

The neuropsychological and behavioural profiles of HIV-infected HAART-naïve children.

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**ABSTRACT**

One of the most serious consequences of HIV-infection is its impact on the central nervous system (CNS). This CNS impact often results in neuropsychological deficits in children. Children born with HIV are prescribed highly active antiretroviral therapy (HAART) as they start to show HIV-related symptoms at a young age. Asymptomatic children born with HIV may only present with symptoms in late childhood and therefore remain HAART-naïve until this time. Few studies have focused on the cognitive and behavioural development of HAART-naïve children, often unaware of the underlying impact that HIV infection has on the CNS. The aim of this study was to investigate the neuropsychological and behavioural profiles of HAART-naïve children. Participants were 12 HAART-naïve children, aged 6 to 11 years. Each participant was assessed using a battery of neuropsychological tests to evaluate general intellectual functioning and functioning within the cognitive domains of language, executive function, visual perception, memory, processing speed and motor function. Behaviour was assessed using the Achenbach Child Behaviour Checklist that was completed by each participant's parent or caregiver. Results show that HAART-naïve children scored within the average range on tests of general intellectual functioning; however, they showed impairments in specific cognitive domains. Behaviour was also impaired. Despite being termed asymptomatic, this study has suggested that HAART-naïve children do experience underlying CNS impairments manifest in behavioural and cognitive functioning. This study is an important contribution to understanding of HIV infection and CNS progression in children.

*Keywords:* HAART-naïve; HAART; HIV; pediatric HIV infection; asymptomatic; children; CNS impairments

The Human Immunodeficiency Virus (HIV) has a severe impact on the lives of children throughout the world. There are currently about 2.5 million children living with HIV and about 420, 000 new infections each year among infants and children. One of the most serious consequences of HIV infection is its impact on the central nervous system (CNS). This results in neurocognitive abnormalities, both in adults and children (Kovacs, 2009). Children born with HIV (perinatal transmission) may begin to present these abnormalities within a few months of birth. However, there are other children born with HIV who may only present with HIV-related symptoms and cognitive deficits in late childhood and early adolescence. These children are referred to as asymptomatic HIV-infected children (Dunkley-Thompson, Figueroa, & Christie, 2006). Asymptomatic children have rarely been reported in literature and it is suggested that these children make up a small subset of the HIV-infected population (Judd et al., 2009).

Antiretroviral drugs, more specifically Highly Active Antiretroviral Therapy (HAART), can inhibit the progression of HIV, improving general health and daily functioning (Brown & Lourie, 2000). HIV-infected children who may only present with cognitive deficits later in life are not treated with HAART while they remain asymptomatic and are therefore referred to as HAART-naïve children. In resource-limited countries such as South Africa, the number of children with access to HAART is unknown, although it is estimated to be very low (Meyers et al., 2007). Therefore, South Africa provides a population of HAART-naïve children, some of whom will be asymptomatic without any previous exposure to antiretroviral drugs. Despite this potentially large population of asymptomatic HAART-naïve children in South Africa, studies of the behavioural and cognitive profiles of these children are limited and further research needs to be done in this field. This kind of research will provide a more comprehensive picture as to how presentation and disease progression manifests in asymptomatic HAART-naïve children, contributing to the literature on HIV-infection in children.

The following literature review will focus on the neuropsychological and behavioural profiles of asymptomatic, HAART-naïve children. I will firstly delineate some of characteristics of HIV-infected children and how disease progression differs from adult HIV-infection. The review will then briefly discuss treatment of HIV infection using HAART. This review will also discuss cognitive and behavioural functioning of HAART-naïve children, highlighting certain limitations as well as confounding factors that influence this research. This review will thereby propose that further study in this area of research would be invaluable to child health care.

## **LITERATURE REVIEW**

### **HIV infection and CNS-related consequences**

HIV, the virus that causes Acquired Immune Deficiency Syndrome (AIDS), was initially thought to only affect the immune system (Byers, 2001). We now know, however, that HIV-infection has a direct impact on the central nervous system (CNS), causing the development of CNS-related disease and disorders. This impact can manifest in a variety of ways, ranging from mild cognitive impairment of general intellectual functioning to severe deficits in specific cognitive domains. It may also manifest in behavioural and emotional impairment (Kovacs, 2009).

### **Neuropsychological profile of HIV-infected children**

Many studies have focused on the neuropsychological consequences of HIV infection in the adult brain; however this research cannot be applied to HIV-infected children. The neuropsychological impact of HIV on the adult brain differs to the impact seen in children, with regard to developmental deficits, progression and severity of disease. HIV infection acquired by perinatal transmission occurs when the immune system is at its most immature and still undergoing development. Children with this type of transmission have earlier and more severe manifestations of CNS disease and a more rapid disease progression than adults (Kovacs, 2009). The exact impact of HIV on the developing brain is different in each child but the neurologic manifestations of HIV generally include impaired brain growth, loss or plateauing of developmental milestones and progressive motor dysfunction. Typically, associated impairments are found in the cognitive domains of motor function and language. Global neurocognitive impairments have not been typically identified. Attentional dysregulation and social-emotional deficits have also been reported (Willen, 2006). In summary, developmental abnormalities manifested by neurological and neuropsychological problems are characteristic of children with symptomatic HIV infection (Wolters, Brouwers, Civitello & Moss, 1997).

It is commonly believed that CNS abnormalities associated with perinatally HIV-infected children are primarily caused by direct infection of macrophages and microglia by the HIV virus. It is hypothesized that this infection leads to neurotoxicity, neuronal damage and disturbances between cells, thus causing structural abnormalities (Willen, 2006). The most common structural abnormalities include cortical atrophy, basal ganglia calcifications and white matter irregularity (Van Rie, Harrington, Dow & Robertson, 2007).

### **Treatment of HIV infection**

As mentioned above, HIV-infected children can develop severe cognitive deficits that impact upon their daily functioning. The introduction of HAART, defined as a combination of at least three antiretroviral drugs, is recommended for the treatment of HIV-related symptoms, such as lowered immune system, nausea, headaches and body aches (Koekkoek et al., 2006). It has been found that HAART restores the immune system, increasing the CD4 count (amount of white blood cells) in children. HAART has also been used in HIV-infected children to inhibit or slow the progression of HIV and to thus improve general functioning (Brown & Lourie, 2000). Although HAART may be an effective way to slow the progression of HIV infection, it is unfortunately not widely available to the entire HIV-infected population.

### **Symptomatic and Asymptomatic HIV-infected children**

HIV-infected children presenting with symptoms of HIV should (if HAART is available to them) be put onto HAART as soon as possible. This is especially important with perinatally infected symptomatic children, who, as noted above, may have more rapid and severe disease progression. These children would therefore need HAART to slow this progression (Bagenda et al., 2006). However, it has been recognized that there are a group of these children who are 'slow progressors' (Dunkley-Thompson et al., 2006, p. 295). These HIV-infected children are also described as being asymptomatic, remaining immunologically and clinically stable for long periods of time after birth. These children may only present with neuropsychological deficits in late childhood or early adolescence (Armstrong, Seidel & Swales, 1993).

It is not entirely clear why some children remain asymptomatic, but there are suggestions that factors such as immunologic reactivity, education, environmental factors, lack of resources and even a different strain of HIV may play a role in the different rates of HIV progression (Bagenda et al., 2006). Nevertheless, this group of asymptomatic children represents a subgroup of HIV-infected children with a less progressive disease progression (Van Rie et al., 2007). Few studies have focused on the neuropsychological profiles of 'slow progressors' with HIV infection and the precise presentation of deficits seen are not entirely known (Armstrong et al., 1993).

### **Studies of the cognitive profiles of HAART-naïve children**

Few studies in the field of HIV neuropsychology have focused on HAART-naïve children specifically. Even fewer studies have focused on the neuropsychological and behavioural profiles of HAART-naïve children (Bagenda et al., 2006). Participants usually include asymptomatic HIV-infected children, some of whom have started HAART and others who are still HAART-naïve. For these reasons, the literature has not been entirely consistent with the findings reported.

Bagenda et al. (2006) investigated Ugandan children, aged 6-12 years, who were asymptomatic, perinatally HIV-infected and who had never received any antiretroviral treatment. They compared those children to a control group of HIV-negative children. Although scoring slightly lower on academic achievement measures and showing more signs of acute illness and malnutrition, the infected HAART-naïve children still scored well within the average range on tests of neuropsychological function. These tests primarily included measurement of sequential-processing, simultaneous-processing and memory.

Similar results are seen in a longitudinal study investigating the effects of HAART on HIV-infected children and psychomotor functioning (Koekkoek et al., 2006). Included in this study was an HIV-infected group of children including both HAART-treated and HAART-naïve children. This study found that at baseline, HAART-naïve children were faster on reaction-timed tasks compared to HAART-treated children. This study suggested that HAART-naïve children may show relatively normal development (Koekkoek et al., 2006).

Another study of asymptomatic HIV-infected children showed relatively normal performances on tests of general intellectual functioning and language, however executive function impairments were present (Bisiachhi, Suppiej & Padova, 2000).

Koekkoek, de Sonnevilla, Wolfs, Licht & Geelen (2008) administered global intelligence tests as well as a series of neuropsychological tests to 22 perinatally HIV-infected children. All the children were asymptomatic but only some were HAART-naïve. All the children scored in the average range compared to age appropriate norms on tests of general intellectual functioning, but cognitive domains of executive function, working memory and processing speed were seen as impaired. This study suggests that deficits in HAART-naïve children exist in specific cognitive domains. In the case of this study, the most severe impairment was seen in the domain of executive function.

A similar study supports these findings with the investigation of 14 children, only some of whom were asymptomatic. The children were administered a battery of neuropsychological tests and it was found that despite normal cognitive development, these

children showed subtle motor impairments. The children's impairments were attributed to compromised executive functioning and slowed information processing (Blanchette, Lou Smith, King, Fernandes-Penny & Read, 2002). Finally, a group of 8 children (ages 6-12) born with HIV and classified as asymptomatic, were investigated. The results of the neuropsychological tests administered suggested the presence of some learning disorders, as well as major memory and perceptual deficits. (Fundaro, Miccinesi, Baldierei, Genovese & Segni, 1998).

The studies described above suggest that asymptomatic HAART-naïve children may show relatively normal neurocognitive development. However, what has further been suggested is that although asymptomatic HAART-naïve children may score in the average range on tests of general intellectual functioning, they may also show subtle deficits in several cognitive domains. The domains most likely to be impaired are visual perception, executive function, memory, language, processing speed and motor function (Brown & Lourie, 2000). These outcomes suggest that despite a child being described as asymptomatic, HIV infection still has an impact on certain aspects of the CNS, causing several deficits in certain cognitive domains (De Baets et al., 2007). These findings underscore the importance of investigating specific cognitive domains in addition to general intellectual functioning. Asymptomatic children may have been classified as such due to their scores on global measures and the underlying deficits may, therefore, not be recognised.

### **Studies on the behavioural profiles of HAART-naïve children**

There has been little research done in the area of behavioural profiles of HAART-naïve children. It is often difficult to include HAART-naïve children in studies as children are often put onto HAART despite being asymptomatic. This is especially the case in developed as compared to developing world countries, where resources allow for this. There is limited literature concerning the behavioural profiles of HAART-naïve children, as it is very difficult for researchers to control for multiple influences that may impact upon emotional and behavioural functioning. Most children with HIV are living in locations with limited resources where experience of trauma, life stressors and family problems are experienced on a daily basis (De Baets et al, 2007). This is especially the case for perinatally infected children as they come from an HIV-infected family. It is therefore difficult to establish the causal relationship between HIV infection and behaviour (Mellins et al., 2003). Literature has shown, however, that HIV-infected children in general do commonly show more disruptive behaviour, particularly with regards to attention, concentration and emotional withdrawal. In

addition, HIV-infected children may also show more subjective distress than their peers and show additional symptoms of anxiety and depression (Brown & Lourie, 2000).

A study of clinically and immunologically stable HIV-infected children showed that the children experienced more frequent behavioural problems than appropriate as compared to childhood norms. Although it has not been thoroughly investigated, the literature seems to suggest that HAART-naïve children will show findings consistent with what is seen in a symptomatic HIV-infected person – showing substantial difficulties in emotional and behaviour functioning (Nozyce et al, 2006). However, this area has not been fully researched, and further research with specific focus on HAART-naïve children is needed.

In summary, the number of studies involving HAART-naïve children is limited and their findings are fairly inconsistent. The majority of the literature shows HAART-naïve children as showing low average general intellectual functioning, while there is some evidence to suggest that there may be subtle deficits in specific cognitive domains. Further research is also needed with regards to the behavioural profiles of HAART-naïve children and whether their behavioural are more similar to that of healthy children or symptomatic HIV-infected children.

### **Social and environmental factors**

There are various other social and environmental factors, to be described below, often not taken into account when considering HIV infection (Martin, Wolters & Toledo-Tamula, 2006). There is evidence to suggest that progression of HIV-infection in children is significantly related to social and environmental factors and not always directly related to the virus (Brown & Lourie, 2000). An extreme difficulty involved in understanding HIV infection in children is determining other factors that can play part in the progression and presentation of HIV symptoms. These factors include low level of maternal literacy, poor socioeconomic conditions and poor quality of the care given to the child (Alvarez & Rathore, 2007). South Africa is good example of a resource-limited country where neurological development may be greatly influenced by the environment in which the child lives. Additional factors such as malnutrition and exposure to disease and toxins add to the likelihood that children will experience developmental delays or cognitive impairments (Armstrong et al., 1993).



### **Summary and conclusion**

In conclusion this literature review has explored the impact of HIV infection in both symptomatic HIV-infected children and asymptomatic HIV-infected children. Importantly, HIV infection does not only affect the immune system but also neuropsychological and behavioural functioning. It is suggested that most of the literature surrounding the study of asymptomatic HAART-naïve children is fairly recent and inconsistent. It is not clear why HAART-naïve children have a slower disease progression, but it has been suggested that despite being termed asymptomatic these children have underlying impairments in certain cognitive domains. The domains suggested in the reviewed studies are visual perception, executive function, memory, language, processing speed and motor function. Furthermore, these children may show average general intellectual functioning which often masks these subtle deficits. South Africa provides a potential population of HAART-naïve children and further study of neuropsychological and behavioural profiles of these children will be an invaluable contribution to the research of HIV progression and childcare.

### **RATIONALE FOR RESEARCH**

This research is part of a larger study that aims to correlate neuroimaging structural abnormalities, as detected by diffusion tensor imaging (DTI), of HIV-infected HAART-naïve children with their cognitive and behavioural profiles. This study will contribute to further understanding of HAART-naïve children's neuropsychological and behavioural profiles within this larger study.

HIV infection is a huge public health problem, especially in South Africa. Therefore any further assistance in management and intervention in this field is a valuable contribution. This study may also aid in creating awareness of this population of asymptomatic HIV-infected children and aid in earlier detection of HIV in children and adolescents unaware of their HIV status. It will also help to inform the literature of how HIV-infection progresses in these asymptomatic children in terms of their behavioural and cognitive profiles. Findings from these investigations could improve the management of HIV-infected children and could inform and consequently improve educational and psychosocial interventions for both asymptomatic and symptomatic children (Martin et al., 2006).

As seen in the literature, many studies do not have participants that are exclusively HAART-naive, many of the participants were described as asymptomatic but had already been started on HAART. For this reason, none of the reviewed studies have been able to effectively compare general intellectual functioning as well as cognitive functioning in

specific cognitive domains for HAART-naïve children specifically. This kind of research would provide a more comprehensive picture as to how presentation and disease progression manifests in asymptomatic HIV-infected children. Furthermore, the behavioural profile of HAART-naïve children has not been properly explored thus far in the literature.

Finally, a study with specific focus on HAART-naïve children has never been done before and South Africa provides a unique sample to be used. Although the prevalence of HAART being administered to children in South Africa has increased, the accurate percentage of children receiving this treatment is not known (Meyers et al., 2007). It is estimated that despite sub-Saharan Africa being home to more than 90% of HIV-infected children, less than 5% of these children have ever received antiretroviral treatment (Da Baets et al., 2007). This provides a South African population of children who have never had access to HAART and therefore a potential HAART-naïve group.

### **SPECIFIC AIMS**

The major aim of this study was to investigate the neuropsychological and behavioural profiles of HAART-naïve children by comparing these profiles to data collected for matched Low SES and High SES healthy children on the same neuropsychological measures.

Therefore this study proposed the following aims:

- 1) To conduct a study on HIV-infected HAART-naïve children, using a data from healthy Low SES and High SES controls for comparison. These groups were matched on as many variables as possible.
- 2) To study the neuropsychological and behavioural profiles of HAART-naïve children by using neuropsychological assessments of both general intellectual functioning and functioning within specific cognitive domains.

### **HYPOTHESES**

The hypotheses tested in this study, included the following.

1. Hypothesis 1: In terms of general intellectual functioning (IQ):

- a) The HAART-naïve group will score within average IQ range for children of this age.
- b) The control groups will show IQ scores within the average range but these will be higher than the HAART-naïve group.

2. Hypothesis 2: In terms of functioning in specific cognitive domains:

- a) The HAART-naïve group will show subtle deficits on measures of visual perception, memory, language, processing speed, motor function and executive functions.

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b) The healthy control group will show no impairments in any cognitive domains.

3. Hypothesis 3: In terms of behavioural and emotional functioning:

a) HAART-naïve group will show substantial difficulty in behavioural and emotional assessment.

b) The healthy group will show normal behavioural and emotional development.

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## DESIGN AND METHODS

### Design

This study was a quasi-experimental, cross-sectional, between-group comparison of cognitive and behavioural functioning in three groups: an HIV-infected HAART-naïve group, and two control groups: a Low SES control group and a High SES control group.

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### Participants

The sample included 12 children, from the ages of 6 to 11 years, who were HIV infected and HAART-naïve and whose parents provided informed consent for their participation. The participants were recruited from a Isoniazid (INH) prophylaxis study of children with HIV at RXH, the Infectious Diseases Clinic at RXH, and from Groote Schuur Hospital. These children had already completed medical history and diagnostic examinations. Children on HAART or who had been on HAART previously were excluded from this group. This and a minimum age of 6 years old were the only exclusion criteria for this study. Participants were Xhosa-speaking, except for one participant who was able to speak English.

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There are two control groups used for this study. Due to time constraints and availability of participants, I was unable to collect my own control data. These control groups, therefore, were comprised of participants from archival data who had been administered the same tests as administered to my sample.

The first group, called the Low socioeconomic status (SES) control group (LSES), consisted of 12 South African children who matched the HAART-naïve group in terms of age, language and SES. These participants are HIV-negative and served as the first control group.

The second control group is the High SES control group (HSES) and consisted of 12 South African children matched only on age. These participants were from a medium to high SES and spoke English or Afrikaans. These participants were also HIV-negative and served as the second control group.

### Materials and Measures

Each participant was assessed using a battery of neuropsychological tests designed to evaluate general intellectual functioning, as well as the specific cognitive domains of attention, motor functioning, language, visual perception and visuospatial abilities, memory,

and executive functioning. Parents or caregivers of the participants were asked to complete a behavioural assessment checklist. All instruments used are standardized, with good psychometric properties, and are commonly used in pediatric neuropsychology research and clinical assessment internationally and in South Africa.

Test instructions were translated into Xhosa. The translation process included forward- and back-translation (authentication) where the translated test instructions were translated into English again. This was to ensure that there are no discrepancies between the original and translated instructions and that the instructions remain culturally suitable in the Xhosa translation.

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Socioeconomic status (SES) was defined for these participants according to annual household income. Low income was defined as household income of less than R100 000 per year. Medium income was defined as household income of between R100 001 and R230 000 per year. High income was defined as household income of between R230 001 and above per year.

This study received approval from the University of Cape Town (ethics ref 299/2005, see Appendix A). Written informed consent was obtained from the parent/caregiver of each participant. Confidentiality was maintained throughout this study, with no risk of social, physical or psychological harm to the participants.

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### General Intellectual Functioning

General intellectual functioning was estimated from the four subtests of the *Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999)*. The *Block Design* subtest requires the participant to replicate, within a time limit, modeled or printed 2D geometric patterns using two-colour cubes, thereby measuring perceptual organization. The *Matrix Reasoning* subtest measures non-verbal fluid reasoning. In this test the participant was required to indicate the missing piece from the choice of five possibilities to complete a series of incomplete grid patterns. The *Vocabulary* subtest measures expressive language capabilities. The participant was asked to give oral definitions of words. This subtest also includes some low-end items that require the participant to name a picture shown to them by the examiner. Finally, the *Similarities* subtest measures verbal conceptualization and abstract reasoning. In this test, the participant was required to either state the way in which two concepts are the same or to point to one of four pictures that is most similar to three target items.

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### **Attention, Tracking and Processing Speed**

Three subtests from the *Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003a)* were used to measure cognitive processes in this domain. The *Coding (CD)* subtest measures speed of mental and graphomotor processing. The participant was required to copy, as quickly as possible within a time limit, symbols that are paired with either geometric shapes or numbers. The *Symbol Search (SS)* subtest is a relatively pure measure of processing speed. The participant was required to scan a group of symbols and then indicate whether a target symbol is present in that group. The participant must complete as many of these items as possible within a specified time limit. The *Digit Span (DS)* test measures attention, concentration and working memory for verbal material. The participant was required to repeat a sequence of numbers in either the order in which they were orally presented by the examiner (*DS Forward*) or in the reverse order (*DS Backward*).

### **Motor Functioning**

The *Fingertip Tapping* subtest from the *NEPSY-II* (Korkman, Kirk, & Kemp, 1998) was used to measure self-directed manual motor speed. The first task on this subtest requires the child to make a circle with the tips of his/her thumb and index finger, opening and closing it as fast as he/she can until he/she makes 20 correct repetitions. The second part of the subtest requires that the child tap his/her index fingertip, then middle fingertip, then ring fingertip, then little fingertip on the tip of their thumb, making a circle with each finger. The participant must do this as fast as possible; the examiner records how long it takes to complete five correct sequences. Participants always complete both tasks with the dominant hand before attempting them with the non-dominant hand.

The *Grooved Pegboard Test* (Matthews & Klove, 1964) measures eye-hand coordination and motor speed. Participants were presented with a metal board with a matrix of 25 holes (in a 5 x 5 array) with randomly positioned slots, and with 25 pegs, each with a ridge along one side. The pegs must be rotated to match the holes before they can be inserted. The participant's task, then, is to insert the metal pegs into the slots as quickly as possible and in sequence. Children are only required to complete the first two rows of pegs. The examiner records time to completion, first with the dominant hand and then with the nondominant hand.

## **Language**

The *Boston Naming Test – Short Form (BNT-2-SF4)*; Mack et al., 1992) assessed the participant's visual confrontation naming ability. This test requires the participant to look at black and white line drawings of common objects and name them. The names of the objects range in difficulty from simple, high frequency vocabulary words to rare words.

## **Visual Perception and Visuospatial abilities**

The *Rey-Osterrieth Complex Figure (ROCF)*; Rey, 1941) is a standardized measure of visual memory, visuo-constructional ability, as well as organization and planning. The ROCF involves the copying of a two-dimensional image, changing pencil colours every 30 seconds. Once the copy is made, the card is removed from the participant's view, and the participants are asked to redraw the image from memory after a 3-minute delay. After a 30-minute delay, the participants are again asked to redraw the image from memory.

The scoring system used in this study is the Rey (1941) 36-point scoring system, which measures how accurately the participants were able to copy and recall the figure. According to this scoring system, 18 details of the figure are used to score the participants' drawings.

## **Learning and Visual Memory**

The immediate and delayed recall trials of the *ROCF* was used visual perceptual and memory abilities of the participants. The administration of this test is described above.

## **Executive Functioning**

The *NEPSY-II Inhibition* subtest was used to measure the inhibition of automatic responses. In this test the participant will look at a series of black and white shapes and arrows and name either the shape or direction or give an alternate response, depending on the colour of the shape or arrow. The *Delis-Kaplan Executive Function System (D-KEFS)*; Delis, Kaplan, & Kramer, 2001) measures key components of executive function. The Letter Fluency and Category Fluency subtests assess fluent productivity in the verbal domain. For verbal fluency the participant is required to produce as many words that begin with a specified letter in one minute. Similarly, in category fluency, the participant is required to produce as many possible words from a semantic category (e.g. animals or fruit and vegetables) within one minute.

## Behaviour

The *Child Behaviour Checklist (CBCL)* (Achenbach & Rescorla, 2001) requires a parent (or caregiver) to rate the child's problem behaviours and competencies. This instrument is suitable for use in children aged 6-18 years. The first section of the CBCL consists of 20 items enquiring about the child's competence in various domains of functioning; the second section of 120 items enquires about the presence of behavioural and emotional problems. The two indices that are focuses on in this study, given by the CBCL parent reports, are Total Competence and Total Problems.

A score of less than 40 on the Total Competence index indicates that the child is in the borderline range and requires assistance with what should be age-appropriate activities. A score of less than 35 indicates clinical range for this scale. Within the Total Competence scale are three subscales that are categorized as Activities, School and Social. A score of less than 35 on any of these subscales indicates that children have borderline impaired functioning in that subscale and a score of less than 30 indicates clinical impairment.

For the Total Problems scale the outcomes of the parent's ratings are captured on three major scales: (1) Internalizing scale – indicates the presence of depression/withdrawal, anxiety and other somaticising behaviours; (2) Externalizing scale – indicates the presence of cruel, aggressive, or delinquent behaviours; (3) Total Problems scale - picks up on any other problem behaviours, such as immaturity or hyperactivity (Achenbach & Rescorla, 2001). A score between 60-65 on any of these scales indicates behaviours in a borderline range and a score more than 65 indicate behaviours in a clinical range.

## Procedure

A list of possible participants was identified with help from the administrators of the INH prophylaxis study in HIV children at RXH. After potential participants had been contacted and informed consent obtained from their parents/legal guardians, a date and time for assessment was scheduled.

This assessment took place on a weekday morning at the RXH HIV unit. The battery of neuropsychological tests was administered by a trained Xhosa interpreter. The child's fatigue, effort, and motivational levels were monitored, and he/she was allowed to take breaks from testing where necessary. Children were accompanied by their parents or caregivers to the appointment, but those individuals remained in a separate room during the neuropsychological assessment. The CBCL was administered to the parent while the child was completing the neuropsychological tests. If a child was, for any reason, unable to

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continue with the assessment it was terminated immediately and an alternate time was scheduled. Each assessment session took between three to four hours.

After the completion of the tests, if parent/caregiver requested feedback from the assessment, a brief summary of the child's test scores was given to the parent/caregiver.

## **DATA ANALYSIS**

I have already mentioned that I have used two control groups from archival data in order to compare the HAART-naïve group to a South African population. Each control group differed in terms of which neuropsychological tests they were administered and not every test I used in my battery was administered to both of the groups. The first control group, the Low SES group, had previously been administered the BNT, verbal and category fluency tests, and therefore this group was compared to the HAART-naïve group on the results of these tests. Independent sample t-tests were used for these comparisons.

The second control group, the High SES control group was administered the D-KEFS and RCF tests and therefore this group was compared to the HAART-naïve group on the results of these tests. Again, independent sample t-tests were used for these comparisons. The specific cognitive domains investigated were assessed using the results of these t-tests.

For the assessment of general intellectual functioning, the WASI test was administered to all 3 groups and therefore 3 separate one-way ANOVAs were performed to ascertain whether there was a significant effect between the groups on scores of VIQ, PIQ and FSIQ. In order to find out where the significant differences were, planned comparisons were used to compare the VIQ, PIQ and FSIQ scores obtained by the HAART-naïve group against each of the control groups. The control groups were also compared against one other. These planned comparisons allowed for fewer comparisons and thereby reduced the number of tests ordinarily done using a post hoc test, providing a greater statistical power against type-II errors (Roberts & Russo, 1999).

Furthermore, I had specific predictions about the scores obtained by each group that I also wanted to explore. The pattern of the WASI scores were predicted to show a linear trend, the HAART-naïve group scoring the lowest, the Low SES group scoring higher than the HAART-naïve group and the High SES group scoring the highest. This linear trend indicates the values of the WASI scores will increase or decrease steadily as a function of the group they are in. If a linear contrast effect truly exists, I was more likely to discover it by asking a focused question rather than an omnibus one. Therefore, linear contrast analyses were also performed to investigate if this trend did exist (Rosenthal, Rosnal & Rubin, 2000).

The tests that were not administered to either of the control groups were compared to international norms using descriptive statistics. Measures of central tendency (mean, median and mode) were calculated and histograms and graphs of normal distribution were obtained to ensure that any outliers were detected.

For all comparisons, effect sizes were calculated using a formula elaborated from Aaron, Kromfey & Ferron (1998), specifically used for small sample sizes.

## RESULTS

In this section, the demographic and clinical characteristics of the HAART-naïve group and the two control groups will be presented. Following this, descriptive statistics and results for all the statistical analyses done will be presented in Table 2. The results will then be elaborated on, first in terms of general intellectual functioning and then according to specific cognitive domains. Finally the findings of behavioural and emotional assessment for the HAART-naïve group will be presented. When not otherwise specified, all assumptions for the following statistical analyses were upheld.

Table 1.

*Demographic and clinical characteristics of the HAART-naïve group, LSES group and HSES group.*

Variable	HAART-		
	naïve (n=12)	Low SES (n=12)	High SES (n=12)
Age (months)	114.74(18.21)	115.42(16.25)	115.42(18.37)
Sex (Female: Male)	6:6	7:5	7:5
Language (Xhosa: English: Afrikaans)	11:1:0	11:1:0	0:9:3
Handedness (R:L:X)	12:0:0	11:0:1	12:0:0
SES (low: medium: high)	12:0:0	12:0:0	2:3:7

*Note.* Age means are presented with standard deviations in parentheses.

For handedness, R:L:X means ratio of right- to left- to cross-handedness.

Table 2.  
Descriptive statistics and results for all neuropsychological tests administered

	HAART-naïve	LSES	HSES	F/t	P	r
<b>General intellectual functioning</b>						
WASI VIQ <sup>c</sup>	91.80(19.53)	94.20(12.53)	106.70(6.56)	3.31	0.052	0.44
WASI PIQ <sup>c</sup>	77.50(10.04)	85.10(12.04)	97.50(11.30)	8.18	0.002**	0.62
WASI FSIQ <sup>c</sup>	82.70(11.95)	88.00(10.33)	102.00(6.36)	10.52	0.0005***	0.66
<b>Executive Function</b>						
D-KEFS verbal fluency <sup>c</sup>	14.80(6.14)	24.60(7.14)	----	-3.29	0.004**	0.36
D-KEFS category fluency <sup>c</sup>	8.00(1.83)	12.10(3.18)	----	-3.53	0.002**	0.36
NEPSY-II Naming <sup>d</sup>	2.33(2.06)	----	----	----	----	----
NEPSY-II Inhibition <sup>d</sup>	4.56(1.88)	----	----	----	----	----
NEPSY-II Switching <sup>d</sup>	3.22(2.28)	----	----	----	----	----
<b>Language</b>						
BNT <sup>a</sup>	8.00(1.13)	9.92(1.62)	----	-3.36	0.003**	0.36
<b>Attention and Processing Speed</b>						
WISC Digit Span <sup>b</sup>	6.00(2.53)	----	9.73(2.28)	-3.63	0.002**	0.36
WISC Processing Speed <sup>c</sup>	10.40(3.37)	----	19.10(3.84)	-5.38	0.00004***	0.22
<b>Motor Function</b>						
Grooved Pegboard DH <sup>c</sup>	96.60(40.59)	----	----	----	----	----
Grooved Pegboard NDH <sup>c</sup>	105.20(33.21)	----	----	----	----	----
Fingertip Tapping DH <sup>a</sup>	8.92(2.57)	----	----	----	----	----
Fingertip Tapping NDH <sup>a</sup>	7.75(2.05)	----	----	----	----	----
<b>Visual Perception</b>						
ROCF copy <sup>e</sup>	21.31(6.58)	----	24.25(5.95)	-0.94	0.365	0.22
<b>Learning and Memory</b>						
ROCF recall <sup>e</sup>	14.75(4.76)	----	15.00(4.30)	-0.11	0.913	0.03
ROCF delay <sup>e</sup>	11.69(4.22)	----	14.00(5.23)	-0.97	0.347	0.22

Comment [A9]: Total IQ scores?

Comment [A10]: Did you exclude the data of those participants you stopped at 5mins?

Notes: Means are presented with standard deviations in parentheses. DH refers to dominant hand. NDH refers to non-dominant hand. <sup>a</sup> For this comparison, n=12. <sup>b</sup> For this comparison, n=11. <sup>c</sup> For this comparison, n=10. <sup>d</sup> For this comparison, n=9. <sup>e</sup> For this comparison, n=8. \*p<0.05, \*\*p<0.01, \*\*\*p<0.001

## General intellectual functioning

### WASI

Three separate one-way ANOVAs were used to compare Verbal IQ (VIQ), Performance IQ (PIQ) and Full Scale IQ (FSIQ) scores of the HAART-naïve group, the Low SES group and the High SES group. All the assumptions for ANOVA were met with one exception: Levene's homogeneity of variance statistic was  $<.05$  for VIQ. However ANOVA is a robust statistical procedure, especially in the case where the sample sizes are equal (Tredoux & Durrheim, 2002). As all other assumptions were upheld the parametric analysis was continued.

With regard to VIQ, as can be seen from Table 2, the one-way ANOVA detected no statistically significant between-group differences. A set of planned pairwise comparisons showed that (a) there was no statistically significant difference between the performance of the HAART-naïve participants and the Low SES participants,  $t(18) = -0.39$ ,  $p = 0.70$ ,  $r = 0.08$ , (b) there was a statistically significant difference between performance of the HAART-naïve participants and the High SES participants,  $t(18) = -2.39$ ,  $p = 0.02$ ,  $r = 0.34$ , and (c) there was no statistically significant difference between the performance of the Low SES participants and the High SES participants,  $t(18) = 2.001$ ,  $p = 0.05$ ,  $r = 0.33$ .

With regard to PIQ, as can be seen from Table 2, the one-way ANOVA detected a statistically significant between-group difference. A similar set of planned pairwise comparisons as described above showed that (a) there was no statistically significant difference between the performance of the HAART-naïve participants and the Low SES participants,  $t(18) = 1.52$ ,  $p = 0.14$ ,  $r = 0.15$ , (b) there was a statistically significant difference between performance of the HAART-naïve participants and the High SES participants,  $t(18) = -4.01$ ,  $p = 0.0004$ ,  $r = 0.35$ , and (c) there was a statistically significant difference between the performance of the Low SES participants and the High SES participants,  $t(18) = 2.48$ ,  $p = 0.02$ ,  $r = 0.35$ . These results suggest that the HAART-naïve children do more poorly on performance tasks and verbal tasks, with VIQ and FSIQ scores being within the average range and PIQ scores being below the average range.

With regard to FSIQ, as can be seen from Table 2, the one-way ANOVA detected statistically significant between-group difference. A final set of planned pairwise comparisons as described above showed that (a) there was no statistically significant difference between the performance of the HAART-naïve participants and the Low SES participants,  $t(18) = 1.06$ ,  $p = 0.298$ ,  $r = 0.22$ , (b) there was a statistically significant difference between performance of the HAART-naïve participants and the High SES

**Comment [KGFT11]:** Remember your entire manuscript should be left aligned (not justified) and have 1-inch (2.54 cm) margins

**Comment [KGFT12]:** Should not be italicized.

**Comment [KGFT13]:** You may need to put a footnote here about why you can/should continue with your planned comparisons even if the omnibus F is not significant. Ask me for a book explaining that.

**Comment [KGFT14]:** Always give p to at least 2 decimal places.

participants,  $t(18) = -4.19, p = 0.0003, r = 0.33$ , and (c) there was a statistically significant difference between the performance of the LSES participants and the High SES participants,  $t(18) = 3.14, p = 0.004, r = 0.36$ .

Using the results of the omnibus F-tests done for VIQ and PIQ, a linear contrast analyses was performed to estimate if this linear trend did exist. The results of the contrast analyses for VIQ scores were:  $F_{contrast}(1, 63) = 5.74, p_{contrast} = 0.012, r_{contrast} = 0.29^1, r_{effect} = 0.28$ . The results for the contrast analyses for PIQ scores were:  $F_{contrast}(1, 63) = 16.06, p_{contrast} = 0.00017, r_{contrast} = 0.45, r_{effect} = 0.45$ .

Both linear contrasts were found to be significant for both VIQ and PIQ. This shows that there is a linear trend in the data that indicates the dependent variable values (the scores on the WASI) increase steadily as a function of the independent variable, in this case, the groups. It was expected that the HAART-naïve would score the lowest, followed by the Low SES group and then the High SES group would score the highest. This was shown to be true.

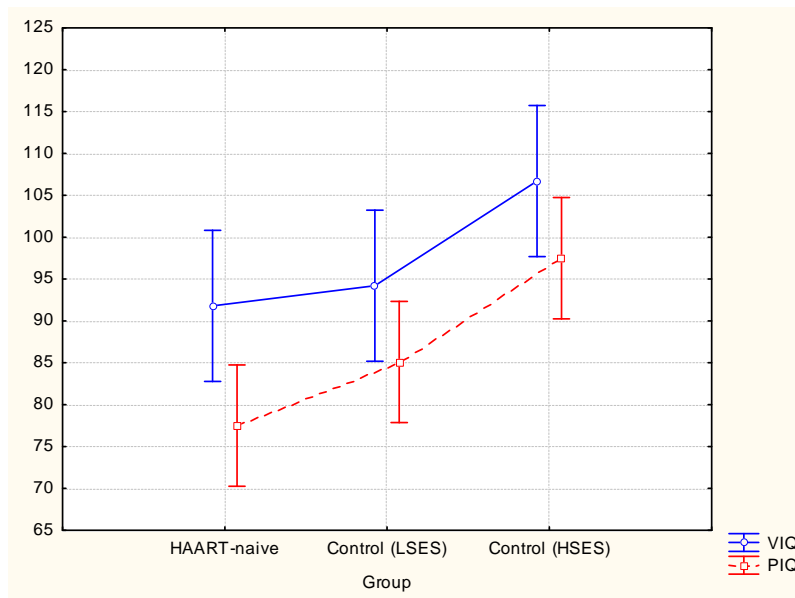


Figure 1. WASI VIQ and PIQ scores showing a linear contrast across all three groups

<sup>1</sup>  $r_{contrast}$  is a partial correlation of the outcome measure and the lambda weights associated with the groups, after controlling for the effect of all other between group differences.  $r_{effect\ size}$ , however, is a measure of the effect without partially out other between-group variation (Rosenthal, Rosnow, & Rubin, 2000).

## Executive Function

### *Verbal and Category fluency*

Independent sample t-tests were used to compare the scores of verbal fluency and category fluency tests between the Low SES and HAART-naïve groups. For verbal fluency, the HAART-naïve group had significantly lower scores than the Low SES group (see Table 2). The same is observed for category fluency as the HAART-naïve group scored significantly lower than the Low SES group.

### *Inhibition*

Inhibition scores were compared against international means. Inhibition was scored using three tasks: Naming, Inhibition and Switching. When considering the classification of these scores as described in the test manual (see Appendix B), the mean scores (refer to Table 2) for Naming and Switching are classified as 'well below expected level'. The mean score for Inhibition is as classified as 'below expected level'. This suggests that the HAART-naïve did do more poorly on this test of executive function.

**Comment [A15]:** You need to include a table in the appendix that lists the various categories that scores may be classified as and provide a reference for it.

## Language

### *BNT*

In order to assess the domain of language, the BNT scores of the HAART-naïve group were compared to Low SES group scores on this test. An independent samples t-test found that the HAART-naïve group did significantly worse than the Low SES group.

## Attention and Processing Speed

### *Digit Span*

Digit span scores of the HAART-naïve group and the High SES group were compared using an independent samples t-test. There was a statistically significant difference between the groups, with the HAART-naïve group scoring lower than the High SES group. The medium effect size ( $r=0.36$ ) seen for these groups suggests there is a substantial significant difference between the groups.

### *Processing Speed*

Processing speed was scored by adding the WISC Coding scores and the WISC Symbol Search score. These scores of the HAART-naïve group and High SES group were once again compared using a t-test. It was found that there was a statistically significant difference between the groups, with the HAART-naïve group scoring lower than the High SES group.

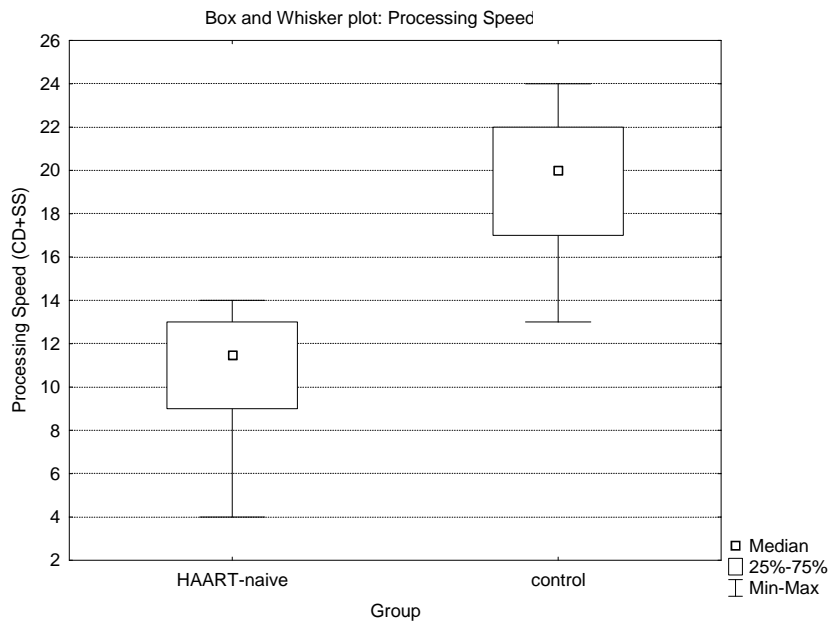


Figure 2. Difference between the High SES control group and the HAART-naïve group on scores of processing speed.

Comment [A16]: In the figures, please label the control group as either low or high SES

## Motor Function

### Grooved Pegboard

The Grooved Pegboard test scores (measured in time) obtained by the HAART-naïve group were compared to international norms according to the descriptive statistics present in the Grooved Pegboard user's manual (see Table 3 and 4 in Appendix C).

Each participant of the HAART-naïve group was compared to normative mean age and sex-appropriate scores to determine performance on this test. 4 of the HAART-naïve participants showed below average scores for this test, with both their dominant and non-dominant hands. All these scores were more than 2 standard deviations below the normative mean age-appropriate scores. 6 children scored within the average range for the test compared with normative scores, however, the HAART-naïve consistently scored below normative scores.

### Fingertip tapping

Fingertip tapping scores were compared against international norms (see Appendix B). These scores showed that the HAART-naïve group scored more poorly when using their non-dominant hand than when using their dominant hand. The mean score for the dominant hand (see Table 2) is considered to be at the expected level. The non-dominant hand mean scores

Comment [A17]: Please check these scores



showed that these children scored within the borderline range between expected level and below expected level.

### Visual Perception

*ROCF copy trials*

**Comment [A18]:** This is a consistent mistake, even in previous drafts

Table 5.

*Each HAART-naïve participant compared to normative scores for RCF copy trail*

Participant	Age	Raw scores	Normative scores for	
			age M(SD)	Description
1	9.5	24.5	30.86(4.36)	Below Average(2)
2	10.11	16.5	33.24(3.51)	Below average (5)
3	11.1	15	33.99(2.99)	Below average (5)
4	8.2	28	27.43(5.18)	Average
5	10.6	20	33.24(3.51)	Below Average (3)
6	8.9	18.5	29.34(4.75)	Below Average (2)
7	6.11	15	18.99(6.67)	Average
8	11	33	33.99(2.99)	Average

*Note:* Number in brackets (in the description) refers to the number of standard deviations the raw score is below the mean.

In order to see how the HAART-naïve group did on these tests, raw scores were compared to the normative age-appropriate scores for each participant (see Table 5). 5 children showed below average scores with more than 2 standard deviations below the mean. 4 children were reported as average. An independent samples t-test was also performed to compare the difference between the High SES group and HAART-naïve group. It was found that there was no statistically significant difference between the groups on this test, although the HAART-naïve group did score lower than the High SES group.

### Visual Memory

*ROCF Recall and Delay trials*

Similarly with the copy trial these scores were also compared against age-appropriate scores for each participant. 3 out of 8 children scored below average for Immediate Recall trails. For the Delayed recall, 5 children scored below average (See table 6 and 7 in Appendix D).

Finally, independent samples t-tests were conducted to compare the difference between the High SES group and the HAART-naïve group on the Immediate Recall and Delayed Recall trials of the ROCF. It was found that there were no statistically significant differences between the groups but in both cases the HAART-naïve group did score lower than the High SES group.

## Behaviour

### CBCL scores

Table 4.

*Descriptive statistics for scores on the CBCL scales.*

	HAART-naïve (n=7)
Total Competence Scale	37.57(6.13) B
<i>Activities</i>	36.86(4.74)
<i>Social</i>	48.86(7.47)
<i>School</i>	34.29(9.12) B
Total Problems Scale	63.29(8.67) B
<i>Externalizing</i>	58.71(9.48)
<i>Internalizing</i>	67.29(6.92) C

**Comment [A19]:** This entire section should be part of the methods section. You should only report results in the results section

**Comment [A20]:** Your description says that scores more than 65 are borderline and those more than 70 are clinical?

*Notes.* Means are presented with standard deviations in parentheses. B indicates a score in the borderline range. C indicates a score in the clinical range.

As shown in the above table, the HAART-naïve group show borderline problems in the **Total Competence Scale**. When looking at the results more closely, the subscale most impaired was school. These results indicate that the participants are having difficulty at school, such as repeating grades, attending special classes and having problems with schoolwork. Most of the participant's caregivers or parents did explain that their child was struggling at school.

**Comment [A21]:** Again, decide whether this is capitalised or not and maintain that throughout

Furthermore, parents or caregivers reported Internalizing behaviours in the clinical range. These behaviours include somatic complaints, withdrawal and depression. These results suggest asymptomatic HIV-infected children are experiencing more Internalizing behaviours as compared to Externalizing behaviours. However, although Internalising behaviours are clearly in the clinical range, it is important to note that the standard deviation of the average Externalising behaviour scores indicated that two of the participants also fall within the clinical range for this subscale. These scores suggest that the HAART-naïve group

are experiencing behavioural and emotional problems, especially in terms of Internalizing behaviours.

## DISCUSSION

### Hypotheses 1: General Intellectual Functioning

**Comment [A22]:** Please ensure that the hypotheses here match those stated in the introduction

Previous research within the field of paediatric HIV infection has shown varying results in terms of the general intellectual functioning of HAART-naïve children. The majority of studies reviewed found both asymptomatic and HAART-naïve children to score in the average range on scores of general intellectual functioning (VIQ, PIQ and FSIQ), suggesting that intellectual functioning is somewhat spared in these children (Koekkoek et al., 2008). Although general intellectual functioning may be spared, IQ scores were shown to generally be in the low average range (Bagenda et al., 2006). This was, therefore, my first hypothesis, that HAART-naïve children would score within the low average range on tests of general intellectual functioning as well as lower than both the control groups.

The results of this study showed that when compared to the Low SES group (using planned comparisons), there was no significant differences between the groups on scores of VIQ, PIQ and FSIQ. According to the qualitative description of WASI (Wechsler, 1999) IQ scores (see Appendix E) VIQ scores for the HAART-naïve were classified as average (90-109) and FSIQ scores were classified as being in the low average (80-89) range. These scores show support for my hypothesis that HAART-naïve children will show average, although low, general intellectual functioning. However, although FSIQ and VIQ were within the normal range, PIQ scores fell within the borderline range (70-80) which lies between low average and below average. These PIQ scores do not support the literature as there is no indication as to why HAART-naïve children would do particularly poorly on tests of PIQ.

This difference in PIQ scores of these HAART-naïve children suggest that HAART-naïve children did better on verbal tasks than nonverbal tasks. Other literature found contrasting results as their participants scored lower on verbal tasks than nonverbal tasks (Fundaro et al., 1998). As there were subtle impairments in the cognitive domains of processing speed and motor function (to be discussed) and considering that the nonverbal tasks measuring PIQ (Matrix reasoning and Block Design) are timed and require motor coordination, it is suggested that deficits in these domains may be the reason for the poor performance on PIQ. Furthermore, poor performance was also seen on tasks of visual perception and organisation as measured by the copying trial of the ROCF task (to be discussed). This seems to reflect a consistent poor performance by the HAART-naïve group on tasks measuring perceptual organization.

Although there was a difference in VIQ and PIQ scores, FSIQ score still fell within the average range for scores of intellectual functioning, supporting my first hypothesis.

Further comparisons were made between the HAART-naïve group and the High SES group. The HAART-naïve IQ scores were significantly lower than the High SES IQ scores. Interestingly, when the Low SES and High SES group PIQ and FSIQ scores were compared it was also found that there was a significant difference between the groups. For VIQ, there was no significant difference between the HAART-naïve and High SES group, however the effect size was moderate for this test,  $p=0.005$ ,  $r=0.33$ , suggesting that with a larger sample size the difference between these two groups could become significant. This is an important point because it shows that even though both the Low SES and High SES group consists of typically developing individuals, there are clear differences in their performance on general intellectual functioning. One suggestion is that their performance differences could in fact be due to the factor of SES. This is again supported by the significant linear contrast which shows that the test scores changed as a function of the different groups. Consideration of SES is important, as I cannot necessarily only attribute low IQ scores to the impact of HIV infection on the neurodevelopment of these children.

**Comment [A23]:** You need to say how they differed

As mentioned it is difficult to determine whether low scores can be attributed to other factors such as low SES (Blanchette et al., 2002). The children coming from low SES backgrounds (HAART-naïve group and low SES group) are likely to be living in impoverished environmental and social conditions. These types of conditions, for example low level of maternal literacy, poor financial conditions and poor quality of care, may play a role in developmental delays or cognitive impairments (Alvarez & Rathore, 2007). In South Africa, it is often the case that low SES families, with HIV-infected children, do not have access to the appropriate educational and medical services. These HAART-naïve children, therefore, may not be getting the appropriate support needed to stimulate their cognitive and general functioning (Meyers et al., 2007). The HAART-naïve participants most likely did not have the same educational and learning opportunities as the participants from the high SES group. Therefore, one can see how the effects of HIV infection on the CNS are confounded by these other factors. SES is therefore a factor to be mindful of throughout this discussion.

**Comment [A24]:** low SES - lowercase l for low, same for high SES

## **Hypothesis 2: Cognitive domains**

With the average scores of HAART-naïve children in general intellectual functioning (FSIQ), numerous studies have described impairments found in certain cognitive domains (Brown & Lourie, 2000). The most commonly hypothesised areas of impairment are visual perception, executive function, memory, language, processing speed and motor function (Koekkoek et

al., 2008). Thus, this is the basis of my hypothesis that predicts impairments in these specific cognitive domains for HAART-naïve children. Further predictions are that the Low SES and High SES control groups will show no impairments in these cognitive domains. As different tests were compared to different groups and some to international norms, these results were not easily interpreted. However, the results do tend towards supporting my hypothesis of subtle impairments in certain cognitive domains.

Within the domain of executive function, verbal and category fluency scores were compared against the Low SES group scores. It was found that the HAART-naïve group did significantly worse than the Low SES control group. The effect size was moderate for both these tests (refer to Table 2) suggesting that there was a substantial difference between these groups. For these groups, SES, language and age were a common and therefore it is more reasonable to assume that this difference can be attributed to HIV infection .

Executive function was further tested using the NEPSY-II inhibition compared against international norms. Results showed that the HAART-naïve group scored in the category of 'below the expected level' for all subtests of this test. It is therefore suggested that the results for the cognitive domain of executive function tend towards impairment in this domain, thus supporting the current literature and hypothesis.

In terms of the language domain for the HAART-naïve group, scores compared against the Low SES group show significantly poorer scores on this test for the HAART-naïve group. These results suggest that HAART-naïve children do show impairments in this cognitive domain.

Tests of processing speed and attention, although compared to the High SES group, showed significant differences between the scores showing some difficulty for the HAART-naïve children in this domain.

It was expected that tests of motor function would show impaired performance, which is in support of the literature (De Baets et al., 2007). For the Grooved Pegboard test, some children showed substantially below average scores for both dominant hand and non-dominant hands. Further, Fingertip tapping tests showed average scores for the dominant hand and borderline scores for the non-dominant hand. It is hard to determine the severity of impairment for this domain, however HAART-naïve children, although sometimes scoring in the average range, did have poorer scores than international norms. These results tend towards some difficulty experienced by HAART-naïve children in this domain.

For ROCF scores (visual perception and visual memory) raw scores were compared to age-appropriate international means. These comparisons suggest that the majority of

participants show below average performance on the ROCF Copy trial indicating some difficulty in the domain of visual perception. As mentioned, above, impairment in this cognitive supports the low scores seen in PIQ. The results for the Recall and Delay trials also indicated some difficulty for participants in this domain, especially with regard to the Delayed trails. When the HAART-naïve group was compared to the High SES group on all three trials, of Copy, Recall and Delay, although there was no statistically significant difference between the groups the HAART-naïve group did score lower on all trials. Again, this tends towards the idea that the HAART-naïve group are showing some subtle impairment in the domain of visual perception and visual memory. The effect sizes for these tests were generally low and therefore the lack of significant difference could be due to the small sample size of only 8 participants in each group.

In summary a general trend was that no matter which groups or normative scores the HAART-naïve children were being compared to, most of these children did show some difficulty in the cognitive domains of visual perception, memory, executive function, language, processing speed and motor function.

### **Hypothesis 3: Behavioural profiles**

The literature regarding behavioural and emotional functioning of HAART-naïve children specifically is limited; however the literature regarding asymptomatic HIV-infected children suggests that they do show more frequent behavioural problems (Noyzce et al, 2006). In fact, HIV-infected children in general do show more behavioural and emotional impairment (Brown & Lourie, 2000). In line with this, the hypothesis for behavioural functioning is that the HAART-naïve group will show significant behavioural difficulties. The majority of the parents or caregivers completing the CBCL questionnaires reported more problems than typically reported of children in the age range of 6-11 years old. The outcomes showed the HAART-naïve children were experiencing substantial problems at school. Many of the participants had repeated grades and needed special classes. This falls in line with the difficulties seen in specific cognitive domains, which could play a role in poor school performance. This could be one of the reasons why HAART-naïve children are struggling at school.

Internalizing behaviours were identified in these children, such as depression, anxiety, withdrawal and somatic complaints. These behaviours were reported more frequently than typically expected in typically developing children of this age range. Externalising behaviours such as cruel or aggressive behaviours were also present. This brings into light the

**Comment [A25]:** comment on externalising behaviours too

psychological effects of HIV infection in children as studies have shown high rates of emotional and behavioural problems in HIV-infected children in general. The literature reports the same pattern of impaired internalising behaviour for HIV-infected symptomatic children (Noyze, 2006). A crucial point here is that it is hard to establish the causal relationship between HIV-infected children and behaviour (Mellins et al., 2003). It is difficult to determine the social and environmental influences these children are experiencing. They are likely to be living in poverty stricken and resource-limited settings. In South Africa especially we need to be aware of the circumstances in which these children live and how this could confound their behavioural profiles. Further investigation should compare behavioural functioning to a healthy control group matched as closely as possible.

### **The bigger picture**

This study of the neuropsychological and behavioural profiles of HAART-naïve children is one of the first from a developing country such as South Africa. Despite the consistent trend of low IQ scores, PIQ and FSIQ scores were classified as being in the average range. In addition, the HAART-naïve group did show some degree of impairment in all the cognitive domains investigated. Despite being a study specific to South African children, results seem to be largely consistent with universal studies done on asymptomatic and HAART-naïve children. This may suggest that the translations and adaptations used in this study were fairly successful in estimating the extent of HIV impact on the CNS of HAART-naïve children.

These results, therefore, support an important finding that has been pertinent throughout this study, that despite a child being described as asymptomatic and HAART-naïve, HIV infection may still have an impact on certain aspects of the CNS functioning (De Baets, 2007). Why children remain asymptomatic or show slow progression of HIV-related symptoms is not clear, but this study supports a growing trend towards investigating general intellectual functioning as well functioning of specific cognitive domains in order to gain a more inclusive picture of HIV progression and its impact on neuropsychological functioning (Bagenda et al., 2006). This study has suggested that general intellectual functioning may be found to be spared; but without further investigation, the specific underlying impairments seen in specific cognitive domains would not be recognized. It is suggested that global measures such as the WASI (ref) may not be sensitive enough to reflect other deficits in specific cognitive domains (Martin et al., 2006). It is important that the neuropsychological tests administered are a true reflection of neuropsychological function investigated (Brickman, Cabo & Manlu, 2006).



This study has suggested that HAART-naïve children do experience underlying CNS impairments manifest in behavioural and cognitive functioning. It may be that children who are thought of as ‘slow progressors’ may in fact be more symptomatic than generally considered and further research in this field would be invaluable to South African child care of HAART-naïve, HIV-infected children. If we are able to identify asymptomatic children as experiencing cognitive and behavioural impairments in everyday life, this could aid in the management of these children. This would allow for intervention programmes that could help them at school as well as help their families cope with this type of HIV progression.

### **Limitations and Future Direction**

This study was part of a larger study and due to time constraints and limited resources it had a small sample size. I was also unable to test my own control group, matched on all of the necessary variables. I used archival data that came in the form of two groups, which often made interpreting results quite difficult. However, future research will allow the testing of a South African control group that are closely matched to the 12 participants used in this study. This will make the outcome of this study clearer. I also intend to increase my sample size as the small group affects the generalizability of my results. These issues can be quite easily addressed next year when this study continues. A further limitation was seen with the administration of the CBCL which was not translated into Xhosa. Consequently, many parents were unable to fill out this questionnaire themselves and only 7 full questionnaires were used in this study. Translation or allocation of time to help parents fill out of the CBCL will be considered in future.

### **CONCLUSION**

This study of HAART-naïve children is one of few studies that have been able to include a purely HAART-naïve group of children. Due to the control groups used, interpretation of results was difficult but it is reasonable to suggest that this group of HAART-naïve children did show general intellectual functioning in an average, although lower, range as well as impairments in the majority of cognitive domains investigated. Behaviour was also seen as impaired, supporting the original hypothesis, although it is important to take into consideration the impact of environmental and social factors on South African children. The essential finding, however, is that this research of neuropsychological and behavioural profiles of HAART-naïve children is important for better understanding of HIV infection and the impact it has on children who are seemingly healthy. There is a need for better

understanding and treatment of asymptomatic HIV-infected children. Future research in this area will help to determine how to appropriately manage these children as well as add to the ever growing research done in the field of paediatric HIV infection.

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## **Appendix A**

## Ethical Approval Form

UNIVERSITY OF CAPE TOWN



**Health Sciences Faculty**  
**Research Ethics Committee**  
 Room E52-24 Groote Schuur Hospital Old Main Building  
 Observatory 7925  
 Telephone [021] 406 6492 • Facsimile [021] 406 6411  
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24 January 2008

REC REF: 299/2005

**Prof H Zar**  
 School of Child and Adolescent Health  
 Paediatric Medicine  
 Red Cross Hospital

Dear Prof Zar

**PROJECT TITLE: EXTENDED FOLLOW-UP STUDY: LONG TERM STUDY OF 2 ISONIAZID (INH) PROPHYLACTIC REGIMENS WITH CONCOMITANT COTRIMOXAZOLE (CTX) IN HIV-INFECTED CHILDREN-IMPACT ON MORBIDITY, MORTALITY, BACTERIAL RESISTANCE AND INCIDENCE OF TUBERCULOSIS**

Thank you for your letter to the Research Ethics Committee dated 21<sup>st</sup> January 2008.

Thank you for the progress report. We **approve** your request to extend the follow-up period for further two years.

Please note that we have closed the study: "strategies for prevention of opportunistic infections in HIV – infected South African children: comparison of 2 trimethoprin-sulphamethaxazole (TMP-SMX) prophylaxis regimens with and without concomitant isoniazid- impact on morbidity, mortality, bacterial resistance and incidence of tuberculosis"-Ref 057/2002. There has been some confusion between the two studies (original trial and long-term follow-up) in our files.

This study is **approved** to continue until 30 January 2009.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

**Please quote the REC. REF in all your correspondence.**

Yours sincerely

**PROF M BLOCKMAN**  
**CHAIRPERSON, HSF HUMAN ETHICS**

**Appendix B**



Table 5.

*Qualitative Descriptions of NEPSY-II Scaled Scores*

Scaled Score	Classification
13 – 19	Above Expected Level
8 – 12	At Expected Level
6 – 7	Borderline
4 – 5	Below Expected Level
1 – 3	Well Below Expected Level

*Note.* Taken from *NEPSY-II* (Korkman, Kirk & Kemp, 2007).

**Appendix C**

Table 3.

*Grooved Pegboard dominant hand scores for HAART-naïve children compared to normative scores*

Participant	Sex	Age (years)	DH raw scores	Normative scores for	
				age M(SD)	Description
1	Male	10.5	152	83.00(36.50)	Below average (2)
2	Female	9.5	113	90.00(54.00)	Average
3	Female	8.3	48	38.00(10.40)	average
4	Female	11.5	126	79.00(17.00)	below average (3)
5	Female	10.11	162	84.00(18.10)	below average (5)
6	Male	11.1	91	76.00(18.10)	average
7	Male	8.2	51	38.00(9.02)	below average (2)
8	Female	10.6	94	84.00(18.10)	average
9	Male	6.11	65	58.00(33.90)	average
10	Male	11	67	76.00(18.10)	average

*Notes:* DH refers to dominant hand. Number in brackets (in the description) refers to number of standard deviations the raw score below the mean.

Table 4.

*Grooved Pegboard non -dominant hand scores for HAART-naïve children compared to normative scores*

Participant	Sex	Age (years)	NDH raw scores	Normative scores for age M(SD)	Description
1	Male	10.5	125	90.00(28.90)	below average (2)
2	Female	9.5	120	96(50.6)	average
3	Female	8.3	68	47(26.8)	average
4	Female	11.5	132	92(24.8)	below average (2)
5	Female	10.11	169	92(24.4)	below average (3)
6	Male	11.1	105	86(31)	average
7	Male	8.2	66	41(14.6)	below average (2)
8	Female	10.6	104	92(24.4)	average
9	Male	6.11	66	64(33.9)	average
10	Male	11	97	90(28.9)	average

*Notes:* NDH refers to non -dominant hand. Number in brackets (in the description) refers to number of standard deviations the raw score is below the mean.

## Appendix D

Table 6.

*ROCF Recall trial scores for HAART-naïve children compared to normative scores.*

Participant	Age	IR raw score	Normative scores	
			for age	Description
1	9.5	14	18.60(5.42)	Average
2	10.11	7.5	20.79(5.48)	Below average (3)
3	11.1	14	21.90(5.49)	Below Average (2)
4	8.2	18	27.43(5.18)	Below Average (2)
5	10.6	18.5	20.79(5.48)	Average
6	8.9	14.5	17.41(5.39)	Average
7	6.11	9.5	10.48(5.19)	Average
8	11	22	21.90(5.49)	Average

*Notes:* IR refers to Immediate Recall trial. Numbers in brackets (in description) refers to the number of standard deviations the raw score is below the mean

Table 7.

*ROCF Delay Recall trial scores for HAART-naïve children compared to normative scores.*

Participant	Age	DR raw score	Normative scores	
			for age	Description
1	9.5	11.00	18.56(5.49)	Below average (1)
2	10.11	4.50	20.74(5.51)	Below average (3)
3	11.1	17.50	21.80(5.44)	Average
4	8.2	17.50	15.93(5.33)	Average
5	10.6	11.00	20.74(5.51)	Below average (2)
6	8.9	10.50	17.36(5.43)	Below average (1)
7	6.11	10.00	10.06(4.77)	average
8	11	11.50	21.80(5.44)	Below Average (2)

*Notes:* DR refers to Delayed Recall trial. Numbers in brackets (in description) refers to the number of standard deviations the raw score is below the mean.

## Appendix E

Table 8.

*Qualitative Descriptions of WASI Scores*

IQ Scores	Subtest Scaled Score	Classification
130 and above	16 – 19	Very Superior
120 – 129	14 – 15	Superior
110 – 119	12 – 13	High Average
90 – 109	8 – 11	Average
80 – 89	6 – 7	Low Average
70 – 79	4 -5	Borderline
69 and below	1 – 3	Extremely Low

*Note.* Taken from *Wechsler Abbreviated Scale of Intelligence* (Wechsler, 1999)