

The exploration of neuropsychological disorders in HAART- naïve young adults in South
Africa

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ABSTRACT

Previous studies have reported that Human Immunodeficiency Virus type 1 (HIV-1) directly affects the nervous system and the brain, and subsequently, it compromises patients' cognitive ability which in turn decreases their functional status and survival time. Using a variety of neuropsychological tests, the aim of this study was to investigate the impact of HIV-1 on neurocognitive ability of HAART-naive young adults in Cape Town, South Africa, where clade C of the virus prevails. HAART-naive individuals are people who are not taking antiretroviral treatment (ARVs). Participants were 24 HIV seropositive (HIV+) and 24 HIV seronegative (HIV-) individuals recruited from a clinic in Khayelitsha. They were matched on age, gender, socio-economic status (SES), language, and education. Those who had a history of substance use and pre-existing mental illness were excluded from the study. Results were similar to the previous findings from both developing and developed countries. Participants in the HIV+ group performed more poorly on some tests of motor functioning, attention, processing speed, and executive functioning. The findings reflected that subtle cognitive impairment is present in South African HAART-naive individuals.

Keywords: HIV-1; HAART-naive; HIV-1 associated dementia; Mild Neurocognitive Disorder ; clade C; Cognitive impairment; South Africa.

The World Health Organisation estimates that 33 million people worldwide were living with HIV in 2007. Sub-Saharan Africa had 22 million people living with HIV, with nearly 6 million of them residing in South Africa. In 2003 alone, there were relatively 370,000 AIDS associated deaths (UNAIDS, 2004). This is the highest number of deaths in any one country within a year. Because of the large number of infected people in this country, it is important that we understand the nature of the disease, especially its effects on cognitive ability of the patients.

HIV-1 affects many parts of the body during the failure of the immune system, which is associated with the progression of the disease. The Central Nervous System (CNS) and the brain are ones of these affected areas. The purpose of the current study was to examine the cognitive functioning, particularly the neuropsychological performance of HIV + individuals. More specifically it was to look at the cognitive ability of HAART- naive young adults just prior to starting HAART in Cape Town, South Africa , where HIV -1 clade C is dominant.

This review of the relevant literature begins with a brief overview of effect of HIV on the CNS. Secondly, it focuses on HIV-associated neurocognitive disorders (HAND). Thirdly, it delves into the cognitive problems of HAART- naïve individuals with HIV-1. Then, variation in HIV-associated cognitive disturbances across different countries is examined, and finally, the effects of HIV-1 on cognitive ability in Africa in previous studies are looked at.

THEORETICAL BACKGROUND

The Effect of HIV-1 on the Central Nervous System

HIV-1 is a neurotrophic virus that has an adverse impact on the brain and CNS. In the early stages of infection it enters the brain via HIV-infected monocytes and other infected CD4 cells which differentiate into macrophages. The virus replicates in these cells, and thereafter infects other cells such as microglia, oligodendrocytes, astrocytes, and neurons. Furthermore, the presence of HIV-1 in the brain influences an inflammatory cascade that results in neuropathological changes such as dendritic simplification, loss of synaptic density, and neurodegeneration in the frontal cortex, hippocampus, basal ganglia and deep white matter (Moore et al., 2006).

The most dramatic impact of HIV-1 on the CNS in the early stages of infection is manifested in cognitive disturbances, namely, asymptomatic neurocognitive impairment (ANI), then mild neurocognitive disorder (MND), ultimately, these cognitive disturbances can develop into full-blown HIV-associated dementia (HAD). Such cognitive impairment if remains untreated results in decreased patient's quality of life, poor medication adherence, and shorter survival time (Ellis et al., 1997; Tozzi et al., 2007).

HIV-Associated Neurocognitive Disorders (HAND)

Table 1

Criteria for HIV-Associated Neurocognitive Impairment

HIV-associated asymptomatic neurocognitive impairment (ANI)

1. ANI is defined by performance at least 1 SD below the mean of demographically adjusted normative scores in at least two domains (attention-information processing, language, abstraction-executive, complex perceptual motor skills, memory including learning and recall, simple motor skills or sensory perceptual abilities); these criteria specify that at least five cognitive domains be examined or observed. Finally, the impairment does not occur solely as part of a delirium such as vascular insult, confusional state secondary to opportunistic CNS disease, drug effect, or other systematic disorders.
- 2 The cognitive impairment does not interfere with every day function.
- 3 The cognitive impairment does not meet criteria for delirium or dementia
- 4 There is no evidence of another pre-existing cause for the ANI

HIV-associated mild neurocognitive disorder (MND)

- 1 Acquired mild-to-moderate impairment in cognitive function documented by a score of at least 1SD below demographically corrected norms on tests of at least two different cognitive domains.
- 2 The cognitive impairment interferes, at least mildly, with activities of daily living
- 3 The impairment does not meet criteria for delirium or dementia
- 4 The impairment is not fully explained by comorbid conditions.

HIV-associated dementia

- 1 Acquired moderate to severe cognitive impairment, documented by a score at of least 2 SD below demographically corrected normative means in at least two different cognitive areas.
 - 2 Marked difficulty with activities of daily living due to the cognitive impairment
 - 3 The impairment does not meet criteria for delirium
 - 4 The impairment is not adequately explained by comorbid conditions.
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Antinori et al. (2007)

HIV-associated asymptomatic neurocognitive impairment (ANI)

HIV- associated cognitive impairment has been divided in three broad types by Antinori et al. (2007) which are given in table 1. The term HIV-associated asymptomatic neurocognitive impairment refers to the early stages of HIV-1 infection. This stage is characterised by subtle cognitive impairment, and the quality of life of patients is still not affected at this point. Gopukumar et al. (2008) illustrate that at this stage the progress of cognitive impairment remain stable for a while despite the decline in CD4 cell count and viral load increase. The affected brain processes are sub-cortical and frontostriatal patterns, and usually, the levels of CD4 counts are still quite high, and may range from 200 to 500. This stage may last up to 10 years after diagnosis (Gupta et al., 2007; Grassi, Perin, Borella, & Mangoni 1999).

In general, previous research acknowledges the manifestation of minor cognitive impairment in the asymptomatic stage (Antinori et al., 2007; Gupta et al., 2007; Odiase et al., 2006). These studies suggest that asymptomatic patients may experience minor alterations in their cognitive functioning such as executive functions, motor skills, speed of processing, and memory which are not severe enough to interfere with patients' daily activities. In contrast, Price (1996) reported that at this stage the memory of patients may be affected in a way that could interfere with their ability to carry out their normal activities. Additionally, Grant (2008) point out that, the asymptomatic patients may exhibit exaggerated tremor and gait disturbance. Nevertheless, he postulates that motor difficulties are frequently observed in more advanced HIV-1 stages. He further suggests that in the asymptomatic stage, a failure to

accomplish motor skills is associated with progression to HAD (Grassi, et al., 1999; Salawu et al., 2008; Tartar et al., 2004; Wilkie, et al., 1998).

Furthermore, consensus is lacking regarding the clinical causes of the minor cognitive impairment observed in asymptomatic stage, and that may be due to differences in samples of interest. Hence, in an attempt to understand the causes of minor cognitive impairment, the stage of the disease, and levels of CD4 count have been used interchangeably by different studies. For instance, some studies have reported no relationship between CD4 cell count, and neuropsychological impairment (Clifford et al., 2007). Whereas others have found individuals with CD4 cell less than 200 to be more impaired on a variety of neuropsychological tests compared to individuals with CD4 cell counts higher than 200 (Gupta et al., 2007). And some studies have reported neuropsychological performance as being solely dependent on the stage of the disease (Grassi, et al. 1999; Price, 1996; Salawu et al., 2008). Since the asymptomatic stage is characterised by subtle cognitive impairment, and quality of life of the patients is still not disturbed, it is suggested that a more sensitive neuropsychological test battery is needed (Wilkie et al., 1998).

HIV-associated mild neurocognitive disorder (MND)

The ANI and MND are the most prevalent forms of HAND occurring in 30%-60% of HIV+ individuals (Grant, 2008). MND diagnosis is similar to ANI but requires mild impairment in daily activities and in neuropsychological performance. Patients may show cognitive, behavioural and motor problems. Two of the following deficits may be experienced: impaired attention, mental slowing, slowed movement, incoordination or personality change and irritability Delis et al. (1995). Delis and colleagues in their study found that patients with mild neurocognitive disorder were more impaired in tests of memory and learning compared to the HIV+ control group who did not meet the criteria of MND. They also suggested a great involvement of subcortical areas at this stage.

HIV-associated dementia (HAD)

As mentioned previously, neuropsychological impairment in HIV+ people can range from ANI and MND to HAD. HAD is largely found at the later stages of infection. Usually, the level of CD4 count is very low, and may be less than 200. HAD is a neurological syndrome characterised by abnormalities in cognition, motor performance, and behaviour. Specifically, HAD results in extreme difficulties in attention, concentration, speed of processing

information, mental flexibility, verbal learning and memory, as well as motor speed (Grant, 2008; Gupta et al., 2007). Additionally, Ances & Clifford (2008) point out that HAD may also result in social withdrawal that may be mistaken as depression.

HAD becomes detrimental to the lives of patients by resulting in lack of productivity, poor medication adherence, low quality of life, diminished self-care, and subsequently, it may lead to death. For instance, Childs et al. (1999) illustrates that the survival time after the diagnosis of HAD prior to HAART administration was very low, ranging from 3 to 6 months. This clearly indicates that if it remains untreated it can be dangerous.

HAD is the most prevalent form of dementia in the world, and is becoming a major concern in sub-Saharan Africa as well. For example, in a study by Wong et al. (2007) in Uganda it was detected in 31% of the participants. This statistic is disconcerting, and seems to give credence to Sacktor et al.'s (2005) argument that HAD will be the leading cause of dementia in the world, particularly, in people who are younger than 40.

Possible causes of HAD

HAD is caused by direct adverse effect of the virus on the brain such as chronic leptomenigeal and abnormalities of white matter rather than opportunistic infections (Price, 1996). It may also be caused by exposure of CNS to the virus, low levels of CD4 cell count, as well as immunosuppression, which is thought to be perhaps the most critical variable in the prediction of the severity of HAD (see Heaton et al., 2008; Sacktor, et al., 2006).

There are also other possible factors which may lead to severe HAD other than biological factors such as older age, low levels of education, unemployment, gender and decreased availability of health care, and poor nutritional status (Heaton et al., 2008; Wong et al., 2007). Additionally, Tozzi et al. (2007) demonstrate that low levels of education may increase the occurrence of HAD. In their study they found that less educated patients were more likely to have difficulties in attention, concentration, speed processing, verbal memory, and mental flexibility. They further suggested that this may be due to the possibility that educated people have a greater ability to hide their cognitive difficulties compared to less educated people.

HIV-Associated Cognitive Impairment in HAART -Naive Adults

Grant et al. (1987) state that 50% of all untreated HIV+ patients have cognition, behavioural, and motor deficits. Some studies report a prevalence of cognitive or motor dysfunction in more than 20% of all patients, whereas others have found approximately 5% or less.

Recently, Gupta et al. (2007) found that 60.5% of the participants in their study had mild to moderate cognitive deficits in the domains of learning and memory, fluency, and working memory.

Furthermore, previous studies have asserted the prevalence of poor motor skills and memory in HAART-naive individuals. For instance, Heaton et al.'s study (as cited in Wilkie et al., 2003) postulate that HIV+ untreated patients have difficulties with recalling recently acquired information such as names of people they have met recently, and that, subsequently they begin to develop difficulties with fine finger movements, and walking (Clifford et al., 2007). Moreover, the symptoms detected in HAART-naive individuals may become severe, interfere with daily activities, and thereafter, may lead to severe disability, and can only be reduced by HAART.

HAART is a combination of two or more different classes of ARVs. However, its effectiveness is not well known in many sub-Saharan countries because it is still not well studied yet, and still not administered in other areas (Parsons, Braaten, Hall, & Robertson, 2006; Sacktor et al., 2006). Most importantly, Tozzi et al. (2007) argue that even though HAART may reverse cognitive impairment, but it is not enough to treat it. For instance, in their study they found that patients who started it at a low baseline, and advanced cognitive impairment were more likely to be resistant towards HAART despite its long term administration. Thus, they suggested that HAART should be given as soon as HIV-associated cognitive impairment is diagnosed to avoid potentially irreversible neurological damage.

Variation in HIV-1 Associated Cognitive Impairment Across Countries

Previous studies have suggested that the frequency and severity of HIV-1 associated cognitive symptoms varies from region to region due to clade variation (e.g. Mishra et al., 2008; Sacktor et al., 2006; Wong et al., 2007). In other words, the cognitive difficulties experienced by HIV+ people who live in developed regions such as Europe, America, and Australia where clade B prevails, may differ in severity compared to the cognitive difficulties experienced by HIV + people in developing countries, where clade A, D and C dominate. In sub-Saharan Africa, opportunistic conditions such as tuberculosis, cryptococcal disease, syphilis, and the high frequency of malaria, poverty, and lack of education may worsen the

manifested cognitive impairment in HIV + individuals (Sacktor et al., 2006). On the other hand, in developed countries the pathology in CNS white matter may worsen the difficulties in speed of processing, and motor functioning, and such pathology is known to induce the levels of HAD (Robertson et al., 2007).

Clade C is prevalent worldwide, particularly, in developing countries such as southern and eastern Africa, India, Nepal and China (Liner, Hall, & Robertson, 2007; Valcour, et al., 2007). It affects more than 50% of HIV+ individuals worldwide (Mishra et al., 2008). And in South Africa it is responsible for 92% of HIV-1 infections (Van Harmelen et al., 1999). Surprisingly, despite that it is the less studied clade compared to clade B. Clade B is the most studied clade because in developed countries there are enough resources to conduct such studies. Thus, little is known about the nature of clade C.

However, the few previous studies that have been conducted in India have suggested that clade C is associated with low levels of neuropsychological impairment than clade B (Chandra et al., 2006; Gupta et al., 2007). For instance, Gupta and colleagues in their study of HAART-naive adults in India have found that none of the participants had severe cognitive difficulties such as HAD. Contrarily, Joska, Fincham, Stein, Paul & Seedat (2009) in their study conducted in Cape Town in South Africa, where clade C dominates found HIV-associated cognitive impairment to be prevalent, and using the HIV Dementia Scale (HSD), HAD was detected in 23.5% of the participants.

Various factors that lead to low levels of cognitive difficulties in clade C

Gupta et al. (2007) point out that there are various factors that may contribute towards the low levels of neuropsychological abnormalities in clade C compared to clade B. They mentioned: (1) the conserved dicysteine motif of the Tat protein; (2) the less amount of the damage to the neuronal cells; (3) as well as the lack of inflammatory response.

Nevertheless, Gupta and colleagues suggested that some factors accountable for the nature of manifested cognitive deficits in clade B are present in clade C as well, e.g. the levels of CD4 cell count and immunosuppression. They further state that the cognitive domains vulnerable in clade B are vulnerable in clade C too.

HIV-Associated Cognitive Impairment in Africa

There are more than 20 million individuals living with HIV-1 in sub-Saharan Africa (Sacktor et al., 2006). Approximately 2 million people die from HIV/AIDS-related causes annually, while 15 000 new cases of HIV-related cognitive impairment such as ANI, MND and HAD

are reported annually (Odiase et al., 2006). Sacktor (in press) cautioned about the alarming rate of cognitive impairment in this region, particularly, HAD and its danger. Judging from his study conducted in Uganda, he estimated that across sub-Saharan Africa shortly, there will be more than 8 million people living with HAD. He further argued that in this region HAD remains an under-recognised condition that needs to be studied and treated carefully.

Despite the prevalence of HIV-1 and HAND in sub-Saharan Africa, relatively, few studies have been published about its adverse effect on cognitive ability of HIV+ individuals in this region. There has been always more focus on HIV-related diseases, such as tuberculosis and cryptococcal meningitis (Sacktor et al., 2005).

Nevertheless, few previous studies conducted in this region have pointed out the existence of HAND, which is similar in occurrence to the one suggested by studies from developed countries (Price, 1996; Salawu et al., 2008; Wilkie et al., 2003). For instance, HIV+ individuals in Uganda reflected deficits in verbal learning and memory, attention, speed of processing, and executive functioning compared to HIV- individuals. Furthermore, fine and gross motor performance were being more compromised in patients with HAD compared to those without HAD (Robertson et al., 2007). Likewise, Clifford et al. (2007), who studied asymptomatic HAART-naïve individuals in Ethiopia, found that finger-tapping performance using dominant hand was significantly slower in HIV+ than HIV- participants. These findings clearly indicate that severe cognitive impairment is not uncommon in sub-Saharan region.

RATIONALE FOR RESEARCH

The purpose of the currently proposed study was to examine the impact of HIV-1 on neurocognitive functioning of HAART-naïve young adults in the Western Cape region of South Africa, where clade C prevails. It is important to study HAART-naïve individuals because cognitive impairment detected in them is associated with higher risk of mortality (Ellis et al., 1997). For example, Wilkie et al. (1998) found that, in their study of 119 HIV + HAART-naïve homosexual men who were in asymptomatic stage, 71.4% of participants who had minor cognitive alteration died within 3 years of assessment compared to their HIV + counterparts whose cognitive ability was intact.

Clifford et al. (2007) postulate that the risk for mortality detected in early stages of HIV infection can only be reduced by administration of treatment as early as possible. They further cautioned that the late delivery of treatment in developing countries is detrimental to

the lives of patients as it may expose them to irreversible brain damages (Gupta et al., 2007; Tartar et al., 2004).

A second important reason for conducting the present study is that the literature reviewed above provides a clear indication that there is limited consensus regarding the causes, prevalence and severity of HIV-associated cognitive impairment in HAART-naïve individuals. This lack of consensus may be due to the differences in sample of interest, used neuropsychological tests, and clade variation. Therefore, the findings of the studies conducted in India, America, Uganda, and Ethiopia may fail to clearly reflect the difficulties being faced by HAART-naïve South Africans.

A unique feature of the current research is that it is the first South African study in the field of HIV neuropsychology to focus only on individuals who are not on ARVs. Therefore, data gathered from this study will contribute to the literature by pointing out the similarities and differences between HIV-associated cognitive impairment in South Africa versus other countries. Furthermore, from a more clinical perspective, the data gathered from the current study will also point to the real difficulties encountered by HAART-naïve HIV-positive South Africans, and will render their cognitive difficulties better understood so that more appropriate and effective interventions and assessment tools might be designed.

SPECIFIC AIMS AND HYPOTHESES

The aim of this study was to critically explore and describe the cognitive profile of Xhosa-speaking HAART-naïve individuals in the Western Cape. I hypothesize that: (1) the HIV + group will show cognitive deficits in some cognitive domains compared to HIV - group. The main reason for such cognitive difficulties is that HIV-1 affects particular brain regions in infected individuals; (2) within the HIV+ group; increased cognitive impairment will be associated with severe immunosuppression and lower CD4 count

DESIGN AND METHODS

Design

This research was part of a larger study being done in the Department of Psychiatry at the University of Cape Town looking at the cognitive effects of anti-retroviral. It took a form of a quasi experimental cross-sectional study. Cognitive abilities of two groups (HIV + and HIV - group) were compared on variety of neuropsychological tests. Additionally, within each group there were roughly equal numbers of males and females, because the literature review points out that, sex differences have influence in cognitive performance. There was one independent variable (HIV status: HIV + or HIV -), and several dependent variables (performance on each of the administered neuropsychological tests).

Participants

Participants were 24 males and 23 females recruited from a public clinic in Khayelitsha. The Khayelitsha clinic provides a voluntary testing and counselling service for individuals who wish to know their HIV status. Participants were informed about the study by posters and fliers. The HIV + group ($n = 24$) were participants both in asymptomatic and symptomatic stage, who were not taking ARVs. There was also a control HIV - group ($n = 24$). An attempt was made to match both groups on age, education, gender, SES, race and home language. Another advantage is that both groups were from the same community. All participants were between 19 and 34 years old, with a minimum education level of Grade 7.

Exclusion Criteria

The following exclusion criteria was used for participation in the study.

- a. Schizophrenia or bipolar disorder.
- b. Presence of uncontrolled medical condition, such as poorly controlled diabetes mellitus, epilepsy, active tuberculosis requiring admission or non-standard treatment .
- c. Presence of an identified central nervous system neurological condition, such as lymphoma, or untreated neuro-syphilis or cryptococcal infection. However, patients who have had such conditions and who were supposed to have been fully treated were included.
- d. Patients who have abused alcohol or other psycho-active substances within the preceding three months: “current alcohol abuse/dependence”.
- e. History of a head injury with a duration of loss of consciousness of >30 minutes, AND/OR requiring overnight admission to hospital.

- f. And patients who refused to sign informed consent were also excluded

Materials

The neuropsychological test battery used was translated into Xhosa by the Stellenbosch Language Laboratory. The battery has focused on cognitive domains that previous studies (Dawes et al., 2008; Grant., 2008; Wilkie et al., 2003) have reported as being vulnerable to HIV-1 infection. Although the implemented neuropsychological test battery originates from developed countries, it has been used in sub-Saharan Africa. Moreover, this battery is regarded as valuable in the diagnosis of neuropsychological impairment in developing countries (Clifford et al., 2007; Odiase et al., 2006; Robertson et al., 2007; Sacktor et al., 2006). A description of the tests in the battery is given below.

Motor function

The *Successive Finger Taps Test* (Reitan, 1969) is used to assess motor functions. The examinee was instructed to touch each finger to the thumb of the dominant hand. This had to be done for five consecutive rounds. The same task was then repeated using the non-dominant hand. The test took 5 minutes.

The *Grooved Pegboard Test* (Lafayette Instrument Company, 1989) requires more complete visual motor co-ordination than most pegboards. It has 25 slotted holes; each row has five holes that matches with pegs of the board. The examinee was required to fill all the holes of the board with the pegs, first using the dominant hand, then with non-dominant hand. The time limit was 5 minutes.

Learning and memory

The *Hopkins Verbal Learning Test* (HVLT; Brandt, 1991) is designed as a brief test of auditory verbal learning and memory. Firstly, the examiner read a list of 12 words aloud, then asked the examinee to memorise those words as they were going to be asked. In the first round this test is conducted in three consecutive trials. Then, after three minutes the examinee is reminded to recall those words again. Lastly, after 30 minutes, the examiner read a list of words, some of them were in the list read earlier on, and some were not; the participant had to say yes if a particular word was there, and no if it was not.

The *Rey-Osterrieth Complex Figure* (ROCF; Rey, 1941) is used to assess visuo-constructional ability, visual memory, planning and organisation. The examinee was instructed to copy ROCF changing crayons in every 45 seconds. When done with copying,

the card was removed from the examinee's view. After three minutes the examinee was asked to redraw the image without seeing it, and again after 30-minutes.

The *Brief Visuospatial Memory Test* (BVMT) is used to measure visual memory. The examinee was shown a page that had six figures to memorise for 10 seconds. Then, asked to draw each figure exactly the way it appeared on the page without the page being exposed to him or her. This task was conducted in three consecutive trials. Time limit was 10 minutes. In a delayed recall, the examinee was shown a page with a variety of figures, some were in the page exposed before, and some were not, therefore the examinee had to state whether a shown figure was there or not.

Attention

The *WMS III Mental Control subtest* (Wechsler, 1945) is used to measure the examinee's ability to recall over learned information and to mentally manipulate that information. The examinee was required: (1) to count from 1 to 20 backward and forward; (2) to recite the alphabet; (3) then to alternate them with numbers for in stance 1A, 2B, 3C and so forth; (4) then to recite days of the week and the months of the year backward and forward. The time limit was 5 minutes.

The *WMS III Spatial Span subtest* (Wechsler, 1997) is used to measure attention. Subtest materials include a board with nine numbered blocks attached in no particular order. The examiner touched the sequence of blocks (starting from a span of two), and then instructed the examinee to do the same. If successful, one block was added. In second trial, the examinee had touch the blocks backward. This subtest was discontinued if the participant failed two consecutive rounds at any level. Time limit was 10 minutes.

The *Mental Alternation Test* is modelled on the Trail making Test. It is used to assess the accuracy and speed (Emad & Justin, 2002). In trial one the examinee was required to count from one to 20. In trial two, to recite alphabets, and then in trial three to alternate between numbers and letters e.g. 1A, 2B, 3C and so forth.

Speed of processing

WAIS III Digit Symbol Coding and WAIS III Symbol Search (Wechsler, 1997) measures clerical efficiency, visual motor coordination, and processing speed.

The *Digit Symbol Coding*, the examinee was shown a paper with boxes; each box had a number in the upper part, and a special mark in the lower part. Then, told to look down the page where the squares had numbers in the top part but empty at the bottom part, in each of

the empty squares he or she had to put a mark that matched with that particular number. Time limit was two minutes

WAIS III: Symbol Search, the participant was required to scan a group of symbols, and then indicate whether a target symbol was present in that group. The participant had to complete as many of these items as he or she could within two minutes.

Executive function

The *Trail Making Test A* (Strauss, Sherman, & Spreen, 2006) is used to test processing speed in the information processing domain. It is sensitive to deficits in sustained attention or information processing speed, and also requires visual scanning and psychomotor speed. The examinee was given a paper with circled numbers beginning from number one to number 25. He or she had to connect the circles starting from circle number 1, 2, 3 until number 25 in a chronological way without lifting up the pen. There was no time limit for this task; however the examinee was requested to work as quickly as possible.

The *Colour Trail Making Test* (D'Elia, Satz, Uchiyama, & White, 1996) is a culturally fair equivalent of the Trail Making Test (Lee, Cheung, Chan, & Chan, 2000). It is used to assess flexibility of thinking on a visual-motor task. In the first part, the examinee was given a paper with numbered coloured circles starting from 1, 2, 3 until 25, and instructed to connect them. The second part of the test was identical except that the examinee had to join the numbers with alternate colours (e.g., pink 1, to yellow 2, from yellow 2 to pink 3, until 25). In both cases the participant was not allowed to lift up the pen. There is once again no time limit, but the examinee has to work as quickly as possible.

The *Stroop Test* (Golden, Freshwater, & Golden, 2003) is divided into three parts. In the *Stroop Word Test*, the participant is given a list of words written in black ink and required to read as many words as possible within 45 seconds.

The *Stroop Colour Test*, the participant was given a page with list of colours (green, red and blue) and required to read those colours within 45 seconds.

The *Stroop Colour Word Test*, the participants had to call out the colour of the ink in which a word is printed. The colour of the ink is never the same as the word, which is always a colour. Time limit is 45 seconds.

Language

Animal Fluency test (Spreeen & Strauss, 1998) was used to test for word fluency in examinee's language. He or she was instructed to name the list of animals that comes to mind in one minute.

Fruit and Vegetable Fluency test, the examinee was instructed to name the list of fruit and vegetables in one minute.

Intelligence

The *WASI Block Design subtest* (Wechsler, 1981) is used to assess Visuospatial function. The examinee copied a series of designs made by the examiner initially, and then copied from a two-dimensional depiction in a book, with red and white-coloured blocks. Time limit was based on the complication of the design.

The *Matrix Reasoning subtest* (Wechsler, 1999) required the examinee to select one correct piece of a missing picture from a series of options.

The *Similarities subtest*, the examinee was given two words, and asked to indicate in what way were they similar.

Procedures

All testing was conducted in a room in J-block at Groote Schuur Hospital, which is the outpatients unit of the Department of Mental Health and Psychiatry. Informed consent was obtained from all the participants prior coming to the hospital. When the participants arrived at hospital in the morning, they were given refreshments. Thereafter, the testing started immediately at 08H30, and it took approximately 3 hours to complete. The same battery of tests was conducted on both HIV (+) and HIV (-) participants. The tests were grouped together according to the cognitive domain they fell under, as follows: (1) in motor cognitive domain there was Successive Finger Tapping and Grooved Pegboard; (2) learning and memory tests were HVLT total, delayed recall and recognition, BVLTL total, recognition, delayed recall, RCF 3 and 30 minutes; (3) attention and working memory tests were MAT, WMS Mental Control, WMS Spatial Total, TMTA and Colour Trails 1; (4) processing speed included Digit Symbol Coding and Symbol Search; (5) verbal fluency included Animal and Fruit and Veg; and (6) in executive functions there was RCF copy, Stroop Interference Test, Colour Trails 2 and Spatial Span backwards.

Tests were conducted by technicians who are fluent in Xhosa, under the supervision of a trained clinical psychologist to facilitate accuracy of administration. Participants were informed of the purpose of testing, which had already been conveyed in the written informed consent forms. They were told that they were not going to be paid for participating on the study, and that they were only going to be given a reimbursement for travelling expenses. There was no noise or any form of distraction in the testing room. The participants were asked to try to do their best in whatever they were asked to do.

At the end of the testing session, participants were thanked, and any questions which they had were answered.

Data Analysis

Using SPSS, all the data was scored, checked for missing scores, and cleaned. Descriptive statistical analysis was performed to organize and summarize the data, and to produce measures of central tendency (mean, median and mode), variance, and normality of distributions. An independent *t*-test was conducted to assess for differences in education and age between HIV + group and HIV - group. A Chi-square test was used to assess for differences in gender ratio between the HIV + and HIV - group.

The raw scores were converted to Z-scores in order to be able to compare the performance of the HIV + group to the HIV - group. The number of HIV + participants scoring more than 1 standard deviation (SD) and 2 standard deviations (SD) below the mean were reported for each test using Frequency measures. This was done to give an indication of where these scores would fall in terms of the levels of HAND - e.g. MND and HAD.

One-way MANOVA (multivariate analysis) was conducted to find out what differences there were between HIV + and HIV - groups on the neuropsychological tests. No co-variates were added because there were no significant differences in gender, age or education levels between control and HIV+ group. The tests were grouped by cognitive domain in order for the MANOVA's to be performed.

RESULTS

The present study consisted a sample of 24 HIV + young adults, the age variation was ranging from 19 to 34 years. The participants' education was between 7 to 13 years, the control group included 24 participants matched in terms of age, gender, and education with

the experimental group. There were no significant differences in gender, age, and education between the experimental and control group. See table 2

Table 2

Demographic Characteristics of the HIV+ and HIV- groups

Variables	HIV+ (n = 24)	HIV- (n = 24)	Significance
Education	11.21 (1.351)	11.38 (1.663)	$p = .554$
Age	28.38 (3.739)	26.33 (4.584)	$p = .263$
Gender (M:F)	6:18	11:12	$p = .104$

Table 3 shows the means and standard deviations for each dependent variable used in this study for both groups.

Table 3

Descriptive Statistics

Domain/Tests	HIV+ M (SD)	HIV- M (SD)
Motor Functions		
Successive Finger Tapping dominant	9.71 (4.57)	7.59 (2.00)
Successive Finger Tapping non-dominant	9.53 (2.53)	8.20 (2.53)
Grooved Pegboards dominant	87.25 (50.73)	76.86 (27.09)
Grooved Pegboards non-dominant	91.75 (35.29)	80.83 (9.20)
Learning and Memory		
HVLT total	21.42 (4.73)	22.25 (3.80)
HVLT delayed recall	6.63 (2.84)	7.75 (2.40)
HVLT recognition	10.17 (2.22)	11.00 (1.65)
BVLT total	18.63 (8.72)	18.70 (7.66)
BVLT delayed recall	8.00 (3.53)	8.40 (2.91)

BVLT recognition	5.25 (1.07)	5.60 (.94)
RCF 3 minutes	17.52 (7.99)	19.15 (6.52)
RCF 30 minutes	16.94 (8.00)	19.60 (6.73)
Attention and Working Memory		
MAT	18.33 (5.98)	18.00 (5.45)
WMS Mental Control	21.38 (6.24)	20.54 (4.74)
WMS Spatial Span Total	11.46 (3.26)	12.79 (3.79)
TMTA	57.70 (27.13)	43.74 (12.40)
Colour Trails 1	51.05 (21.11)	48.77 (16.62)
Processing Speed		
WAIS Digit Symbol Coding	46.21 (14.89)	50.54 (11.06)
WAIS Symbol Search	20.08 (6.11)	24.04 (6.11)
Verbal Fluency		
Animal Fluency	13.33 (3.74)	14.67 (4.44)
Fruit and Veg Fluency	15.13 (4.50)	14.58 (4.14)
Excutive Functions		
RCF copy	30.07 (6.52)	32.39 (3.00)
Stroop Word	74.30 (21.00)	80.14 (22.23)
Stroop Colour	46.39 (15.13)	56.32 (9.04)
Stroop Colour Word	31.00 (11.21)	32.64 (8.97)
Colour Trails 2	128.29 (98.98)	93.85 (20.99)
Spatial Span backward	5.13 (1.77)	5.59 (2.32)
Intelligence		
WASI Similarities	10.25 (5.59)	11.27 (5.30)
WASI Block Design	19.00 (8.86)	23.77 (6.37)
WASI Matrix Reasoning	16.33 (11.82)	17.81 (9.33)

Note. WASI = Wechsler Abbreviated Scales of Intelligence; WMS = Wechsler Memory Scale; WAIS = Wechsler Adult Intelligence Scale; BVMT = Brief Visuospatial Memory Test; HVLT Hopkins Verbal Learning Test; RCF = Rey Complex Figure; TMTA = Trail Making Test part A; MAT = Mental Alteration Test.

In order to test Hypothesis 1, a variety of tests were done. The HIV+ participant's scores were converted to Z-scores using the means and standard deviations of the control group in order to assess how many scores might fit into the MND and HAD levels of HAND.

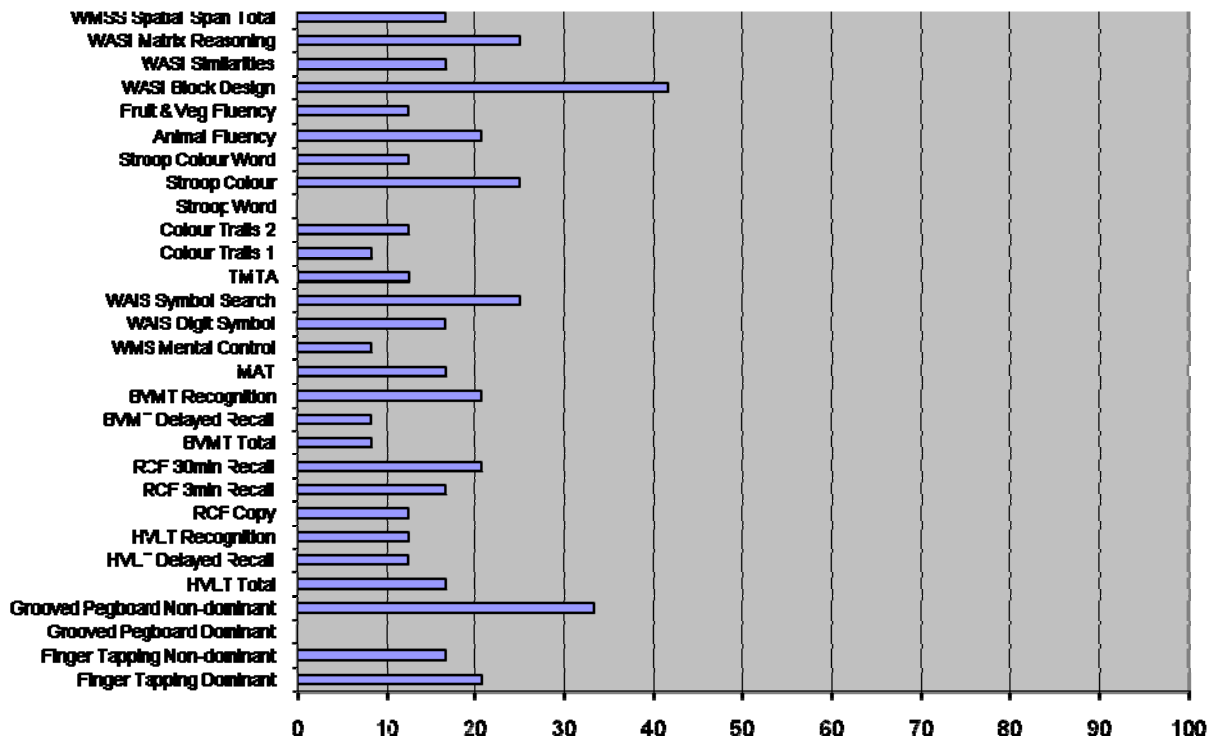


Figure 1 Percentages of HIV+ participants on one standard deviation below the mean

The graph shows that in mild cognitive impairment, Grooved Pegboard Non-dominant, Finger tapping dominant, BVMT recognition, WAIS Symbol search, RCF 30 minutes recall, Stroop Colour, Animal Fluency, WASI Block Design, and WASI Matrix Reasoning tests have more than 20% of people falling one standard deviation below the mean of the control sample. This suggests that these tests discriminate well between HIV+ and HIV- people.

Whereas, BVMT Total, BVMT Delayed Recall, WMS Mental Control, and Colour Trail 1 have less than 10% of people falling one standard deviation below the mean of the control sample. They do not discriminate well between HIV+ and HIV- people.

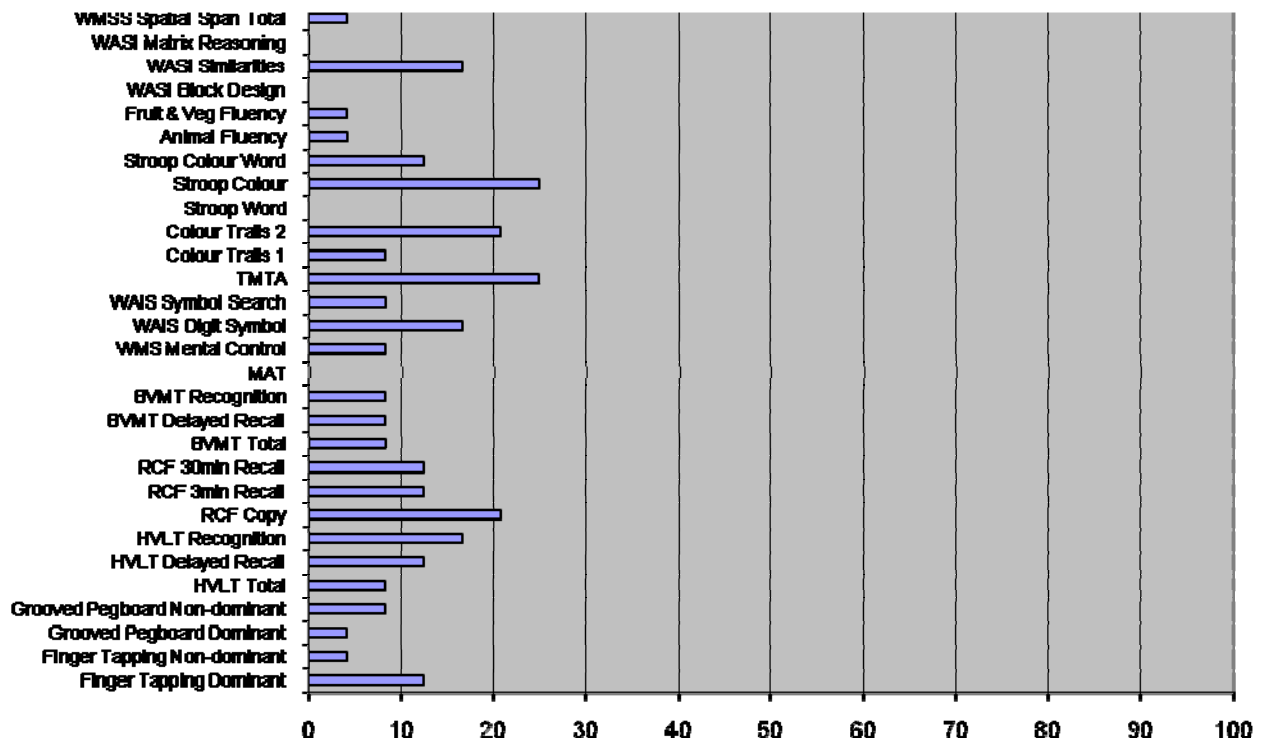


Figure 2 Percentages of HIV+ participants on two standard deviation below mean

This graph shows that Stroop Colour, TMTA, Colour trails 2, and RCF copy tests have more than 20% of people falling two standard deviation below the mean of the control sample.

These tests discriminate well between HIV+ and HIV- people.

While, Grooved pegboard dominant, Finger tapping non-dominant, Animal, Fruit and Vege fluency, and WMS Spatial Span Total tests have less than 5% of people falling two standard deviation below the mean of the control sample. Therefore, they do not discriminate well between HIV+ and HIV- people.

MANOVAs were then performed by cognitive domains. All assumptions were upheld. Homogeneity of variance: Levene's test was not significant for most of these tests. However, TMTA, BVMT recognition, RCF copy, Colour Trials 2 and Stroop Word were significant. Graphs were normal and groups were independent as each group consisted of different individuals. Thus, the risk of Type I errors was reduced.

As presented in table 4 MANOVA results showed that statistically significant differences exist between the HIV + and HIV - group across the administered neuropsychological tests.

Table 4

Significant Dependent Variables for HIV + group

Test	Significance	F	Effect size
Successive Finger Tapping dominant	$p = .046$	4.202	.085
TMTA	$p = .027$	5.253	.102
WAIS Symbol Search	$p = .030$	5.026	.099
Stroop Colour	$p = .011$	7.056	.141

To confirm the second hypothesis the Pearson correlation was performed to assess the relationship between CD4 count and neuropsychological performance. The results are presented in table 5.

Table 5

Pearson Correlation

Tests	r
Stroop Word	.445
Stroop Colour	.482
Stroop Colour Word	.467

DISCUSSION

The current study assessed the impact of HIV-1 on cognitive ability of HAART-naive young adults in the Western Cape region, South Africa where clade C of the virus prevails. This study was a quasi-experimental comparison of HIV+ and HIV- groups on performance of a variety of neuropsychological tests.

Many previous studies have demonstrated that HIV-1 has a negative impact on cognitive ability of the HIV+ untreated individuals (Odiase et al., 2006; Tartar et al., 2004; Wilkie et al., 1998). It is generally accepted that the decline in cognitive ability in HIV+ individuals is due to the direct negative effect of HIV-1 on the CNS and the brain. The brain processes vulnerable to HIV-1 are subcortical and frontostriatal regions (e.g. Chandra et al., 2006; Gopukumar et al., 2008; Gupta et al., 2007; Price, 1996; Salawu et al., 2008)

Because of the negative impact of HIV-1 on the CNS and the brain, my first hypothesis was that the HIV+ group was going to be more impaired on a variety of neuropsychological tests compared to the HIV- group. As hypothesised, the neuropsychological performance of the HIV+ group was impaired in some of the administered tests compared to the HIV- group. However, on some tests the performance of the HIV+ group remained intact. The neuropsychological tests that appeared to be significantly vulnerable to HIV-1 were: TMT A which is a measure of attention, followed by Successive Finger Tapping with dominant hand, a measure of motor functions, then, WAIS Symbol Search which measures speed of processing, and lastly the Stroop Colour test which measures executive functions. These results support findings by previous researchers (e.g. Grant et al., 1987; Grant, 2008; Robertson et al., 2007) which illustrate that motor skills, attention, processing speed, and executive functions are vulnerable to HIV-1. Additionally, Mishra et al. (2007) postulate that the impairment in motor and executive functions in HIV+ individuals is due to significant neuronal death in the basal ganglia, cerebral cortex as well as hippocampal regions.

The results of the current study showed the presence of HIV-associated cognitive impairment in HAART-naive individuals, however, they did not convey any presence of severity. For instance, the effect sizes of all the significant tests were very small; none of them were more than .2. Nevertheless, even though the effect sizes of the significant variables were small, the findings of this study are alarming in terms of the severity of cognitive impairment experienced by HAART-naïve South Africans. In relation to these findings, Grant (2008) speculates that TMT A test tends to be intact in HIV+ patients except in cases of HAD. He further cautions that the impairment of motor skills in HIV+ patients is an alarming signal of HAD. Similarly, Clifford et al. (2007) and Robertson et al. (2007) in their studies of HAART-naive individuals conducted in Ethiopia and Uganda, motor impairment was associated with advanced stage of the virus, and HAD. Therefore, the findings of this study clearly indicate that HAART-naive South Africans are vulnerable to HAD.

The International HIV Dementia Scale (IHDS) was used to assess HAD. According to Sacktor et al. (2005), the IHDS is a sensitive screening test for HAD both in developed and developing countries. Looking at the above provided graphs, the results show that the Stroop Colour test is the only test for this sample that has a large (>20%) number of HIV+ participants that fall both one and two standard deviations below the mean of the HIV- participants. It is also noticeable that Colour Trails 2 and the RCF Copy Test, which are both

tests of executive function, are well represented in the 2SD group. The other test in this group is the TMTA, which is a test of attention.

Furthermore, motor function tests (Grooved Pegboard and Finger Tapping with dominant and non-dominant), memory tests (BVMPT recognition and RCF 30 min recall), intelligence (WASI Block Design and Matrix Reasoning), word fluency (Animal and Fruit and Vege fluency) and speed of processing (WASI Symbol Search and Digit Symbol Coding) tests are useful at teasing out deficit at the 1SD level. Consequently, most tests discriminated well between the HIV+ and HIV- group in this study. Nevertheless, some tests of cognitive domains such as working memory, learning and memory, and verbal fluency did not appear to be significantly vulnerable to HIV-1 in both 1 and 2 SD below the mean. Therefore, it is possible that other studies which may perhaps use larger samples could find the opposite.

In terms of working memory, Grant (2008) states that there has been conflicting evidence regarding the presence of working memory impairment in HIV-1. In this study it was not significantly affected by HIV-1, and that was surprising considering that most studies have reported its prevalence in HIV-1 (Ances & Clifford, 2008; Gupta et al., 2007; Wilkie et al., 1998).

Variation in neuropsychological performance due to differences in levels of CD4 cell count, and immunosuppression has been reported (Chandra et al., 2006; Gupta et al., 2007; Odiase et al., 2006) Thus, my second hypothesis was that the HIV+ participants with low levels of CD4 cell count were going to show more neuropsychological impairment compared to the HIV+ participants with high levels of CD4 cell count. The results showed no great relationship between CD4 count and neuropsychological performance. For instance, out of all administered tests there was a moderate correlation between CD4 count and one test only, the Stroop Test.

In terms of the nature of clade C-associated cognitive impairment, the findings of this study confirm the speculations that clade C is associated with less neurotropism. For example, Gupta et al. (2007) in their study of HAART-naive individuals none of their participants had severe cognitive impairment. Thus, they suggested that clade C is associated with low levels of cognitive impairment compared to clade B. However, one thing worth noting before generalizing their findings is that their inclusion criteria was strictly only for the patients in the asymptomatic stage. And, generally, the asymptomatic stage is associated with low levels of cognitive impairment. Thus, it is not surprising that none of their participants had HAD.

Unlike their study, in this study the symptomatic patients were included as well; therefore the outcomes that show lack of severity of cognitive impairment in HIV+ individuals were not expected. However, the possible explanation of such surprising findings may be the lack of power in this study as well as quite a large number of employed tests. And that, make it harder to be assertive about the lack of severity in cognitive impairment in HIV+ individuals living in this country. And also, because Joska et al. (2009) in their study conducted in Cape Town which had larger sample found that HAD was present in 23.5% of their participants. Their findings were consistent with findings from developed countries, where clade B dominates (Grant, 2008; Wilkie et al., 1998).

Although the cognitive deficits in the studied sample were relatively subtle, they may have important clinical and public health implications. It is worth noting that these deficits are more likely to affect patient's functional status such as maintaining employment and also result in lack of medication adherence which may of course decrease their survival rates.

Cautiously, even though the results of the current showed the presence of subtle cognitive impairment in HAART-naive individuals, some of the tests that came up to be significantly affected by HIV-1, are the same tests that previous studies have reported their impairment to be associated with HAD. Thus, the findings of this study make a call for initiation of similar studies in this country which will yield more understanding about the nature of severity of cognitive impairment not in HAART- naive individuals only but about the nature of clade C-associated cognitive impairment as well.

I believe that the findings of this study are reliable because: (1) the selected battery of tests was brief and sensitive to neuropsychological impairment (see Ances & Clifford, 2008; Antinori et al., 2007; Grant, 2008; Lezak, 2004); (2) the control group was well-matched with the experimental group as they also lived in the same area; and (3) since low levels of education may be mistakenly seen as neuropsychological impairment, I ensured that I recruit people who at least have a minimum education of grade 7. As Antinori et al. (2007) suggest that to control for the effect of education in neuropsychological performance participants should at least have 5 years of education. Thus, I avoided any occurrence of neuropsychological misdiagnosis due to low levels of education of the participants.

Limitations and Future Research

Limitations of this study are that, firstly it is the part of a larger study. Due to time constraints, I could not cover all cognitive domains vulnerable to HIV-1 as suggested by

previous studies. I have concentrated mainly on the cognitive domains that many studies have reported to be in high risk. Thus, it is possible that the cognitive domains excluded from this study were going to yield different outcomes.

Secondly, my sample was very small, while the number of used tests was quite huge. Therefore, the findings of this study may not be generalized to the larger population. Thirdly, there was no prior study from this country conducted on this topic to be used as guidance. I was solely dependant on studies from other countries which may fail to depict the problems faced by South African HAART-naive individuals.

Another limitation was that the implemented neuropsychological tests originate from developed countries, and may not be appropriately transferred to the population studied in the present study. Ances & Clifford (2008) explain the limitations of the use of neuropsychological test battery in developing countries that originate from developed countries in this way “it is time intensive, expensive, and difficult to organise, and its use can be problematic in a variety of circumstances. Because norms need to consider a large variety of social, educational, and environmental factors, local norms are required in the developing world and are often unavailable” p. 457. Thus, it is possible that the deficits shown by HIV+ patients in this study were also induced by the cultural bias of the employed tests. It may happen that the results of the current study could have been different if the used tests were initially developed for South African population.

Furthermore, the reviewed studies in the topic were not from South Africa, despite the startling increase of HIV-1 that the country is currently experiencing. Therefore more studies about the nature of cognitive impairment in South African HAART-naive individuals are needed in order to help to identify the similarities and/or differences between them and those from other countries. This knowledge will also help to decide when exactly these HAART-naive individuals should start taking treatment. Such understanding will result in maximization of both their quality of life and their survival rates (Clifford et al., 2007; Mishra et al., 2008).

Most importantly, since clade C prevails in this country, there is an overarching need for studies similar to this one to be conducted in order to fully comprehend its effect on cognitive ability of HIV + patients. Studies about the nature of clade C are necessary, generally, not only in South Africa but in other countries as well so that comparison can be made as there is lack of consensus regarding the severity of cognitive impairment in this clade. Gupta et al. (2007) also made a similar request. Additionally, such studies should be longitudinal and follow ups should be made as well.

Lastly, this study showed the presence of neuropsychological impairment in South African HAART-naïve individuals as well as the high risk of HAD. HAART is known to reduce these cognitive impairment. Therefore, access to health care facilities in this country need to be improved. There should be many hospitals with adequate resources that will not inhibit clinicians from optimally using their research skills. For instance such improvement could also allow HAART to be produced locally.

CONCLUSION

HIV-1 is more likely to reach the CNS and the brain soon after infection has occurred, and subsequently, it has a negative impact on cognitive ability of HIV+ individuals. In South Africa there has been very little research based on the effect of HIV-1 on cognitive ability, especially on HAART-naïve patients. The current study has shown that HAART-naïve young adults living in this country in the Western Cape region are vulnerable to HIV-related cognitive impairment even though they were subtle. The HIV+ group performed more poorly on some tests of motor functioning, attention, speed of processing, and executive functioning compared to the control group. Most importantly, the cognitive domains affected in the studied participants, previous studies have reported that they signal a presence of severe impairment which could be detrimental in patient's functional status or even lead to death in extreme cases if not treated.

Furthermore, the relationship between CD4 cell count and neuropsychological performance was assessed. Most tests showed no relationship between CD4 count and neuropsychological performance, there were only three significant tests, namely, Stroop Word, Stroop Colour, and Stroop Colour Word. This may be due to the lack of power in this study; perhaps if there was an adequate sample maybe they could have been different. Fortunately, the larger study, which this study is a part of, has a larger sample of 200 HIV+ people and it is a follow up study. Therefore, it will yield more knowledge about the nature of cognitive impairment experienced by HAART-naïve individuals in this country.

Lastly, since neuropsychological impairment seems to be present in South African HAART-naïve individuals, there should be frequent neuropsychological examination for all HIV+ patients shortly after diagnosis of HIV-1 has occurred. Those who show decline should be given HAART, and an appropriate additional treatment to help them compensate for deficits in their daily functioning. Moreover, such free additional treatment would be of great help, especially in patients from low SES communities like Khayelitsha. Cautiously, HAART should be given as early as possible because Tozzi and colleagues point out that patients who

start it late are more likely to be resistant regardless of its long term administration. Even though HAART may seem expensive it is better for the government to spend money preventing the deterioration of HIV-1 than spending money on sick patients because of the late administration of HAART.

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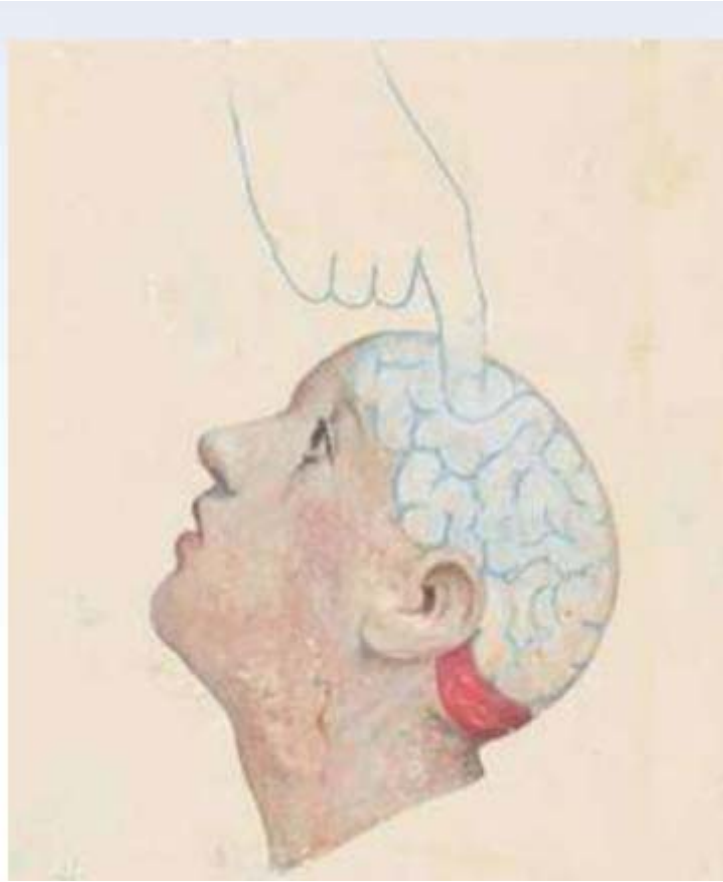
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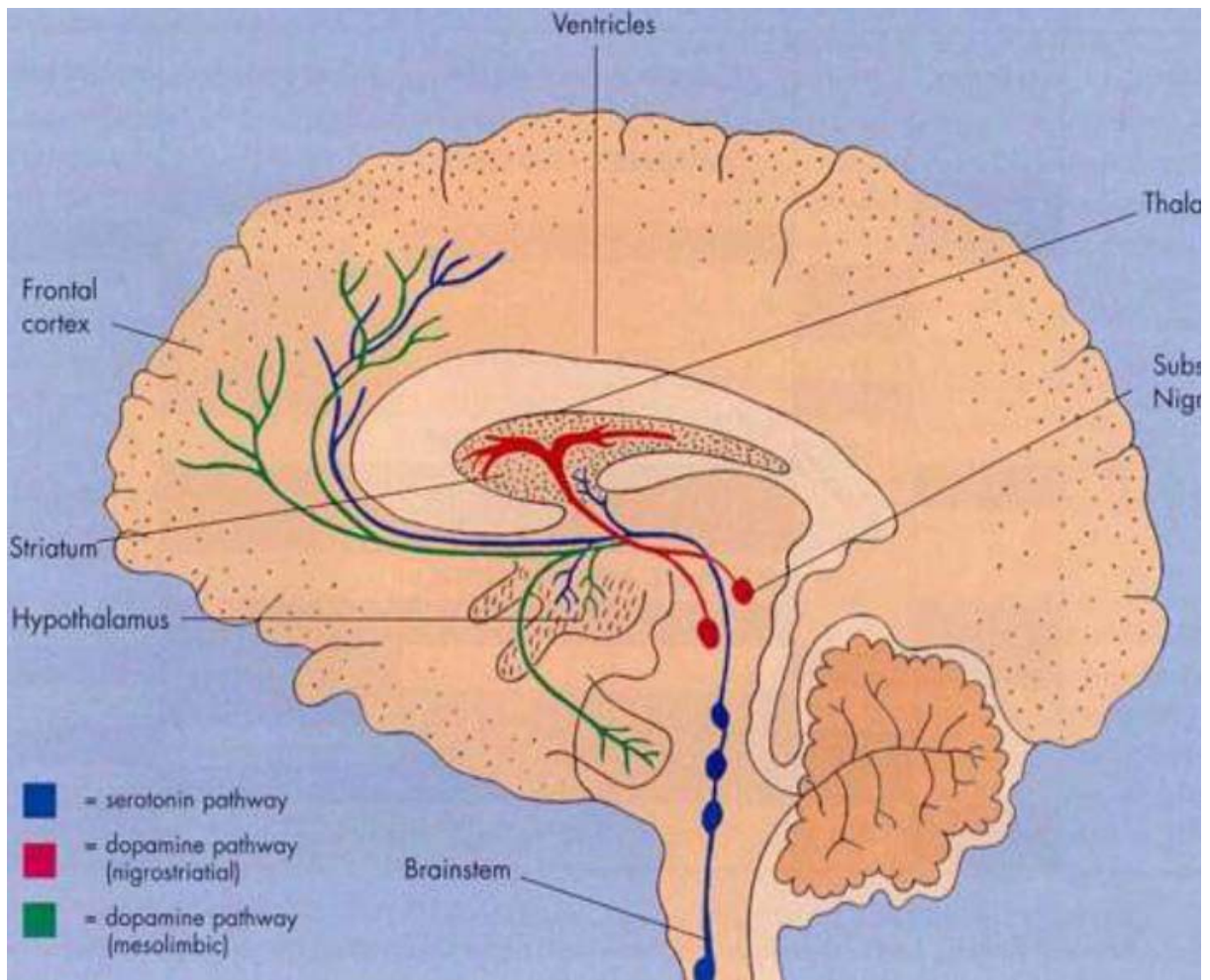
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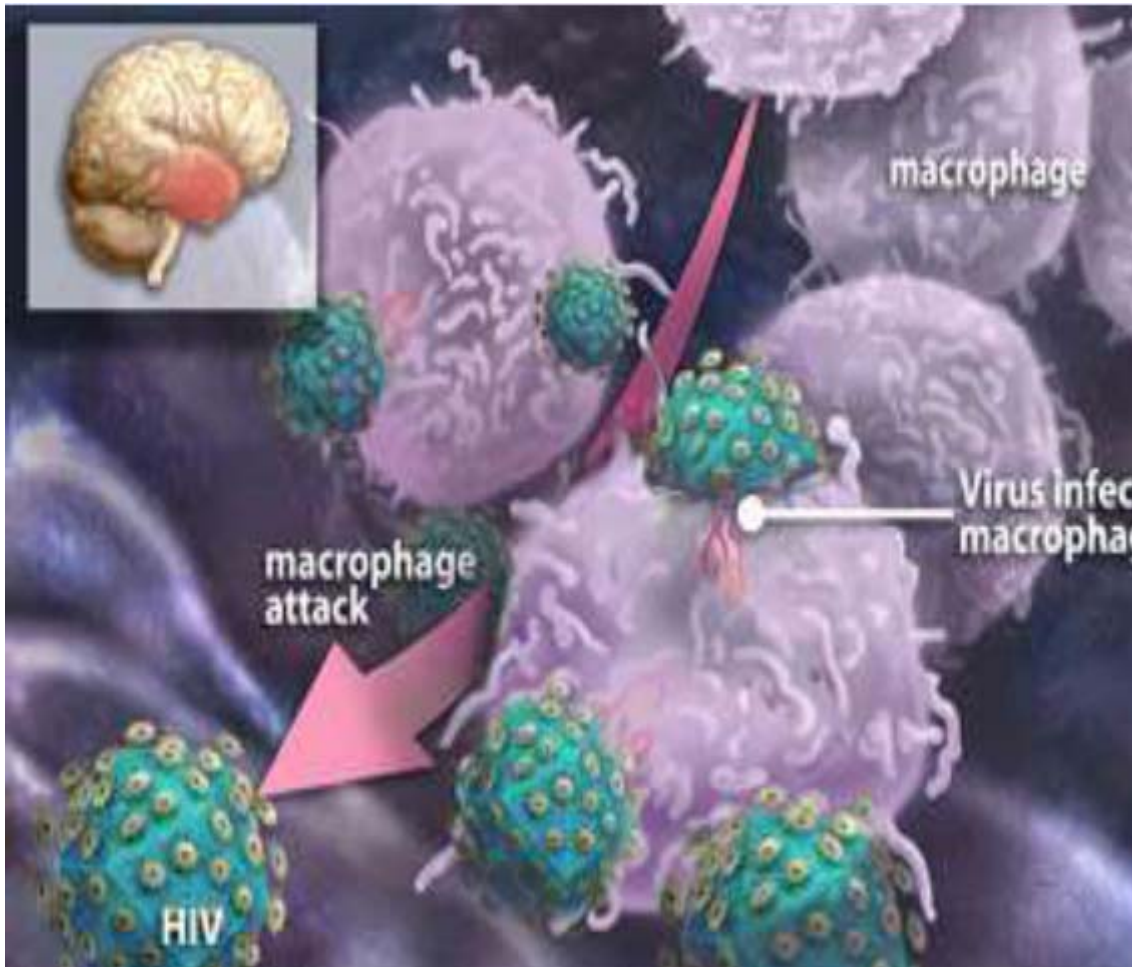
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Grant (2008) argues that even though executive and attention deficits are prevalent in HIV CNS disease almost any function can be affected. Thus,

Wechsler, D. (1945). A standardized memory scale for clinical use. *Journal of Psychology*, 19, 87–95.

HAND is the most common preventable and treatable cause of dementia, and has been noticed since the early recognition of HIV-1. According to Odiase et al. (2006) it ranges from 12 % to 87 % among HIV+ patients. There are three forms of HAND as suggested by American Academy of Neurology (AAN) (Antinori et al., 2007). Table one shows a criteria for each of them, then below they are discussed in depth.