 2002, 26.5% of pregnant women were HIV positive (Department of Health, 2003). Whilst this estimate among antenatal women attending clinics rose to 30.2% in 2010, it is thought this could have been due to increased awareness and increased testing rather than increased

incidence (Department of Health, 2010). Nevertheless, the restriction of ARV treatment in the South African public sector resulted in many children unnecessarily inheriting the virus from their mothers through vertical transmission. Furthermore many of these children born prior to 2004 would have received delayed ARV treatment and may have only received treatment based on the severity of clinical symptomology and/or viral load, suggesting that neurological damage may have already occurred (Coovadia, 2009). Studies from the US show that ARV-naïve children placed onto HAART after presenting symptomatically show greater neurocognitive deficits compared to children who are placed on ARVs from birth (Laughton et al., 2010). Within a South African context of lower socioeconomic status, limited resources, poverty and a different HIV-1 clade, not much is known about the impact of this delay in treatment upon cognitive functioning.

2.6 HIV-1 Infection and Psychomotor Functioning

Whilst the extent of cognitive deficits in HIV infection is appreciated, the current study, as part of a larger study, will be limited to the effects on psychomotor functioning. This includes simple psychomotor functions such as motor speed and manual dexterity as well as more complex psychomotor functions which involve an integration of skills, such as graphomotor (being able to draw or write) and visuomotor (coordination of hand and eye) functioning. These will be discussed in more detail in the Methods section.

2.6.1 The development of motor functions.

Post-natally the human brain undergoes rapid growth and maturation during childhood and adolescence incorporating all that is learnt and experienced during this time. This indicates a time of significant neuroplasticity and is largely dependent on environmental stimulation, together with genetic predisposition. Different regions of the brain mature at different times

(critical periods) allowing cognitive functions to "come online" at specific times in development. Developmental insults such as injury, infection or disease can hamper or restrict maturation during these periods.

The first areas of the brain to mature are the primary cortical motor and sensory regions, undergoing a burst in synaptogenesis and myelination during the first two years of life (De Luca & Leventer, 2008). Myelination proceeds from the posterior (occipital) to the anterior (frontal) regions and from the inferior to the superior regions, ensuring areas involved in sensory processing and motor skills are developed before the need for abstraction and association, in line with Piaget's (1953) theories of cognitive development. These processes are innate but highly influenced by external environmental stimulation such that the World Health Organisation has developed references for appropriate developmental milestones for children from disadvantaged or under stimulated areas, such as those in this study (WHO Multicentre Growth Reference Study Group, 2006).

According to this reference, between the ages of four to nine months a child should be able to sit without support and learn to stand with assistance between the ages of five to 11.5 months. Crawling should develop from five to 13.5 months leading to walking with assistance from six to 14 months. A child should be able to stand alone from the ages of seven to 17 months and learn to walk unassisted from eight months and by 18 months. These suggest a time range for development of such skills that is greater than what is expected for children from developed countries and indicate the neuroplasticity of such developments.

Piaget (1953) theorised that children progress through different sensorimotor and cognitive stages; that development of each stage provides the basis for the next. This implies that

development of early sensory and motor functions is necessary for the later development of higher order processing. Several studies have shown that the timing and acquisition of developmental motor milestones may affect later cognitive, emotional and social development (Biringen, Emde, Campos & Appelbaun 1995; Bushnell & Boudreau, 1993; Murray et al., 2006). Other studies have shown, however, that early fine and gross motor abilities are not predictive of future motor functioning but that early gross motor functioning (e.g. crawling, walking) may be representative of later cognitive functioning, particularly working memory and processing speed (Piek, Dawson, Smith & Gasson, 2008; Wijnroks & van Veldhoven, 2003).

If an infant is born prematurely or there is some disruption in development, it has been suggested that, with appropriate remediation and environmental stimulation from an early age, the neuroplasticity of the developing brain can be exploited and some functions may still evolve appropriately (Anderson, Northam, Hendy & Wrennall, 2001). However, this is not likely to be the case for children born into poverty and low socioeconomic circumstances where resources for appropriate remediation and environmental stimulation are limited. Therefore, in such conditions one would expect a disruption in development to hold persisting consequences.

2.6.2 Areas of the brain involved in psychomotor function.

The following two sections will give a brief overview of the motor system and how it is affected by HIV infection. It will illustrate the multiple areas involved in psychomotor functioning and demonstrate that an integration of cerebral regions is necessary for optimal voluntary and controlled movements.

Alpha motor neurons provide the primary interaction between muscles and the nervous system (Gazzaniga, Ivry & Mangun, 2009). They receive input from sensory fibres in the muscles (e.g. reflex actions) as well as from the descending fibres that originate in cortical and subcortical structures in the brain (e.g. voluntary actions). Several cortical and subcortical areas of the brain are involved in the execution of movement. The motor system involves pyramidal and extrapyramidal tracts; grey matter of the spinal cord; nerves to innervate muscles; and the cerebellum and basal ganglia (Waxman, 2010). The pyramidal, or corticospinal, tracts originate in the prefrontal cortex whereas the extrapyramidal tracts originate in the brain stem. Sensory information is received and processed in the somatosensory cortex. It is then relayed to the dorsolateral prefrontal cortex where, together with input from the basal ganglia, movement is planned. Information is sent through the premotor and supplementary motor areas for sequencing and further planning and then through to the primary motor cortex for execution (Crossman & Neary, 2010). The primary motor cortex has important connections with the cerebellum, the basal ganglia and the motor nuclei of the thalamus in order to mediate movement (Crossman & Neary, 2010). In the corticospinal tract, the Betz cells of the primary motor cortex pass through the internal capsule, the cerebral peduncle, the basis pontis and the pyramids of the medulla oblongata, and these are essential for fine motor skills, precision and executive of discrete movements (Afifi & Bergman, 2005). The corticopontocerebellar tract originates from several cortical areas, in particular the primary sensory and motor cortices, and passes through the internal capsule, cerebral peduncle and basis pontis. From there it projects through the pontine nuclei to the cerebellum where it is involved in the rapid correction of movement (Afifi & Bergman, 2005). The corticobulbar tract, on the other hand, controls the muscles of the face. There are other corticofugal tracts whose function are to feedback to the sensorimotor cortex and mediate motor control (Waxman, 2010).

The basal ganglia consist of subcortical nuclei including the striatum (caudate and putamen), globus pallidus (internal and external capsules), subthalamic nuclei and substantia nigra (pars reticulate and pars compacta) (Rothwell, 2011). Its role in movement control is through loop connections through the thalamus with the cortex, rather than direct sensory inputs and motor outputs. It is thought that the basal ganglia, through these loop connections receives excitatory input and its output plays more of a general inhibitory role in movement so that "appropriate movements are facilitated whereas others are suppressed" (Rothwell, 2011, p.307). It is not involved in the initiation of movement, but rather to "bias the motor system towards certain patterns of movement" (Rothwell, 2011, p.307). The striatum sends inhibitory signals to the internal part of the globus pallidus which projects to the ventral nuclei of the thalamus and then back to the cerebral cortex (Waxman, 2010). Lezak, Howieson and Loring (2004) argue that "lesions here do not result in loss of the ability to move, but rather disrupt the integration of the motor components of complex acts, producing discontinuous or uncoordinated movements and impaired motor skills, and may also affect limb strength" (p.77).

The cerebellum is connected with several of the motor system regions to allow for smooth, coordinated unconscious movements, including feedback of executed movements, and control of muscle tone (Waxman, 2010). The cortical areas of the brain are involved in conscious movement whereas the subcortical areas, such as the cerebellum and basal ganglia, are more concerned with the automatic regulation of movement (Zillmer et al., 2008). Research has shown that the development of motor skills, coordination, reflexes and muscle tone are consistently and significantly affected by HIV infection (Drotar et al., 1997).

2.6.3 Motor areas affected by HIV.

HIV predominantly infects the pathways between the frontal cortex and the basal ganglia – two areas critical for intact motor function – as well as the corpus callosum – necessary for the exchange and integration of information (Gongvatana et al., 2009; Woods, Moore, Weber & Grant, 2009). Autopsy studies in seropositive adults and children have indicated extensive neuropathology and calcifications in the basal ganglia and white matter which, in addition to neuronal loss and tissue necrosis, are a result of a build-up of infected macrophages (Belman et al., 1985; 1986; Tardieu, 1998). It is hypothesised that HIV results in extensive vascular disruption of the blood-brain barrier of the basal ganglia and eventually calcium deposition. Furthermore, Joseph and Spiegel (2007) argue that HIV "shows a preference for the basal ganglia" (p.78). Clinically, individuals with HIV infection may develop a disturbance in motor coordination (such as a tremor or a disturbance of gait). Infection of the CNS by HIV causes a cascade of inflammatory events resulting in demyelination, axonal loss and atrophy. It is thought that subcortical damage to the striatum may be a result of the excitotoxic release of Quinoline acid by the activated macrophages and microglial cells (Hähnel, 2009).

In a recent study using diffuse tensor imaging in seropositive adults, Pfefferbaum, Rosenbloom, Rohlfing, Kemper, Deresinski and Sullivan (2009) reported finding axonal compromise in the internal and external capsules of the globus pallidus, the superior and inferior cingulate bundles that connect the frontal and subcortical regions and the posterior regions of the corpus callosum.

Therefore, HIV appears to have significant detrimental effects in several of the brain areas involved in executing appropriate motor movement.

2.6.4 Psychomotor deficits in HIV-1 infected children and adolescents.

Motor development is significantly affected in vertical HIV infection (Sherr et al., 2009; Wachsler-Felder & Golden, 2002). It is important to acknowledge that the timing of HIV infection has different effects, either on already emerged functions or, as in the case of vertical infection, on later developing functions (Armstrong et al., 1993). If a function such as motor ability is delayed, one would expect an impact on future emerging skills (i.e. writing, reading) as the development of the brain and central nervous system is a sequential process. Blanchette et al. (2002) argue that impairments may become worse as more complex functions emerge over time.

Significant developmental delays in psychomotor functioning have been found in HIV-infected children in the first two years of life (Blanchette et al., 2002; Chase et al., 2000; Gay et al., 1995). HIV positive infants score significantly lower than HIV negative infants on the psychomotor development index of the Bayley Scales of Infant Development (Aylward, Butz, Hutton, Joyner & Vogelhut, 1992; Chase et al., 2000; Drotar et., 1997; Foster, Biggs, Melvin, Walters, Tudor-Williams & Lyall, 2006; McGrath et al., 2006). Deficits in fine and gross motor ability are often reported in vertically-infected children including "inappropriate muscle tone (hypertonicity/hypotonicity), reduced flexibility and muscle strength, spasticity and poor control, and a loss of previously attained motor milestones" (Armstrong et al., 1993, p.95). Chase et al. (2002) found significant motor deficits as early as four months of age. Therefore, there is a considerable amount of literature demonstrating the negative effects of vertical HIV infection on early motor development.

Although a limited number of studies have investigated the neurodevelopment of HIV positive children in sub-Saharan Africa, Abubakar, Van Baar, Van de Vijver, Holding and

Newton (2008) noted, in their review of seven published African studies, that "the magnitude of impairment in motor and mental development is similar to that observed in children in the West" (p.884). Furthermore, they reported that all the studies they reviewed revealed significant differences in motor development between HIV positive children and controls, with some appearing as early as six months of age suggesting a similar profile to that of Western seropositive children.

Many South African children, however, differ from their Western counterparts in that they are ARV-naïve or only placed on ARV treatment at a later age, particularly those born prior to the ARV-rollout. In a study of vertically infected, ARV-naïve, South African infants between the ages of 18 and 30 months, significant motor developmental delays were reported (Baillieu & Potterton, 2008). One would expect some of these children to develop severe disease progression, similar to their Western counterparts. Whilst some do not survive past infancy, others appear to not demonstrate as severe a disease progression and survive past childhood (Bagenda et al., 2006). Bagenda et al. (2006) demonstrated that a group of vertically-infected, ARV-naïve Ugandan children (aged six to 12 years) performed within the normal range of cognitive ability, including psychomotor functioning, even though these children displayed developmental motor delays earlier in life. They argue that the neurodevelopmental progression of HIV in older children is static compared to younger children and that determining factors include the timing of infection *in utero*, the viral load and the biogenetic makeup of the child as well as the virus subtype. They conclude that these factors, together with social, economic, medical and emotional support contribute to their lack of neurodevelopmental impairment. It has been shown that CNS insult early in development can be "overcome" due to the plasticity of the developing brain. It is possible

that in such instances, non-infected areas of the brain have assumed the role of infected areas, compensating for the earlier perceived motor deficits.

Even though the adult HIV literature demonstrates that psychomotor retardation is a core feature of HAD (Sacktor et al., 1996), there is a considerable lack of information regarding vertically-infected HIV positive adolescents. The effect of HIV infection on the infant and early developing brain as well as the adult "developed" brain has been researched extensively. The effect of earlier infection on adolescence, a period of cortical fine-tuning, however, has not been explored. In the age of HAART, where individuals are living longer, it is therefore important to explore if vertical HIV infection may have possible ongoing neuropsychological deficits

2.6.5 Psychomotor deficits in HIV-1 infection and ARV treatment.

Although the introduction of ARVs has resulted in general improvement in overall cognitive ability and life expectancy (Brouwers et al., 1997; Martin, Pitrak, Novak, Pursell & Mullane, 1999; Smurzynski et al., 2011; Suarez et al., 2001), there seem to be conflicting arguments regarding the improvement of psychomotor skills. HIV is a multifactorial disease; therefore elements such as timing of infection, viral load, genetic composition, general health, timing of treatment and adherence to treatment will all affect response to treatment.

Several studies in the paediatric HIV literature have indicated that abnormal neurological signs and motor difficulties persist even after infants are initiated on HAART (Foster et al., 2006; Smith, Adnams & Eley, 2008). On the other hand, significant improvements in the cognitive, emotional and behavioural functioning of HIV-1 infected children have also been found following the advent of ARVs (Armstrong et al., 1993; Tardieu, 1998; Wachsler-

Felder & Golden, 2002). Tardieu (1998) argues that ARVs are only beneficial to late-occurring HIV-1 encephalopathy in children and it is argued that the age of starting HAART is an important predictor for neuropsychological outcome (Smith et al., 2008). Shanbhag, Rutstein, Zaoutis, Zhao, Chao and Radcliffe (2005) argue that if HAART is initiated in early infancy, cognitive deficits can be significantly reduced.

Additional studies of school-aged vertically-infected children and adolescents further demonstrate persistence of fine motor and motor strength deficits (Blanchette et al., 2002) as well as CT abnormalities associated with cognitive deficits (Martin et al., 2006), despite being on HAART. Both studies concluded that vertically-infected children with CT scan abnormalities were at higher risk for poorer cognitive functioning, particularly visual-motor deficits.

On the other hand, studies in the adult HIV literature have demonstrated an improvement in psychomotor speed following ARV treatment (Ferrando, Rabkin, Van Gorp, Lin & McElhiney, 2003; Sacktor, Skolasky, Lyles, Esposito, Selnes & McArthur, 2000). Ferrando et al. (2003) suggested that the subcortical structures involved in psychomotor speed, such as the basal ganglia, are sensitive to the benefits of potent ARVs.

However, in their review of the adult literature, Cysique and Brew (2009) reported that, whilst several studies have demonstrated improvement in psychomotor speed and fine motor coordination following HAART treatment, a "non-negligible proportion of individuals" (p.176) demonstrated neuropsychological decline suggesting that HAART is not necessarily effective for all HIV positive individuals and that it depends on the penetration efficacy of the ARVs, initial viral load and $CD4^{+}$, adherence to treatment as well as other additional factors.

It seems that ARVs do not necessarily improve cognitive functioning in the paediatric or the adult HIV populations as several factors such as timing of infection, viral load and genetic composition play significant roles. It appears that the earlier HAART is initiated, the better the outcome. Additionally, it would be expected that HIV-1 infection has a different effect on the developing brain compared to the developed brain. Unfortunately little is known about what occurs in between – when the major developmental gains have been achieved but before mastery has occurred – a period when the brain is still developing – adolescence. With early treatment intervention, HAART can have a considerable amelioration effect on the developing and developed brain. However, the consequences of delayed HAART initiation have not been established, particularly in the population of South African adolescents who were born vertically-infected prior to the ARV rollout in 2004.

2.7 Rationale for the Study

The human immunodeficiency virus is a continuing global health epidemic and is still highly prevalent in South Africa. Despite the introduction of antiretroviral treatment in the late 1980s to delay the disease progression, access to this treatment was restricted to South Africans up until the mid-2000s. Therefore, many South African children born HIV positive during that time would have had delayed access to ARVs. Some of these children have survived through early childhood and are now entering, or are in, adolescence. Very little is known about the effects of HIV on the adolescent brain and particularly an adolescent brain on delayed ARV treatment.

The neuropsychological developmental effects of HIV-1 infection are extensively documented in the paediatric literature. In particular, mention is made of detrimental delays in psychomotor function. The importance of this cannot be underestimated as the

development of the brain is a sequential process – one function is disrupted and it effects the development of future functions. Additionally, the effects of HIV-1 infection on the adult brain are also well-documented with degeneration of motor skills being an early indicator of HAD.

This study forms part of a larger cohort investigating the neuropsychological profile of vertically-infected HIV positive adolescents, who, although currently on a managed HAART programme, received delayed initiation of treatment. The aim of this study is to explore whether there are possible ongoing motor deficits in these young adolescents with delayed ARV treatment.

2.7.1 Research question.

Are there differences in psychomotor function in HIV positive adolescents on a delayed HAART programme compared to HIV negative adolescents in Johannesburg, South Africa?

2.7.2 Research aims.

- To describe the fine psychomotor functioning of HIV positive adolescents on a managed but delayed HAART programme.
- To describe the fine psychomotor functioning of a contrast group of HIV negative adolescents.
- To compare or identify group differences in fine psychomotor functioning between a group of HIV positive adolescents on antiretroviral treatment with regard to a contrast group of HIV negative age, gender, education and socioeconomically-matched adolescents.

2.7.3 Hypotheses.

The central hypothesis for this research was:

- There are statistically significant differences between the means of the two groups regarding psychomotor function performance.

The following is the list of null sub-hypotheses used, which were either confirmed or rejected:

- Null Sub-Hypothesis 1: There are no statistically significant differences between the means of the dominant hand performance in the Finger Tapping Test between the two groups.
- Null Sub-Hypothesis 2: There are no statistically significant differences between the means of the non-dominant hand performance in the Finger Tapping Test between the two groups.
- Null Sub-Hypothesis 3: There are no statistically significant differences between the mean rank scores of the dominant hand performance in the Grooved Pegboard Test between the two groups.
- Null Sub-Hypothesis 4: There are no statistically significant differences between the mean rank scores of the non-dominant hand performance in the Grooved Pegboard Test between the two groups.
- Null Sub-Hypothesis 5: There are no statistically significant differences in mean rank scores of the errors made in the dominant hand between the two groups in the Grooved Pegboard Test.
- Null Sub-Hypothesis 6: There are no statistically significant differences in mean rank scores of the errors made in the non-dominant hand between the two groups in the Grooved Pegboard Test.

- Null Sub-Hypothesis 7: There are no statistically significant differences between the mean rank scores of the Digit Symbol-Coding subtest of the WISC-R between the two groups.
- Null Sub-Hypothesis 8: There are no statistically significant differences between the mean rank scores of errors made in the Digit Symbol-Coding subtest of the WISC-R between the two groups.
- Null Sub-Hypothesis 9: There are no statistically significant differences between the means of the results of the Block Design subtest of the WISC-R between the two groups.
- Null Sub-Hypothesis 10: There are no statistically significant differences between the mean rank scores of the Mazes subtest of the WISC-R between the two groups.
- Null Sub-Hypothesis 11: There are no statistically significant differences between the mean rank scores of the errors made in the Mazes subtest of the WISC-R between the two groups.
- Null Sub-Hypothesis 12: There are no statistically significant differences between the mean rank scores of the ROCFT Copy between the two groups.
- Null Sub-Hypothesis 13: There are no statistically significant differences between the mean rank scores of the time taken to complete the ROCFT Copy between the two groups.
- Null Sub-Hypothesis 14: There are no statistically significant differences between the mean rank scores of the time taken to complete the TMT A between the two groups.
- Null Sub-Hypothesis 15: There are no statistically significant differences between the mean rank scores of the number of errors made in the TMT A between the two groups.

- Null Sub-Hypothesis 16: There are no statistically significant differences between the mean rank scores of the time taken to complete the TMT B between the two groups.
- Null Sub-Hypothesis 17: There are no statistically significant differences between the mean rank scores of the number of errors made in the TMT B between the two groups.
- Null Sub-Hypothesis 18: There are no statistically significant differences between the mean rank scores of the difference between TMT A time and TMT B time between the two groups.
- Null Sub-Hypothesis 19: There is no statistically significant relationship between i) years on HAART; ii) CD4+ count at HAART initiation; iii) viral load at HAART initiation; and iv) WHO stage of diagnosis at HAART initiation and performance on psychomotor function subtests.
- Null Sub-Hypothesis 20: There is no statistically significant relationship between current combination of ARVs and performance on psychomotor function subtests.

Additional areas of qualitative investigation included:

- Null Sub-Hypothesis 21: There is no statistically significant relationship between observed tremors in the Grooved Pegboard Test and HIV status.
- Null Sub-Hypothesis 22: There is no statistically significant relationship between observed difficulty in picking up pegs in the Grooved Pegboard Test and HIV status.
- Null Sub-Hypothesis 23: There is no statistically significant relationship between observed difficulty in manipulating pegs in the Grooved Pegboard Test and HIV status.
- Null Sub-Hypothesis 24: There is no statistically significant relationship between observed slow movement in the Grooved Pegboard Test and HIV status.

- Null Sub-Hypothesis 25: There is no statistically significant relationship between pencil grip used in the Mazes WISC-R subtest and HIV status.
- Null Sub-Hypothesis 26: There is no statistically significant relationship between line quality in the Mazes WISC-R subtest and HIV status.
- Null Sub-Hypothesis 27: There is no statistically significant relationship between strategy used in the Mazes WISC-R subtest and HIV status.

3. Methods

3.1 Research Design

3.1.1 Variables.

3.1.1.1 HIV status.

An HIV positive status is determined by the presence of the HI virus, HIV antibodies and HIV antigens detected in tests such as ELISA, Western Blot or Rapid Tests, and/or HI virus antigen tests. An HIV negative status is determined by the consistent absence of the HI virus, HIV antibodies and HIV antigens in such tests.

In the present study, an HIV positive status was diagnosed in the HIV positive sample using the above tests by a health care practitioner at the hospital where the adolescents received the managed HAART programme. The researcher had access to the participants' medical files to confirm this.

Due to ethical and legal reasons, the researcher could not enquire about HIV status or administer diagnostic tests on the contrast sample. Therefore, HIV negative status was assumed if the participant was not repeatedly absent from school as a result of possible secondary HIV infection or if the participant was not taking any chronic medication.

3.1.1.2 Psychomotor functions.

Intact psychomotor functions provide the means of acting on thoughts, goals and needs. There are different types of movement: reflex actions, automatic repetitive actions, semiautomatic actions and voluntary actions. This research will focus on voluntary actions which involve planned, anticipated and goal-directed movements. These can be divided into simple psychomotor skills requiring little coordination or complex psychomotor skills

requiring higher motor control and cortical processes (Zillmer et al., 2008). Simple psychomotor skills include manual dexterity and motor speed whereas more complex psychomotor skills include the ability to integrate visuoperceptual information with a motor outcome or response, as well as the ability to initiate, shift, maintain and inhibit movements.

This research utilised tests of psychomotor function that are commonly used in South Africa. The Finger Tapping Test is a measure of manual dexterity and motor speed; the Grooved Pegboard Test is a measure of manual dexterity, motor speed and complex motor co-ordination. Other motor tests from the full neuropsychological battery are measures of a combination of several cognitive functions including motor speed, manual dexterity, and visual motor coordination and integration such as the Digit Symbol-Coding, Mazes and Block Design subtests of the WISC-R, the Rey Osterrieth Complex Figure Copy Test and the Trail Making Test. Furthermore, qualitative observations were made regarding motor tremors, pencil grip, line quality and manipulation of objects. These tests will be described in more detail in the Instruments section.

3.1.1.3 Extraneous variables.

The following variables were controlled for in this study:

3.1.1.3.1 Age.

Age was used as an inclusion and matching variable. Participants between the ages of 13 and 16 years of age were included in both groups to avoid potential age effects or differences from affecting the results. This particular age range was used due to this age group being regarded as the period of early adolescence. Additionally, the research aimed to look at the possible ongoing effects of neuropsychological deficits on a delayed HAART programme;

this age group of HIV positive adolescents were born prior to the rollout of ARVs in South Africa and were therefore all on delayed ARV treatment.

3.1.1.3.2 Level of education and language proficiency.

In order to ensure no significant differences in baseline intelligence due to differing levels of education as well as to ensure similar language proficiency, all participants were required to have a minimum of four years of English-medium schooling in a government school. Therefore education was used as an inclusion and a matching variable to minimise any differences in intelligence due to educational status. Additionally, all participants were second-language English speakers and so this was also used as an inclusion and matching variable.

3.1.1.3.3 Socioeconomic status.

Socioeconomic status was utilised as an inclusion and a matching variable and was determined using the Socio-Economic Deprivation Questionnaire of the Senior South African Individual Scale-Revised. All participants were Black South African adolescents living in low socioeconomic areas of Johannesburg.

3.1.1.3.4 Adult-headed households.

All participants came from adult-headed households and not child-headed households or institutions. This variable was controlled for to minimise emotional, behavioural and cognitive effects of living in such circumstances.

3.1.1.3.5 Vertical acquisition of HIV infection.

Vertical acquisition of HIV infection (i.e. from the mother) was utilised as an inclusion criteria for the experimental group. This is the most common form of HIV transmission in children in South Africa; however, other methods of transmission include sexual intercourse and blood transfusion. These were excluded to minimise differences according to method of acquisition. Vertical acquisition of HIV infection was confirmed in the participants' medical files.

3.1.1.3.6 First line HAART.

First line HAART was utilised as an inclusion criteria for the experimental group. If a child receives second line HAART, it is due to them not being receptive to or experiencing significant side-effects from the initial first line treatment. Therefore, only participants on first line HAART were utilised in this study to minimise effects of adverse responses to treatment.

3.1.1.3.7 Previous medical history.

To exclude differences due to any previous complicating neurological or medical conditions, only participants without a prior history of head injury, Meningitis, or comorbid conditions such as Down Syndrome, Autism or Epilepsy were included in the study.

3.1.1.3.8 Substance use.

Participants currently using or who had previously used drugs and/or alcohol were excluded from the study. This criterion was utilised to avoid differences due to the effects of substance use and/or abuse.

There are many variables that could have impacted neuropsychological performance but it was not possible to control for all these variables due to time constraints and personal communication with the attending consultants at the clinic indicated that controlling for such variables would further limit access to a sample population. The following variables were therefore not controlled for and it must be acknowledged that they may have had an effect on the performance of the participants:

3.1.1.3.9 Duration and type of ARV treatment.

All participants in the experimental group were on a delayed HAART programme and, although date of onset of treatment was recorded, duration of treatment varied and was not controlled for. Additionally, whilst all participants in the experimental group were on first line HAART, the drug regimens varied and, although recorded, were not controlled for. Duration and type of treatment were not controlled for due to considerable variation between individual participants and so would have limited the sample size further.

3.1.1.3.10 $CD4^+$ count and viral load.

$CD4^+$ count and viral load prior to HAART initiation and at time of testing was recorded but not controlled for. This may have had an effect on motor performance as low $CD4^+$ count and high viral load have been associated with worse neurocognitive functioning but controlling for this would have limited the sample size even more.

3.1.1.3.11 Environment.

Whilst attempts were made to minimise distractions and administer assessments in a quiet and well-lit environment, this was not always possible in the hospital or the school setting.

Therefore, this may have affected performance and so must be considered when interpreting results.

3.1.1.3.12 Individual factors.

Individual factors such as personality features, mood at time of testing, motivation for testing as well as adaptive functioning were not controlled for. These are all known to affect test performance. Furthermore, previous exposure to neuropsychological testing was not explored but was not controlled for as it would limit the sample size.

3.1.1.3.13 Fatigue.

Whilst participants were given breaks during testing, fatigue was not evaluated and could have had a negative effect on test performance. This must therefore also be considered when interpreting results.

3.1.2 Design.

This research did not attempt to manipulate the variables in any way. Therefore, the research design was a non IV-manipulated cross-sectional quasi-experimental post-test only contrast group design.

3.2 Sample

The HIV positive group consisted of 30 HIV positive adolescents whereas the contrast group consisted of 70 HIV negative adolescents. The groups were matched for age, gender, level of education and socioeconomic status. Whilst all attempts were made to obtain as many participants as possible, the inclusion criteria proved to be somewhat restrictive. The sample consisted of Black adolescents between the ages of 13 and 16, whose second language was

English and who currently lived in low socioeconomic circumstances. To minimise the extraneous impact of language proficiency in testing second language speakers, all participants had completed at least four years of English-medium schooling. Adolescents without a parent or guardian (i.e. in an institution or a child-headed household) were excluded from the study due to ethical and neurobiological reasons. Based on similar neurobiological reasoning, additional exclusion criteria included any form of neurological compromise such as Epilepsy, Meningitis, and Traumatic Brain Injury, psychiatric conditions and substance abuse. This was to keep the integrity of the internal validity so that the results of the instruments reflected the deficits caused by HIV and not by any other confounding cause. Both participants in the HIV positive and the HIV negative groups were sampled through convenience, purposive and snowball sampling methods.

All participants in the HIV positive group attend a managed HAART programme at a hospital in Johannesburg, South Africa. They attend the programme every three months where they receive a check-up by the treating physicians and nurses (including $CD4^+$ count and viral load measurement), medication, a support group, as well as dietary counselling, psychological counselling and psychiatric consultation if deemed necessary. They were accompanied by a parent or guardian who was given and signed a letter of consent, which included information regarding the research, to agree to the participation of their child or ward in the study.

Participants for the contrast group were obtained from the same school in the Orlando area of Soweto reported on by Skuy, Schutte, Fridjhon and O'Carroll (2001). Parents or guardians of the adolescents had received and signed a letter of consent, which included information regarding the research, agreeing to the participation of their child or ward in the study. Included in the letter was a request that should their child or ward be on chronic medication,

repeatedly absent from school, HIV positive, ever suffered a head injury, ever had any neurological impairment, or be living outside of the nuclear family structure, a response to the request for participation was not necessary. In this way the exclusion criteria that applied to the HIV positive group was operationalised in the HIV negative contrast group.

The following tables depict distribution in age, gender and educational level of the participants in both the HIV positive and HIV negative groups.

Table 2

Age of participants

HIV Status		13	14	15	16	Mean	Total
Positive	Frequency	11	8	10	1	14.03	30
	% within HIV status	36.7	26.7	33.3	3.3		100%
Negative	Frequency	18	23	21	1	14.08	63
	% within HIV status	28.6	36.5	33.3	1.6		100%
Total	Frequency	29	31	31	2	14.06	93
	% within HIV status	31.2	33.3	33.3	2.2		100%

Table 3

Gender of participants

HIV Status		Male	Female	Not recorded	Total
Positive	Frequency	14	16	0	30
	% within HIV status	46.7	53.3	0	100%
Negative	Frequency	33	33	4	70
	% within HIV status	47.1	47.1	5.7	100%
Total	Frequency	47	49	4	100
	% within HIV status	47	49	4	100%

These two tables indicate the mean age of the HIV positive group was 14.03 years and the mean age of the HIV negative group was 14.08 years. Additionally, there was roughly an equal amount of boys (47%) as girls (49%) in the sample.

Table 4

Current grade of participants

HIV Status		7	8	9	10	11	Total
Positive	Frequency	13	8	6	3	0	30
	% within HIV status	43.3	26.7	20	10	0	100%
Negative	Frequency	8	19	41	1	1	70
	% within HIV status	11.4	27.1	58.6	1.4	1.4	100%
Total	Frequency	21	27	47	4	1	100
	% within HIV status	21	27	47	4	1	100%

Table 5

Percentage of participants who have repeated a grade

HIV Status		Yes	No	Total
Positive	Frequency	9	21	30
	% within HIV status	30	70	100%
Negative	Frequency	15	55	70
	% within HIV status	21.4	78.6	100%
Total	Frequency	24	76	100
	% within HIV status	24	76	100%

These two tables indicate the majority of the HIV positive group (43.3%) were in grade 7 at the time of testing and the majority of the HIV negative group (58.6%) were in grade 9 at the time of testing. Additionally, the majority of both the HIV positive group (70%) and the HIV negative group (78.6%) had never repeated a grade. All participants also had at least four years of English-medium schooling.

The following table depicts the medical information of the HIV positive participants.

Table 6

Description of HIV positive participants' medical data

	N	Minimum	Maximum	Mean	Std. Dev.
Age initiated HAART	30	2	14	8.73	2.92
$CD4^+$ count at initiation	30	16	6239	564.07	1106.91
Viral load at initiation	30	25	1100 000	222 656.23	305 966.93
$CD4^+$ count currently	29	21	1013	625.82	268.85
Viral load currently	30	25	240 000	12 195.17	45 726.53

Table 6 indicates that the average age a HIV positive participant was initiated on HAART was 8.73 years (S = 2.92) confirming the late initiation of this sample population. In addition, this information indicates the significant effect of HAART on the reduction of $CD4^+$ count as well as viral load.

Table 7

WHO stage at time of HIV diagnosis

WHO stage	Frequency	%
I	6	20
II	4	13.3
III	6	20
IV	4	13.3
Unknown/Not recorded	10	33.3

Whilst the majority of participants' WHO stage at diagnosis was not recorded in their medical files (33.3%), some individuals were at a late stage IV (13.3%) before being initiated on HAART.

Table 8

Frequency of ARV regimen

ARVs	Frequency	%
ABC, 3TC, EFV	15	50
D4T, 3TC, EFV	10	33.3
Other	4	13.2
Not recorded	1	3.3

The ARV regimen of Abacavir (ABC), Lamivudine (3TC) and Efavirenz (EFV) was the first-line treatment of choice for most individuals (50%). This is the standard ARV treatment in South Africa for children three years or older (Department of Health, 2010*)*.

3.3 Instruments

As previously mentioned, this study forms part of a larger study to investigate the neuropsychological profile of HIV positive adolescents on a delayed HAART programme in Johannesburg, South Africa. Nevertheless, for the purpose of this study, only the instruments utilised to assess psychomotor function will be discussed here.

The Finger Tapping Test and the Grooved Pegboard Test are widely used measures of fine motor co-ordination and speed (Lezak et al., 2004). Burton, Sepehri, Hecht, VandenBroek, Ryan and Drabman (2001) argue that motor speed can also be used as an indicator of

cognitive ability. Complex psychomotor functions such as graphomotor and visual-motor coordination were measured using subtests of the Weschler Intelligence Scale for Children Revised (WISC-R) – Digit Symbol-Coding; Block Design; and Mazes, the Rey Osterrieth Complex Figure Test (ROCFT), and the Trail Making Test.

3.3.1 The finger tapping test.

The Finger Tapping Test (FTT) (1992) is a measure of simple psychomotor speed and simple manual dexterity (Lezak et al., 2004). Impairments in psychomotor functioning can be detected using the FTT (Shimayama, Ninchoji, & Uemura, 1990). The participant is required to tap a key attached to a counter as fast as possible using the index finger of their dominant hand for ten seconds in five consecutive trials. This exercise is subsequently repeated with the non-dominant hand. The resultant score for each hand is the average of the five consecutive trials (Morrison, Gregory, & Paul, 1979). Should the non-dominant hand yield a speed of <80% than that of the dominant hand, impairment in the contralateral hemisphere is indicated. Should the speed of the dominant hand equal or be slower than the non-dominant hand, impairment is suggested in that contralateral hemisphere.

The FTT generally shows high reliability coefficients (.9), with men generally displaying a higher coefficient than women (.94 and .86 respectively) (Lezak et al., 2004). Combined reliability coefficients in both dominant and non-dominant hands are also shown to be high at .8 (Prigatano & Hoffmann, 1997). These results indicate this is a reliable measure of simple motor speed and manual dexterity.

3.3.2 The grooved pegboard test.

The Grooved Pegboard Test, developed by Kløve (1963), measures manual dexterity, psychomotor speed as well as visual-motor coordination (cited in Lafayette Instrument Company, 2002; Lezak et al., 2004). Additionally, it correlates highly with types of work requiring speed, finger dexterity and manual dexterity. It can assist in identifying lateralised impairment as a right/left ratio of more than 1.0 may indicate specific hemisphere impairment (Bornstein, 1986; Haaland, Cleeland & Carr, 1977). The complexity of this test makes it sensitive to disease progression, such as that of HIV infection (Miller et al., 1990; Stern et al., 2001).

The pegboard is placed in front of the participant and they are asked to match the groove of the pegs with the groove of the board by placing the pegs into the holes. They must first use only their dominant hand and the second trial involves only their non-dominant hand. The examiner records the time taken to completely fill all 25 peg holes; the number of unintentional drops (errors) of a peg; as well as the number of correctly placed pegs for each hand. These three scores are summed to get a total score. Although participants were not asked to repeat the test, test-retest reliability coefficients are .67 to .86 in normal individuals, suggesting good reliability (Levine, Miller, Becker, Selnes & Cohen, 2004). The following qualitative information was also recorded in the current study: presence of a tremor (resting, intention, essential or tension); any difficulty picking up pegs; any difficulty fitting pegs into the holes; as well as if the participant demonstrated significantly slow movement.

3.3.3 WISC-R subtests.

The WISC-R subtests used in this study are all components of the Performance IQ (PIQ). Digit Symbol-Coding involves symbol-associated learning, memory, as well as fine visual-

motor co-ordination and speed (Lezak et al., 2004). The participant is asked to fill in blank spaces with a symbol according to a key of symbols and numbers. They are given a trial period of seven blank spaces and are then asked to fill in as many as they can in 120 seconds. The administrator totals the number of spaces filled in correctly.

Block Design is a construction test where the participant is asked to use blocks to construct designs in a booklet. Each design is timed. It involves having to visualise and reason in terms of spatial relationships and construct a design, as well as visual-motor co-ordination.

Mazes involve planning, visuospatial and visuomotor abilities. The participant is asked to trace through a series of nine mazes of increasing difficulty without entering any blind alleys. There is a time limit to each maze and. In this study total maze score was recorded according to the WISC-R manual. A separate score of errors was also recorded and included entering of blind alleys as well as crossing over of lines and pencil lifts. Qualitative information was also recorded for this test: pencil grip (dynamic, static, clutch); line quality (controlled, shaky, jerky, other); strategy (no planning, pre-planned, deliberated, start at end of maze and work backwards).

The raw scores of the WISC-R subtests were converted into their corresponding scaled scores using the WISC-R manual (Wechsler, 1974).

Overall internal consistency reliability coefficients have been generated where PIQ has a reliability coefficient of .90, Verbal IQ (VIQ) of .94, and Full Scale IQ (FSIQ) of .96 respectively. Correlation coefficients for the Verbal subtests range from 0.63 for Similarities to .80 for Digit Span, while correlation coefficients for the Performance subtests range from

.59 for Picture Completion to .80 for Object Assembly (Franzen, 2000). The WISC-R is a valid measure to use with a population with neurological impairment as it delineates profiles of skills and deficits (Hale, 1981).

The use of the WISC-R over the more modern WISC-IV was decided on as the WISC-R was the only Wechsler scale with adequate norms for an adolescent South African population at the time of the study (Skuy et al., 2001). Additionally, it was also decided that the WISC-R was a more valid and reliable measure than the Senior South African Individual Scale-Revised, particularly as there were available norms for Black adolescents whose first language was not English. It must be noted that Skuy et al. (2001) reported significantly lower scores on the subtests of the WISC-R compared to the normative sample in the manual with the South African adolescent sample achieving mean scores in the Borderline to Below Average range. It was therefore felt necessary to utilise a measure with appropriate norms to elicit relevant and fair findings.

3.3.4 Rey Osterrieth complex figure test.

The Rey Osterrieth Complex Figure Test (ROCFT) evaluates the participant's visuomotor construction and integration ability, visual memory and executive function mediated by the prefrontal lobe (Shin, Park, Park, Seol & Kwon, 2009). It is made up of three conditions. In the initial condition, the participant is given the Complex Figure to copy which is, amongst other skills, an assessment of their visuomotor and graphomotor abilities. The time taken to complete the copy was recorded and the 36-point Rey-Osterrieth/Taylor scoring method used to measure performance (Lezak et al., 2004). The subsequent phases form part of a memory component and so were not utilised in this study and will not be described here.

The split-half and coefficient alpha reliabilities of the Copy condition were found to be > .60 and correlational and factor analytic studies support its validity (Strauss, Sherman & Spreen, 2006). A study conducted by Skuy et al. (2001) found that the mean standard of the copies on a South African Soweto sample yielded lower scores (M = 31.27, S = 3.14) than the American norms (M = 35.1, S = 1.5).

3.3.5 Trail making test.

The Trail Making Test (TMT) consists of Part A which assesses complex visual scanning, visuomotor tracking and speed and Part B which assesses scanning, visuomotor tracking and speed, divided attention and cognitive flexibility (Lezak et al., 2004). In Part A, the participant is asked to connect consecutively numbered circles on a page. In Part B, the participant is asked to connect consecutively numbered circles and lettered circles alternately. In both conditions, the participant is encouraged to do this as quickly and accurately as possible without lifting the pen from the page. Errors are recorded in terms on incorrect connections. Reliability coefficients are usually > .60 (Lezak et al., 2004) indicating this is a reliable measure.

3.4 Data Collection Procedure

Ethical clearance was obtained from the University of the Witwatersrand Medical School to conduct the research in a hospital and a school in the Johannesburg area. The researchers underwent standardised test training as a group by one of the neuropsychology professors at the University of the Witwatersrand. It was decided that each researcher administer a full test battery rather than each researcher administer specific tests. This was decided upon in order to develop rapport between participant and researcher, to minimise time taken to complete the battery and to reduce participants' anxiety. Furthermore, this meant the test battery could be

administered in the same order for each participant to minimise the contraindicating effects of fatigue.

At the hospital, the researchers were granted access to the medical files of the adolescents attending the clinic on the days of data collection. The researchers perused the files to look for suitable participants. If an individual met the inclusion criteria, their accompanying parent or guardian was approached and the scope of the study as well as the process of assessment explained. If they agreed for their child or ward to participate in the study, they were given a consent form to sign and the participant an assent form to sign.

Once a participant was selected and the appropriate consent and assent forms signed (Appendices one to four), a researcher administered the full test battery to the participant whilst another conducted a collateral interview with the parent or guardian (Appendix 9, Part B) and obtained the relevant information from the participant's file (Appendix 9, Part A). The order in which the test battery was administered was as follows: the **Finger Tapping Test**, the **Grooved Pegboard Test**, the **ROCFT Copy**, three minutes of conversation/biographical questions, the ROCFT immediate recall, the RAVLT trials I to VII, **Trail Making Test A**, **Trail Making Test B**, the ROCFT delayed recall, the ROCFT recognition, the RAVLT delayed recall, the RAVLT recognition, the COWAT, the Stroop Delis-Kaplan version and then the Wisconsin Card Sorting Test (WCST). Participants were then given a break and light refreshments were provided. Testing then recommenced with the **WISC-R** which was administered according to the standardised order. Following testing, the participant was asked questions from the biographical questionnaire (Appendix 9, Parts B and C) and was asked to complete the Beck's Youth Inventory-II (Appendix 9, Part D). The total time for assessment took approximately four to five hours.

With regard to the contrast group, the teachers explained the participant information sheet (Appendix 7) to the pupils who then took home the parent/guardian information sheet (Appendix 5), parent/guardian consent form (Appendix 6) for them to read and, if they agreed to their child/ward participating, signed the appropriate forms. The children who brought back signed consent forms to school participated in the study during the school holidays so as to not disrupt their school timetable. The above procedure of the neuropsychological battery and interviews was the same.

3.5 Data Analysis

The assessments of both the HIV positive and negative groups were scored utilising the above-mentioned procedures found in the test manuals. These results were entered into The Statistical Package for the Social Sciences (SPSS) version 17 and analysed using this to provide insights from the data obtained.

Demographic information regarding the participants' gender, age, language, current grade, as well as HIV-related variables such as $CD4^+$ count at HAART initiation was explored and reported.

The distribution of the data was analysed using the Kolmogorov-Smirnov Test of Normality which assesses the normality of the distribution of the results in a population of two independent samples (Pallant, 2005). A non-significant result indicates normality of distribution whereas a significant result indicates non-normal distributions. When the data was non-normally distributed, non-parametric statistical analyses were used. However, when the data was normally distributed, parametric statistical analyses were used.

Parametric tests make several assumptions about the data being analysed: that it is normally distributed; that there is homogeneity of variance (each population has the same variance); and that the results or observations of each population are independent of one another – therefore parametric tests assume that both populations (e.g. HIV positive and HIV negative groups) are normal and have the same error variance. Thus, they can only differ in their means; the null hypothesis being $x_1 = x_2$. Non-parametric tests do not require assumptions of normality of population distributions and are therefore preferable when the data is not normally distributed as well as when such a small sample is used. However, they do still require independence of samples.

This research utilised independent samples t-tests for normally distributed data and Mann-Whitney U tests for non-normally distributed data to compare means of the two populations. These tests were used as the two population samples were mutually independent, with similar shapes and equal variances.

A Phi Coefficient was used to explore the relationship between qualitative observations of the Grooved Pegboard Test and: HIV status and tremor; HIV status and difficulty picking up pegs; HIV status and slow movement; HIV status and difficulty fitting pegs; as dichotomous variables were used for each correlation. A Cramer's V Coefficient was then used to explore the relationship between qualitative observations of the WISC-R Mazes subtest and: HIV and line quality; HIV and strategy used; and HIV and pencil grip; as there were differing levels for each variable.

A cross-tabulation was performed to explore relationships between uncontrolled but measured variables such as "years on HAART", "$CD4^+$ count at HAART initiation", "viral

load at HAART initiation", and "WHO stage at HAART initiation" and performance on the motor subtests. A Spearman's Rank Correlation Coefficient was used to determine significance of the relationships between non-normally distributed data and a Pearson's Product Moment Correlation Coefficient for normally distributed data. Lastly, the CPE 2010 rankings of the different combination of ARVs were calculated and a cross-tabulation performed to explore any relationship between penetration efficacy of drug regimen and motor performance.

Furthermore, as studies have indicated that South African adolescents perform significantly below their Western counterparts in various measures of neuropsychological functioning, overall means of scores were used to compare to normative data when statistically significant results were not found. When statistically significant differences were found between means of the HIV positive and HIV negative groups, the individual group means were utilised to compare to normative data. This is, however, discussed in more detail in the discussion section.

3.6 Ethical Considerations

As previously mentioned, ethical clearance was obtained from the University of the Witwatersrand's Medical School as well as from the University of the Witwatersrand's School of Human and Community Development.

Participants were above the age of assent, but not above the age of consent. They were therefore required to fill in an assent form (see Appendices 4 and 8) and their legal guardians were required to fill in a consent form (see Appendices 2 and 6).

Confidentiality was rigorously maintained and any further information needed was obtained in collaboration with the medical officer consulting on the case. As the participants needed to be physically present for the testing, there could not be full anonymity but their data was coded so no names were used. For the statistical analyses, the names and codes were kept by the main supervisor. Participants were provided with the contact details of free counselling services at the University of the Witwatersrand if any participant, for any reason, experienced distress during or after testing.

All of the tests performed were non-invasive and therefore no foreseeable harm could have befallen the participants from participating, thus upholding non-maleficence. As the testing process took a few hours, lunch and refreshments were provided for the participants and their guardians. Participants were also reimbursed for their travelling costs as they often had to stay longer than they had anticipated.

Permission for testing the HIV group was obtained from the clinic where testing took place and permission from Department of Education and the school itself was also obtained for testing the contrast group.

4. Results

The following section will describe the findings of this study. As this research is comparative and experimental in nature, the results will be presented in tabular form. Firstly, descriptive information of the various motor subtests will be presented, followed by the results of the test for normality of data distribution. Then the more in-depth statistical analyses for the individual motor subtests will be presented. Interpretation and discussion of these findings will be presented in the next section.

Table 9

Descriptive statistics of the motor subtest results of the HIV positive and HIV negative groups

Subtest		N	Mean	SD	Range	Median	Min	Max
Finger Tapping Test	Positive	30	35.43	8.22	31.8	35.5	20.4	52.2
Dominant Hand	Negative	69	36.47	7.11	42.2	36	22.2	64.4
Finger Tapping Test	Positive	30	31.85	7.43	29.8	31.9	18	47.8
Non-Dominant Hand	Negative	69	33.85	5.88	26	33.4	22.4	48.4
Grooved Pegboard Test	Positive	30	79.03	25.52	139	72	58	197
Dominant Hand	Negative	68	70.69	12.15	78	69.5	51	129
Grooved Pegboard Test	Positive	30	92.67	42.42	238	85	62	300
Non-Dominant Hand	Negative	68	79.46	17.68	122	77	54	176
Grooved Pegboard Test	Positive	30	.53	1.20	5	.00	0	5
Dominant Hand Errors	Negative	68	.59	.82	3	.00	0	3
Grooved Pegboard Test	Positive	30	.63	.99	4	.00	0	4
Non-Dominant Hand	Negative	68	.59	.93	5	.00	0	5
Errors								

Table 9 continued:

Descriptive statistics of the motor subtest results of the HIV positive and HIV negative groups

Subtest		N	Mean	SD	Range	Median	Min	Max
WISC-R Digit Symbol-	Positive	27	4.81	2.77	10	5	0	10
Coding Scaled Score	Negative	69	5.23	3.14	12	5	1	13
WISC-R Digit Symbol-	Positive	27	1.07	2.39	9	.00	0	9
Coding Errors	Negative	69	.87	2.07	11	.00	0	11
WISC-R Block Design	Positive	26	5.58	2.75	10	5	1	11
Scaled Score	Negative	63	7.43	3.12	17	8	1	18
WISC-R Mazes Scaled	Positive	27	9.37	3.2	13	9	3	16
Score	Negative	69	8.61	3.20	14	8	3	17
WISC-R Mazes Errors	Positive	29	6.07	4.46	19	6	0	19
	Negative	69	7.71	3.90	16	7	0	16
ROCFT Copy	Positive	30	23.75	6.88	26	25.5	9	35
	Negative	70	28.96	3.94	18	30	17	34
ROCFT Time	Positive	17	5.39	1.84	7	5.13	3	10
	Negative	58	4.50	1.60	8.92	4.23	2.08	11
TMT A Time	Positive	30	65.53	22.43	82	59.5	36	118
	Negative	70	44.65	17.18	77	41.5	21	98
TMT A Errors	Positive	30	.47	.78	3	.00	0	3
	Negative	70	.26	.61	3	.00	0	3
TMT B Time	Positive	30	148.43	62.83	270	129	65	335
	Negative	70	102.79	55.09	300	88.5	1	301
TMT B Errors	Positive	30	2.57	3.58	15	1.50	0	15
	Negative	70	.86	1.52	7	.00	0	7

TMT B – A Difference	Positive	30	82.90	61.67	291	72	-13	278
	Negative	70	58.14	44.12	272	45	-26	246

One can see from the above findings that in several subtests, the full sample was not necessarily tested for whatever reason. This will be discussed in the following section but must be borne in mind and for each subsequent finding the number of participants included in each analysis will be presented.

Due to the small sample size of the HIV positive group (N=30), one cannot assume that the data was normally distributed. Therefore, the Kolmogorov-Smirnov Test for Normality of distribution of data was performed on the individual motor subtests in the neuropsychological battery. These results are presented in Table 10:

Table 10

Kolmogorov-Smirnov Test for normality of data distribution for the tests of psychomotor function

Test	HIV status	N	Statistic	Significance
Finger Tapping Test Dominant Hand	Positive	30	.08	.20
	Negative	69	.08	.20
Finger Tapping Test Non-Dominant Hand	Positive	30	.08	.20
	Negative	69	.07	.20
Grooved Pegboard Test Dominant Hand	Positive	30	.21	.00**
	Negative	68	.14	.00**
Grooved Pegboard Test Non-Dominant Hand	Positive	30	.25	.00**

	Negative	68	.16	.00**
Grooved Pegboard Test Dominant Hand Errors	Positive	30	.41	.00**
	Negative	68	.35	.00**
Grooved Pegboard Test Non-Dominant Hand Errors	Positive	30	.34	.00**
	Negative	68	.34	.00**
WISC-R Digit Symbol-Coding	Positive	27	.10	.20
	Negative	69	.17	.00**
WISC-R Digit Symbol-Coding Errors	Positive	27	.36	.00**
	Negative	69	.37	.00**
WISC-R Block Design	Positive	26	.14	.20
	Negative	63	.09	.20
WISC-R Mazes	Positive	27	.18	.03*
	Negative	69	.13	.01*
WISC-R Mazes Errors	Positive	29	.18	.02*
	Negative	69	.09	.20
ROCFT Copy	Positive	30	.14	.15
	Negative	70	.16	.00**
ROCFT Copy Time	Positive	17	.20	.08
	Negative	58	.14	.01*
TMT A Time	Positive	30	.21	.00**
	Negative	70	.11	.04*
TMT A Errors	Positive	30	.39	.00**
	Negative	70	.48	.00**
TMT B Time	Positive	30	.19	.01*

	Negative	70	.20	.00**
TMT B Errors	Positive	30	.24	.00**
	Negative	70	.30	.00**
TMT B – A Difference	Positive	30	.17	.04*
	Negative	70	.15	.00**

* = $p < .05$

**= $p < .01$

This indicated that the results of some of the tests were not normally distributed as the Kolmogorov-Smirnov value was less than .05. Therefore, non-parametric tests were used to explore differences between the HIV positive and HIV negative groups in these measures and parametric tests were used to explore differences between those tests that were normally distributed.

The following section will describe more in-depth analysis of the results of the performance of participants in the various motor subtests.

An independent samples t-test was conducted to compare the results of the Finger Tapping Test in both the HIV positive and HIV negative groups (Table 11).

Table 11

Independent samples t-test comparing mean results of the Finger Tapping Test

Hand	HIV status	N	Mean	SD	t	df	Sig.
Dominant	Positive	30	35.43	8.22	-.64	97	.52
	Negative	69	36.47	7.11			
Non-Dominant	Positive	30	31.85	7.43	-1.43	97	.16
	Negative	69	33.85	5.88			

The results in Table 11 indicate there were no statistically significant differences in manual dexterity and motor speed between the HIV positive and the HIV negative groups, therefore accepting null sub-hypotheses one and two.

To compare these results to normative data one can use the overall group means for the dominant and non-dominant hands as statistically significant differences were not found between groups. Therefore, the overall samples' mean for dominant hand performance was 36.16 (S = 7.44) and the overall samples' mean for non-dominant hand performance was 33.24 (S = 6.42).

A Mann-Whitney U test was conducted to compare mean rank scores on the Grooved Pegboard Test in the HIV positive and negative groups as the findings of the Kolmogorov-Smirnov test revealed these results to be not normally distributed. The results are presented in Table 12.

Table 12

Mann-Whitney U Test comparing mean rank scores of the Grooved Pegboard Test

Hand	Status	N	Mean Rank	Mean	SD	*U*	Asymp. Sig.
Dominant	Positive	30	56.00	79.03	25.52	825.00	.13
	Negative	68	46.64	70.69	12.15		
Non-Dominant	Positive	30	58.90	92.67	42.42	738.00	.03*
	Negative	68	45.35	79.46	17.68		

* = $p < .05$

These results revealed a statistically significant difference between the non-dominant hand scores in the HIV groups (U = 738.00, $p < .05$) but no significant difference between dominant hand performance. Therefore null sub-hypothesis three was accepted indicating no statistically significant difference between speed of performance between groups for the dominant hand. Null sub-hypothesis four was rejected and the alternate hypothesis accepted, indicating that the HIV positive group (M = 92.67, S = 42.42) performed significantly slower than the HIV negative group (M = 79.46, S = 17.68) in the non-dominant hand on the Grooved Pegboard Test.

As significant differences were found between groups in non-dominant hand performance, individual group means were used in a later comparison of normative data. However, as significant differences were not found between groups in dominant hand performance, the overall mean (M = 73.24, S = 17.65) was used.

A Mann-Whitney U test was performed to investigate the difference in mean rank score errors between the HIV groups in the dominant and non-dominant hands (Table 13).

Table 13

Mann-Whitney U Test comparing mean rank scores of errors made between groups in the Grooved Pegboard Test

Hand	Status	N	Mean Rank	Mean	SD	*U*	Asymp. Sig
Dominant	Positive	30	44.93	.53	1.20	883.00	.22
	Negative	68	51.51	.60	.82		
Non-Dominant	Positive	30	49.87	.63	1.00	1009.00	.92
	Negative	68	49.34	.60	.93		

These results, shown in table 13, indicated no statistically significant difference in mean rank score errors made between the two groups in either the dominant or the non-dominant hand and so null sub-hypotheses five and six were accepted, suggesting that number of errors made in either the dominant or the non-dominant hand was independent of HIV status.

In terms of qualitative observations in the Grooved Pegboard Test, only essential tremors were observed in types of tremors. Therefore, from now on tremor refers to an essential tremor. The results of a Pearson's Phi Coefficient exploring the relationship between HIV status and qualitative Grooved Pegboard observations revealed substantially small positive correlations between HIV status and tremors ($r_\phi = .27$, $p < .01$); difficulty picking up pegs ($r_\phi = .22$, $p < .05$); and slow movement ($r_\phi = .31$, $p < .01$). Therefore, null sub-hypotheses 21, 22 and 24 were rejected and the alternate hypotheses accepted which state that there is a significant difference between groups in observed tremors, difficulty picking up pegs and slow movement, with more abnormalities observed in the HIV positive group. This suggests a possible relationship between HIV infection and complex motor coordination.

The results of a Mann-Whitney U test comparing mean rank scores of performance on the Digit Symbol-Coding and Mazes subtests of the WISC-R are presented in table 14.

Table 14

Mann-Whitney U Test comparing mean rank scores of performance on the Digit Symbol-Coding and Mazes subtests of the WISC-R

Test	Status	N	Mean Rank	Mean	SD	*U*	Asymp. Sig
Digit Symbol-	Positive	27	46.78	4.81	2.77	885.00	.70
Coding	Negative	69	49.17	5.23	3.14		
Digit Symbol-	Positive	27	49.76	1.07	2.39	897.50	.73
Coding Errors	Negative	69	48.01	.87	2.07		
Mazes	Positive	27	54.06	9.37	3.2	781.50	.22
	Negative	69	46.33	8.61	3.20		
Mazes Errors	Positive	29	40.4	6.3	4.46	736.50	.04*
	Negative	69	53.3	7.87	3.99		

* = $p < .5$

As previously mentioned, Mazes score was determined by time taken to complete each maze and number of errors in terms of entering of blind alleys (incorrect pathways). In this study, a separate measure of errors were also assumed to include crossing over of lines and pencil lifts, therefore explaining the discrepancy between frequency of Mazes scaled scores and frequency of Mazes errors. The results of these findings led to the acceptance of null sub-hypotheses seven, eight and ten, meaning no statistically significant differences were found in mean rank scores between groups in the Digit Symbol-Coding subtest, number of errors made in this subtest as well as in the mean rank scores of the Mazes subtest. However, a

statistically significant difference was found between mean rank scores of number of errors made in the Mazes subtest (U = 736.50, $p < .05$). Therefore, null sub-hypothesis 11 was rejected and the alternate hypothesis accepted, stating a statistically significant difference was found between mean rank scores of the number of errors made on the Mazes subtest, in favour of the HIV positive group.

An independent samples t-test comparing the performance of the two groups in the Block Design subtest was also statistically significant [$t(88) = -2.93$, $p < .01$]. Therefore, null sub-hypothesis nine was rejected and the alternate hypothesis accepted, meaning there were statistically significant differences between the means of the results of the HIV positive and HIV negative group on the Block Design subtest of the WISC-R, in favour of the HIV negative group.

In terms of qualitative information regarding the Mazes, the following was noted: pencil grip, line quality and strategy. These were cross-tabulated against HIV status. No statistically significant differences were found in line quality and strategy between the HIV positive and the HIV negative groups with the majority of adolescents demonstrating a controlled line quality (90%). Unfortunately 51% of the participants' strategy in completing the mazes was not recorded. Nevertheless, 30% demonstrated no planning, 16% pre-planned, 2% deliberated and 1% started at the end of the maze and worked backwards. A Cramer's V coefficient indicated a weak positive correlation between pencil grip used and HIV status ($\phi_c = .29$, $p < .05$) with 33% of HIV positive participants using a static grip and 67% using a dynamic grip compared to 81% of HIV negative participants who used a dynamic grip and only 11% of HIV negative participants who used a static grip.

As significant differences were not determined between groups for the WISC-R Digit Symbol-Coding and Mazes subtests, mean overall scaled scores can be assumed, indicating a mean overall scaled score of 5.09 for Digit Symbol-Coding (S = 3.05), and 8.87 for Mazes (S = 3.31) to later compare with normative data. As significant differences were found between groups for the WISC-R Block Design subtest, it can be assumed these are two separate populations. Therefore, separate scaled scores indicated a mean of 5.58 (S = 2.75) for the HIV positive group and 7.43 (S = 3.12) for the HIV negative group.

The results of a Mann-Whitney U test comparing group differences in mean rank scores on the ROCFT Copy score as well as time taken to complete the ROCFT Copy is presented in Table 15.

Table 15

Mann-Whitney U Test comparing mean rank scores of performance on the ROCFT Copy as well as time taken to complete the ROCFT Copy

Test	Status	N	Mean Rank	Mean	SD	*U*	Asymp. Sig
ROCFT Copy	Positive	30	33.32	23.75	6.88	534.50	0.00**
	Negative	70	57.86	28.96	3.94		
ROCFT Time	Positive	17	46.65	5.39	1.84	346.00	.06
	Negative	58	35.47	4.50	1.60		

** = $p < .01$

A statistically significant difference was found between groups in the mean rank scores of the ROCFT Copy score (U = 534.50, $p < .01$). Therefore, null sub-hypothesis 12 was rejected and the alternate hypothesis accepted, meaning there was a statistically significant difference

between the mean rank scores of the groups' ROCFT Copy score with the HIV positive group performing significantly lower (M = 23.75, S = 1.26) than the HIV negative group (M = 28.96, S = .47).

Although there is a discrepancy between frequency of recorded times and frequency of recorded Copy scores, a statistically significant difference was not identified in mean rank scores between groups in time taken to complete the ROCFT Copy therefore null sub-hypothesis 13 was accepted.

In order to compare these results with normative data, separate group means for the ROCFT Copy was utilised as a statistically significant difference was found between groups.

The results of a Mann-Whitney U test comparing mean rank scores of time and errors on the Trail Making Test Parts A and B between the HIV positive and negative groups is presented in table 16. Additionally, differences between TMT A and TMT B was calculated and group mean rank scores compared.

Table 16

Mann-Whitney U Test to compare mean rank scores of times and errors between groups in the TMT A and B

	HIV status	N	Mean Rank	Mean	SD	*U*	Asymp. Sig.
TMT A time	Positive	30	70.68	65.53	22.43	445.00	.00**
	Negative	70	41.87	44.65	17.18		
TMT A errors	Positive	30	55.67	.47	.14	895.00	.11
	Negative	70	48.29	.26	.07		
TMT B time	Positive	30	68.53	148.43	62.83	509.00	.00**
	Negative	70	42.77	102.79	55.09		
TMT B errors	Positive	30	61.20	2.57	.65	729.00	.01**
	Negative	70	45.91	.86	.18		
TMT B –	Positive	30	59.85	82.90	61.67	769.50	.04*
TMT A	Negative	70	46.49	58.14	44.12		

* = $p < .05$

** = $p < .01$

These results revealed statistically significant differences in mean rank scores between groups in the time taken to complete the TMT A ($U = 445.00$, $p < .01$) and the TMT B ($U = 509.00$, $p < .01$). Therefore, null sub-hypotheses 14 and 16 were rejected and the alternate hypotheses accepted which state that there are statistically significant differences between the two groups' time taken to complete the TMT A and B, in favour of the HIV negative group. In terms of errors made, statistically significant differences were found in errors made in the TMT B between groups ($U = 729.00$, $p < .05$), therefore rejecting null sub-hypothesis 17 and

accepting the alternate hypothesis. This suggests the HIV positive group made significantly more errors (M = 2.57, S = .65) in the TMT B than the HIV negative group (M = .86, S = .18). Statistically significant differences were not found in errors made in the TMT A between groups therefore null sub-hypothesis 15 was accepted. The comparison of mean rank score differences between TMT B and TMT A times between groups revealed a statistically significant result (U = 769.50, $p < .05$) and so null sub-hypothesis 18 was rejected and the alternate hypothesis accepted, meaning there was a greater difference between TMT A and B times in the HIV positive group (M = 82.90, S = 61.67) than the HIV negative group (M = 58.14, S = 44.12).

In order to compare the results of these population samples against normative data, individual group means were utilised for TMT A time and TMT B time as statistically significant differences between groups were found.

A cross-tabulation was performed to explore possible relationships between "years on HAART", "$CD4^+$ count at HAART initiation", "Viral load at HAART initiation" and "WHO stage at HAART initiation" and the various motor subtests in the neuropsychological battery. A Spearman's Rank Correlation Coefficient indicated a weak positive correlation between number of years on HAART and TMT B time (ρ = .39, $p < .05$) and a moderate positive correlation between number of years on HAART and the difference between TMT A time and TMT B time (ρ = .47, $p < .01$). Furthermore, a moderate positive correlation was found between initial viral load and number of errors made on the Digit Symbol-Coding subtest (ρ = .58, $p < .01$).

The Antiretroviral CNS Penetration Effectiveness 2010 rankings (Letendre et al., 2008; Levin, 2011) for the combination of ARVs were calculated. As 50% of the HIV positive sample were taking ABC, 3TC and EFV and 33.3% were taking d4T, 3TC and EFV, the remaining combinations were grouped as "other." A cross-tabulation was performed to explore any relationships between the different CPE rankings – 8 for the ABC, 3TC and EFV combination and 7 for the d4T, 3TC and EFV combination – and the motor subtests. No statistically significant results were found.

5. Discussion

In 1987, the introduction of Azidothymidine (AZT, or Zidovudine) as treatment to delay the progression of HIV infection resulted in a dramatic reduction in AIDS-related deaths in the US and UK (AVERT, n.d.). With the introduction of combined antiretroviral treatment (cART or HAART) in 1992, HIV was no longer seen as an imminent death sentence. Unfortunately, however, ARVs were restricted in the South African public sector until 2003/4 (Cornell et al., 2009). Hundreds of innocent children were infected with the virus via the second most common mode of infection in South Africa, vertical mother-to-child transmission, before the ARV rollout. There must therefore be a significant population of vertically-infected HIV positive children and adolescents in South Africa who were not placed on ARVs from birth. Very little is known about the neuropsychological profile or implications of delayed ARV treatment of this specific population. However, personal communication with consulting physicians and nurses at an adolescent clinic in Johannesburg suggested this specific population did experience neuropsychological difficulties.

This research formed part of an overriding project that aimed to investigate the neuropsychological profile of a population of South African vertically-infected HIV positive adolescents who were not initiated on antiretroviral treatment from birth. It explored cognitive domains such as attention, visuospatial function, memory, language, executive function as well as fine psychomotor function, the focus of this particular project. This current research project asked the question “are there significant differences in psychomotor function in HIV positive adolescents on a delayed HAART programme compared to HIV negative adolescents in Johannesburg, South Africa?” The adult and paediatric HIV literature demonstrates significant fine motor deficits in HIV positive populations. Therefore, it was hypothesised that an adolescent population of vertically-infected individuals would also

exhibit deficits in fine psychomotor functioning, in comparison to a HIV negative contrast group. The aim of this research project was to explore the above question as well as describe the fine psychomotor functioning of a population of South African vertically infected HIV positive adolescents on delayed HAART in comparison to the fine psychomotor functioning of a population of South African HIV negative adolescents.

5.1 Simple Psychomotor Functions

The Finger Tapping Test is a frequently used measure of simple motor speed and simple manual dexterity and is regularly used in neuropsychological testing to detect subtle motor or other cognitive impairments (Lezak et al., 2004; Strauss et al., 2006). In the current study, no significant differences were found between the dominant or the non-dominant hands' performance in the two groups, suggesting vertical HIV infection did not have persisting effects on simple motor speed or manual dexterity. Although Blanchette et al. (2002) reported subtle but significant differences in simple motor speed and manual dexterity between an HIV negative group and an HIV positive group of vertically-infected adolescents, their very small sample sizes may have affected their results. Nevertheless, the finding of the current study is inconsistent with this previous result.

The Finger Tapping Test is often used to detect laterality of brain lesions or dysfunction as well as disturbances in the cerebellar, basal ganglia and cerebral regions (Lezak et al., 2004; Strauss et al., 2006), suggesting it is likely to be affected by HIV infection. However, the results of this current study do not support this hypothesis. It is important to consider that this measure is also affected by "levels of alertness, impaired ability to focus and maintain attention, problems with generating responses, or generalised slowing of responses" as well as medication (Strauss et al., 2006, p.1048). Nevertheless, there were no significant

differences between the means of the two groups. Therefore, deficits in simple motor speed and manual dexterity did not appear to persist in vertically-infected, HIV positive adolescents. It is possible that, prior to HAART initiation, the HIV positive group may have experienced deficits in simple motor speed and manual dexterity and that treatment with ARVs ameliorated these difficulties, as is found in the adult HIV literature (Ferrando et al., 2003; Sacktor et al., 2006). However, participants were not assessed prior to HAART initiation so this could not be determined in the current study.

The Grooved Pegboard Test is frequently used in HIV neuropsychological batteries as it is sensitive to psychomotor slowing due to brain impairment from HIV infection (Lezak et al., 2004). The results of this study, however, did not indicate significant differences between groups in the dominant hand performance but rather statistically significant differences were only found in non-dominant hand performance between the two groups, with the HIV positive group performing significantly slower than the HIV negative group. A possible explanation for this could be that the motor areas in the primary motor cortex responsible for the dominant hand compensated for potential damage due to HIV infection by assuming connections in the less frequently stimulated motor areas responsible for the non-dominant hand in the primary motor cortex. As the dominant hand is required to be more directive and utilised more frequently (i.e. in writing), the neuronal circuitry may have rearranged itself as a compensatory mechanism to produce optimal functioning. Conversely, both hands may have been significantly slower prior to HAART initiation and the onset of ARVs, coupled with more frequent use, resulted in greater improvement in performance in the dominant hand rather than the non-dominant hand.

The adult HIV literature has reported psychomotor retardation in the non-dominant hand as demonstrated by the Grooved Pegboard Test as well as improvement following HAART initiation (Ferrando et al., 2003; Sacktor et al., 2000). Blanchette et al. (2002), however, did not report differences in Grooved Pegboard performance between vertically-infected HIV positive children and a control group. The results of this study therefore contradict both the adult literature, as non-dominant hand slowing persisted despite HAART, and the paediatric literature as differences in non-dominant hand performance were reported between groups, suggesting that, even with HAART, deficits in manual dexterity, motor speed and visual motor co-ordination persisted in the non-dominant hand.

If the slowed performance in the HIV positive group were due to the effects of medication, one would expect both the performance of the dominant and non-dominant hands to be significantly slower than those of the HIV negative group, which was not the case in the current study. It has been reported that a defective performance in the Grooved Pegboard Test may be predictive of HAD (Stern et al., 2001). These results therefore need to be explored further in longitudinal studies.

Clinical observations in the Grooved Pegboard Test indicated positive correlations, albeit weak ones, between HIV status and difficulties in picking up pegs, an essential tremor and slowed movement. However, no statistically significant differences were revealed between errors made in either the dominant or the non-dominant hand performance between the two groups. This could be because errors are recorded as peg dropping, which suggests a difficulty in peg manipulation, rather than in picking up pegs, which was not found to correlate with HIV status. These results are, however, clinical observations suggesting there is a strong possibility for inter-rater differences and perhaps an underestimation of clinical

difficulties. Nevertheless, the results do suggest that vertically-infected HIV positive adolescents may have some difficulty with complex motor co-ordination despite HAART.

5.2 Complex Psychomotor Functions

The measures of complex psychomotor functioning that were used in this research involved an integration of cognitive processes such as visual perception, working memory, executive functions as well as intact fine motor skills. In terms of the WISC-R subtests used in this study, a significant difference between groups was found only in the Block Design subtest, where the HIV positive group performed worse than the HIV negative group. This measure requires visual-perceptual reasoning, problem solving abilities as well as intact visual-motor integration and coordination. In looking at this measure alone, however, it is difficult to discern which of these function(s) is impaired.

The two other subtests from the WISC-R that were utilised in this study – Digit Symbol-Coding and Mazes – did not elicit significant differences in mean performance between the two groups. This is inconsistent with findings in the adult literature where significant deficits in the WAIS-III version of the Digit Symbol-Coding were found in a demographically similar HIV positive population (Lawler et al., 2010). However, a control or contrast group was not utilised in their study. On the other hand, these results are consistent with the findings of Blanchette et al. (2002) who did not find significant differences between results of vertically-infected HIV positive children on HAART and a control group on the WISC-III Digit Symbol-Coding subtest. It seems that, whilst performance on this measure may be affected in HIV positive adults on HAART, performance of vertically-infected HIV positive adolescents on HAART is not significantly different from HIV negative adolescents. This may perhaps be related to the impact of the virus on the developing child brain compared to the developed

adult brain in that "in the former case, injuries disrupt the acquisition of developmental abilities; in the latter case, previously acquired abilities break down" (Zillmer et al., 2008, p.273). It appears that, whilst the development of brain areas and such cognitive functions may be so severely affected by HIV infection (Armstrong et al., 1993; Belman et al., 1985; Chase et al., 2000; Civitello, 2003; Dickson et al., 1993; Epstein et al., 1987; Wachsler-Felder & Golden, 2002), in some cases it appears that this is not so adversely affected. It is likely, as previously mentioned, that multiple factors are involved including timing of infection, viral load of the mother, as well as genetic make-up of the mother and child – factors which were not explored in the current study but may provide insightful information in future studies on why such ARV-naïve children are able to progress into adolescence, seemingly impervious to the devastating effects of vertical HIV infection.

In another study comparing neuropsychological performance of: HIV-infected individuals with haemophilia; HIV negative individuals with haemophilia; and a control group of individuals without haemophilia or HIV, it was found that the HIV positive group performed significantly better than both the HIV negative group and the control group on the Mazes subtest (Thompson et al., 1996). Interestingly, in the current research, whilst a significant difference was not elicited, the mean scaled score for the HIV positive group was higher than that for the HIV negative group, suggesting better performance. Furthermore, a significant difference in mean errors made (including crossing over of lines, pencil lifts and entering of blind alleys) between groups was found, with the HIV negative group making more errors than the HIV positive group. This is an interesting result and suggests perhaps impulsivity, poor self-regulation as well as poor psychomotor speed.

This finding was surprising as impulsivity is a feature often associated with HIV positive children, even those on ARVs (Nozyce et al., 2006). Furthermore, Scharko (2006) found an average prevalence of 28.6% of comorbid Attention Deficit Hyperactivity Disorder (ADHD) – a disorder with impulsivity as a main feature – in HIV-infected children. Additionally, Zeegers, Rabie, Swanevelder, Edson, Cotton and van Toorn (2010) reported a higher prevalence of comorbid ADHD in HIV-infected children in the Western Cape, South Africa, compared to the general population of children in other developing countries. However, the results of this current study suggested greater impulsivity and worse planning in the HIV negative group. This could be a result of the ARV medication, such as Efavirenz whose side-effects include drowsiness and inattention (Koekkoek et al., 2006), causing those on this medication to be less impulsive. Unfortunately, the strategy of the participants was not always recorded so this could not be accurately determined.

A statistically significant difference was found between groups in the ROCFT Copy, a measure of visual-motor organisation and integration, with the HIV negative group achieving a higher score than the HIV positive group. A significantly lower copying ability could be due to poor motor ability, poor visual spatial ability and/or poor attention (Strauss et al., 2006). Poor complex integration of visual and motor information could be a result of the deterioration of white matter fibre integrity as shown using diffusion tensor imaging in a recent study of a similar population of HIV positive adolescents in Cape Town, South Africa (Hoare et al., 2012). Whilst the current study did not suggest major deficits in fine motor abilities, it appears that when an integration of information or functions is required (such as visual and motor skills), performance is impaired. This was also supported by the results of the TMT B. Whether this is due to a delay in HAART initiation is not known and future research should compare the results of vertically-infected HIV positive adolescents on

delayed HAART with those of vertically-infected HIV positive adolescents on HAART from birth.

Interestingly, there was no statistically significant difference in mean time taken to complete the ROCFT Copy between the two groups. It must be noted, however, that the sample population for this comparison was a lot smaller than that for the ROCFT Copy as time taken to complete the Copy was not always recorded. Nevertheless, this finding of the current study does suggest that graphomotor speed was not impaired in the vertically-infected HIV positive group.

Results of the comparison of mean time to complete the TMT Parts A and B revealed significantly faster times in the HIV negative group compared to the HIV positive group. This suggests significantly worse attention, visual tracking and psychomotor speed, mental flexibility and working memory in the HIV positive group. TMT performance is known to be sensitive to mild traumatic brain injury with psychomotor slowing in patients compared to control subjects, so it is a commonly used measure in adult HIV neuropsychological batteries and is associated with vocational outcome (Lezak et al., 2004; Strauss et al., 2006). TMT B performance has been found to be moderately negatively correlated with motor speed (-.42) and moderately positively correlated with manual dexterity (.46) suggesting a significant motor component (Skeel, Nagra, Van Voorst & Olson, 2003). Together, the findings of the complex psychomotor function subtests of the current study suggest that it is the integration of functions that is impaired in the HIV positive group compared to the performance of the HIV negative group.

Calculating the difference between TMT B time and TMT A time for each participant allows one to control for speed of processing, although "a low score on Trails B relative to Trails A does not necessarily imply reduced cognitive efficiency but may reflect the increased demands on motor speed and visual-perceptual processes" (Strauss et al., 2006, p.668). Nevertheless, the results of this study indicated a significant difference between mean TMT B – TMT A between groups suggesting that the increased cognitive demands were considerably more challenging for the HIV positive group. This is supported by the finding that more errors were also made by the HIV positive group in TMT B compared to the seronegative group. It could be that this significant discrepancy between groups is due to a reduced ability to integrate information as a result of the deterioration of white matter fibres. Therefore, although these results do not necessarily suggest a direct deterioration in psychomotor functioning, as previously mentioned, when the combination of visual-perceptual skills, working memory as well as fine motor coordination is required, performance appears to be negatively affected by vertical HIV infection, despite delayed HAART.

Whilst the extraneous variables "years on HAART", "$CD4^+$ count at HAART initiation", "viral load at HAART initiation" and "WHO stage at HAART initiation" were not controlled for, it was hypothesised they may have had an effect on neuropsychological performance. Interestingly, unusual results were found. A weak positive correlation between "years on HAART" and TMT B time and a moderate positive correlation between "years on HAART" and difference between TMT B and TMT A times were found suggesting more years on HAART was related to a greater (slower) TMT B time as well as a greater difference between TMT B and TMT A times. This was an unexpected result but it could be related to negative side-effects of the ARV medication such as slowed processing speed. Additionally, a moderate positive correlation between "viral load at HAART initiation" and WISC-R Digit

Symbol-Coding errors made was found suggesting perhaps a connection with difficulties in visual-motor integration.

As CNS penetration effectiveness has been found to influence neuropsychological performance, the CPE (2010) rankings of the experimental groups' ARV regimen were calculated and a possible relationship with psychomotor functioning explored. No statistically significant results were found suggesting, as the CPE rankings of the participants' ARV regimens were relatively high, they are able to effectively penetrate the CNS blood-brain barrier and exert ameliorating effects on the necessary neuronal components.

5.3 Comparison of the Current Study's Results with International Normative Data

Initially, this research did not intend to compare its results with international normative data but rather to compare the results of the experimental group with those of the contrast group. Nevertheless, it was subsequently discovered that several of the mean scores of these two populations were below the international normative data and so it was decided to evaluate these results in comparison.

According to normative data for the Finger Tapping Test, developed by Findeis and Weight (1994), the mean score of a 14 year old for the dominant hand is 44.38 (S = 6.8) and 40.67 (S = 6.1) for the non-dominant hand. The findings of the present study suggest that this South African sample (of both HIV positive and HIV negative adolescents with a mean age of 14 years) performed below the international normative mean in both the dominant (M = 36.16, S = 7.44) and the non-dominant (M = 33.24, S = 6.42) hands. Additionally, the normative data in the manual for the Grooved Pegboard Test (Lafayette Instrument Company, 2002) indicates that the mean score of a 14 year old for the dominant hand is 65.88 (S = 11.88) and

70.66 (S = 8.31) for the non-dominant hand. The results of the current study revealed that non-dominant hand performance for both the HIV positive (M = 92.67, S = 42.42) and the HIV negative (M = 79.46, S = 17.68) groups was below the manual normative mean. Furthermore, the overall group mean for dominant hand performance (M = 73.24, S = 17.65) was below the manual normative mean.

As significant differences were not found between groups on the WISC-R Digit Symbol-Coding and Mazes subtests, the combined group scaled scores were used to compare to the manual norms: M = 5.09, S = 3.05 in the Digit Symbol-Coding subtest and M = 8.87, S = 3.31 in the Mazes subtest. Similar to the results of the simple psychomotor function subtests, the mean scaled score for the WISC-R Digit Symbol-Coding subtest is well below what is expected for this age group, according to the WISC-R manual norms (M = 10, S = 3). Although this result is lower than that found in a study by Skuy et al. (2001) with a similar demographic population, it is still within the Borderline range. The mean scaled score for the WISC-R Mazes subtest in the current study fell within the Low Average range described in the manual (M = 10, S = 3). It was, however, slightly higher than the mean scaled score of the similar population in the Skuy et al. (2001) study. It is possible that the Mazes task has become a more familiar task for this population of individuals with increased exposure in schools, resulting in an improved performance.

As significant differences between group means were found for the WISC-R Block Design subtest, separate group means were used to compare against manual norms. The results of the current study indicated that the mean scaled score for the HIV positive group (M = 5.58, S = 2.75) fell within the Borderline range and the mean scaled score for the HIV negative group (M = 7.43, S = 3.12) fell within the Low Average range. Therefore both groups performed

below international norms. Interestingly, in comparison with the previous findings of Skuy et al. (2001) of a similar HIV negative adolescent population, the HIV positive group in the current study performed below this finding but the HIV negative group performed better than this previous group.

A statistically significant difference was found in ROCFT Copy score between groups and so separate group means were used to compare to a normative score for 14 year olds (M = 33.53, S = 3.18) according to the Taylor scoring criteria (Strauss et al., 2006). The results of the current study indicated that both the mean HIV positive group score (M = 23.75, S = 6.88) and the mean HIV negative group score (M = 28.96, S = 3.94) were below this normative mean. In relation to a previous study by Skuy et al. (2001), the HIV negative group in the current research performed in the same range as this previous group, whereas the HIV positive group performed worse than the average range of the previous group.

Furthermore, TMT A and TMT B times for the current study were compared against international normative data (TMT A: M = 25.7, S = 8.8; TMT B: M = 49.8, S = 15.2) (Strauss et al., 2006). It was found that both the HIV positive (TMT A: M = 65.53, S = 22.43; TMT B: M = 148.43, S = 62.83) and the HIV negative (TMT A: M = 44.65, S = 17.18; TMT B: M = 102.79, S = 55.09) groups in the current study performed significantly slower than their international counterparts in both the TMT A and the TMT B. Interestingly, the HIV positive group but not the HIV negative group performed significantly slower than a similar previous population in both the TMT A and the TMT B (Skuy et al., 2001).

These results concur with previous research which revealed that adolescents from low socioeconomic conditions in sub-Saharan Africa perform significantly below their Western

counterparts on several neuropsychological measures (Rushton & Jensen, 2003; Skuy et al., 2001). Like many cognitive domains, simple motor speed and manual dexterity is affected by IQ, level and quality of education (Nell, 2000; Strauss et al., 2006). It is well-documented that the quality of education between higher socioeconomic and lower socioeconomic schools in South Africa is hugely disparate. Even though it is almost 20 years post-Apartheid, former Department of Education and Training (DET) schools often still do not have the equivalent highly qualified teachers or teaching equipment that private schools or former Model C schools do. Thus, quality of education is likely to be a factor affecting fine motor performance in this particular South African population. However, other developmental factors are likely to be of importance such as the types of toys available to stimulate the development of gross as well as fine motor control; parental/guardian education and the amount of time they spent furthering the gross and fine motor control of their children/ward; the accessibility of professionals such as occupational therapists and phyiostherapists to treat any perceived delays in motor development; and the accessibility of nursery schools or pre-schools where social interaction and stimulation enhances motor development. All of these opportunities and factors are widely available and accessible in Western countries but not in the lower socioeconomic areas of South Africa from where this population sample originate. Therefore, it is likely these are also contributing factors in terms of why this population performed significantly below the average of their Western counterparts.

This is a significant and continuous issue regarding neuropsychological testing in South Africa and therefore emphasises the need for South African-developed norms for such measures as well as culturally-appropriate measures. Additionally, one must exercise considerable caution when interpreting results according to Westernised norms. In individual settings, one must take into account the cultural, developmental, educational and medical

history of the individual. In quantitative research, however, qualitative information is not frequently sought as standardised tools are required.

5.4 Implications of these Findings

The overall finding that this population of HIV positive and HIV negative South African adolescents performed well below the Western normative sample in both measures of simple motor speed, simple manual dexterity and visual-motor coordination implies poor development of fine psychomotor skills. As previously mentioned, motor functions are one of the earliest skills to develop so that an infant can move around, grasp novel objects, follow moving objects; explore its environment. As the brain matures sequentially, the development of future skills depends on intact and appropriate attainment of earlier skills. For example, psychomotor skills are involved in every day scholastic and vocational functioning such as reading, writing and typing. If this population of individuals are experiencing slowed simple motor speed and manual dexterity, it is suggested that appropriate interventions be placed. For example, basic psychoeducation at pre- and post-natal clinics can teach and encourage mothers and caregivers to promote physical development such as regularly changing the infant's position and increasing time spent on their stomach to develop gross motor functions. Additionally, as the child gets older and starts exploring, reaching and grabbing for objects, to encourage play with different types and sizes of objects; scribbling, drawing and colouring; use of building blocks; use of playdough; use of puzzles; buttoning up clothes; cutting paper with scissors; and doing up shoelaces. Whilst it is recognised that this population of individuals grew up in low socioeconomic environments and therefore resources are limited, these examples are inexpensive and don't always require purchasing extra material; objects found in the home can be used. It is necessary, however, for the government's health and education departments to emphasise the importance of stimulation during development,

particularly its long-lasting consequences. Furthermore, as neuropsychologists, one is aware of the importance of early childhood stimulation, and so one should be involved in promoting childhood development in the neonatal clinics.

A significant difference in non-dominant hand performance was found between groups in the Grooved Pegboard Test. It is suggested that HIV positive children be encouraged to use their non-dominant hands as much as possible (e.g. brushing teeth, drawing) to strengthen the neuronal connections. Additionally, the HIV positive adolescents performed worse than the HIV negative adolescents in several tasks where an integration of functions was needed. It may be useful to include psychoeducational and occupational therapy groups or sessions at the HIV adolescent clinic to show the individuals specific strategies to break tasks down into separate components, as well as how to develop their own strategies to do this. Furthermore, ball throwing and catching should be encouraged to enhance visual-motor coordination.

5.5 Limitations of the Study

As the current study was part of a larger research project, several researchers were involved. Whilst each researcher was familiar with the standardised procedure, unfortunately not all required information was recorded; some researchers used different methods of recording information; and some researchers used different-sized stimuli which could have affected participants' performance. Therefore, sample sizes were not always the same, meaning it was difficult to compare results between measures.

Due to the strict inclusion and exclusion criteria and the time restraints, only a small sample of HIV positive participants was collected. Additionally, the clinic where participants

received their medication and where they were approached for the study only holds an adolescent clinic one day a week, therefore limiting assessment opportunities.

Even though the use of the WISC-R as opposed to the WISC-IV was previously explained, this measure is significantly outdated and its verbal measures, in particular, cannot be considered a valid representation of those abilities in this specific population born in the late 1990s or 2000s.

As with all neuropsychological measures, it is very difficult to isolate individual cognitive abilities as the brain functions as an integrative system (Luria, 1973). The results of this study do imply that the integrative functioning of the brain is what appears to be impaired in vertical HIV infection however further studies are required.

5.6 Future Research

Firstly, in order to gain a better understanding of a bigger population of South African vertically-infected HIV positive adolescents on delayed HAART, a larger sample needs to be sought and assessed. Very little is known about the persisting neuropsychological deficits in these individuals and so future research is necessary to continue the current study.

Furthermore, in the current research it is not known whether psychomotor functioning has improved, declined or remained the same compared to before initiation of HAART. The literature points to significant motor and other developmental delays due to vertical HIV infection (Aylward et al., 1992; Chase et al., 2000; Foster et al., 2006; McGrath et al., 2006; Msellati, Lepage, Hitimana, Van Goethem, Van de Perre & Dabis 1993; Smith et al., 2008). It is quite possible that, whilst this population may not have experienced significantly

detrimental psychomotor delays, they did experience some delay and poor development of psychomotor skills, which was ameliorated by HAART. However, 33.3% of the seropositive adolescents were recorded as being at or below WHO Stage II at time of HAART initiation, suggesting a significantly low level of functioning. The results of this study do support those of Bagenda et al. (2006) who found similar findings in a longitudinal study of vertically-infected ARV-naïve children. It appears that this specific population of vertically-infected adolescents may have a strain of HIV that may not be as neurotropic as those in the US, allowing them to progress and develop, sometimes until the age of 13, before beginning antiretroviral treatment. Studies have, however, shown contradicting evidence with regards to neurocognitive impairment in predominantly HIV Clade C infected regions, such as Sub-Saharan Africa (Lawler et al., 2010). Some argue that HIV Clade C is not as neurologically harmful as other Clades whereas other studies suggest that it is no less neurotropic than other Clades (Lawler et al., 2010). In accordance with Bagenda et al. (2006), it is likely that multiple factors are involved, including the timing of infection *in utero*, the viral load of the mother, the biogenetic makeup of the child and mother, and the virus subtype. Nevertheless, longitudinal studies of vertically-infected children and adolescents on delayed HAART in South Africa would be useful to answer some of these questions.

6. Conclusion

The HIV epidemic has wreaked devastation throughout South Africa; millions are dying and thousands of children have inherited this disease from their mothers. Whilst significant efforts have been made to reduce the prevalence of mother-to-child transmission, little is known about the long-lasting neuropsychological effects of vertical transmission. Furthermore, little is known about vertically-infected adolescents on delayed HAART. The current study investigated the possible ongoing effects of vertical HIV infection on fine psychomotor functioning in a population of South African adolescents on delayed HAART. The findings indicate that, whilst this HIV positive sample did not perform significantly worse than an HIV negative contrast sample on measures of fine psychomotor functioning, the overall fine psychomotor functioning of this population was poor in comparison to their Western counterparts. In terms of complex psychomotor functioning, the HIV positive sample frequently performed significantly worse than the HIV negative contrast sample, suggesting that integration of skills impeded performance. Various developmental and remedial recommendations were made. Whilst HIV continues to ravage through South Africa, it is imperative that more research be performed to explore and investigate the implications, the long-term consequences and the social and economic burden of this disease, particularly of this specific strain of the virus. Additionally, longitudinal studies of neuropsychological, emotional and behavioural functioning of vertically-infected individuals are necessary as they are the future of this country.

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8. Appendices

Appendix 1: Parent/Guardian Information Sheet (Experimental Group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4556

Dear Parent/Guardian,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Masters degree at the University of the Witwatersrand. Our area of focus is young adolescents attending the [redacted] Clinic for treatment. We would like to invite your child/ward to take part in this study.

We are doing neuropsychological evaluations of adolescents attending the [redacted] Clinic. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses pertaining to mental processes such as memory, judgement, processing and reasoning.

If you, as the guardian/parent agree to allow your child/ward to participate, they will be required to complete some neuropsychological tests which are made up of drawing tasks, repeating lists of words and numbers, identifying colours as well as trying their hand with some cards. This may take between four to five hours to complete with rests in between. Your child will be provided with light refreshments half way through the tests.

Participation is voluntary, and no individual will be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and your child as the participant is guaranteed. The information from the tests will be coded and names will not be assigned to the information. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback can be given as the participants are on a managed treatment programme therefore test results will be supplied to the medical practitioner to be used at their discretion. The grouped data collected may be used in publications or conference presentations, but no data that identifies your child will be used.

Please note that your child is free to stop the procedure at any time and no negative consequences will follow. He/she may simply say they would no longer like to participate. The information your child provides will be kept confidential in a locked cabinet according to the regulations set out by the Health Professions Council of South Africa. The regulations

state that the information must be kept for two years if there is a publication and six years if the research is not published.

The tests will be administered in a room provided by the Psychology department at [redacted] Hospital after your child/ward has seen the doctor at the [redacted] Clinic.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints, compliments or queries you can address them to the HREC on 011 717 1234.

In order to facilitate the smooth running of our research, we need your permission to access your child/ward's file at the clinic so as to obtain the duration, as well as the type of treatment your child/ward is currently on and the other treatments they have been on in the past.

If your child/ward seems to be suffering from any psychological stress as a result of the testing they will be referred to the Emthonjeni Centre at the University of the Witwatersrand. You may additionally contact the centre for psychological services after the research is complete if your child is suffering any psychological stress. For referral to one of the training psychologists at the Emthonjeni Centre please contact Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice, Kelly Holland, 0118722372

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas, Aline Ferreira Correia 0117174524

Appendix 2: Parent/Guardian Consent Form (Experimental Group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development
Private Bag X3, Wits, 2050, Johannesburg, South Africa
Tel: (011) 717 4500 Fax: (011) 717 4559

I, Mother/Father/Legal Guardian of

_____, give consent for my child/ward to participate in this study

I understand that:

- There is no risk or harm that could come to my child/ward from taking part
- Participation is voluntary
- My child/ward, or I, may choose to stop the testing at any time for any reason with no penalty or loss of benefits
- My child's/ward's results will remain confidential
- No positive or negative consequences will follow from choosing to, or not to, participate

By allowing my child/ward to participate I state that:

- My child/ward has no history of Epilepsy, Meningitis, or have suffered a serious head injury
- All the relevant information about this research has been explained to me and my child/ward clearly and simply and I understand the information
- The researchers have access to my child's file at the clinic in order to get the demographic and medical information they require

Signed: _____ Date: _____

Assigned Participant Number: _____

Appendix 3: Participant Information Sheet (Experimental Group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South Africa

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4556

Hello,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Master's degree in Neuropsychology at the University of the Witwatersrand. Our area of focus is young adolescents attending the [redacted] Clinic. We would like to invite you to take part in this study.

Your parent/guardian has to give consent to let you take part in the study and you will also need to give us assent (your permission) to participate in the study.

We are doing neuropsychological evaluations of adolescents attending the [redacted] Clinic. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses in mental processes such as your memory, judgement, processing and reasoning

You will be asked to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards. This may take between four to five hours to complete with rests in between. You will be provided with light refreshments half way through the tests.

Participation is voluntary and you won't be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and you as a participant is guaranteed. Your name will not be on any of your information from the study. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback can be given. The grouped data collected may be used in publications or conference presentations, but no data that identifies you will be used.

Please note that you will be free to stop the procedure at any time and no negative consequences will follow. You can simply tell the test administrator that you do not want to continue anymore. The information you provide will be kept confidential according to the rules and regulations of the Health Professions Council of South Africa. The regulations state that the information must be kept for two years if there is a publication and six years if the research is not published.

In order to facilitate the smooth running of our research we would like to have permission to have access to your file at the clinic to find out the type of treatment you are on and how long you have been using it and other treatments you have had in the past.

While we are doing the different tests, if you feel sad, uncomfortable or scared or nervous we will refer you to see a training psychologist at the Emthonjeni Centre at the University of the Witwatersrand. You can also call the Emthonjeni Centre at any time after you have participated and speak to Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints, compliments or queries, you can address them to the HREC on 011 717 1234.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice, Kelly Holland, 0118722372

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas, Aline Ferreira Correia 0117174524

Appendix 4: Participant Assent Form (Experimental Group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development

Private Bag X3, Wits, 2050, Johannesburg, SA

Tel: (011) 717 4500 Fax: (011) 717 4559

Hello,

We (Kelly, Daniel, Shona, Stephanie, Urvashi, Cindy and Jessica) are all students at Witwatersrand University and we are doing a study on adolescents attending the [redacted] Clinic for treatment.

We are doing neuropsychological evaluations of adolescents attending the [redacted] Clinic. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses of their mental processes such as your memory, judgement, processing and reasoning

We would like you to take part in the study. If you agree to join in, you will be asked to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards.

If you are happy to take part we would like you to please sign below to say if you would like to participate. If you decide not to, that is okay and no one will be upset. If you decide to join and then later change your mind and want to stop, this is okay too.

Would you like to participate (*Tick **one** box*)

Yes, I am willing

No, I do not want to

Signing at the bottom of this form means that you agree to take part in this research.

Thank you very much,

Signed (You can just write your name): _____

Date: _____

Assigned Participant Code: _____

Appendix 5: Parent/Guardian Information Sheet (Contrast group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South A

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4

Dear Parent/Guardian,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine and Kelly Holland. We are conducting research for the purpose of obtaining a Master's degree in Neuropsychology at the University of the Witwatersrand. Our area of focus is young adolescents. We would like to invite your child/ward to take part in this study.

We are doing neuropsychological evaluations of adolescents attending the school. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses of their mental processes such as memory, judgement, processing and reasoning.

If you, as the guardian/parent agree to allow your child/ward to participate, they will be asked to complete some neuropsychological tests which include drawing tasks, repeating some lists of words and numbers, identifying some colours as well as trying their hand with some cards. This may take between four to five hours to complete with rests in between. Your child/ward will be provided with light refreshments half way through the tests.

Your child/ward's participation is voluntary and no individual will be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and your child/ward as the participant is guaranteed. The information from the tests will be coded and names will not be assigned to the information. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback will be given. The grouped data collected may be used in publications or conference presentations, but no data that identifies your child/ward will be used.

Please note that you will be free to stop the procedure at any time and no negative consequences will follow. Your child/ward may simply say that he/she no longer wishes to participate. The information your child provides will be kept confidential in a locked cabinet according to the regulations set out by the Health Professions Council of South Africa. The regulations state that the information must be kept for two years if there is a publication and six years if the research is not published.

The tests will be administered in a room provided by the school. The tests will be conducted after school and will not interrupt learning.

If your child/ward seems to be suffering from any psychological stress as a result of the testing they will be referred to the Emthonjeni Centre at the University of the Witwatersrand. You may additionally contact the centre for psychological services after the research is complete if your child is suffering any psychological stress. For referral to one of the training psychologists at the Emthonjeni Centre please contact Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints, compliments or queries, you can address them to the HREC on 011 717 1234.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland, 0118722372

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas and Aline Ferreira Correia, 0117174524

Appendix 6: Parent/Guardian Consent Form (Contrast Group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development
Private Bag X3, Wits, 2050, Johannesburg, SA
Tel: (011) 717 4500 Fax: (011) 717 4559
Medical Ethics number: M120268

I, Mother/Father/Legal Guardian of
_____, give consent for my child/ward to participate in this study.

I understand that:

- There is no risk or harm that could come to my child/ward from taking part
- Participation is voluntary
- My child/ward, or I, may choose to stop the testing at any time, for any reason, with no penalty or loss of benefits
- My child's/ward's results will remain confidential
- No positive or negative consequences will follow from choosing to, or not to, participate

By allowing my child/ward to participate I state that:

- My child/ward has no history of Epilepsy, Meningitis, HIV infection, neurocognitive impairment, serious head injury nor are they taking chronic medication
- My child/ward does not live outside a nuclear family unit
- All the relevant information about this research has been explained to me and my child/ward, clearly and simply, and I understand the information

Signed: _____ Date: _____

Assigned Participant Code: _____

Appendix 7: Participant Information Sheet (Contrast Group)

School of Human and Community Development

Private Bag 3, Wits 2050, Johannesburg, South A

Tel: 27 (0)11 717 4524/5 Fax: 27 (0)11 717 4

Hello,

Our names are Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland. We are conducting research for the purpose of obtaining a Masters degree in Neuropsychology at the University of the Witwatersrand. Our area of focus is young adolescents. We would like to invite you to take part in this study.

Your parents have to give consent to let you be part of the study and you will also need to give us assent (your permission) to participate in the study.

We are doing neuropsychological evaluations of adolescents attending the school. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses of their mental processes such as memory, judgement, processing and reasoning.

If you agree to participate, you will be required to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards. This may take between four to five hours to complete with rests in between. You will be provided with light refreshments half way through the tests.

Participation is voluntary and you will not be advantaged or disadvantaged in any way for choosing to, or not to, participate.

Please be assured that confidentiality about the results between the researcher and you as a participant is guaranteed. The information we receive from the tests will only be seen by us and our research supervisors. No individual feedback can be given. The grouped data collected may be used in publications or conference presentations, but no data that identifies you will be used. This means nothing will have your name on.

Please note that you will be free to stop the procedure at any time and no negative consequences will follow. You can simply tell the test administrator that you do not want to continue anymore. The information you provide will be kept confidential according to the regulations of the Health Professions Council of South Africa. The regulations state that the information must be kept for two years if there is a publication and six years if the research is not published.

While we are doing the different tests, if you feel sad, uncomfortable or scared or nervous we will refer you to see a training psychologist at the Emthonjeni Centre at the University of the

Witwatersrand. You can also call the Emthonjeni Centre at any time after you have participated and speak to Ntabiseng Modikane on 011-717-8663 or 011-717-4513.

The tests will be administered in a room provided by the school. The tests will be conducted after school and will not interrupt your learning.

This research project was approved by the Human Research Ethics Committee (HREC) at the University of the Witwatersrand. If you have any complaints you can report them to the HREC on 011 717 1234.

Should you have any further questions, please feel free to contact any of us, or our supervisors at the below mentioned telephone numbers and we will be happy to assist.

Thank You and Kind Regards,

Daniel Greenslade, Urvashi Chiba, Shona Fraser, Stephanie MacIlwaine, Cindy Van Wyk, Jessica Rice and Kelly Holland, 0118722372

Supervisors: Enid Schutte, Kate Cockcroft, Marilyn Lucas and Aline Ferreira Correia, 0117174524

Appendix 8: Participant Assent Form (Contrast group)

UNIVERISTY
OF THE
WITWATERSRAND,
JOHANNESBURG

School of Human and Community Development

Private Bag X3, Wits, 2050, Johannesburg, SA

Tel: (011) 717 4500 Fax: (011) 717 4559

Medical Ethics number: **M120268**

Hello,

We (Kelly, Daniel, Shona, Stephanie, Cindy, Jessica and Urvashi) are all students at Witwatersrand University and we are doing a study on adolescents at your school.

We are doing neuropsychological evaluations of adolescents attending your school. A neuropsychological evaluation involves using standardised tests to be able to describe an individual's cognitive strengths and weaknesses of their mental processes such as memory, judgement, processing and reasoning.

We would like you to take part in the study but need your permission to do so. If you agree to participate, you will be required to complete some drawing tasks, repeat some lists of words and numbers, identify some colours as well as try your hand with some cards.

If you are happy to take part we would like you to please sign to say you would like to participate. If you decide not to, that is okay and no one will be upset. If you decide to join and then later change your mind and want to stop, this is okay too.

Would you like to participate (*Tick **one** box*)

Yes, I am willing

No, I do not want to

Signing at the bottom of this form means that you agree to take part in this research.

Thank you very much,

Signed (You can just write your name): _____

Date: _____

Assigned Participant Code: _____

Appendix 9:

PART A: Participant Screening

(Only if all boxes ticked, proceed to details below)

Criteria for inclusion	
Age 13.5 upto but less than 16 years	
Vertically acquired	
First Line HAART	
No Traumatic Brain Injury, Meningitis or co-morbid conditions such as Downs Syndrome, Autism, Epilepsy *(* Note ADHD and HIVE **not** excluded)*	
Non-institutionalised (in family-type setting)	
Minimum of 4 years of schooling in English medium (includes repeated grades)	

Date……

Code……..

1. Gender: Male 1 Female 2

2. D.O.B:……. 3. Age:……(to confirm D.O.B)

4. Home Language: Sotho 1 Zulu 2 Xhosa 3 English 4 Afrikaans 5 Other 6

5.	Age at which HAART initiated	
6.	WHO stage of HIV at diagnosis	
7.	CD4 count at time of HAART initiation	
8.	Viral load at time of HAART initiation	
9.	Current CD4 Count	
10.	Current Viral Load	
11.	Also add names of HIV medication details – dosage and names Any other chronic medication (eg. Ritalin etc).	

PART B: Biographical Questionnaire

Collateral/Home Information

I am going to ask you some questions about the home and family

12. Where does your ward/child live?.....

13. Can you talk about the type and number of rooms in the house?

	Yes	No
Bedroom?	1	0
If yes, how many?		
Bathroom?	1	0
Kitchen?	1	0
Living room?	1	0

14. Who lives at home with the child?

	Yes	No	
Mother ?	1	0	
Father?	1	0	
Grandmother?	1	0	
Grandfather?	1	0	
Mother's boyfriend?	1	0	
Father's girlfriend?	1	0	
Brothers?	1	0	How many?
Sisters?	1	0	How many?
Aunts?	1	0	How many?
Uncles?	1	0	How many?
Other?			

15. Who is the person that takes care of your ward/child most of the time?

Mother	1
Father	2
Grandmother	3
Grandfather	4
Aunt	5
Uncle	6
Sister	7
Brother	8
Mother's boyfriend	9
Father's girlfriend	10
Other	11……

16. Do the parents or guardians work?

	Yes	No	If Yes: What kind of work do they do?
Mother / female guardian only	1	0	
Father /male guardian only	1	0	
Both parents (mother and father)	1	0	

		Yes	No	Don't know
17	Have at least one of the parents/guardians passed grade 8?	1	2	3
18.	Are there more than 20 hardcover booked in the home?	1	2	3
19.	Does at least one of the parents/guardians read a newspaper or magazine once a week?	1	2	3
20.	Does the child/ward usually receive a present from their parents/guardians on their birthday?	1	2	3
21.	Is the attitude of the parents/guardians towards schooling positive or at least neutral?	1	2	3
22.	Is there enough money at home for basic things like food, clothes?	1	2	3
23.	Is there enough money to buy expensive things? (e.g. plasma TV)	1	2	3

	Is there:	Yes	No
24.	a TV that is working at home?	1	0
25.	a radio that is working at home?	1	0
26.	a hot water tap inside your home?	1	0
27.	a flush toilet?	1	0
28.	a parent/guardian who has their own car?	1	0
29.	a vegetable garden at home?	1	0
30.	electricity in the home?	1	0
31.	gas at home?	1	0
32.	a fridge at home?	1	0
33.	a bed that the child/ward sleeps on by himself/herself?	1	0
34.	a bedroom that the child sleeps in?	1	0
	If not, in what room does he/she sleep in?		
35.	Is he child sleeping alone in the bedroom?	1	0
	If not, who do you share it with?		

Does the child eat:

	Yes	No	What does he/she usually eat?
36.1 Breakfast?	1	0	
36.2 Lunch?	1	0	
36.3. Dinner?	1	0	

		Yes	No	Don't know
37.	Did the mother have any problems during her pregnancy with the child?	1	2	3
38.	Were there any problems during the birth?	1	2	3
39.	Did the child learn to walk, talk etc at an around the right age?	1	2	3
	Comments			

		Yes	No	If so, when and for what?
	Has the child/ward ever received:			
40.	psychotherapy?	1	0	
41.	physiotherapy?	1	0	
42.	occupational therapy?	1	0	
43.	speech therapy?	1	0	
44.	had your eyes tested?	1	0	
45.	had any other forms of treatment?	1	0	
	If so, what?			

Could you tell me about the languages spoken at home.

46. Language Context Information

Languages Used	**Home**	**School**	**Friends**	**Mom**	**Dad**	**Grandparents**
English						
Afrikaans						
Zulu						
SeSotho						
Xhosa						
(Tshivenda) Venda						
(Setswana) Tswana						
Siswati						
Ndebele						
(Xitsonga) Tsonga						
(Sepedi) Northern Sotho						

PART C: Participant Questions:

I need some background information before we start. I am going to ask you some questions about you starting with the languages you speak

47. Participant languages:

Languages	Read	Write	Speak
English			
Afrikaans			
Zulu			
SeSotho			
Xhosa			
(Tshivenda) Venda			
(Setswana) Tswana			
Siswati			
Ndebele			
(Xitsonga) Tsonga			
(Sepedi) Northern Sotho			

I'm going to ask you some questions about your school

48. What language do you learn in at school? …….(should be English but check)

49. What grade are you currently in? ……

50. Have you ever repeated a grade at school?

Yes	1	Which Grade?
No	0	

51. Have you been absent from school this year?

Yes	1	Why?
No	0	

52. What do you do straight after school?..……

53. What do you do when you get home from school?
……
……

		Yes	No	Don't know
54.	Do you smoke?	1	2	
55.	Do you drink alcohol?	1	2	
56.	If so, how much in a week?			

57.	Do you take drugs?	1	2	
58.	If so, how often and what?			
59.	Do you exercise regularly?	1	2	
60.	Are you in a relationship?	1	2	

Now I'm going to ask some questions about which hand you use to do things

		Left	Right	Both	Not sure
	Which hand do you usually use…				
61	To write a letter legibly				
62.	To throw a ball				
63.	To cut with scissors				
64.	To deal playing cards				
65.	To hammer a nail into wood				
66.	To turn a door handle				
67.	To unscrew a jar				
68.	To hold your toothbrush				
	Which foot do you use				
69.	To kick a ball				
70.	To step on a bug				
	Which eye do you use				
71.	To look through a vuvuzela				
72.	To look through a hole				

PART D: BECK'S YOUTH INVENTORY-II

Here is a list of things that happen to people and that people think or feel. Read each sentence carefully, and circle the one word (Never, Sometime, Often or Always) that tells about you best.

THERE ARE NO RIGHT OR WRONG ANSWERS

		0	1	2	3
1	I work hard	Never	Sometimes	Often	Always
2	I feel strong	Never	Sometimes	Often	Always
3	I like myself	Never	Sometimes	Often	Always
4	People want to be with me	Never	Sometimes	Often	Always
5	I am just as good as other kids	Never	Sometimes	Often	Always
6	I feel normal	Never	Sometimes	Often	Always
7	I am a good person	Never	Sometimes	Often	Always
8	I do things well	Never	Sometimes	Often	Always
9	I can do things without help	Never	Sometimes	Often	Always
10	I feel smart	Never	Sometimes	Often	Always
11	People think I'm good at things	Never	Sometimes	Often	Always
12	I am kind to others	Never	Sometimes	Often	Always
13	I feel like a nice person	Never	Sometimes	Often	Always
14	I am good at telling jokes	Never	Sometimes	Often	Always
15	I am good at remembering things	Never	Sometimes	Often	Always
16	I tell the truth	Never	Sometimes	Often	Always
17	I feel proud of the things I do	Never	Sometimes	Often	Always
18	I am a good thinker	Never	Sometimes	Often	Always
19	I like my body	Never	Sometimes	Often	Always
20	I am happy to be me	Never	Sometimes	Often	Always
				BSCI-Y Total RS	

Here is a list of things that happen to people and that people think or feel. Read each sentence carefully, and circle the one word (Never, Sometime, Often or Always) that tells about you best, especially in last two weeks.

THERE ARE NO RIGHT OR WRONG ANSWERS

		0	1	2	3
21	I worry someone might hurt me at school	Never	Sometimes	Often	Always
22	My dreams scare me	Never	Sometimes	Often	Always
23	I worry when I'm at school	Never	Sometimes	Often	Always
24	I think about scary things	Never	Sometimes	Often	Always
25	I worry people might tease me	Never	Sometimes	Often	Always
26	I am afraid I will make mistakes	Never	Sometimes	Often	Always
27	I get nervous	Never	Sometimes	Often	Always
28	I am afraid I might get hurt	Never	Sometimes	Often	Always

29	I am worried I might get bad grades	Never	Sometimes	Often	Always
30	I worry about the future	Never	Sometimes	Often	Always
31	My hands shake	Never	Sometimes	Often	Always
32	I worry I might go crazy	Never	Sometimes	Often	Always
33	I worry people might get mad at me	Never	Sometimes	Often	Always
34	I worry I might lose control	Never	Sometimes	Often	Always
35	I worry	Never	Sometimes	Often	Always
36	I have problems sleeping	Never	Sometimes	Often	Always
37	My heart pounds	Never	Sometimes	Often	Always
38	I get shaky	Never	Sometimes	Often	Always
39	I am afraid that something bad might happen to me	Never	Sometimes	Often	Always
40	I am afraid that I might get sick	Never	Sometimes	Often	Always
				BAI-Y Total RS	

Here is a list of things that happen to people and that people think or feel. Read each sentence carefully, and circle the <u>one</u> word (Never, Sometime, Often or Always) that tells about you best, especially in last two weeks.

THERE ARE NO RIGHT OR WRONG ANSWERS

		0	1	2	3
41	I think that my life is bad	Never	Sometimes	Often	Always
42	I have trouble doing things	Never	Sometimes	Often	Always
43	I feel that I am a bad person	Never	Sometimes	Often	Always
44	I wish I were dead	Never	Sometimes	Often	Always
45	I have trouble sleeping	Never	Sometimes	Often	Always
46	I feel no one loves me	Never	Sometimes	Often	Always
47	I think bad things happen to me	Never	Sometimes	Often	Always
48	I feel lonely	Never	Sometimes	Often	Always
49	My stomach hurts	Never	Sometimes	Often	Always
50	I feel like bad things happen to me	Never	Sometimes	Often	Always
51	I feel like I am stupid	Never	Sometimes	Often	Always
52	I feel sorry for myself	Never	Sometimes	Often	Always
53	I think I do things badly	Never	Sometimes	Often	Always
54	I feel bad about what I do	Never	Sometimes	Often	Always
55	I hate myself	Never	Sometimes	Often	Always
56	I want to be alone	Never	Sometimes	Often	Always
57	I feel like crying	Never	Sometimes	Often	Always
58	I feel sad	Never	Sometimes	Often	Always
59	I feel empty inside	Never	Sometimes	Often	Always
60	Think my life will be bad	Never	Sometimes	Often	Always
				BDI-Y Total RS	

Here is a list of things that happen to people and that people think or feel. Read each sentence carefully, and circle the one word (Never, Sometime, Often or Always) that tells about you best.

THERE ARE NO RIGHT OR WRONG ANSWERS

		0	1	2	3
61	I think people try to cheat me	Never	Sometimes	Often	Always
62	I feel like screaming	Never	Sometimes	Often	Always
63	I think people are unfair to me	Never	Sometimes	Often	Always
64	I think people try to hurt me	Never	Sometimes	Often	Always
65	I think my life is unfair	Never	Sometimes	Often	Always
66	People bully me	Never	Sometimes	Often	Always
67	People make me mad	Never	Sometimes	Often	Always
68	I think people bother me	Never	Sometimes	Often	Always
69	I get mad at other people	Never	Sometimes	Often	Always
70	When I get mad I stay mad	Never	Sometimes	Often	Always
71	When I get mad I have trouble getting over it	Never	Sometimes	Often	Always
72	I think people try to control me	Never	Sometimes	Often	Always
73	I feel people try to put me down	Never	Sometimes	Often	Always
74	I feel mean	Never	Sometimes	Often	Always
75	I feel like exploding	Never	Sometimes	Often	Always
76	I think people are against me	Never	Sometimes	Often	Always
77	I get angry	Never	Sometimes	Often	Always
78	When I get mad I feel mad inside my body	Never	Sometimes	Often	Always
79	I hate people	Never	Sometimes	Often	Always
80	I get mad	Never	Sometimes	Often	Always
				BANI-Y Total RS	

Here is a list of things that happen to people and that people think or feel. Read each sentence carefully, and circle the one word (Never, Sometime, Often or Always) that tells about you best.

THERE ARE NO RIGHT OR WRONG ANSWERS

		0	1	2	3
81	I steal	Never	Sometimes	Often	Always
82	Other people get me into trouble	Never	Sometimes	Often	Always
83	I think about running away from home	Never	Sometimes	Often	Always
84	I do mean things	Never	Sometimes	Often	Always
85	I break into cars, houses or other places	Never	Sometimes	Often	Always
86	I fight with others	Never	Sometimes	Often	Always
87	I like getting people mad	Never	Sometimes	Often	Always
88	I skip school	Never	Sometimes	Often	Always

89	I hate listening to other people	Never	Sometimes	Often	Always
90	I argue with adults	Never	Sometimes	Often	Always
91	I hurt people	Never	Sometimes	Often	Always
92	I like being mean to others	Never	Sometimes	Often	Always
93	I break the rules	Never	Sometimes	Often	Always
94	I like it when people are scared of me	Never	Sometimes	Often	Always
95	I like to hurt animals	Never	Sometimes	Often	Always
96	I like to bully others	Never	Sometimes	Often	Always
97	I tell lies	Never	Sometimes	Often	Always
98	I like to trick people	Never	Sometimes	Often	Always
99	I break things when I am mad	Never	Sometimes	Often	Always
100	I swear at adults	Never	Sometimes	Often	Always
				BDBI-Y Total RS	