

Investigating verbal/visual memory and the compound effect of negative life events on HIV-positive HAART treated children and adolescents.

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### **Abstract**

In South Africa, both the prevalence of children living with HIV and the number of children exposed to traumatic life events is alarming. HIV infection and significant exposure to trauma follows a particular pattern of neuropathology and results in impairments in a wide range of domains. This results in poor performance on neuropsychological assessments. The current study focused on one cognitive domain, memory, specifically visual and verbal memory. I investigated the compound effect of exposure to traumatic events and HIV-infection on performance on the Hopkins Verbal Learning Test (HVLT) and the Rey Complex Figure Test (RCFT). Between group differences were analyzed using one way ANOVAs and Mann-Whitney *U* tests, where applicable, for a sample of HIV-infected HAART treated children ( $n = 14$ ) and matched HIV-negative controls. Within the HIV-infected HAART treated sample, I compared those who were identified as having more exposure to negative life events to those who did not. Results showed that although there were some significant differences related to HIV status and memory, there were no significant differences for the HIV-infected HAART treated children in terms of the relationship between exposure to negative life events and memory.

*Keywords: HIV infection; HAART treated; experiencing negative life events; visual memory; verbal learning and memory*

Worldwide, approximately 3.4 million children are infected with the human immunodeficiency virus (HIV) (World Health Organisation (WHO), 2012). According to UNAIDS (2012), approximately 28% of children infected are on antiretroviral therapy (ARV). The majority (more than 90%) of those infected are in Sub-Saharan Africa, particularly in South Africa (Potterson et al., 2009).

There is consensus that HIV affects memory domains, both visual and verbal memory (Foley, Ettenhoffer, Wright & Hinkin, 2008; Hoare et al., 2012; Martin et al., 2006; Schiller, Foley, Burns, Seller & Golden, 2009). The severity of HIV infection correlates with the degree of impairment within the memory domain. HIV predominantly affects individuals from low socioeconomic backgrounds. Additionally, in low socioeconomic backgrounds, individuals may be exposed to a number of stressors. Significant exposure to traumatic events in childhood and adolescence has also been shown to result in cognitive impairments in memory, particularly if trauma is enduring (Aas et al., 2012; Navalta, Polcauri, Webster, Boghossian & Teicher 2006). Studies on the neuropsychological deficits of children infected with HIV are limited and are less established than studies on adult HIV-infected individuals (Hoare et al., 2012; Wachler- Felder & Golden, 2000). Therefore, there is need to explore the compound effect of HIV-infection and exposure to traumatic events on verbal and visual memory. In order to investigate this topic further it is important to consider the following sections:

### **HIV Infection and Memory**

**The neuropathology of HIV infection in the developing brain.** The period between childhood to adolescence is marked with many developmental changes due to maturation. Although the size of the brain does not grow noticeably, there is a re-organisation of regulatory systems and myelination due to increased white matter in frontal lobes and prefrontal cortex. These processes continue until early adulthood and are influenced by many factors such as genetics, and environmental factors including overall health. HIV-infection affects the developing brain and disrupts processes of maturation. Given the neuropathology of HIV-infection and the vulnerable nature of the developing brain, particularly in the basal ganglia and cerebral white matter, this is likely to result in impairment in complex mental processing (Casey, Getz & Galvan, 2008; Martin et al., 2006; Steinberg, 2005). HIV is a neurotrophic virus that causes devastating neurological impairments to the developing brain. The effects of the virus are further compounded by the opportunistic infections that occur as a consequence of the related

immune suppression (George et al., 2009). Brain imaging of HIV-infected children reveal that cerebral atrophy and ventriculomegaly (also referred to as hydrocephalus, a brain condition that follows when the lateral ventricles become dilated with cerebrospinal fluid) are common (George et al., 2009).

After the lungs, the brain is the second most affected organ by HIV (Masliah, De Teresa, Mallory & Hansen, 2000). HIV affects the brain by penetrating the blood-brain barrier and entering the central nervous system (CNS). This results in immune activation and production of viral and inflammatory proteins. The most severe form of HIV associated tissue damage occurs in the CNS, because of the absence of sufficient innate viral control mechanisms and immunities thus allowing for active viral replication (Buescher, Gross, Gendelman & Ikezu, 2007). These inflammatory responses secreted from the virus infected mononuclear phagocytes, ultimately leading to a decline in executive functioning, memory, psychomotor and attention domains. The virus itself results in neurodegeneration and causes significant neuronal death in the basal ganglia and hippocampal regions (Woods et al., 2009).

Studies have shown that HIV-positive individuals have significantly lower volumetric measures of total white matter and total grey matter, with fronto-striato-thalamo-cortical circuits in particular, severely affected. In addition, pattern of HIV-infection has been documented as subcortical in nature affecting the basal ganglia, thalamus, rostral brainstem nuclei and projections from these areas to the cortex and frontal lobes (Foley et al., 2008; Woods et al., 2009).

**HIV-infection and highly active antiretroviral therapy (HAART).** HAART refers to an aggressive treatment regime offered to HIV-infected individuals. It has been shown to achieve immune reconstruction and delay the advancement of opportunistic diseases caused by HIV by suppressing viral replication (Yao et al., 2013). Prior to the introduction of antiretroviral therapy (ART) in 1995, approximately 50% of HIV-positive children died before the age of two and those who lived until adolescence were typically ‘slow progressors’ (Brady et al., 2012; Newell et al., 2004). The advent of ART has resulted in less severe outcomes for HIV-populations, and in particular, with neurocognitive sequelae (Joska et al., 2012; Sacktor et al., 2006).

**HIV-infection, Clade C, and neurocognitive outcomes.** In South Africa and India, most HIV infections are of the clade-C strain. This particular strain has been linked with better neurocognitive outcomes compared to outcomes associated with the clade-B strain, a strain

predominantly found in areas such as North America and Europe. Preclinical studies have shown that a defect in the dicysteine motif of the clade-C tat protein may decrease the neurotoxic effects of the HIV infection (Mishra, Vetriavel, Siddappa, Ranga & Seth, 2008).

**The neural correlates of HIV infection and memory impairment.** HIV infection is known to affect frontal, subcortical, and mesial temporal regions of the brain that have been linked to memory function (Woods et al., 2009). During memory tasks, there is activation in the following areas: the inferior temporal cortex, the temporo-occipital junction, the left parietal gyrus and the left anterior cingulate gyrus: all of which are implicated in HIV disease progression (Smith & Jonides, 1997).

Research shows that the hippocampus, which plays a significant role in memory, is particularly vulnerable to HIV infection (Navalta et al., 2006; Stein, Koverola, Hanna, Torchia & McClarty, 1997). Memory is an umbrella concept; it is divided into subsystems based on the ideas of encoding, storage and retrieval. Optimum functioning of the memory system is highly contingent on successful functioning of other domains, namely executive functioning and attention (Zillmer, Spiers & Culbertson, 2008).

It has been established that poor performance for HIV-infected individuals on memory tests occurs as a result of damage in frontostriatal, subcortical circuits, and the hippocampus, as HIV infection progresses. Various memory domains, including both verbal and visual memory, are compromised (Grant, 2008; Hoare et al., 2012; Wright et al., 2011; York et al., 2001).

Verbal memory is a comprehensive term used to refer to the memory of language in different forms. Researchers frequently test this form of memory by asking participants or patients to attempt to recall lists of words or a story (Lezak, Howieson, Bigler & Tranel, 2012). Verbal memory impairment linked to HIV infection has persisted despite the advent of HAART in both children and adults (Wright et al., 2011). However, there are a very limited number of pediatric studies as compared to adult studies for this domain. In these studies, results show that HIV-positive participants perform significantly more poorly on the recall of verbal material when compared to normal controls. Results show that HIV-positive participants perform significantly more poorly on the recall of verbal material when compared to normal controls. For example, a study by Peavy et al. (1994) in adults explored the nature of verbal memory impairment across three groups namely: an HIV-positive asymptomatic, HIV-positive symptomatic, and a healthy control group. These researchers administered the California Verbal

Learning Test (CVLT) and found significant differences between the HIV-positive symptomatic group and the healthy control group. Peavy et al. (1994) postulated that this difference may be a result of impairment on measures of acquisition and retention. Compared to the control group, the HIV-infected symptomatic group was less likely to use a semantic clustering strategy to support recall of information therefore resulting in the poorer recall performance (Peavy et al., 1994). Semantic clustering is the inclination to sequentially recall semantically related words (Cofer, Bruce, & Reicher, 1966). Riedel et al. (1992) further demonstrated that the deficits seen in HIV-infection on verbal memory reflect spared recognition but decreased recall of verbal memory in a comparison between haemophiliacs seropositive for HIV and healthy adult controls. Comparison between HIV-positive (who were classified as either good or poor adherers to HAART) and healthy controls yielded significant differences on the CVLT (Wright et al., 2011). The good and poor adherers presented with encoding deficits when compared with the healthy controls. However, the poor adherence group displayed retrieval deficits when contrasted to the control group. Encoding difficulties mainly accounted for a substantial decrease in delayed recall in the good adherence group. Interestingly, encoding and retrieving deficits accounted for the diminished delayed recall in poor adherers compared to the normal controls (Wright et al., 2011).

Moreover, Blanchette et al. (2002) did not find significant differences on immediate or delayed story recall between school-age HIV positive (asymptomatic, mildly symptomatic and AIDS) and control siblings.

Visual memory is the process of recalling information a person has seen (Lezak et al, 2012). Research on visual memory and HIV-infection in adults and children has yielded conflicting results. For example, Riedal et al. (1992) found that the subcortical profile of memory deficits in HIV-infected adults showed a sparing of visual memory. However, in a study by Garrido, Fernández, Foltz, Rodríguez Castro, and Carrera Fernández (2012), researchers explored the cognitive performance of HIV-positive adults found that there were significant differences between the seropositive and seronegative groups on the immediate and delay trials of the RCFT. The majority of the seropositive participants were receiving some form of ART.

A similar discrepancy is reported among pediatric studies. For example, in one study conducted with school-age children, researchers found that there were no significant differences between HIV-infected children (all on a form of HAART treatment) and healthy controls, on the immediate and delayed recall trials of the Rey Complex Figure Test (RCFT) (Blanchette, Smith,

King, Fernandes-Penney & Read 2002). However, in other studies, visual memory is reportedly compromised in HIV-infected children. This is seen in HIV-infected participants who perform significantly poorer than healthy control participants on the RCFT. For example, research by Fundaro et al. (1998) on asymptomatic HIV-infected and seroreverted school-age children found significant differences between the groups on their recall of the RCFT. Researchers found that the HIV asymptomatic group performed poorer than the seroreverted group on the recall (immediate) of the RCFT. Similarly, Hoare et al. (2012) found that HIV- infected school-age children who received limited/no treatment in the form of HAART performed worse than healthy matched controls on the delayed recall trial of the RCFT. Further, Bisuacchi, Suppiej and Laverda (2000) in school-age children, found visuospatial and memory difficulties most evident in children with full-blown Acquired Immune Deficiency Syndrome (AIDS) compared to asymptomatic children who reported mainly executive functioning impairment in attention/working memory.

In summary, HIV infection can result in much impairment in memory amongst a host of other domains. Memory in HIV-infected individuals can be compromised in other ways too, however. For example, it has been established that prolonged and multiple experiences of trauma in childhood and subsequent adolescent years also negatively affects memory (Aas et al., 2012; Bremner, 1995). Children who are infected with HIV also experience trauma related to their health condition, as well as due to broader factors such as low socio-economic status, living conditions, nutrition, and access to education. In most cases, these stressors endure for a long period of time (Sternberg & Grigorenko, 2001). There is insufficient research which investigates the compound effect of exposure to trauma and HIV-infection on memory in children. The following section will explore how exposure to trauma affects the brain and subsequently memory.

### **Traumatic Events and Memory**

**Pathophysiology of trauma and the brain.** Trauma is defined as experiences that overwhelm the psychological and biological coping mechanisms of an individual. Furthermore, trauma may be any event that is deemed emotionally taxing (American Psychological Association (APA), 2000). Trauma refers to adverse events that result in distress as well as the distress itself (APA, 2000). Experiences that are likely to result in trauma in childhood and adolescence include neglect, maltreatment, abuse (sexual, emotional and physical), bereavement,

chronic sickness within with the family unit, lack of significant affection and love from friends and family, and poor performance in school (APA, 2000). Experiencing trauma in childhood and the subsequent adolescent years affects the brain in many ways because the mechanisms that mediate stress-responses are still developing (Rinne- Alber, van der Wee, Lamers- Winkelman & Vermeiran, 2013). The biological stress-response is a mechanism designed for normal adaptive responses to stressful life events. This enables physiological and behavioural changes within the body to ensure survival in the face of mild, temporary and controlled stressors (Bremner, 1999; Delima & Vimpani, 2011). On-going exposure to trauma activates a prolonged biological stress response (Delima & Vimpani, 2011). This biological stress-response is facilitated by the limbic-hypothalamic pituitary adrenal axis, a system that mediates the interaction of the peripheral body through the sympathetic and hormonal tissues that regulate the body's response to threats that are on-going (Delima & Vimpani, 2011).

During childhood, the brain is still developing and is vulnerable to the experience of on-going stress, which particularly affects brain areas such as the prefrontal cortex, hippocampus, and the corpus callosum (De Bellis, 2001; Delima & Vimpani, 2011; Rinne- Alber, van der Wee, Lamers- Winkelman & Vermeiran, 2013). Prolonged exposure to trauma, at this stage, can result in structural and functional brain changes in these areas (Delima & Vimpani, 2011). The hippocampus is one of the most vital brain regions and is affected by responses to stress hormones (released during traumatic experiences) and glucocorticoids (Bremner, 1999; Bremner et al., 1995; Zola-Morgan & Squire 1990). The hippocampus also mediates new learning and memory; therefore prolonged stress (or exposure to trauma) may damage it, leading to poor performance on neuropsychological tests in this domain (Bremner, 1999).

The development of the human brain is an intricate process that extends into early adulthood and can be strongly influenced by experiences. Differentiation of brain structures during development takes place through the formation of new neurons, dendrites and synapses, the careful 'pruning' of neurons, dendrites and synapses, and the myelination of neurons. These processes are influenced by neuronal hormones like the stress hormones, cortisol and catecholamines (Teicher, 2002; Teicher, Andersen, Polcari, Anderson & Navalta, 2002). Research has shown that structure and functioning of the developing brain are highly vulnerable to the effects of adversity, particularly in certain critical time windows especially during childhood (Teicher, 2002; Teicher et al., 2002).



The effects of trauma are organised across four main categories namely: cognitive, affective, behavioural and somatic- physiological (Armsworth & Holaday, 1993). This study, focused mainly on the cognitive category, and more specifically, the memory domain. A few studies have compared the different cognitive profiles of school aged children who have experienced traumatic events and those that have not (Bücker et al., 2012). A few studies have investigated cognitive function in mistreated, abused, or neglected children and found impairments in executive function (memory) and verbal ability, as well as poorer school performance (Pears & Fisher, 2005). Bücker et al. (2012) and explored the effects of childhood traumatic events on adults and found results consistent with the hypothesis that childhood traumatic events are linked with poor cognitive functioning in attention, immediate verbal memory and working memory.

**Trauma and memory.** Childhood trauma has been linked with poorer outcomes across cognitive domains in adult patients with schizophrenia and bipolar disorders (Rinne- Alber, van der Wee, Lamers- Winkelman & Vermeiran, 2013). Traumatic experiences significantly affect brain regions especially those that are important to memory function, such as the hippocampus and amygdala (Bremner et al., 1995). Findings from neuroimaging studies show that participants who have been exposed to traumatic life events and subsequently develop posttraumatic stress disorder (PTSD) have smaller hippocampi, when measured in terms of volume. This reduction in volume explains the deficits shown in neuropsychological tests of memory function (Bremner, 1999). Similarly, Bücker et al. (2012) found that specific impairment in cognitive functions that have been linked with the hippocampus and prefrontal cortex, areas that are the most vulnerable to prolonged trauma effects and have been shown to be affected in previous studies of childhood trauma (Etain et al., 2008). These findings support the view that traumatic life events interferes with brain development that results in long lasting changes in the development and functionality (Aas et al., 2012). A study by Clarke et al. (2012) that explored the effect of early life stress (ELS) in adults infected with HIV and healthy controls with ELS. The researchers use the Early Life Stress Questionnaire which explored experiencing adverse 17 life events before the age of 18 years and a healthy control group. Adverse life events included family conflict, abuse, bullying, and neglect. Results showed that HIV-infection and high ELS exposure have combined effects group scores on the psychomotor/processing, although no there were significant results for memory functioning. Research by Clarke et al. (2012) offers strong evidence that high ELS

contributes significantly to structural brain and neurocognitive anomalies in HIV-positive participants.

In the visual memory domain, for example, researchers report significant difference in the results of participants who had been exposed to trauma and developed PTSD and those did not develop PTSD with regards to visual memory tasks. Participants who had been exposed to trauma and developed PTSD performed poorly on the Rey complex Figure Test (RCFT) than healthy controls (Bremner et al., 2003; Yasik et al., 2007). With regards to verbal memory, there is limited published research on the effects of traumatic events in childhood and subsequent adolescence on verbal memory.

There have been no studies to my knowledge conducted on visual and verbal memory in relation to experiencing negative life events with HIV-infected children and adolescents. Most research has been done in children with a history of trauma in childhood and has explored their subsequent impairments (Etain et al., 2008; Bückner et al. 2012; Rinne- Alber et al., 2013). Clarke et al. (2012) conducted a retrospective study on HIV-positive adults who had experienced early adverse life events and found that high ELS contributes profoundly to structural brain and neurocognitive anomalies in HIV-positive participants.

### **HIV-Infection and Childhood Stressful Life Events - What are the Implications?**

Research has shown that neuropsychological impairment and traumatic life events are common among individuals with HIV-infection (Trapanier et al., 2003; Pence et al, 2012). There are significant differences on neuropsychological tests between patients who report childhood trauma and are HIV-infected compared to those who are HIV-negative and not exposed to trauma on measures of executive functioning, attention and memory abilities (Pence et al., 2012).

**Rationale.** It is evident that both HIV and childhood trauma are significant contributors to memory impairment in children. This is evident in the domains of verbal and visual memory. There is very little research on exposure to traumatic events and its relation to memory within HIV positive individuals, and children specifically, in South Africa and globally. The current study is important because it does not take a retrospective approach utilized in (Clarke et al., 2012). This study will explore participants current accounts of traumatic life events they experience. In addition, Clarke et al., (2012) focused on adult and this study focuses on a much younger population (children and adolescents. It is of particular interest and importance that research of this type is conducted in South Africa because of the high prevalence of both these

factors in the country. The compound effects associated HIV infection and exposure to trauma have far reaching costs on a child's performance and schooling outcomes; hence the need for this research.

**Specific aims and hypotheses.** The current study is nested within a larger research project examining the integrity of neural pathways, and associated neuropsychological, neuropsychiatric, and behavioural characteristics, of vertically-infected HIV-positive, HAART-naïve children, in a cohort of children in Cape Town, South Africa. The current study looked at whether significant exposure to childhood trauma exacerbated performance in neuropsychological tests of visual and verbal memory in HIV-infected children. This study had three main aims:

1. To investigate the visual and verbal memory functioning in HIV-positive HAART-treated children and adolescents compared to HIV-negative controls
2. To investigate the levels of traumatic life events experienced by both HIV-positive and HIV-negative children and adolescents who are socioeconomically and demographically matched.
3. And lastly to explore the impairment caused by the compound effect of HIV-infection and trauma exposure on tests of verbal and visual memory in a sample of HIV-positive HAART-treated children and adolescents who report more life events vs. those who report fewer negative life events

Given these aims, the following hypotheses were tested:

*Hypothesis 1:* HIV-infected children and adolescents will perform more poorly than HIV-negative controls on neuropsychological tests of visual and verbal memory.

*Hypothesis 2:* There would be significant difference in traumatic events reported between HIV-positive and HIV-negative participants.

*Hypothesis 3:* HIV-positive children and adolescents who have been exposed to substantial traumatic events and are HIV-positive will perform significantly poorer on neuropsychological tests of visual and verbal memory compared to HIV positive children and adolescents who have not been exposed to significant traumatic events.

## **Methods**

## **Research Design and Setting**

The current study employed a quasi-experimental, quantitative, and cross-sectional design. There were two groups in the study: a HIV-positive and a matched HIV-negative group, with both groups reporting some degree of exposure to negative life events.

The independent variables were HIV status and exposure to negative life events. Experiencing significant negative life events in this study was defined as being subjected to events that are emotionally taxing and result in distress including abuse (sexual, physical emotional), maltreatment, bereavement, chronic sickness within with the family unit, lack of significant affection and love from friends and family, and poor performance in school (APA, 2000). The dependent variables were the achieved by participants on the neuropsychological tests of verbal and visual memory. All testing procedures were carried out at the Red Cross War Memorial Children's Hospital (RXH) and the Department of Psychiatry and Mental Health at University of Cape Town.

## **Participants**

As part of the larger study, HIV-infected participants were recruited via referrals from the RXH, the Infectious Disease Clinic at Groote Schuur Hospital (GSH), and HIV clinics in disadvantaged communities, including Nyanga, Khayelitsha, and Mitchells Plain. The control group participants were recruited from schools within the same disadvantaged communities such as Langa, Phillipi, Mfuleni, and Gugulethu and via word-of-mouth.

The sample comprised of 14 HIV-infected children and adolescents (aged 6-17 years) and 14 HIV-negative children and participants. Care was taken to ensure that both groups were matched on age, sex, race, handedness, socioeconomic bracket, education, and home language as far as possible.

The total number of participants enrolled in the larger study between June 2010 and June 2013 was 120 ( $n = 86$  HIV-positive participants;  $n = 34$  HIV-negative participants). I excluded 72 participants ( $n = 52$  HIV-positive participants;  $n = 20$  HIV-negative participants) from the original dataset because they did not complete the traumatic life events measure. An additional 10 participants were excluded from this project because they had HIV and encephalopathy or they were HAART naïve (all HIV-infected participants for this study were on HAART treatment). The remaining 38 participants included 14 HIV-positive HAART-treated

participants. These participants were carefully matched to 14 HIV-negative participants for investigation.

**Inclusion criteria.** In terms of the HIV-infected group, children who were vertically infected, HIV-positive and were currently medically stable were included for the current study. HIV-infected participants were selected if there were taking HAART treatment for at least six weeks prior to the commencement of their assessment. Additionally, HIV-infected children who had been exposed to negative life events were recruited. In terms of the HIV-negative group, children were enrolled in the study if they were healthy and met the distinct developmental milestones for their age. For both groups (HIV-infected and the matched control group), children were recruited for the study if they between the age of 6 and 17 and if they were English-, Xhosa- or Afrikaans-speaking.

**Exclusion criteria.** In terms of HIV-infected group, participants who were physically or medically ill were not considered for participation in the study. However, some participants were considered only after their immediate medical needs were taken care of and they are deemed stable. Children who were HIV-positive and HAART naïve or had encephalopathy were not selected for this study. Participants who were HIV-positive and had any other chronic illnesses such as cancer or diabetes were also not included. Furthermore, HIV- positive participants who had developmental impairments not related to HIV-status and were not able to speak English, Afrikaans, or IsiXhosa were excluded from the study. With regards to the HIV-negative group, participants who presented with developmental impairments and fell outside the target age range (between 6 and 17) were not deemed eligible for the study. For both groups, children and adolescents were excluded if they had a current or history of drug and alcohol abuse. Exclusion criteria also included history of traumatic brain injury in which the participant lost consciousness for more than 30 minutes.

## **Measures**

Neuropsychological testing is a well-established and non-invasive technique for detecting the effect of HIV infection on the CNS (Gupta et al., 2007; Rourke, Halman, & Bassel, 1999). Verbal and visual memory, the outcome variables for this study, were assessed using the Hopkins Verbal Learning Test (HVLT) and Rey Osterrieth Complex Figure (ROCF), respectively.

**Socio-Demographic Questionnaire.** This questionnaire was developed by the research team of the larger study. It recorded information about race, language, age, handedness, education, medical history and living conditions (including location, size of house or dwelling and the number of people residing in it) of the participants recruited into the study. Furthermore, this questionnaire noted information about the participants' current grade and if they had repeated a grade. A copy of this questionnaire is included (see Appendix A).

***The Hopkins Verbal Learning Test- Revised (HVLTR)***. The HVLTR was used to briefly assess the participant's verbal learning and memory. This instrument is used in both clinical and research settings (Strauss, Sherman & Spreen, 2006). The test was designed by Brandt and Benedict (2001) and typically comprises of six alternate forms each consisting of 12 nouns with four words drawn from different semantic categories. These semantic categories include four-legged animals, precious stones and human dwellings. The categories differ across the six forms (Strauss et al., 2006). In this study the precious stone section was replaced with items of clothing.

The test includes three learning trials (immediate recall), a delayed recall trial and a yes/no recognition trial. First, the examiner reads the word list with a 2-second interval between each word and asks the participant to verbally repeat the words in any order. Second, in a delayed recall trial (without warning after a delay of 20 – 25 minutes), the examiner asks the test-taker if they can verbally recall any words from the list in any order. For the learning trial, the examiner reads a list of words over three trials and asks the participant to verbally repeat the words immediately. The participant's total learning recall is calculated by summing a participant's performance across the three trials. In all the different stages of the testing the examiner does not provide cues to aid the test-takers recall. Lastly, the test includes a yes/ no delayed recognition trial. Here the examiner reads a word list consisting of 12 non-target additional words (these have been added to the original target words) the non-target words are drawn from a similar semantic category as the target words). The examiner asks the participant to state whether a word was on the list or not. Reliability and validity (construct and discriminant) of this test was established as measure of verbal memory in the clinical and research setting (Woods et al., 2005). Studies that have used the HVLTR as a measure of verbal learning and memory have shown that HIV-positive, clade B-infected adults perform

significantly more poorly compared to HIV-negative on the free recall trials (total learning) and on the delayed recall trial (Carey et al., 2004; Maki et al., 2009; Woods et al., 2005).

***The Rey Osterrieth Complex Figure Test (ROCF)***. It is widely used to assess visual-spatial constructional ability and visual memory (Lezak, Howieson, Bigler & Tranel, 2012; Strauss et al., 2006). It is widely used in clinical and research settings. The complex figure was developed by André Rey in 1941 and later standardized by Paul-Alexandre Osterrieth in 1944. The administration of this test is over three stages but for the purpose of this study only the 2<sup>nd</sup> and 3<sup>rd</sup> trials are important as they tap into visual memory. First, the examiner reveals the figure to the participant and instructs them to copy it on a blank sheet of paper for a minimum of 2.5 minutes and a maximum of 5 minutes. Second, after 3 minutes the examiner asks the test-taker to draw the figure from memory. There is no time limit on this trial. Lastly, after a delay of 30 minutes, participants are asked to draw the figure from memory. Again, there is no time limit on this trial. During each of the trials the examiner does not cue the test-taker. This measure has been deemed suitable for use with people aged 6-89 years. Reliability (intrarater and interrater) of the ROCF has been established (Lieberman, Stewart, Seines & Gordon, 1994). The ROCF has been used successfully in Canada (Blanchette et al., 2002), Italy (Fundaro et al., 1998), as well as South Africa with HIV-infected children (Hoare et al., 2012). Reliability and validity of these tests has been established (Bruce & Echemendia, 2003; Strauss et al., 2006).

***Adolescent Life Events Questionnaire (ALEQ)***. The ALEQ, developed by Hankin and Abramson (2002), consists of 70 items that assess exposure to traumatic or stressful life events in different areas of the participants' life in the last three months. The ALEQ assesses negative life events across four categories, namely: Family and Parents, Romantic Relationships, School and Classes as well as Friends and Social Activities. Participants are required to answer either yes/no on the questionnaire and to add any other events that may have been traumatic for them at the end of the checklist (in the event that the statements in the questionnaire were not exhaustive) (see Appendix B). According to Hankin & Abramson, (2002), the internal consistency of the ALEQ is .94 and the test-retest reliability over two weeks was .65. Convergent validity of the ALEQ was established with other measures assessing the varying levels of exposure to potentially traumatic events. The ALEQ was tested and was found to significantly correlate with other recognized measures of the traumatic events, namely, the Traumatic Life Events Questionnaire (TLEQ) (Gray, Litz, Hsu, & Lombardo, 2004). The ALEQ is typically used to

assess the various negative life events adolescents (between 13-18 years) encounter. Given that the majority of participants in this sample were below this age, statements 30 through to 40 from the Romantic Relationships section of the questionnaire were removed. This was done because this cohort was not expected to be in Romantic Relationships and, therefore the ALEQ was out of 60. The ALEQ has been used predominantly in American populations to predict depressive symptoms (Calloway, 2010; Young, 2012). There is no report of its use in a South African context. With regards to a cut off score, the ALEQ is not clear, however. Young (2010) reports 6 or more events to predict depressive symptoms in adolescents. The more negative life events reported has been correlated with greater depressive symptoms (Calloway, 2010; Young, 2012).

### **Procedure**

All participants completed a full medical history screening and laboratory blood tests as part of their routine medical examination at a clinic visited regularly. As most participants were recruited via referrals from hospitals, community clinics and schools, they are informed via telephone of the study and were asked whether they wanted to participate. Upon confirmation of participation, a date for testing was set. Participants were collected from the nearest clinic or police station in the area they resided and brought to either RXH or the Department of Psychiatry and Mental health. Upon arrival, participants were welcomed and given consent and assent forms. A qualified interpreter was present to explain the consent and assent form to the participants, when required.

After informed consent and assent was arranged (see Appendix B and C), the child was taken to a separate room for testing and parents were allowed to remain in the social worker's office. Either a social worker or an examiner (both competent and trained in neuropsychological testing) was always present during different phases of the testing process. The testing was done in the participants' preferred language. The examiner was trained in neuropsychological testing and was proficient in the participants' home language

Each child was assessed individually in a private, quiet room, free of any distractions, provided at RXH or the Department of Psychiatry and Mental Health, UCT. The examiner established rapport with each child before testing commenced. The overall protocol of the study involved the administration of a comprehensive neuropsychological testing battery. The



neuropsychological battery assessed many domains. However, for the purpose of this study only memory specifically the visual and verbal memory was analyzed.

Given the exhausting nature of the neuropsychological battery, a 10-15 minute break (where refreshments were provided) was given to the participant whenever necessary. A 30-45 minute lunch break was allocated at mid-day (refreshments were served). If the participant felt that he/she was unable to complete the session in one day, testing was discontinued for that particular day and the participant was given an appointment to return at another time. For the current project, all participants completed their neuropsychological test battery in one day.

### **Ethical Considerations**

The larger study was granted ethical approval by the Human Research Ethics Committee of the Faculty of Health Sciences at UCT (HREC REF: 406/2010). The study was conducted according to Medical Research Council guidelines on good clinical practice (2003) as well as the Declaration of Helsinki Guidelines (Seoul, 2008), which provide detailed guidelines that relate to the ethical conduct of studies involving human subjects. The current study followed the University of Cape Town's (UCT) guidelines for ethical research with human subjects.

**Consent, voluntary participation, and confidentiality.** Consent and assent forms were provided in English for the HIV-positive and negative participants (See Appendix C & D). Provision was made for an interpreter (proficient in IsiXhosa, Afrikaans and English) to explain the informed consent and assent forms to the participants. Written informed consent and assent forms, seeking permission for both the child and parent/guardian to participate in the study was obtained from each child and parent/guardian before enrolling them in the study. Participants were reminded that their participation in the study was entirely voluntary and that they were allowed to withdraw their participation at any time. If participants withdrew from the study, they were not discriminated against in any way and care was taken to ensure that their access of future medical care or research participation would not be compromised. Participants were assured that all the information collected during the testing procedures would be kept confidential and no actual names would be used if any part of the study was published.

In the interest of confidentiality, each child was assigned a non-identifiable assessment number and any information linked to their identity was password and lock protected. Participants and parents/caregivers were debriefed and thanked separately following

participation in the study. Each parent was given the option of receiving feedback in writing or via telephone with regards to their child's performance.

**Risks and benefits for participants.** There were no real risks to participants involved in the completed study. There was the possibility that some children would become slightly fatigued during the assessment. However, they were encouraged to take breaks if they needed to and would receive refreshments during those breaks.

The primary benefit to both the child and the parent is that information collected will be used to assess the degree of impairment as well spared abilities on a developmental and neuropsychological level in the children and adolescents. Parents/guardians, who felt that their child needed further intervention, were referred to the relevant health care department for further clinical assessment and intervention initiation. Each parent/guardian was reimbursed with R50 cash for travelling and a R50 Pick 'n Pay gift voucher for meal costs. Children were given with a T-shirt and certificate upon completion of the neuropsychological test battery (See appendix E).

**Debriefing.** All participants were debriefed and thanked for their contribution at the end of their participation in the study. Parents/guardians received a take-home information sheet containing background information related to the study. In addition to this, parents were given the opportunity to ask questions and express any opinions with regard to the study. Lastly, they were given contact details of the primary investigator (Dr. Jackie Hoare) in case they had any further questions about the study.

### **Statistical Analysis**

The Statistical Package for the Social Sciences™ (SPSS), Version 21 was used to analyze the data. Detailed descriptive statistics of the data was computed to gain a better understanding of the central tendency, variation and distribution (Field, 2009). Preliminary tests were explored to assess whether assumptions of parametric tests were upheld or not, namely normality and homogeneity of variance (Field, 2009).

For the main analysis, I used between-group comparisons to compare the performances of the HIV-positive and HIV-negative participants, and HIV-positive individuals with exposure to trauma vs. those without exposure to trauma, on tests of verbal and visual memory. I used either one way analysis of variance (ANOVA) or a Mann-Whitney U test depending on whether parametric test assumptions were violated or not. This was done for each of the tests trials. For between group evaluations of categorical variables, a chi-square test of contingency was used.

However, I used Fisher's exact test for these analyses where at least 50% of cells had expected counts of less than 5.

A significance level of  $\alpha < 0.05$  was set unless stated otherwise. I calculated the appropriate effect size estimates for all between-group comparisons. Effect sizes were understood as being small (0.20), medium (0.50), or large (0.80), according to convention (Cohen, 1988).

## Results

### Sample Characteristics HIV-positive vs. HIV-negative participants.

Table 1 shows the sociodemographic characteristics of the HIV-positive and HIV-negative groups under investigation. The groups were matched on age, race, gender, handedness and socioeconomic bracket as far as possible. The table also shows that there were no significant differences between groups in terms of demographic information provided.

Table 1

*Sociodemographic characteristics of the current sample (N = 28)*

| Variable   | Group                    |                          | F/ X <sup>2</sup> | p    | ESE               |
|--|--------------------------|--------------------------|-------------------|------|-------------------|
|  | HIV-positive<br>(n = 14) | HIV-negative<br>(n = 14) |                   |      |                   |
| Age  | 10.07 (2.58)             | 9.86 (2.90)              | .045              | .83  | 0.08 <sup>a</sup> |
| Repeated Grade (yes/no)  | 8:5                      | 5:9                      | 1.29              | .44  |                   |
| Sex (female/male)  | 7:7                      | 8:6                      | .144              | .50  |                   |
| Handedness (left/right)  | 2:12                     | 1:13                     | .373              | 1.00 |                   |
| Home Language<br>(IsiXhosa/Afrikaans/English)                  | 13:0:1                   | 12:2:0                   | 2.60              | .48  |                   |
| Race (Black/Coloured)  | 13:1                     | 12:2                     | .373              | .10  |                   |
| Socio-economic bracket<br>R0-35 000/R36-50 000/ R51-<br>80 000 | 10:3:1                   | 11:3:0                   | .491              | .49  |                   |

*Note.* For the variable *Age*, means are presented with standard deviations in parentheses. ESE = Effect size estimate. <sup>a</sup>Effect size estimate using Cohen's *d*. \**p* < .05.

### A comparison of verbal and visual memory in HIV-positive and HIV-negative participants.

Tables 2 and 3 show the results of a series of one-way ANOVAs and Mann-Whitney *U* tests, relevant to the *hypothesis 1* which predicted that HIV-positive participants would perform significantly poorer than matched healthy controls on verbal and visual memory. In terms of verbal memory, the hypothesis largely not confirmed. There were no significant between-group differences on the delayed and recognition trials of the HVLT and these comparisons were associated with a very small effect size. Table 2 shows that there were no significant between-group differences on the delayed and recognition trials of the HVLT and these comparisons were associated with a very small effect size. There was, however, a significant between-group

difference for the total learning score of the HVLТ. There was a medium effect size for this result. With regard to visual memory, the *a priori* predictions were not confirmed on both the immediate and delayed recall trails of the RCFT (See table 3). Both trial comparisons were associated with a small effect size.

Table 2

*Between-Group Comparisons: Verbal Memory (N =28)*

| HVLТ outcome variable                   | Group                             |                                    | <i>F/ U</i> | <i>p</i> | ESE   |
|---|-----------------------------------|------------------------------------|-------------|----------|-------|
|   | HIV- positive<br>( <i>n</i> = 14) | HIV - negative<br>( <i>n</i> = 14) |             |          |       |
| Learning / Encoding<br>Immediate Recall | -.72 (.90)                        | -.03 (.95)                         | 6.02*       | .01      | 0.43  |
| Memory / Retrieval<br>Delayed Recall    | -.29 (.009)                       | -.28 (.009)                        | 3.71*       | .06      | 0.00  |
| Recognition trial<br>Recognition        | -.28 (.01)                        | -.28 (.002)                        | 71.5**      | .100     | -0.00 |

*Note.* In the columns, means are presented with standard deviations in parentheses. HVLТ-R = Hopkins Verbal Learning Test-Revised ESE = effect size estimate; in this case, Cohen's *d*. The *p*-values listed are one-tailed in all cases since there were a priori predictions of significant between-group differences (i.e., measure of verbal memory) \*Estimate of effect size using Cohen's *d*. \* is to denote One way ANOVA *F* statistic and \*\* Mann-Whitney *U* statistic. *Z* scores were used in these analyses.

Table 3

*Between-Group Comparisons: Visual Memory (N =28)*

| RCF outcome variable                  | Group                             |                                  | <i>F/ U</i> | <i>p</i> | ESE  |
|---------------------------------------|-----------------------------------|----------------------------------|-------------|----------|------|
|                                       | HIV- positive<br>( <i>n</i> = 14) | HIV-negative<br>( <i>n</i> = 14) |             |          |      |
| Memory / Encoding<br>Immediate Recall | -1.82 (1.19)                      | -1.85 (1.06)                     | .004*       | .47      | 0.10 |
| Memory /Retrieval<br>Delayed Recall   | -1.91 (.90)                       | -1.70 (.95)                      | .339*       | .28      | 0.10 |

*Note.* In the columns, means are presented with standard deviations in parentheses. RCF = Rey Complex Figure Test. ESE = effect size estimate; in this case, Cohen's *d*. The *p*-values listed are one-tailed in all cases since there were a priori predictions of significant between-group differences (i.e., measure of visual memory). \* is to denote One way ANOVA *F* statistic and \*\* Mann-Whitney *U* statistic. *T* scores were used in this comparison.

## Experiences of Traumatic Events between HIV-positive and HIV-negative Participants

For *Hypothesis 2* it was predicted that there would be significant difference in negative life events reported by both the HIV-positive and the HIV-negative group, with the HIV-positive group reporting more negative life events than the HIV-negative group. Table 4 shows that results of these analyses. This hypothesis was only confirmed for the School and Classes category. The majority of the comparisons had small effect sizes except the School and Classes category, which was associated with a medium effect size.

Table 4  
*Between-Group Comparisons: Exposure to Trauma (N =22)*

| ALEQ CATEGORIES               | Group                            |                                 | <i>F / U</i> | <i>p</i> | ESE   |
|-------------------------------|----------------------------------|---------------------------------|--------------|----------|-------|
|                               | HIV-positive<br>( <i>n</i> = 13) | HIV-negative<br>( <i>n</i> = 9) |              |          |       |
| Family and Parents            | 3.31 (2.95)                      | 3.56 (1.50)                     | 50.50        | .30      | -0.15 |
| School and Classes            | 2.85 (1.95)                      | 1.56 (1.33)                     | 2.95*        | .05      | 0.35  |
| Friends and Social Activities | 2.85 (1.51)                      | 2.89 (1.76)                     | .004*        | .95      | 0.04  |
| ALEQ Total                    | 9.00 (4.89)                      | 8.11 (2.26)                     | 55.50        | .42      | -0.05 |

*Note.* In the columns, means are presented with standard deviations in parentheses. ESE = effect size estimate; in this case, Cohen's *d*. The *p*-values listed are one-tailed in all cases since there were a priori predictions of significant between-group differences (i.e., measures of verbal and visual memory). The romantic relationships section was excluded from the analysis as majority of children were not involved in romantic relationships. (Data was analysed for 13 HIV+ and 9 HIV- due to an administration error). \* is to denote One way ANOVA *F* statistic and \*\* Mann-Whitney *U* Test statistic.

**Sample characteristics: HIV-positive participants exposed to negative life events vs. those who were not.** Table 5 shows the sociodemographic information for the HIV-positive participants who experienced trauma in terms of negative life events and those that did not. The table shows that there were no significant differences in the demographics of the participants in this analysis.

Table 5  
*Sociodemographic characteristics of the current sample (N = 13)*

| Variable  | HIV positive          |                      | F/ X <sup>2</sup> | p    | ESE               |
|---|-----------------------|----------------------|-------------------|------|-------------------|
|   | > 6 events<br>(n = 8) | ≤ 6 event<br>(n = 5) |                   |      |                   |
| Age   | 9.50 (2.07)           | 11.40 (3.20)         | 1.71              | .21  | 0.36 <sup>a</sup> |
| Repeated Grade (yes/no) <sup>c</sup>                                    | 4:4                   | 4:1                  |                   | .56  |                   |
| Sex (female/male) <sup>c</sup>  | 5:8                   | 2:3                  |                   | .59  |                   |
| Handedness (left/right) <sup>c</sup>                                    | 1:7                   | 1:4                  |                   | 1.00 |                   |
| Home Language <sup>c</sup><br>(IsiXhosa/Afrikaans/English) <sup>c</sup> | 8:0:0                 | 4:0:1                |                   | 1.00 |                   |
| Race (Black/Coloured) <sup>c</sup>                                      | 8:0                   | 4:1                  |                   | .38  |                   |
| Socio-economic bracket<br>R0-35 000/R36-50 000/ R51-<br>80 000          | 6:2:0                 | 3:1:1                | 1.73              | .70  |                   |

*Note.* For the variable *Age* is presented with standard deviations in parentheses. ESE = Effect size estimate. <sup>a</sup>Estimate of effect size using Cohen's *d*. *p* < .05. (Data was analysed using 8 participants for the trauma group and 5 for the non-trauma group from the number of negative life events participants reported on the ALEQ). <sup>c</sup> denotes analyses where Fisher's Exact Test value was not reported.

### **A comparison of verbal and visual memory in HIV-positive participants with or without exposure to negative life events.**

*Hypothesis 3* predicted that children and adolescents who were HIV-positive and had been exposed to more traumatic life events would perform poorer on verbal and visual memory tests compared to those that had experienced fewer significant traumatic life events although infected with HIV. Table 6 below, shows the results for these comparisons. For verbal memory, the prediction was not confirmed as there were no significant results across three trials of the HVLT. The total learning and recognition trial were associated with a medium effect size and the recognition trial with a very small effect size. With regards to visual memory, again the hypothesis was not confirmed. There were no significant differences between the groups on the two trials of the RCFT. There were medium effect sizes associated with these comparisons.

Table 6  
*Between-Group Comparisons: Verbal and Visual Memory (N =28)*

|                      | HIV positive                  |                               | <i>F/U</i> | <i>p</i> | ESE  |
|----------------------|-------------------------------|-------------------------------|------------|----------|------|
|                      | > 6 events<br>( <i>n</i> = 8) | ≤ 6 events<br>( <i>n</i> = 5) |            |          |      |
| Immediate            |                               |                               |            |          |      |
| Learning / Encoding  |                               |                               |            |          |      |
| Immediate Recall     | -.46 (.94)                    | -1.15 (.85)                   | 1.72*      | .10      | 0.36 |
| Memory / Retrieval   |                               |                               |            |          |      |
| Delayed Recall       | -.28 (.010)                   | -.29 (.008)                   | 2.28*      | .07      | 0.00 |
| Recognition trial    |                               |                               |            |          |      |
| Recognition          | -.28 (.004)                   | -.29 (.022)                   | 20.00**    | .47      | 0.00 |
| RCF outcome variable |                               |                               |            |          |      |
| Memory / Encoding    |                               |                               |            |          |      |
| 3 Minute Recall Copy | -1.59 (.95)                   | -2.44 (1.45)                  | 1.63*      | .11      | 0.34 |
| Memory /Retrieval    |                               |                               |            |          |      |
| 30 Minute Delay Copy | -1.74 (.79)                   | -2.46 (.77)                   | 2.57*      | .06      | 0.42 |

*Note.* In the columns, means are presented with standard deviations in parentheses. HVLTR = Hopkins Verbal Learning Test-Revised and RCF = Rey Complex Figure Test. ESE = effect size estimate; in this case, Cohen's *d*. The *p*-values listed are one-tailed in all cases since there were a priori predictions of significance between-group differences (i.e., measures of verbal and visual memory). \* denotes One way ANOVA *F* statistic and \*\* *U* statistic. *Z* scores were used for the HVLTR comparison and *T* scores for RCFT.

### Discussion

The main purpose of this study was to examine the compound effect of HIV-infection and exposure to negative life event on verbal and visual memory between HIV-positive HAART treated and healthy matched controls and within an HIV-positive group of participant.

#### Effect of HIV infection on Verbal and Visual Memory

For *Hypothesis 1*, it was predicted that HIV-infected participants would perform more poorly on verbal and visual memory trials compared to HIV-negative participants.



For verbal memory the hypothesis in this instance was not supported except for the immediate recall trial (total learning) of the HVLVT. There was a significant between-group result for the immediate recall trial of the HVLVT. The HIV-positive participants perform poorer compared to their HIV-negative counterparts for this component of the HVLVT. This finding suggests that the HIV-positive group did not learn as many words or improved improved their learning at a slower rate than (over the total learning trial) the HIV-negative participants. Research has shown that attention and processing speed is often implicated in HIV-positive individuals and this may result in slower performance or learning rate on this neuropsychological measure (Sacktor et al., 2006). This explanation is reasonable for this study because on average the HIV-positive participants learn fewer words across the three learning trials compared to the HIV-negative group (Heaton et al., 1995; Tozzi et al., 2005).

However, there were no significant difference for the delayed recall and recognition trial of the HVLVT. This result is consistent with the literature, although factors such as attention and processing speed could explain this finding.

In terms of visual memory, I did not find any significant results in both trials of the RCFT. Research on visual memory in HIV-positive participants has achieved conflicting results. Results obtained in this study are consistent with literature from North America. For example, a pediatric study by Blanchette et al. (2002) in Canada did not find significant differences between on visual memory between HIV-positive HAART treated and healthy controls. Conversely, Fundaro et al. (1998) and Hoare et al. (2012) found significant differences on visual memory between school-age HIV-positive children who were on limited or no treatment in the form of HAART. Findings from research by (Bisuacchi et al., (2000) and Hoare et al. 2012 suggest that visual impairment in HIV-infected individuals may be a feature associated with severe disease progression to AIDS or in individuals who are not on any form of treatment. In this current sample all HIV-positive individuals had to have been on a form of HAART for at least 6 weeks prior to participating in the larger study. A study by Cohen et al. (2001) showed that HAART improved neurocognitive outcomes over time. HAART treatment may serve as a buffer against poor cognitive outcomes (Cohen et al., 2001). The explanation given above could explain the non-significant between the two groups. Furthermore, clade C which is the strain of HIV that typically affects majority of individuals has been linked with better cognitive outcomes.

Another explanation could relate to the clade sequencing of participants. Although, clade sequencing was not available on this sample, it seems reasonable to assume that the participants were infected with the clade C strain. It has been put forward that more than 90% of infected individuals in the Cape Town area are infected with the clade C virus (Jacobs et al., 2006). Research by Mishra et al., (2008) has shown that a defect in the dicysteine motif of the clade C tat protein may decrease the neurotoxic effects of the HIV infection neurocognitive outcomes and this may explain why in some trials, there are no significant differences between the controls and the HIV-positive group for example, on all trials of the RCF (immediate and delayed recall). In summary, taken together, therefore, the performance on tests of learning and memory indicate that both HIV-positive and HIV-negative groups are able to learn and recall both audio-verbal and visual-spatial information, although the HIV-positive individuals show slower initial learning of the word lists for the audio verbal memory task.

### **Experiences of traumatic life events between HIV-positive and HIV-negative**

For *Hypothesis 2*, I predicted that HIV-positive participants would report more negative life events compared to HIV-negative participants. There was a significant difference on the School and Classes category of the ALEQ with HIV-positive participants report more negative life events compared to HIV-negative participants. For example, HIV-positive participants mainly reported items such as failing a test, receiving a bad report (for school term), failing to understand material being taught at school and struggling to complete homework expected. It might be that HIV-positive children are likely to be ill and in hospital more often compared to HIV-negative participants. Hence, HIV-positive participants are likely to miss school more often compared to HIV-negative participants. Moreover, HIV-infection (the disease process) has been shown to have far-reaching consequences for a child's academic performance therefore it may be linked with some of the schooling problems reported (Hoare et al., 2012).

Attentional and information processing difficulties with HIV-positive individuals may also impact negatively on academic performance. The non-significant results observed in the Family and Parents together with the Friends and Social Activities categories of the ALEQ between the two groups could be due to the fact that all participants were recruited from the same social-economic backgrounds. Research has shown that individuals from low socioeconomic tend to experience similar negative life events (Young, 2012).

### **Compound effect of negative life events and HIV-infection on visual and verbal memory**

*Hypothesis 3* predicted that there would be a significant difference between HIV-positive children and adolescents who had experienced many negative life events compared to those who had not. The *a priori* prediction was not confirmed. An analysis of HIV-positive participants who reported greater than 6 negative traumatic life events and those who reported less than 6 negative life events did not yield significant results. Results in this comparison did not yield significant differences for any of the trials of visual and verbal memory. The sample size for this comparison was very limited but effect sizes for some of the comparisons were medium, suggesting that with a larger sample size these results could reach significance. Also this result must be interpreted with caution because the ALEQ, a measure of negative traumatic events employed in this study did not distinguish the severity of these negative life events which has been shown to result in cognitive deficits in memory (Stein, Koverola, Hanna, Torchia, & McClarty, 1997; Teicher et al., 2004).

#### **Limitations**

The primary measure for negative life events in the study was the ALEQ. This test was developed in USA for that distinct adolescent population. This measure was used in line with the protocol of the larger study. It was approved for use in the study as there were no other measures deemed suitable for to assess child appropriate traumatic events. This may have hindered results because the test was not adapted for a South African population. The team in the larger study, in which the current study is nested, did not have special rights to adapt the test and it was used in its original format. Some items in the test many have not been culturally applicable for example:

11. *Have to do chores/ work you don't want to do.* \_\_\_\_\_

27. *Your parents grounded you.* \_\_\_\_\_

43. *Got a bad report card.* \_\_\_\_\_

44. *Didn't get to take a class you wanted to take.* \_\_\_\_\_

45. *Didn't make the honour roll when you wanted to.* \_\_\_\_\_

These items may have been difficult to understand for the participants although examiners assisted participants as much as they could. In addition to this, this measure only explores negative life events in the preceding three months which some may argue is not sufficient enough. In light of these limitations it may be useful to obtain rights to adapt North American based measures to South African populations and also use comprehensive measure of negative

life events because it is reasonable to assume that negative life events in the HIV sample have been occurring in this population for a significant amount of time.

Additionally, the scale did not tap into criminal types of negative life events (trauma) such as being a victim of rape, sexual abuse/assault, robbery which are likely to have affected participants considering the high prevalence of child abuse in South Africa. Although at the end of the ALEQ, additional space was allocated for participants to state other traumatic events that may have occurred and were not captured by the categories in the measure. The limitations associated with the ALEQ are also relevant to hypothesis 2. Future research may benefit if they employ a more comprehensive measure for negative life events. In addition, looking at severity of negative life events may prove more useful than the number of negative life events.

In the current study, I did not have access to biological information such as Viral Load and CD<sub>4</sub> count. This information is useful although some studies have shown this information is not linked performance on neuropsychological measures. In future it may be useful to include this information to add to the growing body of literature on viral load and CD<sub>4</sub> count on performance. In future, this research this could be useful information to obtain because researchers can explore differences (if any) in performance on neuropsychological tests of HIV-infected participants with a high CD<sub>4</sub> count and viral load and those with a low CD<sub>4</sub> count and viral load.

The differences observed between the groups in this sample are attributed to HIV-infection, as this disease mechanism is in one group and not the other. However, it may be useful to include a third group of participants with a managed chronic illness, (for example, epilepsy or cancer) to ascertain if the differences seen in the current study maybe reflective of merely having a disease or rather is the neurocognitive pattern of HIV infection. Therefore future research may benefit from adding a third group into the study. This group would typically include participant who have a chronic illness. It may be interesting to observe performance on neuropsychological tests across these different groups.

In summary, there were no significant differences for memory performance between the HIV positive and negative groups or for the HIV positive individuals with or without exposure to trauma. Hence, I was unable to demonstrate a compound effect of HIV infection and negative life events on verbal and visual memory tasks. I have provided possible explanations to account for these findings and there are various aspects of this research that can be explored further with

using more refined methods and measures. However, there is very limited literature on the compound effect of HIV-infection and experiencing negative traumatic events. As both of these factors are particularly prevalent in the South African context, the results from this study reveal that it may be important to investigate this work further.

#### Significant of study

One explanation for the non-significant results could be that HIV-infection has a more profound effect on verbal and visual memory compared to experiencing negative traumatic events in this study. Lastly, to my knowledge, there is hardly any literature on the compound effect of HIV-infection and experiencing negative traumatic events. Results from this study reveal that it may be important to look into this work further.

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## Appendix A

### Life events checklist for adolescents

#### ADOLESCENT LIFE EVENTS QUESTIONNAIRE

**INSTRUCTIONS:** In this questionnaire we are interested in whether certain events have happened to you in the past 3 months. Please answer yes if any of the following events have happened to you in the past 3 months. Answer no if this event did not happen to you in the past 3 months.

#### FAMILY AND PARENTS

1. Your parents divorced. \_\_\_\_\_
2. Your parents separated. \_\_\_\_\_
3. A close family member (parent, brother, sister) hospitalized for serious injury/illness. \_\_\_\_\_
4. A close family member (parent, brother, sister) had an unwanted, unplanned pregnancy. \_\_\_\_\_
5. A close family member (parent, brother, sister) died. \_\_\_\_\_
6. A close family member (parent, brother, sister) was arrested. \_\_\_\_\_
7. You and your family moved to a new town, but you didn't want to move. \_\_\_\_\_
8. You had an argument with a close family member (parent, brother, sister). \_\_\_\_\_
9. A close family member (parent, brother, sister) lost their job. \_\_\_\_\_
10. A close family member (parent, brother, sister) can't work due to injury/illness. \_\_\_\_\_
11. Have to do chores/ work you don't want to do. \_\_\_\_\_
12. Have to take care of brothers/ sisters when you don't want to. \_\_\_\_\_
13. Don't spend as much time with close family members as you want to. \_\_\_\_\_
14. Parents are upset because you haven't lived up to their standards. \_\_\_\_\_
15. You can't seem to please your parents. \_\_\_\_\_
16. You can't seem to get close to one or more family members. \_\_\_\_\_
17. Did something you didn't want to do to please a close family member. \_\_\_\_\_
18. Found out that close family member has been criticizing you behind your back. \_\_\_\_\_

19. Parents put you down. \_\_\_\_\_
20. Seems like your parent are disappointed with you. \_\_\_\_\_
21. Close family member has significant medical or emotional problems (examples: heart disease, cancer, depression, etc.). \_\_\_\_\_
22. Don't receive the love, respect, or interest from parents that you wanted (example: parents didn't notice or compliment you on a good job). \_\_\_\_\_
23. Fight with parents over personal goals, desires, or choice of friends. \_\_\_\_\_
24. Your parents force you to achieve things you don't want to do. \_\_\_\_\_
25. Close family members withdraws love or affection from you. \_\_\_\_\_
26. Parents criticized you or yelled at you for not doing well in school. \_\_\_\_\_
27. Your parents grounded you. \_\_\_\_\_
28. Your parents won't let you go out with your friends. \_\_\_\_\_
29. You get in a fight with your parents over friends/ boyfriend/ girlfriend. \_\_\_\_\_

## **RELATIONSHIPS**

30. A boyfriend/girlfriend breaks up with you, but you still want to go out with them. \_\_\_\_\_
31. Became pregnant/ made someone pregnant when you didn't want to. \_\_\_\_\_
32. Had a baby that you didn't plan or want. \_\_\_\_\_
33. Don't have a boyfriend/ girlfriend when you want one. \_\_\_\_\_
34. Got in a fight/ argument with a boyfriend/ girlfriend. \_\_\_\_\_
35. Can't seem to please girlfriend/ boyfriend when you want to. \_\_\_\_\_
36. Girlfriend/ boyfriend criticizes you. \_\_\_\_\_
37. Can't seem to get close to your boyfriend/girlfriend when you want to. \_\_\_\_\_
38. Found out that boyfriend/ girlfriend has been criticizing you behind your back. \_\_\_\_\_
39. Found out that boyfriend/ girlfriend has been cheating on you. \_\_\_\_\_
40. Did something to please you boyfriend/ girlfriend that you didn't want to do. \_\_\_\_\_

**SCHOOL AND CLASSES**

41. Did poorly on, or failed, a test or class project. \_\_\_\_\_
42. Do not have time to do well in school (example, working too many hours at work). \_\_\_\_\_
43. Got a bad report card. \_\_\_\_\_
44. Didn't get to take a class you wanted to take. \_\_\_\_\_
45. Didn't make the honour roll when you wanted to. \_\_\_\_\_
46. Had a bad teacher. \_\_\_\_\_
47. Didn't understand the material the teacher was teaching you. \_\_\_\_\_
48. Have to attend a class that you don't like. \_\_\_\_\_
49. Didn't complete required homework assignment for class. \_\_\_\_\_
50. Got in trouble with the teacher or principal. \_\_\_\_\_
51. Didn't get accepted for an extracurricular activity you wanted to be a part of. \_\_\_\_\_

**FRIENDS AND SOCIAL ACTIVITIES**

52. Don't have as many friends as you would like to. \_\_\_\_\_
53. Aren't friends with the people you want to be friends with. \_\_\_\_\_
54. Don't get invited to parties. \_\_\_\_\_
55. Don't get invited to dances when you want to go. \_\_\_\_\_
56. Didn't have anyone to go out with on the weekends when you wanted to go out. \_\_\_\_\_
57. You had an argument with a close friend. \_\_\_\_\_
58. Your friends don't seem to understand you. \_\_\_\_\_
59. People don't call you when they are going out. \_\_\_\_\_
60. Don't have time to spend with your friends when you want to be with them. \_\_\_\_\_
61. Don't talk or share feelings with your friends. \_\_\_\_\_
62. Got in a fight/ argument with your friends. \_\_\_\_\_
63. Friends pressure you to do things you don't want to do. \_\_\_\_\_

- 64. A close friend was arrested. \_\_\_\_\_
- 65. A close friend had an unwanted, unplanned pregnancy. \_\_\_\_\_
- 66. A close friend was hospitalized for a serious injury/illness. \_\_\_\_\_
- 67. A close friend died. \_\_\_\_\_
- 68. A close friend moved away. \_\_\_\_\_
- 69. You can't seem to get close to one of your friends. \_\_\_\_\_
- 70. Close friends withdraw their affection from you. \_\_\_\_\_

Please list any other stressful, negative event(s) that you can remember happening to you since you started school:

- .
- .
- .
- .
- .
- .
- .

THANK YOU.



## **Appendix B**

### **Informed consent/assent form for parent and child**

**pHIV DTI: Version 3, September2010, Positive group 1**

PATIENT INFORMATION AND CONSENT FORM FOR THE STUDY

**Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.**

HIV Positive patients

**Principal Investigator:** Dr J Hoare

Dear Participant

**You and your child are requested to participate in a medical research study that is being done at Red Cross Children's Hospital in the School of Child and Adolescent Health, University of Cape Town. The following describes the study and you and your child's role. Please take some time to read the information presented here carefully, and feel free to ask any questions.**

#### **Background**

We are doing a study on how HIV affects children's learning, development and behaviour. We want to compare tests of development (learning, memory, language and attention), psychosocial scales (trauma, life events, depression, anxiety and adaptability) and brain scans from children with HIV to children who do not have HIV.

If you are willing to allow your child to participate in this study, your child must be *HIV positive and currently not physically ill*.

HIV infection may cause slow development in a child. This can be either because of the virus itself or infections that the child may get. Even if a child seems well and is going to school, the HIV infection may affect some functions - like interfering with learning, with good memory, with doing mathematics, and with attention and behaviour.

We also want to learn about how caring for a child affects you as a parent. Parents, who have to care of a HIV-positive child, may experience more stress and difficulties than parents whose children do not have HIV. We want to compare test of parental stress of parents of children who are HIV-positive, to parents of children who are HIV-negative.

Children are often exposed to different kinds of trauma under various circumstances. We would like to find out more about the kinds of trauma certain children may experience.

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**Purpose of the Study**

The aim of this study is to measure tests of development (learning, memory, language, attention) and tests of behaviour and brain scans in healthy HIV-positive children and in healthy HIV negative children. The HIV-positive children's performance will be compared to the performance of healthy HIV-negative children. This will improve our understanding and management of children with HIV.

### **Procedures in the Study**

Your involvement in the study will require you to visit the study doctor/team on three occasions. Two of the sessions will take place at Red Cross Children's Hospital (RXH), and during these sessions neuropsychological, developmental and behavioural tasks will be completed by your child. This includes the brain scan, but this will be done at Tygerberg Hospital.

### **Confirmation of HIV diagnosis**

If you are invited to participate in this study, it means that your child has already been diagnosed as being HIV positive, and has been referred to this study. Your child is unique in that he/she will have acquired the infection via mother to child transmission, and not via a blood transfusion or unhygienic needles.

Your child is currently attending a clinic for regular check-ups. With your permission, we will contact the clinic which you and your child are attending to gain access to information in your clinic folders. During the course of your participation you will be asked certain medical questions regarding your child most recent CD4 count, viral load, and current treatment regime.

### **Neuropsychological and psychological testing**

The study research assistant will ask your child to complete a number of pencil and paper tests which involve some writing and drawing as we test their memory, concentration and planning abilities. Many of these are like a normal IQ test that your child may have completed at school. All of these tests are important and will help us to determine if HIV has any effects on these aspects for your child's brain. This session will take approximately 2½ - 3 hours long. At another session your child will be asked questions about what kinds of things they have experienced in their everyday lives, as well as questions about their emotional state.

While your child completes these tasks, we will ask you as the parent / guardian to complete psychological measures pertaining to your child's overall development, as well as your experiences as a parent. These tests are important and will help us to determine the amount of stress and anxiety you may experience as a parent, and how this relates to your child's development.

***Brain scanning procedure***

All brain scans will be done at a specialized facility at Tygerberg Hospital. A special brain scan (an MRI scan) will be done on your child – this examination is not harmful and it is not painful. Your child will be asked to lie still on a special bed while the scanner takes the pictures of your child's head - this will be for a maximum of 30 minutes. Some children may find the machine a bit scary. If your child is very anxious or scared or unable to lie still for that long, we will not continue with the examination.

***Neurological examination***

Your child will be required to undergo a neurological examination which will be performed by a study doctor. The purpose of this examination is to check that your child's sensory and motor responses, and also their reflexes, are functioning properly and that there is no damage to their nervous system. To test this, the doctor will ask your child to do a series of playful activities, for example touching their nose or their ankles. These tasks are not harmful to your child. If your child is anxious, you may accompany him/her in the examination room.

***Procedure for drawing of bloods***

This part of the study involves the long-term storage of DNA (genetic) taken from a sample of your child's blood for future analysis. Genetic material, also called DNA, can be obtained from small samples of blood. Previous studies have shown that HIV infection can have damaging effects on the brain. We are however unsure as to how serious these effects may be in young children. In this part of the study, we hope one day to be able to use genetic material, such as we will be collecting, to assist us in identifying genes that will tell us what people may be particularly vulnerable to experience harmful effects, and what genetic patterns are likely to make people more susceptible to becoming infected with the HIV virus. Before the brain scan is done, a registered nurse will draw a small amount of blood from your child. This procedure will not be harmful to your child. Your child may feel a light prick when the needle is inserted into his/her arm, but will not experience any pain. The needle is connected to a thin plastic pipe and the blood then flows into a small blood sample tube. The test will require about 1 teaspoon of blood, and is performed only once.

Your blood will only be used for genetic research that is directly related to this study looking at diffusion tensor in HIV-infected children. Also if the researchers wish to use your stored blood for *additional research in this field* they will be required to apply for permission to do so from the Human Research Ethics Committee at UCT. If you do not wish your blood specimen to be stored after this research study is completed you will have an opportunity to request that it be discarded when you sign this consent form.

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***Follow ups***

You and your child may be asked to attend a follow up session. If you are asked to come for a follow up, it will be one year from the date of your first enrolment to this study. The study procedures for the follow up will be the same as for this time.

**Your Part in the Study**

While your child is being tested by members of the study team, you will also be asked to complete questions by another member of the study. You will complete a general demographics form, and other psychological tests pertaining to your child's mental health and yours. These tests are not harmful, but may ask some sensitive questions about your life. Our researchers will do all they can to emotionally support you while you complete these forms. It is important for us that you answer these questions truthfully, so that we can better understand you as a parent, and your needs.

For the first session, a trained research assistant will interview your child at RXH. During this session your child will complete the neuropsychological tasks previously described. During the second session, a registered social worker will interview your child about their behavioural and emotional well-being. Your child will then be given another appointment to go Tygerberg hospital, on a day that is convenient for you, where the brain scan will be done. We will try to arrange these sessions so as to not interfere with your child's normal school routine. These sessions may be booked after school hours where possible. Transport money and food vouchers will be provided for you and your child for each these visits.

**Risks to You and Your Child**

There are only low or minimal risks associated with your participation in this study. If you feel tired at any point during any of the visits, you should please ask your study doctor/psychologist for a rest. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessments at another time.

There are no direct risks in having blood taken for genetic testing.

Furthermore, there are no known risks for your child for either the psychological tests or the brain scan.

The brain scan does not involve any radiation.

**Benefits to You and Your Child**

Although there is no direct benefit for you or your child, the results of this research may help to inform us to what the common school and behaviour problems are that healthy HIV-positive children can have. This will help us to decide if we need to consider extra treatments and/or interventions for these children.

### **Confidentiality**

You and your child's test results will be kept confidential (private) and will only be used by the members of this study for the purpose of research. If any information from this study gets published, we will make sure that your personal details will remain confidential at all times.

This study has been approved by the Committee for Human Research of the University of Cape Town (UCT). It will be conducted according to Medical Research Council guidelines on good clinical practice (2003) as well as the Declaration of Helsinki Guidelines (Edinburgh, 2000), which provide detailed guidelines that relate to the ethical conduct of studies involving human subjects.

### **Voluntary Participation**

You and your child's participation are entirely voluntary. You or your child is not under any obligation to participate. If you choose not to allow your child to participate, it will not affect you or your child negatively or prevent your right to future health care services. You have the right to withdraw your child from the study at any time.

**You have the right to ask questions at any time about any aspect of the study. If you have any queries, you can contact Jackie Hoare on 021 404 2134/2164**

**You are entitled to a signed copy of this document.**

If you agree to take part, please complete the following section:

pHIV DTI: Version 3, September2010, Positive group 6

#### ASSENT OF MINOR

I (Name of Child/Minor) \_\_\_\_\_ have been invited to take part in the above research project entitled: Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.

The study doctor/nurse and my parents have explained the details of the study to me and I understand what they have said to me.

- They have also explained that this study will involve 3 assessments which include interviews, filling questionnaires, a physical examination, blood sampling, and a brain scan.
- I also know that I am free to withdraw from the study at any time if I am unhappy.
- By writing my name below, I voluntarily agree to take part in this research project. I confirm that I have not been forced either by my parents or doctor to take part.

---

Name of child (To be written by the child if possible)

pHIV DTI: Version 3, September2010, Positive group

#### DECLARATION BY PARENT/LEGAL GUARDIAN

By signing below, I (name of parent/legal guardian) \_\_\_\_\_ agree to allow my child (name of child) \_\_\_\_\_ who is \_\_\_ years old, to take part in a research study entitled: Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.

I declare that:

- I have read or had read to me this information and consent form and that it is written in a language with which I am fluent and comfortable.
- If my child is older than 7 years, he/she must agree to take part in the study and his/her ASSENT must be recorded on this form.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is voluntary and I have not been pressurised to let my child take part.
- I may choose to withdraw my child from the study at any time and my child will not be penalised or prejudiced in any way.
- My child may be asked to leave the study before it has finished if the study doctor or researcher feels it is in my child's best interests, or if my child does not follow the study plan as agreed to.
- I understand that genetic material will be collected from blood samples

I agree that my child's blood sample can be stored for research purposes, subject to the approval of the Human Research Ethics Committee (HREC) of UCT, provided that all information is kept confidential. I can choose to request at any time that my stored sample be destroyed. I have the right to receive confirmation that my request has been carried out.

OR

Please destroy my blood sample as soon as the current research project has been completed. (Tick the option you choose)

Signed at (place) \_\_\_\_\_ on (date) \_\_\_\_\_ 20\_\_\_\_

\_\_\_\_\_  
Signature of parent/legal guardian

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DECLARATION BY INVESTIGATOR

I (name) \_\_\_\_\_ declare that:

- I explained the information in this document to

(name of child and parent) \_\_\_\_\_

I encouraged him/her to ask questions and took adequate time to answer them.

- I am satisfied that he/she adequately understand all aspects of the research, as discussed above.
- I did/did not use an interpreter (if an interpreter is used, then the interpreter must sign the declaration below).

Signed at (place) \_\_\_\_\_ on (date) \_\_\_\_\_ 20 \_\_\_\_\_

\_\_\_\_\_  
Signature of investigator

DECLARATION BY INTERPRETER

I (name) \_\_\_\_\_ declare that:

- I assisted the investigator (name) \_\_\_\_\_

to explain the information in this document to

(name of parent/legal guardian) \_\_\_\_\_

using the language medium of Afrikaans / Xhosa.

- We encouraged him/her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the parent/legal guardian fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.

Signed at (place) \_\_\_\_\_ on (date) \_\_\_\_\_ 20 \_\_\_\_\_

\_\_\_\_\_

Signature of interpreter

pHIV DTI: Version 3, September2010, Positive group

#### **PARTICIPANT INFORMATION LEAFLET**

We are doing a study on children's learning, development and behavior.

We also want to learn about how caring for a child affects you as a parent.

#### **Procedures in the Study**

Your involvement in the study will require you to visit the study doctor/team on three separate occasions. Two sessions at RXH and another session at TBH.

#### **Neuropsychological and psychological testing**

The study research assistant will ask your child to complete a number of pencil and paper tests which involve some writing and drawing as we tests their memory, concentration and planning abilities. This session will take approximately 2½ - 3 hours long. While your child completes these tasks, we will ask you as the parent / guardian to complete psychological measures pertaining to your child's overall development, as well as your experiences as a parent.

#### **Brain scanning procedure**

All brain scans will be done at a specialized facility at TBH. A special brain scan (an MRI scan) will be done on your child – this examination is not harmful and it is not painful. The scan will take about 30 minutes.

#### **Neurological examination**

You child will be required to undergo a neurological examination which will be performed by a study doctor. The purpose of this examination is to check that your child's sensory and motor responses, and also their reflexes, are functioning properly and that there is no damage to their nervous system.

#### **Risk and Benefits**

There are no major risks involved in participating in this study. You and your child will be making a valuable contribution to the field of medical and psychological knowledge. Transport money and food vouchers will be provided for each of your visits. All your personal information and test results will be kept strictly confidential



Questions and queries:

Bulelwa Mtukushe

(Tel) 021 404 7625 / 021 404 7626

**Appendix C**  
**Informed consent/assent form for parent and child**

pHIV DTI: Version 4, September2012, Negative group

**PATIENT INFORMATION AND CONSENT FORM**

FOR THE STUDY

**Diffusion Tensor Imaging of HIV Affected Children and Their  
 Psychocognitive and Behavioural Profiles.**

HIV Negative controls

**Principle Investigator:** Dr J Hoare

Dear Participant

**You and your child are requested to participate in a medical research study that is being done at Red Cross Children's Hospital in the School of Child and Adolescent Health, University of Cape Town. The following describes the study and you and your child's role. Please take some time to read the information presented here carefully, and feel free to ask any questions.**

**Background**

We are doing a study on how HIV affects children's learning, development and behaviour. We want to compare tests of development (learning, memory, language and attention), psychosocial scales (trauma, life events, depression, anxiety and adaptability) and brain scans from children with HIV to children who do not have HIV.

You may participate in this study if your child is *healthy and not HIV positive*.

Infection may cause slow development in a child. This can be either because of the virus itself or infections that the child may get. Even if a child seems well and is going to school, the infection may affect some functions - like interfering with learning, with good memory, and with attention and behaviour.

We also want to learn about how caring for a child affects you as a parent. Parents, who have to care of a positive child, may experience more stress and difficulties than parents who have children who are negative. We want to compare test of parental stress of parents of children who are negative, to parents of children who are positive.

Children are often exposed to different kinds of trauma under various circumstances. We would like to find out more about the kinds of trauma certain children may experience.

pHIV DTI: Version 4, September2012, Negative group

**Purpose of the Study**

The aim of this study is to measure tests of development (learning, memory, language, attention) and tests of behaviour and brain scans in healthy positive children and in healthy negative children. The positive children's performance will be compared to the performance of healthy negative children. This will improve our understanding and management of children with HIV.

### **Procedures in the Study**

Your involvement in the study will require you to visit the study doctor/team on three occasions. Two of the sessions will take place at Red Cross Children's Hospital (RXH), and during these sessions neuropsychological, developmental and behavioural tasks will be completed by your child. The brain scan will be done at the third session, and this will take place at Tygerberg Hospital's (TBH) Cape Universities Brain Imaging Center (CUBIC).

### **HIV testing procedure**

Since your child is a healthy HIV negative participant in this study, with your permission we are going to do a very simple screening procedure to test for HIV infection. It is important that we are able to exclude HIV as a confounding factor when looking at the development of normal healthy children. This test will be done at your first study visit, prior to doing any of the neuropsychological tasks.

If your child is negative, he/she will be enrolled into this study with your permission as parent/guardian. If your child tests positive, he/she will still be able to participate in this study, but only after his/her immediate medical needs have been taken care of. Having an HIV test done can cause feelings of anxiety and worry. These kinds of feelings are normal. We will take every step possible to ensure that you are comfortable with having your child take the HIV test. We will perform an HIV rapid test, which will require your child to have a finger prick for a drop of blood. The test results are immediately available. As part of this procedure, you and your child will be counselled both prior to taking the test and afterwards, regardless of the test outcome.

### **What are your rights?**

- To make your own decision about whether to be tested for HIV or not;
- To be provided with all the information necessary regarding harm and risks of taking or not taking an HIV test
- To be given an opportunity and time to ask any questions related to the infection and have them answered to your satisfaction; this includes any questions that your child might have

- To have a session of counselling for you and your child before and after the result of the test is known

- To have your child's test results treated in confidence

To ask ANY questions about any part of this study

If as a result of your participation in this research study your child is initially diagnosed as positive, the results will be revealed to you. This can either be done privately or together with your child. You will then be referred by the study doctor to the Infectious Disease Family Clinic at Groote Schuur Hospital or to your local clinic for immediate counselling and medical treatment.

If your child has already had a recent HIV test, he/she will not need to redo the test to participate in this study, but with your permission, we will have to gain access to the information from the clinic at which he/she was tested.

### **Neuropsychological and psychological testing**

The study research assistant will ask your child to complete a number of pencil and paper tests which involve some writing and drawing as we tests their memory, concentration and planning abilities. Many of these are like a normal IQ test that your child may have completed at school. All of these tests are important and will help us to determine if HIV has any effects on these aspects for your child's brain. This session will take approximately 2½ - 3 hours long. At another session you child will be asked questions about what kinds of things they have experienced in their everyday lives, as well as questions about their emotional state.

While your child completes these tasks, we will ask you as the parent / guardian to complete psychological measures pertaining to your child's overall development, as well as your experiences as a parent. These tests are important and will help us to determine the amount of stress and anxiety you may experience as a parent, and how this relates to your child's development.

**Brain scanning procedure**

All brain scans will be done at a specialized facility at Tygerberg Hospital. A special brain scan (an MRI scan) will be done on your child – this examination is not harmful and it is not painful. Your child will be asked to lie still on a special bed while the scanner takes the pictures of your child's head - this will be for a maximum of 45 minutes. During that time your child may rest and close his/her eyes. Having an MRI scan done is a safe procedure if you and your child have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects. A formal screen for this will be done by one of the study research assistants prior to the scanning session. When the magnet inside the machine is switched on, it will make some loud banging noises. At this time you will feel nothing and the noise is not harmful to you or your child in any way. Your child will be given soft ear plugs to wear during the procedure to minimize possible discomfort associated with this experience. Some children may find the machine a bit frightening. If your child is very anxious or scared, you will be allowed to accompany your child inside the scanning room. We will make sure that it is safe for both you and your child to go inside the MRI scanning room and to undergo scanning. Your child may feel slightly dizzy immediately after the scan. This is completely normal. The radiographers at the scanning centre are qualified and trained to be alert to the effects of the scanning procedure on participants. Your child's need will be attended to immediately, should the need arise. We will make every effort to ensure that your child is comfortable doing the scan. Materials will be provided to prepare your child before the scan, for example a flow diagram for the scanning procedure, as well as a video. If your child is still afraid or unable to lie still for that long, we will not continue with the examination.

**Follow ups**

You and your child may be asked to attend a follow up session. If you are asked to come for a follow up, it will be one year from the date of your first enrolment to this study. The study procedures for the follow up will be the same as for this time.

**Your Part in the Study**

While your child is being tested by members of the study team, you will also be asked to complete questions by another member of the study. You will complete a general demographics form, and other psychological tests pertaining to your child's mental health and yours. These tests are not harmful, but may ask some sensitive questions about your life. Our researchers will

do all they can to emotionally support you while you complete these forms. It is important for us that you answer these questions truthfully, so that we can better understand you as a parent, and the difficulties you experience while caring for your child.

For the first session, a trained research assistant will interview your child at RXH. During this session your child will complete the neuropsychological tasks previously described. During the second session, a registered social worker will interview your child about their behavioural and emotional well-being. Your child will then be given another appointment to go Tygerberg hospital, on a day that is convenient for you, where the brain scan will be done. We will try to arrange these sessions so as to not interfere with your child's normal school routine. These sessions may be booked after school hours where possible. Transport money and food vouchers will be provided for you and your child for each these visits.

### **Risks to You and Your Child**

There are no risks involved in doing an HIV test. However, waiting for and receiving the test result may be a difficult time because of the complex emotions involved in a time such as this. If you are in need of support, please telephone the study contact (investigator) who gave you this information before you had the test done.

If you or your child feels tired at any point during any of the visits, you should ask your study doctor/psychologist for a rest. If for some reason you are unable to complete a visit on a particular day we may reschedule to complete the assessment at another time.

Furthermore, there are no known risks for your child for either the psychological tests or the brain scan. The brain scan does not involve any radiation.

### **Benefits to You and Your Child**

Although there is no direct benefit for you or your child, the results of this research may help to inform us to what the common school and behaviour problems are that healthy HIV-positive children can have. This will help us to decide if we need to consider extra treatments and/or interventions for these children.

We acknowledge that we cannot provide intervention or treatment, as part of this study. If it is detected that your child has developmental delay, we will provide you will a detailed report, and with your permission we will forward it to the relevant educational department to be dealt with accordingly. A detailed report will be important in determining what type of intervention your child may need. Further treatment for your child will be at your own expense.

**Confidentiality**

You and your child's test results will be kept confidential (private) and will only be used by the members of this study for the purpose of research. If any information from this study gets published, we will make sure that your personal details will remain confidential at all times.

This study has been approved by the Human Research Ethics Committee (021 406 6492) of the University of Cape Town (UCT). It will be conducted according to Medical Research Council guidelines on good clinical practice (2003) as well as the Declaration of Helsinki Guidelines (Edinburgh, 2008), which provide detailed guidelines that relate to the ethical conduct of studies involving human subjects.

**Voluntary Participation**

You and your child's participation are entirely voluntary. You or your child is not under any obligation to participate. If you choose not to allow your child to participate, it will not affect you or your child negatively or prevent your right to future health care services. If you do not want your child to be tested for HIV, this means that you and your child will not be able to participate in this study. The reason for this is that it is important that we are able to exclude HIV disease as a factor in our findings and your child's performance. You have the right to withdraw your child from the study at any time.

**You have the right to ask questions at any time about any aspect of the study. If you have any queries, you can contact Jackie Hoare on 021 404 2134/2164.**

**You are entitled to a signed copy of this document.**

If you agree to take part, please complete the following section:

**ASSENT OF MINOR**

I (*Name of Child/Minor*) \_\_\_\_\_ have been invited to take part in the above research project entitled: **Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.**

The study doctor/nurse and my parents have explained the details of the study to me and I understand what they have said to me.

- They have also explained that this study will involve 3 assessments which include interviews, filling questionnaires, a physical examination including a blood test, and a brain scan.
- I also know that I am free to withdraw from the study at any time if I am unhappy.
- By writing my name below, I voluntarily agree to take part in this research project. I confirm that I have not been forced either by my parents or doctor to take part.

---

Name of child (**To be written by the child if possible**)



*al guardian*) \_\_\_\_\_ agree to allow my child (*name of child*) \_\_\_\_\_ who is \_\_\_ years old, to take part in a research study entitled: **Diffusion Tensor Imaging of HIV-positive Children and Their Psychocognitive and Behavioural Profiles.**

I declare that:

- I have read or had read to me this information and consent form and that it is written in a language with which I am fluent and comfortable.
- If my child is older than 7 years, he/she must agree to take part in the study and his/her ASSENT must be recorded on this form.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to let my child take part.
- I may choose to withdraw my child from the study at any time and my child will not be penalised or prejudiced in any way.
- My child may be asked to leave the study before it has finished if the study doctor or researcher feels it is in my child's best interests, or if my child does not follow the study plan as agreed to.

Signed at (*place*) \_\_\_\_\_ on (*date*) \_\_\_\_\_ 20 \_\_\_\_

\_\_\_\_\_  
Signature of parent/legal guardian

**DECLARATION BY INVESTIGATOR**

I (*name*) \_\_\_\_\_ declare that:

· I explained the information in this document to

(*name of child and parent*) \_\_\_\_\_

I encouraged him/her to ask questions and took adequate time to answer them.

· I am satisfied that he/she adequately understand all aspects of the research, as discussed above.

· I did/did not use an interpreter (*if an interpreter is used, then the interpreter must sign the declaration below*).

Signed at (*place*) \_\_\_\_\_ on (*date*) \_\_\_\_\_ 20 \_\_\_\_\_

\_\_\_\_\_  
Signature of investigator

**DECLARATION BY INTERPRETER**

I (*name*) \_\_\_\_\_ . declare that:

· I assisted the investigator (*name*) \_\_\_\_\_

to explain the information in this document to

(*name of parent/legal guardian*) \_\_\_\_\_

using the language medium of Afrikaans/Xhosa.

· We encouraged him/her to ask questions and took adequate time to answer them.

· I conveyed a factually correct version of what was related to me.

· I am satisfied that the parent/legal guardian fully understands the content of this informed consent document and has had all his/her questions satisfactorily answered.

Signed at (*place*) \_\_\_\_\_ on (*date*) \_\_\_\_\_ 20 \_\_\_\_\_

\_\_\_\_\_  
Signature of interpreter

pHIV DTI: Version 4, September2012, Negative group

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We also want to learn about how caring for a child affects you as a parent.

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Your involvement in the study will require you to visit the study doctor/team on three separate occasions. Two sessions at RXH and another session at TBH.

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#### **Risk and Benefits**

There are no major risks involved in participating in this study. You and your child will be making a valuable contribution to the field of medical and psychological knowledge. Transport money and food vouchers will be provided for each of your visits. All your personal information and test results will be kept strictly confidential

#### **Questions and queries:**

Bulelwa Mtukushe

(Tel) 021 404 7625 / 021 404 7626