Neuropsychological Profiles of Older Adults with Human Immunodeficiency Virus (HIV): A Comparison with Controls

by

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A mini-dissertation submitted in partial fulfillment of the

requirements for the degree

M.A Research Psychology

in the

Department of Psychology at the

UNIVERSITY OF PRETORIA

FACULTY OF HUMANITIES

SUPERVISOR: Prof. N. Cassimjee

October 2014

ACKNOWLEDGEMENTS

I would like to express my deepest appreciation and gratitude to the following people:

- Prof Cassimjee, for providing me with an opportunity to learn and grow under your mentorship. Your continual encouragement, wisdom and commitment to the highest standards have inspired me.
- My colleague and friend Stacey Jedlinski for inspiring my effort despite the work pressures we were facing together.
- The staff at the clinic, particularly Sister De Gama and Sister Borens. Your assistance and warm reception were very much appreciated.
- McMaster University, specifically Patrick Bennet and Allison Sekuler for hosting me in your lab. I was very inspired by the work you do and your contribution to psychology. Thank you to Betty Ann Levy as well for being a great host in Canada.
- Dr Inger Fabris-Rotelli and Jacqui Sommerville at the statistics department for your helpful assistance.
- My wonderful mother, for being a pillar of strength and support. You have always believed in me and this has given me encouragement beyond words. I love you.
- Kearabetswe Motswai for loving me, pushing me and laughing with me throughout this entire journey. I am so blessed that I get to walk the rest of my life journey with you.

My greatest thanks go to my Lord and Saviour Jesus Christ for His strength that has carried me through.

DECLARATION OF ORIGINALITY

I declare that this mini-dissertation, which I hereby submit for the degree MA Research Psychology at the University of Pretoria, is my own work and has not been previously submitted by me for another degree at another university.

FINANCIAL ASSISTANCE

Financial assistance provided by the National Research Foundation (NRF) in respect to the costs of this study is hereby acknowledged. Opinions or conclusions that have been expressed in this study are those of the writer and must not be seen to represent the views, opinions or conclusions of the NRF.

ABSTRACT

There is a greater need to understand the neuropsychological profile of older HIV-infected individuals. Despite the inception of antiretroviral medication, milder forms of neuropsychological impairments appear to exist. Furthermore, the neuropsychological impairments seen in healthy older adults seem to have a similar pattern to those seen in HIV patients. The current exploratory study set out to compare the global and specific neuropsychological profiles of older HIV positive individuals (experimental group) to older HIV negative individuals (control group). The quasi-experimental design was employed to preliminarily assess for possible significant differences in the relevant neurocognitive domains. Participants were recruited by convenience sampling from a primary health care center in a semi-urban community. The neuropsychological battery used included the Dementia Rating Scale-2, Symbol Digit Modalities Test, Stroop Color and Word Test and the Delis-Kaplan Executive Function System. The sample size used for data analysis was 50 (experimental group: n=33; control group: n=17).Mann-Whitney U tests were used to compare the groups, with the aid of the bootstrap resampling technique. Results indicated that the HIV positive group showed significantly poorer performance on measures of executive function, psychomotor processing, memory, visuo-spatial/constructional ability and global neurocognitive function. Future studies on the older HIV positive population should be conducted - with more detailed neuropsychological tests and larger samples. A better understanding of the neuropsychological profile of the older cohort may have possible treatment policy implications which will contribute to better health and quality of life outcomes.

Keywords: HIV, neuropsychological functioning, neurocognitive, aging

TABLE OF CONTENTS

LIST OF TABLES

LIST OF GRAPHS

CHAPTER 1: INTRODUCTION

1.1 Introduction

The following mini-dissertation is an account of research conducted to preliminarily explore the neuropsychological profiles of older individuals with the human immunodeficiency virus (HIV) as compared to a control group. The first chapter presents a background to the research, specifies the problem statement, hypotheses and describes the practical significance of the study. A brief account of the methodology employed as well as an overview of the subsequent chapters is provided.

1.2 Problem Statement

An estimated 5.6 million people were living with HIV and/or Acquired Immunodeficiency Syndrome (AIDS) in South Africa in 2009. This prevalence is one of the highest in the world (UNAIDS, 2011). After revision of data from Demographic Health Surveys (DHS) and extrapolation of data from the Joint United Nations Programme on HIV/AIDS, Negin and Cumming (2010) reported that approximately 3 million people aged 50 and older were said to be living with HIV in sub-Saharan Africa in 2007. This represents 14.3 percent of the approximately 21 million people aged 15 years and older who were infected with HIV during this period. South Africa was amongst one of the five countries with the highest number of older adults living with HIV in sub-Saharan Africa.

It is thus clear that the older HIV population is increasing. HIV was previously associated with severe impairments in neuropsychological functioning largely before the implementation of highly active antiretroviral treatment (HAART) (Woods, Moore, Weber, & Grant, 2009). HAART played a pivotal role in decreasing the more severe neuropsychological manifestations of HIV, such as HIV dementia, which has a dramatic

impact on quality of life and survival (Cystique & Brew , 2009). As a result of HAART, people infected with HIV are now living longer. This is in addition to the increasing rates of infection in the older cohort. However, milder forms of neuropsychological impairments have been shown to persist (McArthur, Steiner, Sacktor, & Nath, 2010). Furthermore, the nature of the relationship between neuropsychological functioning and HIV status remains unclear to a large extent (Wendelken & Valcour, 2012).

Normal aging is generally reflected in an overall decline in neuropsychological functioning (Salthouse, 2004). Advancing age may somehow modify the neuropsychological presentation of HIV; resulting in a potentially greater risk for neuropsychological impairment in HIV positive older individuals. A need for research thus exists to better understand the neuropsychological manifestations of HIV in the older cohort (Hardy & Vance, 2009).

Neuropsychological research in HIV has centred on neurocognitive constructs that have direct relevance to neural systems affected by HIV. Neurocognitive domains that have been reported to be vulnerable to both the effects of HIV and aging were assessed in the current study. These include *attention (*ability for focused behaviour); *psychomotor processing* (ability to process information regarding movement); *executive function* (ability to respond to a novel situation in an adaptive manner) and *memory* (capacity to retain, encode and retrieve information), *visuo-spatial/constructional ability* (ability to detect, understand, manipulate and integrate visual stimuli in the context of its environment) and *processing speed* (the speed of completion of a neurocognitive task with reasonable accuracy) (Foxcroft & Roodt, 2009; Lezak, Howieson, Bigler, & Tranel, 2012; Woods, Moore, Weber, & Grant, 2009). International studies often assess *language* as a neurocognitive domain; however the assessment of language was not the direct focus of the current study. This is because language often results in cultural biases due to the multicultural and multi-lingual context in

South Africa (Singh et al., 2010). This is more so evident with regard to the disadvantaged older population group, who have variable levels of functional literacy because of the historical imbalances of education within South Africa.

1.2.1 Research Question

The primary aim in the study was to preliminarily compare the neuropsychological functioning (global and domain-specific) of older HIV positive (HIV+) adults to older HIV negative (HIV-) adults. The following research question was addressed:

Research question: Are there significant differences in the neuropsychological performance of older HIV+ individuals as compared to older HIV- individuals?

Sub-question 1: Are there significant differences in global neuropsychological performance of older HIV+ individuals as compared to older HIV- individuals?

Sub-question 2: Are there significant differences in domain-specific (attention, executive function etc.) neuropsychological performance of older HIV+ individuals as compared to older HIV- individuals?

1.2.2 Objectives

Specific objectives of the research were:

- To measure the global neuropsychological performance of older HIV+ and HIV- individuals
- To measure domain-specific neuropsychological performance of older HIV+ and HIV- individuals
- To compare the neuropsychological performance (global and domain-specific) of older HIV+ individuals and HIV- individuals.

1.3 Overview of Methodology

The objectives mentioned above were pursued using a quantitative, quasi-experimental research design. The pre-existing older HIV+ group was non-randomly assigned to the experimental group, while the older HIV- group was assigned to the control group. A neuropsychological battery consisting of the Dementia Rating Scale-2 (DRS-2), the Symbol Digits Modalities Test (SDMT), the Stroop Colour and Word Test (Stroop CW) as well as the Delis-Kaplain Executive Function System: Trail Making Test (D-KEFS, TMT) was used to measure the relevant constructs. Convenience sampling was used in order to obtain the HIV+ sample from a primary health care centre in a semi-urban community. The HIV- negative sample was obtained from the same community as well as the primary health care centre. Participants who had any other comorbidity that affected their neuropsychological functioning were excluded from the study. Descriptive and inferential statistical techniques were used to analyse the data.

1.4 Significance of the Study

There is a twofold reason for studying an aging HIV sample. Firstly, neurobiological parallels seem to be evident between HIV infection and aging (Ances et al., 2010). Secondly, research indicates that the presence of latent reservoirs in the brain, which store viral variants and produce persistent low grade viral replication, may be responsible for impairing neurocognition. The aging of the brain enhances the burden for metabolic, neurologic and neuropsychiatric/neuropsychological conditions (Gonzales & Cherner, 2008). Among older adults, neuropsychological impairment may be specifically detrimental for everyday outcomes; for example, older adults with HIV-associated neurocognitive disorders (HANDs) evidence poor medication adherence, financial management (Doyle, Weber, Atkinson, Grant, Woods, & (HNRP), 2012) and even earlier mortality (Wilkie et al., 2003).

Gonzales and Cherner (2008) and Patel and Crane (2011) reported that their recent observations with regard to aging with HIV have significant bearing on modification of long term management of HIV infected individuals and mental health policies. They go on to suggest that further generation and revision of data would enable more effective treatment of older HIV+ individuals who present with unique health needs.

Clade C (subtype C) of HIV is the least studied of the various clades, yet it is the most prevalent in sub-Saharan Africa, where the majority of HIV+ individuals reside (Otiti-Sengeri et al., 2010). Knowledge of HANDs in general is limited in developing countries (McArthur, Steiner, Sacktor, & Nath, 2010). Research about neuropsychological functioning in the older cohort with HIV in developing countries would thus aid in expanding existing knowledge.

1.5 Chapter Overview

The research study is presented in five chapters. Chapter 2 presents a review of literature regarding neuropsychological function in HIV and aging. Chapter 3 discusses the research methodology employed with specific reference to sampling methods, measurement instruments and data analysis techniques. Chapter 4 presents the findings of the study with regards to the sample composition as well as the statistical techniques. Chapter 5 reviews the main findings in the context of current literature, the limitations of the study, relevant recommendations for future research and a conclusion.

CHAPTER 2: THEORY AND LITERATURE REVIEW

2.1 Introduction

Increasing numbers of older people with HIV are under treatment and care. This is both due to the availability of effective highly antiretroviral therapy (HAART) or combination antiretroviral therapy (cART), as well as increasing numbers of new transmissions and diagnoses in older individuals. In the past, mortality due to AIDS-related infections was predominant; but has decreased dramatically in patients receiving treatment (Fisher & Cooper, 2012). HIV dementia has also been dramatically reduced since the initiation of HAART; however data from recent studies suggests that mild neuropsychological impairment still occurs in a significant proportion of people with treated HIV (Heaton, et al., 2010; Simioni et al., 2010) and is more widespread among people who are HIV+ than people who are HIV- (Heaton et al., 2011). Neuropsychological conditions in HIV patients that are related to old age in the general population have led to the supposition that normal neurocognitive aging may be accelerated in HIV patients (Fisher & Cooper, 2012).

Chapter 2 aims to provide a review of literature pertaining to older individuals that are infected by HIV. The theoretical framework of cognitive reserve will serve as a basis of understanding neuropsychological domains that are affected by both aging and HIV. Different variations of the virus will be taken into account as well as comorbid factors that occur.

2.2 Healthy Neurocognitive Aging

As the adult population of HIV+ individuals continues to grow older, researchers and clinicians are developing a greater interest in the unique health care needs of older adults with HIV. It is well established that neuropsychological function is one factor of general health and well-being that is compromised in older HIV-infected individuals. However, it is also

well-established that in healthy older adults without HIV or other acute neurological conditions, decline across spectrums of neurocognitive domains occur (Welsh-Bohmer, et al., 2009; Zimmerman & Brickman, 2009). It is therefore both a challenge and of scientific importance to systematically explore and understand the neurocognitive profile of those that are both aging and have HIV. To assist in the understanding of this complex relationship, neurocognitive changes that accompany healthy aging have to be characterised (Zimmerman & Brickman, 2009).

As people age, they change in countless ways, both on a biological and psychological level. Some of the changes encountered may be for the better, but others not (Glisky, 2007). The word "cognitive" comes from the Latin *cognoscere*; which means "to know". Neurocognitive processes are thus a fundamental aspect of the human experience, which assist in mediating individuals' understanding of both themselves and their relation to the broader environmental and social context. Deterioration of neurocognitive abilities may thus have detrimental effects on the psychological well-being of affected individuals and their caregivers (Zimmerman & Brickman, 2009). There is ample evidence that alterations in brain structure and function are intimately tied with alterations in neurocognitive function. The intricacy of both neural and neurocognitive functions, however, makes exact mapping between brain and behaviour difficult, and so these relations remain largely speculative, although ultimately testable. Although the relationship between brain and neurocognition is a dynamic one and thus may change throughout the lifespan, changes in these two domains are ultimately related (Glisky, 2007).

Aging can in no way be considered a causal factor of neuropsychological impairment, but it is rather viewed as a dimension along which factors that cause neuropsychological impairment operate. Fluid or processed-based neuropsychological abilities have been

observed to decline with age, both in cross-sectional and longitudinal studies. These include speed of processing, reasoning, attention, memory encoding and retrieval and are of use in the completion of most basic tasks (Birren & Schaie, 2006). Neuropsychological function is one factor amongst several contributing to successful functioning in most activities. Other factors such as motivation, persistence and various personality characteristics are also important. These may either be unrelated to age or may follow different age trajectories than measures of neuropsychological functioning (Fisher & Cooper, 2012).

It is important to note that just as age-related changes in brain structure and function are not uniform across individuals or the whole brain, age-related changes in neurocognition are not uniform across all neurocognitive domains or across all older individuals. The following section will outline the major neurocognitive domains affected by aging (Glisky, 2007).

2.3 Neurocognitive Domains and Neuropsychological Tests

The term *attention* broadly refers to complex, multifaceted cognitive processes that orientate the individual toward a stimulus (Zimmerman & Brickman, 2009). Attention involves several different processes that are related aspects of how an individual becomes receptive to stimuli and how that individual may process the incoming or attended-to excitation (whether internal or external) (Lezak, Howieson, Bigler, & Tranel, 2012). Some form of attention is involved in virtually all neurocognitive domains, except when task performance has become automatic or habitual. Assessment of various forms of attention is thus an important aspect of neuropsychological evaluation. This is because attentional processes frequently support performance on many other tests of neurocognitive function, such as memory and executive function. Deficits in attention therefore usually have broad effects in one's ability to function effectively in everyday life (Glisky, 2007).

Defining attention is a difficult task to do, as there are many aspects that relate to it, however, several characteristics have been identified that are salient with the concept of attention (Lezak, Howieson, Bigler, & Tranel, 2012). Although not exhaustive, the primary components of attention that will be briefly explained are selective attention, sustained attention and divided attention. Selective attention refers to the ability to attend to some stimuli while ignoring other stimuli that are irrelevant to the task at hand. Selective attention can be assessed by tasks such as the Stroop test, where participants are asked to name the colour of an ink in which an incongruent colour word is printed (i.e. word "yellow" is printed in blue). The name of the different colour tends to create interference. This causes errors and an increase in response times because to perform well in these kinds of tasks, people have to select the relevant stimulus or dimensions for processing and ignore the irrelevant ones (Glisky, 2007).

Findings with regard to selective attention are not entirely consistent across studies and may differ across tasks. In general, older adults appear to be slower than younger adults in responding to the targets in tasks that test selective attention. Older adults may not be differentially affected by distraction. Glisky (2007) hypothesizes that the deficits found in many of these tasks can be largely attributed to a general slowing of information processing in older adults rather than selective attention deficits per se. However, there continues to be an ongoing debate about whether age-related behavioural increase in interference on a selective attention task is due to declining neurocognitive control or general slowing (Samanez-Larkin, Robertson, Mikels, Carstensen, & Gotlib, 2009).

Memory refers to the ability to explicitly or implicitly recall information that has been encoded in the recent or distant past (Zimmerman & Brickman, 2009). The capacity for memory and learning and the intentional access to this store is central to all neurocognitive

functions. Severely impaired memory isolates an individual from emotionally or practically meaningful contact with the world about them. Furthermore, it deprives the individual of a sense of personal continuity, rendering them passive and helplessly dependent. Mildly to moderately impaired memory also has a disorientating effect (Lezak, Howieson, Bigler, & Tranel, 2012).

Older individuals have been found to be particularly vulnerable to memory slips and errors that can have serious consequences (i.e. taking the same medicine twice). There are possible links between memory impairments and these are associated with aging and neuropsychological deficits in frontal lobe functioning. There is also an age-related pattern of memory errors that is characteristic of old age, which resembles the pattern found in patients suffering frontal lobe lesions. Pansky, Goldsmith, Koriat and Pearlman-Avnion (2009) found an age-related decline in the amount of retrieved information in older adults as compared to younger adults, with regard to memory quantity. This refers to the amount of information that can be recalled or recognised after a retention interval.

Executive function is a multifaceted neuropsychological construct consisting of a set of higher-order neurocognitive processes that allow higher organisms to make choices and to engage in purposeful, goal-directed and future-orientated behaviour (Suchy, 2009). Executive function is generally assumed to include monitoring and control of one's own behaviour in terms of the ability to suppress irrelevant information, the ability to shift between mental sets or tasks and to control attention. Executive function thus includes higher cognitive processes such as reasoning and planning. Some of the age-related impairments in memory functioning appear to be linked to executive functioning (Pansky, Goldsmith, Koriat, & Pearlman-Avnion, 2009).

Lezak, Howieson, Bigler and Tranel (2012) claim that so long as executive functions are intact; a person can sustain considerable neurocognitive loss and still continue to be independent, constructively self-serving and productive. When executive functions are impaired, the person may no longer be capable of satisfactory self-care, performing useful work independently or even maintaining normal social relationships, regardless of how well-preserved the neurocognitive capacities are. In other words, impairments in executive functions will tend to show up globally, thus affecting all aspects of behaviour. This is reported in a study by Johnson, Lui and Yaffe (2007), which examined 7717 elderly women over a 6 year period, and reported that those with executive function impairment had significantly worse activities of daily living as well as an increased risk of mortality.

Executive function depends critically on the prefrontal cortex, which exerts its broad-reaching controlling influence via extensive reciprocal connections with posterior cortical regions. An economical explanation of neurocognitive aging ascribes a causal role to executive control deficits - what has been called the frontal lobe hypothesis of aging. In support of this hypothesis, both structural and functional neuro-imaging studies have revealed a preferential decline in older adults in the volume and function of prefrontal brain regions (Glisky, 2007).

Psychomotor processing or function can be described as the ability to process information regarding movement (Lezak, Howieson, Bigler, & Tranel, 2012). Aging is associated with selective losses in function related to psychomotor function (Welsh-Bohmer et al., 2009). Closely related to psychomotor processing is *psychomotor speed*; which can be defined as the amount of time it takes an individual to process a signal, prepare a response and execute that response (Lezak, Howieson, Bigler, & Tranel, 2012). A 10 year follow-up community study

found that psychomotor speed was a domain that deteriorated the earliest in their non-demented elderly sample (Dodge, Du, Saxton, & Ganguli, 2006).

Visuo-spatial/Constructional Abilities can be defined as the ability to detect, understand, manipulate and integrate visual stimuli in the context of its environment (Woods, Moore, Weber, & Grant, 2009). A distinction can be made between spatial information and object information in terms of the "where" and "what" systems. The visual system comprises of two different streams. The dorsal stream processes spatial or "where" information for object localisation, whereas the ventral stream processes visual or "what" features (such as shape, colour, luminance) for object recognition. All kinds of processes and information useful to locate positions and directions in the environment can be defined spatial/constructional. To encode the position of an object, a second object is required for reference (Iachini, Iavarone, Senese, Ruotolo, & Ruggiero, 2009).

Processing speed can be defined as the speed of completion of a given neurocognitive task (attention, executive function task etc.) with reasonable accuracy. Processing speed is regarded as a leading indicator of age changes in memory and spatial ability by Finkel, Reynolds, McArdle and Perderson, (2007). It is well established in literature that processing speed declines with advancing age (Birren & Schaie, 2006; Salthouse, 2004).

Although these neurocognitive functions have been reviewed separately above, it is abundantly clear that they overlap and interact in interesting and complex ways. For example, neurocognitive abilities such as memory and visuospatial ability are presumed to be dependent on whether central capabilities such as attention and executive function are intact (Martin, Thomson, Blizzard, Wood, Garry, & Srikanth, 2009).

Another neurocognitive domain affected by age is *Language* (Welsh-Bohmer et al., 2009). International studies often assess *language* as a neurocognitive domain; however the assessment of language results in cultural biases due to the multicultural and multi-lingual context in South Africa. This is particularly more so evident with regard to the older population, which is prone to illiteracy, due to the historical imbalances of education within South Africa (Singh et al., 2010). This domain will therefore not be explicitly covered within the scope of this preliminary study.

2.4 Cognitive Reserve: A Framework of Neurocognitive Aging

Aging can be viewed as a condition of decreasing cognitive reserve (Cherner et al., 2004). The cognitive reserve model suggests that the brain actively attempts to cope with brain damage by using pre-existing cognitive process or by enlisting compensatory processes (Stern, 2009).In other words, cognitive reserve refers to the ability to optimise or maximise performance through differential recruitment of brain networks, which perhaps reflects the use of different cognitive strategies. Individuals with high cognitive reserve would thus be more successful at coping with the same amount of brain damage than those with low cognitive reserve. This makes brain function, as opposed to brain size (or structure), the relevant variable. This implies that same amount of brain pathology or damage will have different effects on different people, even when brain size or structure is held constant (Cosentino & Stern, 2013).

Despite the popularity of the concept of cognitive reserve, there are many aspects of this construct that have yet to be fully elaborated. Some of these issues relate to the fact that the manner in which cognitive reserve affords protection from pathology is not fully understood. It is known that in some individuals, there is a discrepancy between brain changes or pathology and cognitive change such that in some individuals, cognitive function remains

relatively preserved in the face of pathological markers. Therefore, individuals with high cognitive reserve are not necessarily protected from developing pathology, but rather they are spared the clinical effects of such pathology. Thus, when we refer to a preservation of a cognitive function such as memory, we refer to memory itself and not the integrity of the brain areas underlying that cognitive function. A complete model of cognitive reserve would have to integrate the complex interactions between genetics, the environmental influences on brain reserve and pathology and the ability to actively compensate for the effects of pathology (Cosentino & Stern, 2013; Stern, 2009).

Neuropsychological theories of aging are very limited because most research relating to brain behaviour has been addressed to pathological conditions such as Alzheimer's or Parkinson's disease (Sanchez Rodriguez & Rodriguez Alvarez, 2003). The cognitive reserve model however, provides a reasonable supposition that aging in the context of HIV/AIDS may confer increased vulnerability to brain dysfunction (Cherner et al., 2004). This is because a high level of variability is exhibited in HIV associated neurocognitive compromise with regard to factors such as speed of progression, severity of decline and areas of primary focus. While several factors appear to play a role in central nervous system (CNS) deterioration (i.e. CD4 cell count, viral load etc.), none have been found to fully explain the large degree of variability in ultimate neurocognitive presentation. With such factors held constant across individuals, a subset of HIV infected individuals go on to exhibit a variety of neurocognitive syndromes, while others do not. Such variability suggests multi-dimensional factors that mediate the effects of HIV and neurocognitive aging (van Gorp & Root, 2008).

2.5 HIV Infection and Alterations in Neurocognition

Acquired immune deficiency syndrome (AIDS) was first identified in 1981. Throughout the 1980s and mid-1990s, newly diagnosed AIDS cases increased worldwide, peaking in the

United States in 1993 and then exhibiting a slow decline to the present. At the core of HIV infection is the suppression of human immune response through the reduction of cell-mediated immunity, leading to an increased susceptibility to infectious disease and illness. The mechanism of HIV-related immunosuppression lies in the large-scale suppression of CD4+ helper T cells, which serve to coordinate and control the immune response. This leaves the individuals infected with HIV vulnerable to disease and illness, unchecked by the human immune response (van Gorp & Root, 2008; Kojic & Carpenter, 2009).

Opportunistic infections are the most common manifestation of immunosuppression. In addition, CNS damage has also been shown to result from AIDS and HIV infection, with an often progressive course of CNS deterioration having been identified with disease progression. HIV penetrates the blood brain barrier and infiltrates the CNS in the earliest stages of infection. At autopsy, 76 percent of HIV-infected individuals have been found to exhibit significant CNS pathology related to both primary HIV infection and secondary opportunistic infections. (van Gorp & Root, 2008; Kojic & Carpenter, 2009). When examined on post mortem, atrophy and/or abnormalities were found in various brain regions and structures, including the basal ganglia, hippocampus and corpus callosum within the brains of HIV+ individuals. Furthermore, there are inflammatory changes; excessive accumulation of astrocytes, known as astrocytosis or gliosis; demyelination, loss of the protective insulation surrounding neuron axons; and build-up of amyloid precursor proteins. MRI scans of HIV positive individuals have also indicated that neurocognitive impairment was associated with atrophy of grey matter and abnormal white matter (The Body: The Complete HIV/AIDS Resource, 2009).

Neurocognitive deterioration has been recognized in individuals infected with HIV since the year in which AIDS was recognized as a clinical entity. In these early years of the AIDS

epidemic, patients with neurocognitive impairment were often severely demented and this was viewed as an indication of impending mortality. Although initial studies of the severe neurocognitive deterioration described the clinical onset of symptoms as dangerous in most cases, many dementia cases had abrupt accelerations sparked by opportunistic infections, thus obscuring conclusions regarding a possible direct relationship between HIV and neurocognitive deficits (Woods, Moore, Weber, & Grant, 2009). Severe neurocognitive deterioration now seldom develops in persons who begin HAART prior to developing moderately severe immunodeficiency. Severe neurocognitive deterioration has thus rarely been recognized in patients in whom the CD4 count has never fallen below 200 cells/mm^3 (Kojic & Carpenter, 2009).

2.6 HIV-Associated Neurocognitive Disorders

The diagnosis of a particular neurocognitive disorder due to HIV must be determined by assessing at least five areas of neurocognitive functioning known to be affected by HIV. For example, executive function, episodic memory, speed of information processing, motor skills, attention/working memory, language and sensoriperception (McArthur, Steiner, Sacktor, & Nath, 2010). The revised criteria allows for three possible research diagnoses, namely HIV associated dementia (HAD), mild neurocognitive disorder (MND) and Asymptomatic neurocogntive impairment (ANI). For a more in-depth explanation of the diagnostic nomenclature refer to Antinori et al. (2007).

HAD (formerly referred to as the AIDS dementia complex) is characterised by marked impairment in neurocognitive functioning in at least two neurocognitive domains, but typically in multiple domains. The neurocognitive impairment produces marked interference in day-to-day functioning. This includes activities at work, home, social activities and the like (Grant, 2008). In individuals on HAART, the prevalence of HAD is low, ranging between 2

to 8 percent as reported by McArthur, Steiner, Sacktor and Nath (2010). Sacktor, Nakasujja, Robertson and Clifford (2007) reported that HAD occurs in 10-15 percent of HIV+ individuals in advanced infection. This illustrates that HAD is more common in the late stages of infection. This disorder has a dramatic impact on quality of life and survival (Singh et al., 2010).

MND is less severe and is characterised by impaired neuropsychological function in at least two domains or areas of neurocognitive functioning. These abnormalities typically result in mild impairments at work or in activities of daily living. According to McArthur, Steiner, Sacktor and Nath (2010), MND can be identified in 20 to 30 percent of HIV positive adults. Implications for this disorder are significant and associated with shortened survival, reduced adherence to antiretroviral medication and worse employability. The presence of MND is predictive of HIV encephalitis (Joska et al., 2012; McArthur, Steiner, Sacktor, & Nath, 2010).

ANI is characterised by measurable neuropsychological impairment in at least two ability domains (Grant, 2008) that is unrecognisable by the individual, or fails to impact neuropsychological functioning (Joska et al., 2012). According to McArthur, Steiner, Sacktor and Nath (2010), ANI occurs in about 30 percent of HIV infected individuals and in some sense can be considered a presymptomatic form of HANDs, comparable to the presymptomatic phases of Alzheimer disease. The neurocognitive impairment occuring should not interfere with everyday functioning (Grant, 2008).

It is important to note that for all these neurocognitive disorders, neurocognitive impairment should not be associated with delirium or other co-morbid conditions (Liner, Ro, & Robertson, 2010).

The temporal progression of HANDs has apparently been altered by HAART, with most patients now having a static form of neurocognitive impairment, rather than rapidly progressive dementia. In addition, the presentation of the disease appears to have switched from a sub-cortical disorder, predominantly affecting memory and speed of cognitive processing, to one that may have a mixed pattern of involvement with both sub-cortical and cortical involvement. Without treatment, HANDs commonly progress slowly over few months and are rarely acute in their presentation. Typically, there is a combination of cognitive, behavioural and motor dysfunction - but the initial symptoms may be absent (ANI) or subtle (MND) and are often overlooked unless specific screening is conducted. In the early stages, short term memory loss, mental slowing, reading and comprehension difficulties, and apathy are common complaints. Gait disturbance, with stumbling and tripping is common. Tremor and impairment of fine manual dexterity develops in most patients (McArthur, Steiner, Sacktor, & Nath, 2010; Singh et al., 2010).

HANDs are of public health concern as they remain prevalent in society today (Singh, et al., 2010; Woods, Moore, Weber, & Grant, 2009). Neuropsychological testing has traditionally been used to measure the progression of HANDs in the western context; however HANDs occurs globally (McArthur, Steiner, Sacktor, & Nath, 2010). Ideally, these domains would be assessed using a performance-based neurocognitive battery and interpreted using demongraphically-appropriate normative data, although the criteria also allows the use of mental status exams (i.e. HIV Dementia Scale) in resource limited settings (Woods, Moore, Weber, & Grant, 2009).

It is not possible to accurately and confidently classify neuropsychological impairments resulting from HIV into a diagnosis of HANDs (i.e. ANI, MND etc.), more so within the South African context (Singh et al., 2010). As a diagnosis of HAND often rests on

determining the presence or absence of declines in everyday functioning, it is important to consider many intricacies and complications in assessing functional impairments. A review by Woods, Moore, Weber and Grant (2009) explains that there are no worldwide agreed-upon clinical measures of everyday functioning. Performance-based assessments of everyday functioning are sometimes used in research settings, but the shortage of normative data of HIV seronegative individuals, coupled with lengthy administration protocols make it unlikely that the current available measures will be widely used in the clinical setting. In the South African context, this problem is worsened by the limited norms for this specific population from which comparisons can be drawn and diagnoses made (Singh et al., 2010). It can thus be more practical to focus on the level of neuropsychological functioning in individuals with HIV, against comparative control groups to preliminary assesses neuropsychological performance.

2.7 Variations of HIV and Neurocognitive Performance

Within different regions of the world, different clades or subtypes of HIV predominate. In the western context (i.e. North America, Europe and Australia), clade B of the disease is most prevalent. Clade C is predominant in India and much of Asia. Clades A, C and D are the predominant subtypes in East Africa (Boivin et al., 2010), whereas in sub-Saharan Africa - where two-thirds of HIV infected individuals reside (Otiti-Sengeri, Colebunders, Kempen, Ronald, Merlen, & Katabira, 2010) - clade C is most prevalent. Although the prevalence of HANDs is well established in some regions, there is less evidence on the prevalence and risk factors in areas where clade C HIV predominates, such as South Africa (Joska et al., 2011).

Sacktor et al. (2009) provided some of the first evidence that HIV clades may differ in terms of neurocognitive pathogenesis by examinining the relationship between HIV clades and the severity of HIV-associated neurocogntive impairment among HIV-infected adults initiating

antiretroviral therapy in a single clinic in Uganda. They concluded that HIV dementia may be more common in adults with clade D than than those with clade A. Boivin et al. (2010) compared the neurocognitive impact between clade A and D and it came to light that individuals with clade A demonstrated poorer neurocognitve performance than individuals with clade D. They went on to suggest that clade-specific neurocognitive deficits may reflect age-related differences in the neuropathogenesis of HIV. However, the study only investigated Ugandan children (6-12 years) who were HAART-naïve. One can therefore speculate that different clades possibly result in different neuropsychological manifestations of HIV (Joska et al., 2012), thus making the study of clade C important to diversify existing literature.

2.8 HIV-Associated Neurocognitive Disorders in Africa

It cannot be assumed that HIV+ patients in Africa exhibit the same declines as patients in high-resource settings. This is because in addition to different clades of the virus, there are differences that may influence neurocognitive functioning, such as nutrition, history of parallel diseases and varying HIV strains among other possibilities (Robertson et al., 2007). Limited studies have examined the neurocognitive functioning of HIV patients in sub-Saharan Africa.

Wong et al. (2007) set out to measure the frequency and associated risk factors of HIV dementia in an HIV clinic in Uganda. From a sample of 78 HIV positive individuals, 31 percent of these individuals had HIV dementia - leading the authors to conclude that HIV-dementia is common in HIV+ Ugandan individuals that attended the AIDS clinic. Advanced age and low CD4 count were the only variables identified as significant risk factors and thus more associated with HIV dementia (Wong, et al., 2007). This is consistent with studies by Cohen et al. (2010) (mean age = 48.6 years, SD = 7.5) and Jernigan et al. (2011) (mean age =

44.1 years, SD 7.9 years); which have reported that lower CD4 count is associated with structural brain tissue damage, brain volume loss and lower volumes of cerebral white matter and subcortical grey matter. Robertson et al. (2007) compared the neuropsychological test scores of 110 HIV+ patients (mean age = 36.72 years; SD = 8.71) to 100 control participants (mean age = 27.48; SD = 9.14) in Uganda and found significant group differences on measures of attention, verbal learning and memory, speed of processing, attention and executive functioning between HIV+ and HIV- participants.

In a Botswana study by Lawler et al. (2010) (n = 120; mean age = 37.5 years; SD = 6.5), 38 percent of individuals met the criteria for dementia on the International HIV Dementia Scale, despite the fact that 97.5 percent of the participants were receiving HAART for an average of two years and were asymptomatic from the perspective of subjective complaints and everyday activities. A subsequent study by Lawler et al. (2011) with similar results found that 37 percent of HIV+ patients met criteria for neurocognitive impairment following a comprehensive neuropsychological test battery and structured psychiatric interview. From a sample of 60 HIV+ individuals on HAART medication (mean age = 37.5; SD = 6.2) and 80 demographically matched HIV- control paticipants (mean age = 35.8 years; SD = 6.7), the authors concluded that neurocognitive impairment is an important feature of HIV infection in resource-limited countries after finding that HIV+ individuals were impaired for all neurocognitive-motor ability areas compared to matched, uninfected control subjects. The small sample size in the study was the main limitation.

In a South African study (n = 536, mean age = 33.98 years, SD = 7.92), HANDs were present in 23.5 percent of the sample and was associated with older age, a low educational level among those with post-traumatic stress disorder (PTSD) and alcohol abuse. Limitations for this study was that detailed neuropsychological assessement was not performed and therefore

formal diagnoses of various types of neurocognitive disorders could not be made. This restricted the authors' ability to comment on the effect of reported variables on milder forms of the neurocogntive disorder (Joska, Fincham, Stein, Paul, & Seedat, 2010).

2.9 Aging with HIV

2.9.1 Prevalence of HIV in the Elderly

The aging factor within HIV has long been one that has transformed throughout the years. In an analysis of cases between 1991 and 1995, older persons with HIV were more likely to present with encephalopathy and wasting syndrome and were more likely to die within one month of presentation (Kalayjian & Al-Harthi, 2009). Due to marked improvements in survival as a result of HAART, persons older than 50 years represent a rapidly growing segment of the prevalent HIV-infected population. While the number of HIV cases in general has levelled off, the proportion of HIV diagnoses in adults 50 years and older is steadily increasing (Hardy & Vance, 2009). Individuals who are 50 years and older have represented approximately 12% of the newly diagnosed AIDS cases in the USA since 2005 (Wendelken & Valcour, 2012). It is estimated that by the year 2015, about 50 percent of people living with HIV/AIDS in the USA will be over the age of 50 (Justice, 2010; Patel & Crane, 2011).

After revision of data from Demographic Health Surveys (DHS) and extrapolation of data from the Joint United Nations Programme on HIV/AIDS, Negin and Cumming (2010) reported that approximately 3 million people aged 50 and older were said to be living with HIV in sub-Saharan Africa in 2007. This represents 14.3 percent of the approximately 21 million people aged 15 years and older who were infected with HIV during this period. South Africa was amongst one of the five countries with the highest number of older adults living with HIV in sub-Saharan Africa.

Wendelken and Valcour (2012) report that since the initiation of HAART, the population has shifted from a predominantly young demographic (91 percent below age 45 years in 1996), to an older, aging population with approximately one half of HIV+ individuals currently over 45 years of age. A person diagnosed HIV+ and aged 20 years in developed countries can be alive and well into their sixties. This is because these settings are well-equipped to deal with an aging HIV+ population and with the availability of specialised care (Justice, 2010). HIV has thus evolved from a sub-acute and ultimately terminal disease to one characterized by long-term chronic illness.

According to Justice (2010), in an area where antiretroviral treatment is accessible, a 35 year old HIV infected individual initiating HAART at a CD4 count below 100 cells/ mm^3 is expected to live up to 62 years of age. Furthermore, if that same individual starts HAART at a CD4 count above 200, he/she is expected to live an additional 10 years. In developing countries, such as South Africa, the WHO (World Health Organisation) guidelines recommend initiation of therapy at a CD4 count threshold of 200 cells/mm^3 (Kojic & Carpenter, 2009). A review by Justice (2010) suggests that life expectancy would be even longer were an individual to start HAART at a CD4 count above 350 or even 500 cells/mm^3. Timely antiretroviral treatment therefore has a profound effect on longevity and aging with HIV.

2.9.2 Conceptualizing "Aging" in HIV

Most developed countries have accepted the chronological age of 65 years as a definition of 'elderly' or an older person (Orimo, Ito, Suzuki, Araki, Hosoi, & Sawabe, 2006); however due to the nature and complex rapid historical progression of HIV, it is not surprising that older adults tend to be conceptualized as slightly younger in HIV studies than the usual definition of an "elderly" adult. This results in a more youthful cohort than that which is

typically studied in geropsychology (Doyle, Weber, Atkinson, Grant, Woods, & (HNRP), 2012). The age cut-off of 50, although arbitrary, is widely used due to its prognostic validity in identifying a subset of people who experience a greater rate of HIV disease progression and who are more likely to experience neurocognitive impairment (Kalayjian & Al-Harthi, 2009).

Negin and Cumming (2010) suggested that indicators of the prevalence of HIV infection should be expanded to included people 49 years of age and older to better reflect the aging of the HIV positive population. Becker, Lopez, Dew and Azeinstein (2004) and Cherner et al. (2004) employed the standard way of defining older adults within the context of their study as those that are 50 and older; while the CASCADE Collaboration group defined older HIV patients as those that are 45 years or older during the time of infection or seroconversion (Patel & Crane, 2011). Kissel, Pukay-Martin and Bornstein (2005) also defined 45 years and above as ‘older’.

2.9.3 Chronicity and Aging in HIV

The duration of HIV (chronicity) in an individual is a confounding factor that is somewhat related to age. Chronicity is of great importance when attempting to clarify the neuropsychological effects of aging in the context of HIV. HIV+ individuals can be classified as either chronic or acute (Ances et al., 2009). Chronic HIV individuals are those who have experienced seroconversion more than a year ago and acute refers to those who have experienced seroconversion less than a year ago. This categorisation is based on the widely used classification system by Fiebig et al. (2003). Wendelken and Valcour (2012) report that older adults tend to have a longer overall duration of infection and possibly a longer duration of exposure to HAART. Similarly, individuals who become infected at older ages may have

unique neuropsychological risk factors in part due to delayed diagnosis, and thus may have been living with HIV for a longer period.

2.9.4 Co-morbidities in HIV and Neurocognition: Implications for Aging

People with HIV infection are frequently faced with coexisting conditions that complicate the course of their illness (Gonzales & Cherner, 2008). These conditions often serve as possible contributors to neuropsychological impairment other than HIV and aging as they also affect brain functioning (Joska, Fincham, Stein, Paul, & Seedat, 2010). These include substance abuse, neurological conditions affecting the brain (i.e. stokes, seizure disorders or traumatic brain injury) or severe psychiatric conditions and hepatitis C (Gonzales & Cherner, 2008; Joska et al., 2012). Substance abuse usually affects neurocognitive functioning through common neural pathways that include basal ganglia and prefrontal cortex structures thought to be preferentially affected by HIV. In addition, different drug classes may have unique effects on neuropsychological functioning based on the neurotransmitter systems they most affect (Gonzales & Cherner, 2008).

Individuals who are singly infected with hepatitis C exhibit deficits in neuropsychological functioning similar to those observed among HIV+ individuals. The Center for Disease Control (CDC) reports that approximately 25-30 percent of HIV infected individuals in the United States are also infected with hepatitis C. Rates reported from the EuroSIDA study encompassing several European countries are similar. There is therefore a possibility of interaction of both HIV and hepatitis C in the presentation of neuropsychological functioning (Gonzales & Cherner, 2008). The prevalence of hepatitis C in the South African population is however considerably low. Joska et al. (2010) report that in one community HIV study of over 500 patients, none of the individuals tested positive for hepatitis C.

2.9.5 Antiretroviral Therapy and the Aging Hypothesis in HIV

Untreated HIV has been associated with changes in the immune system that are similar to those observed in the elderly. The extent to which antiretroviral treatment reverses these changes is not yet known (Fisher & Cooper, 2012). This may be because penetration of antiretroviral medication into the CNS is limited by the blood brain barrier and blood cerebrospinal fluid barriers - and this may lead to ineffective treatment of virus in the CNS (Liner, Ro, & Robertson, 2010). Despite the success of HAART, research indicates the presence of latent reservoirs in the brain, which store viral variants and produce persistent, low grade viral replication that may be responsible for impairing neurocognition (Gonzales & Cherner, 2008; Liner, Ro, & Robertson, 2010). Both HIV and aging have been associated with elevated markers of inflammation and coagulation. These markers remain elevated in patients on HAART and have been related to mortality in patients with HIV (Fisher & Cooper, 2012).

Conversely, individual drugs could also contribute to premature neuropsychological deterioration or aging. Thymidine analogues have been associated with mitochondrial dysfunction and telomere shortening (Fisher & Cooper, 2012). A randomized, double blind controlled trial by Gutierrez-Valentia et al. (2009) reports that Efavirenz (an antiretroviral drug) is associated with hangover-like symptoms, impaired concentration and hallucinations - suggesting that antiretroviral treatment may play a role in affecting neuropsychiatric stability.

The course of neuropsychological impairment in HIV is reported to be equivocal. This is evident in studies that found a significant proportion of individuals who with age or prolonged antiretroviral treatment, show neuropsychological improvement (Ernst et al., 2009; Woods, Moore, Weber, & Grant, 2009). On the contrary a review by Patel and Crane (2011) report that HAART may be associated with poorer neuropsychological function over time.

There are several confounding factors that hinder a clear interpretation of the role of antiretroviral medication. Several of these are related to the behaviour of the HIV patient. For example, neuropsychological impairment has been linked to decreased HIV medication adherence, independent of age (Justice, 2010). Kalayjian and Al-Harthi (2009) report that adherence to antiretroviral medications appears to be at least as good, if not better in older patients as compared with their younger counterparts. It is thus rather difficult to accurately determine to what extent aging may be contributing to impairment in neuropsychological functioning in HIV (Justice, 2010).

Other confounding factors include differences in baseline neurocognitive impairment in studies. These differences may also affect outcomes as subjects with greater baseline deficits tend to respond to antiretroviral treatment with more improvement (Liner II, Ro, & Robertson, 2010). Practice effects in longitudinal studies may play a role, as individuals may show improvement in neuropsychological testing, but this being a reflection of their increasing competency in the tests as opposed to a reflection of their neuropsychological health (Gravetter & Forzano, 2009).

2.9.6 Neuropsychological Aging in HIV

2.9.6.1 Brain Metabolism: Evidence of Combined Effects of HIV and Aging

Neuropsychological aging and HIV appear to present additional risk for brain abnormalities compared to HIV alone. Results from Chang et al. (2004) showed that HIV and aging had additive effects on markers of inflammation and glial activation in white matter and basal ganglia as detected by proton magnetic resonance spectroscopy (MRS).

Ances et al. (2010) however, investigated interactions between HIV and aging and their effects on brain function demands through the use of functional magnetic resonance imaging (fMRI) in the visual cortex and found conflicting evidence. Twenty-six HIV-infected participants and 25 HIV seronegative participants were investigated and it was found that although HIV serostatus and age independently affected fMRI measures, no interaction occurred. This was illustrated by a decrease in baseline cerebral blood flow in both HIV infection and aging. A number of limitations existed within this study. The first being that many of the participants had a history of substance abuse or illegal recreational drug use, however, approximately equal numbers of control subjects and experimental subjects met these criteria. Secondly, although the cross-sectional cohort was modest in size, a larger sample size may have demonstrated different results. Thirdly, the impact of HAART on aging could not be analysed because most of the older HIV+ participants were receiving medications. Despite these limitations, the study found that cerebral blood flow in the HIV-infected brain is comparable to that seen in the uninfected brain 10 to 15 years older. The authors thus found the study to be of value in terms of highlighting the potential role of fMRI in the evaluation of possible impacts of HIV infection and aging on brain infection (Ances et al., 2010).

Results from studies presented above have evidently been conflicting. The majority of these studies suggest that age may detrimentally impact neurocognitive performance. This increases the risk for clinically relevant neurocognitive dysfunction. In other words, findings so far from these studies are more robust or relevant for clinical outcomes than they are for neuropsychological findings. This is because most studies are limited in power or methodological approaches (Kalayjian & Al-Harthi, 2009).

2.9.6.2 Neurocognitive Domains Affected by Aging in HIV

Several research groups have investigated the effects of aging on the development of neurocognitive deterioration in HIV. These studies have primarily been conducted within the western context. A number of key findings include a study by Doyle, Weber, Atkinson, Grant, Woods and (HNRP) (2012) reporting that older HIV-infected adults evidence mild neuropsychological impairments at disproportionately higher rates and show the greatest impairment in neurocognitive domains of psychomotor function, executive functioning and memory. The older participants were aged 50 and older and the younger participants were aged 40 and younger. The older sample had a higher proportion of Caucasians, more years of formal education and a higher rate of hepatitis C co-infection. HIV disease-related differences included lower nadir CD4 cell counts and a longer estimated duration of infection.

Sacktor, Nakasujja, Robertson and Clifford (2007) reported that age was associated with lower performance in tests of memory, executive functioning and motor performance in older HIV+ individuals with and without neuropsychological impairment in comparison to younger HIV+ individuals. A review by Wendelken and Valcour (2012) suggests that age may be modifying the overall manifestation of neuropsychological impairment brought on by HIV.

2.9.6.3 Comparing the Neuropsychological Performance of Older HIV+ Individuals with Controls

Several comparative studies assessing neuropsychological performance in the older cohort between HIV+ and HIV- individuals have been conducted. A study conducted by Woods et al. (2013) examined 50 HIV+ individuals aged 50 and older and 50 HIV- controls on a visual temporary order memory task. The HIV+ group had significantly worse memory impairment accross all temporal separations. The impairment was independently associated with clinical

deficits in executive function and delayed retrospective memory. Sorlini et al. (2014) also found significantly worse neurocognitive performance in executive function, processing speed and verbal learning for elderly HIV+ women compared to elderly matched HIV- women. The study compared 20 HIV+ women (median age = 72, range 67.5-77.7) and 21 HIV- women (median age = 76, range 69.5-77.5).

Wilson et al. (2013) investigated a group of aging HIV-infected patients (n=12, range 50-69 years) on HAART and a matched-group of uninfected controls (n=12, range 50-70 years) using magnetoencephalography (MEG) during a psychomotor and motor task. MEG is a non-invasive neuroimaging method that quantifies the magnetic fields that naturally emanate from populations of active neural cells in the neocortex. Key findings include sharply reduced beta activation in the primary motor cortices and the supplementary motor areas of HIV-infected individuals during the psychomotor and motor tasks respectively. These beta reductions in fundamental regions for motor control were accompanied by significantly stronger responses in higher-order brain centers, such as the right medial prefrontal cortex. This may reflect some form of compensatory mechanism in HIV-infected participants.

Magnetoencephalography was also used in another study by Becker et al. (2013) to measure neural activity during the resting state in 15 HIV-infected older patients and a demographically matched group of 15 uninfected controls. HIV-infected individuals showed decreased beta oscillations in the superior parietal lobule relative to heathy controls. These regions function to integrate sensory information related to visuospatial ability (Lezak, Howieson, Bigler, & Tranel, 2012).

2.11 Conclusion

In summary, it is clear that advancing age brings about a compromise in a number of neurocognitive domains. HIV is also related to some form of compromise in neuropsychological function. The specific differences in neuropsychological profiles of older HIV positive adults as compared to healthy controls needs further clarification. The following chapter provides the research methodology utilised to preliminarily investigate this.

CHAPTER 3: RESEARCH METHODOLOGY

3.1 Introduction

The main purpose of this study was to compare the neuropsychological profiles of an older cohort of HIV+ individuals and HIV- individuals. Differences in neuropsychological functioning between HIV+ and HIV- older individuals were expected; however the more pertinent issue would be to preliminarily assess whether those differences are in fact significant and whether they occur globally (i.e. across neurocognitive domains) or are domain-specific. Furthermore, the neuropsychological pattern of these differences was to be examined.

Chapter 3 describes the use of the cross-sectional, quasi-experimental design employed to investigate the main aims of the study. This chapter continues to detail the convenience sampling strategy employed to recruit the relevant participants from a primary health care facility as well as the neuropsychological research instruments that were used to assess these participants. The data analysis techniques are also described in detail. Due to the sensitive nature of HIV, it was thus of the utmost importance for the entire research process to be one that shows respect and honesty towards all parties involved. Specific ethical issues that are pertinent to this particular study are thus outlined in this chapter in addition to relevant limitations related to the study design.

The following main hypothesis was investigated:

Research hypothesis (Ha_1): There are significant differences in the neuropsychological functioning (global and/or domain-specific) of older HIV+ individuals in comparison to older HIV- individuals.

Null hypothesis (Ho_1): There are no significant differences in the neuropsychological functioning (global and/or domain-specific) of older HIV+ individuals in comparison to older HIV- individuals.

The pre-existing independent variable in this instance is the HIV status (positive or negative) and the dependent variable is the neuropsychological performance of the individuals.

Based on the above hypothesis, the following primary aims of the study were investigated:

a) To preliminarily explore whether there are significant global or domain specific differences in the neuropsychological performance of older HIV+ as compared to older HIV- individuals.

The secondary aims of the study were as follows:

a) To compare the global neuropsychological performance of older HIV+ and older HIV- individuals.
b) To compare the domain-specific neuropsychological performance of older HIV+ and older HIV- individuals.

3.3 Defining Terms

The variables that were used to test hypotheses in this study may take on many forms and conceptualizations, thus it is important to define what each of these terms mean within the context of this study.

3.3.1 Older Adults

For the purposes of the current study, age was operationalized in terms of chronological age. The most widely accepted definition of an older adult in developed countries is someone over the age of 65 (Orimo, Ito, Suzuki, Araki, Hosoi, & Sawabe, 2006). In HIV studies however, older adults tend to be conceptualized as slightly younger than the usual definition of an

elderly adult. Within the context of this study, the population of older adults that were aimed at being studied were those that are over the age of 45, as adapted from these referenced studies (Kissel, Pukay-Martin, & Bornstein, 2005; Patel & Crane, 2011).

3.3.2 Experimental Group and Control Group

The experimental and control groups were assigned in terms of HIV status. If an individual was undergoing treatment at the Wellness Centre at the community HIV clinic and their medical records indicated a positive HIV result, they formed part of the experimental group. If an individual was part of the community and their medical records at the clinic did not indicate a positive HIV test, they formed part of the control group.

3.3.3 Chronicity

It was not always possible to ascertain the exact time when an individual contracted HIV; however an attempt was made to make use of participants who have been infected with HIV longer than a year, as they are considered to have chronic HIV as opposed to acute HIV (Ances et al., 2009; Fiebig et al., 2003). Patients' medical records usually indicated the date of the first positive diagnosis at the clinic, and this was used to calculate the chronicity. Making use of chronic HIV patients is in line with the nature of the study because it is exploring the longer term effects of HIV.

3.3.4 Neuropsychological Performance

Neuropsychological functioning refers to the functioning of the brain, as it relates to specific psychological processes and behaviour (D'amato & Hartlage, 2008). Neuropsychological functioning is inferred by neuropsychological performance. Within the context of this study, neuropsychological performance was operationalized by means of neuropsychological tests

that assess domains which have been reported to be affected by both HIV and aging (Doyle, Weber, Atkinson, Grant, Woods, & (HNRP), 2012; Sacktor, Nakasujja, Robertson, & Clifford, 2007). These domains include *attention*, *psychomotor processing*, *executive function*, *memory*, *visuospatial/constructional abilities*, *processing speed and global neurocognitive function*. Specific neuropsychological tests and their applicability to measuring neuropsychological performance will be further discussed in the research methodology section below.

3.3.6 Demographic Variables

Demographic variables within this study included age (as discussed above), gender, ethnic group, education level and employment status. Eating habits and sleeping habits were also taken into account when collecting data.

3.3.7 Clinical Variables

Medical records provided clinical variables such as CD4 count, plasma viral load (copies per mL), the date of the HIV test which revealed a positive diagnosis (to determine chronicity) and the date of first antiretroviral medication treatment (to determine the duration on antiretroviral medication).

3.4 Research Design

3.4.1 Quasi-Experimental Design

The quasi-experimental design was used to investigate possible differences between HIV+ (experimental) and HIV- (control) older individuals. Comparisons were made to assess whether there are significant differences between the experimental and control group with regard to their global and domain-specific neuropsychological performance. A characteristic

of the quasi-experimental design is that assignment to the experimental and control group is not random (Shadish, Cook, & Campbell, 2001). This is because the individuals' pre-existing HIV status determined which group they would be placed in.

It is likely that individuals in the experimental group (HIV+) may possess some other characteristic other than HIV, which can influence their neuropsychological performance, as opposed to those in the control group (HIV-). This is characteristic of the quasi-experimental research design, in that it usually contains confounding variables that cannot be adequately controlled for because of practical reasons. (Gravetter & Forzano, 2009). This implies that one cannot completely rule out some alternative explanations for the results obtained. During interpretation of the data, other variables and explanations that have not been adequately controlled for will be taken into consideration (Leedy & Ormrod, 2013).

An inherent strength in the quasi-experimental design is that it helps protect the ethical rights of the people within the study. This was immensely important, especially for the HIV+ population. It would have been unethical and even impossible to manipulate the HIV variable in order to investigate its effects. This particular design allowed for studying a condition (HIV) that is already present, since randomization would be impractical and even more so unethical (Leedy & Ormrod, 2013). To minimize bias and provide considerable control over non-random assignment, the experimental and control groups were matched in terms of age, gender, ethnicity, socio-economic status and educational level (Gravetter & Forzano, 2009).

3.5 Research Methodology

3.5.1 Sampling

Participants were selected using convenience sampling from a semi-urban community health centre in Pretoria, based on their availability and willingness to participate. According to

Maree and Pietersen (2007), this sampling strategy is ideal for exploratory research, because it provides an inexpensive and efficient approximation of the truth. Convenience sampling however does not result in representative samples.

Eighty three participants were recruited for the study from August 2013 to December 2013; however 25 did not meet the minimum requirements of the study as outlined by the exclusion criteria below. The remaining 58 participants consisted of 33 HIV+ participants and 25 HIV- participants who were eligible for the study. The experimental group consisted of HIV+ individuals who were consecutively enrolled during routine outpatient visits. The control group consisted of HIV- individuals obtained by means of convenience sampling. This sample consisted of the following individuals whose medical records could be obtained from the clinic: caregivers, family members and other community dwelling volunteers and patients that were willing to participate and had complete and accessible medical records. All participants were aged 42 and above.

The sample size used for the final data analysis consisted of 33 HIV+ and 17 HIV- (n = 50) protocols. This sample was still relevant to the preliminary nature of the current study (see review by Hardy & Vance, 2009). A larger sample size could not be collected due to practical considerations such as time frame, cost, patient accessibility and incomplete medical information.

Participants were not included in the study if they had any health issues that may have impacted upon their ability to complete the tests administered and any other factors that may have impacted upon their neuropsychological performance other than HIV. Participants were thus asymptomatic from the perspective of subjective complaints.

The following exclusion criterion was adhered to in selecting appropriate participants:

3.5.2 Exclusion Criteria

a) Diagnosed major psychiatric disorder, including bipolar illness, schizophrenia and active major depression.
b) A head injury with a loss of consciousness for more than 30 minutes.
c) Major neurologic disease such as multiple sclerosis, epilepsy, major stroke or current delirium.
d) An opportunistic brain infection.
e) Recent (within the last 3 months) history of substance abuse
f) Cytomegalovirus (CMV) retinitis, other overt retinal conditions or ocular opportunistic infections.
g) Dementia

3.5.3 Participant Recruitment

Participant recruitment took place at a primary health care facility in Pretoria. This primary health facility has a 'wellness centre' which specialises in mainly stable HIV patients that are already on a long term treatment plan for antiretroviral medication. This is where the majority of HIV+ patients were recruited from.

Nurses screened for possible candidates for the study, briefly introduced them to the purpose of the study and what is expected. Patients who were interested and felt they fit the inclusion criteria would be given a pamphlet containing brief information about the assessment and a tear-off slip with a space provided for the contact details of the patient (contact number and/or e-mail address).

Depending on the schedule of the patient, they would come in to the private consulting room to give the researcher the tear-off slip as well as attend an information session about the

nature of the study. If the participant was comfortable with the process at the information session, they were then be given consent forms to sign, upon which it was indicated that their medical records would also be accessed. The testing would then proceed. If the patient was comfortable with the process, but could not proceed with testing at that point for some or other reason, they would provide a return date when they would come again for the assessment.

3.5.4 Administration Conditions

The collection of data was done with a trained co-researcher. If some of the conditions in the exclusion criteria were revealed during the intake conversation or completion of the socio-demographic questionnaire, participants were thanked for their participation in the study and further testing was discontinued

3.6 Research Instruments

3.6.1 Socio-Demographic Questionnaire

The socio-demographic questionnaire was used to obtain basic medical information as well as socio-demographic information as detailed above (see appendix A).

3.6.3 Medical Records Checklist

The following information was collected from the patients' medical records: Socio-demographic variables (gender, age, race, level of education and employment status), clinical variables (HIV status, date of first HIV test, date of first ARV treatment, viral load, latest CD4 count) and comorbid conditions (tuberculosis, opportunistic infections, cancer, etc.) (see appendix A).

3.6.2 Health-Related Quality of Life Questionnaire

The EQ-5D questionnaire was used as a self-report indicator of anxiety and/or depression. The EQ-5D questionnaire is an assessment of general health-related quality of life. This simple generic measure of health is a widely standardized test instrument (Rabin & de Charro, 2001). The EQ-5D measures five domains that contribute to a single index measure, namely mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The domain of interest in the current study was anxiety/depression. This self-reported measure was included to ascertain that there were no significant differences between the two groups on self-reported mood. The EQ-5D questionnaire has been used in the HIV population in both the international (Delate & Coons, 2001; Stavem, Frøland, & Hellum, 2005; Wu et al., 2002) and South African settings (Hughes, Jelsma, Maclean, Darder, & Tinise, 2004; Robberstad & Olsen, 2010).

3.6.2 Neuropsychological Battery

3.6.2.1 Criteria for Selection of Neuropsychological Battery

The neuropsychological battery used in the present study was selected based on measures that assessed functioning across several neurocognitive domains to explore the stated hypotheses. The neuropsychological battery assessed domains that previous studies (Carey et al., 2004; Hardy & Vance, 2009; Valcour, Paul, Neuhaus, & Shikuma, 2011; Wilkie et al., 2003) reported as being vulnerable to HIV infection and aging. The following neuropsychological test battery was also been selected due to practical issues and constraints such as time and fatigue factors. HIV+ patients at these primary health care centers often spend the entire day going through various examinations; thus it was of importance to make the testing process as efficacious as possible. Although these tests described below originate from developed

countries, they have been used in sub-Saharan Africa and are regarded as valuable in the assessment of neuropsychological impairment (Singh et al., 2010; Foxcroft & Roodt, 2009).

The neuropsychological assessment took between 30 to 60 minutes to administer - depending on the pace of the patient. Tests were chosen and administered in the order presented below to decrease testing time and ensure the best possible transition between measures.

3.6.2.2 Dementia Rating Scale-2 (DRS-2)

The Dementia Rating Scale-2 (DRS-2; Jurica, Leitten, & Mattis, 2001) is an assessment of general or global neurocognitive function at lower levels of ability. It is a frequently used measure of mental status among older adults with neurocognitive impairment (Schmidt, Lieto, Kiryankova, & Salvucci, 2006). This test and its predecessor (DRS; Mattis, 1988) were designed specifically for assessment of low levels of neurocognitive functioning, where other instruments tend to show floor effects. The test consists of 36 tasks and includes 32 stimulus cards, which are used in completing several of the tasks (Jurica, Leitten, & Mattis, 2001). The five DRS-2 subscales of the test provide information about specific abilities and are explained below.

A global measure of dementia is derived from subscales of specific neurocognitive capacities. The subscales include measures of attention (i.e. digit span), initiation and perseveration (i.e. performing alternating movements, copying repeated patterns, and semantic fluency), construction (i.e. copying designs), conceptualisation (i.e. similarities) and verbal and nonverbal short term memory (i.e. sentence recall, design recognition) (Jurica, Leitten, & Mattis, 2001; Strauss, Sherman, & Spreen, 2006).

The reported test-retest reliability for the DRS-2 is a correlation coefficient of 0.97, with subscale correlation coefficients ranging from 0.61 to 0.94 in a sample of dementia of the

Alzheimer's type. The lowest reliability was for the attention subscale. The reported split-half reliability (internal consistency) coefficient was 0.90 in a sample of people with either organic brain syndrome or senile dementia. The Mini-Mental State Examination (MMSE) is a brief screening instrument used to evaluate neurocognitive status. The DRS is reported as displaying greater sensitivity to change than the MMSE in patients with severe dementia (Jurica, Leitten, & Mattis, 2001). In studying the convergent validity of the DRS, Brown et al. (1999) found statistically significant correlations between DRS subscales and the subscales of other well-validated measures in a sample of patients with Parkinson's Disease. This indicated acceptable levels of convergent and divergent validity.

The DRS has rarely been used in the HIV population. Kovner, et al. (1992) recommended that the DRS may be a useful screening tool in this population - following a study of HIV drug-induced HIV+ individuals. Bottiggi et al. (2007) also recommeded the DRS for the bedside evaluation of patients suspected of having HIV-dementia or milder forms of it. Antinori et al. (2007) - the leading authors in the classification of HANDs - recommend the Mattis Dementia Rating scale as a mental status examination in HANDs.

3.6.2.3 Stroop Colour and Word Test (Stroop CW)

The Stroop Colour and Word Test (Golden & Freshwater, 2002) measures *executive function*. Executive function is a multifaceted neuropsychological construct that consists of a set of higher-order neurocognitive processes that allow higher organisms to make choices and to engage in purposeful, goal-directed and future-oriented behaviour (Suchy, 2009). According to Strauss, Sherman and Spreen (2006), executive function is a form of cognitive control which assesses the ease with which a person can maintain a goal in mind and suppress a habitual response in favour of a less familiar one.

The Stroop Colour and Word Test consists of a Word Page with 100 colour words (red, green, blue) printed in black ink; a Colour Page with 100 Xs printed in either green, red or blue ink; and a Colour-Word Page with 100 words from the first page (red, green, blue) printed in colours from the first page (the colour and the word do not match). The participant looks at each sheet and moves down the columns, reading words or naming the ink colour as quickly as possible within a time limit of 45 seconds. The test yields 3 scores based on the number of items completed on each of the three stimulus sheets. The last score (Colour-Word Page) requires the participant to ignore the word but mention the colour the word is printed in. This assesses executive function as a measure of cognitive control – the ease with which a person can maintain a goal in mind and suppress a habitual response (reading out the word) in favour of a less familiar one (reading out the colour) (Strauss, Sherman, & Spreen, 2006; Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006).

Golden (1975) reported test-retest reliabilities of 0.89 (Word), 0.84 (Colour) and 0.73 (Colour-Word; n = 450) for the group administered version of the test; and reliabilities of 0.86, 0.82 and 0.73 respectively (n = 30) for the individual version (Golden, 1975; Golden & Freshwater, 2002). However, the interset interval and the characteristics of the subjects were not described (Strauss, Sherman, & Spreen, 2006). Franzen, Tishelman, Sharp and Friedman (1987) gave this test to 62 healthy individuals on two occassions, spaced one or two weeks apart. The coefficients were 0.83 for the Word score, 0.74 for the Colour score and 0.67 for the Colour-Word score.

3.6.2.4 Symbol Digits Modalities Test (SDMT)

This neuropsychological test measures *psychomotor speed*. Psychomotor speed can be defined as the amount of time it takes an individual to process a signal, prepare a response and execute that response (Lezak, Howieson, Bigler, & Tranel, 2012). The SDMT involves

the conversion of meaningless geometric designs into written and/or oral responses (Smith, 1982). The written version of this test was used in the current study.

In this test, participants were required to identify nine different symbols corresponding to numbers 1 through 9. Participants had to practice writing the correct number under the corresponding symbol. They then manually filled the blank space under each symbol with the corresponding number. The participants were given 90 seconds to complete the administration (Lezak, Howieson, Bigler, & Tranel, 2012; Sheridan et al., 2006).

The test-retest reliability was 0.80 for the written SDMT and 0.76 for the oral SDMT. A correlation of 0.82 was obtained between written and oral forms of the SDMT - on the initial testing and 0.84 on retesting. This lends support for the equivalency of the two forms (Smith, 1982).

3.6.2.5 Delis-Kaplan Executive Function System (D-KEFS) Trail Making Test (TMT)

The D-KEFS provides a standardized assessment of higher-level cognitive functions, called *executive functions* in children, adolescents and adults between the ages of 8 and 89. The D-KEFS is composed of the following nine stand-alone tests that can be administered individually or in a group: Trail Making Test; Verbal Fluency Test; Design Fluency Test; Color-Word Interference Test; Sorting Test; Twenty Questions Test; Word Context Test; Tower Test; and Proverb Test (Homack, Lee, & Riccio, 2005). The authors state that these tests were selected to be sensitive to many of the types of executive impairment seen in patients with disorders affecting the brain (Lezak, Howieson, Bigler, & Tranel, 2012).

The nine tests composing the D-KEFS are either relatively new tests that the authors developed or adaptations of procedures that have been used as long-standing measures used in past experimental studies (Homack, Lee, & Riccio, 2005). For the purposes of this study -

a long standing measure - the Trail Making Test - was used to measure executive function in participants. This test consists of 5 conditions, namely a visual cancellation task (condition 1) and a series of connect-the-circle tasks (condition 2-5). Condition 1 assesses visual scanning; condition 2 assesses number sequencing, condition 3 assesses letter sequencing, condition 4 assesses number-letter sequencing (task-switching) and condition 5 assesses motor speed. The primary executive function task is number-letter sequencing (condition 4); which is a means of assessing flexibility of thinking on a visual-motor sequencing task. The other four conditions of this test allow the examiner to quantify and derive normative data for several key component processes necessary for performing the switching task. Thus the examiner can determine whether a deficient score on the switching condition is related to a deficit in cognitive flexibility and/or to impairment in one or more underlying component skills (Delis, Kaplan, & Kramer, 2001).

Internal consistency on the D-KEFS TMT was somewhat low to moderate, varying from 0.57 to 0.81. Schmidt (2003) noted that only 17% of the reliability values published in the D-KEFS manual were above the 0.80 value. This has been a popular criticism of the D-EKFS system, but does not pose a serious concern because of the general difficulties associated with measuring executive function (Shunk, Davis, & Dean, 2006).

3.6.2.6 Summary of the Relevant Neuropsychological Domains

Although the above-mentioned tests were used to assess neuropsychological domains, it is important to note that each test related to the main research hypothesis in a unique way. The table below is a summary of the main variables in the data analysis as related to the relevant domains.

Table 3.1: Neuropsychological domains assessed in the neuropsychological test battery

Domain	Test name	Variable assessed
Attention	DRS-2	DRS-2-Attention
	Stroop	Stroop Colour-Word Score (selective attention)
	D-KEFS	D-KEFS Visual Search (TMT 1)
Executive Function	Stroop CW	Stroop Colour-Word Score
	D-KEFS	D-KEFS Task-Switching (TMT 4)
	DRS-2	DRS-2-Initiation/ Perseveration
		DRS-2 Conceptualisation
Psychomotor Processing	D-KEFS	D-KEFS Motor Speed (TMT 5)
	SDMT	SDMT Primary Task
Memory	DRS-2	DRS-2 Memory Subscale
Visuo-Spatial/Constructional Abilities	DRS-2	DRS-2 Construction
	D-KEFS	D-KEFS Visual Search (TMT 1)
Global Neurocognitive Functioning	DRS-2	DRS-2 Total Score
Processing Speed	SDMT	SDMT Task
	Stroop	Stroop Colour-Word Score
	D-KEFS	D-KEFS Visual Search (TMT 1)
		D-KEFS Task-Switching (TMT 4)
		D-KEFS Motor Speed (TMT 5)

3.6.2.7 Neurocognitive Domains as Assessed by the Test Battery

Attention was measured by the score given for the digit span exercise in the DRS-2 attention subscale. Digit span tasks have traditionally been considered to measure attentional abilities (Groth-Marnat, Gallagher, Hale, & Kaplan, 2000; Lezak, Howieson, Bigler, & Tranel, 2012). *Executive Function* was assessed by the number of items completed in the colour-word condition of the Stroop test (Golden & Freshwater, 2002) as well as time it took to complete the task-switching condition of the TMT (Delis, Kaplan, & Kramer, 2001; Homack, Lee, & Riccio, 2005). The initiation, perseveration and conceptualisation subscales of the DRS-2 are also umbrella terms under the term of executive function (see Allain et al., 2005; Baddely, 1986; and Lezak, Howieson, Bigler and Tranel, 2012), thus the scores given on these subscales served as indicators of executive function.

Psychomotor processing was measured by the SDMT - as the number of symbols correct in a set time (Lezak, Howieson, Bigler, & Tranel, 2012; Smith, 1982). Furthermore, the measurement of psychomotor speed was supported by the D-KEFS motor speed condition which was measured as the amount of time it took to complete the motor task (Delis, Kaplan, & Kramer, 2001). *Memory* was measured by the DRS-2 memory subscale (Jurica, Leitten, & Mattis, 2001) based on the score given for remembering verbal and non-verbal material. *Visuo-spatial/constructional abilities* was assessed by the score given on the construction subscale in the DRS-2 (Jurica, Leitten, & Mattis, 2001). Furthermore, the assessment of visuo-spatial/constructional abilities was supported by measuring the time it took to complete the visual search condition of the D-KEFS TMT (Delis, Kaplan, & Kramer, 2001). *Global neurocognitive function* was measured by the total score given on the DRS-2 (Jurica, Leitten, & Mattis, 2001) which represented the mental status of the older adults with suspected neurocognitive impairment (Schmidt, Lieto, Kiryankova, & Salvucci, 2006). *Processing speed* was indicated by the scores obtained on the five-timed tests, as a measure of reaction

time. These included the primary task score of the SDMT, the colour-word score of the Stroop and the amount of time it took to complete the visual search, the task-switching and motor speed conditions of the TMT.

3.7 Data Analysis

Quantitative data analysis was conducted using the Statistical Analysis Software (SAS) in conjunction with the Statistical Package for the Social Sciences (SPSS) version 21. Preliminary data analysis was conducted on the 58 participants (33 HIV+ and 25 HIV-) who met the inclusion criteria. The main aim of this analysis was to assess the distribution of the sample. Furthermore, preliminary data analysis was conducted to determine whether the two groups were statistically comparable in terms of the demographic variables. All other demographic variables were comparable; however, the non-parametric Mann-Whitney U test indicated a significantly younger experimental group. All the individuals over the age of 60 in the control group were thus excluded from the analysis, leaving an age-matched sample of 33 HIV+ and 17 HIV- individuals (all under the age of 60).

For this new sample (n=50), descriptive statistics were used to explore the nature of the data. The distribution of the data was evaluated by means of the Kolmogorov-Smirnov test, skewness and kurtosis (Pallant, 2010). Crosstabs were conducted to summarise categorical demographic variables (gender, ethnicity, education). Age comparability was also ascertained by means of a Mann-Whitney U test.

The Mann-Whitney U test is a nonparametric alternative of the t-test (Pallant, 2010) which was used to compare the neuropsychological performance (neurocognitive test scores) between the two groups. The t-test could not be used because the clinical population data violated two of the assumptions of parametric techniques; i.e. the sample was not normally distributed and sample size was small (Field, 2009). The Mann-Whitney U test converts the

scores of the continuous variable to ranks across the two groups. It then evaluates whether the ranks for the two groups differ significantly. Due to the scores being converted to ranks, the actual distribution of the ranks does not matter. Furthermore, this technique compares medians and not means (Pallant, 2010).

Due to the small sample size of the control group (n=17), the current study made use of an additional nonparametric technique called the bootstrap resampling method. "Bootstrapping" refers to making inferences about a sampling distribution of a statistic (i.e. U statistic) by resampling the same sample with replacement, as if it were a finite population. The degree of accuracy of the inferences made is dependent on how well the resampling distribution mimics the original sampling distribution. Due to the distribution of the control group, 17 combination samples (bootstrap samples) were resampled (explained further in chapter 4). Hypothesis tests (using the Mann-Whitney U test in this instance) were then conducted on these to compare the experimental and control group based on their neuropsychological scores (Chernick & LaBudde, 2011; Davison & Hinkley , 2006).

3.8 Ethical Considerations

3.8.1 Ethical Approval for the Study

Ethical approval to conduct the study was granted by the Postgraduate Committee (12 February 2013) and the Research Ethics Committee (25 June 2013) at the University of Pretoria. Once ethical approval had been granted by the university, full permission was granted by the Department of Health (Tshwane Research Committee, 2nd July 2013) for the research study to commence at the community primary health care facility.

3.8.2 Confidentiality and Anonymity

HIV is a sensitive issue, as there is often a lot of stigma attached to those that are affected by it. The researcher therefore maintained the responsibility for respect and honesty towards the participants at all stages of the research process. The confidentiality and anonymity of the participants was maintained throughout the study. It is not ethical to directly recruit a participant based on their HIV status; therefore potential participants were firstly approached by the relevant medical professional and an appropriate recruitment procedure was followed.

Participation was strictly voluntary and no coercion to participate took place. Participants were explicitly made aware of their right to withdraw from the study at any stage, with no questions asked. It was communicated to participants that information gathered during the course of the research process would only be used for the purpose of the current study. The data gathered would thereafter be stored in an archiving facility at the University of Pretoria for 15 years. If the potential participant felt comfortable with the proceedings, they were given consent forms to sign and then testing took place. Information and measurements obtained from each participant were not referred to by the participant's name at any stage during the study to ensure anonymity. This was achieved through assigning numerical codes to the information gathered from the participants (Gravetter & Forzano, 2009).

3.9 Conclusion

Chapter 3 introduced details of the quasi-experimental design used. A detailed description of the method for collecting and analysing data as well as the measuring instruments used was provided. Data was collected by means of convenience sampling technique from a primary health facility. Data analysis was then performed on 33 HIV+ participants and 17 HIV- participants. Chapter 4 will detail the results of the descriptive and inferential statistics performed on the neuropsychological data.

CHAPTER 4: RESULTS

4.1 Introduction

The following chapter presents findings of statistical analyses conducted on neuropsychological data collected from older HIV+ (experimental group) and older HIV- (control group) individuals. The discussion will begin with a description of the demographic information for the overall sample as well as the older HIV+ and older HIV- groups respectively. The discussion will then continue to detail the findings with respect to the neuropsychological profile comparisons between the two groups.

4.2 Preliminary Data Analysis

During the period between August 2013 and December 2013, a total of 83 participants were recruited and/or tested for the study. From this pool of recruited participants, 25 participants were not considered in the data analysis because they either did not sufficiently meet the inclusion criteria of the study or they could not complete a satisfactory amount of the assessment.

Preliminary analysis was conducted on the remaining 58 participants; consisting of 33 HIV+ and 25 HIV- participants. The mean age was 49.64 (SD 4.54) for the HIV+ sample and 56.52 (SD 8.48) for the HIV- sample. The Mann-Whitney U Test confirmed a statistically significant younger HIV+ group as compared to the HIV- group, U = 213.5, z = -3, p = 0.001. Further analysis between the two groups indicated that the HIV+ group performed significantly poorer than the HIV- group on subscales of initiation/perseveration (U=284.5; z = -2; p=0.045), conceptualisation (U= 242.5; z=0.008; p=0.008) and global neurocognitive function (U=275.5; z=-2; p = 0.032). Results for the remaining domains indicated no significant differences.

Because neuropsychological impairments generally increase with age (Salthouse, 2004), it would be expected that a significantly younger group of participants (HIV+) should perform better on most, if not all of the assessments. Preliminary results (indicating that the younger HIV+ group showed poorer neuropsychological performance than the older HIV- group) served as an indicator that further comparison analyses can and should be conducted after correcting for age comparability. After excluding all participants 60 years and older (these were only in the control group), comparison using the Mann-Whitney U test was conducted on the remaining 50 participants (33 HIV+ and 17 HIV-) and showed no significant age differences. The descriptive statistics for this sample are described below.

4.3 Demographic Information

The entire sample was collected from a semi-urban community on the outskirts of Pretoria with individuals of similar socio-economic status. The entire sample consisted of individuals from the Black ethnic group. In terms of gender; the older HIV+ group consisted of 33% males and 67% females; while the older HIV- group consisted of 24% males and 76% females. In terms of employment, 52% of the HIV+ sample reported being employed, while 53% of the HIV- sample reported being employed. There were no significant differences ($p = 0.076$) in the years of education between the HIV+ and HIV- groups. The two groups also had no significant differences ($p = 0.169$) in terms of age. In terms of self-reported mood states between the two groups, both groups scored on the lower end of the anxiety/depression scale, indicating that they felt little or no anxiety and/or depression. There were no significant differences ($p = 0.767$) between the older HIV+ group and the older HIV- group in these scores. More detailed information is provided in Table 4.1 and Table 4.2 below.

Table 4.1: Demographic factors for the experimental and control group

Demographic Factors	Magnitude (older HIV+)	Magnitude (older HIV-)
Gender	Female: 22 (67%)	Female: 13 (76%)
	Male: 11 (33%)	Male: 4 (24%)
Ethnicity	Black: 33 (100%)	Black: 17 (100%)
Employment Status	Employed: 17 (52%)	Employed: 9 (53%)
	Unemployed/retired/other: 16 (48%)	Unemployed/retired/other: 8 (47%)
Education (in years)	Mean:9.82 SD: 3.07	Mean:11.53 SD: 2.38
Age	Mean:49.64 SD:4.54	Mean: 52.18 SD: 5.92

Note: SD = standard deviation, n = 50

Table 4.2: Comparison data for education, age and anxiety/depression: Mann-Whitney U Test

Variable	Median (HIV+)	Median (HIV-)	U	Z	p-value
Education	10	12	196.5	-1.8	0.076
Age	49	53	213.5	-1.3	0.169
Anx/Deppr	1	1	268.0	-0.3	0.767

Note: Sig level at $p < .05$.

4.4 Clinical Variables

Clinical variables were collected in order to obtain a clearer picture of the medical profile of the HIV+ individuals included in the study. The variables included the duration of the illness (chronicity), the duration on HAART, the CD4 count and the viral load. This information could not be collected for every participant due to incomplete medical records; however what could be obtained is detailed below.

4.4.1 Chronicity

Chronicity was determined by means of the earliest dated test that confirmed an HIV positive result. Information about the duration of the illness (chronicity) could be obtained for 26 of the 33 HIV positive participants. From the 26 participants, 20 could be classified as having chronic HIV (having HIV for longer than a year). The chronicity for all participants ranged from 0 to 152 months (over 12 years). The mean for this variable was 41 months (SD 37.7); however the median would be more suitable to report as it is less sensitive to outliers. The median chronicity was 24 months. This illustrates that the representative person in this sample had a chronicity of 2 years and thus can be classified as having chronic HIV.

Information regarding the duration that the individual was on HAART was determined by means of the date given for initiation of HAART at the clinic. The duration of HAART for the participants ranged between 0 and 152 months (over 12 years). The mean duration was 36 months (3 years, SD 42). The median, which is not as sensitive to outliers, was 24 months (2 years). This indicates that a representative individual in the sample has been on ARV treatment for 2 years (similar to chronicity). This similarity is expected as most HIV+ individuals attended the clinic in order to receive treatment.

4.4.2 CD4 Count and Viral Load

Information regarding the CD4 count was available for 31 of the 33 participants. The mean CD4 count was 415 (SD = 231.6). The CD4 count ranged between 12 and 850, with a median of 403. Information regarding the plasma viral load was not sufficiently provided in the medical records. Of the 33 HIV+ participants, 46% (15 participants) had no records of their viral load. 42% (14 participants) had a lower than detectable limit for their viral load. This means that for 42% of the HIV+ group, the individuals were in a more stable and healthy

condition because the virus was suppressed beyond a detectable amount. The remaining participants (12%; 4 participants) had varying amounts for their viral load.

4.4.3 Descriptive Statistics

The following section provides a summary of the distribution of scores obtained from the DRS-2; SDMT, Stroop CW and D-KEFS TMT for the experimental and control groups respectively.

Table 4.3: Descriptive statistics for neuropsychological performance (older HIV+)

Variable	N	Median	Mean	SD	Min	Max
DRS-2 Attention	33	34	33.91	2.53	25	37
DRS-2 Initiation/Perseveration	33	31	30.82	5.30	21	37
DRS-2 Construction	33	6	5.85	0.36	5	6
DRS-2 Conceptualisation	33	31	30.97	4.53	20	39
DRS-2 Memory	33	23	22.55	2.46	17	28
DRS-2 Total	33	125	124	11.37	101	142
SDMT	31	27	26.00	9.49	8	50
Stroop (CW)	30	23	23.03	8.98	4	42
TMT 1	31	39	42.54	17.75	25	91
TMT 4	30	240	200.2	54.45	68	240
TMT 5	30	61	67.43	27.66	33	137

Note: N = sample size, SD = standard deviation

Table 4.4: Descriptive statistics for neuropsychological performance (older HIV-)

Variable	N	Median	Mean	SD	Min	Max
DRS-2 Attention	17	34	34.18	2.04	27	36
DRS-2 Initiation/Perseveration	17	36	34.00	4.00	23	37
DRS-2 Construction	17	6	5.88	0.33	5	6
DRS-2 Conceptualisation	17	37	35.18	4.07	24	39
DRS-2 Memory	17	24	23.65	1.80	19	25
DRS-2 Total	17	132	132.29	9.51	103	141
SDMT	16	32	32.19	9.85	13	47
Stroop (CW)	15	31	27.47	11.07	4	42
TMT 1	16	31	32.75	9.90	14	53
TMT 4	16	180	173.81	68.97	85	240
TMT 5	16	52.50	57.06	29.63	19	150

Note: N = sample size, SD = standard deviation

An inspection of the distribution of the scores for the tests was done in order to determine the appropriate statistical techniques that can be used for inferential statistical analysis (see appendix C). For the DRS-2, the global scores for both samples were reasonably normally distributed based on the inspection of the histograms and the Kolmogorov-Smirnov value of 0.193 and 0.146 for the HIV+ sample and HIV- samples respectively. However, for the attention, initiation/perseveration, construction, conceptualization and memory subscales of the DRS-2, either one or both the samples were not normally distributed based on inspection of the data. For all the subscales, either one or both of the groups had a negatively skewed distribution of scores. Pallant (2010) states that many scales and measures used in the social

sciences have scores that are skewed; either positively or negatively. This does not necessarily indicate a problem with the scale, but rather reflects the underlying nature of the construct being measured.

The distribution of the scores for the SDMT (primary task) was reasonably normal for both the older HIV+ and older HIV- samples (Kolmogorov-Smirnov value of 0.200 for both). The same can be said for the Stroop Colour and Word Test (colour-word trial) (Kolmogorov-Smirnov value of 0.104 and 0.200 for the HIV+ sample and HIV- sample respectively).

For the Trail Making Test, the first, fourth and fifth task were considered for analysis as they were related to the relevant domains for the study. The first task (visual scanning) had a distribution that was not normal for the HIV+ sample but a normal distribution for the HIV- sample. The fourth task (task switching) had a distribution of scores that was not normal for both the groups. The fifth task (motor speed) had a distribution that was normal for the HIV+ group (Kolmogorov- Smirnov value of 0.200 and fairly normally distributed histogram.). For the HIV- group, the Kolmogorov-Smirnov value indicated a distribution that was not normal (0.04).

To sum up, not all the subscales of the DRS-2 were normally distributed. The SDMT and Stroop Colour and Word Test were reasonably normally distributed. Lastly for the TMT, either one or both the samples were not normally distributed on the set tasks. Based on inspection of the data in terms of the distributions of scores, nonparametric statistics were chosen for the inferential analyses. This is because most of the distributions were not normal. The sample size of the control group was below 30 (Pallant, 2010). The assumption of normality and a large sample size for parametric techniques was therefore violated (Field, 2009).

4.5 Group Comparisons: Mann-Whitney U Test

The following table (Table 4.5) indicates the results of comparisons of neuropsychological performance between the older HIV+ and the older HIV- group (n=50) based on the Mann-Whitney U test. This comparison was done prior to the bootstrap resampling technique. The results of the comparison done after the bootstrap resampling technique are presented in Table 4.11.

Table 4.5: Summary of the Group Comparisons: Mann-Whitney U test

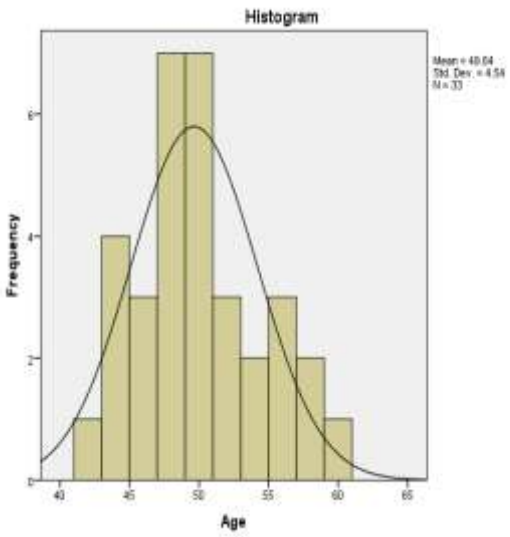
Variable	Median (HIV+)	Median (HIV-)	U	Z	p-value
DRS-2 Attention	34	34	259.0	-0	0.654
DRS-2 Initiation/Perseveration	31	36	173.5	-2	**0.027**
DRS-2 Construction	6	6	271.0	-0	0.746
DRS-2 Conceptualisation	31	37	128.5	-3	**0.002**
DRS-2 Memory	23	24	192.5	-2	0.066
DRS-2 Total	125	132	153.0	-3	**0.009**
SDMT	27	32	155.0	-2	**0.036**
Stroop (CW)	23	29	196.5	-1	0.315
TMT 1	39	31	167.0	-2	0.069
TMT 4	240	180	195.0	-1	0.263
TMT 5	61	52.50	183.5	-1	0.192

Note: Sig level at $p < .05$

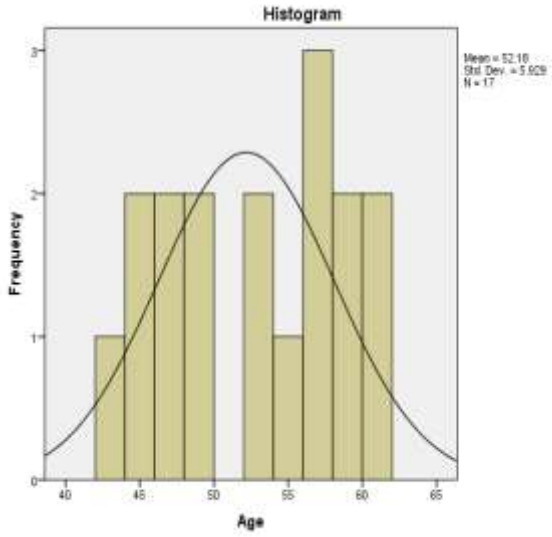
4.6 Hypothesis Testing: Bootstrap Method

The second non-parametric approach (bootstrapping) was used to repeatedly draw combination samples from the original sample, with replacement. The basic concept was to produce several combination samples of the same size as the original sample. Each of these samples is known as a "bootstrap sample" (Good, 2005; Walters & Campbell, 2004). The neuropsychological scores from these bootstrap samples (from the experimental and control group) were then compared to each other using the Mann-Whitney U Test.

The experimental and control group were comparable in terms of age; however the two groups did not have similar age distributions (see Figure 4.1 and 4.2 below).



Graph 4.1: Age distribution (HIV+) (n=33)



Graph 4.2: Age distribution (HIV-) (n=17)

The original sample was then altered in order to have similar distributions between the experimental and control group. Below is a table of the original sample (Table 4.6) and the altered sample (Table 4.7).

Table 4.6: Frequencies of age intervals (prior to bootstrap resampling)

Age	Control (HIV-)	Experimental (HIV+)	Total
41-45	3	7	10
46-50	4	15	19
51-55	3	6	9
56-60	7	5	12
61-65	0	0	4
66-70	0	0	3
71-75	0	0	1
Total	17	33	58

Table 4.7: Frequencies of age intervals (altered sample for bootstrap resampling)

Age	Control (HIV-)	Experimental (HIV+)	Total
41-45	3	7	10
46-50	4	15	19
51-55	3	6	9
56-60	2	5	7
61-65	0	0	0
66-70	0	0	0
71-75	0	0	0
Total	12	33	45

Due to the composition of each interval in the data, there was a maximum of 21 different combinations of 2 out of 7 (for the 56-60 age interval - control group) for selection and hypothesis test analysis. The Mann-Whitney U Test results of each of the 21 bootstrap samples are evidenced in the three tables below.

Table 4.8: Mann-Whitney U Test: Bootstrap samples 1-7

Domain	Sample1	Sample2	Sample3	Sample4	Sample5	Sample6	Sample7
DRS2Att	0.380864	0.621226	0.380864	0.327697	0.380864	0.380864	0.809930
DRS2Init	**0.017377**	**0.037600**	**0.009303**	**0.024978**	**0.005133**	**0.005133**	0.070004
DRS2Constr	0.732442	0.949545	0.732442	0.732442	0.732442	0.732442	0.949545
DRS2Concept	**0.003577**	**0.028716**	**0.002967**	**0.002698**	**0.002698**	**0.002967**	**0.032910**
DRS2Memory	0.423924	0.517850	0.423924	0.423924	0.423924	0.423924	0.517850
TotalDRS2	**0.012804**	0.055072	**0.007252**	**0.012804**	**0.005605**	**0.006113**	0.098253
SDMT	0.080663	0.182691	**0.037085**	0.075894	**0.042559**	**0.037085**	0.276946
StroopCW	0.341582	0.630589	0.670225	0.476596	0.314083	0.300880	0.314083
TMT1	0.127282	0.276946	0.071431	0.146413	0.141622	0.071431	0.414045
TMT4	0.690391	0.690391	0.341582	0.532454	0.355876	0.355876	0.690391
TMT5	0.611143	0.573050	0.432698	0.695416	0.432698	0.690391	0.482935

Note: significant at $p < .05$

Table 4.9: Mann-Whitney U Test: Bootstrap samples 8-14

Domain	Sample8	Sample9	Sample10	Sample11	Sample12	Sample13	Sample14
DRS2Att	0.534460	0.454105	0.534460	0.534460	0.809930	0.713445	0.809930
DRS2Init	**0.020141**	**0.048637**	**0.011837**	**0.011837**	**0.045657**	0.093013	**0.028716**
DRS2Constr	0.732442	0.732442	0.732442	0.732442	0.949545	0.949545	0.949545
DRS2Concept	**0.003577**	**0.003259**	**0.003259**	**0.003577**	**0.028716**	**0.026792**	**0.026792**
DRS2Memory	0.423924	0.423924	0.423924	0.423924	0.517850	0.517850	0.517850
TotalDRS2	**0.016120**	**0.026792**	**0.012804**	**0.013838**	0.062179	0.093013	0.055072
SDMT	0.067141	0.130889	0.080663	0.067141	0.157133	0.281511	0.173860
StroopCW	0.341582	0.203770	0.123412	0.116641	0.630589	0.441165	0.288042

TMT1	0.127282	0.244796	0.231706	0.127282	0.276946	0.480086	0.445502
TMT4	0.341582	0.532454	0.355876	0.355876	0.341582	0.532454	0.355876
TMT5	0.355876	0.591348	0.355876	0.591960	0.327651	0.551762	0.327651

Note: significant at $p < .05$

Table 4.10: Mann-Whitney U Test: Bootstrap samples 15-21

Domain	Sample15	Sample16	Sample17	Sample18	Sample19	Sample20	Sample21
DRS2Att	0.809930	0.454105	0.534460	0.534460	0.454105	0.454105	0.534460
DRS2Init	**0.028716**	**0.028716**	**0.006661**	**0.006661**	**0.017377**	**0.017377**	**0.003577**
DRS2Constr	0.949545	0.732442	0.732442	0.732442	0.732442	0.732442	0.732442
DRS2Concept	**0.028716**	**0.002698**	**0.002698**	**0.002967**	**0.002451**	**0.002698**	**0.002698**
DRS2Memory	0.517850	0.423924	0.423924	0.423924	0.423924	0.423924	0.423924
TotalDRS2	0.055072	**0.014942**	**0.007252**	**0.007252**	**0.012804**	**0.012804**	**0.006113**
SDMT	0.157133	0.062317	**0.034575**	**0.029975**	0.071131	0.062317	**0.034575**
StroopCW	0.275567	0.476596	0.314083	0.300880	0.183398	0.173780	0.103953
TMT1	0.276946	0.146413	0.141622	0.071431	0.268891	0.146413	0.141622
TMT4	0.355876	0.225687	0.137842	0.137842	0.237235	0.237235	0.145513
TMT5	0.554424	0.407247	0.229288	0.416631	0.407247	0.674071	0.416631

Note: significant at $p < .05$

The overall results are indicated in Table 4.11 below.

Table 4.11: Hypothesis test summary

Variable	95% CI	Sig (p-value)	Decision
Attention	min 0.328, max 0.810	0.065	Retain H_0
Initiation/Conceptualisation	min 0.004, max 0.093	**0.000**	**Reject H_0**
Construction	min 0.732, max 0.950	**0.000**	**Reject H_0**
Conceptualisation	min 0.002, max 0.033	**0.000**	**Reject H_0**
Memory	min 0.424, max 0.518	**0.000**	**Reject H_0**
Global Neurocognitive Func.	min 0.006, max 0.098	**0.000**	**Reject H_0**
Psychomotor Processing	min 0.030, max 0.282	**0.000**	**Reject H_0**
Executive Function (Stroop)	min 0.104, max 0.670	0.052	Retain H_0
Visual Search	min 0.071, max 0.480	**0.004**	**Reject H_0**
Task-switching	min 0.138, max 0.690	**0.027**	**Reject H_0**
Motor Speed	min 0.229, max 0.695	0.629	Retain H_0

Note: significant at $p < .05$; CI = confidence interval; one sample Komolgorov-Smirnov Test was used.

4.5.1 Executive Function

For the *executive function* domain, the older HIV+ group performed significantly poorer than the older HIV- group on measures of task-switching (D-KEFS TMT) ($p = .027$). Furthermore the older HIV+ group performed significantly poorer than the control group for initiation/perseveration (DRS-2) ($p = .000$), which was indicated by verbal generative fluency, auditory articulation of vowel and consonant patterns, alternating motor movements and simple graphomotor skills. The conceptualization subscale on the DRS-2 indicated that the older HIV+ group performed significantly poorer (p. = .000) than the older HIV- group in

their ability of abstract concept formation skills and the ability to identify similarities and differences among sets of objects presented visually and verbally. Cognitive flexibility, as measured by the Stroop Colour and Word condition indicated lower scores in the older HIV+ group as compared to the older HIV- group, however the difference was not statistically significant (p = .052).

4.5.2 Psychomotor Processing

For the *psychomotor processing* domain, the older HIV+ group performed significantly poorer than the older HIV- group (p = .000) as measured by the SDMT. The motor speed condition of the TMT however did not indicate any significant difference between the two groups (p = .629).

4.5.3 Memory

The older HIV+ group showed a significantly poorer performance (p =.000) than the control group in their orientation ability (to time, day, date and situation) as well as their forced-choice recognition memory of a verbal and visual nature.

4.5.4 Attention

In the DRS-2, the attention subscale consisted of forward and backward digit span, as well as the ability to attend to and execute verbal and visual commands of varied complexity. Even though the older HIV+ group had lower scores than the older HIV- negative group, no significant differences were observed between the two groups (p = .065). The visual search task in the TMT measured attention by means of searching for a target stimulus and identifying it among non-targets. The ability of the older HIV+ group to preferentially process some information over other information was significantly poorer (p = .004) than the ability of the older HIV- group to do the same. The Stroop Test, which is also a measure of

selective attention, indicated a lower scores for the older HIV+ group in comparison to the older HIV- group, however the difference was not statistically significant (p = .052).

4.5.5 Visuo-spatial/Constructional Abilities

The older HIV+ group performed significantly poorer than the older HIV- group on their ability to copy simple visual designs as indicated by the DRS-2 construction measure (p = .000). Furthermore, the visual search condition of the TMT also indicated a significantly poorer performance (p = .004) by the older HIV+ group in comparison with the older HIV- group.

4.5.6 Global Neurocognitive Function

In terms of the overall level of neurocognitive function, the five DRS-2 subscales, namely attention, initiation/perseveration, construction, conceptualization and memory yielded a composite score which indicated that the older HIV+ adults performed significantly poorer than the older HIV- group (p = .000) for global neurocognitive function.

4.5.7 Processing Speed

The older HIV+ group completed a significantly smaller number of symbols in the allotted time compared to the older HIV- group. Likewise, the older HIV+ group took significantly longer amount of time to complete the visual scanning as well as the task-switching condition. Three out of four tests (SDMT, TMT visual search, TMT task-switching) indicated that the older HIV+ group had slower processing speed in comparison to the older HIV- group, based on the slower reaction times. The Stroop test indicated that the older HIV+ group completed fewer items in the designated time; however the differences between the two groups were not significant. The motor speed condition of the TMT was not a neurocognitive measure per se, however it served as an indicator that both the older HIV+

group and the older HIV- group had similar motor abilities. One can thus reasonably assume that the processing speed deficits observed were not an indicator of motor deficits, but rather an indication of the respective neurocognitive abilities of both groups (underlying component processes).

4.7 Conclusion

Chapter 4 presented demographic information and clinical variables for the sample. Results of the tests of comparisons using the non-parametric Mann-Whitney U technique with the aid of the bootstrap resampling technique were also detailed. A discussion of these results in line with literature, as well as the limitations and recommendations thereof are presented in the following chapter.

CHAPTER 5: DISCUSSION AND CONCLUSION

5.1 Introduction

The aim of this study was to compare the neuropsychological performance of older HIV+ adults as compared to older HIV- adults. Overall results in this particular sample suggested that older HIV+ adults show poorer neuropsychological performance than older HIV negative adults on measures of executive function, psychomotor processing, memory, visuo-spatial/constructional ability, global cognitive function and processing speed. Older HIV+ adults appeared to be performing similarly to older HIV- adults in selective attention (an aspect of executive ability) and component motor abilities. This chapter provides a discussion of the overall results in the context of relevant literature. This chapter also takes account of the strengths and limitations of this study; gives recommendations for future research and offers a final conclusion.

5.3 Differences in Neuropsychological Performance

5.3.1 Global Neurocognitive Function

The current study indicated that older HIV+ individuals perform significantly poorer in overall neurocognitive function than the older HIV- individuals. This result was also reflective of the fact that most of the neuropsychological domains assessed in the current study (executive function, psychomotor processing, memory, processing speed, visuo-spatial/constructional ability) indicated a significantly poorer performance for the older HIV+ individuals as compared to the older HIV- group.

A recent study demonstrated that older HIV+ adults produce greater dispersion or intraindividual variability in performance across a range of tests. The authors proposed that this may be reflective of cognitive dyscontrol to which this population is vulnerable, perhaps

driven by the combined effects of aging and HIV infection on prefrontostriatal systems (Morgan, Woods, Delano-Wood, Bondi, Grant, & The HIV Neurobehavioral Research Program, 2011). The following sections discuss the specific neurocognitive domains in more detail.

5.3.2 Executive Function and Attention

In the current study, older HIV+ adults presented with poorer neuropsychological performance in domains of executive functioning than older HIV- adults. A cross-sectional study by Sorlini et al. (2014) reported that older individuals showed poorer neurocognitive performance than age-matched HIV- controls in domains of executive function as well as speed of processing and verbal learning. The study was however only looking at women who were 65 years of age and above. This trend of neurocognitive performance was also evident in patients with a low viral load.

The nature of neurocognitive changes in HIV infection have been characterized as a subcortical dementia which mainly affects the prefrontal striatal system. In other words, the earliest signs and symptoms of neurocognitive deficits in HIV are often related to executive dysfunction (Kissel, Pukay-Martin, & Bornstein, 2005). Woods et al. (2013) also reported that older HIV+ individuals (≥50 years) perform poorer on measures of memory tasks that are related to executive function as compared to age-matched controls.

Sacktor et al. (2007) suggested that among HIV+ patients, age may be associated with greater impairment in executive functioning. However, they could not conclusively report whether this was a consequence of advanced age in itself, or age-associated comorbidities such as coexisting cerebrovascular or neurodegenerative disease. On the contrary, Kupprat et al. (2013) reported that HIV+ individuals have consistently longer times on the Trail-Making Test B regardless of age and education when compared to the norms. What is clear from the

current study is that executive function is impaired among older HIV+ individuals in comparison to older HIV- individuals. However, whether increasing is a clinical correlate of the disease is beyond the scope of the current study.

Executive function is often complex to accurately measure (Miyake & Friedman, 2012). Miyake, Friedman, Emerson, Witzki and Howerter (2000, p.87) state that executive functions are "separable but moderately correlated constructs". This was evident in that the Stroop test, which is one measure of executive function, did not yield significant differences between the two groups, while the rest of the measures of executive function (TMT, DRS-initiation/perseveration, conceptualisation etc.) indicated significant differences.

Executive functions are theoretically thought to be divided into three components. These components include set formation (i.e. working memory and generativity), set shifting (i.e. cognitive flexibility) and set maintenance (i.e. response selection, inhibition, initiation and attentional vigilance) (Suchy, 2009). There are a wide variety of assessments which are believed to measure executive functions. These assessments often tap into different components of executive functions. In addition, these assessments are often indicators of other components which are not part of executive functions (Miyake & Friedman , 2012). For example, the Wisconsin Card Sorting Test-categories achieved (WCST-CA) is thought to be an indicator of set formation (generativity) and set shifting (cognitive flexibility), however it does not indicate set maintenance. Furthermore, the WCST-CA is also known to indicate visuo-spatial ability - which is a non-executive function component. The Trail Making Test-part B (TMT-B) is known to be an indicator of set formation (working memory), set shifting (cognitive flexibility) and set maintenance (attentional vigilance). Furthermore this test measures non-executive components such as visuo-spatial ability, language and processing speed. The Stroop Colour and Word Test also measures non-executive function components

similar to those of the TMT-B. In terms of executive function components, the Stroop Colour and Word Test is known to only be an indicator of the set maintenance component (response selection, inhibition and attentional vigilance). It is thus clear that different executive function assessments indicate different components of executive functions. It is highly likely that not all executive function components may be compromised in the older HIV+ population. Furthermore, it is also likely that some tests may not be sensitive enough to pick up the relevant executive deficits in this older HIV+ population.

In the current study, both the older HIV+ and older HIV- groups performed similarly in the domain of attention. It is reported that in HIV, simple attention, as measured by continuous performance tasks such as the Digit Span Test, tends to be preserved except in cases of frank dementia (Grant, 2008; Hardy & Hinkin, 2002). Furthermore, the attention subscales (digit span, counting distraction and visual attention) were not timed tasks and thus performance scores may not be attenuated by slow processing speed or cognitive load. Conclusions made regarding attention may have been limited to the measure used (Levine, Hardy, Barclay, Reinhard, Cole, & Hinkin, 2008). On the other hand, the results may be indicating that simple attention may not be heavily reliant on executive processing in the older HIV+ population, and complex attention may be compromised due to greater demand on higher-order processing.

Another aspect of attention processing is selection, where some information is preferentially processed over other information. A way to indicate selective attention is the visual search task where a target stimulus must be searched and identified among non-targets (Hinkin et al., 2002). In the current study, the older HIV+ adults performed poorer than the control group on this measure of attention. A study by Vance, Wadley, Crowe, Raper and Ball (2011)

concluded that older adults with HIV perform significantly worse on measures of visual search, than a demograpahically matched sample.

The Stroop Test is also a good example of selective attention processing (Hardy & Hinkin, 2002). In the current study, there were no differences in the performances of older HIV+ individuals and older HIV- individuals for attention as measured by the Stroop Test. Martin et al. (1992) found that the traditional Stroop Test only differentiated slightly between individuals in the early stage of HIV-infection and seronegative controls, while the computerized version could differentiate between the two groups. These results cannot be directly compared to the current study as they did not exclusively focus on older adults as in the current study. However, Hardy & Hinkin (2002) propose that the neuropsychological symptomatology of HIV is more related to higher order attentional deficits.

Relative to other neuropsychological constructs, such as memory and language, the nature and neuroanatomical substrates of attention are poorly understood. As a consequence, methods used to assess attention have not been adequately defined to date (Levine, Hardy, Barclay, Reinhard, Cole, & Hinkin, 2008). The consequence is that the precise effects of HIV upon attentional systems remain unclear.

5.3.3 Memory

In the current study, the older HIV+ group showed poorer performance on the memory domain, in comparison to the older HIV- group. Some aspects of memory measured in the current study were verbal. In that regard, similar results were obtained by Sorlini et al. (2014), who reported that older HIV+ individuals performed poorer on measures of verbal learning than age-matched controls. The current study included recognition memory of a visual nature. Similar results by Woods et al. (2013) also found that older HIV+ patients had worse memory impairment of a visuospatial nature than older HIV- patients.

A review article by Grant (2008) made a general conclusion that memory impairment is not among the most prominent neurocognitive problems encountered in HIV; and whether it is detected very much depends on the nature and difficulty of the task and conditions of testing. Scott et al. (2006) also reported that only a small proportion of HIV-infected persons display evidence of rapid forgetting - which is sometimes evident in persons with HAD. This may be different in the older population. Results from the current study suggested that in the older population, memory impairment may be more a factor in HIV+ individuals in comparison to HIV- individuals. Despite the limited evidence provided by traditional neurocognitive markers of rapid hippocampal neurodegeneration in HIV, there is considerable neuropathological evidence that hippocampal neurons are affected in advanced HIV disease (see review by Woods, Moore, Weber, & Grant, 2009). Moreover, impaired executive organising skills may underlie the differences in memory skills found between the two groups. According to Woods et al. (2013), HIV is associated with deficits in strategic aspects (executive function-related) of memory encoding and retrieval in the older HIV+ population. In other words, in this particular population, poor memory appears to be linked to some executive dysfunction (Pansky, Goldsmith, Koriat, & Pearlman-Avnion, 2009).

5.3.4 Psychomotor Processing, Motor Speed and Speed of Processing

In the current study, the older HIV+ group showed significantly poorer performance than the older HIV- group in their psychomotor processing abilities. A study by Wilson et al. (2013) investigated a group of aging HIV-infected patients (n=12, range 50-69 years) on HAART and a matched-group of uninfected controls (n=12, range 50-70 years) using magnetoencephalography (MEG) during a psychomotor and motor task. Sharply reduced beta activation in the primary motor cortices and the supplementary motor areas of the older HIV-infected individuals compared to the controls were observed during the psychomotor and

motor tasks respectively. On the other hand, Morgan and Ricker (2008) reported that psychomotor speed, a prominent symptom in both clinical observation and objective neuropsychological measures, appears to be partly improved by the increased efficacy of HAART regiments.

One should bear in mind that the current study indicated poorer performance in the psychomotor processing of the older HIV+ group compared to the control group; however the motor speed performance of both groups were similar. One can make a tentative assumption that there were no significant motor deficits in the older HIV+ group in comparison to the older HIV- group. This may be an indication that the poorer performance in psychomotor speed was not related to slower component process motor abilities in the older HIV+ group, but rather an indication of their higher order cognitive processing capabilities.

It is widely held that slowed information processing and slowed movement are the most prominent features of neuropsychological impairment in individuals with AIDS. Motor slowing was a required feature of HAD in the early diagnostic formulations (Antinori et al., 2007). Some authors have also argued that slowed information processing and slowed movement are the cardinal symptoms of HAND (Hardy & Hinkin, 2002). Severe movement abnormalities are however not frequently observed in association with HIV infection, but occasionally emerge in individuals with HAD (Mirsattari, Berry, Holden, Ni, Nath, & Power, 1999) or CNS opportunistic infections that affect the nigrostriatal dopaminergic system (Tse, Cersosimo, Gracies, Morgello, Olanow, & Koller, 2004). More investigations should therefore be conducted to clarify the effects of these two domains in the context of HIV, more specifically in the older population.

The current study indicated a slower speed of processing for the older HIV+ group in comparison to the older HIV- group. The study mentioned earlier by Sorlini et al. (2014) also

indicated a significantly lower speed of processing for older HIV+ women in comparison to age and gender-matched controls. Generally, a longer duration of HIV infection is reported as being associated with a poorer speed of processing, in addition to lower current CD4 T cell count (Vance, Fazeli, & Gakumo, 2013). In addition to psychomotor processing, the measure used in the current study (the SDMT) included visual scanning, executive abilities and more complex involvement of integrated brain systems. Slower speed of processing in the older HIV+ group as compared to the older HIV- group may not be attributable to mood. This is because the subjective report of anxiety/depression indicated no significant differences between the groups. However one should bear in mind that a caveat is not a comprehensive measure of anxiety/depression.

5.3.5 Visuospatial/Constructional Abilities

Comparisons indicated a significantly poorer performance in visuo-spatial/constructional ability for the older HIV+ group as compared to the HIV- group. Scott et al. (2011) indicated no interactional effects between HIV and aging on visuoconstruction. A few earlier studies of HIV infection indicated evidence of possible mild deficits in spatial neurocognition, including visuoconstruction and visuospatial skills (Poutiainen, Iivanainen, Elovaara, Valle, & Lahdevirta, 1988). Subsequent studies have indicated that subtle deficits are consistently present, even in the absence of basic visual dysfunction. Deficits seem to occur in spatial abilities linked to executive difficulties that rely more heavily on the integrity of the fronto-striato-parietal networks.

Becker et al. (2013) used magnetoencephalography (MEG) to measure neural activity during resting state in 15 HIV-infected older patients and a demographically matched group of 15 uninfected controls. Results indicated that HIV-infected individuals had decreased beta oscillation activation in the superior parietal lobes of older HIV+ individuals compared to

matched controls. These regions function to integrate sensory information related to visuospatial ability (Lezak, Howieson, Bigler, & Tranel, 2012). A study by Woods et al., (2013) also indicated that visuospatial ability as related to temporal order memory is significantly poorer in older HIV- individuals as compared to older HIV+ individuals.

5.7 Summary of Main Results

The current study illustrated that an older HIV+ group performed significantly poorer than an older HIV- group on several neurocognitive domains. The executive function domain indicated significantly poorer performance in measures of initiation/perseveration, conceptualization and task-switching. Memory performance was also significantly poorer for the older HIV+ group. Furthermore, the psychomotor processing domain also showed poorer performance in the older HIV+ group as compared to the older HIV- group. In terms of visuo-spatial/constructional ability, the older HIV+ group performed significantly poorer as well. Finally, the older HIV+ group had lower scores in global neurocognitive function as compared to the older HIV- group. No significant differences between the two groups were observed for simple attention, selective attention and motor speed.

5.8 Limitations of the Study and Implications for Future Research

Most of the limitations encountered in the current study were due to practical constraints. The length of the neuropsychological assessment, time constraints and the specificity of the cohort being assessed resulted in a small sample size. Nonparametric comparison techniques were thus used after correcting for age comparability. This resulted in analysis of an even smaller sample size. Future studies should make use of larger sample sizes.

Several challenges were encountered in ascertaining the HIV status of the participants. This was due to methodological aspects that were related to ethical issues pertaining to HIV. It is thus recommended that in future research, bearing the methodological and ethical issues in

mind, alternative methods be used to ascertain HIV status. It is possible that some individuals in the HIV- sample may have been HIV+. However, due to ethical constraints, the participant's medical records were taken as the final authority in terms of sampling.

In addition to the HIV status, there were also challenges pertaining to the clinical variables. Although the access to the participants' medical records was granted, there was not a sufficient account of the CD4 count and viral load data for all the HIV+ participants. It was not always possible to determine the exact duration that HIV patients had been infected (chronicity). The earliest positive HIV test in the file was noted to determine the chronicity. It was likely that a patient may have had the illness longer than indicated; however the guiding principle was to acquire as many patients as possible that are chronic (infected longer than a year) (Ances et al., 2009). Future work in HIV should try to more adequately rule out relevant clinical variables as confounding factors in neuropsychological functioning.

There was also no direct assessment of mood conducted to completely rule it out as a confounding factor. However, on EQ-5D questionnaire, both the older HIV+ group and the older HIV- group indicated similar levels of self-reported anxiety and depression. Further investigations should include a more comprehensive assessment of psychological status.

Neurocognition remains an important health outcome worthy of investigation for HIV+ individuals (Ances & Ellis, 2007). Additional research should continue to examine the neuropsychological and functional differences between individuals with and without HIV in the older cohort. Possibly more longer-term studies can give clarity to the neuropsychological performance trajectories of this population. This would be of particular relevence in the sub-Saharan context (where clade C of the virus predominates), as more research has focused on clade B in the western context. It would also be beneficial to identify more relevant methods of classifying HIV-related neurocognitive impairment that are sensitive to the relatively mild

and variable patterns of neurocognitive deficits in individuals with HIV (Blackstone et al., 2012). Furthemore, due to the varying nature of the virus in different groups, as well as the cultural factors, it is important for studies going forward to establish context-specific norms (Singh et al., 2010). This will aid in more accurate diagnoses of HANDs in underresourced developing countries.

5.9 Conclusion

The current study set out to investigate the older HIV population, which to date have had limited inclusion in neuropsychological studies. The main objective was to identify which neurocognitive domains were affected by HIV in comparison to a control group. In view of the preliminary nature of the current study, the pattern of neurocognitive impairment in this specific sample of older HIV+ individuals compared to demographically matched controls appears to be related to executive function, psychomotor processing, memory, processing speed, visuo-spatial/constructional ability and global neurocognitive function. Future work should closely examine the profiles of older individuals with HIV, with larger sample sizes. A better understanding can provide relevant information toward providing suitable long-term treatment and care for these individuals.

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APPENDIX A: INSTRUMENTS

University of Pretoria – Department of Psychology

Project Description: Neuropsychological Performance, Visual Ability and Health-Related Quality of Life

Desktop Research: Medical Records Checklist

Participant Number: #_____

CLINICAL VARIABLES

HIV Status (positive/negative): _____

Date of First HIV test: _____ Viral Load: _____

Date of First ARV Treatment: _____ Latest CD4count:_____

WHO Stage: _____

COMORBID CONDITIONS

TB? *Yes/No* _____ Opportunistic infections? *Yes/No*_____

Cancer? : *Yes/No* Type: _____ Other? *Yes/No* Type: _____

SOCIO DEMOGRAPHIC VARIABLES

Gender: _____ Race: _____

Age: _____ Marital Status: _____

Education: _____ Employment Status: _____

Additional Comments, if any?

_____

_____

_____

_____

_____

Socio- demographic Questionnaire

Please fill out the following information below:

1. Gender
☐ Male
☐ Female

2. Age
When is your date of birth?
Year _____Month _____Day ____

3. Race
☐ Black
☐ White
☐ Indian
☐ Coloured
☐ Other (please specify) _____

4. Marital Status
☐ Single
☐ Married
☐ Divorced or Separated
☐ Widowed

5. Education
Highest level of education:
☐ Primary
☐ Secondary
☐ Tertiary
☐ Other (please specify) _____

6. Employment Status
☐ Employed
☐ Unemployed
☐ Student
☐ Retired
☐ Unable to work
☐ Other (please specify) _____

7. Please tick any of the following that apply to you:

☐ History of substance abuse (e.g. drug addiction/alcohol) in the past 3 months.
☐ History of mental health problems (e.g. depression, anxiety, schizophrenia).
☐ Head injury (severe, where loss of consciousness for more than 30 minutes).
☐ Seizure disorders (e.g. epilepsy).
☐ Problems experienced with your eye-sight (vision). Please specify _____
☐ Sexually Transmitted diseases (STI)

8. Please specify how often you eat a day? (e.g. 3 meals a day)

_____

_____

_____

9. When was your last meal?

_____

_____

_____

10. How many hours of sleep did you have the previous night?

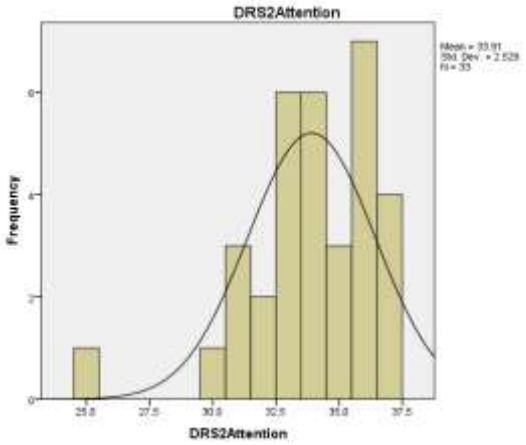
_____

_____

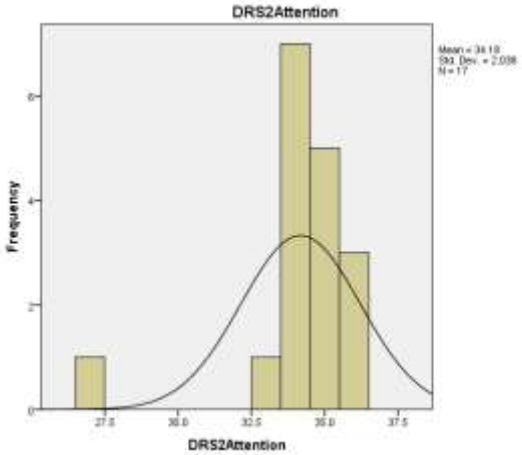
_____

Thank you

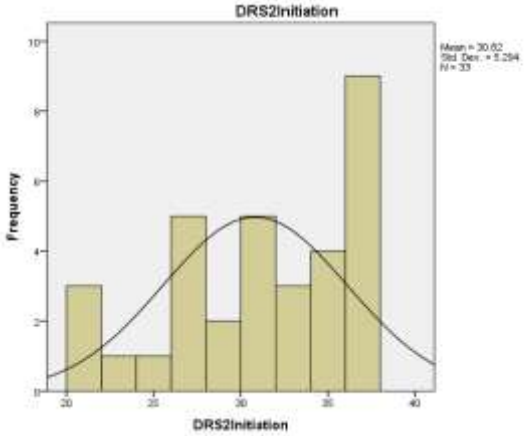
APPENDIX B: GRAPHS: Histograms for Experimental and Control Groups



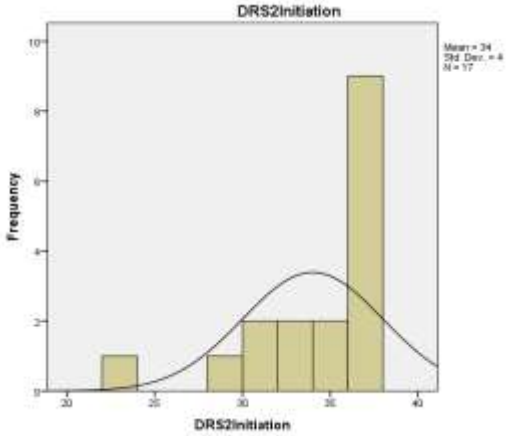
Graph 1: DRS-2 Attention (Experimental)



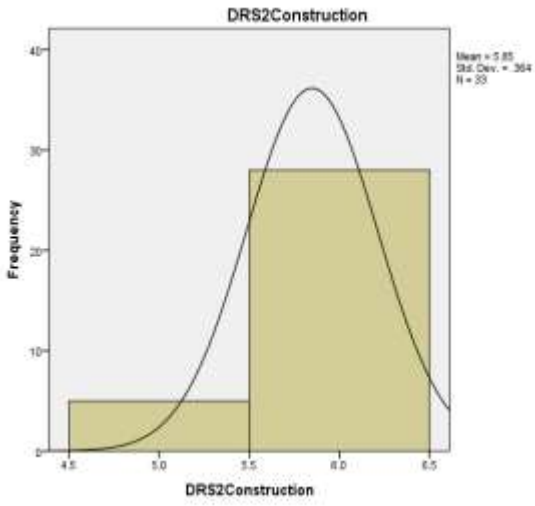
Graph 2: DRS-2 Attention (Control)



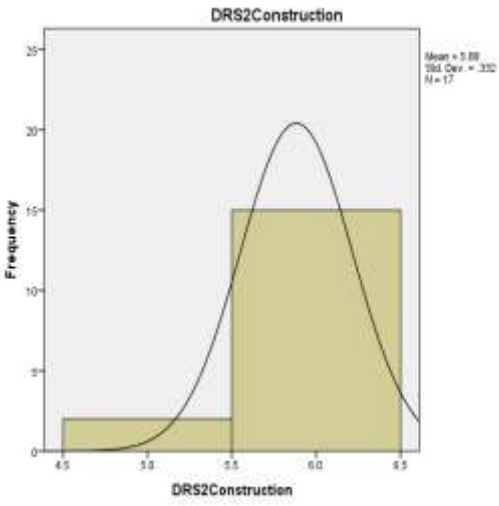
Graph 3: DRS-2 Initiation/Pers (Experimental)



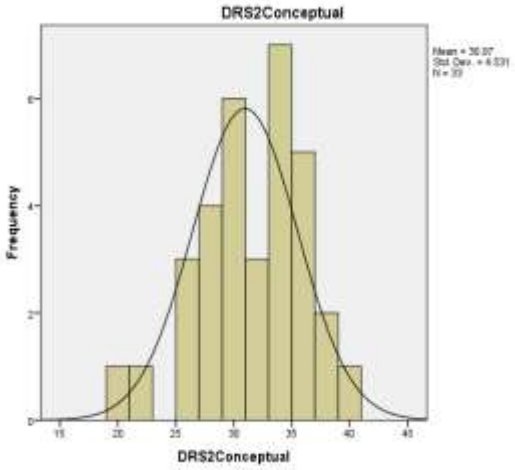
Graph 4: DRS-2 Initiation/Pers (Control)



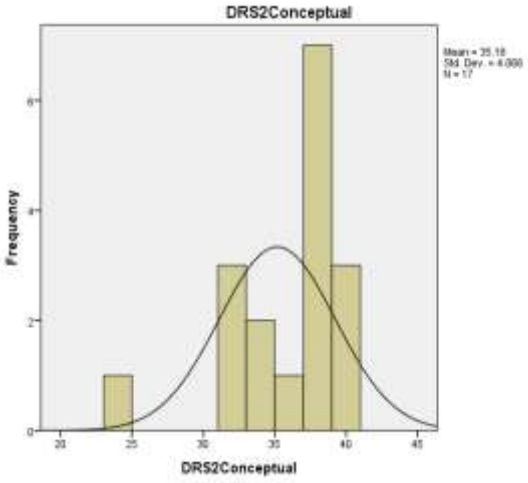
Graph 5: DRS-2 Construction (Experimental)



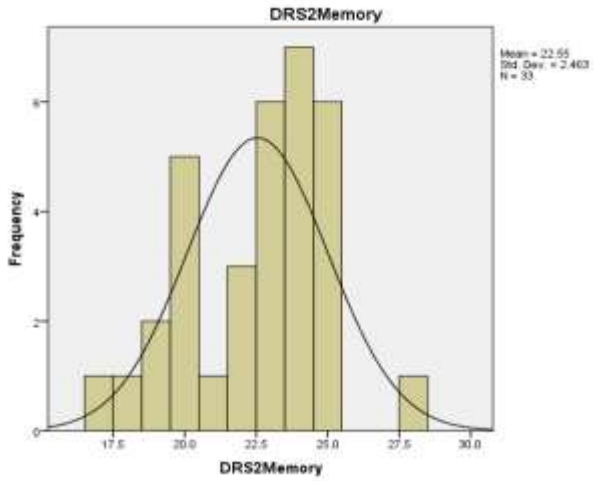
Graph 6: DRS-2 Construction (Control)



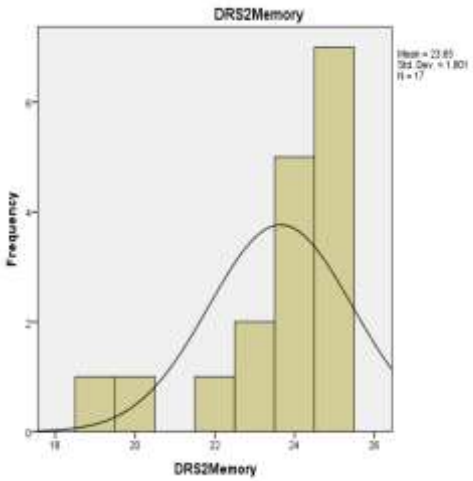
Graph 7: DRS-2 Conceptual (Experimental)



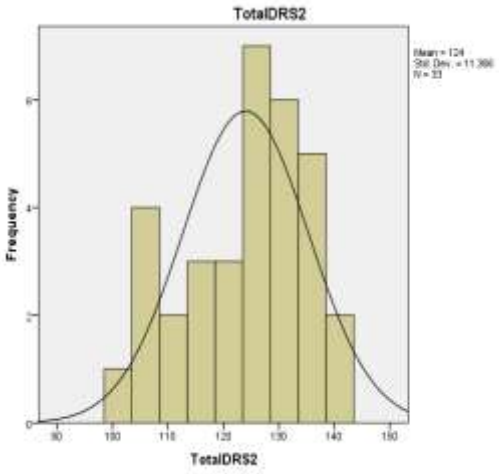
Graph 8: DRS-2 Conceptual (Control)



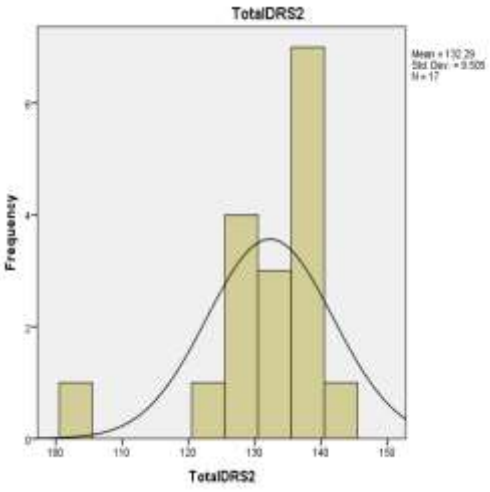
Graph 9: DRS-2 Memory (Experimental)



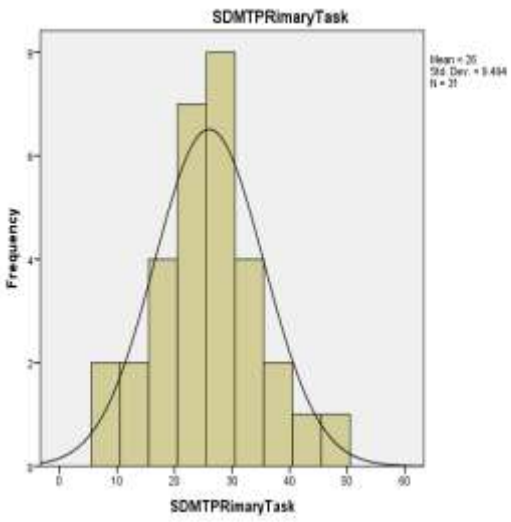
Graph 10: DRS-2 Memory (Control)



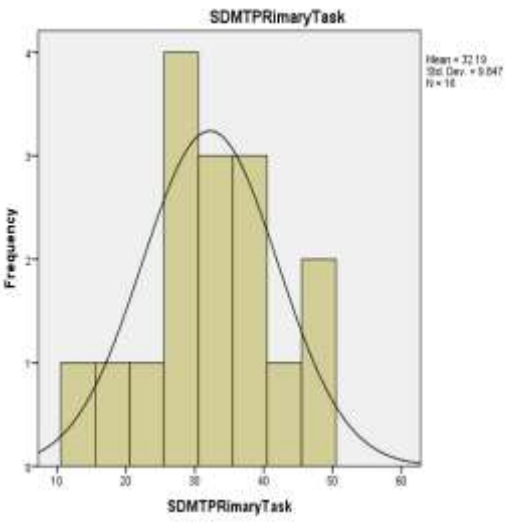
Graph 11: DRS-2 Total (Experimental)



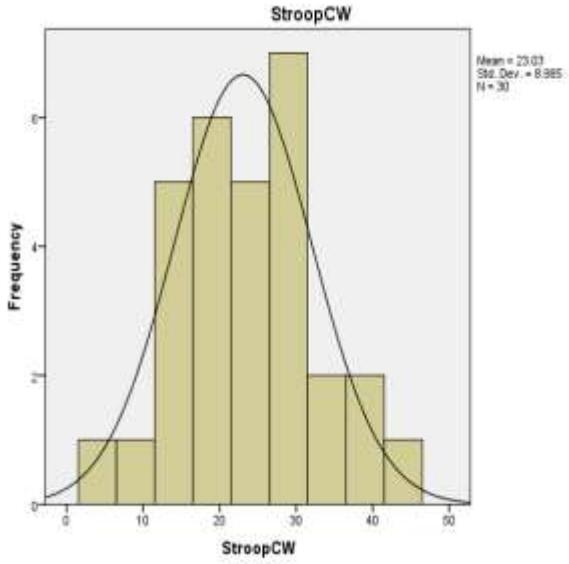
Graph 12: DRS-2 Total (Control)



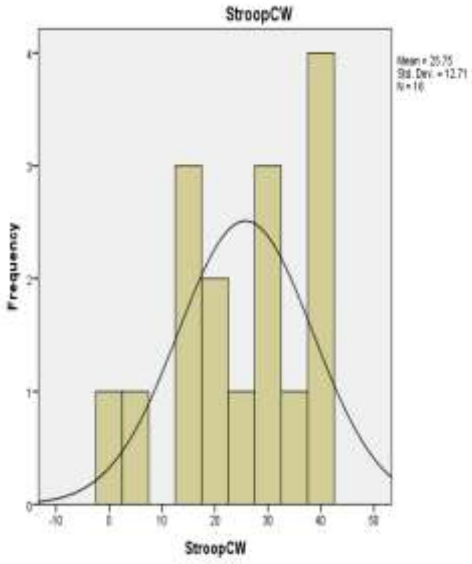
Graph 13: SDMT (Experimental)



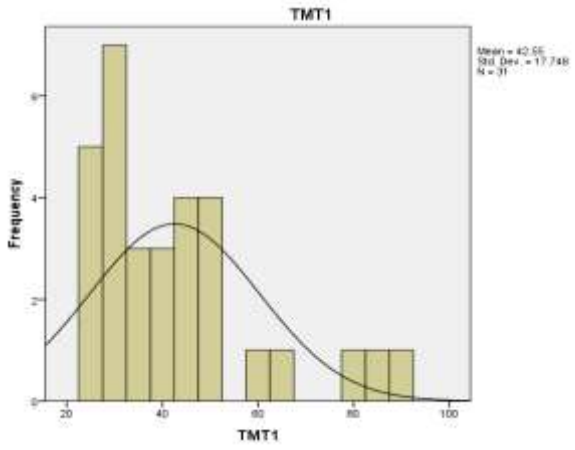
Graph 14: SDMT (Control)



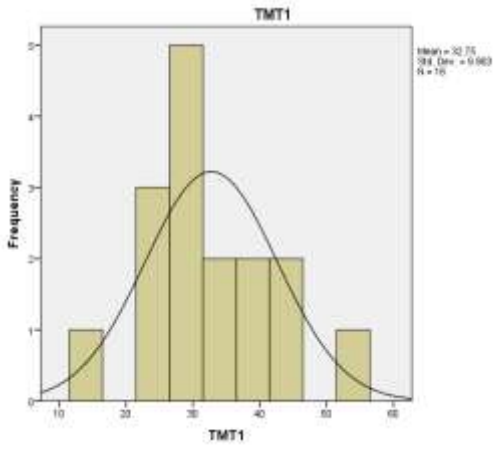
Graph 15: Stroop (Experimental)



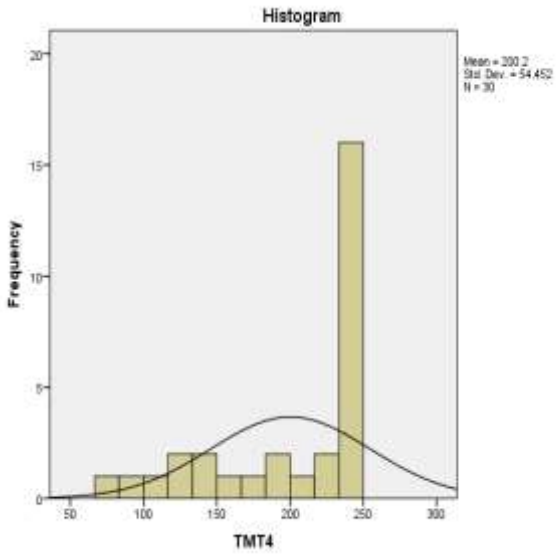
Graph 16: Stroop (Control)



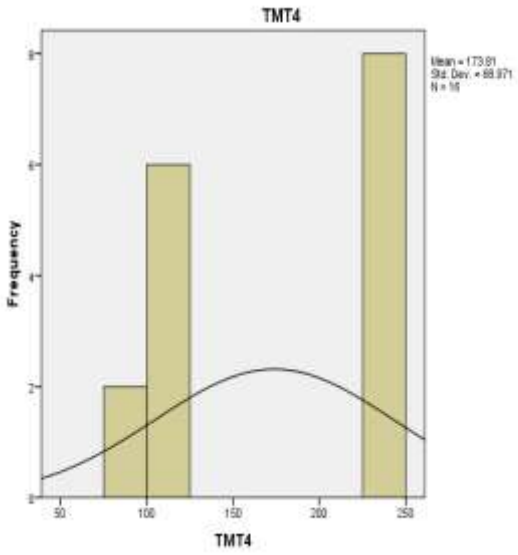
Graph 17: Visual Search TMT (Experimental)



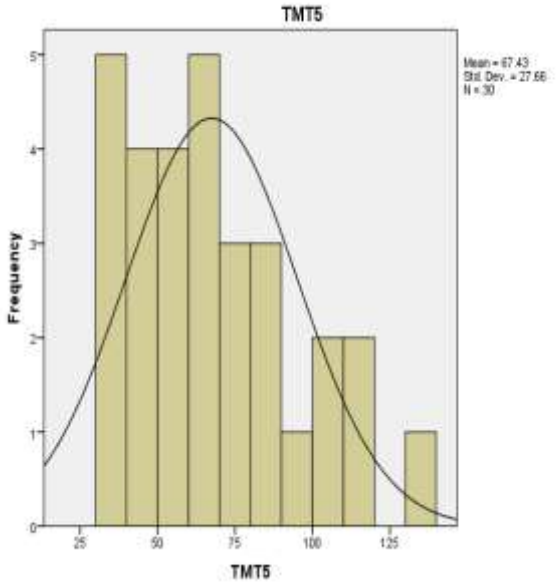
Graph 18: Visual Search TMT (Control)



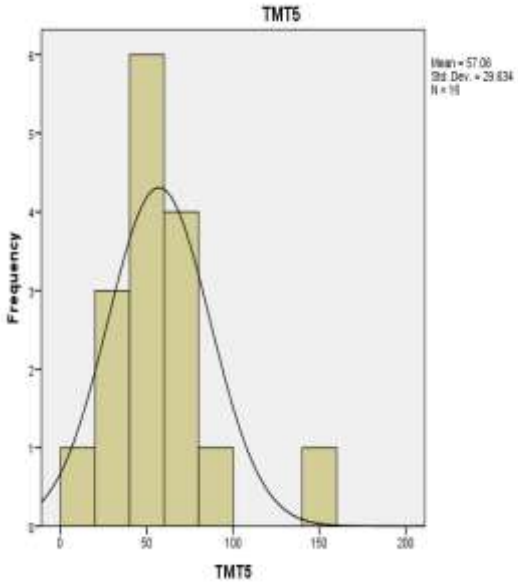
Graph 19: Task-Switching TMT (Experimental)



Graph 20: Task-Switching TMT (Control)



Graph 21: Motor Speed TMT (Experimental)



Graph 22: Motor Speed TMT (Control)