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# The neurocognitive profile of HIV infected adults attending Lufuno Neuropsychiatric Clinic as measured by the brief neuropsychological cognitive examination

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# The Neurocognitive Profile of HIV Infected Adults Attending Lufuno Neuropsychiatric Clinic as Measured by the Brief Neuropsychological Cognitive Examination.



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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, in partial fulfilment for the degree of MMED Psychiatry

Johannesburg 2020

**Candidates Declaration**

I, Dr Thato Lekati Motsitle Kalane, declare that this research report is my own work. It is being submitted for the degree of MMED Psychiatry in the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

...Thato Kalane...

The .9th. day of ...November.., 2020

## Abstract

Sub-Saharan Africa is home to the largest population of individuals infected with the Human Immunodeficiency Virus (HIV). Therefore, there is a high number of individuals who are at risk of developing HIV Associated Neurocognitive Disorder (HAND) and HIV Associated Dementia (HAD). This high number makes the need for neuropsychological screening in public healthcare vital. South African clinicians are challenged by few neuropsychological tests that are available to screen for HAND and HAD, as not all screening tests can be used on all populations and cultures, and for all budgets and clinical practices. Furthermore, South Africa is predominantly populated with clade C HIV which has a specific neurocognitive profile. Consequently, the aim of this study was to explore the neurocognitive profile of HIV infected adults attending the Lufuno Neuropsychiatric Clinic at Tara H. Moross Hospital as measured by the Brief Neuropsychological Cognitive Examination (BNCE) as an alternative screening tool for HAND and HAD. The results were then compared to the neurocognitive profiles of the Montreal Cognitive Assessment (MoCA) and International HIV Dementia Scale (IHDS) as they are currently the most widely used screening tools for HAND and HAD in South Africa. Demograghic data were also included to determine whether they had an impact on the patients' neurocognitive screening test outcomes. All statistical analyses were conducted using R software. All tests were two-tailed, and statistical significance was accepted when alpha was smaller than or equal to 0.05. When screening for HAND using the BNCE, the results showed that more individuals scored significantly low for Constructive Praxis, Shifting Set, Incomplete Pictures, Similarities, Attention, and Working Memory. For the MoCA, individuals scored significantly low on Visuospatial, Abstraction, and Delayed Recall subtests; while Attention, Language, Orientation, and Naming were relatively intact. For the IHDS, significantly more patients scored low for Psychomotor Speed, and Memory Recall, while Motor Speed was relatively

intact. Comparing the BNCE and the MoCA showed similar results in the same cognitive domains except for Attention, which was not significant in the MoCA. Comparing the IHDS was difficult as it only has 3 subtests and is largely biased towards Memory and Motor Speed, nevertheless for total scores, it was in keeping with the BNCE and the MoCA. The results showed that the BNCE was an adequate screen for HAND when compared to the MoCA and IHDS as the degree of impairment was equally measured across all three tests. With regards to demographics, all the participants were adults infected with HIV, with more of the sample being middle-aged individuals, the majority were black, female and had a higher education. More were employed, did not have a substance history, did not have co-morbidities, and had been on antiretroviral drugs (ARVs) for only a short period of time. Females had poorer BNCE scores while participants with a matriculation had better BNCE scores. Duration of treatment and CD4 count did not impact the outcome of BNCE scores.

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# Chapter 1: Introduction

South Africa remains one of the countries most affected by the Human Immunodeficiency Virus (HIV), with a total number of 7.97 million people living with HIV as of October 2019. At the end of 2019, the percentage of adults infected with HIV in South Africa equalled 19.07%. (1) HIV is known to cause neurocognitive deficits which may be significant enough to cause Major Neurocognitive Disorder (MNCD). It has been well established that HIV affects the subcortical areas of the brain and results in syndromes collectively known as HIV Associated Neurocognitive Disorders (HAND), of which HIV Associated Dementia (HAD) is the most severe. (2) This insult to the brain causes neuronal damage which has great implications for the patient's health and their social and occupational interactions. This neuronal damage puts the patient at high risk to default on their antiretroviral therapy regimen (ARVs) and may increase the development of other medical comorbidities, all of which eventually may contribute to a poor quality of life.

This leads to further financial burden on the state because of the need for an increased health budget. The introduction of ARVs for the treatment of HIV has led to a decrease in the development of HAND. However, even with these advances in medicine, HAND remains a problem and must be successfully screened to improve its clinical outcomes. South Africa is currently faced with the challenge of limited resources in clinical practice and requires screening tools that are efficient, time conservative, and practical to use within a South African context. The current study will investigate the Brief Neuropsychological Cognitive Examination (BNCE) as a comprehensive screening tool for HAND in a South African population. The results were compared to screening measures currently being used in public healthcare clinics, namely the MoCA and the IHDS, in order to determine internal consistency reliability.

**Literature Review**

The Human Immuno-Deficiency Virus (HIV) is known to cause neurocognitive deficits which may be significant enough to cause Major Neurocognitive Disorder (MNCD). (2) This results in the syndromes HAD and HAND. The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) classifies neurocognitive disorder due to HIV as follows:

- The criteria are met for major or mild neurocognitive disorder.
- There is documented infection with HIV.
- The neurocognitive disorder is not better explained by non-HIV conditions, including secondary brain diseases such as progressive multifocal leukoencephalopathy or cryptococcal meningitis.
- The neurocognitive disorder is not attributable to another medical condition and is not better explained by a mental disorder. (2)

Although the introduction of ARVs for the treatment of HIV has led to a decrease in the development of severe forms of HAND, they remain a clinical problem. (2) These diagnoses have serious implications with regards to an individual's neurocognitive functioning which may impact upon social and occupational functioning. Known complications in cognition that an individual may experience with HAD and HAND are executive dysfunction and a slowed processing speed. (2) This may lead to an increase in nonadherence of medication (2) as well as social difficulties such as unemployment, the consequence of which may be family burden. (3)

### *The Prevalence of HIV in South Africa*

There are currently an estimated 7.97 million individuals infected with HIV in South Africa. (1) Up to 90% of these infections are caused by HIV-1 clade C strain. (4,5) At the end of 2019, Statistics South Africa estimated that 19.07% of the total South African adult population was infected with HIV. (1) Significantly more people are diagnosed with HIV each year than are on treatment. It was reported that 90% of infected South Africans in 2018 were aware of their HIV status and 68% of them were receiving ARVs. Furthermore, 87% of individuals who had been diagnosed were virally suppressed. This is because of the country's large ART programme which is funded by South Africa's health fund. (1) A challenge that South Africa is presently facing is that individuals that are exposed to HIV are not being tested and tend to present to hospital when they are already ill. (1) At some point during the course of their illness, most of the individuals infected with HIV will be diagnosed with a psychiatric disorder depending on the stage of the HIV disease. (2, 6) South Africans infected with HIV have been found to be five times more likely to experience a psychotic disorder when compared to individuals who are HIV-negative. (6) This is likely due to the impact of clade C HIV on the brain. Figures further suggest that 17% to 25% will present with some form of cognitive impairment. (7) The resultant cognitive impairment has been found to interfere with executive functioning, evident in social and occupational situations, as well as affect ARV adherence since patients tend to forget to take medication. (2)

### *Effects of Clade-C HIV on Neurology*

It is well documented that HIV-1 has a significant impact on the brain. (2,8) HIV-1 is divided into four groups, mainly M, N, O and P. Group M is further sub-divided into clades A, B, C, D, E, F, G, H, J and K. The international distribution of these clades is specific to every region, and hence there will be a unique severity of illness in each region. (9) One study suggested that clade D may be the most virulent, followed by clades B, C and A. (10)

However, alternative studies have proposed that the prevalence of HAND is not specific to a clade. (10) Group M is reported to be a cause for a greater number of the infections (9). Clade B of group M is highly prevalent in North America and Europe, but clade C is found all over the world. (9) Much existing research has found HIV 1 - clade C to be the most prevalent strain in India and sub-Saharan Africa, contributing to 90% of infections in South Africa. (4,5) A study in Kwa-Zulu Natal, which included 72 treatment naïve patients, showed that all had clade C HIV. (11) Another study in Cape Town, which included 140 HIV treatment naïve patients, showed that 95% of the sample were infected with clade C HIV, while 3.6% were infected with clade B HIV. (12)

The central nervous system (CNS) is infected within days of the HIV-1 clade C virus infecting the body. The virus infects perivascular macrophages and microglia, which is the main site for viral replication. Macrophages and microglia release viral proteins which include cytokines and chemokines. These viral proteins have been shown to be toxic to astrocytes and neurons in the brain. (13,14). Although neurons cannot be infected by HIV-1, they can be directly damaged by several proteins. (15) It is also thought that the microphages and microglia produce inflammatory factors that release glutamate and other excitatory amino acids that cause neural excitotoxicity, injury and subsequent death. (13, 14).

The clade C virus crosses the blood-brain barrier and, although it spreads widely throughout the brain, it mostly affects the striatum, vascular, cortical grey and white matters. (8,16) The disturbance of function in these areas has been found to cause significant impairment in higher order cognitive functions, where processing speed, memory and attention appear to be more severely affected than others. (16,17) These cognitive defects are collectively known as HIV Associated Neurocognitive Disorder (HAND). (6) A South African study examining the Magnetic Resonance Imaging examinations (MRIs) of 28 individuals showed that clade C HIV affects the white matter, thalamus and cortical grey

matter, supporting the concept that clade C HIV causes neuronal damage and subsequent HAND. (18) A recent study in Southern African countries involving clade C viruses reported that the virus still had the Tat di-cysteine motif (CC) at positions 30 and 31. This protein is found in most clade B viruses and is responsible for the increased neurotoxicity of clade C virus. The same protein has been found to be missing in clade C viruses in India, and this is why neurocognitive disorders in that region are not common. (10,19)

HIV-associated Neurocognitive Disorder (HAND) applies to a number of syndromes which describe neurocognitive impairments caused by HIV. In 2007, the US National Institutes of Health Working Group reviewed and changed the diagnostic criteria to include three syndromes, namely Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV Associated Dementia (HAD) which is the most severe. (20) The DSM 5 criteria separates this into Major or Mild Neurocognitive Disorder due to HIV infection (NCD). (2) HAD commonly affects individuals in the late stages of HIV and occurs in 10-15% of HIV affected individuals. (21) More commonly found are the less severe forms of neurocognitive disturbance, mainly ANI and MND which affect 30-60% of HIV infected individuals depending on their disease stage, and these leads to an impairment in higher order cognitive functions. (22) This is supported by a Cape Town study which included 283 clade C HIV infected individuals where 42.4% had MND and 25.4% had HAD. (23)

The cognitive functions implicated include motor skills and information processing, learning and memory, attention and working memory, executive function, visuospatial function, and speech and language. (24) These have been found to arise as a development of the white matter connections in the brain which are affected by HIV (8,24), thereby disrupting cognitive function. (8) It is well documented that clade C HIV preferentially affects white matter, and thus causes degeneration of myelination. This has an impact on the

subcortical circuits - including the basal ganglia and caudate nucleus – and on frontal lobe functions as well as right parietal lobe functions. (25) A South African study using Diffusion Tensor Imaging (DTI) to examine white matter damage in clade C HIV-positive individuals supports past research showing that individuals with clade C HIV have white matter abnormalities. (26) It also demonstrated injury to the corona radiata, corpus collosum, and superior and inferior longitudinal fasciculus, with consequential disruption to several cognitive profiles. (26) The resultant deficits in the subcortical structures are as follows:

1. Motor skills and information processing:

These are mediated by the frontal cortex, subcortical circuits, and basal ganglia. Clade C HIV causes injury to these areas, especially significant calcification in the basal ganglia. (26) The predominant concern with difficulties with motor skills tends to be slowed information processing and slowed movement. (2, 24) Slowness in motor skills can be demonstrated in finger tapping, (24) which was tested in the International HIV Dementia Scale (IHDS). Slowness in information processing can be seen qualitatively in trail making on the MoCA (24) and the BNCE. Chorea, myoclonus, dyskinesia, and dystonia are rarely seen unless opportunistic infections affect the nigrostriatal pathway. (27)

2. Learning and memory:

The clade C virus has been found to impact on learning and memory, which are largely mediated by the frontal and temporal lobes. (25,26) These defects may be measured on tasks which include word lists and simple and complex designs. (27) Prospective memory, dependent on frontal systems, is also affected. This refers to the individual's ability to carry out a future plan and encompasses an executive functioning component. Memory functioning involves encoding, consolidating the information, and retrieving it. Patients with HAD present with rapid forgetting which demonstrates an encoding problem. (27)

3. Attention and working memory

In the early stages of HIV, the functions of attention and working memory are preserved but become affected as the disease progresses to HAND. (24 , 27) Patients will usually complain of not being able to concentrate when given instructions. Working memory refers to the ability to store information temporarily and further manipulate it and underlies most executive functioning. Difficulty in these functions is associated with inflammation of the fronto-striatal areas affected by clade C HIV. This inflammation is as a result of white matter injury by demyelination. (25,27)

4. Visuospatial functioning

Impairment in spatial abilities is demonstrated by tasks that measure the individual's point of reference. (27) Visual processing has been found to be affected by HIV, thereby increasing the disturbance of everyday functioning, such as driving, following routes or estimations of depth and distance. (27) The role of the parietal cortex in the integration of information required by the visuospatial domain is structurally specialised with high ratios of white to grey matter, particularly in the right hemisphere. Clade C HIV is known to preferentially affect white matter tracts in the brain, (18) thus the structures underlying visuospatial functioning are largely at risk. (8) Affected patients are likely to have further difficulty integrating visual information.

5. Speech and language

This profile is largely mediated by the left temporo-parietal area and is typically not affected in adults infected with clade C HIV. Aphasia, alexia and agraphia tend not to be evidenced in HAD. (24 , 27)

6. Executive function

Executive function refers to an individual's higher order functioning including the ability to solve complex problems and demonstrate self-motivated, goal-directed behaviour. (27) These functions are mediated by the frontal cortex, particularly the dorsolateral prefrontal, orbitofrontal, and ventromedial prefrontal cortices. (8) HIV causes neuronal injury to the frontal cortex resulting in difficulties in executive function. (26) Executive function is assessed by abstraction, reasoning and problem solving. When HAND progresses to HAD, patients present with a decrease in cognitive planning, impairment in response inhibition, and a decrease in abstract reasoning. (8 , 24)

With the high prevalence of HIV, as well as the profound and diffuse impact that HIV has on the brain, it is imperative to have a tool that can efficiently and effectively screen for HAND.

***Screening for HAND***

South Africa is faced with the challenge of limited neuropsychological tests that are specific to the South African population. (3) Consequently, it is difficult to compare local findings with those of international literature because South Africa has a different HIV clade, predominantly clade C, which also has a different neurocognitive profile to those found in international literature. (8) The difficulty also includes language barriers, the level and quality of education of the participants, that testing is available mostly in English while South Africa has 11 official languages, and a lack of familiarity with assessment tools among testers. (3) It is thus important to find a valid screening tool that may be compared and contrasted with results found in the international literature. (3)

In addition, clinical practice faces a number of challenges with regard to the standardised battery of tests. (28) Neurocognitive assessments are time-intensive, and a full

diagnostic workup may be costly. In resource-limited settings, the only screening tool available might be a clinical examination. This demonstrates a need for the accessibility of more efficient screening tools that can be used during routine visits. (29) These tools should enable the clinician to successfully screen for HAND. (28, 29) They also need to be brief and practical to use, as well as have high specificity and sensitivity for milder forms of HAND. (29) Improving screening tools will ultimately allow clinicians to give better care to individuals affected with the virus. (29) The most widely used screening tool for HAND in the South African clinical setting is the HIV Dementia Scale (HDS), International HIV Dementia Scale (IHDS) and the Montreal Cognitive Assessment (MoCA). (3) Although the HDS has been validated in South Africa, it is not common in local clinics as it needs the administrator of the test to be trained, while the IHDS is largely biased towards motor and memory function. (24) Thus, these tools may have limited clinical utility in the South African setting, as they might be unable to pick up the milder forms of HAND. (30) For the purpose of this study, the IHDS and the MoCA will be discussed in more detail as they will be used in comparison with the BNCE.

**The International HIV Dementia Scale (IHDS) and the Montreal Cognitive Assessment (MoCA) as Screening Tools for HAND**

The IHDS was designed to screen for subcortical dementia, particularly caused by HIV. It was intended for global use as a brief and easily administered screening tool. (31) The sensitivity of the instrument refers to the ability of the IHDS to correctly identify those individuals affected with HAND, while the specificity refers to the ability of the IHDS to identify those without the illness. A review done by Zipursky ascertained that the IHDS was not ideal for screening milder forms of HAND. (29) The IHDS is highly recommended as a screening tool for detecting HAD in areas that are limited in resources. (24) A South African validation study on a population with clade C HIV showed a sensitivity of 45% and a

specificity of 79% when the score was <10. (10) If the score was measured at <11, then sensitivity improved to 72% and specificity decreased to 46%. (32) The drawback is that it is less reliable in detecting milder forms of HAND as it focuses mainly on motor and memory function, problematically excluding executive function. (24) Nevertheless, it appears that currently the IDHS is the most widely used screening tool in Southern Africa for assessing HAND.

The MoCA is a screening tool with high sensitivity and specificity for Mild Cognitive Impairment (MCI). (24) It was developed as a screening tool for individuals who present with mild cognitive complaints related to diseases that affect cognition like Alzheimer's Disease. (33) The MoCA has been validated in many countries as being superior in screening for mild cognitive impairment (MCI). (33) It is widely used in South African clinics to screen for HAND, since it assesses many of the cognitive domains affected by HIV, especially executive function. (3) One of the drawbacks is that it does not evaluate motor function, which is one important function affected by HIV. In a study conducted in a South African population with HIV using the MoCA. (3) The study found that the MoCA showed good promise in detecting HAND but had to be adjusted to suit a South African population before it could be validated for screening HIV, as a low level of education contributed to low scores. (3)

Since South Africa has a unique population and is faced with unique socio-economic challenges, the need arises to have screening tools that are culturally relevant and practical for use. (3) The BNCE will be the focus of this study, to determine whether it offers a brief and more comprehensive screening tool for HAND and HAD. To date, no study in South Africa has been done to establish its efficiency in screening for HAND and HAD.

**The Brief Neuropsychological Cognitive Examination (BNCE)**

The gold standard for screening for HAND is a full battery of tests, but that often proves to be too expensive and time costly in low resourced settings with a high patient load. (34) Furthermore, it has been found that some patients seen in clinics do not have the attention span and concentration to sit through a lengthy evaluation. (34) Many patients attend clinics before their working day starts and would need one or two full days away from work to sit for these assessments. Unfortunately, this is not feasible in a country stricken with poverty. As a result, the BNCE was developed to offer a more comprehensive, non-expensive, and time-conserving screen for cognitive impairment. It is completed within 30 minutes and is particularly useful in relating the neurocognitive profiles of psychiatric and neurological patients. (34)

The BNCE consists of two parts. Part 1 assesses lower order cognitive function such as Orientation, Presidential Memory, Naming, Comprehension and Constructive Praxis. Part 2 comprises higher order cognitive functions, most of which are affected by HIV. These include Shifting Set, Incomplete Pictures, Similarities, Attention and Working Memory. In terms of psychometric properties, reliability of a test refers to the consistency and accuracy of results when used in different individuals. The reliability of the BNCE was tested in hospital patients using two methods, namely the test-retest correlation and inter-rater reliability. The results of the assessments were then correlated. For both methods, the reliability was high at .95 and .97. (34) The closer the score is to 1, the more reliable the test. In another study using a different set of hospital patients and a different method, reliability using the test-retest correlation was found to be high at ranges between .64 and .97. (34)

The validity of a test is the degree to which the tool measures what it claims to measure. Concurrent validity refers to the extent to which the results of a particular test or measurement correspond to those of a previously established measurement for the same construct. This was established by correlating the subtests in Part 1 of the BNCE to other

established tests testing the same cognitive functioning. (34) The correlated tests included the Mini-Mental State Examination (MMSE) with Orientation, the Wechsler Memory Scale with Presidential Memory, the Boston Naming Test and the Full Scale and Performance IQ scores with Naming, and finally the Performance IQ with Constructive Praxis. The correlations between the two scores on each subtest were high and demonstrated the usefulness of the BNCE in evaluating cognitive impairment in psychiatric and neurological patients. (34)

Construct validity refers to the degree to which a test measures what it claims or reports to be measuring. The BNCE and the Wechsler Adult Intelligence Scale - Revised (WAIS-R) were measured for construct validity, as both test for similar cognitive abilities, but they have different indications. The results showed that the BNCE was straightforward and did not require the patient to have an extensive education. (34) It assesses neurocognitive deficits in patients with pathologies, while the WAIS-R measures cognitive function in individuals without pathology. The WAIS-R covers a greater range of information processing and also gives information about the patient's level of cognitive impairment. (34)

Discriminant validity tests whether concepts that are not supposed to be related really are unrelated. A study was done to establish how well the BNCE can discriminate between two groups of individuals with cognitive impairment secondary to either a psychiatric illness or a neurological illness, and a third non-impaired group. (34) The MMSE and the BNCE was administered to all three groups. The average scores in the three groups showed that the BNCE scores are able to discriminate between patients with either a primary psychiatric disorder or a neurological cause. Although the BNCE cannot replace a full battery of tests, it can suggest the presence and severity of illness, level of function of the affected individual, and determine whether the impairment is secondary to a neurological cause. (34)

Therefore, the BNCE has been shown to be reliable and comprehensive in establishing the cognitive profiles of psychiatric and neurological patients. It is also quick to

administer, is impartial to language and culture, and the clinicians who use it do not need to have specialised neurological training. Thus, this study is important since it determines whether the BNCE is an appropriate screening tool for the South African population because HIV is so prevalent, HAND and HAD remain such a problem, and few tools have been validated for screening HAND in South Africa. The high prevalence of neurocognitive deficits along with their significances for the HIV infected individual's employment, activities of daily living, adherence to medication, need for placement, substance use and driving ability, requires a better understanding of the neurocognitive profile of HIV. In the current clinical setting, the experience has been that it is not sufficient to use just the MoCA and the IHDS alone. The MoCA was designed to test for MCI in diseases such as Alzheimer's, Parkinsonism and Huntington's (33), while the IHDS is largely biased towards memory and movement impairment. (24) Therefore, there is a gap in available screening items.

# Chapter 2: Methodology

## 2.1. Aim

The aim of the study was to establish and describe the neuropsychological profile of HIV in a sample of HIV reactive individuals on a managed ART program attending the Lufuno Neuropsychiatric Clinic using the BNCE, thereby determining whether the BNCE is adequate for screening this profile.

## 2.2. Study Objectives

This study comprised a number of objectives:

i) To assess the neuropsychological profile of HIV as measured by the BNCE.

ii) To determine whether the BNCE is adequate for screening this profile by comparing it to the profiles of the IHDS and/ or the MoCA.

iii) To determine whether the patients' demographic data has an impact on neurocognitive screening test outcomes.

The BNCE was selected as a potential screening assessment for a number of reasons. Although the B of cognitive abnormalities than most screening tests. This has a major advantage over the IHDS which focuses only on motor and memory impairment. The BNCE separates Part 1 and Part 2 scores so that an individual's ability to process conventional information that is used more often can be contrasted with their ability to process new and incomplete information. Each particular score can be used by itself to pinpoint pathology in various domains, which is important as the severity of the symptoms of HAND depends on the stage of illness.

The BNCE may be used to identify whether the source of cognitive impairment is as a result of prima because locally, assessment of HIV-positive individuals presenting with cognitive impairment is challenged by a lack of screening tests that are comprehensive, time efficient

and normed on the South African population. In addition, South Africa's prevalence of clade C HIV differs from other clades in its neuropsychological profile. A major advantage of the BNCE over the MoCA is that a particular level of education is not a requirement. (34) This is significant for this study as it was anticipated that the study population would have a poor socio-economic and educational background.

### 2.3. Study Design

The study aimed to describe the neuropsychological profile of HIV-positive adults as measured by the BNCE. The profile of performance on each of the subtests of the BNCE was examined, and no attempts were made to manipulate them in any way. Therefore, the design of the proposed study was retrospective, descriptive, and non- experimental. The study was based on file records.

### 2.4. Setting

The study was done at Lufuno Neuropsychiatric Clinic, located at the tertiary institution Tara H. Moross Hospital (hereafter referred to as Tara). Lufuno comprises of three clinics, namely the Lufuno Neuropsychiatric Clinic, an HIV Clinic and a Voluntary Counselling and Testing (VCT) Clinic. Lufuno Neuropsychiatric Clinic provides tertiary level neuropsychiatry services to the surrounding area, offering an integrated service for patients with comorbid mental illness, with certain neurological conditions, and with HIV. This was the site for this research.

The HIV clinic provides outpatient HIV/AIDS management, which includes dispensing ARVs to the surrounding community. Patients are referred via the Department of Health. Patients receive ARVs and treatment of HIV-related illnesses, but not treatment for other chronic conditions that can be treated at Primary Health Care level. The VCT Clinic is a walk-in service for any member of the public who requests HIV/AIDS information, testing,

counselling, and health education. Rapid HIV tests are used. The general profile of patients in the clinic range from privileged to underprivileged, young to elderly.

## 2.5. Study Sample

The sample utilised in the study comprised of 70 HIV-positive adults over the age of 18 years, who attended Lufuno Neuropsychiatric Clinic, and who had been administered the BNCE and either the MoCA or the IHDS. The study sample comprised an adult population as a means of controlling for potential neurodevelopmental confounds. The adult brain is relatively stable in terms of neuropsychological functioning as the structures underpinning cognition have developed and specialised. In addition, the BNCE is indicated for individuals over the age of 18. The study adhered to relatively stringent inclusive and exclusive criteria.

### *Inclusion Criteria*

1. HIV-positive patients at any stage of the illness.

2. HIV-positive patients on any HAART regimen.

3. Any CD4 and viral load was acceptable.

4. A fully completed BNCE with at least a fully completed MoCA and or IHDS.

### *Exclusion Criteria*

1. Patients less than 18 years of age.

2. Patients with any neurological complication not related to HIV.

3. Patients with any primary DSM 5 psychiatric disorders.

## 2.6. Procedure

The data was collected at Lufuno Neuropsychiatry Clinic. The HIV medical officer assisted with screening for relevant patients. The first 70 files which met with the criteria were separated. Data was collected over one month.

## 2.7. Data Management

A data sheet was designed to facilitate data collection from medical records. Categorical data included the scores on the different profiles as they appeared on the BNCE, namely Orientation, Presidential Memory, Naming, Comprehension, and Constructive Praxis from Part 1. Part 2 included Shifting Set, Incomplete Pictures, Similarities, Attention and Working Memory. The variables included the following demographics: age, gender, race, level of education, employment status, starting CD4 count, duration of treatment, alcohol and substance intake, and medical comorbidities. Categorical data are further explained below.

***Part 1 of the BNCE***

Part 1 assesses lower order cognitive function and includes the following subtests:

Orientation: The items relate specifically to the current time, place, and facts about the patient. Orientation is independent from short-term memory. It is information that has been overlearned and is only affected in severe cognitive impairment. (34)

Presidential Memory: Presidential icons are chosen to test long term memory. These are learned items which are easy to retrieve, and where the influence of gender, age, level of education and ethnicity is minimised. Patients with amnestic disorders will present with impairment in Presidential Memory. (34)

Naming: This subtest measures the ability to identify the parts of the body that are not frequently talked about, like the earlobe, eyelashes, fingernails and eyebrows. In this way, mild disturbances in Naming can be picked up, and the influence of memory disturbance in

Naming is minimised. Patients with various types of aphasia arising from the Sylvian fissure in the dominant hemisphere often present with naming disorders. (34)

Comprehension: This subtest asks the patient to point to the hand-ear-eye, starting with the dominant hand and moving to the non-dominant hand. Aphasic disorders may be identified, and this will further assist in determining the different types of language disorders resulting from the various types of dysarthria. It works on the principle that commands have to be understood in order to be carried out. Impairments are seen in semantic aphasia related to the parietal lobe, and in Wernicke's and Broca's aphasias related to frontal and temporal lesions. (34)

Constructive Praxis: Patients are asked to copy three figures onto a blank page. A missing component, an added component, or a component added to the wrong point are errors. The subtest also minimises the influence of education, skills before illness, and a patient's individual experiences. Two of the drawings cannot be encoded verbally, but are rather copied from models instead of verbal instruction. This minimises the verbal component of the testing. Impairment in this subtest is usually seen with lesions of the parietal lobe and possibly the frontal lobe, especially in the premotor region. (34)

At the end of Part 1, total scores out of 15 are added up for Part 1.

***Part 2 of the BNCE***

Part 2 of the BNCE assesses higher order functions, many of which are affected by clade C HIV. It includes the following subtests:

Shifting Set: This comprises three activities. In the first, the patient is asked to copy then draw from memory three different figures. An addition, removal, and/or addition to the wrong point is seen as an error. The second test asks the patient to show two fingers when the examiner shows one and vice versa demonstrating a measure of reciprocal motor function.

The third test asks the patient to name the months of the year backwards. The Shifting Set subtest measures the ability of the patient to change or shift from an established pattern of responding. Impairment in shifting is seen in disorders of the frontal and fronto-subcortical circuits. Attention, registration, and working memory can contribute to poor performances in this subtest. (34)

Incomplete Pictures: An incomplete picture is shown to the patient to identify. The complete one is then shown to the patient as a learning trial followed by another round of the same incomplete picture. This subtest involves the processing of incomplete information. Patients with visual agnosia will likely have impairment in Incomplete Pictures. The occipital and frontal lobe are responsible for visual agnosia. This subtest further diminishes the role of memory disturbances making it a relatively pure test of visual recognition and frontal lobe functioning. (34)

Similarities: In this subtest the patient is asked to identify the common functional feature of different objects and the social features of humans. It is a variant of a verbal reasoning test that is widely used in neuropsychiatry and neuropsychology. Impairment in frontal lobe function is likely to result in poor performance in verbal reasoning ability. (34)

Attention: This subtest evaluates visual attention using an untimed tracking test, as well as verbal concentration using calculation and backward calculation. Letters are not included to minimise the influence of education. Impairment in attention is related to lesions of the frontal lobe or subcortical structures. In the instance of errors in calculation, parietal lobe lesions maybe involved. (34)

Working Memory: This subtest involves the repetition of three words memorised after a certain period. Impairment involves lesions in the limbic system, the subcortical and mesencephalic structures, and the frontal lobe. (34)

At the end of Part 2, total scores are added out of a maximum of 15, then combined with total scores from Part 1 to make up a total score out of 30. A score between 28-30

suggests there is no impairment. Scores between 22 -27 show a mild impairment. Patients with scores in the no impairment and mild impairment range are likely able to live independent lives. A score between 10-21 shows moderate impairment while a score between 0-9 shows severe impairment. Patients in the moderate and severe ranges are usually unable to live independent lives. The pattern of scores across the domains of functioning provide a neurocognitive profile. Therefore, the neuropsychological impairments that are demonstrated in clade C HIV may be determined by the pattern of performance on the BNCE in addition to the overall severity scores.

***Montreal Cognitive Assessment (MoCA)***

The categorical variables captured for the MoCA are outlined as follows:

Visuospatial/Executive: In this subtest trail making, copy a cube and clock drawing are included. Trail making assesses visuo-motor and visuo-perceptual abilities as well as the flexibility of the mind. (24) Impairment is a result of lesions in the frontal lobe. (27) Copy a cube tests for spatial planning and visuo-motor coordination. Impairment in these abilities result from lesions in the frontal and parieto-occipital lobes. (27) Clock drawing assesses planning, conceptualization and visuo-constructive abilities. (24) Impairment involves lesions to the frontal, parietal and temporal lobes. (27)

Naming: Word finding, visuo-perceptual and semantic memory are assessed in this subtest using three animals that are not common. (24) Impairment involves lesions to the occipital and frontal lobe. (27)

Attention: In this subtest, retention of auditory stimuli and working memory as well as executive processing is assessed by evaluating concentration and calculation using the letter A tapping and serial seven calculation. (24) Frontal and parietal lobe dysfunction results in poor attention. (27)

Language: The subtest is assessed by sentence repetition. (24) This function is mediated by the left temporo-parietal frontal circuits. (27) The letter F fluency is also

assessed as part of language. (24) Language impairment is related to frontal and temporal lobe dysfunction. (27)

Abstraction: Semantic knowledge and conceptual thinking are assessed in this subtest using two items that are similar. (24) Lesions in the frontal and temporal area result in difficulties with conceptual thinking. (27)

Delayed recall: Encoding and retrieval memory is assessed by recalling five nouns five minutes after the individual learns them. (24) Encoding is mediated by the hippocampus while retrieval memory is mediated by the medial parietal and frontal white matter tracts and subcortical structures. (27)

Orientation: The items relate specifically to the current time, place, and facts about the patient. Orientation is independent from short-term memory. It is information that has been learned often and is only affected in severe cognitive impairment. (24)

The total score for the MoCA is 30. A score below 26 is suggestive of a Major Neurocognitive Disorder.

***International HIV Dementia Scale***

Categorical data for the IHDS are explained below:

Motor Speed: Finger tapping at a timed speed is used to test motor speed. (24) Impairment is as a result of dysfunction to the frontal cortex, subcortical circuits and the basal ganglia. (27)

Psychomotor Speed: Slowed information processing as well as motor skills are assessed by alternating hand sequencing which is timed. (24) Impairment is as a result of dysfunction to the frontal cortex, subcortical circuits and the basal ganglia. (27)

Memory Recall: In this subtest, encoding and retrieval memory is assessed by recalling four learned items. (24) Encoding is mediated by the hippocampus while retrieval memory is mediated by the medial parietal and frontal white matter tracts and subcortical structures. (27)

The total score for the IHDS is 12. A score of 10 and below is significant of a Major Neurocognitive Disorder. (24)

Data were collected over a period of one month at Lufuno Neuropsychiatric Clinic. The first seventy files from HIV-positive patients with possible neurocognitive presentation who met the inclusion and exclusion criterion were selected. The data were summarised on a data-capturing sheet, included in the appendix.

After the data were collected, a computerised Excel spread sheet was created. This included all the demographic data and all scores from the BNCE, the MoCA and the IHDS. The Part 1 and Part 2 scores of the BNCE were plotted separately and then totalled up for the final score. The data were then plotted onto the spreadsheet in categorical scores before data analyses could be conducted.

**2.8. Data Analyses**

All statistical analyses were conducted using R software (R studio version 0.99.903; https://www.rstudio.com/). R software is an open source programming language and software environment for statistical computing and graphics. All tests were two-tailed, and statistical significance was accepted at values equal to or less than 0.05.

Using the Shapiro-Wilke test, the data collected was assessed to see if any abnormalities could be detected. It was then visualised using Q-Q plots. Q-Q plots is a graphical technique for determining if two data sets come from populations with a common distribution. The data from for the study was collected from assessments of categorical scores. Generalised Linear Model (GLM) analyses were used. GLM are used to analyse non-normal data. They are statistical approaches that consider how dependant variables are influenced by fixed factors and continuous predictors like demographics.

Statistical analyses used in each of the three objectives are outlined below:

Objective 1: To assess the neuropsychological profile of HIV-positive patients, the BNCE scores in Part 1 and Part 2 were analysed separately to assess whether the category scores differ from each other, using a GLZ test with a binomial function or confidence interval. (GLZ is a form of GLM which takes the idea of a general linear model even further).

Objective 2: To assess whether the BNCE is adequate for screening the neuropsychological profile of clade C HIV patients, the scores obtained from the BNCE were compared with the scores of the IHDS and the MoCA. Analyses comprised of 1-sample tests which assessed significant differences between the BNCE profile scores and the scores of other tests.

Objective 3: Demographic parameters were recorded to determine their impact on the categorical variables.

Sample sizes: A sample size of 45 was the minimum required to detect statistical significance at the 5% level.

**2.9. Funding**

The study was self-funded.

Budget for project:

1. Stationary (paper, photocopying) R1 000

2. Printing R500.

3. Transport R1 500

4. Statistician R3 000

5. Editing R5600

Total R11600

## 2.10. Ethics

Permission to conduct this research was obtained from the Human Research Ethics Committee (Non-Medical) at the University of the Witwatersrand. The study was retrospective; therefore, no patient-doctor contact took place. The patients' records were in the possession of Lufuno Neuropsychiatric Clinic, and all data were collected in the form of codes, hence preserving patient confidentiality. As part of the clinic's intake procedure, all patients are required to consent to the administration of the BNCE and also to the use of their scores for research purposes. The BNCE was purchased by Tara and can be used by Tara for research purposes.

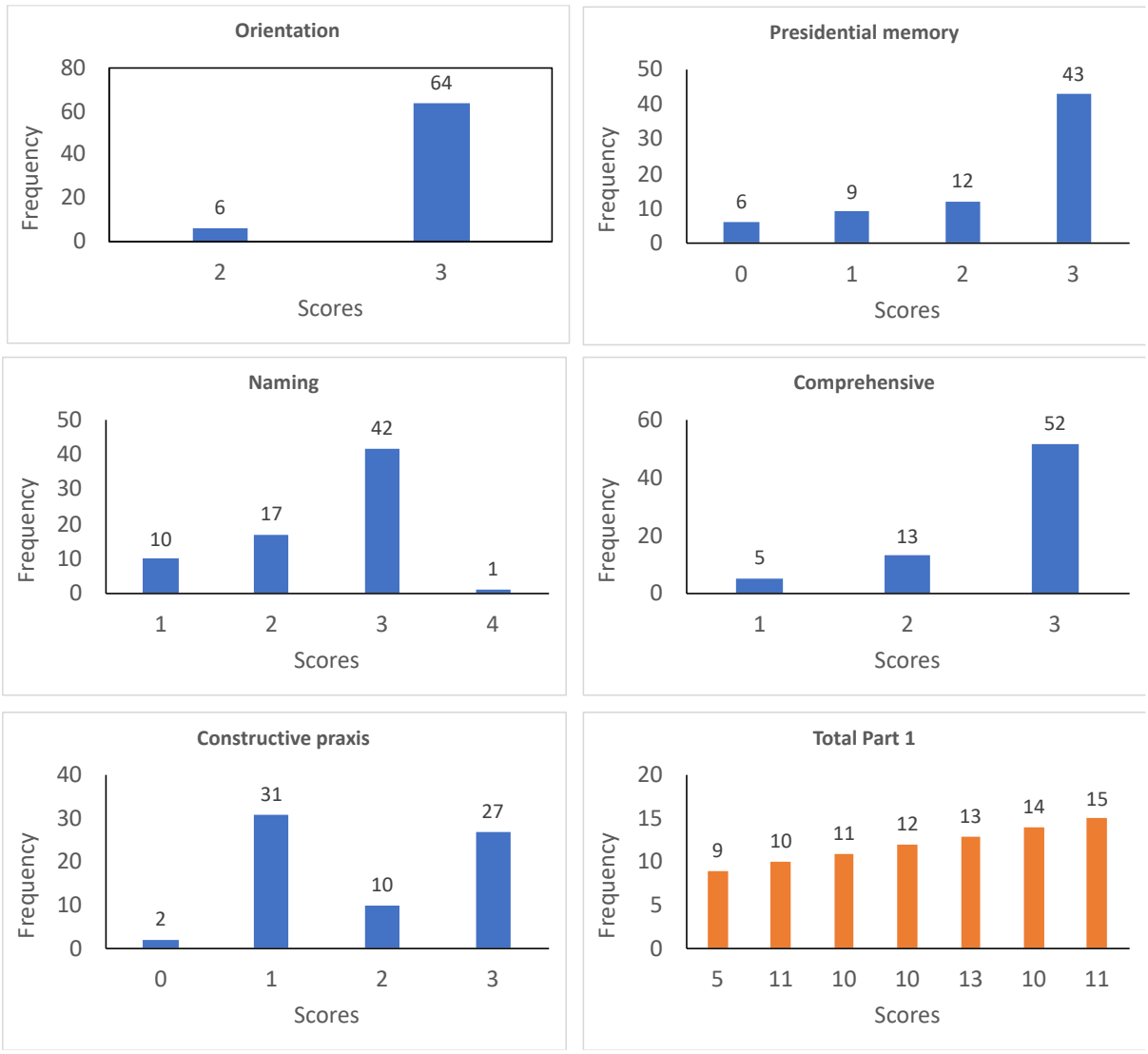
## Chapter 3: Results 3.1. Data analyses

The questionnaire data were captured in Microsoft Excel. The neurocognitive profiles for the BNCE, the IHDS and the MoCA were plotted as frequencies on bar charts. Descriptive analyses of the socio-demographic and clinical variables were shown by percentage (categorical variables) in pie charts and a table.

All statistical analyses were conducted using R software (R version 3.4.2; https://www.r-project.org). Tests were two-tailed probability values and statistical significance accepted when $\alpha \leq 0.05$. The data set for this study was generated mainly from assessments of categorical scores. Categorical data are usually non-normal. Thus, non-parametric chi-squared contingency tests were used to analyse count data per socio-demographic/clinical profile and for the neurocognitive profiles. Mann-Whitney U analyses were used to assess BNCE total scores for gender, education level and CD4 count. Spearman rank analyses were used to compare BNCE total scores against duration of stay.

### 3.1.1 Neurocognitive Profile per the BNCE

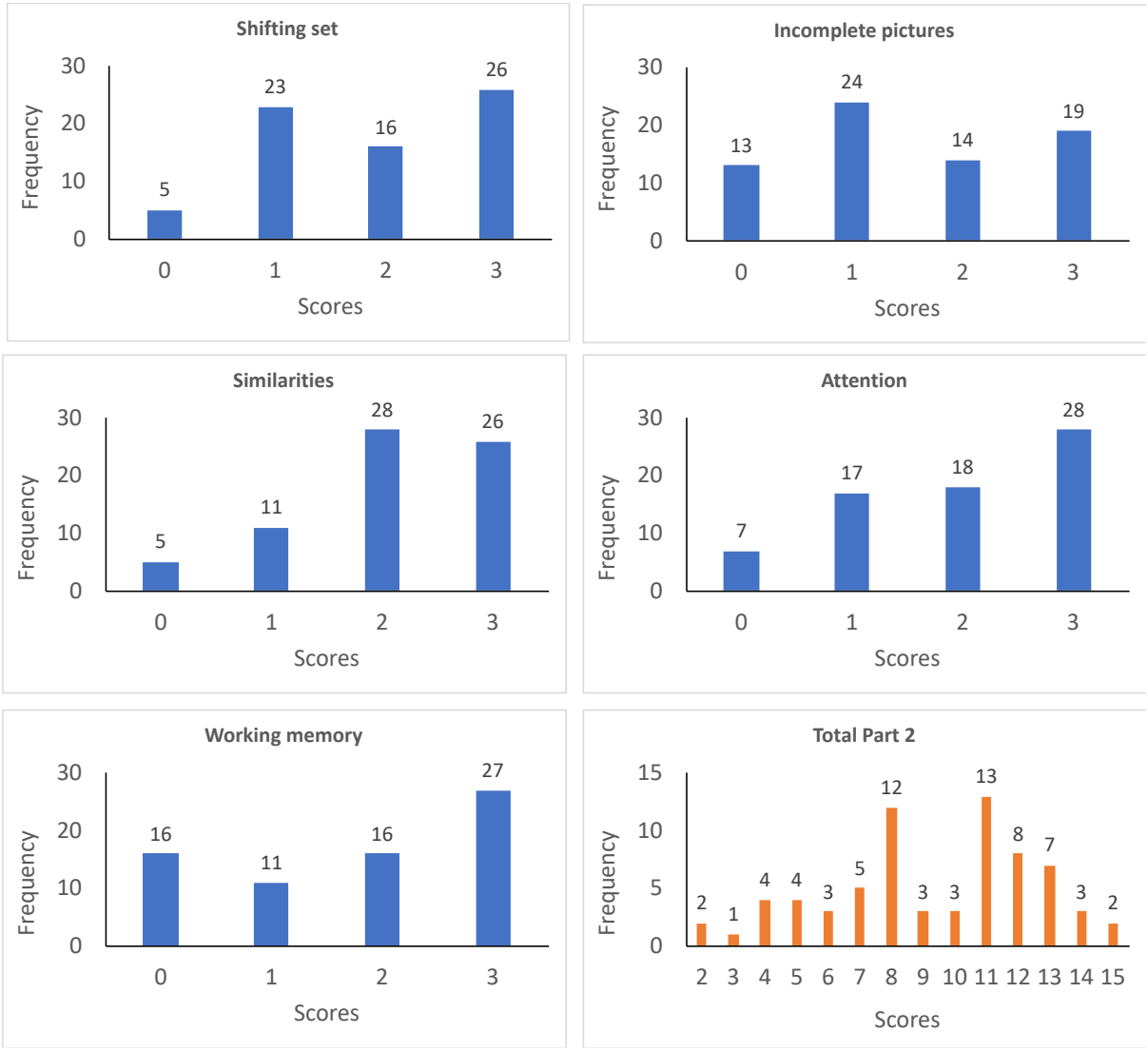
Figure 3.1. The number of patients (frequency) per component and Part 1 total scores per the BNCE neurocognitive profile.




The scoring on the BNCE is as follows: 3 represents no impairment, 2 is indicative of mild impairment, 1 reflects a measure of moderate impairment and 0 indicates severe impairment. For Part 1 scores, all component scores differed significantly from chance or had statistical value. Significantly more patients scored 3 in the Orientation ($\chi^2_1 = 48.06$, $p < 0.001$ ;), Presidential Memory ($\chi^2_3 = 13.41$, $p = 0.004$), Naming ($\chi^2_3 = 37.53$, $p < 0.001$), and Comprehension subtests ($\chi^2_2 = 54.2$, $p < 0.001$; Figure 3.1) which indicates that no cognitive

impairment is demonstrated. In the Constructive Praxis subtest, patients predominantly scored 1 or 3, which were significantly greater than other scores ($\chi^2_3 = 27.36$, $p < 0.001$). This suggests that a subset of patients present with moderate cognitive impairment on the Constructive Praxis subtest. However, total scores for Part 1 did not differ significantly from chance ($\chi^2_7 = 3.60$, $p = 0.825$ ;) and there was therefore no statistical value.

Figure 3.2. The number of patients (frequency) per component and Part 2 total scores per the BNCE neurocognitive profile

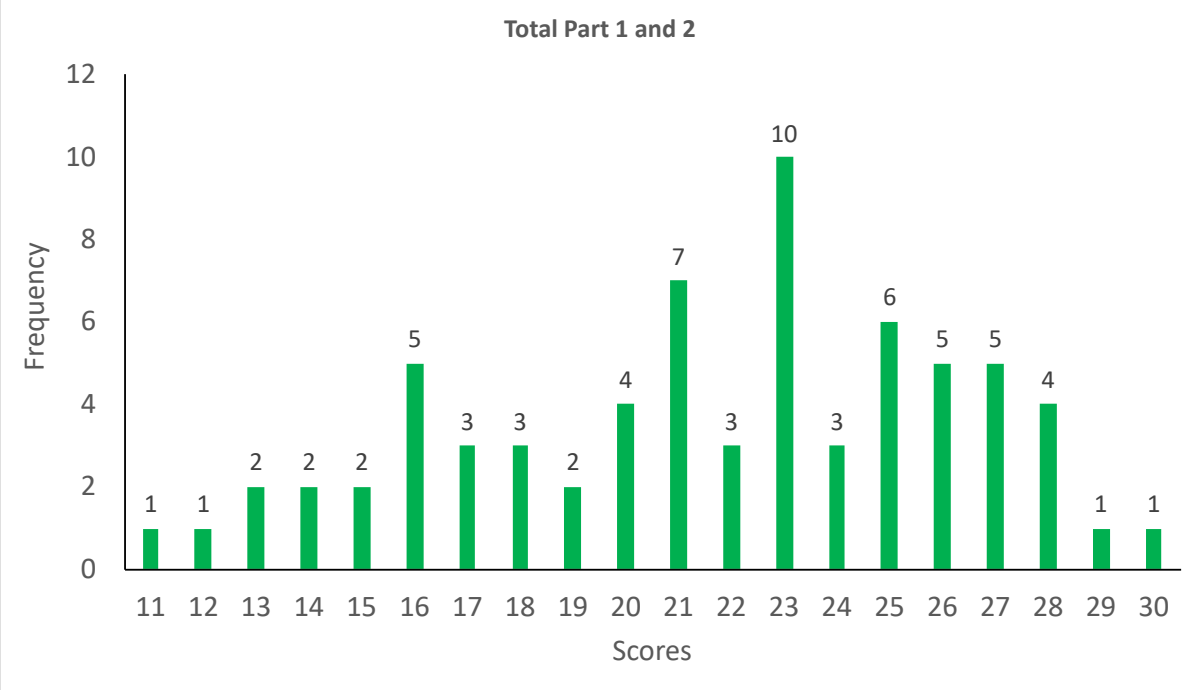



The Shifting Set subtest from Part 2 of the BNCE demonstrated that significantly more patients scored between 0 and 2. While there were a number of patients who demonstrated no impairment on this particular subtest, it seems the majority of the patients had mild to severe impairment ($\chi^2_3 = 10.79$, $p = 0.013$). In addition, the results on the Similarities subtest demonstrated a similar pattern where there was a high proportion of patients who had no impairment in this domain; however, the majority of the results suggest

mild to severe impairment ($\chi^2_3$ = 17.64, p < 0.001). While the scores for the Incomplete Pictures ($\chi^2_3$ = 4.27, p = 0.233), Attention ($\chi^2_3$ = 6.33, p = 0.100), and Working Memory ($\chi^2_3$ = 2.67, p = 0.445) tests did not differ significantly from chance, a much higher proportion of patients scored within the severe to moderate impairment range.

For the total scores for Part 2, significantly more patients scored 8 out of 15 and 11 out of 15 ($\chi^2_{13}$ = 36.56, p < 0.001;).

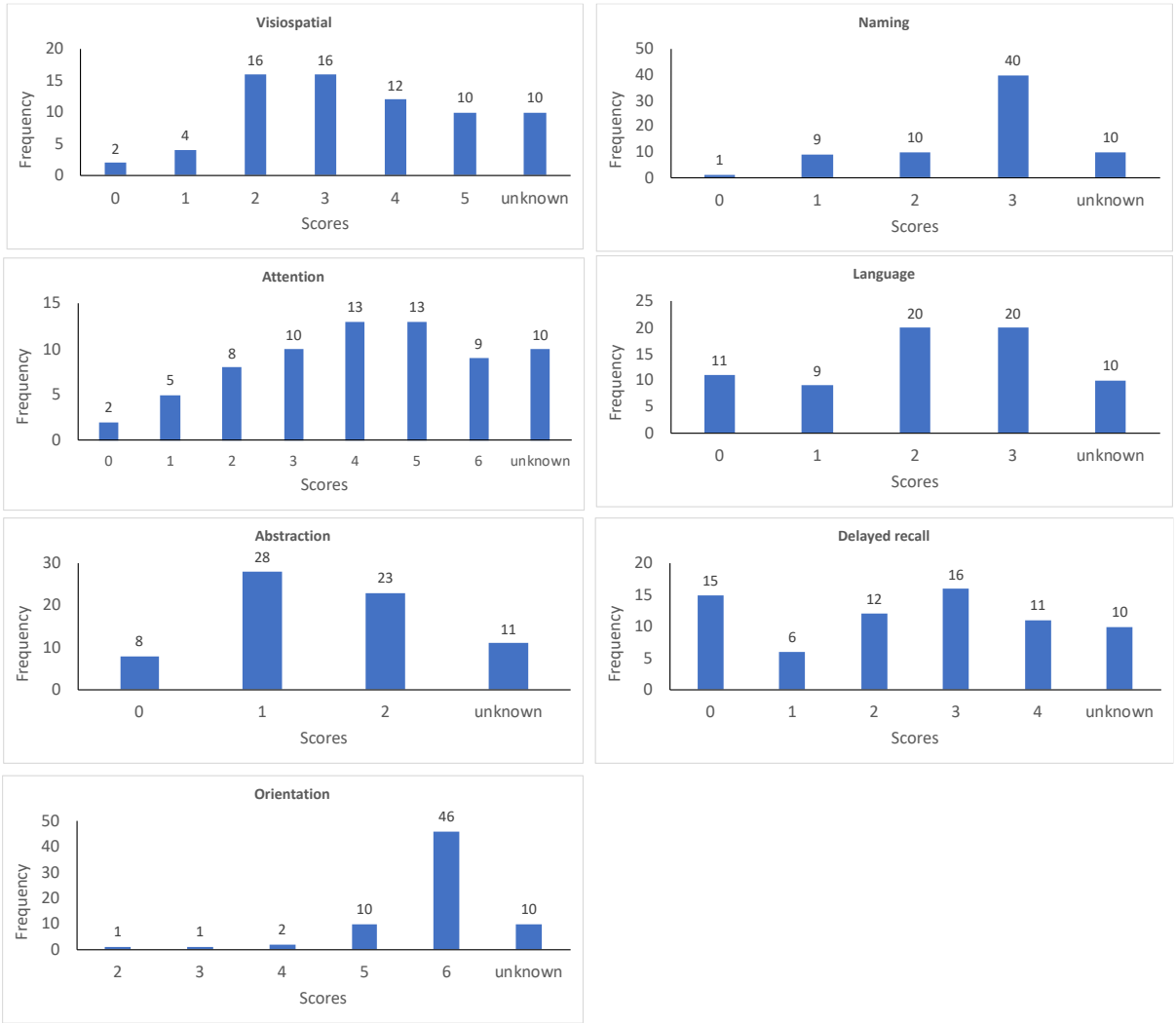
Figure 3.3. The number of patients (frequency) per Parts 1 and 2 total scores per the BNCE neurocognitive profile.




Combining the total of Parts 1 and 2 scores showed a trend ($\chi^2_{19}$ = 29.43, p = 0.059). Most patients scored 23 out of a total of 30 which signified a mild impairment (lower limits).

### 3.1.2 Neurocognitive profile for the MoCA

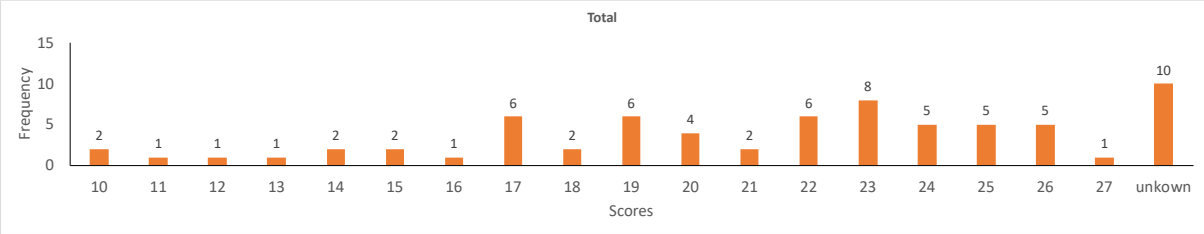
Figure 3.4. The number of patients (frequency) per component scores per the MoCA neurocognitive profile




Analyses of neuropsychological test performances were completed, which provided a more detailed characterisation of the pattern of impairment in various cognitive domains. In the Visuospatial tests, significantly more patients scored 2 and 3 ($\chi^2_4 = 17.60$, $p = 0.007$) which shows some impairment. Most patients scored 3 for Naming ($\chi^2_4 = 64.43$, $p < 0.001$) which shows no significant impairment. For Abstraction, most patients scored 1 ($\chi^2_3 = 13.19$,

p = 0.004) which shows some impairment. Significantly more patients scored 6 in Orientation ($\chi^2_5$ = 129.03, p < 0.001; Figure 3.) which shows no significant impairment. Scores for Attention ($\chi^2_7$ = 11.64, p = 0.113) were predominantly 4 and 5 which did not indicate impairment. Most patients scored 3 and 2 for Language which showed little or no impairment; Language ($\chi^2_4$ = 8.71, p = 0.070). For Delayed Recall ($\chi^2_3$ = 5.60, p = 0.347) the majority of patients scored 3 or 4 which showed little or no impairment.

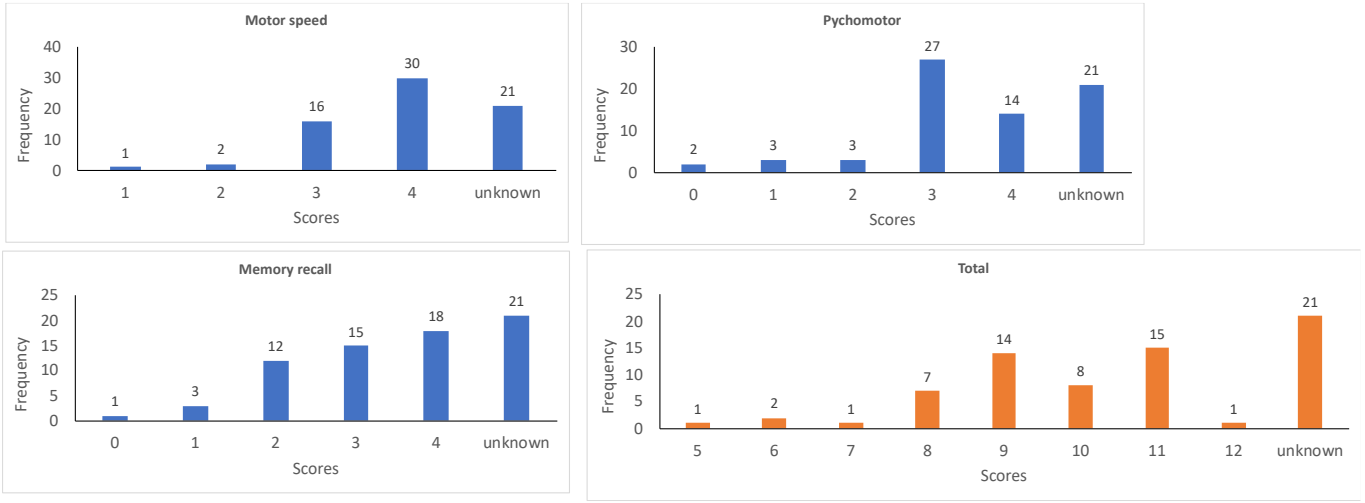
Figure 3.5. The number of patients (frequency) per total scores per the MoCA neurocognitive profile




For the total MoCA scores, the overall scores predominantly fell below 23 which suggest a range of severe to mild cognitive impairment, ($\chi^2_{18}$ = 35.14, p = 0.009).

### 3.1.3. Neurocognitive profile of the IHDS

Figure 3.6. The number of patients (frequency) per component and total scores per the IHDS HAND profile




The IHDS measures three entities, namely Psychomotor Speed, Memory Recall, and Motor Speed. Motor Speed seemed largely unaffected. There was significant impairment in Psychomotor Speed and Memory Recall.

For the IHDS scores, all components and the total score were significant. Specifically, significantly more patients scored 4 for Motor Speed ($\chi^2_4 = 44.43$, $p < 0.001$), which showed no significant impairment. More patients scored 3 for Psychomotor Speed ($\chi^2_5 = 48.97$, $p < 0.001$), which shows some impairment. A significant number of patients scored 3 and 2 on the Memory Recall which showed some impairment ($\chi^2_5 = 28.06$, $p < 0.001$).

Of the results a significant number of patients scored below 10 which is indicative of a MNCD ($\chi^2_8 = 56.26$, $p < 0.001$).

### 3.1.4. Comparisons between the BNCE and variables

Comparisons were made between BNCE total scores and four variables: gender, education, CD4 counts and duration of treatment. The data for the gender suggested that females had significant median (middle value separating the higher half from the lower half of a data sample) values than males (females = 12 vs. males = 14) for Part 1 total BNCE scores (U=345.5, p=0.030). This suggests that for Part 1 of the BNCE, the females scored less than the male which is significant of females having more severe impairment. There were no significant differences between median values for females (8) and males (11) in the Part 2 total BNCE scores (U=386, p=0.101). Both genders had no difference in impairment. However, in the overall total BNCE scores for Parts 1 and 2, females again had significantly lower median values than males (females = 12 vs. males = 14; U=352.5, p=0.037). This suggest that females present with more severe impairment.

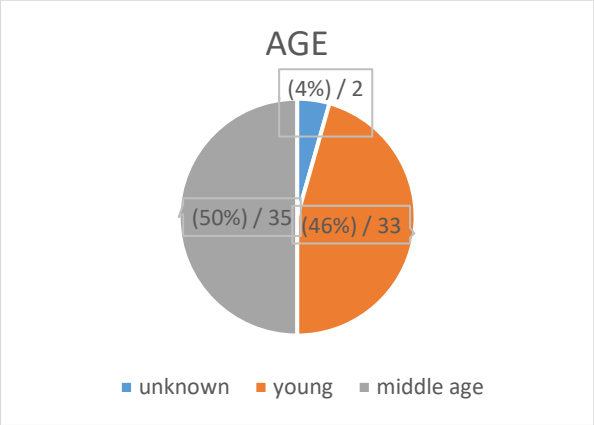
For education, unknown responses were omitted, leaving 29 patients with matriculation and 32 patients without in the analyses. For all BNCE total scores, patients with matriculation had higher median (middle value) values than those without. This suggest that patients with a matriculation scored better in the BNCE. Specifically, Part 1 total (U=306.5, p=0.022; matric = 13; <matric = 11.5) Part 2 total (U=243.5, p=0.001; matric = 11; <matric = 8), and overall total (U=235.5, p<0.001; matric = 24; <matric = 20).

For CD4 counts, unknown responses were again omitted, leaving 32 with <200 and 25 >200 (the single 200 count was included in the > 200 group for statistical purposes). For all BNCE total scores, there was no significant differences between patients with <200 and >200 CD4 counts. Specifically, Part 1 total (U=339.5, p=0.464; <200 = 12.5; >200 = 12) Part 2 total (U=335.5, p=0.425; <200 = 11; >200 = 8), and overall total (U=332.5, p=0.397; <200 = 23; >200 = 21).

For the duration of treatment, data from 70 patients were used in the analyses (excluding unknown responses). There was no significant correlation between duration of treatment and BCNE scores for Part 1 (r=0.05, p=0.706), Part 2 (r=-0.06, p=0.668) and total (r=-0.18, p=0.176) scores. These analyses indicated that a long or short duration of treatment did not predict BNCE scores.

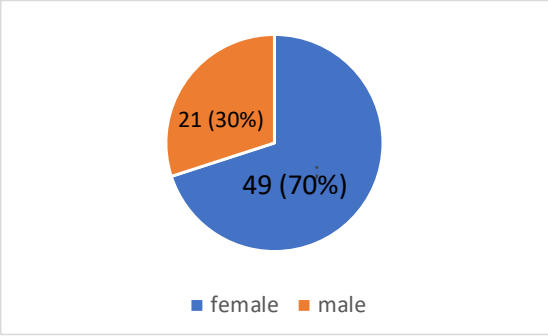
### 3.1.5 Socio-demographic profile

Figure 3.7. The age profile of patients considered in the study



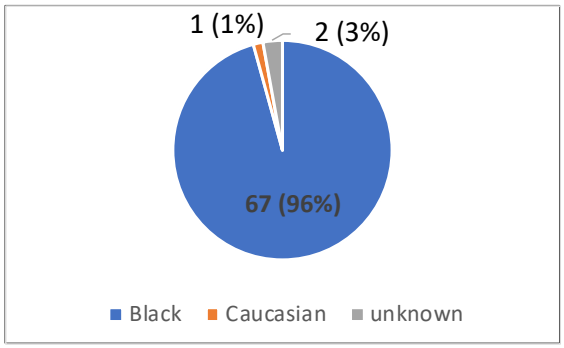

In terms of the demographic variables, age groups were as follows: young age (18-39 years), middle age (40-59 years) and elderly ≥60 years. There were 35 patients (50%) who were middle-aged, while 33 patients (46%) were of a younger age. There were no elderly patients in the sample. A small number of 2 patients (4%) in the study did not have their ages included in the files.

Figure 3.8. The number of female and male patients considered in the study



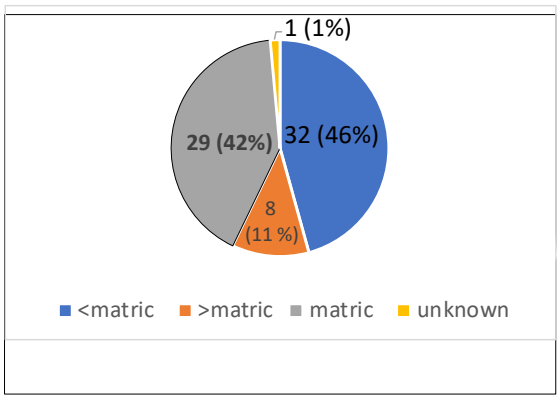
Significantly more patients were female than male ($\chi^2_1$ = 11.20, p < 0.001 ;). 21 patients (30%) were male while 49 patients (70%) were female.

Figure 3.9. The race distribution of patients considered in the study



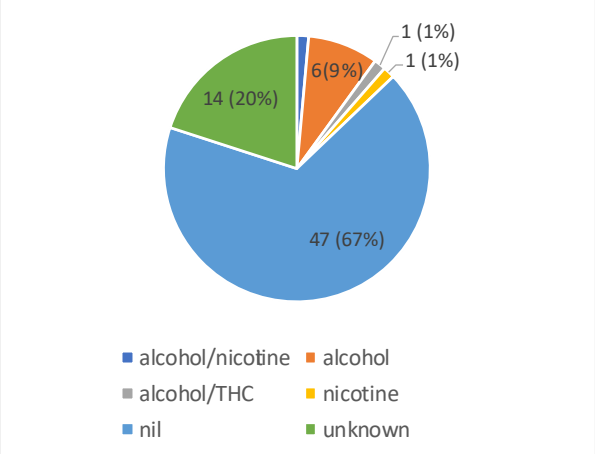

Significantly more patients were Black than Caucasian, and the race of two patients was unknown ($\chi^2_2$ = 122.60, p < 0.001; Figure 3.3) 67 patients (96%) were Black,1 patient (1%) was Caucasian and the race of 2 patients (3%) was unknown.

Figure 3.10. The education profile of patients considered in the study



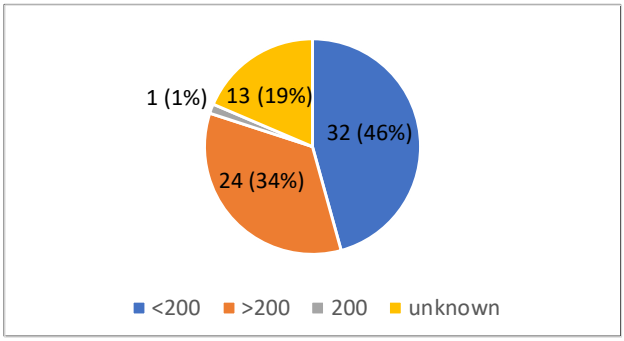
Most patients had matriculated. However, the distribution of patients did not differ significantly from chance ($\chi^2_3 = 5.46$, $p = 0.14$). There were 32 patients (46%) who did not have a matriculation. Another 29 patients (42%) had matriculated. There was a small number of 8 patients (11%) who had achieved a higher education , while the education background of one patient (1%) was unknown.

Figure 3.11. The alcohol/substance use distribution of patients considered in the study



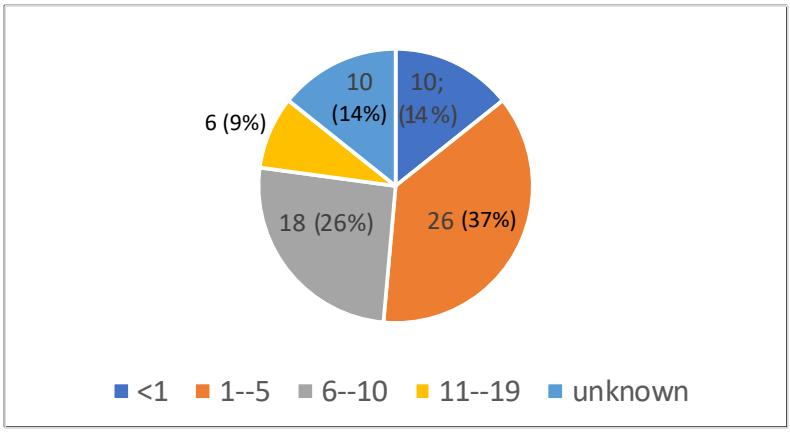

Most patients (n = 47; 67%) reported not drinking alcohol or taking substances. This number was significantly greater than those who reportedly did take alcohol/substances ($\chi^2_5 = 139.49$, $p < 0.001$;). Only 6 patients (9%) reported taking alcohol , 1 patient (2%) took both alcohol and nicotine while 1patient (1%) reported taking alcohol and cannabis and 1 patient (1%) reported using nicotine. There were 14 patients (20%) whose substance history was unknown in the study sample.

Figure 3.12. The CD4 profile of patients at admission



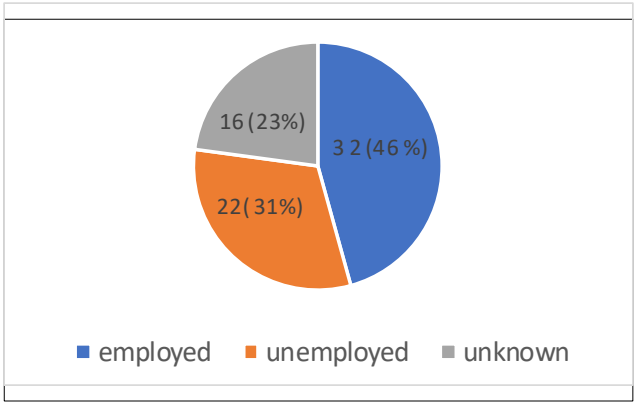
Significantly more patients (32), corresponding with 46%, had a starting CD4 count of less than 200, rather than a start of 200 which only 1 patient (1%) presented with. 24 patients (34%) had a starting CD4 count greater than 200 and the CD4 count of 13 patients (19%) was unknown ($\chi^2_3 = 29.99$, $p < 0.001$).

Figure 3.13. The duration of treatment (in months) of patients considered in the study in months.




Significantly more patients (n = 26; 37%) were on antiretroviral medication treatment for 1-5 months when they first consulted at the clinic ($\chi^2_4 = 18.29$, $p = 0.001$). There were 18 patients (26%) who had been on treatment between 6 and 10 months, while 6 patients (9%) were on treatment between 11 and 19 months. 10 patients (14%) had been on treatment for less than a month, and the treatment duration of another 10 (14%) was unknown.

Figure 3.14. The employment status of patients considered in the study.



A greater percentage of the sample (46%), which amounts to 32 patients were employed but whether or not the patients were employed did not differ significantly from chance ($\chi^2_2 = 5.60$, $p = 0.061$). There were 22 patients (31%) which were unemployed. The employment status of the remaining 16 patients (23%) was unknown.

In terms of comorbidities, the following diagnoses were considered:

Table 3.1 The number of patients with different comorbidities

| Comorbidities | |
|---|---|
| Anaemia | 1 |
| Diabetes Mellitus | 1 |
| Extrapulmonary Tuberculosis | 3 |
| Haemorrhoids | 1 |
| Herpes Zoster | 1 |
| Hypertension | 5 |
| Hypothyroidism | 2 |
| Nil | 45 |
| Pulmonary Tuberculosis | 1 |
| Stomach Ulcers | 1 |
| Unknown | 9 |

The majority of the patients (45) did not report comorbidities, which differed significantly from chance ($\chi^2_{13} = 299.86$, $p < 0.001$). 9 patients were unknown. 5 patients had hypertension, 1 was anaemic, 1 had diabetes mellitus, 1 had pulmonary TB while 3 had extra

pulmonary TB, and 1 had herpes zoster. 2 patients had hypothyroidism .1 patient had stomach ulcers and 1 other patient had haemorrhoids.

## Chapter 4: Discussion

The aim of this study was to establish and describe the neuropsychological profile of HIV in a sample of HIV reactive individuals who are on a managed ART program and who attend the Lufuno Neuropsychiatric Clinic. The Brief Neuropsychological Cognitive Examination (BNCE) was used to determine whether it is an adequate screening tool for this profile in comparison to the frequently used screening tools, namely the MoCA and the IHDS.

The following objectives were identified:

i) To assess the neuropsychological profile of HIV as measured by the BNCE.

ii) To determine whether the BNCE is adequate for screening this profile by comparing it to the profiles of the IHDS and the MoCA.

iii) To determine whether the patients' demographic data has an impact on neurocognitive screening test outcomes.

HIV in South Africa has reached unprecedented numbers and because of the resultant severity of HAND and HAD, it has become imperative to make use of adequate screening regimes for such disorders. This research is significant due both to the noted gap in screening for HAND and HAD in South Africa, and for the necessity to better understand the profile of HIV. It appears that it is insufficient to use only the IHDS with the MOCA as screening tools to assess for HAND and HAD within the current South African context.

### The neurocognitive profile as measured by the BNCE

The main aim of the study was to investigate the neurocognitive profile of HIV individuals as measured by the BNCE. Research has shown that clade C HIV preferentially

affects white matter integrity. The white to grey matter ratios are found to be higher in the parietal lobe which is important in the interpretation of information required by the visuospatial domain. In individuals with HAND, this visual-spatial processing is affected with further impairment in hand eye coordination which impact upon drawings. (8, 27) There were significantly lower scores in Constructive Praxis for Part 1 of the BNCE. Constructive Praxis relies heavily on intact parietal lobe functioning, particularly the right hemisphere. This is likely because of higher ratios of white to grey matter. HIV causes degeneration of myelination in white matter. Therefore, the structural integrity of the parietal lobe is compromised, leading to a deficit in visual-spatial functioning. All the other profiles of Part 1 - including Orientation, Presidential Memory, Naming and Comprehension - were largely unaffected. Again, this is in keeping with the literature, suggesting that HIV does not generally impair these functions. (27)

In Part 2, low scores are seen for Shifting Set, Incomplete Pictures, Similarities, Attention and Working Memory. Shifting Set is related to pathology of the frontal and fronto-subcortical circuits, which would contribute to difficulties in domains such as executive function, attention, and working memory. Shifting Set tests the ability of the individual to shift from an established pattern of responding. Research has shown that HIV causes neuronal injury to the frontal and fronto-subcortical circuits, resulting in impairment in cognitive planning, impairment in response inhibition, decrease in abstract reasoning, and decreased concentration when given instructions. (8, 26) Consequently, patients in the present sample appeared to have difficulty with their executive functions.

Impairment in Incomplete Pictures is seen in individuals with prefrontal and occipital pathology. It involves the processing of incomplete information which is mediated by the occipital and frontal lobe together. HIV generally does not affect the occipital lobe, while the frontal lobe may be affected by neuronal damage due to white matter distribution in this

region. (26) This results in individuals failing to complete pictures as a result of impairment in the frontal lobes which use executive functioning to complete the picture through reasoning processes. (27) This is also in keeping with research that the frontal lobe is highly affected by clade C HIV. (8, 27)

Similarities assesses the ability to identify underlying concepts and provides a measure of verbal reasoning ability. An impairment in this area suggests further pathology in the frontal lobe. Poor performance is seen in identifying a common functional feature between objects and the social feature of humans. As mentioned earlier, HIV is known to cause neuronal damage in the myelination of the white matter tracts in the frontal lobe. (26) As a result, further executive functions are likely affected with resultant impairment in abstract reasoning, in keeping with studies around the effect of HIV on the frontal lobe. (8, 27)

Attention is a further frontal lobe function. Studies have shown that, although in the early stages of HIV attention is not affected, as the illness progresses impairment in attention is seen. (27). Deficits in attention are related to lesions of the frontal lobe or subcortical areas, which largely rely on white matter tract integrity for processing. (25, 26, 27) The parietal lobe may also be affected in some instances. Impairment in working memory occurs as a result of lesions in the limbic system, the subcortical and mesencephalic structures, as well as in the frontal lobe. This is in keeping with research demonstrating that memory deficits are present in the late stages of HAND. (24) The disturbance in attention and working memory develop as a result of inflammation of the fronto-striatal areas, due to the white matter demyelination caused by HIV. (25, 26)

The above results were compared to those of the MoCA and the IHDS.

**The neurocognitive profile as measured by the MoCA**

Analyses of neuropsychological test performances for the MoCA showed significant impairment in Visuospatial, Abstraction and Delayed Recall subtests in this study's sample. Attention, Language, Orientation, and Naming appeared to be mostly intact. This pattern of performance has been seen previously in individuals with HAND. It has been established that cognitive functions including motor skills and information processing, learning and memory, attention and working memory, executive function, visuospatial function, and speech and language, that have been found to arise as a development of the white matter connections in the brain are preferentially affected by HIV. (8, 24) The MoCA evaluates many of these domains that are affected by HIV.

Recent studies have shown that the visuospatial domain is affected in the later stages 2Wsawof Retroviral Disease (24). Memory function is also commonly impaired in HAND and can worsen as the illness progresses. (24, 27) Another study showed that attention and concentration are spared in the early phase of HAND and will only be affected in advanced illness (24, 27). Language is generally preserved, but there may be expressive language deficits as the illness progresses (27). Orientation is largely unaffected in HAND.

The above results were mostly in keeping with the results of the BNCE. Language, Orientation and Naming subtests in the MoCA correlate with Part 1 results of the BNCE. Visuospatial, Abstraction and Delayed Recall correlate with BNCE scores for Part 2. There was a mild impairment in Attention in the BNCE, while little or no significant impairment was noted in Attention in the MoCA. The reason for this could be that it was difficult to score the different subtests of the MoCA as the MoCA relies heavily on the overall score, while the BNCE offers total and separate scores for Part 1 and 2. It also gives an interpretation of individual scores. The MoCA scores out of six for Attention, while the BNCE provides a

score out of nine, this suggests that the BNCE assesses the attention construct in more detail than the MoCA.

**The neurocognitive profile as measured by the IHDS**

The IHDS comprises three subtests and focuses mainly on motor and memory function, excluding executive function, which is largely affected by HIV. There was significant impairment in Psychomotor Speed and Memory Recall in this study's sample. These functions are mediated by the frontal cortex, subcortical circuits, and the basal ganglia. Clade C HIV causes injury to these areas, particularly causing significant calcification to the basal ganglia. (26) There is resultant difficulty evidenced by slowed information processing seen in the trail making test in the MoCA and the BNCE and slowed motor movements seen in the finger tapping test in the IHDS. The results are in keeping with results of the BNCE and MoCA. It was difficult to compare Motor Speed as both the BNCE and MoCA do not have an equivalent assessment. The Motor Speed adds an advantage to the IHDS. Another difficulty is that the IHDS does not offer an interpretation for individual scores but offers only interpretation for overall scores.

Overall total scores showed cognitive impairment. This is consistent with research that HIV affects subcortical structures, including the basal ganglia, resulting in movement difficulties, as well as the hippocampus, resulting in memory problems. (26) Total score results are in keeping with the BNCE and MoCA.

The neuropsychological profile of the BNCE for HIV individuals in this study has shown efficacy and is in keeping with literature. Similar results were found when comparing the BNCE and the MoCA, demonstrating consistent neurocognitive profiles. In addition, the BNCE added more in-depth information as it starts with simpler tasks in Part 1 and then progresses onto more complex tasks in Part 2. As a result, it is sensitive to mild cognitive

impairment. It also provided total and separate scores for Part 1 and 2 which allows comparison and contrast the patient's ability to process information that is used more often with new information. The demographic variables showed some impact on the neurocognitive results.

In part, the HIV epidemic is influenced by the HIV reactive individual's socio-economic status, which includes their access to education, their increased potential for substance use, the comorbidities they are prone to, and how available ARVs are to them. Several studies to date have reported that risk factors for developing HAD include a low CD4 count, advancing age, a lower level of education (23), and drug and alcohol abuse. (35) Therefore, these variables were included in the study in order to determine whether they impacted upon the results.

In the study sample, the majority of the sample was middle-aged, which correlates with studies that advance in age is a risk factor for HAND. (23) The majority of the sample was also noted to be female. This correlates with previous studies which have noted that young women become infected with HIV at least 5 to 10 years earlier than males. (36) In another study, it was found that women between the ages of 15 and 24 had a prevalence of 11.4% compared to the 2.9% prevalence in males of the same age. (1,37) When correlating gender and total scores for the MoCA and the BNCE, the current study shows that total scores for women were lower than for males which suggests that females presented with more severe impairment. This is in keeping with another study which reported that women infected with HIV were more at risk to a decline in cognition because of added socio-economic factors, including unemployment and poverty, raising children alone, and sometimes sexual abuse. (38)

Furthermore, studies have evidenced that socio-economic and educational history in South Africa are widely varied, with half of the population being underprivileged. (39) Many

of these individuals have been educated in poor conditions, often with no basic essentials and inadequate sanitation. This has resulted in illiteracy in a third of the country's population. (40) The current unemployment level of 29.1% further exacerbates the problem. (41) In this study, 46% of patients had not matriculated. A greater number had matriculated, with a small number among them having received higher education. This was in keeping with the sample of employed patients; however, this inconsistency with the general population could result from the study taking place at Tara, which is located in an area where some of the patient population are financially privileged. In all three scores - Part 1, Part 2 and total BNCE – the correlation between BNCE scores and educational background showed that the patients who had matriculated, as well as those who had higher learning, scored higher than those who had not matriculated.

A large portion of the sample (67%) reported that they took no substances, and just 9% took alcohol. This was unexpected in terms of the majority of research which reports that substance use disorder is widespread in people living with HIV (35), and that alcohol use is the most common substance of abuse. (35) The same study showed that alcohol was a risk factor for developing HAND. (35) This may be as a result of the added injury to the brain as a result of alcohol.

In the current study, the greatest percentage (46%) of the sample had a starting CD4 count of less than 200 when they first started attending the clinic. Research has shown that individuals with a CD4 count of less than 200 are at a greater risk for developing HAND, and hence screening should be performed more regularly. (6) However, in this study correlations between the patients' CD4 counts and BNCE scores were not significant, possibly because the CD4 counts were recorded while the patients were already on ARVs. This is important as it could demonstrate the neuroprotective impact that ARVs have on CD4 count and cognitive function.

It is also noted in the literature that individuals presenting with HAD and HAND, and who are on an ARV regime, present with neurocognitive problems much later in the course of the illness, which suggests that ARVs have been beneficial in the treatment of HAND. (6) Research has also shown that, since the advent of ARVs, there has been a notable decline in the number of severe HAND cases, but that milder forms of HAND are evident. (2) This may be due to HIV not being adequately controlled in the CNS, HIV strains evolving and becoming drug resistant, the addition of other insults to the brain including alcohol and illicit drugs, previous head injuries, increasing age and infections like syphilis and hepatitis. (2) A correlation done between duration and treatment and BNCE scores were not significant. This could be because the individuals had been on treatment for a short duration of time, namely less than 5 months. A small majority had been on treatment for 11-19 months. With a longer duration of treatment there may possibly be an improved BNCE score. A study done in Cape Town on HAND and ARVs showed that ARVs improve cognition in individuals infected with HIV within one year of initiation. (42).

**Limitations of the Study**

The study was carried out in one centre with a small sample size. There were eight patients with comorbidities that did not meet the exclusion criteria, although they may have had some impact on neurocognitive function. These included hypertension, diabetes mellitus and hypothyroidism. A further limitation was incomplete data capturing in the patient files. There were some files which did not have all of the screening measures. All the files had BNCE tests done, but some lacked IHDS and or MoCA assessments. In some files, demographic data were also incomplete. An explanation for this could be due to time management as all three tests could be taxing to the patients if done at the same time. A recommendation here would be to streamline the process of screening so that all tests are administered.

# Chapter 5: Conclusion

The BNCE demonstrated effective use as an alternative screening tool for determining neurocognitive profiles in HAND when compared to the MoCA and the IHDS. It demonstrated reliability and was comprehensive in establishing the neuropsychological profiles of HIV on a sample of HIV reactive patients on a managed ART program attending Lufuno Neuropsychiatric Clinic. It was also found to be quick to administer, impartial to language and culture, and the clinicians who may use it do not need specialised neurological training. It was found to give a more comprehensive evaluation of the patient than the MoCA and the IHDS. It also correlated with the findings of the MoCA as similar cognitive domains are tested.

The cognitive profile established by the BNCE is consistent with the neurology of HIV. Subsequently, the BNCE appears effective as an alternative screening measure as it demonstrates structure and associated functional impairments in an HIV positive sample.

## Recommendations

All patients must be screened. The BNCE can be used as an alternative or together with the MoCA as it provides more information although it takes 20 more minutes than the MoCA. It was found to be more comprehensive particularly because it uses both individual and total scores for evaluation. It also moves from simpler tasks in Part 1 to more complex tasks in Part 2. This makes it valuable in picking up the milder forms of HAND. Unlike the MoCA, a higher level of education is not needed for the BNCE. This is important as most of the patients in the South African clinic setting are poorly educated. It is also recommended that it can be used together with the IHDS as the BNCE lacks the motor components

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## Appendix A

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Thato Leketi Motsitle Kalane

**HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)**

**CLEARANCE CERTIFICATE NO. M180627**

| | |
|---|---|
| **NAME: (Principal Investigator)** | Thato Leketi Motsitle Kalane |
| **DEPARTMENT:** | Psychiatry<br>Lufuno Neuropsychiatric Clinic<br>Tara the H Moross Centre |
| **PROJECT TITLE:** | The neurocognitive profile of HIV infected adults attending the Lufuno Neuropsychiatric Clinic as measured by the brief Neuropsychological Cognitive Examination |
| **DATE CONSIDERED:** | 29/06/2018 |
| **DECISION:** | Approved unconditionally |
| **CONDITIONS:** | |
| **SUPERVISOR:** | Shona Fraser |
| **APPROVED BY:** | Dr C Penny, Chairperson, HREC (Medical) |
| **DATE OF APPROVAL:** | 07/12/2018 |

**This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.**

**DECLARATION OF INVESTIGATORS**

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 301, Third floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed June and will therefore be due in the month of June each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

5/01/2019
Date

**PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES**

## Appendix B

# BNCE

## Administration and Scoring Form

by Joseph Tonkonogy, M.D., Ph.D.

wps
Test with Confidence

**Client Name:** _____

**ID Number:** _____

**Age:** _____ **Gender:** ☐ Male ☐ Female

**Date of Testing:** _____

**Ethnicity:** ☐ Asian ☐ Black ☐ Hispanic ☐ Native American ☐ White ☐ Other: _____

**Years of Education Completed:** ☐ <12 ☐ 12 ☐ 13 ☐ 14 ☐ 15 ☐ 16 ☐ >16

**Background Notes:** *(referral question; related medical, neurological, or psychiatric conditions; and community adjustment)*

_____

_____

_____

_____

**IQ (if available):** _____ **Date of IQ Assessment:** _____ **Source of IQ:** _____

## BNCE Results

Circle the adjusted score (in bold print) that corresponds to the raw score obtained for each subtest. Sum the circled adjusted scores to obtain row totals, then sum the row totals to obtain Part I and Part II Scores. Add the Part I and Part II Scores together to obtain the Total Score, and divide the Part I Score by the Part II Score to calculate the Validity Index. Connect the circled adjusted scores with a line to create a profile. Consult the BNCE Manual (WPS Product No. W-326D) for a description of how the pattern of results on the BNCE differs for patients with neurological and psychiatric disorders.

**Part I**

| Impairment | Orientation A | Presidential Memory B | Naming C | Comprehension D | Constructive Praxis E | Row Totals |
|---|---|---|---|---|---|---|
| None | 8–9 **3** | 3–4 **3** | 4 **3** | 7–8 **3** | 6 **3** | |
| Mild | 6–7 **2** | 2 **2** | 3 **2** | 5–6 **2** | 5 **2** | |
| Moderate | 4–5 **1** | 1 **1** | 2 **1** | 3–4 **1** | 2–4 **1** | |
| Severe | 0–3 **0** | 0 **0** | 0–1 **0** | 0–2 **0** | 0–1 **0** | **0** |

**Part II**

| Impairment | Shifting Set F | Incomplete Pictures G | Similarities H | Attention I | Working Memory J | Row Totals |
|---|---|---|---|---|---|---|
| None | 8–9 **3** | 7–8 **3** | 3 **3** | 8–9 **3** | 3 **3** | |
| Mild | 7 **2** | 5–6 **2** | 2 **2** | 6–7 **2** | 2 **2** | |
| Moderate | 4–6 **1** | 2–4 **1** | 1 **1** | 3–5 **1** | 1 **1** | |
| Severe | 0–3 **0** | 0–1 **0** | 0 **0** | 0–2 **0** | 0 **0** | **0** |

**Total Score Ranges**

| Impairment | |
|---|---|
| None 28–30 | Patients with scores in this range may be able to live independently. |
| Mild 22–27 | |
| Moderate 10–21 | Patients with scores in this range are usually unable to live independently. |
| Severe 0–9 | |

☐ Part I Score + ☐ Part II Score = ☐ Total Score

☐ Part I Score ÷ ☐ Part II Score = ☐ Validity Index

(Values <0.8 suggest an unlikely pattern of impairment or an aphasic condition that has prevented the patient from demonstrating his or her actual abilities on the BNCE.)

Additional copies of this form (W-326C) may be purchased from WPS. Please contact us at 800-648-8857 or wpspublish.com.

W-326C

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4 5 6 7 8 9

## Part I *Circle the correct response.*

### A. Orientation

| | Incorrect | Correct |
|---|---|---|
| **Time:** "What is today's date?" | | |
| 1. Year | 0 | 1 |
| 2. Month | 0 | 1 |
| 3. Day of month | 0 | 1 |
| 4. Day of week | 0 | 1 |
| **Place** | | |
| 5. "What state is this?" | 0 | 1 |
| 6. "What kind of place (or building) is this?" | 0 | 1 |
| 7. "What is the precise name of this place?" | 0 | 1 |
| **Person** | | |
| 8. "How old are you?" | 0 | 1 |
| 9. "In what year were you born?" | 0 | 1 |

**Orientation Raw Score** (9 max.) ☐

### B. Presidential Memory

| | Incorrect | Correct |
|---|---|---|
| 10. "Who is the President of the U.S. now?" | 0 | 1 |
| 11. "Who was the President before the one now?" | 0 | 1 |
| 12. "Who was the President who was killed in Dallas, Texas?" | 0 | 1 |
| 13. "Who was the President who was killed in Washington many years ago?" | 0 | 1 |

**Presidential Memory Raw Score** (4 max.) ☐

### C. Naming

*For each item, ask* "What is this?" *while pointing to the corresponding part of your hand or head.*

| | Incorrect | Correct |
|---|---|---|
| 14. Fingernail | 0 | 1 |
| 15. Eyebrow | 0 | 1 |
| 16. Eyelash | 0 | 1 |
| 17. Earlobe | 0 | 1 |

**Naming Raw Score** (4 max.) ☐

### D. Comprehension

| | | |
|---|---|---|
| 18. "Raise your right hand" | Fail | Pass |
| 19. "Raise your left hand" | Fail | Pass |

*If the patient fails either Item 18 or Item 19, do not administer the remaining Comprehension items. Otherwise, administer the remaining Comprehension items, but do not include scores for Items 18 and 19 in the Comprehension Raw Score.*

| | Incorrect | Correct |
|---|---|---|
| 20. "Point to your right ear" | 0 | 1 |
| 21. "Point to your left ear" | 0 | 1 |
| 22. "Point to your left ear with your right hand" | 0 | 1 |
| 23. "Point to your right eye with your left hand" | 0 | 1 |
| 24. "Point to my right hand" | 0 | 1 |
| 25. "Point to my left hand" | 0 | 1 |
| 26. "Point to my right hand with your left hand" | 0 | 1 |
| 27. "Point to my left hand with your right hand" | 0 | 1 |

**Comprehension Raw Score** (8 max.) ☐

### E. Constructive Praxis

*Present the Response Booklet to the patient so that only page 3 is showing. Open the Stimulus Booklet so that only Figure CP-1 is showing. Point to Figure CP-1 and ask the patient to copy the figure into the blank space next to the "CP-1" printed in the Response Booklet. After the first figure is copied, proceed in the same way with Figures CP-2 and CP-3. A missing element of the figure, an additional element, or an element attached to the wrong point on an adjacent line are considered errors.*

| | Errors | | |
|---|---|---|---|
| | ≥3 | 1–2 | None |
| 28. Copy Figure CP-1 | 0 | 1 | 2 |
| 29. Copy Figure CP-2 | 0 | 1 | 2 |
| 30. Copy Figure CP-3 | 0 | 1 | 2 |

**Constructive Praxis Raw Score** (6 max.) ☐

**Part II** *Circle the correct response.*

## F. Shifting Set

### Recurrent figures

*Fold the Response Booklet and present it to the patient so that only page 4 is showing. Open the Stimulus Booklet so that only Figure RF-1 is showing. Point to Figure RF-1 and ask the patient to copy the figure into the blank space next to the "RF-1" printed in the Response Booklet. After the figure has been copied, turn the Response Booklet over so that only page 5 is showing. Remove Figure RF-1 and ask the patient to draw the figure from memory in the space provided. Proceed in a similar manner with Figures RF-2 and RF-3. A missing element of the figure, an additional element, or an element attached to the wrong point on an adjacent line are considered errors.*

| | Incorrect | Correct |
|---|---|---|
| 31. Copy Figure RF-1 | 0 | 1 |
| 32. Draw Figure RF-1 | 0 | 1 |
| 33. Copy Figure RF-2 | 0 | 1 |
| 34. Draw Figure RF-2 | 0 | 1 |
| 35. Copy Figure RF-3 | 0 | 1 |
| 36. Draw Figure RF-3 | 0 | 1 |

### Reciprocal motor function

*Say* "When I show you two fingers, you show me one. When I show one finger, you show two fingers." *Administer some trials, showing the patient first one finger, then two fingers, then two fingers again, and finally one finger. Then proceed with Item 37. Place a check in the space provided for each correct or incorrect response that is given by the patient. If motor impairment or apraxia interfere with responding, a verbal response may be given.*

| | Correct | Incorrect |
|---|---|---|
| 37. Two fingers | ☐ | ☐ |
| One finger | ☐ | ☐ |
| One finger | ☐ | ☐ |
| Two fingers | ☐ | ☐ |
| One finger | ☐ | ☐ |

| Errors | | |
|---|---|---|
| ≥2 | 1 | None |
| 0 | 1 | 2 |

### Months backwards

| | ≥1 Month Missed | Correct Sequence |
|---|---|---|
| 38. "Please recite the months of the year backwards, starting with December." | 0 | 1 |

*The correct sequence is December, November, October, September, August, July, June, May, April, March, February, January.*

**Shifting Set Raw Score** (9 max.) ☐

## G. Incomplete Pictures

*Fold the Stimulus Booklet so that only Figure IC-1 is showing, and present it to the patient. Administer Item 39, asking the patient to identify the object represented by the incomplete picture. Do the same with Figures IC-2 through IC-4. Repeat the procedure with Figures IC-5 through IC-8 for Item 40 and Figures IC-9 through IC-12 for Item 41. Record all answers given by the patient.*

39. Teapot _____
Anchor _____
Scissors, shears _____
Glasses, spectacles _____

40. Scissors, shears _____
Glasses, spectacles _____
Anchor _____
Teapot _____

*Item 40 is not scored.*

41. Teapot _____
Anchor _____
Scissors, shears _____
Glasses, spectacles _____

| Number of Objects Correctly Identified | | | | |
|---|---|---|---|---|
| 0 | 1 | 2 | 3 | 4 |

**Incomplete Pictures Raw Score** (8 max.) ☐

## H. Similarities

*Record all answers.*

42. "What do plums and cherries have in common?"

| | Incorrect | Correct |
|---|---|---|
| _____ | 0 | 1 |

43. "What do a hammer and a screwdriver have in common?"

| | | |
|---|---|---|
| _____ | 0 | 1 |

44. "What do a judge and a police officer have in common?"

| | | |
|---|---|---|
| _____ | 0 | 1 |

**Similarities Raw Score** (3 max.) ☐

## I. Attention

### Tracking

*Fold the Response Booklet and present it to the patient so that only page 6 is showing. Instruct the patient to connect the numbers of the initial trial in sequence from 1 to 2, 2 to 3, and so on up to the number 6. Once this trial is completed, turn the Response Booklet over so that only page 7 is showing, and ask the patient to proceed in the same manner with Tracking Test I, connecting the numbers 1 to 12 in sequence. Administer the second trial and Tracking Test II on pages 8 and 9 in a similar manner. This time, ask the patient to connect the numbers in a sequence that alternates between the lowest and the highest numbers: 1 to 6, 6 to 2, 2 to 5, and so on for the trial, and 1 to 12, 12 to 2, 2 to 11, and so on for Tracking Test II.*

45. Tracking Test I

| | Errors | | |
|---|---|---|---|
| | ≥2 | 1 | None |
| Connecting numbers in ascending sequence | 0 | 1 | 2 |

46. Tracking Test II

| | Errors | | | |
|---|---|---|---|---|
| | ≥3 | 2 | 1 | None |
| Connecting numbers in alternating ascending and descending sequence | 0 | 1 | 2 | 3 |

### Working Memory Registration

*In preparation for administering Item 50 (Working Memory), ask the patient to repeat the words* "table," "shoe," *and* "window." *Ask him or her to repeat this list two more times, then say* "Please try to remember these words. Later, I will ask you to repeat them again."

### Calculation

| | Incorrect | Correct |
|---|---|---|
| 47. "How much is 20 minus 5?" _____ | 0 | 1 |
| 48. "How much is 23 minus 7?" _____ | 0 | 1 |

49. "Please count backward by threes, starting at 40—*40 minus 3*—then that number minus 3, and so on."

*Stop the patient after four numbers besides 40 are given. The score is the number of the first three values in the sequence 37, 34, 31, 28 that are correctly given.*

| | Correct | | |
|---|---|---|---|
| | None | 1 | ≥2 |
| _____ | 0 | 1 | 2 |

**Attention Raw Score** (9 max.) ☐

## J. Working Memory

50. "Please repeat those three words I asked you to remember."
Recalled: table_____ shoe _____ window _____

| Number of Words Correctly Recalled | | | |
|---|---|---|---|
| 0 | 1 | 2 | 3 |

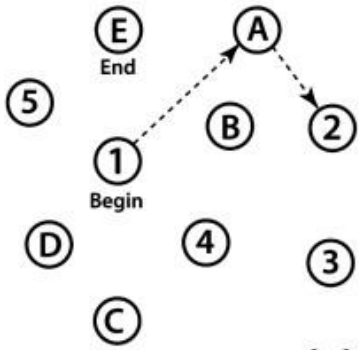
**Working Memory Raw Score** (3 max.) ☐

## Appendix C

**MONTREAL COGNITIVE ASSESSMENT (MOCA)**
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

**VISUOSPATIAL / EXECUTIVE** — POINTS

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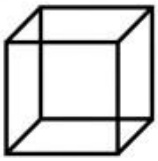


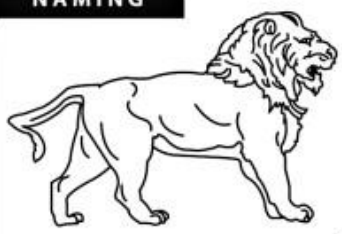
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands

__/5

**NAMING**



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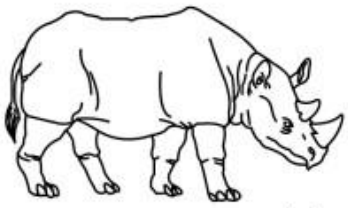

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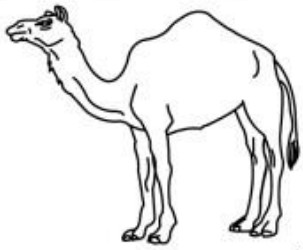

[ ]

__/3

**MEMORY** Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

| | FACE | VELVET | CHURCH | DAISY | RED |
|---|---|---|---|---|---|
| 1st trial | | | | | |
| 2nd trial | | | | | |

No points

**ATTENTION** Read list of digits (1 digit/ sec.).

Subject has to repeat them in the forward order [ ] 2 1 8 5 4

Subject has to repeat them in the backward order [ ] 7 4 2

__/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors

[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B

__/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt**

__/3

**LANGUAGE** Repeat : I only know that John is the one to help today. [ ]

The cat always hid under the couch when dogs were in the room. [ ]

__/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words)

__/1

**ABSTRACTION** Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler

__/2

**DELAYED RECALL**

| | Has to recall words **WITH NO CUE** | FACE [ ] | VELVET [ ] | CHURCH [ ] | DAISY [ ] | RED [ ] | Points for UNCUED recall only |
|---|---|---|---|---|---|---|---|
| **Optional** | Category cue | | | | | | |
| | Multiple choice cue | | | | | | |

__/5

**ORIENTATION** [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City

__/6

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TOTAL __/30

Add 1 point if ≤ 12 yr edu

Administered by: _____

**Appendix D**

Memory-Registration – Give four words to recall (dog, hat, bean, red) – 1 second to say each. Then ask the patient all four words after you have said them. Repeat words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

1. Motor Speed: Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.

    4 = 15 in 5 seconds
    3 = 11-14 in 5 seconds
    2 = 7-10 in 5 seconds
    1 = 3-6 in 5 seconds
    0 = 0-2 in 5 seconds

    ____

2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put hand perpendicular to flat surface on the side of the 5th digit. Demonstrate and have patient perform twice for practice.

    4 = 4 sequences in 10 seconds
    3 = 3 sequences in 10 seconds
    2 = 2 sequences in 10 seconds
    1 = 1 sequence in 10 seconds
    0 = unable to perform

    ____

3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).

    Give 1 point for each word spontaneously recalled.
    Give 0.5 points for each correct answer after prompting
    Maximum – 4 points.

    ____

Total International HIV Dementia Scale Score: This is the sum of the scores on items 1-3. The maximum possible score is 12 points. A patient with a score of ≤ 10 should be evaluated further for possible dementia.

____

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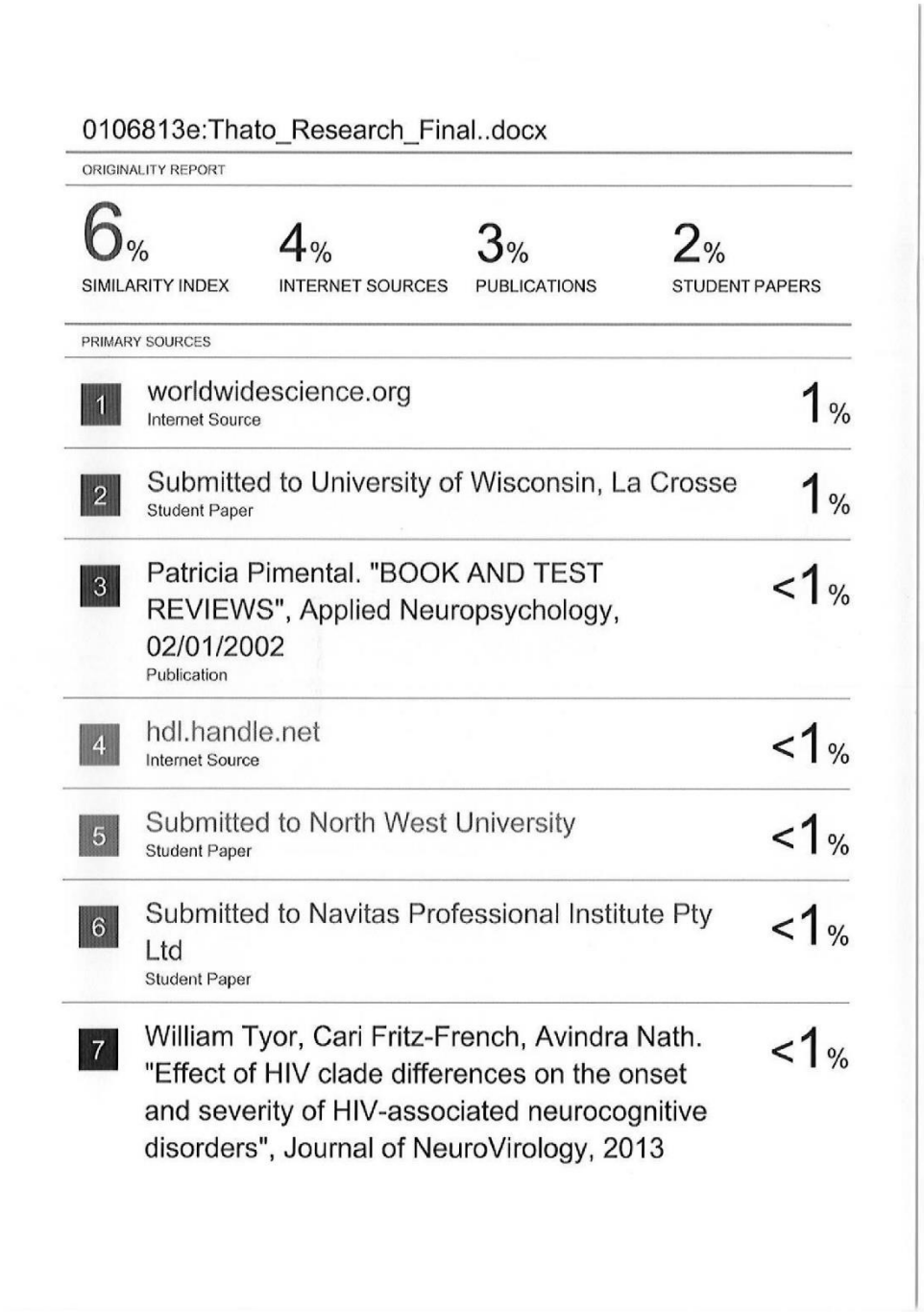
## Appendix E

**Appendix E**



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**Appendix F**

Table 2.1 Data Collection table (BNCE)

BNCE Part 1

| **Categorical data** | Orientation | Presidential Memory | Naming | Comprehension | Constructive Praxis | Total score |
|---|---|---|---|---|---|---|
| **Score** | | | | | | |

Part2

| **Categorical data** | Shifting Set | Incomplete Pictures | Similarities | Attention | Working Memory | Total score |
|---|---|---|---|---|---|---|
| **Score** | | | | | | |

| **Total scores for Part 1 and Part 2** |
|---|
| |

Table 2.2 Data collection table (MoCA)

| **Categorical Data** | Visuospatial/ Executive | Naming | Memory | Attention | Language |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| **Score** | | | | | |
| **Categorical data** | Abstraction | Delayed Recall | Orientation | Total score | |
| **Score** | | | | | |

Table 2.3 Data collection table (IHDS)

| | | | | |
|---|---|---|---|---|
| **Categorical data** | Motor Speed | Psychomotor Speed | Memory Recall | Total score |
| **Score** | | | | |

Table 2.4 Data collection table (Clinical Variables)

| | | | | |
|---|---|---|---|---|
| Age | Gender | Race | Education level | Alcohol/substance intake |
| | | | | |
| Starting CD4 | Duration of treatment | Medical comorbidities | Employment status | |
| | | | | |