

Executive Dyscontrol of Learning and Memory on the HVLТ-R:  
Findings from a clade C HIV-positive South African sample

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## Abstract

South Africa is home to the largest number of people living with HIV in the world. The virus follows a distinct neuropathological and neuropsychological pattern, affecting specific neural structures and neurocognitive functions. One of the neurocognitive functions affected is verbal learning and memory. I explored clade C HIV-positive participants' performance on component processes of a verbal learning and memory test, known as the Hopkins Verbal Learning Test—Revised (HVLT-R). While this test was designed for verbal learning and memory performance, it also taps into various aspects of executive functioning, that can either improve or inhibit performance. My study looked at whether poor performance on the HVLT-R was purely a memory deficit, or whether it was due to aspects of executive dyscontrol related to prefrontostral circuitry damage. I used independent samples *t*-tests to look at group differences between 53 HIV-positive individuals, and 53 HIV-negative individuals.

*Keywords:* clade C; encoding; consolidation; executive dyscontrol; HIV; prefrontostral circuitry; retrieval; verbal learning and memory

## Executive Dysfunction of Learning and Memory on the HVLTR: Findings from a clade C HIV-positive South African sample

The human immunodeficiency virus (HIV) epidemic affects the lives of 33 million people globally. More than two-thirds of all HIV-infected persons reside in sub-Saharan Africa (Hemelaar, Gouws, Ghys, & Osmanov, 2006; WHO, 2009). At a national level, in turn, South Africa contains the world's biggest population of individuals living with HIV, with an estimated 5.38 million (Statistics South Africa, 2011). In light of these epidemiological data, it is not surprising that vast amounts of research attention are trained on people living with HIV.

HIV treatment access, in the form of Highly Active Antiretroviral Therapy (HAART), has resulted in lower mortality rates, and an increased prevalence of individuals who are living with HIV-associated neurocognitive disorders (HAND). For example, 17% of individuals in an HIV-positive, HAART-treated sample drawn from a Cape Town health clinic had mild-to-severe neurocognitive impairment (Ganaseen, Fincham, Smit, Seedat, & Stein, 2008; Robertson, Liner, & Heaton, 2009). Therefore, the arrival of HAART in South Africa has transformed HIV into a chronic (and not fatal) disease, where individuals are actually living with the virus, its associated neurocognitive disorders, and subsequent impact on everyday functioning.

The virus is complex, as demonstrated by its various divisions and subdivisions. Most research focuses on the HIV-1 form, as most people in the world (including South Africa) are infected with this form (Hemelaar et al., 2011). HIV-1 is further divided into three groups, each of which contains different clades, or strains, of the virus (Robertson et al., 2000). Group M is responsible for most infections and diseases globally, and is comprised of 11 clades, labeled subtypes A through F. Furthermore, specific clades proliferate in different geographic regions (Stebbing & Moyle, 2003). For example, clade B is prominent in North and Central America, Western and Central Europe, and Australia, whereas clade C is prominent in Southern Africa (Osmanov et al., 2002; Smith, Kuiken & Korber, 2003; Van Harmelen et al., 1999).

### **Neuropathology of HIV**

In order to understand the various neurocognitive deficits associated with HIV infection, it is necessary to understand the effects of the virus on various brain structures. Of particular importance to this study is the fact that HIV attacks the hippocampus, a subcortical structure associated with the processes of episodic memory encoding and consolidation (Carr,

Jadhav, & Frank, 2011; Cherner et al., 2007; Fujimura et al., 1997; Kircher, 2009; Pomara, Crandall, Choi, Johnson, & Lim, 2001). Episodic memories are those associated with learning and retaining information that has specific spatiotemporal contextual significance (Tulving, 1972). Hence, damage to the hippocampus (e.g., as might follow HIV infection) results in episodic memory deficits.

Neurocognitive deficits associated with HIV infection are also related to prefrontostriatal circuitry damage (Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008). Of particular importance to this study is the fact that such damage is associated with what is termed executive dyscontrol (the inability, or a deficiency in the ability, to use executive control) over episodic memory processes such as encoding and retrieval (Woods, Scott, et al., 2005). On tasks of episodic verbal learning and memory, executive dyscontrol can lead to impairments in free recall, erratic learning over learning trials, decreased utilization of organizational strategies such as semantic clustering, and the frequent occurrence of repetition errors (Gongvatana et al., 2007; Peavy et al., 1994; Woods, Scott, et al., 2005).

These learning, memory, and executive functioning deficits are, among others, characteristic of the neuropsychological profile of HAND.

### **Classifications of HIV-Associated Neurocognitive Disorders (HAND)**

Before detailing the specific neuropsychological pattern associated with HIV infection, it is important to understand the various classifications of HAND. The three categories of HAND are asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD). ANI is the mildest form of HAND. Characteristics of ANI include deficits (defined by age- and education-adjusted test performance of 1 standard deviation below the mean) in any two cognitive domains. To fit the diagnostic criteria for ANI, these cognitive deficits should not interfere with successful completion of activities of daily living, and they cannot be the result of delirium, dementia, or any other neurological or medical etiology (Antinori et al., 2007).

MND is a more severe form of HAND. It features the same diagnostic criteria as ANI, except for the fact that cognitive impairment must interfere with successful completion of activities of daily living. Hence, individuals diagnosed with MND experience difficulties functioning at home, at work, or in social settings. As in the case of ANI, cognitive impairment cannot be due to delirium, dementia, or any other neurological or medical etiology (Antinori et al., 2007).

The most severe form of HAND is HAD, which presents with noticeable impairment in multiple cognitive domains. Impairments in the learning of new information, in information processing, and in attention abilities are characteristic of this form of the disorder. Here, impairment is defined as age- and education-adjusted test performance of 2 or more standard deviations below the mean. These cognitive deficits are associated with severe problems with activities of daily living in the home, at work, or in social settings. As in the cases of ANI and MND, cognitive impairment cannot be associated with delirium, dementia, or any other neurological or medical etiology (Antinori et al., 2007).

### **Neuropsychology of HIV**

As is clear from the review above, deficits in neuropsychological functioning are characteristic of all HAND categories. The nature of these deficits can be traced to the damage the virus inflicts on particular brain structures, such as the medial temporal and prefrontal lobes discussed earlier. Hence, the cognitive domains affected by the virus include attention, information processing speed, psychomotor ability, language, executive functions, and learning and memory (Grant, 2008; Gupta, Woods, Weber, Dawson, & Grant, 2010; Kim, Miles, Huber, & Feit, 2008; Robertson, Liner, & Heaton, 2009; Wood, Moore, Weber, & Grant, 2009).

**Attention, information processing, and psychomotor ability.** Typically, the first cognitive domain assessed for impairment on a neuropsychological test battery is complex attention (Grant, 2008; Woods et al., 2009). Complex attention is needed as processing demands from the environment increase. It takes the form of either sustained attention (the ability to maintain focus on a specific task over for a certain amount of time; see, e.g., Sarter, Givens, and Bruno (2001)), or divided attention (the ability to attend to more than two tasks simultaneously; see, e.g., Uncapher and Rugg (2005)). Complex attention is especially vulnerable to impairment under time constraints. Bradyphrenia, or slow information processing, as well as bradykinesia, or slow movement, are typical features of HAND. Hence, individuals with HAND tend to perform poorly on timed tests of psychomotor ability.

**Language and executive functions.** Language is relatively spared in HIV, although verbal fluency is affected (Grant, 2008; Robertson et al., 2009). That is to say, individuals diagnosed with HAND experience difficulties generating words to phonemic or semantic cues under time constraints. Verbal fluency is often categorized as an executive function, as it relates to generativity (i.e., the ability to self-produce a given action; see, e.g., Robinson, Goddard, Dritschel, Wisley, and Howlin (2009)). Multiple other executive functions,

including abstraction, set shifting, response inhibition, and decision-making, are impaired in HIV (Kim et al., 2008).

**Learning and memory.** Specific types of learning and memory are susceptible to impairment in HIV. Affected individuals struggle with explicit learning tasks, as they experience difficulties recalling newly learned information on episodic memory tasks (Grant, 2008; Wood et al., 2009). Prospective memory (the ability to remember to perform a future action) is particularly susceptible to impairment (Gupta et al., 2010). Problems with prospective memory have a severe impact on activities of daily living, including medication adherence, employment and household duties, financial management, and social relationships.

### **Verbal Learning and Memory Performance in HIV**

As mentioned previously, one particular domain of cognitive functioning affected by HAND is verbal learning and memory (Grant, 2008; Wood et al., 2009). Most evidence for HIV-positive individuals' poor performance on verbal learning and memory tasks comes from clade B-infected populations. For instance, White et al. (1997) showed that HIV-associated dementia (HAD) patients were impaired, relative to both HIV-positive non-demented and HIV-negative controls, on the acquisition and recall components of a list-learning task. Similarly, Peavy et al. (1994) reported that HIV-positive symptomatic participants were, relative to HIV-negative controls, significantly impaired on the acquisition and retention components of the same list-learning task.

Neuropsychological studies focusing on clade C-infected individuals from Southern India and China have found the same pattern of impairment in HIV-positive individuals: HIV-positive individuals performed significantly more poorly on verbal learning and memory tasks than HIV-negative individuals (Cysique et al., 2007; Das Gupta et al., 2007; Yephthomi et al., 2006). More specifically, HIV-positive individuals, in comparison to their HIV-negative counterparts, demonstrated significant impairment on the total number of words produced on free recall trials and on the delayed recall trial.

**Hopkins Verbal Learning Test-Revised (HVLT-R).** This instrument (Brandt & Benedict, 2001) is used in both clinical and research settings to examine verbal learning and memory. It is comprised of three learning trials, a delayed recall trial, and a yes/no recognition trial.

The examiner commences administration by reading a list of 12 words, with a 2-s interval between each word. Immediately thereafter, the test-taker is asked to produce, verbally and in any order, as many words as possible from the list. This procedure is repeated

three times, with the same list of 12 words being presented, in the same order, each time. Each of the 12 words belongs to one of three semantic categories: precious stones, human dwellings, and four-legged animals. After completion of these three learning trials, the test-taker is told that he or she might be asked to recall the word list again later in the session.

After a filled delay of 20 to 25 minutes, the examiner administers the delayed recall trial. Here, the test-taker is simply asked to produce, verbally and in any order, as many words as possible from the list. The examiner provides no cues to aid the test-taker's recall.

The recognition trial is administered immediately after completion of the delayed recall trial. The examiner reads a list of 24 words (12 from target list and 12 distracters; 6 of the latter are semantically related to words on the target list), and asks the test-taker to state, as each word is read, whether it was on the target list or not.

Studies utilizing the HVLT-R as a measure of verbal learning and memory have shown that HIV-positive, clade B-infected individuals perform significantly more poorly than their HIV-negative counterparts on the free recall trials and on the delayed recall trial (Carey et al., 2004; Maki et al., 2009; Woods, Scott, et al., 2005). This finding is replicated in clade B-infected HIV-associated dementia (HAD) participants: Scott et al. (2006) showed that those individuals showed significant impairment in total recall across the three learning trials and on the delayed recall trial, in comparison to HIV-positive participants with no signs of dementia and to an HIV-negative group.

### **HVLT-R Component Processes Implicated in Mechanisms of Cognition**

A closer examination of the different task components of the HVLT-R has demonstrated that differentiating between them might help shed light on which fundamental cognitive mechanisms (encoding, retention/consolidation, and retrieval) might be responsible, either singly or jointly, memory impairment (Delis, Jacobson, Bondi, Hamilton, & Salmon, 2003; Poreh, 2000). For example, Delis et al. (2003) showed that there were statistically significant positive correlations between HVLT-R free and delayed recall in both healthy individuals and in Huntington's disease patients. This finding suggests that, because of the amount of shared variance, these two variables are measuring the same cognitive construct. In the same study, however, the correlation between free and delayed recall performance in Alzheimer's disease patients did not reach significance. Therefore, the relationship between these two variables creates the false impression of representing a single cognitive construct. Under some conditions, there does indeed appear to be a great deal of shared variance. The unique variance is only revealed, however, when the cognitive process driving the association is impaired due to neuropathology in brain areas that are responsible for more than one of the

components represented by the outcome variables (in this case, prefrontostriatal circuitry damage).

One example of the clinical utilization of a specific HVLТ-R component process is the use of the semantic clustering index as a determinant of executive dyscontrol in verbal learning and memory. For instance, Bruce and Echemedia (2003) showed that patients with mild traumatic brain injury utilized decreased semantic clustering, in comparison to control patients, 48 hours after their head injury.

Similarly, Woods, Rippeth, et al. (2005) used component processes from the HVLТ-R to determine the cognitive mechanisms related to episodic verbal memory impairment in individuals with methamphetamine dependence. Their results indicated that these patients exhibited impaired learning, delayed recall, and application of semantic clustering, in addition to the frequent occurrence of intrusions and repetitions, relative to a matched control group. On the other hand, there were no significant between-group differences on the component processes of retention, recognition discrimination, or serial clustering. The authors interpreted this finding by noting that, in methamphetamine-dependent individuals, there is executive dyscontrol associated with impaired verbal encoding and retrieval.

### **Organizational Strategies Improve Verbal Learning and Memory Performance**

Performance on verbal learning and memory tests can be improved via the effective use of organizational strategies that assist with learning (Murji et al., 2001). These strategies help test-takers learn and encode (and possibly consolidate) information in particular structured ways that assist with retention of information over time and hence assist with retrieval of those bits of information (Savage et al., 2001). For instance, Gsottschneider et al., (2011) demonstrated that in individuals diagnosed with schizophrenia, the use of *semantic clustering* (an organizational strategy associated with more efficient encoding and subsequent improved retrieval), improved patients' performance on a verbal list-learning task. Therefore, such strategies have the potential to improve delayed recall of previously learned information, especially on verbal list-learning tasks such as the HVLТ-R.

***Impaired semantic clustering in HIV.*** The use of this strategy is classed as an executive functioning ability (Elderkin-Thompson, Mintz, Haroon, Lavretsky, & Kumar, 2006). Researchers record a semantic cluster when, on a list-learning task such as the HVLТ-R, a participant or patient recalls, in direct succession, two words belonging to the same semantic category (Stricker, Brown, Wixted, Baldo, & Delis, 2002).

Numerous studies have shown that, on list-learning tasks, clade B HAND patients tend to use this organizational strategy less frequently than controls. For instance,



Gongvatana et al. (2007) reported that clade B HAD patients used semantic clustering significantly less frequently than HIV-positive patients with neuropsychological impairment, HIV-positive patients with minor cognitive-motor disorder, and healthy controls. This inefficient use of semantic clustering in patients affected by HAD appears to be generalizable to HIV-positive individuals with no HAND classification: Both Peavy et al. (1994) and Woods, Scott, et al. (2005) showed that clade B HIV-positive individuals who were not classified according to HAND categories showed significant impairment, compared to HIV-negative individuals, in the utilization of semantic clustering.

***Self-monitoring errors in HIV.*** Self-monitoring is an individual's ability to check and modify his or her performance on a given task (Bengtsson, Lau, & Passingham, 2009). The ability to self-monitor successfully is classed as an executive functioning ability (Pharo, Sim, Graham, Gross, & Hayne, 2011). Researchers record one type of self-monitoring error (a repetition error) when, on a list-learning task such as the HVLT-R, a participant repeats a word from the original word list that he or she has already recalled. For example, as mentioned previously, methamphetamine-dependent users demonstrated poor self-monitoring errors, through the excessive production of repetition errors, on the HVLT-R (Woods, Rippeth, et al., 2005).

There is little literature on self-monitoring errors in HIV. Woods, Scott, et al. (2005) reported an interesting pattern of data, however: When comparing a clade B sample of HIV-positive individuals to matched HIV-negative controls, there were no significant between-group differences in terms of repetition errors.

Given the literature reviewed above, one reasonable hypothesis is that poor performance on the HVLT-R might arise not only from pure memory deficits but also from executive dyscontrol of memory processes and impaired executive functioning (i.e., less use of semantic categorization and more self-monitoring errors).

### **Summary and Rationale for the Present Study**

Sub-Saharan Africa is home to more than two-thirds of the world's HIV-infected population. Due to the widespread use of HAART medication, there is a high prevalence of South African individuals living with HIV as a chronic disease. This situation warrants extensive research investigating the neuropsychological impairments associated with the virus. These neuropsychological impairments form the basis for classification of the various HIV-associated neurocognitive disorders (HAND), and these disorders follow a specific neuropathological pattern affecting discrete brain structures. Hence, the neuropsychology of

the categories within HAND follows specific patterns of impairment. One area of impairment is the domain of verbal learning and memory.

Such impairment can be traced, at least partially, to HIV-related damage to the hippocampus and to prefrontostriatal circuitry (Chang et al., 2001; Ernst, Chang, Jovicich, Ames, & Arnold, 2002; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008). Damage to the latter, in particular, results in executive dyscontrol of particular component processes of verbal learning and memory performance (Woods, Scott, et al., 2005). This executive dyscontrol (i.e., inefficient executive control over the episodic memory processes of encoding and retrieval) is demonstrated through impairments in free recall, learning, and semantic clustering, and the production of repetition errors, on verbal list-learning tasks (Gongvatana, et al., 2007; Peavy et al., 1994; Woods, Scott, et al., 2005).

Research into the neuropsychology of HIV has focused on clade B-infected populations. Although studies in clade C-infected populations have confirmed a similar pattern of poor performance on tests of verbal learning and memory, none have explored the specific memory profile associated with HIV infection in clade C populations, and none have done so with particular reference to prefrontostriatal circuitry damage and executive dyscontrol. Hence, this is the first study in a clade C-infected population that extends its examination beyond general verbal memory impairment into the possibility of executive dyscontrol of verbal learning and memory, as measured by the specific component processes of the HVLТ-R.

### **Specific Aims and Hypotheses**

Broadly stated, the purpose of this study was to use the various component processes of the HVLТ-R to address the question of whether clade C HIV-positive participants in South Africa show the same pattern of cognitive deficits as the clade B participants who are usually described in the HIV neuropsychology literature. I tested these hypotheses, all of which were based on findings in clade B HIV-positive samples (e.g., Carey et al., 2004; Gongvatana et al., 2007; Maki et al., 2009; Peavy et al., 1994; White et al., 1997; Woods, Scott, et al., 2005):

- 1) HIV-positive individuals will perform more poorly than their sociodemographically matched HIV-negative counterparts on measures of verbal learning (indicative of encoding impairment);
- 2) There will be no statistically significant between-group differences on measures of consolidation of previously-learned information;

- 3) HIV-positive individuals will perform more poorly than their sociodemographically matched HIV-negative counterparts on measures of verbal recall and recognition memory (indicative of impaired retention);
- 4) HIV-positive individuals will perform more poorly than their HIV-negative counterparts on measures of executive functioning (measured, for instance, by their relative inability to utilize organizational strategies such as semantic clustering, and by the relatively frequent occurrence of self-monitoring errors such as repetitions during recall).

The significance of this study is that it examines performance on a widely-used test of verbal learning and memory taking into account not only the conventional recall and recognition measures, but also analyzing the contribution of the various component processes of the HVLTR, such as serial versus semantic clustering and the presence of self-monitoring errors on recall trials. Identifying the nature of poor performance specific to South Africa's clade C HIV-positive population (i.e., answering the question of whether poor performance in clade C HIV is consistent with findings of poor performance on particular aspects of verbal learning and memory in clade B HIV) has important implications for the type of rehabilitation HIV patients should receive in this country.

## **Methods**

### **Design and Setting**

This case-control study compared two groups, one consisting of HIV-positive individuals and one consisting of HIV-negative individuals. All study procedures took place in the Department of Psychiatry and Mental Health at Groote Schuur Hospital.

### **Participants**

This study is part of a large on-going research programme that aims to investigate neurocognitive deficits associated with HIV, clade B type, in South African individuals. The HIV-positive participants in this study were recruited from three primary health clinics (one in Khayelitsha Site C, one in Mitchell's Plain, and one in Woodstock) as part of that research programme. Representatives of the research team invited HIV-positive clinic patients attending pre-Antiretroviral Therapy (ART) counselling visits to participate in the study. Hence, the HIV-positive patients in this study had never been on ART medication, and, furthermore, were not on ART medication at the time of testing.

HIV-negative participants were recruited from voluntary counselling and testing clinics located close to the HIV clinics mentioned above. The research team also allowed snowball recruitment for HIV-negative participants.

The final sample consisted of 106 participants ( $n = 53$  per group). Participants were right- and left-handed Black males and females, between 18 and 42 years of age. Groups were matched on language of test administration (Xhosa), home language (Xhosa), age at the time of testing, and years of education completed successfully.

**Exclusion criteria.** Exclusion criteria were largely consistent across groups, with a few differences. Potential participants were excluded if they refused to sign the informed consent form, or if they were identified with a central nervous system neurological condition, unless fully treated. Other exclusion criteria included uncorrected visual impairment and hearing loss, disability in the upper body that could affect motor performance, and colour-blindness. Individuals who had abused alcohol and/or psychoactive substances during the preceding 3 months, or who had an uncontrollable medical condition such as epilepsy or diabetes mellitus, were not included in the study.

The following additional exclusion criteria were applied specifically to the HIV-positive group: a contra-indication to magnetic resonance imaging (MRI) like claustrophobia, metal implanted inside the body, or pregnancy. Potential HIV-positive participants were also excluded if they had a history of head injury resulting in either a loss of consciousness for more than 30 minutes or overnight hospitalization.

The following additional exclusion criteria were applied specifically to the HIV-negative group: a history of head injury leading to the loss of consciousness for at least 5 minutes, or hospitalization for more than 24 hours. Potential HIV-negative participants with neurologic diagnoses such as multiple sclerosis, encephalitis, Huntington's disease, Parkinson's disease, Alzheimer's disease, or with a history of stroke, brain surgery, or a consult to a professional for thinking or memory problems, were also excluded. Furthermore, potential HIV-negative participants on electroconvulsive treatment, or who were prescribed antidepressant, antipsychotic, or anti-anxiety medications, were excluded.

## **Materials**

**Hopkins Verbal Learning Test-Revised (HVLTR).** The instrument demonstrates strong psychometric properties. Benedict, Schretlen, Groninger, and Brandt (1998) showed that test-retest reliability, with a retest interval ranging from 14 to 134 days ( $M = 46.66$ ,  $SD = 30.1$ ), was in the moderate-to-strong range for learning trial 1 ( $r = .55$ ), learning trial 2 ( $r =$

.67), learning trial 3 ( $r = .78$ ), total recall across learning trials 1 through 3 ( $r = .74$ ), and the delayed recall trial ( $r = .66$ ).

In terms of concurrent validity, Shapiro, Benedict, Schretlen, and Brandt (1999) showed that total recall across the three learning trials and performance on the delayed recall trial correlated strongly with performance on the Wechsler Memory Scale-Revised Logical Memory subtest (Wechsler, 1987;  $r = .75$  and  $.77$ , respectively). In terms of construct validity, the HVLTR demonstrates moderate Spearman's rho correlations of  $.43$  for the semantic clustering HVLTR index and executive functions, and  $-.46$  for the retrieval index and executive functions (Woods et al., 2005).

The HVLTR has been used in a variety of cross-cultural settings, including Southern India (Das Gupta et al., 2007; Yepthomi et al., 2006) and China (Cysique et al., 2007). In South Africa, the version of the HVLTR used in this study has been used to examine the relationship between the Apolipoprotein E genotype and neuropsychological function (Hoare, Westgarth-Taylor, Fouche, Combrinck, et al., 2012), and to examine the relationship between prospective memory impairment and white matter areas in the brain (Hoare, Westgarth-Taylor, Fouche, Spottiswoode, et al., 2012). In both studies, the HVLTR was administered as part of a neuropsychological test battery to assess the specific domain of verbal learning and memory. The HVLTR was modified for use in the current study (and in the studies by Hoare, Westgarth-Taylor, Fouche, Combrinck, et al. (2012) and Hoare, Westgarth-Taylor, Fouche, Spottiswoode, et al. (2012) by three South African neuropsychologists with a great deal of experience testing clinical populations in this country. The modification entailed replacing four items from the original test (all in the semantic category of precious stones: *emerald, sapphire, opal, pearl*) with items deemed more culturally appropriate and more familiar to the participants (all in the semantic category of clothing: *shoes, pants, blouse, and skirt*.) This modification was made after a series of consultative meetings, all held before the launch of the research programme within which this study is nested, focused on the appropriateness of various tests and test items to be included in that programme's protocol.

### **Procedure**

The testing session took place in an isolated, distraction-free room in UCT's Department of Psychiatry and Mental Health. Three examiners were responsible for test administration. Examiner 1 was a 34-year-old male lay counsellor. Examiner 2 was a 28-year-old female lay counsellor, with a diploma in student administration. Examiner 3 was a 37-year-old female nurse. All examiners had a home language of isiXhosa. They were trained

extensively by clinical and neuropsychologists from UCT's Department of Psychiatry and Mental Health, and were supervised in their test administration by these same professionals.

Participants were either transported by one of the recruiters to Groote Schuur Hospital and back home, or took public transport. Upon arrival, they were administered an informed consent form in their home language (See appendix A and B). After reading through and signing the consent form, they were administered a neuropsychological test battery that contained the HVLТ-R. The HVLТ-R was the 12<sup>th</sup> test administered, and was always administered at the same point in every session. The test was administered in participants' test language of preference (isiXhosa, in the case of all participants in this study), which they indicated before the start of the testing session. The entire neuropsychological test session lasted up to 5 hours, depending on how quickly the participant completed the required tasks. Participants were allowed to take a break at any point during the session. Upon completion of the neuropsychological test battery, participants were thanked, remunerated, and returned to their homes.

In terms of data recording, the examiner recorded scores on each learning trial, on the total of the three learning trials, and on the delayed recall trial. For each of those trials, the examiner recorded the order in which words were recalled. For the recognition trial, the examiner recorded the total score and the total number of false positives (including the number of these that pertained to words related to one of the target list's semantic categories (i.e., semantically-related words), and the number that pertained to semantically-unrelated words). The examiner also recorded the total number of intrusions and repetitions committed across learning trials 1-3, on the delayed recall trial, and on the learning and delayed recall trials combined.

### **Ethical Considerations**

The Human Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences granted ethical approval for the research programme within which this study was nested.

Regarding consent and confidentiality, participants read and signed informed consent documents that confirmed (a) their participation was entirely voluntary; (b) they were allowed to withdraw from the study at any point without consequences; and (c) the data they provided would be kept confidential and anonymous. To ensure that these conditions were upheld, each participant was assigned a unique study number. That number, but no other identifying information, was recorded on their testing form. Only researchers involved in the project had access to the key linking participant names with study numbers.

Regarding potential risk associated with the study procedures, no physical, psychological, or social harm was inflicted upon participants. There was a risk of fatigue, given that the neuropsychological testing session could have lasted up to 5 hours in some cases; as noted above, however, participants were allowed to take small breaks throughout the testing session. They were also not obligated to complete all tasks on the neuropsychological test battery; if they wished to skip a task, they were able to do so without penalty.

Regarding benefits of study involvement, participants (a) were remunerated R150 to compensate their transportation costs, (b) took part in a mental health interview, which allowed the research team to diagnose and formulate a treatment plan for any mental health problems, and (c) were afforded the opportunity to have the research team provide them with the support and assistance they required to manage their HIV. Additionally, administration of the comprehensive neuropsychological test battery allowed the research team to detect, and possibly treat, cognitive impairments. Furthermore, this study benefits the scientific community, as it allows researchers to create treatments specific to participants' impairments, and to provide direction for further studies that can broaden scientific knowledge on HIV-associated neurocognitive disorders.

Participants were not debriefed formally, but those with clinical problems or psychological distress were referred to appropriate sources for counselling or assistance.

### **Data Management and Statistical Analysis**

**Power analysis and sample selection.** The sample size was set at  $N = 106$  because a power analysis suggested that this number was adequate to achieve a power of .80, given a medium effect size (Cohen's  $d = 0.50$ ) and an alpha of .05 (Erdfelder, Faul, & Buchner, 1996). Hence, from the total number of participants who had been enrolled in the larger research programme between February 2006 and February 2011 ( $n = 123$  HIV-negative;  $n = 165$  HIV-positive), I selected 53 HIV-positive individuals with a home language of Xhosa who had also been tested in Xhosa. For each HIV-positive participant thus selected, I selected an HIV-negative participant matched for home language, language of test administration, age (within 2 years), and education (within 2 years).

**Calculating semantic and serial clusters.** During administration of the HVLTR, the examiner recorded the order of words recalled by each participant for each of the three learning trials, and for the delayed recall trial. Using those records, I used a method proposed by Stricker et al. (2002) to calculate semantic and serial cluster scores for each of those four trials. These authors' List-Based Semantic Clustering and Serial Clustering Indices control

for the possibility that participants randomly recall words by chance (i.e., that their recall does not utilize any clustering strategy).

The first step in these calculations was to record semantic and serial clusters in the conventional manner. Hence, I recorded a semantic cluster when the participant recalled two words from the same semantic cluster (animals, human dwellings, or clothing) in succession. Similarly, I recorded a serial cluster when the participant recalled two words in succession that appeared in the same order of the target list. In this way, I recorded the number of semantic and serial clusters for each of the three learning trials, and for the delayed recall trial.

The next step was to use the equations presented by Stricker et al. (2002) for List-Based Semantic and Serial Clustering Indices. The formulas to calculate these two indices were created by Frender and Doubilet (1974). The formula for List-Based Semantic Clustering is:  $LBC_{sem} = OBS_{sem} - EXP_{sem}$ , where  $OBS_{sem}$  is the observed semantic cluster scores (the number of semantic clusters I calculated per participant, per trial) and  $EXP_{sem}$  is the expected semantic cluster scores.  $EXP_{sem}$  is calculated according to the following formula:  $EXP_{sem}$  for specific trial =  $[(r - 1) (m-1) / N_L - 1]$ , where  $r$  is the number of correct words recalled on the specific trial,  $EXP_{sem}$  is calculated according to the following formula:  $EXP_{sem}$  for specific trial =  $[(r - 1) (m-1) / N_L - 1]$ . In this formula,  $r$  is the number of correct words recalled on the specific trial,  $m$  is the number of words per semantic category on the HVLT-R original word list (i.e. 4), and  $N_L$  is the total number of words on the HVLT-R list (i.e., 12).

The interpretation of any List-Based Semantic Clustering score is that this calculated value represents the amount of observed clusters that *would* have occurred during recall, if the individual were to randomly recall the target words. Therefore a large negative score means that the participant is using another form of organizational strategy (i.e., one that is not semantic) to recall words. In the case of the HVLT-R, a participant who recalls all 12 words on the target word list, in the exact same order that the words are presented, will have the most negative score.

The formula for List-Based Serial Clustering is:  $LBC_{ser} = OBS_{ser} - EXP_{ser}$ , where  $OBS_{ser}$  is the observed serial cluster scores (the number of serial clusters I calculated per participant, per trial), and  $EXP_{ser}$  is the expected serial cluster scores.  $EXP_{ser}$  is calculated according to the following formula:  $EXP_{ser}$  for specific trial =  $(r - 1) / N_L$ , where, once again,  $r$  is the number of correct words recalled on the specific trial, and  $N_L$  is the number of words on the original word list. The formula for  $EXP_{ser}$  differs from the formula for  $EXP_{sem}$ , as it is



highly unlikely that participants would randomly recall words in a serial clustering manner, even if they were to recall the entire word list at random. Again, the interpretation of scores for this formula is that large negative scores indicate a tendency to recall words in a non-serial manner, whereas positive scores indicate a tendency to recall words serially.

**Outcome variables.** Regarding sociodemographic information, the examiner recorded participants' self-reports of age, years of education, gender, and home language in each individuals' information file. Handedness was also determined by self-report, and was confirmed by the examiner's observations during testing.

Hypothesis 1 stated that the HIV-positive group would perform more poorly than their HIV-negative counterparts on measures of verbal learning (encoding). Therefore, the first set of outcome variables of interest were performance on the following HVLT-R measures: (a) Total Recall (the total number of words recalled correctly on learning trials 1-3); and (b) Learning Slope (the average number of newly recalled correct words for each learning trial).

Hypothesis 2 stated that there would be no significant between-group differences on measures of consolidation of previously learned verbal information. Therefore, the second set of outcome variables of interest were performance on the following HVLT-R measures: (c) Percent Retained (number of words recalled correctly on the delayed recall trial divided by number of words recalled correctly on either trial 2 or 3, depending on which is the highest); (d) Total Intrusions Errors (words produced on the three learning trials and delayed recall trial that were not on the target list); (e) Recognition Discrimination Index (number of true positive words (i.e., number of words identified correctly as being on the target list) minus the number of false positive words (i.e., number of words identified incorrectly as being on the target list)).

Hypothesis 3 stated that HIV-positive group would perform more poorly than their HIV-negative counterparts on measures of verbal recall and recognition memory (retention). Therefore, the third set of outcome variables of interest were performance on the following HVLT-R measures: (f) Delayed Recall (number of words correctly recalled); and (g) Retrieval Index (recognition discrimination index score minus delayed recall score).

Hypothesis 4 stated that the HIV-positive group would perform more poorly than their HIV-negative counterparts on measures of executive functioning. Therefore, the fourth set of outcome variables of interest were (h) Total Repetition Errors (words recalled correctly but repeated on the same trial); (i) Semantic Clustering; (j) Serial Clustering; (k) Semantically Related False Positive Errors (identifying any of the six semantically related non-target words on the recognition trial, as being on the original word list); (l) Semantically Unrelated False

Positive Errors (identifying any of the six semantically-unrelated non-target words on the recognition trial, as being on the original word list).

**Between-group comparisons.** Inferential statistical analysis occurred over two steps. First, to show that the two groups were well matched, I calculated descriptive statistics for group sociodemographic characteristics, and conducted between-group comparisons of those data. Second, to test the study's hypotheses, I used a series of between-group comparisons, one for each of the outcome variables listed above. For each between-group comparison of a continuous variable, I examined the assumptions underlying parametric statistical tests (homogeneity of variance, measured through Levene's test; normally distributed data; independence of observations). If these assumptions were not violated, I used an independent samples *t*-test. If one or more of these assumptions were violated, I used a Mann-Whitney *U*-test. For each between-group comparison of a categorical variable, I used a chi-square test of contingency.

All statistical analyses were conducted using SPSS version 20. Alpha was set to a level of .05 for all decisions determining statistical significance. A Bonferroni corrected *p*-value was used in order to control for familywise errors; this value depended upon the number of dependent variables related to the various hypotheses. I calculated the appropriate effect size estimates for all between-group comparisons. Effect sizes were interpreted as being either small (0.20), medium (0.50), or large (0.80), according to convention (Cohen, 1988).

## Results

### Sample Characteristics

Table 1 displays sociodemographic characteristics of the two groups. As can be seen, the groups were matched successfully on age and years of education. There was a relatively uneven sex distribution across the groups, however, with the HIV-negative group containing a more even male:female split. Overall, the sample was aged between 18 and 42 years ( $M = 29.30$ ,  $SD = 3.76$ ), had between 6 and 12 years of education ( $M = 10.52$ ,  $SD = 1.49$ ), was mostly female ( $n = 78$  females,  $n = 28$  males), and was mostly right-handed ( $n = 99$  right-handed,  $n = 7$  left-handed).

Table 1  
*Sociodemographic Characteristics of the Current Sample (N = 106)*

Variable	Group		$t / X^2$	$p$	ESE
	HIV-positive ( $n = 53$ )	HIV-negative ( $n = 53$ )			
Age	29.36 (3.77)	29.25 (3.77)	0.15	.88	0.03 <sup>a</sup>
Education	10.45 (1.46)	10.58 (1.54)	-0.45	.65	0.09 <sup>a</sup>
Sex (female:male)	46:7	32:21	9.51	.002*	0.30 <sup>b</sup>
Handedness (left:right)	4:49	3:50	0.15	.70	0.04 <sup>b</sup>

*Note.* For the variables *Age* and *Education*, means are presented with standard deviations in parentheses. ESE = Effect size estimate. <sup>a</sup>Estimate of effect size using Cohen's  $d$ . <sup>b</sup>Estimate of effect size using Cramer's  $V$ .

\* $p < .05$ .

### Learning, Memory, and Executive Functioning

Table 2 displays the results of the series of independent-samples  $t$ -tests, or Mann-Whitney  $U$ -tests, relevant to Hypotheses 1, 2, 3, and 4.

As can be seen, Hypothesis 1 (that HIV-positive participants would perform more poorly than their HIV-negative counterparts on HVLT-R measures of verbal learning) was confirmed only partially: There were significant between-group differences on the sum of learning across trials 1-3, with HIV-positive participants performing significantly more poorly than their HIV-negative counterparts. A medium effect size was associated with this comparison. There was, however, no significant between-group difference with regard to Learning Slope, and only a small effect size was associated with this comparison.

Regarding Hypothesis 2 (that there would be no significant between-group differences in terms of consolidation of previously-learned HVLT-R verbal information), the prediction was again confirmed only partially: There were no significant between-group differences on the Percent Retained (small effect size) and Recognition Discrimination Index (medium effect size) measures. There were, however, significant differences (unexpectedly, in favour of HIV-positive group) on Total Intrusion Errors (large effect size).

Regarding Hypothesis 3 (that HIV-positive participants would perform more poorly than their HIV-negative counterparts on HVLT-R measures of verbal memory), the prediction was not confirmed: There were no significant between-group differences on any of these measures, and small effect sizes were associated with each comparison.

Regarding Hypothesis 4 (that HIV-positive participants would perform more poorly than their HIV-negative counterparts on HVLT-R measures of executive functioning), the

prediction was not confirmed. In fact, the HIV-negative participants performed more poorly than their HIV-positive counterparts on some measures: Across the recall trials, they committed more repetition errors (significant at the Bonferroni-corrected  $p$ -value, and associated with a large effect size), and on the recognition trials they produced more semantic and more non-semantic false positives (both significant at the conventional  $p$ -value, but neither at the corrected value, and associated with medium and large effect sizes, respectively).

Regarding serial and semantic clustering, as Table 2 shows there were no significant between-group differences in organizational strategy for retrieval across the learning trials or on the delayed recall trial (associated with small effect sizes). Of note, however, is that participants in both groups tended to use semantic clustering more on the delayed recall trial than on the learning trials: A 2 x 2 repeated-measures ANOVA found a significant main effect of Trial,  $F(1, 99) = 258.24, p < .001$ , partial  $\eta^2 = .72$ , but no significant main effect of Group,  $F(1, 99) = .001, p = .98$ , partial  $\eta^2 < .001$ , and no Group x Trial interaction,  $F(1, 99) = .03, p = .86$ , partial  $\eta^2 < .001$ .<sup>1</sup> In contrast, there were no significant increases (or decreases) in the use of serial clustering from the learning trials to the delayed recall trial.

### **Post-Hoc Exploratory Analyses**

**Nature of intrusion and repetition errors.** To explore intrusion errors further, I conducted Mann Whitney  $U$ -tests to examine whether there were between-group differences in semantic intrusion errors (i.e., intrusions that were from one of the target list's three semantic categories) and in non-semantic intrusion errors (i.e., any other kinds of intrusions). As Table 3 shows, the HIV-negative group produced, across the three learning trials and the delayed recall trial, significantly more semantic intrusions (large effect size). However, the between-group difference with regard to non-semantic intrusions did not reach statistical significance when the Bonferroni correction was applied (medium effect size).

Similar analyses explored the nature of repetition errors produced. As Table 3 shows, the HIV-negative group produced, across the three learning trials and the delayed recall trial, significantly more repetitions within all three semantic categories (large effect size in each case).

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<sup>1</sup>Because Mauchly's Test of Sphericity was statistically significant,  $p < .001$ ,  $\epsilon = 1.00$ , the Greenhouse-Geisser corrected  $F$ -values and degrees of freedom are reported here.

Table 2  
*Between-Group Comparisons: Learning, memory, and executive functioning (N = 106)*

HVLТ-R outcome variable	Group		<i>t</i> / <i>U</i>	<i>p</i>	ESE
	HIV-positive ( <i>n</i> = 53)	HIV-negative ( <i>n</i> = 53)			
Learning / Encoding					
Total Recall	22.45 (3.95)	24.74 (4.14)	-2.91	.002**†	0.56
Learning Slope	3.00 (1.59)	3.15 (1.57)	-0.49	.31	0.09
Consolidation					
Percent Retained	1.08 (1.26)	0.84 (0.17)	1.39	.34	0.26
Total Intrusion Errors	1.40 (1.87)	3.67 (4.23)	-3.55	.002**†	0.69
Recognition Discrimination Index	10.06 (1.39)	9.32 (2.26)	2.02	.010*	0.39
Memory / Retrieval					
Delayed Recall	8.19 (1.79)	8.23 (2.14)	-0.10	.46	0.02
Retrieval Index	1.87 (1.82)	1.09 (2.23)	1.96	.05	0.38
Executive functioning					
Recall trials					
Total Repetition Errors	2.15 (2.17)	4.75 (3.51)	-4.55	< .001***†	0.89
Semantic Clustering <sup>a</sup>					
Learning trials 1-3	0.39 (0.98)	0.43 (1.04)	-0.18	.43	0.04
Delayed recall trial	1.10 (1.52)	1.08 (1.46)	0.07	.48	0.01
Serial Clustering <sup>a</sup>					
Learning trials 1-3	0.17 (0.56)	0.08 (0.51)	-0.77	.21	0.17
Delayed recall trial	0.03 (0.86)	0.15 (0.90)	-.05	.25	0.14
Recognition trials					
Semantic False Positives	1.19 (0.96)	1.56 (1.07)	-1.86	.04*	0.36
Non-Semantic False Positives	0.11 (0.42)	0.33 (0.65)	-2.00	.01*	0.56

*Note.* In the second and third 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 cases where there were a priori predictions of significant between-group differences (i.e., measures of learning, memory, and executive functioning), and two-tailed in cases where there were no such predictions (i.e., measures of consolidation). <sup>a</sup>Data analysed for only 49 HIV-positive participants and 52 HIV-negative participants due to administrator error in recording word order for all participants.

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001. †Significant at Bonferroni-corrected *p* (.05/12 = .004).

Table 3  
*Between-Group Comparisons: Types of intrusion and repetition errors (N = 106)*

HVLТ-R outcome variable	Group		<i>U</i>	<i>p</i>	ESE
	HIV-positive ( <i>n</i> = 53)	HIV-negative ( <i>n</i> = 53)			
Intrusion error type					
Semantic	1.19 (1.68)	2.74 (2.66)	896.00	.001***†	0.69
Non-semantic	0.15 (0.50)	0.76 (2.29)	1189.50	.038*	0.37
Repetition error type					
Clothing	0.64 (0.86)	1.49 (1.59)	934.00	.002***†	0.66
Dwelling	0.66 (0.94)	1.49 (1.61)	927.50	.001***†	0.62
Animal	0.85 (1.23)	1.68 (1.68)	975.50	.004***†	0.56

*Note.* HVLТ-R = Hopkins Verbal Learning Test - Revised. ESE = effect size estimate; in this case, Cohen's *d*. Errors are summed across the three learning trials and the delayed recall trial.

\**p* < .05. \*\**p* < .01. \*\*\**p* < .001. †Significant at Bonferroni-corrected *p* (.05/5 = .01), two-tailed.

**Interactions with sex.** Because the male:female distribution was so lopsided (only 7 of the 53 HIV-positive participants were male, whereas 21 of the 53 HIV-negative participants were male), I created a series of univariate general linear models to investigate whether (a) after accounting for the main effect of Sex, the significant between-group differences reported above remained so, and (b) Group x Sex interactions had a significant effect on the HVLT-R outcome variables where significant between-group differences had been detected. None of these models were significant: For all cases,  $ps > .51$  for main effect of Sex,  $ps > .21$  for Group x Sex interaction, and  $R^2 < .18$ ).

### Discussion

The general purpose of this study was to use the various component processes of the HVLT-R to address the question of whether clade C HIV-positive participants in South Africa show the same pattern of cognitive deficits as the clade B participants who are usually described in the HIV neuropsychology literature. I tested four specific hypotheses, all of which were based on findings in clade B HIV-positive samples. For the most part, the patterns of data observed here did not confirm the a priori predictions; in other words, clade C HIV-positive individuals in this sample showed a different pattern of cognitive impairment on the HVLT-R component processes than clade B HIV-positive individuals are reported to do. More specifically, the clade C HIV-positive individuals studied here were not impaired on certain measures of verbal learning and memory and executive functioning. In fact, on some HVLT-R measures, HIV-positive participants actually performed *better* than their HIV-negative counterparts.

Hypothesis 1 stated that HIV-positive individuals would perform more poorly than their sociodemographically matched HIV-negative counterparts on HVLT-R measures of verbal learning (an impairment indicative of encoding difficulties). Research in clade B samples (Maki et al., 2009; Peavy et al., 1994; White et al., 1997; Woods, Scott, et al., 2005) suggests that HIV-positive individuals perform more poorly on measures of total recall across the learning trials, and on the slope of the learning curve across those trials. Although the clade C HIV-positive individuals in this sample demonstrated poorer performance on the former measure (supported by a large effect size), there were no between-group differences on the latter measure (supported by a small effect size). Therefore, hypothesis 1 was confirmed only partially.

Hypothesis 2 stated that there would be no statistically significant between-group differences on HVLT-R measures of consolidation of previously-learned information. Again,

this hypothesis was confirmed only partially: Clade C HIV-positive participants in this study performed no differently than their HIV-negative counterparts in terms of percentage of learned information retained over a consolidation interval (small effect size) and on the ability to discriminate, on the recognition trial, between words presented before and new words (medium effect size). Taken together, these findings are only partially consistent with clade B HIV research: HIV-positive individuals in those studies show *poorer* performance on the Percent Retained measure, and *comparable* performance on Recognition Discrimination Index (e.g., Woods, Scott, et al., 2005).

Interestingly, Clade C HIV-positive individuals in this sample committed *fewer* intrusion errors than their HIV-negative counterparts, a finding consistent with the pattern reported by Woods, Scott, et al. (2005) for clade B HIV-positive individuals. In that clade B sample, the production of more intrusion errors by HIV-negative participants was associated with their increased utilization of the semantic structure of words during recall (as demonstrated by their greater production of semantic versus non-semantic intrusions).

Post-hoc analysis of this study's data confirmed a similar pattern: the HIV-negative group produced more semantic intrusions than the HIV-positive group across the three learning trials and the delayed recall trial (a comparison supported by a large effect size). In other words, HIV-negative participants demonstrated comprehension of the semantic nature of the word list, but struggled to recall the target words belonging to those categories (Woods, Scott, et al., 2005). As a result, they produced many semantically-related words at both immediate free recall and delayed recall.

Hypothesis 3 stated that HIV-positive individuals would perform more poorly than their sociodemographically matched HIV-negative counterparts on HVLT-R measures of verbal recall and recognition memory (an impairment indicative of retention difficulties). This prediction was disconfirmed: there were no significant between-group differences in terms of performance on the delayed recall trial or on the Retrieval Index measure. This result stands in direct contrast to previous findings in clade B samples (e.g., Scott et al., 2006; Woods, Scott, et al., 2005).

Hypothesis 4 stated that HIV -positive individuals would perform more poorly than their sociodemographically matched HIV-negative counterparts on HVLT-R measures of executive control of learning and memory processes (e.g., semantic clustering). This prediction was not confirmed: HIV-positive participants in this sample produced significantly *fewer* repetition errors than HIV-negative controls, a finding inconsistent with clade B studies



(Woods, Scott, et al., 2005). Similarly, in terms of semantic and non-semantic false positives, HIV-positive participants produced *fewer* false positives of both kinds.

Furthermore, clade B HIV-positive individuals have demonstrated poorer utilization of semantic but not serial clustering (Gongvatana et al., 2007; Peavy et al., 1994; Woods, Scott, et al., 2005), a finding might underlie their weaker performance on tests of verbal learning and memory tests (Woods, Rippeth, et al., 2005). This finding was not replicated in this study: clade C HIV-positive individuals in this sample did *not* demonstrate poorer utilization of either serial *or* semantic clustering.

As reviewed earlier, the prefronto-striatal circuit has been implicated in clade B studies associating executive dyscontrol with poor performance on tasks of verbal learning and memory (Gongvatana, et al., 2007; Peavy et al., 1994; Woods, Scott, et al., 2005). This association is reflected through the diminished use of semantic clustering, and frequent occurrence of repetition errors, that result in poor performance across learning trials and on the delayed recall trial. However, results from this study indicate that clade C HIV-positive individuals *and* HIV-negative individuals did not utilize semantic clustering. Because both groups demonstrate this same pattern, this finding might be due external social factors such as the influence of culture and education. Furthermore, the HIV-positive group produced less repetition errors in comparison to their HIV-negative counterparts; another finding that could be attributed to external factors, or a confounding variable.

The currently observed patterns of data were not confounded by sociodemographic factors of home language, language of test administration, age at the time of testing, and years of education, as the two groups were matched on those factors. There was, however, an uneven distribution of sex across the two groups (many more females than males in the HIV-positive group, and a more even match in the HIV-negative group). This uneven distribution is reflective of the fact that there are significantly more HIV-positive women than HIV-positive men in South Africa (UNAIDS, 2010; CDC, 2008).

Although there have been no suggestions in the literature that speak to the effect of sex on HIV cognition (Maki & Martin-Thormeyer, 2009; Pereda et al., 2000; Robertson et al., 2004), I decided to conduct a post-hoc analysis to confirm that sex did not play a role in any of the statistically significant between-group variables in this study. The analysis duly confirmed that sex was a non-significant predictor of HVLT-R performance in this sample.

An important aspect of this study is that all the HIV-positive individuals in this sample were not on HAART medication at the time of testing. This fact stands in contrast to many previous studies in this field (e.g., Suarez et al., 2001; Tozzi et al., 2005) and notably of

clade B HIV-positive individuals tested using the HVLTR (Woods, Scott, et al., 2005). HAART has been associated with improved cognitive performance in both clade B HIV-positive (Suarez et al., 2001) and clade C HIV-positive (Joska et al., 2010; Joska et al., 2012) individuals. Therefore, findings from this study's untreated HIV-positive sample cannot be attributed to the positive effects of medication, an important factor that is not always controlled for in other HIV studies.

### **Limitations and Suggestions for Future Research**

Although the current study had sufficient power to detect the effects under consideration, and although the research team screened the participants carefully to ensure that potential confounding variables did not contaminate the analyses, there are still some limitations that bear consideration and that suggest caution in interpreting the data. First, IQ and CD4 cell count data were unavailable due to circumstances of the larger ongoing research project in which this study is nested. Regarding IQ, this has been a confounding variable influencing results in various situations, therefore groups should be matched according to this variable. Relatively recent literature (e.g., Dennis et al., 2009) argues that IQ should not always be used as a covariate in studies of neurocognitive functioning, however. The line of reasoning here is that general intelligence, as measured by standard IQ tests, is more characteristic of an aptitude (skill) measure, instead of an achievement and performance measure. This makes years of education completed a better achievement and performance measure, as proven by its association with cognitive functioning (Rindermann, 2008).

Regarding CD4 cell counts, higher counts ( $> 500$  cells/mm<sup>3</sup>) have been associated with better cognitive performance (Ellis et al., 2011), and lower counts ( $< 200$  cells/mm<sup>3</sup>) with poorer cognitive performance (Das Gupta et al., 2007; Harezlack, 2011). Hence, measuring CD4 counts in studies of cognitive function in HIV is critical to interpretation of performance. In the current study, although CD4 counts were not available, it is reasonable to assume that they were not below 200 cells/mm, as none of the participants were HAART-treated.

Another limitation of this study is that the psychometric properties of the modified version of the HVLTR used here have not been demonstrated. As mentioned previously, the HVLTR was modified for this study by replacing the precious stones semantic category with an items of clothing category. Although this change should not, on the face of it, destroy the well-established and strong psychometric properties of the original HVLTR, South African researchers should attempt to validate the modified version, particularly because there is

clinical demand for a psychometrically sound list-learning task in this country (Blumenau & Broom, 2011; Skuy, Schutte, Fridjhon, & O'Carroll, 2001).

A third limitation of this study is that there is no direct comparison of clade B and clade C HVLT-R performance. Although such a comparison was beyond the scope of the current project, burgeoning cross-national collaborations between our research group and laboratories in the global north (see, e.g., Hoare, Westgarth-Taylor, Fouche, Spottiswoode, et al., 2012; Joska et al., 2012) make clade B versus clade C neuropsychological studies imminently possible.

### **Summary and Conclusion**

Findings from a clade C HIV-positive South African sample demonstrated that this strain of the virus produces a different pattern of verbal learning and memory impairment than that produced by clade B of the virus. Specifically, the data here suggest that Clade C HIV-positive individuals are impaired only partially on components of the HVLT-R measuring verbal learning and memory, whereas clade B HIV-positive individuals show full impairment. Furthermore, the clade C HIV-positive participants studied here did not demonstrate the same degree of executive dyscontrol as found in clade B HIV-positive individuals.

This is the first study of clade C HIV neuropsychology to examine specific component processes of a task such as the HVLT-R, and to attempt a finer-grained analysis of neuropsychological performance in HIV. Previous clade C studies (e.g., Das Gupta et al., 2007; Yepthomi et al., 2006) have focused more broadly, using comprehensive neuropsychological batteries and concentrating on composite measures of cognitive function. These studies have only detected patterns of cognitive impairment similar to those reported for clade B samples (e.g., Peavy et al., 1994; White et al., 1997), and have rarely focused on characterising differences in presentation.

Findings from this study have important implications for the clinical setting. Verbal learning and memory impairments in HIV-positive individuals have been associated with difficulties in completing activities of daily living, such as medication adherence (Hinkin et al., 2002) and planning activities, as well as with lower employment rates (Benedict, Mezhir, Walsh, & Hewitt, 2000; Heaton et al., 2003). The data presented here indicate that clade C HIV-positive individuals are able to consolidate, retain, and retrieve information. These intact abilities mean that rehabilitation strategies for HIV individuals can utilize intact cognitive mechanisms to assist with activities of daily living.

Another major significant element of this study is that it examined verbal learning and memory on the HVLT-R in clade C HIV-positive South African individuals who were not on HAART medication. Most of the literature uses mixed HAART groups (Joska et al., 2010, 2012; Suarez et al., 2001), therefore this is one of the few studies with a clean, non-medicated sample.

The current data have important implications for the type of rehabilitation that clade C HIV-positive individuals might receive. Specifically, rehabilitation programs instituted in South Africa, or in any region where clade C proliferates, cannot be based on studies demonstrating patterns of cognitive deficits found in clade B HIV-positive populations; South African rehabilitation programs need to be tailored to the nature of impairments in its HIV-positive population.

Furthermore, findings from this study have important implications for the existing body of HIV neuroscientific literature: it characterizes and distinguishes between specific cognitive mechanisms that are either impaired or unimpaired in verbal learning and memory. Therefore, unlike other clade C HIV studies, the current study did not take the approach of viewing verbal learning and memory as a general cognitive domain that is impaired as a whole. Finally, understanding HIV-associated specific deficits in cognitive mechanisms underlying verbal learning and memory performance is beneficial in order to determine the cognitive status of infected individuals, and to describe how these specific deficits might affect their social, academic, and occupational functioning and activities of daily living.

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## Appendix A

**PARTICIPANT INFORMATION LEAFLET AND CONSENT  
FORM: INTERVIEW AND MRI**

**TITLE OF THE RESEARCH PROJECT:** Neurocognitive disorders in young adults with HIV/AIDS commencing anti-retro-viral treatment in the Western Cape

**PRINCIPAL INVESTIGATOR:** Dr John A. Joska

**ADDRESS:** Department of Psychiatry and Mental Health, J-block, Groote Schuur Hospital, Anzio Road, Observatory, 7925

**CONTACT NUMBER:** 021-404 2164/021-4042151

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

**What is this research study all about?**

- *The study will be conducted at the primary care antiretroviral clinics in Khayalitsha site C, Woodstock and Mitchells Plain. The study aims to include 200 HIV positive people and 50 HIV negative people.*
- *This study will perform a detailed interview when people start taking anti-retrovirals and again at one year, to find out if there are any problems in thinking or moving in people with HIV/AIDS. This is in order to understand why certain people with HIV/AIDS develop these problems. You will also be asked to provide a sample of blood- you will sign a **separate form** to provide this blood sample. You can decide not to give this sample if you wish, without it affecting any treatment you may receive. This blood sample will help us to understand HIV better in the future. Some people will be asked to undergo a brain scan.*

- *Patients who are eligible to enter to the study will be asked to sign this form. They will then have 2 interviews on one day of about 2 hours each, where they will be asked questions about themselves and their mental health. You will be given a break during these interviews and given refreshments. You will perform certain tests, like memory tests and movement tests. The interviews (without blood tests) will be repeated at one year.*
- *Not everyone who comes to the clinic will be asked to participate. We will choose people who are eligible, depending on if they have other mental problems or not..*
- *Apart from the interviews and tests, the study will not offer special treatment or medication. If a mental health problem is found, you will be referred for treatment at your nearest clinic. Any treatment related to HIV/AIDS you will also receive at your normal clinic.*

➤

### **Why have you been invited to participate?**

- *You have been invited to participate, because memory and thinking problems in HIV/AIDS are not properly understood by medical science. Younger people with these problems may demonstrate more clearly why they develop, in order for us to detect and treat these problems better in the future.*

### **What will your responsibilities be?**

- *You will be required to attend the study visits on time and to participate as fully as possible. This means that you will answer questions as fully and honestly as possible. If there are questions you do not want to or cannot answer, you should say so.*

### **Will you benefit from taking part in this research?**

- *You will benefit directly from the study in 2 main ways- first, a detailed mental health interview will be conducted, which will allow us to diagnose and treat any problems you may have. Second, any memory or thinking problems will be diagnosed, which will allow us to treat them if possible, but also to provide you with the assistance you need to manage with HIV/AIDS. In addition, information from this study may allow us to develop possible treatments for these problems, and to develop studies which will help us to understand these problems better.*

### **Are there in risks involved in your taking part in this research?**

- *This study may make you feel uncomfortable as you talk about mental health problems. You may feel embarrassed or shy. Sometimes painful information is shared. Also, some people feel that it is better not to know about memory or thinking problems.*
- *During the second visit in this study you will have a type of brain scan which will be done at the Cape Universities Brain Imaging Centre at Tygerberg Hospital. This scan is called an MRI (magnetic resonance imaging) scan. The scan will require you to lie on your back on a table that will move into the scanning machine for the 85 minutes it will take for the scan. During this time you will be able to close your eyes and rest. You will also be able to talk to the study doctor/assistant at all times during the scan if you should experience any discomfort. The scan is a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study team. As the scan is done in a relatively confined space, occasionally people become anxious. This does*

*not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings before we begin. When the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. At this time you will feel nothing and the noise is not harmful to you in any way. To minimize the possible discomfort associated with this, we will give you some soft earplugs and will also put earphones on so that you can listen to music if you so choose.*

- *These are the main risks. You should feel free to mention your feelings or concerns to any member of the study team*

### **If you do not agree to take part, what alternatives do you have?**

- *You are free not to participate or to withdraw at any time during the study. Your treatment will not be affected in any way. You may continue to attend your clinic. It would be helpful for the study team to let us know why you have decided not to take part, but you are free to not give a reason.*

### **Who will have access to your medical records?**

- *The information collected about you will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.*

### **Will you be paid to take part in this study and are there any costs involved?**

*You will not be paid to take part in the study but your transport costs will be covered for each study visit- The study nurse will give you R150 for this. She will also provide the money it costs to attend the clinic. There will be no costs involved for you, if you do take part.*

### **Is there anything else that you should know or do?**

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact Dr John Joska at tel 021-4042164 if you have any further queries or encounter any problems.
- You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- If you would like a copy of this information and consent form for your own records, please ask a member of the study team to give you one.

## Declaration by participant/guardian/treatment partner (circle)

By signing below, I ..... agree/agree on behalf of..... to take part in a research study entitled: *“Neurocognitive disorders in young adults with HIV/AIDS commencing anti-retro-viral treatment in the Western Cape”*.

I declare that (delete whichever is NOT applicable):

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that my taking part/my relative or friend’s participation in this study is **voluntary** and I/we have not been pressurized to take part.
- I/my relative or friend may choose to leave the study at any time and will not be penalized or prejudiced in any way.
- I/my relative or friend may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) ..... 200\_.

.....  
Signature of participant/guardian/treatment partner

.....  
Signature of witness

## Declaration by investigator

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

- I explained the information in this document to .....
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above

Signed at (*place*) ..... on (*date*) ..... 200\_.

.....  
Signature of investigator



## Appendix B

## **PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM: *INTERVIEW AND NEUROPSYCHOLOGICAL ASSESSMENT: CONTROLS***

**TITLE OF THE RESEARCH PROJECT:** Neurocognitive disorders in young adults with HIV/AIDS commencing anti-retro-viral treatment in the Western Cape

**PRINCIPAL INVESTIGATOR:** Dr John A. Joska

**ADDRESS:** Department of Psychiatry and Mental Health, J-block, Groote Schuur Hospital, Anzio Road, Observatory, 7925

**CONTACT NUMBER:** 021- 404 2164/021- 4042151

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff or doctor any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you do agree to take part.

This study has been approved by the **Research Ethics Committee of the Faculty of Health Sciences of the University of Cape Town** and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

### **What is this research study all about?**

- *The study will be conducted at the primary care antiretroviral clinics in Khayalitsha site C, Woodstock and Mitchells Plain. The study aims to include 200 HIV positive people and 50 HIV negative people.*
- *This study will perform a detailed interview and neuropsychological assessment when people start taking anti-retrovirals and again at one year, to find out if there are any problems in thinking or moving in people with HIV/AIDS. This is in order to understand why certain people with HIV/AIDS develop these problems. We will also do these assessments on the 50 HIV negative people.*
- *You will also be asked for a sample of blood. This will be used to look at your body's response to infection with HIV. Tests of inflammation will be done. This*

*will help us to understand if inflammation is important in the way that problems in thinking and memory happen in people with HIV/AIDS. The study will require about 30 mls (two tablespoons) for this purpose. This will involve minor discomfort at the time taking blood and may cause some reddening and bruising of your arm in this area. You may choose not to participate in this part of the study.*

- *Some people will be asked to have a type of brain scan which will be done at the Cape Universities Brain Imaging Centre at Tygerberg Hospital. This scan is called an MRI (magnetic resonance imaging) scan. The scan will require you to lie on your back on a table that will move into the scanning machine for the 85 minutes it will take for the scan. During this time you will be able to close your eyes and rest. You will also be able to talk to the study doctor/assistant at all times during the scan if you should experience any discomfort. The scan is a safe procedure if you have been screened correctly for the presence of any magnetic material on or inside you such as pace-makers, surgical clips and metal objects in the eyes. A formal screen for this will be done at the screening visit by a member of the study team. As the scan is done in a relatively confined space, occasionally people become anxious. This does not happen often, and if you feel anxious, we will spend time allowing you to get used to the surroundings before we begin. When the magnet in the machine is switched on, it will make some loud banging noises, but you will be clearly warned when this will take place. At this time you will feel nothing and the noise is not harmful to you in any way. To minimize the possible discomfort associated with this, we will give you some soft earplugs and will also put earphones on so that you can listen to music if you so choose*
- *Apart from these tests, the study will not offer special treatment or medication. If a mental health problem is found, you will be referred for treatment at your nearest clinic.*

### **Why have you been invited to participate?**

- *You have been invited to participate, because memory and thinking problems in HIV/AIDS are not properly understood by medical science. We also need to compare these problems in people with and without HIV to see if there are differences.*

### **What will your responsibilities be?**

- *You will be required to attend the study visit on time and to participate as fully as possible. This means that you will answer questions as fully and honestly as possible. If there are questions you do not want to or cannot answer, you should say so.*

### **Will you benefit from taking part in this research?**

- *You will receive little benefit directly from the study. If you do have a mental health problem, we will be able to refer you to someone who may help. Second, if any memory or thinking problems are identified, we will be able to explain these to you. In addition, information from this study may allow us to understand these problems better, and to develop studies which will help us to treat them better.*

### **Are there in risks involved in your taking part in this research?**

- *This study may make you feel uncomfortable as you talk about mental health problems. You may feel embarrassed or shy. Also, some people feel that is it better not to know about memory or thinking problems.*
- *These are the main risks. You should feel free to mention your feelings or concerns to any member of the study team*

### **If you do not agree to take part, what alternatives do you have?**

- *You are free not to participate in the study or to refuse parts of the study.*

### **Who will have access to your medical records?**

- *The information collected about you will be treated as confidential and protected. If it is used in a publication or thesis, your identity will remain anonymous. Only the direct study team will have full access to the information. If we need to refer you to a clinic for treatment, we will provide them with the relevant information needed to treat your condition.*

### **Will you be paid to take part in this study and are there any costs involved?**

*You will not be paid to take part in the study but your transport costs will be covered for the study visit- The study nurse will give you R150 for this. She will also provide the money it costs to attend the clinic. There will be no costs involved for you, if you do take part.*

### **Is there anything else that you should know or do?**

- You should inform your family practitioner or usual doctor that you are taking part in a research study.
- You can contact Dr John Joska at tel 021-4042164 if you have any further queries or encounter any problems.
- You can contact the Research Ethics Committee of the Health Sciences Faculty of the University of Cape Town 021-4066338 if you have any concerns or complaints that have not been adequately addressed by your study doctor.
- If you would like a copy of this information and consent form for your own records, please ask a member of the study team to give you one.

### **Declaration by participant/guardian/treatment partner (circle)**

By signing below, I ..... agree/agree on behalf of..... to take part in a research study entitled: *"Neurocognitive disorders in young adults with HIV/AIDS commencing anti-retro-viral treatment in the Western Cape"*.

I declare that (delete whichever is NOT applicable):

- I have read or had read to me this information and consent form and it is written in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that my taking part/my relative or friend’s participation in this study is **voluntary** and I/we have not been pressurized to take part.
- I/my relative or friend may choose to leave the study at any time and will not be penalized or prejudiced in any way.
- I/my relative or friend may be asked to leave the study before it has finished, if the study doctor or researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) ..... 200\_.

.....  
**Signature of participant/guardian/treatment partner**      **Signature of witness**

**Declaration by investigator**

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

- I explained the information in this document to .....
- I encouraged him/her to ask questions and took adequate time to answer them.
- I am satisfied that he/she adequately understands all aspects of the research, as discussed above

Signed at (*place*) ..... on (*date*) ..... 2005.

.....  
 Signature of investigator      Signature of witness