HIV-Associated Executive Dysfunction:

Positive outcomes for a Clade C sample

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Abstract

HIV infection is more prevalent in South Africa than anywhere else in the world. The virus follows a distinct pattern of neurological impairment, targeting the frontal cortex. Studies emerging from the global north, where the clade B strain of the virus is most prevalent, report that a primary consequence of this neurological attack is impaired executive functioning. There are, however, few studies from regions (including South Africa) where clade C predominates. Such studies are needed because the strains differ neurobiologically, and it is an open question as to whether they also differ in their neurocognitive effects. Furthermore, the effects of antiretroviral treatment on cognition has been contested. Hence, we sought to examine performance of a clade C sample on measures of executive function (specifically, cognitive shifting, problem solving, inhibition, and generativity). HIV-positive (n = 165) and HIV-negative (n = 164) participants were recruited from clinics in the Western Cape. We found that (a) HIV-positive patients performed more poorly than HIV-negative controls on measures of shifting and problem solving, but not on measures of inhibition and generativity, (b) CD4 count and years since diagnosis with HIV were not related to performance on any measure of executive functioning, and (c) a regimen of Highly Active Antiretroviral Treatment was not related to changes in executive functioning over time. These findings, together with the small effect sizes observed, suggest that the executive dysfunction observed in clade C HIV-positive individuals is not consistent with that reported in the clade B literature. Instead, our findings suggest that the clade C subtype presents with a more favourable profile of neurocognitive impairment.

Keywords: clade C; CD4 count; executive function; HAART; HIV; neuropsychology; South Africa

HIV-Associated Executive Dysfunction: Positive Outcomes for a Clade C Sample

The human immunodeficiency virus (HIV) affects approximately 33 million people worldwide, with impoverished and developing areas most affected (Robertson, Liner, & Heaton, 2009). Whereas the number of people infected with HIV in the United States, Western Europe, and Oceania represents only 4% of worldwide infections, the number in Africa, the Middle East, and Asia collectively accounts for over 86% (Hemelaar, Gouws, Ghys, & Osmanov, 2006). South Africa has the highest prevalence of HIV-infection worldwide, with 17.3% of the population aged 15-49 infected with the disease in 2011 (Statistics South Africa, 2011; WHO, 2013).

HIV induces neurological injury and affects areas of the brain involved in multiple domains of cognitive functioning (Woods, Moore, Weber, & Grant, 2009). Neurocognitive impairment is a common, although not universal, feature of HIV infection. Recent research suggests that HIV-associated neurocognitive disorders (HAND) are evident in 30-50% of persons living with HIV (Joska, Westgarth-Taylor, Myer, et al., 2011; Woods, Carey, et al., 2009). In the HIV-positive population in South Africa, the prevalence of two subtypes of HAND (viz., mild neurocognitive disorder (MND) and HIV-associated dementia (HAD)) is approximately 42% and 25%, respectively (Joska, Westgarth-Taylor, Myer, et al., 2011).

Treatment with antiretroviral medication has decreased the severity of the disease and associated mortality rates. Consequently, for many, HIV has become a chronic illness. Therefore, even though treatment has decreased the incidence of severe forms of HAND, more people are living with milder forms of the disorder (Heaton et al., 2011; Robertson et al., 2009). It is thus of increasing importance to investigate the specific patterns of impairment that characterize HIV-associated cognitive impairment.

Neuropathology of HIV

Early in infection, HIV permeates the blood-brain barrier and enters the central nervous system (CNS), resulting in neurodegeneration (Woods, Moore, et al., 2009). Hence, HIV-positive individuals have significantly lower volumetric measures of total white matter and total grey matter, with fronto-striato-thalamo-cortical circuits particularly badly affected. The virus also causes significant neuronal death in the basal ganglia and hippocampal regions. In addition, diffusion tensor imaging studies indicate increased diffusivity and lower

fractional anisotropy; the latter is often particularly evident in individuals with HAND (Heaps et al., 2012; Mishra, Vetrivel, Siddappa, Ranga, & Seth, 2008).

As a result of this physical damage, impairment is evident in a number of cognitive domains, including memory, attention, executive functioning, language, and perceptual ability (Woods, Moore, et al., 2009).

HIV clade variation. The HIV-1 virus consists of several classes, of which group M (major) accounts for 90% of all infections. Group M, in turn, consists of nine subtypes or clades (A-D, F-H, J, and K), of which clades B and C are most predominant (Liner, Hall, & Robertson, 2007). Clade B accounts for approximately 10% of all infections worldwide, and is prevalent in North America, Europe, and Australia; clade C, in contrast, accounts for up to 50%, and is found primarily in Southern and Eastern Africa, India, Nepal, and China (Hemelaar et al., 2006; Liner et al., 2007). In addition, epidemiological studies indicate an increasing prevalence of clade C in Africa and Asia (Gupta et al., 2007).

Clades B and C differ neurobiologically, with clade C showing more favourable outcomes on parameters such as capacity to replicate, neurotoxicity, nucleotide sequencing, and, potentially, in-treatment resistance (Constantino, Huang, Zhang, Wood, & Zheng, 2011; Liner et al., 2007; Yepthomi et al., 2006). Such between-clade biological disparities may have significant implications for HIV transmission, diagnosis, pathogenesis, management, and therapy (Hemelaar et al., 2006). Of importance for neuropsychological studies of HIV, several studies suggest that HIV-associated neurological deficits are more common in clade B than in clade C (e.g., Constantino et al., 2011; Mishra et al., 2008).

Although most of the evidence suggests better outcomes for clade C-infected individuals than their clade B counterparts, some studies conducted in clade C-prevalent areas indicate that HAND may be as common within this subtype (Gupta et al., 2007; Joska, Fincham, Stein, Paul, & Seedat, 2010). Yepthomi et al. (2006) suggest that the clade C viral strain does not allow total defence from the cognitive decline associated with HIV, and that clade C-infected individuals show similar patterns of cognitive compromise as those described for clade B samples.

HIV and Executive Functioning

The term “executive functions” refers to a group of higher-order cognitive abilities involved in complex goal-directed behaviour, commonly linked to frontal systems (Alvarez & Emory, 2006; Stuss & Levine, 2002). One influential model, proposed by Miyake et al. (2000), suggests that executive functioning is comprised of three separable but related factors: shifting, updating, and inhibition. These factors have been implicated in a number of

complex executive function tests. The authors note, however, that their model is not exhaustive, and that it might be complemented by other proposed models of executive function (Koechlin & Summerfield, 2007; Stuss & Levine, 2002). Other processes or tasks that have been reported commonly as components of executive functions include decision-making, abstract reasoning, generativity, and planning (Cattie et al., 2012; Crowe, 1992; Downes, Sharp, Costall, Sagar, & Howe, 1993; Hardy, Hinkin, Levine, Castellon, & Lam, 2006; Heaton et al., 2004; Lezak, 1995; Marcotte et al., 1999).

HIV infection targets the frontal cortex, particularly the dorsolateral prefrontal system (Stuss & Levine, 2002). Consequently, executive functioning is one of the most heavily affected cognitive domains in HIV-positive individuals (Hinkin, Castellon, et al., 2002; Hinkin, Hardy, et al., 2002; Waldrop-Valverde et al., 2006). Executive dysfunction is evident from early infection, and increases in prevalence and severity over time (Iudicello, Woods, Parsons, Moran, Carey, & Grant, 2007; Reger, Welsh, Razani, Martin, & Boone, 2002). Specifically, studies conducted primarily in clade B samples, have shown that HIV infection is associated with difficulties in performance on tests of cognitive shifting and complex sequencing (Heaton et al., 2004; Marcotte et al., 1999; Mindt et al., 2003; Vazquez-Justo, Alvarez, & Ramos, 2003); response inhibition (Hinkin, Castellon, Hardy, Granholm, & Siegle, 1999; Thames et al., 2010; Yadavalli, 2009); decision making (Hardy et al., 2006); abstract reasoning (Heaton et al., 2004; Marcotte et al., 1999); and planning (Cattie et al., 2012).

Not all studies have replicated these results, however. Specifically, Levin, Berger, Didona, and Duncan (1992) did not find any significant impairments in cognitive shifting and abstract reasoning in their clade B HIV-positive sample (N = 122). This negative result may be due to the fact that these researchers studied only asymptomatic HIV-positive individuals who were in early stages of infection and who thus may have not sustained neuronal impairment to a significant degree. However, Baldewicz et al.'s (2004) 8-year longitudinal study also did not find significant impairments in cognitive shifting or inhibition in their clade B HIV-positive sample (N = 59). At the start of the study, all participants were asymptomatic; by the end, 64% (n = 38) were on highly active antiretroviral treatment (HAART). Because combination antiretroviral treatment (cART) has been associated with declines in morbidity and mortality of HIV infection (Heaton et al., 2011), one might speculate that in this case HAART had protective effects on cognitive functioning.

HIV progression and executive functioning. A recognized consequence of HIV infection is depletion of CD4 cells. CD4 lymphocytes perform important functions in the

human immune system. Their responsibilities include helping produce antibodies and cytokines that fight viral infection, and coordinating immune system responses (Yarchoan et al., 1991). HIV-associated CD4 count depletion occurs over time, and has been shown to predict disease progression (Yarchoan et al., 1991). Notably, higher CD4 counts (> 500 cells/mm^3) are associated with better performance on tests of executive function and lower counts (< 200 cells/mm^3) with poorer performance (Muñoz-Moreno et al., 2008; Stern et al., 1991). These relationships hold for populations being treated with cART (Heaton et al., 2011).

ART exists in many forms, all of which are designed to impede disease progression. In clade B studies, the effect of HAART on the CNS has been debated. Some HAART regimens are able to penetrate the blood-brain barrier more readily than others. Penetration of the CNS leads to suppression of viral load in the cerebrospinal fluid. Generally, the literature reports that these HAART regimes are associated with better neuropsychological outcomes (Cysique et al., 2009; Letendre et al., 2008; Smurzynski et al., 2011). However, some studies support the contention that these regimes actually lead to neuropsychological impairments (Marra et al., 2009; Robertson et al., 2010). In a study of immediate relevance to this one, Joska et al. (2012) investigated the effects of HAART on cognition in a clade C sample in South Africa. They found evidence to support the claims of positive HAART effects: Participant performance on neuropsychological tests improved over time following commencement of HAART. However, those researchers used paired-sample *t*-tests to measure performance across time; such analyses do not control for carryover or practice effects. A more accurate picture of the effect of HAART might be found by using more sophisticated analytic methods, such as a regression modeling or estimation of a reliable change index (RCI).

Summary and Rationale for the Present Study

Despite clade C accounting for most worldwide HIV infection and evidence indicating increasing rates of this subtype, most HIV neuropsychology research has been conducted in the United States and Europe, where clade B predominates. Few studies have attempted to replicate these clade B findings in clade C populations, despite the fact that there are well-established clade-specific neuropathological differences. Specifically, little research has investigated executive function in South African clade C-infected individuals.

It is especially important to examine executive functioning because of the consistent reporting of these deficits in the clade B literature, and the fact that this is one of the most highly affected cognitive domains in those samples. Furthermore, knowledge of how this

domain is affected as the disease progresses is useful for assessment and rehabilitation. This relationship is often confounded by treatment with antiretroviral medication, the effect of which is contested; hence, it is also important to investigate the impact of these regimens on cognitive functioning.

Aims and Hypotheses

This study forms part of a larger on-going research programme that aims to investigate neuroimaging and neurocognitive characteristics of the HIV-positive clade C population in South Africa (papers that have emerged from this programme to date include Joska, Westgarth-Taylor, Hoare, et al., 2011; Joska et al., 2012; Joska, Westgarth-Taylor, Myer, et al., 2011; Witten, 2012). First, we examined performance on tests of executive functioning in an ART-naïve sample (individuals who had never been on ART) to see whether the pattern of impairment reported in clade B patients is also present in clade C patients. Second, we examined performance on the same tests in relation to indices of HIV severity (viz., CD4 count and number of years since diagnosis) to see how executive functioning is related to disease progression. Finally, we investigated the impact of HAART by examining the changes in executive function performance over time in individuals commencing treatment. We tested the following hypotheses:

1) HIV-positive ART-naïve individuals will perform more poorly than HIV-negative controls on measures of executive function.
2) CD4 count in HIV-positive ART-naïve individuals will be positively related to performance on measures of executive function.
3) In HIV-positive ART-naïve individuals, the number of years since diagnosis will be negatively related to performance on measures of executive function.
4) Performance on measures of executive function will improve over time in HIV-positive individuals who have started HAART.

Methods

Design and Setting

This quasi-experimental study has both cross-sectional and longitudinal components. The cross-sectional component investigated executive functioning in HIV by comparing scores of HIV-positive individuals against those of HIV-negative controls, and by relating scores to indices of disease severity. The longitudinal aspect compared executive functioning over time in a group of HIV-positive individuals who commenced HAART relative to a

group who remained HAART-naïve. All data were collected in the University of Cape Town's Department of Psychiatry and Mental Health, and all data analyses took place in the UCT Department of Psychology.

Participants

As part of the larger research programme within which this study was nested, HIV-positive participants attending pre-ART counselling visits were recruited from primary health care clinics in Khayelitsha, Mitchell's Plain, and Woodstock between 2008 and 2010. As such, none of the HIV-positive patients had ever been on, or were currently on, any form of ART at the commencement of the study. We do not have data on how many participants were on ART by completion of this phase of the study, but we do know that at least 38% of those who returned for follow-up testing (39 of 103) were on HAART at that time.

HIV-negative participants were recruited in two ways: From voluntary counselling and testing clinics located close to the aforementioned HIV clinics, or through snowball recruitment techniques.

Inclusion criteria. Individuals recruited for the HIV-positive sample were required to (a) have tested HIV-positive in the previous 6 months, (b) have not previously been on HAART, (c) be attending an outpatient clinic, and (d) be able to read and write to a grade 7 level. Individuals recruited for the HIV-negative sample were required to (a) have tested HIV-negative in the previous month, (b) be willing to undergo a confirmatory test, (c) be attending an outpatient clinic, and (d) be able to read and write to grade 7 level.

Exclusion criteria. All potential participants were excluded if they (a) refused to sign the informed consent document, (b) had an active CNS condition, (c) currently abused or were dependent upon alcohol, (d) presented with an uncontrollable medical condition (e.g., a liver, kidney, or heart problem), (e) had contra-indications to magnetic resonance imaging (including metal implants, claustrophobia, or pregnancy), (f) had a history of significant head injury, or (g) presented with a major psychological disorder (such as schizophrenia or bipolar disorder).

The final sample consisted of 329 participants (HIV-positive n = 165; HIV-negative n = 164). Most participants were Xhosa-speaking Black African females, between 18 and 42 years of age. The Results section provides further details of the sample characteristics.

Measures

All of the tests that follow have been used successfully as measures of executive function in South Africa and in other developing economy/low- or middle-income countries (Joska, Westgarth-Taylor, Hoare, et al., 2011; Joska, Westgarth-Taylor, Myer, et al., 2011;

Lin, Chan, Zheng, Yang, & Wang, 2007; Peng, Guo, Li, & Lu, 2010; Sacktor et al., 2006; Wong et al., 2007).

Color Trails Test, Part 2. We used Part 2 of the Color Trails Test (CTT; D'Elia, Satz, Uchiyama, & White, 1996) to measure *cognitive shifting*. This term refers to the ability to switch between mental sets in order to adapt to a changing environment (Moriguchi & Hiraki, 2009), and is one component of Miyake et al.'s (2000) model of executive function. The CTT is a culture-fair version of the Trail Making Test (TMT; Reitan, 1958) as it minimises the influence of language by incorporating colours instead of letters (Spreen & Strauss, 1998).

Part 2 of the CTT requires the participant to draw connections between 50 randomly arranged circles containing the numbers 1 to 25. One set of 25 circles is coloured pink; another set of 25 is coloured yellow. The participant connects the numbers in order, alternating between pink and yellow circles and disregarding the redundant numbers in circles of the alternate colours.

Both the 2-week test-retest reliability and the alternate-form reliability of the CTT are high (r = .79 and r > .80, respectively; Llorente, Williams, Satz, & D'Elia, 2003; Strauss et al., 2006). Convergent validity with the TMT Part B ranges from .50 to .75, depending on language, age, and education of examinees (Lee & Chan, 2000; Lee, Cheung, Chan, & Chan, 2000; Maj et al., 1993).

Wisconsin Card Sorting Test (WCST). This test (Berg, 1948) was designed to assess *problem solving* and *cognitive flexibility*, and is commonly used as a measure of these executive functions (Greve, Stickle, Love, Bianchini, & Stanford, 2005; Heaton et al., 2004; Iudicello et al., 2008; Marcotte et al., 1999; Mindt et al., 2003; Thames et al., 2010; Vazquez-Justo et al., 2003). Furthermore, factor analysis has revealed that performance may also be related to response maintenance (Greve et al., 2002)

The participant is presented with 128 stimulus cards and is required to stack these into categories based on four key cards that differ according to colour, number, and form. Each stimulus card features a different combination of the three categories (colour, number, and form). For example, one card may display three red stars while another might display two green triangles. After the participant places each stimulus card from the deck below one of the key cards, the examiner states whether the placement was 'correct' or 'incorrect.' This decision is based on a sorting rule that is never relayed to the participant. The rule changes each time the participant performs ten consecutive correct sorts. Because each stimulus card contains some combination of colour, number, and form, a 'correct' move is ambiguous more

stimulus cards are placed. The test ends when the participant has made six runs of ten consecutive correct placements, voluntarily states the underlying principle of a changing rule, or has placed more than 64 cards into one category (i.e., underneath only one of the key cards; Lezak, Howieson, & Loring, 2004).

Test-retest reliability for the WCST ranges from .34 to .90 (Ozonoff, 1995; Ingram, Greve, Fishel Ingram, & Soukup, 1999). Alternate-form reliability coefficients are moderate (r = .63; Bowden et al., 1998), and interrater reliability is above .83 in some studies (Axelrod, Goldman, & Woodard, 1992; Greve, 1993) but lower elsewhere (Flashman, Horner, & Freides, 1991). Convergent validity between the number of categories completed on the WCST and error score on the Category Test (DeFilippis & McCampbell, 1997) is moderate (r = -.55; Franzen, 2000). WCST performance also correlates well with frontal lobe activity (Franzen, 2000).

The Stroop test. This test (Stroop, 1935) is a popular measure of inhibitory control (Hinkin et al., 1999; Thames et al., 2010; Vazquez-Justo et al., 2003; Yadavalli, 2009). Inhibitory control ability, or *inhibition*, refers to the ease with which a perceptual set can be changed in order to perform an unusual response while suppressing an automatic one (Spreen & Strauss, 1998). This, too, is a component of Miyake et al.'s (2000) executive function model.

Here, we used the Golden version of the Stroop test (Golden & Freshwater, 2002). Under these administration rules, the test consists of three parts, with the third being of major interest. In the first part, participants are required to read, out loud and as quickly as possible, a series of randomly presented colour names (*red*, *green*, and *blue*) which are printed in black ink, in columns on a single page. In the second part, participants are presented with another single page, this time featuring columns of the item 'XXXX' printed in either red, green, or blue ink. They are required to name the colours, again out loud and as quickly as possible. Finally, in part three of the test, participants are presented with a series of colour names similar to that of part one, but this time printed in coloured ink (the print colour and the colour names never correspond). They are now required to name the colour of the ink while ignoring the written word (again, as quickly and accurately as possible).

This version of the Stroop test has good test-retest reliability (between .62 and .83; Franzen, 2000; Homack, Lee, & Riccio, 2005; Homack & Riccio, 2004) and good split-half reliability (Homack et al., 2005). It also correlates moderately well with other measures of response inhibition (r = .33 - .55; Friedman & Miyake, 2004; May & Hasher, 1998).

Category Fluency test. This test is a measure of *generativity*, a term referring to spontaneous word production under constrained search conditions (Strauss et al., 2006). Although this construct does not form part of Miyake et al.'s (2000) model, it is used frequently as an indicator of executive function (Crowe, 1992; Downes et al., 1993; Lezak, 1995; Marcotte et al., 1999). In the version of the test administered here, participants were first required to name as many different animals as they could, as quickly as possible, for 1 minute. They were then asked to name as many fruits and vegetables as they could, as quickly as possible, for 1 minute (Franzen, 2000).

Test-retest reliability for the Category Fluency test is high for both short and long inter-test intervals ($r > .70$; Basso, Bornstein, & Lang, 1999; Dikmen, Heaton, Grant, & Temkin, 1999; Harrison, Buxton, Husain, & Wise, 2000; Levine, Miller, Becker, Selnes, & Cohen, 2004; Ross, 2003). Correlations between Category Fluency tests using different semantic categories are moderately high ($r = .66$ - $.71$; Delis, Kaplan, & Kramer, 2001; Riva, Nichelli, & Devoti, 2000). Also, convergent validity between the Category Fluency test and the Phonemic Fluency test is moderate to high ($r = .34$ - $.64$; Johnson-Selfridge, Zalewski, & Aboudarham, 1998; Kave, 2005; Kosmidis, Vlahou, Panagiotaki, & Kiosseoglou, 2004; Matute, Rosselli, Ardila, & Morales, 2004; Riva et al., 2000; Tombaugh, Kozak, & Rees, 1999).

Procedure

Three examiners, all with isiXhosa as a home language, administered the tests. Examiner 1 was a 37-year-old female nurse, examiner 2 was a 28-year-old female lay counsellor with a diploma in student administration, and examiner 3 was a 34-year-old male lay counsellor. The examiners administered the tests to all participants in a distraction-free, isolated room in Groote Schuur Hospital's Department of Psychiatry and Mental Health. Clinical psychologists and neuropsychologists from this department provided training to all examiners and supervised test administration.

To reach the test site, participants either used public transport or were provided transport by the research team. The examiner administered informed consent procedures on arrival. These forms (see Appendix A and Appendix B) were available in the participants' home language. The examiner administered a comprehensive neuropsychological test battery, which included all of the tests and measures described above, after those forms had been read and signed and all questions addressed.

The CTT was the 14th test administered in the neuropsychological battery, the Stroop test was 15th, the Category Fluency test was 19th, and the WCST was 20th. Each measure was

administered at the same point in the battery on each occasion. The entire neuropsychological battery took up to 5 hours to complete. Participants were allowed to take a break at any point during the session. Once testing was complete, participants were thanked, compensated for their time, and allowed to leave.

Participants completed the neuropsychological battery for a second time between 7 and 29 months after the first assessment (M = 12.93, SD = 3.13). The administration procedure for the second assessment was identical to that outlined above for the first assessment.

Ethical Considerations

The larger research programme within which the study is nested was granted ethical approval by the Human Research Ethics Committee of the University of Cape Town's Faculty of Health Sciences (see Appendix C).

The consent form signed by each participant contained the assurance that participation in the study was entirely voluntary, that withdrawal at any point would not result in negative consequences, and that the data provided would be kept confidential and anonymous. The examiners assigned each participant a unique study number; that number alone was recorded on his/her testing form. Access to participants' names was limited to researchers involved in the project.

A potential risk to participants was fatigue due to the length of the neuropsychological test battery. To combat this potential fatigue, the examiner allowed breaks at any point in the administration, and participants were not obliged to complete all tasks; they were allowed to skip items without penalty. Additionally, participants were not exposed to any psychological, physical, or social harm.

Regarding benefits, all participants were administered a mental health interview that allowed the research team to diagnose and formulate a treatment plan for any mental health problems. Participants were also provided with support and assistance to manage their HIV, and they received R150 in compensation. Furthermore, the comprehensive neuropsychological test battery administered in the study allowed the research team to identify, and potentially treat, cognitive deficits.

Additionally, this research will benefit the clade C HIV-infected population as it might provide knowledge that can be used to structure appropriate rehabilitation programmes in terms of specific patterns of executive function impairments. This study also adds to scientific knowledge regarding the neuropsychological status of HIV-infected individuals in South Africa.

Those participants who presented with psychological distress, or with clinical levels of any physical, mental, or neurological problems, were referred by the researchers to suitable health professionals (e.g., at the nearest day hospital or clinic) for counselling or support.

Data Management and Statistical Analyses

Scoring and data management. The examiners scored the executive function tests following conventional procedures, as outlined in the respective administration and scoring manuals, with the exception of the CTT Part 2.[1] A member of the research team then entered the raw scores and scaled scores for each test/questionnaire into an MSExcel database. That database also contains sociodemographic and clinical information for each participant.

The principal investigators of the larger study granted us access to the database and to the original data files. Although many of the data we required were available on the database, we used the original files to locate information that had not been recorded previously.

Scores that fell outside of 2 standard deviations from the mean were first checked against the original data files to ensure they had been coded correctly. We found no coding errors. Hence, we retained all such outlying values in our final data analyses, with the exception of one (a performance of 8 standard deviations above the mean on the CTT Part 2) that fell far outside the range of what might be expected clinically. Sample sizes for each analysis differ slightly as we used listwise deletion of missing data in all ANOVA and regression models. The Type I error rate (α) was set at .05 in all cases.

Descriptive statistics. We analysed the data using SPSS version 21. We calculated descriptive statistics for all predictor and outcome variables in order to describe the characteristics of the sample. With regard to these sample characteristics, we looked specifically at the variance and distribution of the data to examine its suitability for use with ANOVA. We calculated correlations using Pearson's correlation coefficient for two continuous variables and Kendall's rank correlation coefficient for at least one categorical variable. We ran two-tailed correlations unless there was a clear prediction in terms of direction of association.

Analysis of cross-sectional data.

Predictor and outcome variables. For Hypothesis 1, predictor variables included all of the sociodemographic variables on which the participants reported (viz., HIV status, age, sex, handedness, home language, years of education completed, and employment status), as

[1]Here, the test administrators followed the normal procedure with this exception: The 10-second rule was not applied. That is, if a participant got stuck on an item for at least 10 seconds, s/he was not directed to the next item.

well as a variable pertaining to whether there was a discrepancy between a participant's home language and the language in which the neuropsychological test battery was administered. For Hypotheses 2 and 3, additional predictor variables were CD4 count and the number of years since a participant was diagnosed with HIV. We used these two variables as proxies for disease severity, or stage of HIV infection.

Outcome variables for the regression analyses were (a) the total time taken to complete the CTT Part 2, (b) the total number of errors, perseverative errors and correct categories completed on the WCST, (c) the total time taken to complete part three of the Stroop test, and (d) the total number of correct words, given the assigned category, generated on the Category Fluency test.

Inferential statistics. We first ran a Principal Component Analysis (PCA) to determine whether our six executive function measures could be reduced, as such reduction would decrease our risk of committing a Type I error.

Hypothesis 1 states HIV-positive ART-naïve individuals will perform more poorly than HIV-negative controls on measures of executive function. To ascertain whether regression analysis was necessary, we used a one-way ANOVA to determine whether there were significant between-group differences on the measures of executive function. We also ran a second one-way ANOVA to determine whether there were systematic between-group differences on the demographic variables outlined above. We ran a hierarchical regression model for each outcome variable found to be significant on the first ANOVA, using as predictors HIV status and those demographic variables found to be significant on the second ANOVA.

We entered the predictor variables in three separate blocks in the following order: [Age, Xhosa, Afrikaans, years of education completed, employment status], language discrepancy, and HIV status. The variables 'Xhosa' and 'Afrikaans' refer to the participants' home language. Specifically, 'Xhosa' refers to whether a participant had a home language of Xhosa or not, coded as 1 for a home language of Xhosa and 0 otherwise. Similarly, 'Afrikaans' refers to whether a participant had a home language of Afrikaans or not, coded as 1 for a home language of Afrikaans and 0 otherwise. Collectively, 92% of the sample (n = 303) spoke either Xhosa or Afrikaans as a home language. Thereafter, demographic variables that were not significantly related to executive function ($p > .10$) were excluded in iterative fashion.

Hypothesis 2 states that CD4 count in HIV-positive ART-naïve individuals will be positively related to performance on measures of executive function, and Hypothesis 3 states

that, in HIV-positive ART-naïve individuals, the number of years since diagnosis will be negatively related to performance on measures of executive function. To test these hypotheses, we conducted hierarchical multiple regression analyses with CD4 count and years since diagnosis as predictor variables. The hierarchical model followed that outlined above, with CD4 count and years since diagnosis in place of the HIV status variable. Again, we excluded demographic variables that were not significant in the initial regression models before running final models.

Analysis of longitudinal data.

Predictor and outcome variables. For Hypothesis 4, predictor variables were CD4 count, years since diagnosis, months between testing, language discrepancy change, and a variable pertaining to whether participants were on HAART or not. The variable 'language discrepancy change' captured whether there was a difference in testing procedure between the first assessment session (Time 1) and the second assessment session (Time 2) in terms of the language in which the test was administered (i.e., whether it was in the participant's home language or not). We calculated outcome variables by subtracting scores at Time 2 from scores at Time 1 on all of the executive functioning measures listed above.

Inferential statistics. We ran a second PCA on the Time 1 – Time 2 change score data to determine whether the same pattern of data as earlier held.

Hypothesis 4 states that performance on measures of executive function will improve over time in HIV-positive individuals who have started HAART. The analysis here followed the same procedure as that of Hypothesis 1. That is, we first ran a series of one-way ANOVAs to determine whether regression analyses were necessary. The only difference here was that we did not look at between-group differences on demographic variables, such as sex, as these would not change over time, and the variable of interest was a change score. The variables we investigated were CD4 count, years since diagnosis, the number of months between testing, and language discrepancy change.

We entered predictor variables into the model in three blocks in the following order: [CD4 count; years since diagnosis], language discrepancy change, and HAART status. Thereafter, variables that were not significantly related to executive function ($p > .10$) were excluded in iterative fashion.

Model diagnostics and power analyses. For all regression analyses, we analyzed residuals and conducted power analyses on each model. Residual analysis did not indicate any concerns with normality or scedasticity, with the exception of the CTT Part 2, which showed non-normality of residuals on the cross-sectional analyses. To correct these

distributions, we used a log transformation (see Appendix F). Power analyses indicated that all final regression models were of sufficient power, $(1 - \beta) > .76$ in all cases, with the exception of the CD4 count and years since diagnosis analyses for the CTT Part 2, $(1 - \beta) = .51$.

Results

Sample Characteristics

Overall, the sample was aged between 18 and 42 years ($M = 27.96$, $SD = 4.77$), and had between 6 and 15 years of education ($M = 10.44$, $SD = 1.62$). Of the 329 participants in the sample, most were female ($n = 236$; 71.73%), most spoke isiXhosa as a home language ($n = 268$; 81.46%), and most were unemployed ($n = 215$; 65.35%). As Table 1 shows, the HIV-positive sample differed significantly from the HIV-negative sample in that, on average, they were older, had lower levels of education, were more likely to be Xhosa-speaking and less likely to be Afrikaans-speaking, and were more likely to be employed. The two groups did not differ significantly in terms of sex or handedness distribution, however: In both groups, most participants were female and right-handed.

Within the HIV-positive sample, 69% ($n = 84$) had a CD4 count below 200 cells/mm^3 and 4% ($n = 5$) had a CD4 count above 500 cells/mm^3.

Table 1
Demographic Variables: Between-group comparisons (N = 329)

Variable	HIV status: Positive (*n* = 165)	HIV status: Negative (*n* = 164)	*df*	F/χ^2	*p*	ESE
Age[a] (years)						
Range	19-36	18-42	1/260.34	40.18	< .001***	.12
M (*SD*)	29.54 (3.64)	26.37 (5.23)				
Education[a] (years)						
Range	6-15	6-13	1/292.64	13.07	< .001***	.04
M (*SD*)	10.15 (1.77)	10.73 (1.4)				
Sex[a]						
Male:Female	42:123	51:113	1/298.56	1.14	.287	.003
Handedness						
Right:Left	150:15	150:14	1/304	0.15	.697	< .001
Home language[a]						
Xhosa:Afrikaans:Other	146:2:17	122:33:9	1/300.24	7.10	.008**	.02
Employment status[a]						
Employed:Unemployed	56:103	35:112	1/303.62	4.85	.028*	.02
Language Discrepancy[a]						
Discrepancy:None			1/249.65	64.09	< .001	0.17
CD4 count						
Range	8-929					
Interquartile Range	117.00-225.50					
M (*SD*)	194.33 (134.62)					
Median	172.00					
Years since diagnosis						
Range	1-10					
M (*SD*)	3.29 (2.43)					

Note. ESE = effect size estimate, calculated using partial eta^2. [a]Brown and Welsh statistics used for significant Levene's test of homogeneity.
*p < .05. **p < .01. ***p < .001.

Analyses of Cross-Sectional Data

Principal component analysis. The PCA extracted one component for all WCST measures, a second component for the Stroop test and CTT Part 2, and a third for the Category Fluency test. The second component, however, is problematic as descriptive statistics showed that, relative to the HIV-negative participants, the HIV-positive participants performed better on the Stroop test but more poorly on the CTT Part 2. We therefore decided that these measures should be analysed separately. The three sub-measures of the WCST collectively accounted for 85.79% of the variance in this test. They all loaded on the component by at least .87 in absolute value. Therefore, the three sub-measures were combined into a single score by converting raw scores to *z*-scores and then weighting them according to their loading on the principal component. Based on previously published findings (e.g. Greve et al., 2002), we suggest that this composite variable is measuring problem-solving ability.

Testing Hypothesis 1. This hypothesis states that HIV-positive ART-naïve individuals will perform more poorly than HIV-negative controls on measures of executive function.

Between-group comparisons. Table 2 displays the results of the between-group comparisons on the outcome variables. The groups differed significantly on all of the outcome variables. Most of these differences were in the predicted direction, in that the HIV-positive sample performed more poorly than the HIV-negative sample. The only exception was the Stroop test; there, the HIV-positive sample completed part 3 of the test (a measure of inhibitory control) more quickly, on average, than the HIV-negative sample.

Multivariate regression analyses. Given that the one-way ANOVAs described above detected significant between-group differences on many of the demographic variables, we conducted multiple regression analyses to determine (a) how much of the variance in outcome variables could be accounted for by variation in demographic variables, and (b) whether group status still accounted for significant variation in outcome variables even after controlling for the effects of demographic variables. We did not enter sex and handedness as predictors into the regression models because there were no significant between-group differences on those variables.

Table 2

Executive Functioning Outcome Variables: Between-group comparisons (N = 329)

	HIV status					
Variable	Positive (n = 165)	Negative (n = 164)	*df*	F/χ^2	*p*	ESE
CTT Part 2						
Time in seconds	121.83 (46.70)	109.13 (44.14)	1/273	13.28	< .001***	.05
WCST						
Composite variable	68.97 (22.55)	55.14 (22.33)	1/273	28.57	< .001***	.10
Stroop						
Time in seconds	27.90 (9.40)	35.31 (9.98)	1/273	48.42	< .001***	.15
Category Fluency						
Correct words	27.53 (7.74)	31.80 (7.00)	1/273	14.55	< .001***	.05

Note. CTT = Color Trails Test; WCST = Wisconsin Card Sorting Test. In columns 1 and 2, means are presented with standard deviations in parentheses. ESE = effect size estimate, calculated using partial eta^2.

*p < .05. **p < .01. ***p < .001.

Table 3
Hypothesis 1: Bivariate correlations between all predictor and outcome variables (73 ≤ N ≤ 329)

	1	2	3	4	5	6	7	8	9	10	11
1. Age	-										
2. Xhosa[a, b]	-.002	-									
3. Afrikaans[a, b]	.01	-.72***	-								
4. Education	-.16***	.04	-.06	-							
5. Employment status[a]	.15***	-.04	-.04	.12**	-						
6. Language discrepancy[a]	.11*	.06	-.19**	.05	.01	-					
7. HIV status[a]	.33**	.18**	-.31***	-.18**	.13*	.42***	-				
8. CTT Part 2	.14*	.18***	-.18***	-.23**	.06	.10**	.14**	-			
9. WCST composite variable	.22***	.15**	-.19***	-.26***	.06	.07*	.27***	.31***	-		
10. Stroop	-.23***	-.23***	.23***	.30***	.02	-.15***	-.29***	-.44***	-.30***	-	
11. Category Fluency	-.08	-.11*	.13**	.28***	-.04	-.23***	-.22***	-.37***	-.27***	.33***	-

Note. CTT = Color Trails Test; WCST = Wisconsin Card Sorting Test. [a]Categorical variable; correlations computed using Kendall's tau-*b*.
[b]Participant's home language.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 3 displays the correlations observed between all demographic and outcome variables that were a part of the regression models. As can be seen, the correlations between demographic variables were generally low (*r* ranged from -.002 to .19). Xhosa and Afrikaans did correlate more strongly, however. When tolerance and VIF values were checked, they did not indicate problems with multicollinearity for these variables. For example, the tolerance value for Xhosa on the CTT Part 2 was .43, which is greater than the acceptable minimum value of .10, as suggested by Field (2009). HIV status showed low-to-moderate correlations with all demographic variables (r = .13 - .42). The cognitive outcome variables showed low correlations with all demographic variables (r = .02 - .28), and low-to-moderate correlations with HIV status (r = .14 - .29). There were moderate correlations between all of the executive functioning tests (r = .27 - .44). These are not problematic, as we ran separate regression models for each outcome variable.

Tables 4-7 display the final regression models that were created after excluding non-significant demographic predictors. Appendix D provides detailed tables of each step of the hierarchical regressions before this exclusion.

In the final models, the remaining demographic variables accounted for between 11% and 24% of the variance in the outcome variables. Education was a consistently significant predictor of executive function, $p < .001$ in all cases. This variable also accounted for most of the variance in each of the models, $sr^2 > .05$, in all cases.

On the CTT Part 2, Afrikaans, education, and language discrepancy collectively accounted for 11% of the variance. HIV status was not a significant predictor, accounting for less than 0.1% of the total variance. For the WCST composite variable, age, Afrikaans, and education accounted for 16% of the total variance. HIV status accounted for an additional 2% and was significantly related to the outcome variable. Out of all the tests, the demographic variables were most predictive of performance on the Stroop test; Xhosa home language, education, and language discrepancy accounted for 24% of the total variance. HIV status was also the most predictive of performance on this test, accounting for 3% of the variance. Finally, education and language discrepancy significantly predicted performance on the Category Fluency test, accounting for 17% of the total variance. HIV status was also a significant predictor, accounting for an additional 1% of the variance.

Therefore, although the initial ANOVA supported the hypothesis, the regression models provided only partial confirmation. In this sample, after taking demographics into account, the HIV status variable contributed significantly to prediction of performance on the CTT Part 2, the WCST, and the Stroop test. As expected, HIV-positive participants

performed more poorly on the CTT Part 2 and the WCST. Although HIV status bore a significant relation to performance on the Stroop test, the direction of association was in the opposite direction to that predicted (i.e., on average, the HIV-positive group performed better than the HIV-negative group). HIV status did not significantly predict performance on the Category Fluency test.

Table 4
Color Trails Test Part 2: Final hierarchical regression model testing Hypothesis 1 (N = 323)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial correlation
Step 1							
Constant	5.27 (0.12)		42.64	< .001***	5.03	5.52	
Afrikaans[a]	-0.25 (0.06)	-0.22	-4.14	< .001***	-0.37	-0.13	-.22
Education	-0.05 (0.01)	-0.25	-4.62	< .001***	-0.08	-0.03	-.25
Step 2							
Constant	5.27 (0.12)		42.82	< .001***	5.02	5.51	
Afrikaans[a]	-0.22 (0.06)	-0.20	-3.71	< .001***	-0.34	-0.11	-.20
Education	-0.06 (0.01)	-0.25	-4.80	< .001***	-0.08	-0.03	-.25
Language discrepancy	0.09 (0.04)	0.12	2.18	.030*	0.01	0.18	.12
Step 3							
Constant	5.26 (0.13)		39.69	< .001***	5.00	5.52	
Afrikaans[a]	-0.22 (0.06)	-0.20	-3.51	.001**	-0.34	-0.10	-.19
Education	-0.06 (0.01)	-0.25	-4.60	< .001***	-0.08	-0.03	-.24
Language discrepancy	0.09 (0.05)	0.11	1.91	.057	0.00	0.18	.10
HIV status	0.01 (0.04)	0.01	0.19	.850	-0.08	0.09	.01

Note. HIV-positive $n = 159$; HIV-negative $n = 164$. In the second column, standard deviations are presented in parentheses. CI = confidence interval. [a]Participant's home language. R^2 for step 1 = .10; ΔR^2 for step 2 = .01 ($p = .03$); ΔR^2 for step 3 < .001 ($p = .85$); overall $R^2 = .12$; overall adjusted $R^2 = .10$; $F(4, 318) = 10.31$, $p < .001$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 5
Wisconsin Card Sorting Test, Composite Variable: Final hierarchical regression model testing Hypothesis 1 (N = 290)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI		Semi-partial correlation
					Lower	Upper	
Step 1							
Constant	1.55 (1.34)		1.16	.248	-1.08	4.18	
Age	0.10 (0.03)	0.18	3.23	.001**	0.04	0.15	.18
Afrikaans[a]	-2.00 (0.44)	-0.25	-4.55	< .001***	-2.87	-1.14	-.25
Education	-0.38 (0.09)	-0.24	-4.41	< .001***	-0.55	-0.21	-.24
Step 2							
Constant	1.67 (1.32)		1.26	.207	-0.93	4.27	
Age	0.06 (0.03)	0.11	1.90	.058	0.00	0.12	.10
Afrikaans[a]	-1.50 (0.47)	-0.19	-3.20	.002**	-2.42	-0.58	-.17
Education	-0.35 (0.09)	-0.22	-4.08	< .001***	-0.52	-0.18	-.22
HIV status	0.93 (0.32)	0.18	2.87	.004**	0.29	1.56	.15

Note. HIV-positive $n = 151$; HIV-negative $n = 139$. In the second column, standard deviations are presented in parentheses. CI = confidence interval. [a]Participant's home language. R^2 for step 1 = .16; ΔR^2 for step 2 = .02 ($p = .004$); overall $R^2 = .18$; overall adjusted $R^2 = .17$; $F(4, 285) = 15.87$, $p < .001$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 6
Stroop Test: Final hierarchical regression model testing Hypothesis 1 (N = 316)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial correlation
Step 1							
Constant	31.18 (5.10)		6.12	< .001***	21.15	41.21	
Age	-0.41 (0.11)	-0.19	-3.68	< .001***	-0.62	-0.19	-.19
Xhosa[a]	-7.65 (1.34)	-0.29	-5.71	< .001***	-10.29	-5.02	-.29
Education	1.73 (0.33)	0.27	5.29	< .001***	1.09	2.37	.27
Step 2							
Constant	29.44 (5.02)		5.86	< .001***	19.56	39.31	
Age	-0.36 (0.11)	-0.17	-3.27	.001**	-0.57	-0.14	-.16
Xhosa[a]	-7.41 (1.32)	-0.28	-5.63	< .001***	-10.00	-4.82	-.28
Education	1.85 (0.32)	0.29	5.73	< .001***	1.21	2.48	.28
Language discrepancy	-4.39 (1.20)	-0.18	-3.66	< .001***	-6.75	-2.03	-.18
Step 3							
Constant	29.17 (4.95)		5.90	< .001***	19.44	38.90	
Age	-0.25 (0.11)	-0.12	-2.20	.028*	-0.47	-0.03	-.11
Xhosa[a]	-6.63 (1.32)	-0.25	-5.02	< .001***	-9.22	-4.03	-.25
Education	1.66 (0.32)	0.26	5.16	< .001***	1.03	2.30	.25
Language discrepancy	-2.68 (1.29)	-0.11	-2.08	.038*	-5.22	-0.14	-.10
HIV status	-3.91 (1.20)	-0.19	-3.26	.001**	-6.28	-1.55	-.16

Note. HIV-positive $n = 154$; HIV-negative $n = 162$. In the second column, standard deviations are presented in parentheses. CI = confidence interval. [a]Participant's home language. R^2 for step 1 = .21; ΔR^2 for step 2 = .03 ($p < .001$); ΔR^2 for step 3 = .03 ($p = .001$); overall $R^2 = .26$; overall adjusted $R^2 = .25$; $F(5, 310) = 22.22$, $p < .001$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 7
Category Fluency Test: Final hierarchical regression model testing Hypothesis 1 (N = 324)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial correlation
Step 1							
Constant	15.74 (2.67)		5.89	< .001***	10.49	21.00	
Education	1.33 (0.25)	0.28	5.27	< .001***	0.83	1.83	.28
Step 2							
Constant	16.49 (2.54)		6.49	< .001***	11.49	21.49	
Education	1.39 (0.24)	0.30	5.80	< .001***	0.92	1.87	.30
Language discrepancy	-5.28 (0.88)	-0.30	-5.99	< .001***	-7.01	-3.54	-.30
Step 3							
Constant	18.45 (2.69)		6.87	< .001***	13.16	23.74	
Education	1.27 (0.25)	0.27	5.19	< .001***	0.79	1.76	.26
Language discrepancy	-4.38 (0.97)	-0.25	-4.51	< .001***	-6.29	-2.47	-.23
HIV status	-1.87 (0.87)	-0.12	-2.14	.033**	-3.59	-0.15	-.11

Note. HIV-positive $n = 163$; HIV-negative $n = 161$. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .08; ΔR^2 for step 2 = .09 ($p < .001$); ΔR^2 for step 3 = .01 ($p = .033$); overall $R^2 = .18$; overall adjusted $R^2 = .18$; $F(3, 320) = 23.97$, $p < .001$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Testing Hypotheses 2 and 3. Hypotheses 2 and 3 relate only to the performance of HIV-positive individuals (n = 60) on the measures of executive functioning. They state, respectively, that CD4 count in HIV-positive ART-naïve individuals will be positively related to performance on measures of executive functiong, and that, in HIV-positive ART-naïve individuals, the number of years since diagnosis will be negatively related to performance on measures of executive function. In each case, then, we predicted that increasing disease severity would be related to poorer performance on measures of executive function.

Table 8 displays information on the predictor and outcome variables for the sub-sample in which these hypotheses were tested. This sub-sample is comparable to that of the full sample[2], except that there were no Afrikaans-speaking participants in it.

Multivariate regression analysis. Table 9 displays the correlations observed between all demographic and outcome variables that were part of these models. Generally, the correlations are comparable to that of the full sample, both in terms of directionality and proportion. Ranges were smaller, which is to be expected given the reduced sample size. CD4 count and years since diagnosis showed low-to-moderate correlations with all demographic variables and outcome measures (r = .01 - .37). They also showed a low correlation with each other (r = .17).

[2] In comparing Table 1 to Table 8: For the larger sample the age ranged from 18-42 years, they had 11 years of education on average, 72% were female, 82% were Xhosa-speaking, and 45% were employed. For the sub-sample the age ranged from 22-35 years, they had 10 years of education on average, 78% were female, 93% were Xhosa-speaking, and 40% were employed.

Table 8
Hypotheses 2 and 3, Sample Demographic, Clinical, and Cognitive Characteristics: Descriptive statistics (N = 60)

Variable	Value(s)
Age (years)	
Range	22 – 35
M (SD)	29.45 (3.38)
Education (years)	
Range	6 – 12
M (SD)	10.23 (1.61)
Sex	
Male:Female	13:47
Handedness	
Left:Right	3:57
Home language	
Xhosa:Other	56:4
Employment status	
Employed:Unemployed[b]	24:32
Language discrepancy	
Yes:No	28:32
CD4 count	
Range	36 – 529
Interquartile range	117-212.75
M (SD)	172.78 (84.92)
Median	165
Years since diagnosis	
Range	1 – 10
M (SD)	3.45 (2.16)
CTT Part 2[a]	
Range	49.37 - 235.81
M (SD)	115.85 (36.92)
WCST composite variable[c]	
Range	-4.52 - 5.01
M (SD)	0.58 (2.75)
Stroop[b]	
Range	13 – 45
M (SD)	28.73 (8.48)
Category Fluency[a]	
Range	14 – 45
M (SD)	28.12 (7.00)

Note. [a]*N* = 59. [b]*N* = 56. [c]*N* = 53. These data were not available for 4 participants because they were not recorded in the original participant folder. CTT = Color Trails Test; WCST = Wisconsin Card Sorting Test.

Table 9
Hypotheses 2 and 3: Bivariate correlations between all predictor and outcome variables ($49 \leq N \leq 60$)

	1	2	3	4	5	6	7	8	9	10	11
1. Age	-										
2. Xhosa[ab]	-.10	-									
3. Education	-.07	.07	-								
4. Employment status[a]	-.04	-.18	.27**	-							
5. Language discrepancy[a]	-.25*	-.02	.17	-.08	-						
6. CD4 count	-.15	.02	.15	-.01	.01	-					
7. Years since diagnosis	-.11	.13	.37**	.10	.11	.17	-				
8. CTT Part 2	-.02	.02	-.15	.05	.10	-.24	-.19	-			
9. WCST composite variable	.03	.08	-.40**	-.10	-.14*	-.12	-.01	.34*	-		
10. Stroop	-.33*	-.17	.42**	.13	.17*	.14	.20	-.23	-.29*	-	
11. Category Fluency	.11	-.07	.43**	.16	-.09	.01	.01	-.22	-.35*	.21	-

Note. CTT = Color Trails Test; WCST = Wisconsin Card Sorting Test. [a]Refers to categorical variables; correlations computed using Kendall's tau-*b*. [b]Participant's home language.
*$p < .05$. **$p < .01$. ***$p < .001$.

Tables 10-13 present results of the final regression models testing Hypotheses 2 and 3. Demographic variables accounted for up to 32% of the variance in the outcome variables. Again, education was the most consistently significant predictor, $p < .003$ in all cases with the exception of the CTT Part 2, $p = .183$ (refer to Table D5 in Appendix D). This variable also accounted for most of the variance in each of the models, $sr^2 > .04$, in all cases of significance.

Performance on the CTT Part 2 was not significantly accounted for by any of the predictor variables. Collectively, CD4 count and years since diagnosis accounted for 8% of the total variance in performance on this test. For the WCST composite variable, education significantly predicted performance, and accounted for 16% of the variance. CD4 count and years since diagnosis were not significant predictors, collectively accounting for only an additional 3%. As for Hypothesis 1, the demographic variables were most predictive of performance on the Stroop test; age, Xhosa home language, and education accounted for 32% of the total variance. Neither CD4 count nor years since diagnosis were significant predictors, accounting for an additional 1%. Finally, education was the only significant predictor on the Category Fluency test, accounting for 18% of the variance. CD4 count and years since diagnosis accounted for an additional 3%.

In summary, neither Hypothesis 2 nor Hypothesis 3 was confirmed: The analyses did not detect a significant association between measures of disease severity and measures of executive functioning.

Table 10

Color Trails Test Part 2: Final hierarchical regression model testing Hypotheses 2 and 3 (N = 59)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial correlation
Step 1							
Constant	4.92 (0.11)		46.09	< .001***	4.71	5.14	
CD4 count	-0.001 (< 0.001)	-0.21	-1.60	.115	-0.002	0.00	-0.21
Years since diagnosis	-0.02 (0.02)	-0.16	-1.26	.213	-0.06	0.01	-0.16

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 = .08; adjusted R^2 =.05. For the final model, $F(2, 56) = 2.48$, $p = .093$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 11

Wisconsin Card Sorting Test, Composite Variable: Final hierarchical regression model testing Hypotheses 2 and 3 (N = 59)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial correlation
Step 1							
Constant	7.20 (2.16)		3.33	.002**	2.86	11.53	
Education	-.65 (0.21)	-0.40	-3.11	.003**	-1.07	-0.23	-0.40
Step 2							
Constant	7.93 (2.25)		3.53	.001**	3.42	12.44	
Education	-0.77 (0.23)	-0.47	-3.30	.002**	-1.23	-0.30	-0.42
CD4 count	-0.002 (0.01)	-0.05	-0.41	.682	-0.01	0.09	-0.05
Years since diagnosis	0.25 (0.18)	0.19	1.37	.176	-0.12	0.69	0.18

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .16; ΔR^2 for step 2 = .03 (p = .368); overall R^2 = .19; overall adjusted R^2 = .14. For the final model, $F(3, 49) = 3.90$, $p = .014$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 12
Stroop Test: Final hierarchical regression model testing Hypotheses 2 and 3 (N = 56)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial Correlation
Step 1							
Constant	6.09 (1.10)		5.49	<.001***	3.86	8.32	
Age	-0.07 (0.03)	-0.31	-2.71	.009**	-0.13	-0.02	-.031
Xhosa[a]	-0.78 (0.36)	-0.25	-2.15	.036*	-1.50	-0.05	-0.25
Education	0.21 (0.06)	0.41	3.63	.001**	0.09	0.32	0.41
Step 2							
Constant	6.02 (1.15)		5.24	< .001***	3.71	8.33	
Age	-0.07 (0.03)	-0.30	-2.57	.013*	-0.13	-0.02	-0.30
Xhosa[a]	-0.81 (0.37)	-0.26	-2.18	.034*	-1.55	-0.06	-0.25
Education	0.20 (0.06)	0.39	3.16	.003**	0.07	0.32	0.37
CD4 count	< 0.001 (0.001)	0.05	0.42	.680	-0.002	0.003	0.05
Years since diagnosis	0.02 (0.05)	0.05	0.41	.684	-0.08	0.11	0.05

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. [a]Participant's home language. R^2 for step 1 = .32; ΔR^2 for step 2 = .01 (p = .828); overall R^2 = .33; overall adjusted R^2 =.26. For the final model, $F(5, 50) = 4.89$, $p < .001$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 13
Category Fluency Test: Final hierarchical regression model testing Hypotheses 2 and 3 (N = 59)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% C.I Lower	95% C.I Upper	Semi-partial Correlation
Step 1							
Constant	9.35 (5.36)		1.74	.087	-1.39	20.08	
Education	1.84 (0.52)	0.43	3.55	.001**	0.80	2.87	0.43
Step 2							
Constant	8.66 (5.51)		1.57	.122	-2.38	19.70	
Education	2.14 (0.56)	0.49	3.80	< .001***	1.01	3.26	0.46
CD4 count	-0.003 (0.01)	-0.03	-0.27	.785	-0.02	0.02	-0.03
Years since diagnosis	-0.55 (0.42)	-0.17	-1.30	.198	-1.39	0.29	-0.16

Note. In column 1, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .18; ΔR^2 for step 2 = .03 (p = .392); overall R^2 = .21; overall adjusted R^2 =.17. For the final model, $F(3, 53) = 4.82$, p = .005.
*p < .05. **p < .01. ***p < .001.

Analyses of Longitudinal Data

Principal component analysis. We conducted a PCA for the scores on the WCST at Time 2. The results were similar to the first PCA: The analysis extracted one component for the three WCST measures, which collectively accounted for 80.62% of the variance in this test. The three variables all loaded on the component by at least .83 in absolute value. Therefore, we combined the scores in the same way as for the scores on Time 1.

Testing Hypothesis 4. Hypothesis 4 relates only to performance of HIV-positive individuals for whom follow-up data were collected (n = 103). The hypothesis states that performance on measures of executive function will improve over time in HIV-positive individuals who have started HAART.

Table 14 displays demographic information for this sub-sample. This sub-sample is, again, comparable to the full sample[3]; again, however, there is a smaller proportion of Afrikaans-speaking participants than in the full sample (there is only one in this sub-sample). The Table also shows that the groups differed significantly on CD4 count, years since diagnosis, and language discrepancy change, but not on months between testing. The HAART-naïve sample had, on average, a higher CD4 count and fewer years since diagnosis, and also contained fewer participants for which the language of testing changed between Time 1 and Time 2 testing.

Between-group comparisons. Table 15 displays the results of the between-group comparisons on the outcome variables. Group performance only differed significantly on the Category Fluency test. This difference was in the expected direction: On average, participants on HAART improved, whereas HAART-naïve participants performed more poorly, over time.

[3] In comparing Table 1 to Table 14: For the larger sample the age ranged from 18-42 years, they had 11 years of education on average, 72% were female, 82% were Xhosa-speaking, and 45% were employed. For the sub-sample the age ranged from 22-35 years, they had 10 years of education on average, 77% were female, 82% were Xhosa-speaking, and 41% were employed.

Table 14

Hypothesis 4, Sample Demographic and Clinical Characteristics: Descriptive statistics and between-group comparisons (N = 103)

	HAART status					
Variable	HAART (n = 81)	HAART-naïve (n = 22)	df	F/χ^2	p	ESE
Age (years)						
Range	22-35	25-35	-	-	-	-
M (SD)	29.26 (3.32)	30.59 (3.42)				
Education (years)						
Range	6-12	7-15	-	-	-	-
M (SD)	10.15 (1.67)	10.27 (1.88)				
Sex						
Male:Female	18:63	6:16	-	-	-	-
Handedness						
Right:Left	74:7	21:1	-	-	-	-
Home language						
Xhosa:Afrikaans:Other	74:1:6	20:0:2	-	-	-	-
Employment status						
Employed:Unemployed	33:44	8:14	-	-	-	-
Language discrepancy change[ab]			1/46.18	6.41	.015*	.04
Discrepancy change:None	29:49	3:19				
CD4 count[a]			1/10.38	4.07	.070*	.18
Range	36-529	85-929				
Interquartile Range	120-214	172-409				
M (SD)	174.98 (82.56)	329.82 (252.12)				
Median	166	198				
Years since diagnosis[a]			1/47.29	41.26	< .001***	.07
Range	1-10	1-2				
M (SD)	3.48 (2.46)	1.29 (0.49)				
Months between testing			1/98	0.27	.602	.003
Range	7-29	7-23				
M (SD)	12.89 (3.11)	13.32 (3.61)				

Note. ESE = effect size estimate, calculated using partial eta^2. [a]Brown and Welsh statistics used for significant Levene's test of homogeneity. [b]Whether there was a change in the language in which the assessmet was conducted between Time 1 and Time 2.

*p < .05. **p < .01. ***p < .001.

Table 15

Hypothesis 4, Performance on Tests of Executive Functioning: Between-group comparisons (N = 103)

	HAART status					
Variable	HAART (n = 81)	HAART-naïve (n = 22)	df	F/χ^2	p	ESE
CTT Part 2						
Time in seconds	6.99 (43.93)	-4.68 (58.97)	1/99	1.04	.311	.01
WCST[a]						
Composite variable	0.71 (2.33)	0.85 (1.53)	1/46.17	0.10	.759	< .001
Stroop						
Time in seconds	-0.58 (8.90)	-2.46 (8.11)	1/97	0.78	.378	.01
Category Fluency						
Correct words	-3.76 (6.42)	0.09 (7.67)	1/100	5.70	.019*	.05

Note. CTT = Color Trails Test; WCST = Wisconsin Card Sorting Test. In columns 1 and 2, means are presented with standard deviations in parentheses. ESE = effect size estimate, calculated using partial eta^2. [a]Brown and Welsh statistics used for significant Levene's test of homogeneity.

*p < .05. **p < .01. ***p < .001.

Multivariate regression analysis. Table 16 displays the correlations. There were low-to-moderate correlations between the predictor variables (r = .02 - .42). The HAART variable displayed low correlations with all of the outcome variables (r = .03 - .23), and the latter displayed low correlations with each other (r = .01 - .15).

Table 17 presents results of the final regression model for predicting change in performance on the Category Fluency test (the only test on which there were between-group differences in performance over time). None of the predictors were significantly related to performance. However, language discrepancy change was significant at the .10 level, accounting for 4.7% of the variance. The HAART variable was also significant at the .10 level, accounting for an additional 3.5% over and above the language discrepancy change. Therefore, in line with the standard of significance used here, Hypothesis 4 was not confirmed: Being on HAART versus being HAART-naïve did not significantly predict performance on any of the measures of executive function over time.

Table 16
Hypothesis 4: Bivariate correlations between all predictor and outcome variables (65 ≤ N ≤ 103)

	1	2	3	4	5	6	7	8	9
1. CD4 count	-								
2. Years since diagnosis	.17	-							
3. Months between testing	.07	.02	-						
4. Language discrepancy change[ab]	-.12	.14	.34***	-					
5. HAART[a]	.23***	-.32**	.03	-.21*	-				
6. CTT Part 2	-.10	-.07	.05	.41	-.05	-			
7. WCST composite variable	< .001	-.07	.05	-.15**	.01	.01	-		
8. Stroop	.03	-.17	-.08	-.05	-.08	.15	.09	-	
9. Category Fluency	.28*	-.15	.02	-.19***	.25***	-.07	.06	-.03	-

Note. CTT = Color Trails Test; WCST = Wisconsin Card Sorting Test. [a]Categorical variables; correlations computed using Kendall's tau-*b*.
[b]Whether there was a change in the language in which the assessmet was conducted between Time 1 and Time 2.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table 17
Category Fluency Test: Final hierarchical regression model testing Hypotheses 4 (N = 99)

Modeling Step / Predictor	B	*β*	*t*	*p*	95% CI Lower	95% CI Upper	Semi-partial correlation
Step 1							
Constant	-1.81 (.82)		-2.20	.030*	-3.44	-0.18	
Language discrepancy change[a]	-3.22 (1.47)	-0.22	-2.20	.031*	-6.14	-0.31	-.22
Step 2							
Constant	-5.82 (2.26)		-2.57	.012*	-10.32	-1.33	
Language discrepancy change	-2.65 (1.48)	-0.18	-1.79	.077	-5.59	0.29	-.18
HAART	3.14 (1.65)	0.19	1.9	.060	-0.14	6.42	.19

Note. HAART $n = 77$; HAART-naïve $n = 22$. In column 1, standard deviations are presented in parentheses. CI = confidence interval. [a]Whether there was a change in the language in which the assessmet was conducted between Time 1 and Time 2.
R^2 for step 1 = .05; ΔR^2 for step 2 = .04 ($p = .060$); overall R^2 = .08; overall adjusted R^2 =.06. For the final model, $F(2, 96) = 4.29$, $p = .017$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Discussion

The purpose of this study was to determine whether the same pattern of executive dysfunction seen in studies of clade B HIV-positive individuals, which dominate the HIV neuropsychology literature, is also evident in clade C HIV-positive individuals. Using various executive function measures and a sample of HIV-positive and HIV-negative individuals, we tested four specific hypotheses. Hypothesis 1 stated that HIV-positive ART-naïve individuals will perform more poorly than HIV-negative controls on measures of executive function. Although research on clade B HIV-positive samples has demonstrated this between-group difference consistently (Hinkin et al., 1999; Iudicello et al., 2008; Thames et al., 2010), our data provided only partial confirmation of the hypothesis. Specifically, the HIV-positive participants in our sample performed more poorly than their HIV-negative counterparts on the WCST and on the Category Fluency test, but not on Part 2 of the CTT or on the Stroop test, after accounting for the effects of demographic variables.

Furthermore, all relationships observed were associated with small effect sizes ($sr^2 <$ .03 in all cases). This result contradicts data reported in previous studies in clade B-prevalent areas: A meta-analysis of the effects of HIV infection on cognitive performance indicated that effect sizes in these studies typically range from .05 to .21 when comparing asymptomatic HIV-positive patients to HIV-negative controls, and from .18 to .65 when comparing symptomatic HIV-positive patients to HIV-negative controls (Reger et al., 2002).

A particular point of interest here was that, in the current sample, HIV-positive participants performed better, on average, than their HIV-negative counterparts on the Stroop test. Previous studies using presumed clade B samples (see, e.g., Hinkin et al., 1999) have reported the opposite pattern (i.e., Stroop performance impairments in HIV-positive participants relative to HIV-negative participants). Although it therefore appears that our finding is anomalous and counter-intuitive, a similar pattern of performance is described in another recent study of clade C HIV-infected individuals. Witten (2012), using a sample recruited from the same larger research programme as the present study, found that HIV-positive individuals performed better than HIV-negative controls on an executive dyscontrol component of a learning and memory task. Witten suggested that one explanation for this unexpected finding was that this relationship may be due to an unobserved confounding variable. We suggest the following: On the one hand, observation of a similar pattern of (unexpected) association on the Stroop test, even given the small effect size observed here, may provide support for the hypothesis that there is in fact a relationship between HIV status and improved performance on certain cognitive tests. More likely, however, the same

confounding variable is present in both the current study and that of Witten (2012); such a situation would not be unexpected due to the fact that the studies used a sample of participants recruited from the same areas and assessed in the same setting and following the same procedure.

In summary, the observed data provided only partial confirmation of Hypothesis 1. Although HIV-positive participants were relatively impaired on measures of shifting and problem-solving ability, they were not impaired on the measure of generativity, and they performed better than controls on the measure of inhibition. Furthermore, being HIV-positive had only a small effect on executive functioning after accounting for demographic variables, regardless of the direction of statistical significance.

Hypotheses 2 and 3 related to the predictive significance of disease severity in executive functioning outcomes. Hence, both of these hypotheses were tested in HIV-positive individuals only. Hypothesis 2 stated that CD4 count in HIV-positive ART-naïve individuals will be positively related to performance on measures of executive function; Hypothesis 3 stated that, in HIV-positive ART-naïve individuals, the number of years since diagnosis will be negatively related to performance on measures of executive function. The data analyses disconfirmed both predictions. Not only were all *p*-values equal to, or greater than, .115, but effect sizes showed no evidence of an effect either ($sr^2 < .04$ in all cases). Again, these relationships were observed after taking into account relevant demographic predictors.

Hypothesis 4 stated that performance on measures of executive function will improve over time in HIV-positive individuals who have started HAART. There was little or no evidence of this relationship in the present study. HAART commencement did not predict changes in performance on most measures, even after accounting for potentially confounding factors. On the Category Fluency test, the HAART variable was marginally significant after accounting for the effects of changing administration procedures. However, this marginal result was also associated with a small effect size, $sr^2 = .04$.

This disconfirmation of Hypothesis 4 contradicts studies that report buffering effects of ARTs, including cARTs (Cysique et al., 2009; Letendre et al., 2008; Smurzynski et al., 2011). In terms of that body of previously published literature, our finding may be explained by the fact that the current sample displayed relatively mild (or, in some cases, no) executive function deficits (based on the findings of Hypotheses 1 to 3). One may speculate that had larger deficits been present pre-HAART, a buffering effect of the medication regimen may have been observed. Indeed, Joska et al. (2012) reported that HAART commencement is

associated with greater cognitive improvements when, at initial pre-HAART assessment, test performance is relatively more impaired.

Of course, the disconfirmation of Hypothesis 4 also stands in contrast to studies that report detrimental effects of HAART (Marra et al., 2009; Robertson et al., 2010). There does not seem to be a ready explanation for this null result in terms of this latter body of literature. We argue, therefore, that the current finding tentatively supports the contention that HAART is associated with better neuropsychological outcomes, as opposed to poorer ones.

Taken together, these findings suggest that, in this sample of clade C HIV-positive individuals, there is (a) no generalized executive dysfunction, (b) only mild impairment (indicated by small effect size estimates) on certain measures of executive function, and (c) no relationship between disease severity and performance on measures of executive function. Furthermore, the effect of HAART on executive functioning over time in HIV remains an open question because our findings were inconclusive, perhaps due to the lack of general impairment in our sample.

One explanation for these findings is that there is, in fact, a relationship between HIV status and some aspects of executive function, but that this relationship is quite weak and is present in only certain domains of executive function. Another explanation is that there is no effect of clade C HIV infection on executive function, and that the observed instances where HIV-positive individuals performed more poorly than HIV-negative individuals can be attributed to a confounding factor: the presence of chronic disease in one group but not the other. Previous studies have noted that diagnosis with a chronic disease, irrespective of what form this disease takes, is associated with poorer performance on cognitive tasks (Elias, D'Agostino, Elias, & Wolf, 1995; Swan, Carmelli, & Larue, 1998), including measures of executive function (for a review, see Schillerstrom, Horton, & Royall, 2005).

Importantly, bias due to omitted variables actually strengthens the findings we report here. Omitted variable bias (OVB) occurs when a variable that is related to both the predictor and the outcome variable is not included in the regression model. This omission influences the relationships observed, and can either increase or decrease the likelihood that a significant relationship will be found.

In terms of the relationship between disease severity (as estimated by, separately, CD4 count and years since diagnosis) and executive function, a potential influencing variable is the level of HIV present in a patient's body, referred to as viral load. Data on viral load were not available for the sample. However, viral load is reported as having a negative relationship with CD4 count and a positive relationship with years since diagnosis, as well as

a negative relationship with executive function scores (Mellors et al., 1997; O'Brien, Hartigan, Daar, Simberkoff, & Hamilton, 1997; Tate et al., 2011). Therefore, the effect of not including viral load in the regression analysis increases the likelihood of finding a significant positive relationship between CD4 count and executive function. In terms of the analysis involving years since diagnosis, the effect on the model would be an increased likelihood of finding a negative relationship. Therefore, the OVB is enhancing, rather than suppressing, the expected relationships. Hence, given that we found no significant relationships between executive dysfunction and either CD4 count or years since diagnosis, we can have increased confidence in our suggestion that the observed data support the null hypothesis that there is, in fact, no relationship between these variables.

Another point of interest is that the sample used in this study is unique in two respects. First, the cohort consisted primarily of female participants; this is often not the case in the reported literature (Joska et al., 2010). Literature from North America suggests that women are generally found to be at a higher risk of developing HIV-related neurocognitive impairment (Liu et al., 1997), although studies done in South Africa suggest there may be comparable outcomes for men and women (Joska et al., 2010). Thus, the overrepresentation of females in this sample should not affect the relationships observed here; if anything, it should overestimate the effect of HIV status on executive functioning for the general population. Second, this sample consisted of individuals who were not on HAART at first assessment. Many studies in this field use samples in which all or some of the participants are on a form of ART (Cysique et al., 2009; Marra et al., 2009). The results produced by those studies are difficult to interpret because ART may protect against some of the negative outcomes of HIV infection (Letendre et al., 2008; Smurzynski et al., 2011). The current study does not suffer from such interpretation difficulty; the fact that the entire sample of HIV-positive participants was treatment-naïve at the first assessment means that the lack of convincing findings for neuropsychological impairment at cross-sectional analysis cannot be attributed to the buffering effects of HAART.

Overall, the results of this study indicate that the pattern of neurocognitive impairment observed in clade C HIV-positive individuals is not consistent with that reported in the clade B literature; our findings suggest that the clade C subtype presents with a more favourable profile of neurocognitive impairment.

An interesting finding, albeit one not related directly to the present research agenda, was that the language discrepancy variable was a marginally significant predictor of function on the CTT Part 2. This is pertinent because the test was designed with the intention of

minimizing the effect of language (Spreen & Strauss, 1998). Further, the inclusion of the language discrepancy variable has important implications for neuropsychological testing in South Africa in general. On the WSCT and Stroop test, those participants who were tested in a language different from their home languages performed more poorly than those tested in their home language—and this on tests that do not have a heavy language component. This finding speaks to the fact that it is important to ensure that tests are administered in an individual's home language before making a clinical diagnosis or before presenting findings in a forensic setting (Fillenbaum, Heyman, Williams, Prosnitz, & Burchett, 1990; Murden, McRae, Kaner, & Bucknam, 1991).

Limitations and Suggestions for Future Research

We have discussed the possible effects of omitting viral load from the analysis on the results of the study; clearly, it would be beneficial to include this variable to directly control for its effect on the relationships observed. This inclusion would allow for more precise estimates, both in terms of effect sizes and statistical significance. Other variables that should be taken into account in future studies are the socioeconomic status and income of the participants, as well as whether they have a history of traumatic life events. Regarding the latter: Although the current study controlled for the effects on cognition of psychiatric disorders such as posttraumatic stress disorder (PTSD) by excluding anyone who presented with such, experience of traumatic life events may or may not later manifest as symptoms of PTSD (Ide & Paez, 2000; Van der Kolk & Courtois, 2005). Importantly, lifetime trauma appears related to impaired performance on cognitive tests (Leserman et al., 2007; Leserman et al., 2005).

A further limitation of this study was the lack of a maturation control group for the longitudinal analysis of executive function test performance. This control would have allowed for a more rigorous assessment of the impact of HIV on executive function over time. Similarly, we advise that future investigations include a control group consisting of individuals who have been diagnosed with a chronic disease that does not affect the frontal systems, such as diabetes or hypertension. In this way, one could determine whether performance on measures of executive function is related to the presence of a disease in general, or of HIV infection specifically.

An important limitation of this study is the absence of a direct comparison between clade B and clade C HIV-positive individuals on performance on measures of executive function. Future research would benefit from collaborations between research laboratories in

South Africa and in North America, in order to ascertain whether there are indeed clade-specific patterns of neurocognitive impairment.

Finally, research in this field would benefit greatly from including measures of instrumental activities of daily living (IADLs). IADLs are everyday tasks that are somewhat complex in nature and involve multiple steps that must be organised, planned, and executed (Cattie et al., 2012). Examples of IADLs include medication adherence, financial management, and management of interpersonal relationships. IADLs have been shown, consistently and over multiple studies, to be related to executive functions (Bowie et al., 2008; Heaton et al., 2004; Mindt et al., 2003) and are a core component of cognitive rehabilitation. Assessing these abilities would provide practical information regarding the benefit of IADL-focused cognitive rehabilitation for HIV-positive individuals.

Summary and Conclusion

Existing literature in the field of HIV neuropsychology consistently demonstrates poor outcomes for HIV-infected individuals on measures of executive functioning. These previously published studies are based almost wholly on samples of (either presumed or confirmed) clade B HIV-positive individuals. However, clade C HIV infection accounts for up to 50% of all infections worldwide. Hence, the major significance of this investigation is that, in this clade C HIV-positive South African sample, the pattern of deficits observed in previous studies is not present. Hence, we suggest that the degree of HIV-related neurocognitive impairment is not equivalent across clades.

The presence of such clade-specific differences has implications for assessment and rehabilitation in clade C prevalent areas, such as South Africa. Basing rehabilitation programmes on studies from clade B-prevalent areas could result in ineffective treatments for cognitive dysfunction. Further research into clade C-specific impairments would aid the tailoring of rehabilitation programmes to fit the profile of clade C HIV impairment.

Furthermore, this study expands the existing scientific literature on the implications of HIV infection for neurocognitive functioning by examining relationships outside of the samples typically investigated. Knowledge of HIV-associated executive (dys)function is expanded here by examining clade C-specific impairments in a sample of individuals who are not on HAART; most literature in this area uses clade B samples in which a proportion of individuals are on ARTs of some form. This study is therefore unique in that it examines functioning in a relatively unexplored cohort of HIV-positive individuals, and that the observed relationships are not obscured by the buffering effects ART.

In conclusion, we report here that clade C patterns of impairment are different, and milder, than those reported in the existing clade B-dominated HIV neuropsychology literature. This finding has important implications for cognitive rehabilitation of HIV-infected individuals in South Africa, and for expanding the existing knowledge base on the clade-specific neuropsychological outcomes of HIV infection.

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Appendix A

Informed Consent Document: Patients

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 is it 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

Informed Consent Document: Controls

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

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- *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

Appendix C

Letter of Ethical Approval

UNIVERSITY OF CAPE TOWN

Health Sciences Faculty
Research Ethics Committee
Room E52-24 Groote Schuur Hospital Old Main Building
Observatory 7925
Telephone [021] 406 6338 • **Facsimile** [021] 406 6411
e-mail: lamees.emjedi@uct.ac.za

07 August 2007

REC REF: 263/2007

Dr J Joska
Psychiatry & Mental Health
J Block

Dear Dr Joska

PROJECT TITLE: NEUROCOGNITIVE DISORDERS IN YOUNG ADULTS WITH HIV/AIDS COMMENCING ANTI-RETRO-VIRAL TREATMENT IN THE WESTERN CAPE

Thank you for your letter to the Research Ethics Committee dated 02 August 2007.

It is a pleasure to inform you that the Ethics Committee has **formally approved** the above-mentioned study including the following documentation:

- Study Protocol.
- Mini International Neuropsychiatric Interview English Version 5.0.0 dated 01 July 2006.
- Participant Information Leaflet and Consent Form Version 1, dated 03 May 2007.

Your comments to the queries raised are noted with thanks.

This serves to confirm that the University of Cape Town Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical Research Council (MRC-SA), Food and Drug Administration (FDA-USA), International Convention on Harmonisation Good Clinical Practice (ICH GCP) and Declaration of Helsinki guidelines.

The Research Ethics Committee granting this approval is in compliance with the ICH Harmonised Tripartite Guidelines E6: Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) and FDA Code Federal Regulation Part 50, 56 and 312.

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

Please quote the REC. REF in all your correspondence.

Yours sincerely

A/PROF. M. BLOCKMAN
CHAIRPERSON, HSF HUMAN ETHICS

lemjedi

Appendix D

Full Hierarchical Regression Models

Table D1
Color Trails Test Part 2: Hierarchical regression model testing Hypothesis 1 (N = 300)

	B	*β*	*t*	*p*	95% C.I		Semi-partial correlation
					Lower	Upper	
Step 1							
Constant	4.99 (0.20)		25.13	< .001***	4.60	5.38	
Age	0.01 (0.00)	0.09	1.55	.123	-0.00	0.02	0.09
Xhosa	0.04 (0.07)	0.04	0.54	.590	-0.10	0.18	0.03
Afrikaans	-0.21 (0.09)	-0.19	-2.34	.020*	-0.39	-0.03	-0.13
Education	-0.05 (0.01)	-0.22	-3.94	< .001***	-0.07	-0.02	-0.22
Employment	0.03 (0.04)	0.05	0.79	.429	-0.05	0.12	0.04
Step 2							
Constant	4.99 (0.20)		25.30	< .001**	4.61	5.38	
Age	0.01 (0.00)	0.07	1.29	.199	-0.00	0.01	0.07
Xhosa	0.06 (0.07)	0.07	0.86	.391	-0.08	0.20	0.05
Afrikaans	-0.16 (0.09)	-0.15	-1.79	.074	-0.34	0.02	-0.10
Education	-0.05 (0.01)	-0.23	-4.13	< .001***	-0.08	-0.03	-0.27
Employment	0.04 (0.04)	0.05	0.87	.386	-0.05	0.12	0.05
Language Discrepancy	0.10 (0.05)	0.13	2.23	.027*	0.01	0.19	0.12
Step 3							
Constant	4.99 (0.20)		25.14	< .001***	4.60	5.38	
Age	0.01 (0.00)	0.07	1.23	.219	-0.00	0.01	0.07
Xhosa	0.06 (0.07)	0.07	0.86	.393	-0.08	0.20	0.05
Afrikaans	-0.16 (0.09)	-0.15	-1.74	.083	-0.35	0.02	-0.10
Education	-0.05 (0.01)	-0.23	-4.00	< .001***	-0.08	-0.03	-0.22
Employment	0.04 (0.04)	0.05	0.86	.389	-0.05	0.12	0.05
Language Discrepancy	0.10 (0.05)	0.13	2.07	.040*	0.01	0.20	0.11
HIV status	-0.00 (0.05)	-0.00	-0.02	.985	-0.10	0.09	-0.00

Note. HIV-positive $n = 153$; HIV-negative $n = 147$. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .11; ΔR^2 for step 2 = .02 ($p = .03$); ΔR^2 for step 3 < .001 ($p = .99$); overall $R^2 = .12$; overall adjusted $R^2 = .10$; $F(7, 292) = 5.82$, $p < .001$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table D2
Wisconsin Card Sorting Test, Composite Variable: Hierarchical regression model testing Hypothesis 1 (N = 272)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	1.71 (1.48)		1.16	.249	-1.21	4.63	
Age	0.10 (0.03)	0.19	3.36	.001**	0.04	0.17	0.19
Xhosa	-0.25 (0.52)	-0.04	-0.48	.633	-1.27	0.77	-0.03
Afrikaans	-2.12 (0.65)	-0.26	-3.25	.001**	-3.40	-0.83	-0.18
Education	-0.41 (0.09)	-0.26	-4.59	< .001***	-0.59	-0.24	-0.26
Employment status	0.27 (0.32)	0.05	0.85	.399	-0.36	0.90	0.05
Step 2							
Constant	1.73 (1.48)		1.16	.245	-1.19	4.65	
Age	0.10 (0.03)	0.19	3.21	.002**	0.04	0.16	0.18
Xhosa	-0.20 (0.52)	-0.03	-0.38	.707	-1.22	0.83	-0.02
Afrikaans	-1.99 (0.67)	-0.25	-2.98	.003**	-3.31	-0.68	-0.17
Education	-0.42 (0.09)	-0.27	-4.63	< .001***	-0.59	-0.24	-0.26
Employment status	0.28 (0.32)	0.05	0.88	.383	-0.35	0.91	0.05
Language Discrepancy	0.28 (0.33)	0.05	0.85	.399	-0.37	0.93	0.05
Step 3							
Constant	1.58 (1.47)		1.08	.283	-1.31	4.48	
Age	0.07 (0.03)	0.13	2.16	.032*	0.01	0.14	0.12
Xhosa	-0.16 (0.52)	-0.03	-0.31	.756	-1.18	0.86	-0.08
Afrikaans	-1.55 (0.69)	-0.19	-2.27	.024*	-2.90	-0.21	-0.13
Education	-0.37 (0.09)	-0.24	-4.03	< .001***	-0.55	-0.19	-0.22
Employment status	0.17 (0.32)	0.03	0.54	.589	-0.46	0.81	0.03
Language Discrepancy	-0.03 (0.35)	-0.00	-0.07	.943	-0.71	0.66	-0.00
HIV status	0.90 (0.36)	0.18	2.47	.014*	0.18	1.61	0.14

Note. HIV-positive $n = 147$; HIV-negative $n = 125$. In the second column, standard deviations are presented in parentheses. CI = confidence interval.
R^2 for step 1 = .15; ΔR^2 for step 2 = .02 ($p = .399$); overall $R^2 = .20$; overall adjusted $R^2 = .18$; $F(7, 264) = 9.15$, $p < .001$.
*$p < .05$. **$p < .01$. ***$p < .001$.

Table D3
Stroop Test: Hierarchical regression model testing Hypothesis 1 (N = 293)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	24.69 (5.53)		4.46	< .001***	13.80	35.57	
Age	-0.39 (0.12)	-0.18	-3.39	.001**	-0.62	-0.16	-0.18
Xhosa	-3.45 (2.02)	-0.13	-1.71	.089	-7.42	0.53	-0.09
Afrikaans	6.54 (2.53)	0.20	2.59	.010*	1.56	11.52	0.14
Education	1.88 (0.34)	0.30	5.53	< .001***	1.21	2.55	0.29
Employment	0.03 (1.21)	0.00	0.03	.979	-2.34	2.41	0.00
Step 2							
Constant	24.65 (5.44)		4.53	< .001***	13.93	35.36	
Age	-0.35 (0.12)	-0.16	-3.03	.003**	-0.57	-0.12	-0.16
Xhosa	-4.35 (2.01)	-0.17	-2.17	.031*	-8.30	-0.40	-0.11
Afrikaans	4.75 (2.55)	0.14	1.86	.064	-0.28	9.78	0.10
Education	1.95 (0.34)	0.31	5.83	< .001***	1.29	2.61	0.30
Employment	-0.15 (1.19)	-0.01	-0.13	.898	-2.49	2.19	-0.01
Language Discrepancy	-4.00 (1.26)	-0.17	-3.18	.002**	-6.47	-1.52	-0.16
Step 3							
Constant	25.89 (5.41)		4.79	< .001***	15.25	36.53	
Age	-0.25 (0.12)	-0.12	-2.09	.037*	-0.49	-0.02	-0.11
Xhosa	-4.65 (1.99)	-0.18	-2.34	.020*	-8.57	-0.73	-0.12
Afrikaans	3.01 (2.61)	0.09	1.15	.250	-2.13	8.15	0.06
Education	1.74 (0.34)	0.27	5.10	< .001***	1.07	2.41	0.26
Employment	0.16 (1.18)	0.01	0.14	.892	-2.17	2.49	0.01
Language Discrepancy	-2.72 (1.33)	-0.12	-2.05	.042*	-5.34	-0.10	-0.10
HIV status	-3.46 (1.29)	-0.17	-2.67	.008**	-6.00	-0.91	-0.14

Note. HIV-positive $n = 148$; HIV-negative $n = 145$. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .22; ΔR^2 for step 2 = .03 ($p = .002$); ΔR^2 for step 3 = .02 ($p = .008$); overall $R^2 = .27$; overall adjusted $R^2 = .25$; $F(7, 285) = 14.74$, $p < .001$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table D4
Category Fluency Test: Hierarchical regression model testing Hypothesis 1 (N = 303)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	16.46 (4.42)		3.73	< .001***	7.77	25.16	
Age	-0.06 (.09)	-0.04	-0.67	.504	-0.25	0.12	-0.04
Xhosa	0.18 (1.60)	0.01	0.12	.909	-2.97	3.33	0.01
Afrikaans	4.07 (2.01)	0.16	2.02	.044*	0.11	8.03	0.11
Education	1.42 (.27)	0.29	5.22	< .001***	0.88	1.95	0.29
Employment status	-1.10 (.96)	-0.07	-1.15	.251	-2.99	0.79	-0.06
Step 2							
Constant	17.11 (4.21)		4.06	< .001***	8.82	25.39	
Age	-0.01 (.09)	-0.01	-0.09	.931	-0.18	0.17	-0.00
Xhosa	-1.01 (1.54)	-0.05	-0.66	.512	-4.04	2.02	-0.03
Afrikaans	1.58 (1.97)	0.06	0.80	.423	-2.30	5.45	0.04
Education	1.47 (.26)	0.30	5.69	< .001***	0.96	1.98	0.30
Employment status	-1.29 (.91)	-0.08	-1.41	.159	-3.09	0.51	-0.07
Language Discrepancy	-5.31 (.95)	-0.30	-5.60	< .001***	-7.17	-3.44	-0.29
Step 3							
Constant	17.82 (4.21)		4.23	< .001***	9.53	26.11	
Age	0.04 (.09)	0.03	0.47	.642	-0.14	0.23	0.02
Xhosa	-1.13 (1.54)	-0.06	-0.74	.461	-4.16	1.89	-0.04
Afrikaans	0.68 (2.02)	0.03	0.34	.737	-3.30	4.66	0.02
Education	1.35 (.27)	0.28	5.09	< .001***	0.83	1.87	0.26
Employment status	-1.11 (.92)	-0.07	-1.21	.227	-2.91	0.69	-0.06
Language Discrepancy	-4.63 (1.02)	-0.26	-4.54	< .001***	-6.63	-2.62	-0.24
HIV status	-1.84 (1.02)	-0.12	-1.80	.073	-3.85	0.18	-0.09

Note. HIV-positive n = 158; HIV-negative n = 145. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .11; ΔR^2 for step 2 = .09 ($p < .001$); ΔR^2 for step 3 = .01 ($p = .073$); overall R^2 = .20; overall adjusted R^2 =.19; $F(7, 295) = 23.97$, $p < .001$. *$p < .05$. **$p < .01$. ***$p < .001$.

Table D5
Color Trails Test Part 2: Hierarchical regression model testing Hypotheses 2 and 3 (N = 55)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	5.28 (0.52)		10.21	< .001***	4.24	6.31	
Age	-0.01 (0.01)	-0.09	-0.64	.527	-0.03	0.02	-0.09
Xhosa	0.07 (0.17)	0.06	0.40	.692	-0.27	0.40	0.06
Education	-0.04 (0.03)	-0.20	-1.39	.170	-0.10	0.02	-0.19
Employment	0.07 (0.09)	0.11	0.72	.477	-0.12	0.25	0.10
Step 2							
Constant	5.13 (0.52)		9.82	< .001***	4.08	6.18	
Age	-0.00 (0.01)	-0.03	-0.18	.861	-0.03	0.02	-0.02
Xhosa	0.09 (0.17)	0.08	0.55	.583	-0.24	0.42	0.08
Education	-0.05 (0.03)	-0.26	-1.73	.091	-0.11	0.01	-0.24
Employment	0.09 (0.09)	0.14	0.95	.345	-0.10	0.27	0.13
Language Discrepancy	0.13 (0.09)	0.21	1.39	.172	-0.06	0.31	0.19
Step 3							
Constant	5.28 (0.54)		9.75	< .001***	4.19	6.37	
Age	-0.01 (0.01)	-0.06	-0.42	.675	-0.03	0.02	-0.06
Xhosa	0.10 (0.17)	0.08	0.58	.568	-0.24	0.43	0.08
Education	-0.04 (0.03)	-0.21	-1.35	.183	-0.11	0.02	-0.19
Employment	0.07 (0.09)	0.11	0.72	.473	-0.12	0.25	0.10
Language Discrepancy	0.11 (0.09)	0.18	1.14	.260	-0.08	0.30	0.16
CD4 count	-0.00 (0.00)	-0.19	-1.29	.202	-0.00	0.00	-0.18
Years since diagnosis	-0.01 (0.02)	-0.03	-0.22	.823	-0.05	0.04	-0.03

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .05; ΔR^2 for step 2 = .04 (p = .172); ΔR^2 for step 3 = .03 (p = .406); overall R^2 = .12; overall adjusted R^2 =-.02; $F(7, 47) = 0.89$, p = .522.
*p < .05. **p < .01. ***p < .001.

Table D6
Wisconsin Card Sorting Test, Composite Variable: Hierarchical regression model testing Hypotheses 2 and 3 (N = 50)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	3.73 (4.87)		0.77	.448	-6.08	13.54	
Age	0.08 (0.12)	0.09	0.63	.531	-0.17	0.32	0.09
Xhosa	1.31 (1.63)	0.11	0.80	.426	-1.97	4.58	0.11
Education	-0.67 (0.24)	-0.41	-2.86	.006**	-1.14	-0.20	-0.39
Employment	0.19 (0.80)	0.04	0.24	.810	-1.42	1.80	0.03
Step 2							
Constant	4.44 (5.03)		0.88	.383	-5.70	14.57	
Age	0.05 (0.13)	0.06	0.41	.685	-0.21	0.31	0.06
Xhosa	1.28 (1.64)	0.11	0.77	.443	-2.04	4.57	0.11
Education	-0.64 (0.24)	-0.39	-2.63	.012*	-1.13	-0.15	-0.36
Employment	0.08 (0.82)	0.02	0.10	.920	-1.57	1.74	0.01
Language Discrepancy	-0.51 (0.81)	-0.09	-0.64	.528	-2.14	1.11	-0.09
Step 3							
Constant	5.63 (5.05)		1.12	.271	-4.56	15.82	
Age	0.05 (0.13)	0.05	0.37	.712	-0.21	0.30	1.18
Xhosa	0.90 (1.63)	0.08	0.55	.584	-2.39	4.19	1.12
Education	-0.77 (0.26)	-0.47	-3.00	.005**	-1.28	-0.25	1.37
Employment	-0.05 (0.82)	-0.01	-0.06	.957	-1.69	1.60	1.22
Language Discrepancy	-0.80 (0.81)	-0.15	-0.99	.330	-2.44	0.84	1.23
CD4 count	-0.00 (0.01)	-0.06	-0.41	.686	-0.01	0.01	1.03
Years since diagnosis	0.36 (0.21)	0.26	1.72	.092	-0.062	0.78	1.27

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .18; ΔR^2 for step 2 = .01 (p = .528); ΔR^2 for step 3 = .06 (p = .217); overall R^2 = .24; overall adjusted R^2 = .11; $F(7, 42) = 1.90$, p = .094.
*p < .05. **p < .01. ***p < .001.

Table D7
Stroop Test: Hierarchical regression model testing Hypotheses 2 and 3 (N = 52)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	32.57 (11.97)		2.72	.009**	8.48	56.66	
Age	-0.68 (0.30)	-0.27	-2.28	.027*	-1.27	-0.08	-0.27
Xhosa	-8.48 (3.85)	-0.27	-2.20	.033*	-16.22	-0.73	-0.26
Education	2.36 (0.65)	0.46	3.63	.001**	1.05	3.67	0.43
Employment	-0.96 (2.17)	-0.06	-0.44	.659	-5.33	3.41	-0.05
Step 2							
Constant	31.80 (12.40)		2.56	.014*	6.84	56.76	
Age	-0.65 (0.31)	-0.26	-2.09	.042*	-1.28	-0.02	-0.25
Xhosa	-8.37 (3.91)	-0.27	-2.14	.038*	-16.23	-0.51	-0.26
Education	2.32 (0.67)	0.45	3.48	.001**	0.98	3.67	0.42
Employment	-0.88 (2.21)	-0.05	-0.40	.693	-5.34	3.58	-0.05
Language Discrepancy	0.60 (2.15)	0.04	0.28	.781	-3.73	4.94	0.03
Step 3							
Constant	31.00 (13.07)		2.37	.022*	4.66	57.35	
Age	-0.63 (0.32)	-0.26	-1.95	.057	-1.28	0.02	-0.24
Xhosa	-8.55 (4.04)	-0.27	-2.12	.040*	-16.69	-0.41	-0.26
Education	2.23 (0.72)	0.43	3.11	.003**	0.79	3.67	0.38
Employment	-0.75 (2.30)	-0.05	-0.33	.745	-5.39	3.88	-0.04
Language Discrepancy	0.69 (2.26)	0.04	0.31	.760	-3.85	5.24	0.04
CD4 count	0.00 (0.01)	0.05	0.36	.724	-0.02	0.03	0.04
Years since diagnosis	0.15 (0.54)	0.04	0.28	.780	-0.94	1.25	0.04

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .33; ΔR^2 for step 2 = .001 (p = .781); ΔR^2 for step 3 = .00 (p = .891); overall R^2 = .34; overall adjusted R^2 =.23; $F(7, 44) = 3.20$, p = .008.
*p < .05. **p < .01. ***p < .001.

Table D8
Category Fluency Test: Hierarchical regression model testing Hypotheses 2 and 3 (N = 55)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	2.15 (10.80)		0.20	.843	-19.55	23.84	
Age	0.32 (0.27)	0.15	1.20	.235	-0.22	0.86	0.15
Xhosa	-2.83 (3.53)	-0.10	-0.80	.426	-9.91	4.25	-0.10
Education	1.82 (0.59)	0.41	3.10	.003**	0.64	3.00	0.39
Employment	0.85 (1.94)	0.06	0.44	.662	-3.04	4.75	0.06
Step 2							
Constant	6.47 (10.93)		0.59	.557	-15.50	28.43	
Age	0.19 (0.28)	0.09	0.67	.505	-0.37	0.74	0.08
Xhosa	-3.39 (3.48)	-0.12	-0.97	.336	-10.38	3.61	-0.12
Education	2.01 (0.59)	0.46	3.41	.001*	0.83	3.19	0.42
Employment	0.36 (1.93)	0.03	0.18	.854	-3.52	4.23	0.02
Language Discrepancy	-3.14 (1.89)	-0.22	-1.67	.102	-6.92	0.65	-0.21
Step 3							
Constant	6.10 (11.32)		0.54	.593	-16.68	28.88	
Age	0.17 (0.28)	0.08	0.60	.554	-0.40	0.73	0.07
Xhosa	-2.65 (3.53)	-0.10	-0.75	.456	-9.76	4.45	-0.09
Education	2.29 (0.62)	0.52	3.67	.001**	1.04	3.55	0.45
Employment	0.33 (1.96)	0.02	0.17	.869	-3.62	4.28	0.02
Language Discrepancy	-3.00 (1.94)	-0.21	-1.55	.129	-6.89	0.90	-0.19
CD4 count	-0.00 (0.01)	-0.05	-0.38	.708	-0.03	0.02	-0.05
Years since diagnosis	-0.61 (0.47)	-0.17	-1.28	.206	-1.56	0.35	-0.16

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .22; ΔR^2 for step 2 = .04 (p = .102); ΔR^2 for step 3 = .03 (p = .384); overall R^2 = .29; overall adjusted R^2 =.18; $F(7, 47) = 2.71$, p = .019.
*p < .05. **p < .01. ***p < .001.

Table D9
Category Fluency Test: Hierarchical regression model testing Hypotheses 4 (N = 56)

					95% C.I		
	B	*β*	*t*	*p*	Lower	Upper	Semi-partial
Step 1							
Constant	-3.21 (2.20)		-1.46	.149	-7.62	1.19	
CD4 count	0.01 (.01)	0.13	0.94	.350	-0.01	0.03	.13
Years since diagnosis	-0.48 (.41)	-0.16	-1.18	.243	-1.29	0.33	-.16
Step 2							
Constant	-2.09 (2.17)		-0.97	.339	-6.44	2.26	
CD4 count	0.01 (.01)	0.11	0.85	.401	-0.01	0.03	.11
Years since diagnosis	-0.32 (.40)	-0.11	-0.81	.424	-1.11	0.48	-.11
Language discrepancy change	-4.06 (1.76)	-0.31	-2.31	.025*	-7.58	-0.53	-.30
Step 3							
Constant	-7.61 (5.56)		-1.37	.178	-18.77	3.57	
CD4 count	0.01 (.01)	0.12	0.93	.359	-0.01	0.03	.12
Years since diagnosis	-0.26 (.40)	-0.09	-0.65	.517	-1.06	0.54	-.09
Language discrepancy change	-3.83 (1.77)	-0.29	-2.17	.035*	-7.37	-0.28	-.28
HAART	4.92 (4.57)	0.14	1.08	.287	-4.26	14.09	.14

Note. In the second column, standard deviations are presented in parentheses. CI = confidence interval. R^2 for step 1 = .04; ΔR^2 for step 2 = .09 (p = .025); ΔR^2 for step 3 = .02 (p = .287); overall R^2 = .14; overall adjusted R^2 =.08; $F(4, 51) = 2.15$, p = .088.
*p < .05. **p < .01. ***p < .001.

Appendix F

Corrections of Non-Normal Distributions

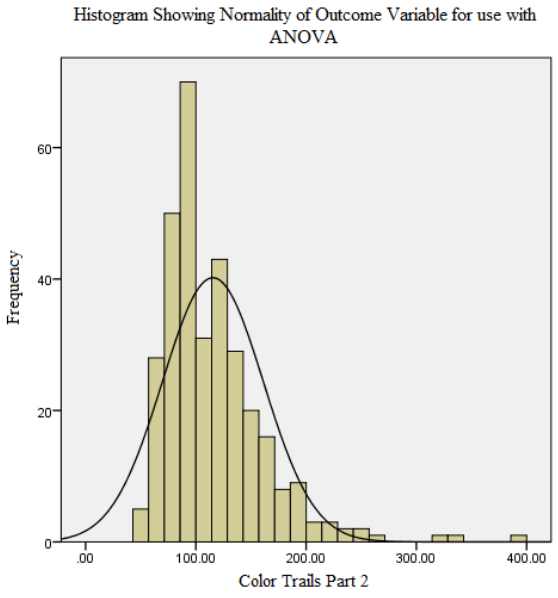

Figure F1. Normality of the Color Trails Test Part 2 testing Hypothesis 1.

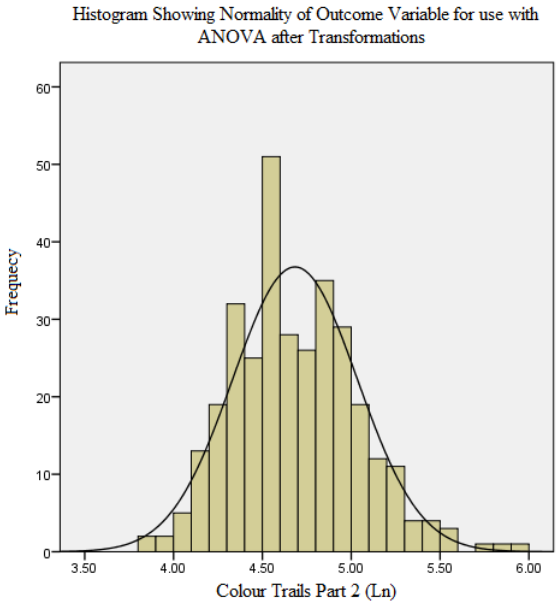

Figure F2. Normality of Color Trails Test Part 2 testing Hypothesis 1 after using a natural log transformation.

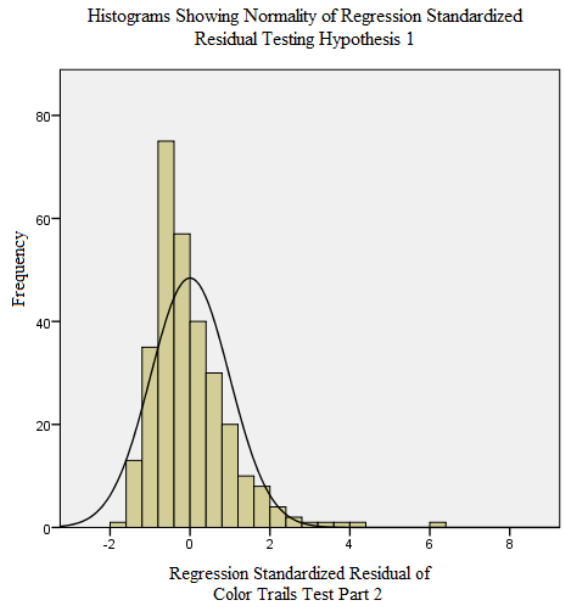

Figure F3. Normality of standardized residual of Color Trails Test Part 2 testing Hypothesis 1.

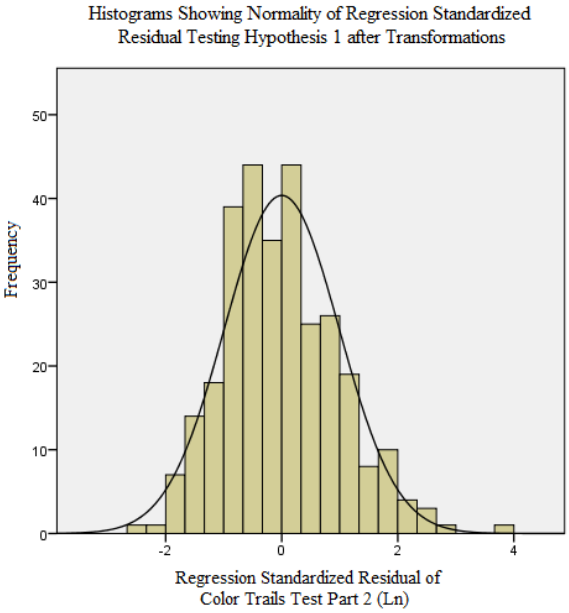

Figure F4. Normality of standardized residual of Color Trails Test Part 2 testing Hypothesis 1 after using a natural log transformation.

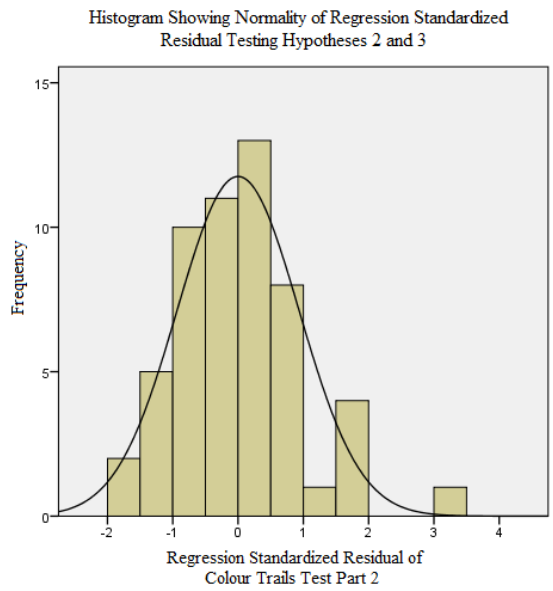

Figure F5. Normality of standardized residual of Color Trails Test Part 2 testing Hypotheses 2 and 3.

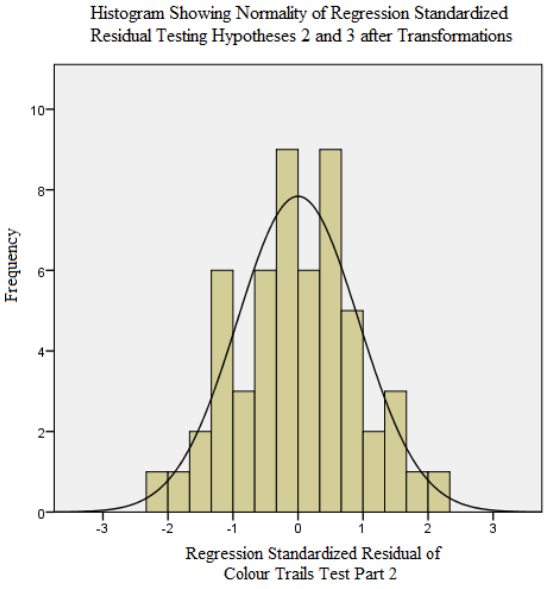

Figure F6. Normality of standardized residual of Color Trails Test Part 2 testing Hypotheses 2 and 3 after using a natural log transformation.

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