The Relationship between Health-Related Quality of Life and Neuropsychological Profiles of Older Adults with Human Immunodeficiency Virus (HIV)

by

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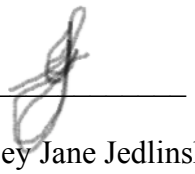
Declaration

I, *Stacey Jane Jedlinski,* declare that this research project entitled, *The Relationship between Health-Related Quality of Life and Neuropsychological Profiles of Older Adults with Human Immunodeficiency Virus (HIV)* is my own work and contains no plagiarism.

All sources have been cited properly and the original authors acknowledged using the American Psychological Association 6th edition referencing guidelines.

This research project is submitted in partial fulfilment of the requirements for the degree of Master of Arts in Clinical Psychology offered by the University of Pretoria. Furthermore, I have not allowed and will not allow anyone to copy my work with the intention of passing it off as his or her own work.



Stacey Jane Jedlinski

Abstract

Advances in the pharmacological treatment of the human immunodeficiency virus (HIV) have resulted in an exponential increase in the number of older individuals living with HIV. However, despite a longer lifespan, milder forms of neuropsychological deficits have been reported. This has implications for the quality of life and everyday functioning in older cohorts with HIV.

The aim of this exploratory study was to investigate the relationship between health-related quality of life (HRQoL), and neuropsychological outcomes in older adults with HIV. Other study objectives included exploring the associations between neuropsychological performance and HRQoL with clinical variables. Participants were recruited through convenience sampling at a semi-urban community clinic. Thirty-four older individuals with HIV were administered a socio-demographic questionnaire, the EQ-5D 5L HRQoL measure and comprehensive neuropsychological battery, comprising the Dementia Rating Scale-2 (DRS-2); Symbol Digit Modalities Test (SDMT); Stroop Colour and Word Test, and the Trail Making Test of the Delis-Kaplain Executive Function System (DKEFS TMT).

Results indicated specific, significant associations between self-reported anxiety/depression, pain/discomfort, self-care, and neuropsychological outcomes. Also, significant associations were noted between clinical variables and four of the neuropsychological measures and two of the health-related quality-of-life variables. Exploratory cluster analysis revealed that age and clinical variables may serve as possible moderator variables.

Keywords: human immunodeficiency virus, neuropsychology, neuropsychological performance, HIV-associated neurocognitive impairment, quality of life, health-related quality of life, older adults, aging, South African context

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Chapter 1: Introduction

1.1 Introduction

This mini-dissertation documents research that explored the relationship between health-related quality of life (HRQoL) and neuropsychological performance in older individuals with HIV. This first chapter introduces background information relevant to this research, specifies the problem statement, justification, aims, objectives, and hypotheses. An overview of the methodology used is provided and the chapter concludes with a summary of subsequent chapters.

1.2 Overview and Problem Statement

The Joint United Nations Program on HIV/AIDS (UNAIDS) estimated that, as at the end of 2012, approximately 35 million people were living with HIV. Furthermore, it was reported that there was an overall decline of newly infected individuals worldwide (UNAIDS, 2012; 2013). Despite these seemingly encouraging findings, the virus continues to raise concern in the global health domain. Sub-Saharan Africa is no exception, and in fact remains the most severely affected region. Reports in 2011 concur that nearly one in every 20 adults (4.9%) is living with HIV in Sub-Saharan Africa, thus accounting for 69% of people living with the virus worldwide (UNAIDS, 2012). Nevertheless, whilst considerable attention has been focused on monitoring HIV infection worldwide, the cohort of older individuals with HIV has thus far been largely neglected in studies. This is surprising since HIV infection in older adults is becoming increasingly common (High, Valcour & Paul, 2006). This also applies to the South African context as a recent study suggest that South Africa is one of the five countries with the highest number of older adults living with HIV in sub-Saharan Africa (Negin & Cumming, 2010).

It is known that HIV is associated with damage to the central nervous system (CNS) which can result in a variety of neurological disorders. These disruptions in brain function have been referred to as HIV-associated neurocognitive disorders (HAND), and accompany a triad of cognitive, behavioural, and motor disturbances (Antinori et al., 2007). The cognitive domains of executive function, speed of information processing, attention, working memory, new learning, motor skills, and retrieval of new information are predominantly compromised in HIV (Dawes et al., 2008; Grant et al., 1987).

However, with the recent advances in drugs such as antiretroviral therapy (ART), combination régime (cART), and highly active antiretroviral therapy (HAART), the severity and spectrum of HAND have changed. The more severe forms of HAND occur less frequently, whilst the subtle forms still persist with a reasonably high prevalence, despite individuals receiving treatment (Robertson, Smurzunski et al., 2007). As a result, there is an underrecognition of minor cognitive impairment in an infected, but treated, population. Secondly, the availability of treatment has allowed HIV to become a chronic but manageable disease (Ances & Ellis, 2007; Tozzi, Balestra, Libertone & Antinori, 2010). This has resulted in an increase in prevalence in an aging population with HIV (Vance, Woodley & Burrage, 2007). The potential interaction between aging and HIV renders older infected individuals more vulnerable to developing cognitive impairment (Valcour, Paul, Neuhaus & Shikuma, 2011). Impairments in cognitive functioning have been associated with individuals with HIV, and include difficulties in managing basic activities of daily living and a decline in health-related quality of life (Tozzi et al., 2003).

It is therefore important to research a population at greater risk of neuropsychological impairment, and to investigate the probable association between these impairments and HRQoL (Tozzi et al., 2003; Osowiecki et al., 2000).

1.3 Justification and Significance of Research

The older population living with HIV is often a group that is neglected in studies (Martin, Fain and Klotz, 2008), and to the researcher's knowledge, limited research is available in this area of work in the South African context. Consequently, this study will contribute to the body of knowledge on neuropsychological outcomes and HRQoL in the South Africa setting, and serve as preliminary work for future studies exploring the impact of HIV in an aging cohort.

1.4 Research Aim, Question, and Objectives

The primary aim of this study is to investigate the association between HRQoL and neuropsychological performance in older individuals with HIV. This aim is deduced from the research question: Is there an association between HRQoL and neuropsychological performance in older individuals with HIV?

The following four specific objectives assist in achieving the aim of the study, and answering the research question:

1. To explore the relationship between neuropsychological performance and clinical variables in older individuals with HIV.
2. To explore the relationship between HRQoL and clinical variables in older individuals with HIV.
3. To explore the relationship between HRQoL and neuropsychological performance in older individuals with HIV.
4. To explore the moderating influences of clinical and socio-demographic variables on the relationship between HRQoL and neuropsychological performance.

1.5 Hypotheses

The following hypotheses were formulated and tested:

1. There is a significant positive association between neuropsychological performance and clinical variables.
2. There is a significant positive association between HRQoL and clinical variables.
3. There is a significant positive association between neuropsychological performance and HRQoL.

1.6 Nature of the Study

A quantitative, correlational research design was utilised. Participants were recruited from a community clinic, in a semi-urban area in Pretoria, using a convenience sampling method. Informed consent was obtained, and various questionnaires were administered in order to collect specific information required for analysis. Thereafter, the data was captured and analysed. Spearman's rank order correlation coefficients were used to evaluate the relationship between the variables, and the moderating effects were tested using exploratory cluster analysis.

1.7 Chapter Overview

The remainder of this mini-dissertation will be divided into the following chapters:

Chapter 2: Literature review. This chapter examines extensive literature pertaining to health-related quality of life and neuropsychological profiles in older individuals with HIV.

Chapter 3: Research methodology**.** This chapter provides an in-depth discussion of the methodological endeavours employed in conducting this research. This includes the research design, description of the participants as well as procedures, measurement instruments, and ethical considerations.

Chapter 4: Results. This chapter presents a summary of the findings obtained after data collection and statistical analysis.

Chapter 5: Discussion and conclusion. This chapter integrates and discusses the findings from this research study in an attempt to answer the research question.

Chapter 2: Literature review

2.1 Introduction

The objective of this chapter is to provide an overview of the major literature pertaining to health-related quality of life and neuropsychological performance in the context of older individuals with HIV.

The chapter begins with a general discussion on neuropsychological impairment in HIV patients. This includes the basic principles of HAND and aspects of assessment, diagnostic characteristics, incidence, prevalence, and major risk factors. The focus then shifts to discussing the specific risk factor of age and its association with HAND. Subsequently, the various neurocognitive domains, known to be affected by HIV and aging, are discussed. Particular attention is given to studies that investigated neurocognitive impairment in older HIV populations, and the impact thereof on the HIV-aging phenomenon and cognitive performance. Lastly, HRQoL is discussed. This includes its definition, measurement, and the various domains that comprise this concept. Following this, HRQoL is further discussed in the context of HIV. Particular attention is focused on the associations found between HRQoL and the neurocognitive profiles of infected individuals. An extensive discussion of these associations in an aging population concludes this chapter.

2.2 Neuropsychological Impairment in HIV

HIV is known to affect the brain at an early stage of infection; the brain is thought to serve as a reservoir for the virus (Ances & Ellis, 2007; Tozzi et al., 2010). This is because the penetration of ART into the CNS is limited by both the blood brain barrier and blood cerebrospinal fluid barrier. This can lead to ineffective treatment of the virus in the CNS (Liner II, Ro & Robertson, 2010). Theoretically, this can result in the development of either indirect symptoms, as a result of an increased susceptibility to other infections, or direct and

distinct neurological symptoms and neuropsychological impairment (Ances & Ellis, 2007). Neuropsychological impairment can be described as a reduction or deficit of cognitive functioning in one or more of the domains of cognition (Lezak, Howieson, Bigler & Tranel, 2012).

In the 1980s, clinicians observed neurological symptoms and mental impairment in a group of advanced HIV-positive patients (Woods, Moore, Weber & Grant, 2009). However, the direct relationship between HIV and cognitive deficits remained poorly understood. This was until a study published by Snider and colleagues (1983) clarified what clinicians were observing. Findings documented complications of HIV infection in the CNS of 50 HIV-positive patients, most of whom exhibited AIDS-related dementia.

Grant et al. (1987) subsequently also provided clarity on the existence of neurocognitive impairment directly attributed to HIV. The findings from their study demonstrated that neurocognitive impairment could be seen across all stages of HIV disease (e.g., medically asymptomatic, symptomatic, and AIDS). This included common neuropsychological problems such as impaired abstract ability, learning difficulty, and slowed speed of information processing. Also, it was argued that probable involvement of HIV in the CNS may begin in the early stages of infection, potentially causing mild cognitive deficits in asymptomatic individuals. Other authors confirm these findings (Heaton et al., 1995; Lunn et al., 1991; Wilkie, Eisdorfer, Morgan, Loewenstein & Szapocznik, 1990). The study by Grant et al. (1987) was one of the first comprehensive publications on HIV-associated neurocognitive deficits/disorders.

2.3 HIV-Associated Neurocognitive Disorders (HAND)

HAND (HIV-associated neurocognitive disorders) is a term used to categorise and describe the presence of chronic CNS HIV infection and its implications for

neurodegeneration of the brain (Tozzi et al., 2010). More specifically, HAND is used to describe a spectrum of neurocognitive disorders related to HIV. This includes changes in cognition, ranging from slowed information processing and forgetfulness to noticeable dysfunction affecting daily living activities (Bloom & Rausch, 1997). It is worth mentioning that terms such as AIDS-related dementia, HIV-associated dementia (HAD), HIV encephalopathy, and AIDS dementia complex are used interchangeably to describe a similar triad of symptoms (psychomotor slowing, memory impairment, and behavioural problems) evident in infected individuals. Nowadays, however, HAND is said to be a more comprehensive title used to describe these symptoms (Grant, 2008; Robertson, Liner & Heaton, 2009).

HAND and the accompanying changes in cognition can be detected through a variety of comprehensive clinical and laboratory-based measures. This is largely dependent on the resources available in the setting where the patients are being evaluated (Antinori et al., 2007). Arguably, neuropsychological assessment is said to be an important tool for diagnosing and categorising the effects of the HIV virus on the central nervous system. This is especially true of resource-limited settings where advanced neuroimaging and laboratory technology are often unavailable (Robertson et al., 2009). The following section will provide a more in-depth discussion on the role of neuropsychological assessment in the identification of HAND.

2.3.1 Neuropsychological assessment in HAND identification

Neuropsychological assessment can be described as one method of detecting and explaining potential brain-based impairment in cognitive function or behaviour. In other words, neuropsychological assessment aims at investigating the brain through studying its behavioural product. This can be done through incorporating aspects of clinical observations

and neuropsychological tests in order to explain brain-behaviour relationships (Lezak et al., 2012; Zillmer, Spiers & Culbertson, 2008).

Traditionally, neuropsychological testing can be defined as recognised, standardised instruments which are sensitive indicators of brain functioning that can provide objective neurocognitive data useful for diagnostic purposes (Zillmer et al., 2007). This can assist in the determination of whether patterns of neurocognitive impairment are most consistent with HIV-associated dementia or other conditions (Ances & Ellis, 2007). Dennis, Houff, Han and Schmitt (2011) report that although hundreds of neuropsychological test measures are said to exist (Lezak et al., 2012), various batteries have been specifically created in order to evaluate neurocognitive function in HIV.

Robertson, Liner and Heaton (2009) suggest that some of the general aims of neuropsychological assessment in HIV-infected populations should include (a) finding neurocognitive impairment directly attributable to HIV; (b) help determine if neurocognitive impairment is associated with co-morbid factors (i.e., psychiatric illness, nutritional deficiencies); (c) allow for the investigation of the relationships between neurocognitive impairment and HIV disease variables such as a history of immunodeficiency (i.e., cluster of differentiation 4 (CD4) count, viral load, biomarkers of HIV neuropathogenesis, and brain pathology); (d) exploring the relationship between HAND and everyday functioning within different population groups; (e) help in determining implications for treatment; (f) determining when treatment should commence in order to protect the CNS from further damage and aid in a continued quality of life, and (g) allow feedback to be available for clinicians and patients on the evaluation of disease progression and effectiveness of treatment.

2.3.1.1 Neuropsychological assessment in South Africa

In the South African setting, accurate identification of neuropsychological impairment is confounded by a number of factors. Local clinics are often unprepared for the large numbers of patients who present with HIV, and often face cultural or language barriers that can hinder the length and accuracy of assessments (Singh et al., 2010). Furthermore, the limited population-specific normative standards and cross-cultural validity hinder clinicians in their efforts to make an accurate diagnosis (Antinori et al., 2007). Yet, Antinori et al. (2007) argue that despite these limitations, and until appropriate normative and standardised data becomes available, algorithms and clinical assessment or judgment can still be used to great effect in establishing the same criteria.

To compensate for the above-mentioned limitations, brief but comprehensive neuropsychological screening batteries are used for the detection of HAND in South Africa. A study by Singh et al. (2010) was one of the first South African studies to recommend a brief battery of standardised neuropsychological tests in order to present locally derived population normative scores for two neuropsychological tests, namely the Trail Making Test (Parts A and B) and the Digit Span Test. Results demonstrated the applicability of a brief 15-minute battery of standardised neuropsychological tests, with locally relevant population norms, that can be conducted by a nonprofessional in the identification of neuropsychological impairment.

In summary, this section addressed the identification of HAND, with particular reference to neuropsychological assessment. As Vally (2011) stipulates, when neuropsychological assessment tools are psychometrically complete, deemed reliable, are valid, and have the appropriate normative data for the population being assessed, they can be

helpful tools for diagnosing and categorising the effects of HIV on the central nervous system.

2.3.2 Current diagnostic nosology of HAND

In 2007, the National Institute of Mental Health and the National Institute of Neurological Diseases and Stroke (Antinori et al., 2007) established a working group to amend the outdated guidelines for assessing/identifying HAND, as originally proposed by the American Academy of Neurology (AAN) AIDS Task Force (Janssen, Cornblath, Epstein & Foa, 1991). The need for revising the diagnostic nosology of HAND came about because of the use of HAART and its impact on the lifespan of an individual living with HIV and the clinical presentation of HAND (Antinori et al., 2007). The reviewed guidelines pay more attention to neurocognitive disturbances, especially in the medically asymptomatic population, as well as the notable interruptions in activities of daily living (ADL) (Antinori et al., 2007).

The reviewed diagnostic guidelines now constitute three specific syndromes, namely (i) asymptomatic neurocognitive impairment (ANI); (ii) HIV-associated mild neurocognitive disorder (MND); and (iii) HIV-associated dementia (HAD). An overview of these syndromes will be discussed below.

2.3.2.1 Asymptomatic neurocognitive impairment (ANI)

ANI refers to mild slowing in mental alertness and loss of concentration (Vally, 2011). In other words, such individuals tend to show an acquired impairment in cognitive functioning (Tozzi et al., 2010). Individuals meet the requirements for a diagnosis of ANI when their neuropsychological performance score, as reflected by detailed neuropsychological testing that explores at least five cognitive domains, is said to be less than

one standard deviation below the mean in demographically adjusted normative scores in at least two of the cognitive domains (Antinori et al., 2007). This can include domains of attention, information processing, language, abstraction-executive functioning, complex perceptual motor skills, memory, simple motor skills, and sensory perceptual abilities. It is also important to note that the cognitive impairment does not interfere with everyday functioning (Antinori et al., 2007). Thus early detection is essential to assess individuals who may be at risk for further cognitive and functional decline.

2.3.2.2 Mild neurocognitive disorder (MND)

For an infected individual to qualify for a diagnosis of MND, mild to moderate neurocognitive impairment should be evident (Antinori et al., 2007). MND is quantified by one standard deviation obtained in at least two of the cognitive domains, as documented by detailed neuropsychological testing that explores at least five cognitive domains (Antinori et al., 2007). Mild difficulties in everyday functioning or activities of daily living should also be described (Antinori et al., 2007; Woods et al., 2009).

Woods, Moore, Weber and Grant (2009) describe and quantify mild difficulties in everyday functioning/activities of an individual who meets at least two of the following criteria: (1) a patient presents with a decline in at least two instrumental activities of daily living which can be as diverse as financial management or bathing, for example, and as measured by self- or proxy report; (2) unemployment or a significant decrease in job performance and responsibilities secondary to the reduced cognitive abilities; (3) a decrease in vocational/occupational functioning, for example an increase in errors or a decrease in productivity; (4) self- or proxy report, suggesting an increase in problems experienced in at least two cognitive ability areas in day-to-day life – Woods et al. (2009) caution against using only this criterion in patients with current depression and self-report; and (5) an individual

scores more than one standard deviation below the mean for performance-based laboratory measures of everyday functioning, for example medical management. The mentioned criterion becomes important when one considers the impact of cognitive impairment on the quality of life of an infected individual. However, this issue will be addressed later in this literature review.

2.3.2.3 HIV-associated dementia (HAD)

Clinically, HAD is considered the more severe form of the three categories. This is due to the marked impairment of everyday functioning, and because it often presents at a later stage of HIV infection (Antinori et al., 2007; Grant, 2008; Tozzi et al., 2010). HAD is characterised by moderate to severe neurocognitive impairment, and is quantifiably diagnosed when an individual obtains a performance score that is at least two standard deviations below the norm of a demographically accounted test in two different cognitive domains (Antinori et al., 2007); these criteria also emphasise the interruptions in activities of daily living (work, home life, and social activities). This is due to the interference of marked cognitive impairment (Antinori et al., 2007).

McArthur, Brew and Nath (2005) suggest the early clinical features of HAD include a combination of a triad of manifestations which encompass areas of cognition (forgetfulness, poor concentration), motor (tremor, ataxia), and behavioural symptoms (agitation and apathy). As the disease progresses, symptoms of dementia, paraplegia, and mutism have been reported (McArthur, Brew & Nath, 2005; Tozzi et al., 2010). This process is often irreversible as it is generally agreed that HAD occurs most frequently in the late stages of the disease, as clinical symptoms evolve insidiously over a period of weeks or months (McArthur et al., 2005).

Notably, a diagnosis of all three forms of HAND requires that the observed neurocognitive impairment and/or functional disturbances cannot be accounted for by co-morbid (non-HIV-related) conditions (Antinori et al., 2007; Robertson et al., 2009).

2.3.3 Incidence and prevalence of HAND

Currently, the influence of ART and HAART has allowed HIV to be considered a chronic but manageable disease, as infected individuals are living longer and receiving long-term treatment (Ances & Ellis, 2007; Tozzi et al., 2010). Yet, recent literature illustrates that despite ongoing treatment and improved longevity, cognitive decline in infected individuals is still prevalent (Robertson & Hall, 2007), particularly the subtle forms of HAND (MND and ANI) which tend to persist, and are estimated as ranging between 30% and 60% of infected individuals (Foley, Ettenhofer, Wright & Hinkin, 2008; Grant, 2008).

However, Foley, Ettenhofer, Wright, and Hinkin (2008) argue that neurocognitive profiles seen in infected individuals have become highly heterogeneous, and increasingly fail to resemble pre-HAART presentations. This variation is likely to be accounted for by differential viral clades (genetic subtypes). These genetic subtypes have different biological properties that could account for the variation of patterns seen in disease progression, neurologic changes, and cognitive arrangements (Foley et al., 2008; Liner, Hall & Robertson, 2007). The following section aims to provide an overview of the presentation of neurocognitive profiles in various population clades worldwide.

The B subtype is highly prevalent in developed countries such as Great Britain, Europe, Australia, some parts of South America, and the United States (Robertson & Hall, 2007). Clades A and D have been reported in Central West Africa and Uganda (Wong et al., 2007). An interesting finding was that clade C reflects an estimated 50% of HIV infections globally, and is associated with rapidly growing epidemics in sub-Saharan Africa and some parts of

Asia (Modi, Hari, Modi & Mochan, 2007; Robertson & Hall, 2007). However, this subtype remains a poorly understood phenomenon and to date, little research has been undertaken to investigate the prevalence, risk factors, and consequences of HAND (Joska et al., 2011). This is largely due to the challenges many of these resource-limited areas are faced with daily. This includes insufficient ART, cultural, socio-demographic differences, and limited normative data on neuropsychological assessment sensitive to neurocognitive impairment (Robertson & Hall, 2007). The following section reviews some of the literature pertaining to the clade C subtypes and neurocognitive profiles in the sub-Saharan Africa/South African context.

Breuer, Myer, Struthers and Joska (2011) conducted a literature review which explored the prevalence of neurocognitive deficits in Sub-Saharan Africa. Results reported that the prevalence of neurocognitive disorders, ranging from 31% to 99% in adults, often occur in the late stages of the disease. Breuer et al. (2011) argue that this variation resulted from the specific tools used, and the clinical status of the patient group.

Furthermore, Modi, Hari, Modi and Mochan (2007) conducted a study to determine the frequency and spectrum of neurological illness in black South African hospital-based HIV-infected (clade C) patients. Of particular interest was that 38% of the patients involved in the study met the diagnostic criteria for HAD. In regards to the more subtle forms of impairment, the prevalence of MND and HAD in HIV-positive participants was 42.4% and 25.4% respectively (Joska et al., 2011). These results are in keeping with other findings emanating from the developing world. In Uganda the frequency of HIV-dementia was 31% (Wong et al., 2007) and in Botswana 37% (Lawler, Mosepele, Ratcliffe et al., 2010).

It can therefore be argued that cognitive impairment, and in particular minor impairment, is underrecognised in large numbers of individuals with HIV on HAART.

Consequently, HAND remains present and raises concern for individuals with HIV in Africa and in the public health sector.

2.3.4 Risk factors of HAND

Literature reveals that there is a need to investigate the potential risk factors for persistent neurocognitive impairment. This is in light of evidence suggesting that infected individuals can live longer, but that HAND continues to persist, despite treatment (Tozzi et al., 2005).

The following risk factors have been associated with HAND: low CD4 count (Tozzi et al., 2005; Wong et al., 2007); lower levels of education (Lawler, Jeremiah, Mosepele et al., 2011); male gender (Joska et al., 2011); and advanced aging (Joska et al., 2011; Lawler et al., 2011; Tozzi et al., 2005; Valcour, Shikuma, Shiramizu, et al., 2004; Wong et al., 2007).

Consequently, the discussion now shifts from describing and identifying the incidence, prevalence, and potential risk factors of HAND to the correlation between aging and HIV.

2.4 HAND and Aging

Since HAART has been shown to improve the survival rates of individuals with HIV, a number of adults are now aging with the virus. As a result, advanced age has become a disconcerting and relevant risk factor for the development of HAND (Ances & Ellis, 2007).

In the United States of America, approximately 25% of reactive patients are 50 years of age or older. This number is expected to increase by 25%, resulting in an overall 50% of people living with HIV/AIDS in the US by 2015 (Smith, 2005). In addition, the number of infected individuals over 65 years of age has doubled between 1994 and 2004 (Stoff, Khalsa, Monjan & Portegies, 2004; Valcour et al., 2011). Yet, despite older adults making up a large and ever-growing proportion of individuals with HIV in the United States, little attention has

been given to researching this population (Martin, Fain and Klotz, 2008). Gonzalez and Cherner (2008) argue that only recently has research in this area increased due to the large number of individuals over the age of 50 years seen in the HIV-infected population. However, to date, little data has been published about older HIV-infected individuals in Africa (Mutevedzi & Newell, 2011; Negin, Mills & Bärnighausen, 2012).

Nevertheless, developing countries such as South Africa will need to make provision for these patients. Hontelez et al. (2011) predict a similar likelihood of an aging HIV population as seen in developed countries. Findings from their microsimulation model study reveal that the prevalence of HIV in patients over 50 years of age will nearly double in the next 30 years, whilst the numbers of infected HIV patients aged over 50 will triple in the same period. Currently, it is estimated that approximately 3 million people over 50 years of age are living with HIV in sub-Saharan Africa, with roughly 9% of this population prevalent in the South African setting (Negin & Cumming, 2010; Wallrauch, Barnighausen & Newell, 2010).

Thus, it is of great importance for local health care systems as well as research to focus on an older HIV-infected population, and to devise creative resources to meet the needs of an increasingly HIV-positive, aging population (Hontelez et al., 2011). Several confounding factors, however, may contribute to making this population a difficult group to study. These challenges involve defining who qualifies as an older adult; which subset of older adults to study; measuring age and aging as a research construct; and ethical and practical dilemmas – to name but a few (Levy, Holmes & Smith, 2003).

2.4.1 Defining ‘older adult’

According to Levy, Holmes and Smith (2003), there are numerous factors that may influence the definition of what one may consider an ‘older adult’. This can include how a

culture may perceive longevity, media influence, mental and physical health, gender, and the notion of maturity. This may become further complicated when one considers HIV in the context of aging and an older population. As a result, defining what constitutes an 'older adult' in the context of HIV-infected individuals tends to differ in literature.

A common convention for defining age, aging or older adulthood in HIV/AIDS research is based on the researcher's sampling decision; this can be influenced by practical considerations (Levy et al., 2003). This is especially true of the South African setting, where studies investigating older HIV-infected populations often rely on clinics to access samples. This is due to easy accessibility of the participants as well as minimal sampling costs. In such circumstances, determining who is defined as an older adult, and who is potentially involved as a subject within HIV/AIDS and aging research, is largely influenced by convenience samples from the lower and upper range of patients that make use of such clinics (Levy et al., 2003).

There are some disagreements amongst authors with regard to the chronological age number selected to determine 'older age'. Gebo (2006) suggests that whilst 50 years of age is not always seen as the threshold to indicate advancing age, the USA Centers for Disease Control and Prevention (CDC) however argue that individuals aged 50 years and older should be considered a separate age group, since this group is much older than the mean age of HIV patients measured early on in the HIV epidemic. However, with the widespread use of antiretroviral therapy, the upper end of the epidemic distribution is beginning to extend into the older age groups (High, Valcour & Paul, 2006). Older individuals with HIV are perhaps aging despite being infected with HIV, or are becoming newly infected at a more advanced age (High, Valcour & Paul, 2006).

Moreover, Negin and Cumming (2010) noted that the International AIDS Society has recently focused on infected individuals between the ages of 15 and 49 years. As a result, a significant number of infected individuals over the age of 50 years and older have been excluded from HIV prevention and testing services. Such notions need to be considered in context when assessing an 'older adult' population affected by a chronic disease.

2.4.2 The influence of normal aging in HIV

Neurobiological parallels have been drawn and documented between normal aging and HIV infection (Ances et al., 2010). Furthermore, both are independently associated with a decline in certain cognitive abilities and the impact on neuropsychological test performance (Cherner et al., 2004; Gonzalez & Cherner, 2008; Valcour et al., 2011). Nevertheless, a number of researchers have postulated that HIV plays an accelerating age-related role in cognitive changes, and potentially predisposes infected individuals to neurodegenerative disorders (Valcour, et al. 2011). Some of these studies are presented and discussed below.

A study conducted by Valcour, Shikuma, Shiramizu et al. (2004) demonstrated that HAD is more frequent in older (25. 2%) compared to younger (13.7%) infected participants. The researchers also adjusted for education, race, substance dependency, viral load, CD4 count, and ART medication. Moreover, the likelihood of having HAD amongst individuals in the older group was 3.26 times that of the younger group. Similar findings have been reported in an international study investigating neurocognitive disorders amongst individuals with HIV (Becker, Lopez, Dew & Aizenstein, 2004). Results concluded that the more severe forms of HAND, namely HAD (23%) were found to be more prevalent amongst individuals over the age of 50.

Conversely, findings from the Multicenter AIDS Cohort Study (MACS) (Van Gorp et al., 1994) who examined a small group of well-educated, asymptomatic HIV subjects,

showed no significant effects of age on HIV-associated impairment. This is likely due to the small sample size which could have been insufficient in revealing more prominent differences. The study did, however, reveal that age was associated with worse performance on timed tests. Comparable findings have been reported in a study conducted by Cysique, Maruff, Bain, Wright, and Brew (2011). The aim of this study was to investigate if there were a linear and/or nonlinear differential age effect on neuropsychological performance between groups of advanced HIV-infected individuals and healthy HIV-negative volunteers. It was suggested that a significant differential effect of age would imply that HIV and age have additional or synergistic effects of cognitive functioning. A non-significant result may suggest a need for reinvestigation, or that potential survivor bias may exist. Results demonstrated no clear combined effect of HIV and age on cognitive function. Similarly, Kissel, Pukay-Martin, and Bornstein (2005) investigated the interaction between age and cognitive impairment in HIV-positive and HIV-negative comparison subjects. Results failed to support the hypothesis that advancing age is a risk factor for the development of HIV-related cognitive impairment.

Although aging and HIV interaction on cognitive impairment reveal mixed findings throughout literature, aging should still be considered an important risk factor or determinant for HAND (Becker et al., 2004; Valcour, Shikuma, Shiramizu, et al., 2004). Research has shown that the combination of aging with HIV places the older HIV-positive adult population at greater risk of neurocognitive impairment and susceptibility to the development of HAND (Cherner et al., 2004; Hardy & Vance, 2009; Valcour, Shikuma, Watters & Sacktor, 2004).

2.4.3 Confounding medical factors in ‘older adult’ populations

Literature reflects that a number of medical complications are associated with an ‘older adult’ HIV-infected population. These factors need to be taken into consideration, as they

may become confounding issues in the progression of HIV in older patients. Firstly, physicians/clinicians often hold inaccurate assumptions about risk behaviour in older populations, and therefore fail to perform more routine screening for HIV/AIDS. Secondly, a missed or latent diagnosis has implications for disease duration or chronicity (Ances et al., 2009) and consequently, antiretroviral treatment tends to be delayed. This compromises treatment efficacy (Grabar, Weiss & Cotagliola, 2006) and becomes problematic in older individuals, especially since they may not respond as well to HAART as their younger counterparts (Gebo, 2006). In other words, it can be said that older infected adults have less capacity for immune recovery. Thirdly, older age in itself is associated with many age-related medical conditions, (e.g., cardiovascular disease, liver failure, kidney failure) (Stoff, 2004). Fourthly, clinicians lack awareness, and their confusion relating to symptoms of opportunistic infections (a group of nervous system disorders encountered during HIV infection) as well as the frequent co-morbid conditions often associated with aging, may impact on screening for HIV (Grabar et al., 2006). HIV-related cognitive decline itself may imitate symptomatic patterns of various diseases such as Alzheimer's disease, Parkinson's disease, or cerebrovascular dementia. Therefore, a differential diagnosis from clinicians is essential (Grabar et al., 2006; Power, Boissé, Rourke & Gill, 2009).

Finally, clinicians are encouraged to consider HIV infection a primary contributor to cognitive impairment in older individuals that seem to be HIV-seronegative/medically asymptomatic (High, Valcour & Paul, 2006). However, the challenge is that limited reliable and valid data is available worldwide on HAND in older HIV-infected adults (Stoff, 2004). Therefore, as Grabar, Weiss, and Cotagliola (2006) argue, more studies of this age group need to be conducted in order to generate specific management guidelines about the prevention, transmission, diagnosis, and treatment of HIV infection in an appropriate manner.

From the discussion above, it is clear that with an aging HIV population on the upsurge, various confounding factors need to be taken into consideration in order to gain a better understanding of the later development of target interventions in HAND and aging. A potentially appropriate place to begin is through an investigation of the neurocognitive profiles of individuals with HIV, as this permits detection of these disorders (Power et al., 2009). The following section will provide an in-depth discussion of the patterns of distribution for neurocognitive impairment in HIV-infected individuals.

2.5 The Neurocognitive Profile of HAND

Dementia due to HIV is typically characterised by a 'subcortical' neurocognitive profile of dysfunction (Ances & Ellis, 2007; Grant 2008; High, Valcour & Paul, 2006). This is due to a disruption in cognitive functions wired by white matter pathways and specific grey matter nuclei that lie deep within the subcortical regions of the brain (High, Valcour & Paul, 2006).

However, a heterogeneous pattern of neurocognitive profiles has emerged (Dawes et al., 2008) as recent reports indicate cognitive defects, characterised by cortical brain regions (Vally, 2011; High, Valcour & Paul, 2006).

This heterogeneous pattern of neuropsychological performance can include problems in executive functioning, speed of information processing, attention and working memory, new learning, motor skills, and retrieval of new information. Moreover, the presentation of this cognitive pattern is not exclusive, and can include deficits in other domains such as language skills, memory (delayed retention), and aspects of visuo-spatial and sensory-perceptual abilities. The latter, however, remain relatively intact in the early stages of the illness (Dawes et al., 2008; Heaton et al., 1995; Reger, Welsh, Razani, Martin & Boone, 2002).

The cognitive domains mentioned above are often the targets for the neuropsychological assessment of HAND, internationally (Robertson et al., 2009; Tozzi et al., 2003) and more recently in resource-limited settings (Kanmogne et al., 2010). The following section will present an overview of HIV-neurocognitive impairment. Specific attention will be given to studies that assess cognitive function as it relates to aging and older individuals with HIV.

2.5.1 Attention, processing speed, and working memory

2.5.1.1 Defining attention, processing speed, and working memory

Attention can be described as a general level of alertness or vigilance. This further includes a general state of arousal, orientation, the ability to focus, divide, or sustain mental processes (Zillmer et al., 2008).

The recent fifth edition of the Diagnostic Statistical Manual (DSM 5) describes three aspects of attention: sustained attention which is considered the preservation of attention over time; selective attention which is the continuance of attention despite competing stimuli and/or distractors; and divided attention which is when an individual attends to two tasks within the same time period (American Psychiatric Association, 2013).

It can be argued that speeds of information processing, short-term memory and working memory are important dimensions that constitute the basics of attentional ability, although various sources differ on this issue (Grant, 2008; Lezak et al., 2012). This is because speed of processing, which is often required in many cognitive operations, requires an individual to have the ability to gather adequate information in order to execute relevant operations within the time allowed (Grant, 2008; Salthouse, 1996). Short-term memory is the temporary holding of newly registered information. It is often equated with simple, immediate span of attention and aspects of immediate/working memory (Lezak et al. 2012; Zillmer et al., 2008).

On the other hand, working memory requires temporary storage and manipulation of information in order to be used for problem solving or other cognitive operations at hand (Lezak et al., 2012).

In the context of neuro-AIDS, research suggests that a more comprehensive definition is required when understanding and assessing attention. Mirsky and Duncan (2001) propose a five-level component process of attention. This includes the ability to (a) focus/execute which involves the ability to focus on a task at hand, despite distractions, and then execute a response as quickly as possible; (b) encode/working memory which includes briefly holding information in memory, and then using it to perform a mental task; (c) attentional shift which involves the ability to move one's attention from one complex stimulus to another; (d) sustain which is to maintain attentional focus for a period of time; and (e) stabilise attention which involves the consistency/stability, with which an individual can respond to specific stimuli. Although this model is not without fault, it is useful in the context of HIV (Woods et al., 2009). Lastly, intact attention is often required for most mental activities (Lezak et al., 2012).

2.5.1.2 Attention, processing speed, and working memory in normal aging

According to literature, normal aging is said to have an impact on attentional processes, including complex attention, speed of information processing, and working memory (Glisky, 2007). In general, simple attention remains relatively intact in individuals 80 years of age (Lezak et al., 2012). More complex forms of attention (i.e., divided attention, the ability to shift, sustain, and select attention) rely on working memory capacity which tends to decline in older adults (Glisky, 2007; Zillmer et al., 2008). This can result in slow responses and an increase in errors in older adults (Lezak et al., 2012).

2.5.1.3 Attention, processing speed, and working memory in HIV

In the context of HIV infection, as with other neurocognitive domains, impairment of attention/working memory and speed of information processing is evident in individuals with HAND (Cysique, Maruff & Brew, 2006; Reger et al., 2002). Reger, Welsh, Razani, Martin, and Boone (2002) suggest that during the initial stages of the disease, basic attention and concentration abilities remain relatively intact. As the disease progresses, mild to moderate deficits in attention/working memory can be noted.

Furthermore, the pattern of deficits in this domain is influenced by the severity of the disease, and the complexity (attentional load) of the task at hand (Vally, 2011; Woods et al., 2009). A common theme, as noted in the review study by Woods et al. (2009), is that deficits in basic attention or seemingly automatic abilities emerge when an infected individual is placed under increased processing demands.

A number of studies suggest that complaints of attention/working memory difficulties in individuals with HIV are strong indicators of cognitive decline (Hardy & Vance, 2009), which may influence everyday functioning and independent living (driving abilities, medication adherence, etc.) (Heaton et al., 2004; Vally, 2011; Woods et al., 2009).

Hardy and Vance (2009) reviewed several studies (Becker et al., 1997; Hardy et al., 1999) on the neuropsychology of HIV/AIDS in older adults. They conclude that older individuals with HIV have deficits in specific cognitive abilities, often involving aspects of attention, cognition, and psychomotor speed.

2.5.2 Learning and memory

2.5.2.1 Defining learning and memory

Memory can be termed the capacity to preserve material, and the ability to apply it adaptively. This process includes the notion of learning which requires information to be retrieved, encoded, and stored (Lezak et al., 2012). The above can be understood in the framework of long-term memory, short-term memory, and prospective memory.

Long-term memory can be described as the ability to learn and retain new information, with unlimited capacity, and remains relatively permanent (Lezak et al., 2012; Zillmer et al., 2008). Various theoretical orientations conceptualise long-term memory into two long-term storage and retrieval systems: declarative and nondeclarative memory systems. Declarative is explicit and consciously accessible memory often divided into episodic memory (individual episodes, autobiographical memory) and semantic memory (memory for information and facts) (Lezak et al., 2012; Zillmer et al., 2008). Nondeclarative memory is usually implicit and procedural forms of memory, for example action, perceptual-motor skills, and conditioned reflexes such as riding a bike (Lezak et al., 2012; Zillmer et al., 2008).

As previously mentioned, short-term memory is the temporary holding of newly registered information. Furthermore, it is often equated with constructs of simple attention and immediate or working memory (Lezak et al. 2012; Zillmer et al., 2008).

Prospective memory is another form of memory. It can be described as the ability to remember to remember (e.g., remembering to take medication). This complex memory system incorporates formation, maintenance, retrieval, and executing the correct objective necessary for success in independent living (Doyle, Weber, Atkinson, Grant & Woods, 2012; Lezak et al., 2012).

2.5.2.2 Learning and memory in normal aging

It is evident that certain aspects of memory and learning change with advancing age, and older populations report difficulty in retrieving information and free recall, compared to recognition (Lezak et al., 2012; Zillmer et al., 2008). Consequently, these deficits in information retrieval may be as a result of poor information encoding in older populations (Brew, Crowe, Landay, Cysique & Guillemin, 2009; Zillmer et al., 2008). Short-term or immediate memory shows only sight age effect (Lezak et al., 2012). However, when an individual is required to mentally manipulate material (working memory), short-term memory becomes more vulnerable with age (Lezak et al., 2012). Memory deficits in older individuals can also be as a result of problems in other cognitive domains, for example, processing speed or reduced attention (Lezak et al., 2012). Tasks involving implicit and procedural memory appear to be less affected by memory deficits. However, these tasks may be performed at a slower rate in older populations (Zillmer et al., 2008). Prospective memory, although mixed findings have been found in literature (Lezak et al., 2012), is thought to be poor and a common complaint in older individuals as a result of difficulty in basic encoding, storage, and retrieval (Lezak et al., 2012; Zillmer et al., 2008).

2.5.2.3 Learning and memory in HIV

In HIV infection, the prevalence of impairment in episodic memory remains relatively high, with estimates ranging from 40% to 60% (Heaton et al., 1995; Woods et al., 2009). Furthermore, deficits in aspects of episodic memory, along with psychomotor slowing, have been observed and have become important indicators for HAND, especially as these deficits are known to worsen as the disease progresses (Reger et al., 2002; Scott et al., 2006; Woods et al., 2009).

Woods et al. (2009) argue that a large proportion of individuals with HIV present with similar patterns of HIV-associated episodic memory deficits in terms of encoding and retrieval profiles. This profile is characterised by impaired immediate and delayed free recall of information, albeit by a relatively better ability to recognise the presented information (Woods et al., 2005). Similar findings have been reported in Botswana where results from a neurocognitive pilot study have shown impaired free recall due to retrieval ineffectiveness, but relatively well-preserved recognition (Lawler et al., 2010). A rapid increase in forgetfulness has also been noted in a small percentage of infected individuals presenting with HAD (Scott et al., 2006; Woods et al., 2009). An earlier study, conducted by Justice et al. (2004), similarly reported memory deficits in an HIV population. Results revealed a higher incidence of memory and neurocognitive problems in HIV-infected individuals of advancing age. Deficits in the above-mentioned aspects of memory could have implications for everyday functioning (Doyle et al., 2012; Woods et al., 2009).

2.5.3 Speech and language

International studies often include domains of speech and language in measures of cognitive ability, specifically within the sphere of HIV-associated neurocognitive impairment. However, in a multi-cultural context such as South Africa, many neuropsychological tests (some of which are language-based) often result in cultural bias (Singh et al., 2010). Therefore, a full overview is not included in this literature review as this domain is not assessed in the current study. For a review of studies exploring this domain, see Vally (2011).

2.5.4 Perceptual-motor abilities

Perceptual-motor abilities constitute a domain that often overlaps with other cognitive domains. For the purpose of this research, visuo-perceptual ability and motor skills will be tested.

2.5.4.1 Defining perception (visuo-perceptual ability)

Visuo-perceptual ability is one aspect of perception often assessed by neuropsychologists. It can be defined as a set of skills that one uses to gather visual information from the external world (environment) and integrate it meaningfully (Zillmer et al., 2008).

2.5.4.2 Defining motor skills

Motor skills can be described as an important component in the process of sensory stimuli response (Zillmer et al., 2008). Motor skills can be divided into abilities of construction, assembly and building, manual dexterity, and strength (Lezak et al., 2012).

2.5.4.3 Perceptual-motor abilities in normal aging

Advanced aging has generally demonstrated a steady decline in visuoperceptual judgment of both spatial and nonspatial objects, and is accompanied by slowing in various aspects of behaviour. Moreover, a decline in simple reaction time and diminished manual dexterity manifest with advancing age. As a result, the decline in coordination of fine motor skills and disruptions in balance/posture often result in a lack of coordination and falls (Lezak et al., 2012).

2.5.4.4 Perceptual-motor abilities in HIV

With regard to visuoperception, it has been widely accepted that spatial cognition is largely unaffected in individuals with HIV (Woods et al., 2009). However, mild deficits in spatial cognition, including visuoconstruction and visuospatial functioning, have recently been noted in individuals with HIV. However, further investigation regarding the etiology of this phenomenon is required (Vally, 2011; Woods et al., 2009).

Psychomotor processing and motor speed slowing can be considered hallmarks of HIV infection (Sacktor et al., 1996). The most prominent features of HIV-associated motor slowing include unsteady gait (walking) disturbances such as stumbling and tripping; bradykinesia (slowed movement); and bradyphrenia (slowed information processing) (Woods et al., 2009; McArthur, Steiner, Sacktor, & Nath, 2010). HIV-associated motor slowing is often evident during actual assessments aimed at monitoring motor skills, such as assessment of gait velocity (Robertson, et al., 2006), finger tapping (Heaton et al., 1995), or indirect tasks which may/may not incorporate motor demands.

A study conducted by Valcour et al. (2008) found that the severe impairment observed on the motor scale of the Unified Parkinson's Disease Rating Scale was prevalent amongst older individuals with HIV. The impairment was most noticeable when slowness-of-hand movement, body bradykinesia, action/postural tremor, and hypomimia (facial expression) were assessed. This finding may have important implications for an aging HIV population.

2.5.5 Executive functioning

2.5.5.1 Defining executive functioning

Executive functioning can be described as higher-order regulatory and supervisory functions necessary for many effective and contextually appropriate cognitive, social, and emotional skills (Lezak et al., 2012; Spreen & Strauss, 1998). It is usually a multi-

dimensional construct comprising a range of processes which include planning, coordination, implementing, organising, and evaluation of tasks and actions (Brew et al., 2009; Lezak et al., 2012).

The DSM 5 provides a more detailed subdivision and definition of the components of executive functioning. This includes planning which is the ability to display forward thinking in light of a problem; decision making which is the performance of tasks that assess the process of deciding in the face of competing options; error utilisation which is the ability to benefit from feedback to gather the rules for solving a problem; inhibition which is the ability to choose a more complex and challenging solution to be correct; and lastly, mental flexibility which is the ability to shift between two concepts, tasks or response rules (American Psychiatric Association, 2013).

2.5.5.2 Executive functioning in normal aging

Executive functioning components such as reasoning, concept formation, and mental flexibility appear to be affected by the normal aging process. Specifically, reasoning with regards to familiar items appears to withstand aging, whereas unfamiliar or complex reasoning may require cognitive reserves that are limited in aging individuals (Lezak et al., 2012). Concept formation, concrete thought processes, and mental flexibility used in abstraction and in forming conceptual links tend to also diminish with age (Lezak et al., 2012).

2.5.5.3 Executive functioning in HIV

Executive dysfunction is considered central to HAND profiles, as is evident from cluster-analysis studies (Dawes et al., 2008). Yet, few studies have assessed the underlying cognitive components of executive dysfunction in HIV, when compared to other cognitive domains (Vally, 2011). Moreover, executive dysfunction becomes more prominent with

disease progression, especially in the latter stages (Reger et al., 2002) and is associated with impairment in everyday functioning (Heaton et al., 2004).

In summary, age and HIV-related changes in cognitive functioning vary across individuals, with some cognitive domains being more susceptible than others. Aging may potentially increase and accelerate early onset of cognitive deficits such as processing speed, working memory, and challenging learning/retrieval that are common to both (Brew et al., 2009). In turn, deficits in neuropsychological performance could impact everyday functioning and quality of life.

2.6 Health-related Quality of Life (HRQoL)

Pharmacological advances have assisted in achieving the primary goal of prolonging the lives of HIV-infected individuals. However, the impact of a chronic disease on daily living (employment, driving abilities, sexual functioning) still needs to be extensively investigated in older adults. Consequently, quality of life (QoL) is one mode of monitoring the progression or impact of a disease, and assessing the effects of treatment. This is particularly important in diseases such as HIV/AIDS (Wu et al., 2000).

2.6.1 Defining health-related quality of life

The World Health Organization (WHO) (Abuse, 1997) defines QoL as follows:

> '… the individuals' perception of their position in life in the context of culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, personal beliefs, and their relationship to salient features of their environment.' (p. 1)

Wu (2000) proposes that when research refers to QoL, it usually implies HRQoL. QoL can be considered a more general term, whereas HRQoL focuses on the aspects of QoL more specifically related to health. In essence, HRQoL can be defined as a multidimensional concept that defines wellbeing in terms of physical, emotional, mental (cognitive), and social functioning, and how a patient may feel about his or her health (Badia & Baró, 1999; Wu, 2000).

2.6.2 Measuring health-related quality of life

Besides defining HRQoL, assessing such a construct can aid in developing guidelines for treatment plans to target diseases, and elicit important information about patient care and implementing interventions (Parsons, Braaten, Hall, & Robertson, 2006). However, in order to achieve this, there is a need for accurate, reliable, and valid instruments to monitor the clinical progress of such interventions. Hence, choosing a measure is often dependent on the defined population, the disease, as well as the type of measuring instrument (Skevington & O'Connel, 2003).

According to Skevington and O'Connel (2003), two broad measures exist, namely generic and specific instruments. A generic instrument can assess a broad range of concerns that are relevant not only to healthy people but also to those with acute and chronic illnesses. In this way, different diagnostic groups (HIV and cancer, for example) can be compared using common constraints. However, the disadvantage of such an instrument is that patients might view the questions as more general and not necessarily applicable to his or her disease. Also, generic instruments might lack the ability to detect or measure change (responsiveness) in a clinical setting (Skevington & O'Connel, 2003). A specific instrument, on the other hand, has been developed to address the specific concerns of a particular disorder (Skevington & O'Connel, 2003).

Because a number of HRQoL measures are viewed as subjective in nature, Jelsma, Mkoka, and Amosun (2008) argue that the term 'health' can be perceived differently between individuals of various cultural groups, resource-limited populations, and health professionals. Furthermore, HRQoL measures developed internationally and adapted to function in a local setting may lack content validity, and results should be interpreted with caution (Jelsma, Mkoka & Amosun, 2008). This becomes imperative in the South African context.

In summary, researchers should consider the studied disease in the context of generic/specific measures, and take into consideration the sample population when deciding on measures that will result in favourable outcomes. The following discussion focuses on understanding health-related quality of life in HIV patients.

2.6.3 HRQoL and HIV

Research indicates that individuals with HIV have considerably lower HRQoL levels than the general population (Miners et al., 2001). Local findings concur that infected individuals measure significantly lower HRQoL scores when compared to individuals without HIV (Hughes, Jelsma, Maclean, Darder & Tinise, 2004; Miners et al., 2001; O'Keef & Wood, 1996). Yet, it can be argued that more empirical research, particularly in developing countries, is required to understand HRQoL in individuals with HIV (Imam, Karim, Ferdous & Akhter, 2011).

2.6.3.1 General domains of HRQoL sensitive to HIV infection

As already established, the general definition of HRQoL comprises several dimensions/domains (e.g., physical, emotional, mental, etc.). HIV is associated with domains pertaining to the physical and the psychological, the level of independence, social interaction, the environment, and spirituality. These associations are said to vary depending on socio-

demographic characteristics (e.g., age, gender, education) and clinical characteristics (e.g., disease-related variables including opportunistic infection, CD4 count) (Basavaraj, Navya, & Rashmi, 2010; Imam et al., 2011).

A review study investigated different HRQoL instruments designed for HIV patients (Badia & Baró, 1999). The study focused on instrument sensitivity to change (i.e., sensitive to detect change in HRQoL over time, either as a result of treatment or illness development) and usefulness as a measure of clinical outcome. Based on this, the authors suggest that the first dimension/domain of HRQoL to show either deterioration or improvement when measured was physical health (incapacity, functional wellbeing, and other symptoms). Other dimensions of overall health and mental health including cognitive function, were also shown to be sensitive to change in HRQoL measures. An interesting finding was that emotional wellbeing demonstrated an improvement after the initial stages of the disease. This may be as a result of means adjustment. However, social aspects, including social functioning, support, and role function are generally less sensitive to clinical change when compared to physical or mental health, and findings in this regard tend to be inconclusive.

The association between the general domains of HRQoL and HIV infection, as described above, inform our knowledge and create a holistic understanding of an infected individual's perception of his or her health and QoL. However, the current study aim is to explore the association between cognitive performance and HRQoL in older individuals with HIV. This relationship has been demonstrated in several studies with younger cohorts (Pandya, Krentz, Gill & Power, 2005; Osowiecki et al., 2000; Tozzi et al., 2003; Tozzi et al., 2004).

2.6.4 HRQoL and cognitive function

The impact of cognitive function on QoL in HIV cohorts has only recently been studied, with Tozzi et al. (2003; 2004) contributing to the majority of literature available. One study in particular (Tozzi et al., 2003) investigated the relationship between HIV-related cognitive impairment and HRQoL. The study measured the variables using a generic HRQoL measure, a battery of neuropsychological tests, and comprehensive neurological and clinical evaluation tools (brain imaging, laboratory testing). Results demonstrated that cognitive impairment (as defined by performance greater than one standard deviation below the normative mean on at least two neuropsychological tests or two standard deviations below the mean on at least one test) is associated with poor QoL. Individuals with more severe cognitive impairment had the highest probability of having poor QoL.

In addition, the ability of HIV-infected individuals to engage in the most basic and important activities of daily living often relies on an individual's intact cognitive reserves or resources. These resources play a fundamental role in an individual's functional capacity (e.g., decision making, problem solving, money management). In turn, compromised cognitive functioning could lead to a loss of independence, and ultimately impact an individual's perceived QoL (Osowiecki et al., 2000; Parsons et al., 2006).

Keeping the above in mind, the following section aims to discuss literature on neurocognitive and HRQoL profiles.

2.6.4.1 HRQoL and neurocognitive profiles in HIV

It can be suggested that the poor performance observed in cognitive abilities, fine motor function, motor speed, speed of information processing, visuospatial scanning, sequential processing, executive function, learning and memory, and attentional abilities have

been associated with a significantly diminished health-related quality-of-life profile in HIV patients (Tozzi et al., 2003; Osowiecki et al., 2000). Interestingly, two sources suggest that measures of psychomotor performance, which are often heavily reliant on sustained attention and visuomotor coordination, are considered a strong predictor of HRQoL (Tozzi et al., 2003; Osowiecki et al., 2000). This may highlight the fundamental importance of sustained attention and visuomotor coordination in an individual's performance in the subtest, and furthermore, the importance of these aspects of cognitive functioning in relation to QoL.

In summary, an individual whose neurocognitive profile presents with deficits in cognitive functioning is less able to employ effective coping strategies to manage the demands associated with his or her health status. Consequently, this is associated with a reduced perceived quality of life (Osowiecki et al., 2000). Therefore, as Tozzi et al. (2003) recommend, improving HRQoL in infected individuals may rely on determining if cognitive functioning is impaired, and whether cognitive function can be improved.

2.6.5 HRQoL and aging with HIV

Since age is said to be independently associated with reduced cognitive performance, a similar relationship is hypothesised in relation to HRQoL of older individuals. In a study by Miners et al. (2001), univariate analysis demonstrated the association between age and HRQoL. Although it was not the main aim of the study, findings showed that scores from the HRQoL measure (EQ-5D utility) was strongly associated with age *(p = . 0001;* younger individuals had higher scores when compared to older individuals). The study did not specify what 'older' individuals meant, however, the mean age was reported to be 36 years and *SD* = 9.0. Furthermore, in a study conducted by Campsmith, Nakashima, and Davidson (2003), linear regression analysis revealed the influence of age on HRQoL through which lower HRQoL scores were associated with older age, amongst other factors.

Doyle et al. (2012) argue that one important aspect not well understood in the context of aging, HIV, and HRQoL is neurocognitive impairment. A handful of studies suggest that a decline in specific neurocognitive domains of psychomotor speed, executive function as well as memory, for example, are predictors of reduced HRQoL in younger and middle-aged HIV-infected adults (Tozzi et al., 2003; Osowiecki et al., 2000). In comparison, older individuals with HIV are faced with a number of additional complications often associated with advanced age and HIV infection (Doyle et al., 2012). However, in the context of older individuals with HIV, little is known about quality of life (Skevington, 2012), and to the researcher's knowledge, few studies have investigated the association between HRQoL and neurocognitive impairment in an older HIV population in the South African context.

In closing, the above-mentioned is of concern in an older population with HIV where the implications of diseases impact on the CNS as well as brain-aging processes, and could result in disruptions in available cognitive resources necessary to carry out basic activities of everyday living. Consequently, this can be detrimental for health-related quality of life.

2.7 Chapter Conclusion

This chapter began with an overview of neuropsychological impairment in HIV, with particular focus on HAND and its implications and associations with an aging HIV population, neurocognitive profiles, and health-related quality of life. Stoff (2004) summarises that neurocognitive disorders may affect disease progression in elderly HIV/AIDS populations, and may result in impairment in the ability to carry out demanding functions – or more generally, diminish an individual's quality of life. Thus, it can be concluded that it is of the utmost importance to research a population which is at greater risk of neuropsychological impairment, as the probable association between these deficits may have a variable impact on HRQoL.

Chapter 3 will discuss the correlational design strategy and methodology used in conducting the current research.

Chapter 3: Research Methodology

3.1 Introduction

This chapter aims to provide a clear outline of the methodology used in conducting this study. The chapter begins with a description of the research aims and objectives. This is followed by the research design which is in accordance with and guided by the research aim, identified variables, and proposed hypotheses. An in-depth discussion of the participants recruited for this study follows. This includes the inclusion/exclusion, the procedures followed in selecting the participants, and a detailed description of all the measurement instrumentation utilised in the study. A section on the statistical analysis and ethical considerations utilised concludes the chapter.

3.2 Research Aims and Objectives

The primary aim of this study was to investigate the association between health-related quality of life (HRQoL) and neuropsychological performance in older individuals with HIV. In order to achieve this aim, the following four specific objectives were formulated:

1. To explore the relationship between neuropsychological performance and clinical variables in older individuals with HIV.
2. To explore the relationship between HRQoL and clinical variables in older individuals with HIV.
3. To explore the relationship between HRQoL and neuropsychological performance in older individuals with HIV.
4. To explore the moderating influences of clinical and socio-demographic variables on the relationship between HRQoL and neuropsychological performance.

3.3 Research Design

A correlational design is considered a method of examining as well as describing the naturally-occurring relationship and/or association between variables, without manipulation by or intervention from the researcher (Gravetter & Forzano, 2009; Spector, 1981). In essence, the purpose of such a design is to establish whether a relationship exists between variables and the nature of that relationship.

In statistics, moderation occurs occasionally when the relationship between two variables depends on a third variable. In such cases, the third variable is referred to as the moderator variable (Gravetter & Forzano, 2009). Moderator variables often influence the strength of a relationship between two other variables (Gogineni, Alsup & Gillespie, 1995). These variables need to be identified.

A limitation of correlational research is that it cannot be used to draw conclusions from a cause-and-effect relationship (Gravetter & Foranzo, 2009). However, this type of design has an advantage in that it is often used in preliminary work, especially where a certain field has not been properly investigated. This has a direct bearing on this study. Whilst extensive research has been conducted internationally, there is a lack of literature specifically dealing with the relationship between health-related quality of life and neuropsychological performance in individuals with HIV in the South African setting.

The purpose of the selected design was therefore to determine whether there is an association between the scores obtained from the HRQoL test, and those obtained from the participant's neuropsychological battery. The moderating effects of demographic and clinical data were also tested.

3.4 Research Hypotheses

The following hypotheses were proposed for this study:

1. There is a significant positive association between neuropsychological performance and clinical variables.
2. There is a significant positive association between HRQoL and clinical variables.
3. There is a significant positive association between neuropsychological performance and HRQoL.

3.5 Participants

The target population for this research study consisted of individuals diagnosed with HIV/AIDS and those that met the study criteria requirements. A local HIV/AIDS specialty clinic, within a semi-urban community health centre (CHC), was approached as a site for accessing the target population. This clinic provides a variety of services to a low socio-economic status community.

Participants were selected from this population, using a convenience sampling method. This relies on a participant's willingness and availability to participate (Gravetter & Foranzo, 2009). Willing participants were referred to the researcher via the medical staff recruitment process.

3.5.1 Participant recruitment process

Prior to data collection, the researcher met with the medical staff of the selected HIV/AIDS specialty clinic. This meeting aimed to devise a participant recruitment system that could be used to inform participants about the study, bearing in mind participants' rights to confidentiality, anonymity, HIV status, and clinic resources as well as their willingness and availability to participate.

It was agreed that medical staff would each be given a card outlining information about the research study, and inclusion/exclusion criteria requirements for suitable candidates. Individuals whom the medical staff deemed suitable candidates were directed to a designated room where the researcher awaited these potential participants to provide them with further details about the study. Alternatively, they were handed a pamphlet explaining the basics of the research study, should they decide to participate at a later stage. The pamphlet was available in English, Afrikaans, and Tswana and contained a 'tear-off' section where interested participants could add their contact details. The 'tear off' slip only required a home/mobile number and/or an email address. This could be placed in a box located in the examination consultation room. The researcher then contacted the potential participant telephonically in order to set up an additional appointment, respecting the participant's availability for a full discussion of the study, matters of confidentiality, and voluntary participation.

3.5.2 Inclusion/exclusion criteria

Participants were included if they had tested HIV positive, as reflected in their medical records. This information was only obtained after informed consent had been received from potential participants. Thus, patients did not require physiological screening to determine their HIV/AIDS status. Furthermore, patients were included in the study if they were able to demonstrate basic literacy and numeracy abilities; were able to provide written informed consent themselves for participation and administration of the questionnaire; and were 45 years of age and older.

Patients were excluded from the study if (a) there was any reported history of substance abuse or dependence (including alcohol) in the previous three months; (b) past psychiatric history; (c) any other conditions that may affect neurocognitive performance such as head

injuries (defined as a loss of consciousness for more than 30 minutes), seizure disorders or cerebrovascular accidents; and (d) presented with severe health profiles (other than those mentioned above) that may jeopardise his or her ability to complete the tests (e.g., extreme coughing and shortness of breath, seizures, lack of coordination, fever, extreme fatigue, severe and persistent diarrhoea).

3.6 Procedures

The researcher obtained the necessary permission from the various authorities before data collection commenced. This included approval by the University of Pretoria's Research and Ethics Committees, Tshwane Research Committee, and permission from the hospital's management in order to gain access to the hospital database and patient files. Furthermore, written permission (via email) was obtained from the EUROQoL group to use the EQ-5D 5L questionnaire.

Before research could proceed as planned, written informed consent was obtained from all individuals willing to participate. A follow-up appointment with the researcher was conducted in a designated room at the clinic during which a full discussion of the study and matters of, amongst others, confidentiality and voluntary participation took place.

Once informed consent was obtained from the participants, the researcher commenced with the administration of the tests. The participants were either assessed by the researcher herself or the co-researcher, as most of the measures follow a strict and standardised administration procedure.

The first measure administered was the socio-demographic questionnaire (see Appendix B). The health-related quality-of-life questionnaire, EQ-5D 5L, was administered

followed by the neuropsychological battery. The test administration took approximately 25 to 40 minutes, and participants were allowed to take a small break between measures.

3.7 Measurement Instruments

3.7.1 Socio-demographic questionnaire

A participant was first required to complete a socio-demographic questionnaire. This questionnaire included a variety of questions used to gather basic demographic, variable information such as age, gender, level of education, employment status, and marital status. The questionnaire also included brief screening questions which corresponded with the exclusion criteria of the study (e.g., history of substance abuse in the past three months; past psychiatric history; history of head injury; seizure disorders, and overt retinal pathology).

The clinical variables and applicable information were collected from the patient's medical file, and documented on a separate record form (see Appendix A). This included the date of the first HIV test (measures, chronicity of the illness), date of the first ART treatment (duration on ARTs), viral load, latest CD4 count (degree of immunosuppression), comorbid conditions such as tuberculosis, opportunistic infections, and cancer. The form provided space for additional comments.

The rationale for selecting the above-mentioned demographic and clinical variables is based on what literature suggests may correlate highly with neuropsychological functioning in HIV (Joska, Fincham, Stein, Paul, & Seedat, 2010).

3.7.2 The health-related, quality-of-life questionnaire

It is acknowledged that a specific HIV instrument, sensitive to HRQoL aspects specifically affected by HIV, was needed. However, the translation and validation of such an

instrument would have taken a considerable amount of time, and therefore health-related quality of life was measured using the generic EQ-5D 5L.

EuroQol, an international research group, originally developed this measure. It has also been validated in several European countries. Furthermore, it is said to be a brief self-report, HRQoL questionnaire used to evaluate an individual's health status in both clinical and economic evaluations. Although the literature highlights the use of the measure in economic evaluations, it can also be employed as a measure of health status in general (noneconomic) health assessments. This is done through the two-paper-based parts that constitute the measure, namely a section that provides a descriptive profile of health, and the EQ-visual analogue scale (EQ-VAS) (Brooks, 1996; EuroQol, 1990).

Three variables can be derived through analysing the above two-paper parts of the measure, namely (1) the EQ-5D profile which can be described as the patient's self-reported health on the dimensions or levels of the descriptive system; (2) the EQ-VAS, the patient's own global rating of his or her overall health on a scale of 0 to 100; and(3) the EQ-5D index profiles that can be summarised using 'value sets' (EQ-5D index) and which reflect the preference of the general public (Devlin, 2013; Krabbe & Weijnen, 2003). The most widely used weights are the York tariffs, generated from a UK-based sample (Dolan, Gudex, Kind & Williams, 1996; Dolan, 1997; Kind, Hardman & Macran, 1999). These weighted EQ index values can range from -0.594 to 1, where the negative values refer to a state of health considered 'worse than death'. This type of variable is often used in economic studies. However, as the aim of this research was a noneconomic study, only variables 1 and 2 were incorporated in the analysis of the data. The following section will discuss the two parts of the measure.

3.7.2.1 The descriptive section

The descriptive section was completed first by the participants. This section permits participants to portray health problems in terms of five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (Brooks, 1996). Each of these domains can be classified according to either a three-level (3L) or the newly developed five-level (5L) version of the EQ-5D. In the three-level version, participants were asked to place a cross or tick next to the appropriate alternative for each of the domains. For example, 1 = no problems, 2 = moderate problems 3 = severe problems. Although participants may attain scores similar to the above 1-3 in the 5L version, they also have the choice of 4 = severe problems and 5 = unable to. This results in a one-digit number, depicting the level for that dimension. The digits for the five domains are combined to express a three- or five-digit number describing the participant's health status. This can be likened to a global summation of a participant's HRQoL score. In the example given by authors Rabin & De Charro (2001), state 21133 would indicate problems with mobility, no problems with self-care or usual activities, and extreme problems with pain/discomfort and anxiety/depression. The 3L version allows for a 243 discrete health status (Brooks, 1996; Rabin & De Charro, 2001). In comparison, the 5L allows for 3, 125 health states (Janssen, Birnie, Haagsma & Bonsel, 2008). This can have implications for the psychometric properties of the different versions (3L and 5L) of the measure (see below).

3.7.2.2 The EQ Visual Analogue Scale (EQ-VAS)

Participants were then asked to complete the EQ-VAS component of the questionnaire which is used to record a participant's state of health. In this section, the participant is instructed to rate his or her own health at that point in time by placing a cross at the appropriate point on the VAS, which is a 20-cm vertical scale that ranges from 0-100,

representing worst imaginable state of health and best imaginable state of health respectively (Brooks, 1996). A three-digit number between 000 and 100 is read off the scale and placed in the empty box next to the words 'your health today'. The EQ-VAS scores are patient-based and not representative of the general population, therefore reflecting the patient's own assessment of his or her health status at that point.

3.7.2.3 Use of the measure in the South African setting and psychometric properties

Although the EQ-5D is considered a non-disease-specific instrument (Brooks, 1996; EuroQol, 1990), growing evidence supports the validity and utility of the EQ-5D measure in a variety of clinical populations, clinical trials, and observational studies including the previous use of the instrument in patients with HIV/AIDS (Delate & Coons, 2001; Wu et al., 2002). The same can be said of the South African setting where local studies have utilised the EQ-5D in various areas. The general agreement between these studies, many of which evaluate HRQoL outcomes in HIV-infected individuals receiving HAART, concludes that the EQ-5D instrument is an appropriate tool for assessing HRQoL in AIDS in Africa (Jelsma, Maclean, Hughes, Tinise & Darder, 2005; Hughes et al., 2004; Louwagie et al., 2007).

In addition to the South African English version, both Afrikaans and Xhosa versions of the questionnaire are available and have been recognised by the EuroQoL group as official translations. The Xhosa version of the test has been deemed reliable and valid for a Xhosa urban-speaking population (Jelsma, Mkoka, Amosun & Nieuwveldt, 2004). However, given the multicultural diversity of South Africa, authors recommend that these three versions continue to be investigated as to ensure cross-cultural validity of the measures (Jelsma & Ferguson, 2004; Mkoka, Vaughn, Wylie, Yelland & Jelsma, 2003).

With regard to the psychometric properties of the EQ-5D, varying data has been found in literature regarding reliability, validity, responsivity, and ceiling effect. However, the

general consensus is that studies have reported good construct validity for the EQ-5D, particularly the use of the measure for HIV-infected populations (Delate & Coons, 2001; Wu et al., 2002). The intraclass correlation coefficient for the measure has revealed a value of 0.78 in a study comparing preference-based utilities from multiattribute utility instruments 15D, with those derived from the EQ-5D and the Short Form 36 (SF-6D) in patients with HIV/AIDS (Stavem, Frøland & Hellum, 2005). Cronbach's alpha for the EQ index was 0.85, indicating a high degree of correlation between the five dimensions. The EQ index correlated well with the VAS scores, revealing a Spearman's $p = 0.48$ and Pearson's $R^2 = 0.29$ (Louwagie et al., 2007). The responsivity of the EQ-5D appears questionable, as suggested in a study conducted by Wu et al. (2002). However, the authors of this study argue that this finding may be as a result of ceiling effect. Other studies have also demonstrated a high ceiling effect for the EQ-5D 3L index component (Stavem, Frøland & Hellum, 2005). It has been hypothesised that this may be as a result of the EQ-5D descriptive system having fewer items and levels. These findings largely pertain to the EQ-5D 3L, as studies that have investigated comparisons between the EQ-5D 3L and the EQ-5D 5L report the latter has less severe ceiling effect, increased discriminatory power, increased reliability, and satisfactory validity (Janssen et al., 2008; Pickard, De Leon, Kohlmann, Cella & Rosenbloom, 2007).

In summary, the researcher has made use of the EQ-5D 5L South African English, Afrikaans, and Xhosa versions.

3.7.3 The neuropsychological test battery

The neuropsychological test battery used in this study complied with the proposal of Joska et al. (2011), namely (1) to include and measure the neurocognitive domains, commonly found in literature, that are the most vulnerable to HIV infection and neuropsychological performance, as well as the targets in the neuropsychological assessment

of HAND such as the work of Antinori et al. (2007), Dawes et al. (2008), and Grant (2008); (2) to include tests that have been used in the international setting in order to make findings comparable; (3) to include tests that have been used in the local/developing setting which take into account the multiple influences that affect neuropsychological testing in South Africa, such as those of Kanmogne et al. (2010) and Robertson, Nakasujja, et al. (2007); and (4) the tests selected were not used to indicate any presence of severity (i.e., to categorise the degree of impairment in accordance with HAND categories) or monitor neuropsychological performance over long periods of time. This was due to limited normative data. Table 1 provides a brief definition of the neuropsychological domains tested in this study.

Table 1

Definition of the Neuropsychological Domains Tested in this Study

Domain	Description of Domain
Attention	Attention is a general level of alertness or vigilance that includes a general state of arousal including orientation verses habituation to stimuli and the ability to focus, divide, or sustain at mental process at hand (Zillmer et al., 2008).
Sustained Attention	Sustained attention is considered to be the preservation of attention over time (American Psychiatric Association, 2013).
Selective Attention	Selective attention is the continuance of attention despite competing stimuli and/or distractors and (American Psychiatric Association, 2013).
Divided Attention	Divided attention is when an individual attends to two tasks within the same time period (American Psychiatric Association, 2013).
Visual Attention	Ability to maintain visual fixation and concentration on a particular stimulus (Lezak et al., 2012)
Working Memory	Working memory requires temporary storage and manipulation of information in order to be used for problem solving or other cognitive operations at hand (Lezak et al., 2012).
Processing Speed	Speed of processing requires an individual to have the ability to gather adequate information in

	order for the relevant operations to be executed within the time allowed (Salthouse, 1996).
Memory	Memory can be termed as the capacity to preserve material and the ability to apply it adaptively (Lezak et al., 2012).
Learning	Learning is the process whereby information is retrieved, encoded and stored (Lezak et al., 2010).
Visuo-Perceptual Ability	A set of skills that one uses to gather visual information from the external world (environment) and integrate it with our other senses in order to make meaning thereof (Zillmer et al., 2008).
Motor Skills /Function Psychomotor Performance	Motor skills is a process of acting on the world in response to sensory stimuli (Zillmer et al., 2008). Motor skills can be divided into the abilities of construction, assembly and building, manual dexterity and strength (Lezak et al., 2012). Psychomotor performance is the coordination and resulted performance of sensory or a cognitive process and a motor activity (Lezak et al., 2012).
Executive Function	Executive functioning include planning, coordination, implementing, organizing, and evaluation of tasks and actions (Brew et al., 2009; Lezak et al., 2012). They can be assessed through neuropsychological measures of abstraction, problem solving, set shift and reasoning (Woods et al., 2009).
Planning	Planning is the ability to display forward thinking in light of a problem (American Psychiatric

	Association, 2013).
Decision-making	Decision-making is the performance of tasks that assess process of deciding in the face of competing alternatives (American Psychiatric Association, 2013).
Error Utilization	Error utilization is the ability to benefit from feedback to infer the rules for solving a problem (American Psychiatric Association, 2013).
Inhibition	Inhibition is the ability to choose a more complex and effortful solution to be correct (American Psychiatric Association, 2013).
Mental flexibility	Mental flexibility is ability to shift between two concepts, tasks or response rules (American Psychiatric Association, 2013).

An in-depth discussion regarding the various assessments used to measure the above-mentioned domains follows.

3.7.3.1 The Dementia Rating Scale-2 (DRS-2)

The Dementia Rating Scale-2 (DRS-2) (Jurica, Leitten, & Mattis, 2004) is said to assess an individual's overall level of cognitive functioning. The measurement, which includes 36 tasks and 32 stimulus cards, comprises five subscale indices. This includes attention (DRS-2 Attention), initiation/perseveration (DRS-2 Initiation/Perseveration), construction (DRS-2 Construction), conceptualisation (DRS-2 Conceptualisation), memory (DRS-2 Memory) and a global neuropsychological score (DRS-2 Total). These five areas are said to be particularly sensitive to behavioural changes, characterised by Alzheimer's disease (Lezak et al., 2012). Furthermore, the original form of the measure has also been used as a screening tool for identifying neuropsychological impairment in an HIV population (Kovner, et al., 1992). The current study supports evidence, endorsing the use of this measure.

During the administration of the measurement, the examiner is required to read aloud the specific instructions for each task to the participant. The participant has to follow each of the given instructions. The DRS-2 is considered fairly brief, despite the 36 tasks that make up the measure. This is because the test is designed in such a way that several items are arranged in hierarchical clusters, meaning that the difficult items are presented first. This can result in the participants disregarding some tasks because they were able to achieve a certain score on the more difficult items.

Test-retest reliability was studied, suggesting a correlation coefficient of 0.97 with subscale correlation coefficients ranging from .61 to .94 (Coblentz et al., 1973). Internal consistency has been reported with alpha coefficients of Attention (.95), Initiation/Perseveration (.87), Conceptualisation (.95) and Memory (.75) (Vitaliano et al.,

1984). Split-half reliability of 0.90 (Gardner, Fisher, Muñoz & Empting, 1981) and further satisfactory construct validity *r-value* ranging from .75 to .82 have been noted.

3.7.3.2 Symbol Digit Modalities Test (SDMT)

The Symbol Digit Modalities Test (SDMT) (Smith, 1982) is a measure that makes use of the exchange of meaningless geometric designs into written and/or oral number responses in order to screen for cerebral dysfunction in both adults and children (Smith, 1982). Furthermore, the SDMT assesses, amongst others, psychomotor speed, attention, complex scanning, and visual tracking (Lezak et al., 2012). For the purpose of this research, only the written component of this measure was used. The measure was composed of three sections, namely the primary task, the immediate recall task, and the delayed recall task.

The primary task requires that participants be handed a sheet of paper on which nine symbols, each paired with a number in the key, appear in the boxes above the unfilled squares waiting for numbers to be written (Lezak et al., 2012). The participant is instructed to substitute a number (written) for randomised presentations of geometric figures (Smith, 1982). The participant has 90 seconds in which to complete as many of the 110 items as possible. The immediate recall task is presented next, and requires that the participant be handed a separate sheet of paper which contains the unmarked last row from the SDMT record form. The participant is instructed to complete the unfilled boxes from memory, and recall as many of the numbers that match the symbols. The delayed recall test is similar to the immediate recall task in that it requires that the participant be handed a separate sheet of paper which contains the unmarked last row from the SDMT record form. However, it differs in that it is administered after a certain period of time after the primary and immediate tasks. For this study, the delayed recall task was administered after the Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT).

With regard to psychometric properties and cultural sensitivity, the SDMT, in a study of normal adults, is reported to have a test-retest correlation of .80 and .76 for the written and oral SDMT respectively (Smith, 1982). Lastly, as Smith (1982) reports, numbers are a universally written language symbol; therefore, the SDMT can be considered a somewhat cultural-free measure. This becomes useful in a culturally diverse country such as South Africa where participants are more likely to speak languages other than English.

3.7.3.3 The Stroop Colour and Word Test

The Stroop Colour and Word Test (Golden & Freshwater, 2002) is said to be a measure of executive function, attention, and concentration as it involves the complex interplay of cognitive flexibility in warding off distractible information and inhibitory control (Lezak et al., 2012). The test comprises three tasks that are consecutively administered.

The Word (W) page task is administered first. Participants are timed and instructed to read as quickly as possible a page consisting of the words 'RED', 'GREEN' and 'BLUE' printed in black ink. The Colour (C) page task is administered next which is a page with 100 XXXXs printed in red, green, or blue ink. Participants are also timed and instructed to name, as quickly as possible, the colour of the ink in which the XXXX is written. Lastly, the Colour-Word (CW) page task is administered. This task consists of a page with a list of colours; however, the colour of the ink is incongruent with the colour of the word listed. The participant is timed and instructed to work as quickly as possible in naming the colour of the ink the words are printed in, disregarding the word that is printed for each item.

Several studies that have investigated the reliability of the Stroop test tend to make use of different forms of the test. However, despite this, there is relatively little difference between the findings in the tests. For example, a study by Franzen, Tishelman, Sharp and Friedman (1987) assessed the test-retest reliability of the commercial version of the Stroop

across two different time intervals. Findings suggest an overall retest reliability of .831 for the Word score, .738 for the Colour score, and .671 for the Colour-Word score. Reportedly, these findings are said to be in line with findings by Jensen (1965) and Golden (1976), with reported reliability coefficients of .86, .82, and .73 for the Word score, Colour score, and Colour-Word score respectively.

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

The Delis-Kaplan Executive Function System Trail Making Test (D-KEFS TMT) (Delis, Kaplan & Kramer, 2001) is a test from the Delis-Kaplan Executive Function System battery. This assessment is aimed at isolating the basic components of performance (e.g., motor or simple sequencing) from the higher order 'executive' components (e.g., multi-tasking or task switching) (Lezak et al., 2012). This is done through the administration of five conditions of which four are visual cancellation tasks (Visual Scanning, Number Sequencing, Letter Sequencing, and Number-Letter Switching), and one is a series of connect–the-circle tasks (Motor Speed). In essence, the D-KEFS TMT measures flexibility of thinking, visual scanning, number sequencing, letter sequencing, and motor speed.

In each of the five conditions, the examiner reads out aloud specific instructions to the participant. The participant is first required to complete a practice task for each of the conditions. This is provided so that the examiner can correct any errors. After completing the practice task, the participant is instructed to complete the timed task for each of the conditions. Time allowed ranges from 150 seconds to 400 seconds, depending on the condition. In the first condition, Visual Scanning, the examinee is required to draw a line through all the 3s on the response sheet. In the second condition, Number Sequencing, examinees are to draw a line connecting numbers 1 to 16 consecutively, whilst ignoring the distractible letters. In the third condition, Letter Sequencing, examinees are to draw a line

connecting letters A to P, whilst ignoring the distractible numbers. In the fourth condition, Number-Letter Switching, examinees are requested to alternate between connecting letters and numbers (i.e., 1-A; 2-B, etc.) Lastly, in condition five, Motor Speed, examinees are instructed to connect circles via a dotted line on the page.

The literature poses a variety of arguments regarding the validity and reliability of the D-KEFS measure itself. Some authors question the reliability and validity of the assessment, suggesting that it is weak (Crawford, Sutherland & Garthwaite, 2008; Schmidt, 2003); whereas the developers (Delis, Kramer, Kaplan & Holdnack, 2004) and other review authors (Homack, Lee & Riccio, 2005) are more confident despite this controversy. Although this research study only made use of the TMT, some studies have reported good construct validity for this item. This is evident in a study by Yochim, Baldo, Nelson, and Delis (2007) which assessed cognitive set shifting in patients with focal lesions in the lateral prefrontal cortex, through measuring patients' performance on the D-KEFS TMT. The study highlighted support for the construct validity of the D-KEFS TMT, suggesting that the measure has the ability to assess set shifting over and above component skills, and to be sensitive to focal frontal-lobe lesions.

It can be suggested that neuropsychological measures are multifaceted, and often measure more than one neuropsychological domain. It is therefore imperative that this study provides a description of the domains that the selected neuropsychological tests measure. This is summarised in table 2.

Table 2: *The Neuropsychological Measures and Domains assessed in this Study*

Test Name	Domain Measured in this Study
DRS- 2 Total	Global Neuropsychological Performance
DRS- 2 Attention	Simple Attention
DRS- 2 Memory	Memory
DRS- 2 Initiation/Perseveration	Inhibition (Executive Function)
DRS- 2 Construction	Visuo-spatial/ Visuo-construction Motor Ability/Function
DRS- 2 Conceptual	Abstract Reasoning Ability (Executive Function)
SDMT Primary Task	Psychomotor Performance Speed of Information Processing Attention Visual Attention Sustained Attention
Stroop Colour Word	Inhibition (Executive Functioning) Error utilization (Executive Functioning) Mental Flexibility (Executive Functioning)
D-KEFS TMT 1 (RT)	Visual Scanning/Search Psychomotor Performance/Psychomotor Speed
D-KEFS TMT 4 (RT)	Psychomotor Performance/ Psychomotor Speed Speed of Information Processing Mental Flexibility (Executive Function) Complex Attention
D-KEFS TMT 5 (RT)	Motor Speed

Note. DRS 2 = Dementia Rating Scale 2; SDMT = Symbol Digit Modalities Test; CW = Colour-Word; D-KEFS TMT = Delis-Kaplan Executive Function System Trail Making Test; RT = reaction time.

3.8 Statistical Analysis

Raw data from each of the questionnaires was captured onto an Excel spreadsheet by the researcher. This data was captured and analysed with the assistance of a professional statistician at the University of Pretoria, Department of Statistics.

3.8.1 Descriptive statistics

Descriptive statistics were derived for all participants on EQ-5D 5L, neuropsychological measures, and clinical/demographic variables which represented a way of organising, simplifying, and summarising the data gathered. The outcome included frequency distributions for each of the variables as well as sample means, standard deviations, and measures of central tendency and dispersion.

3.8.2 Correlational analysis and cluster analysis

Spearman's correlation coefficients were used to specify/assess the relationship between the variables, namely HRQoL. neuropsychological performance, and clinical/demographic variables. Authors Hauke and Kossowski (2011) argue that 'Spearman's rank correlation coefficient (r_s) is a nonparametric rank statistic proposed as a measure of the strength of the association between two variables. It is a measure of monotone association that is used when the distribution of data makes Pearson's correlation coefficient undesirable or misleading.' (p. 89)

Spearman's correlations revealed the presence of multicollinearity; therefore, the appropriate technique for testing for moderation under these conditions will lie within structural equation modelling (SEM). Given the size of the sample ($n = 34$), however, an exploratory cluster analysis was performed. Hassall (2009) summarises cluster analysis as follows:

'… a multivariate technique that identifies groups of participants or objects in a sample or population that is homogenous (or relatively so) and different from other groups of objects or participants in a particular set of variables.' (p. 119)

3.9 Ethical Considerations

- Prior to the commencement of data collection for this study, preliminary permission to gain access to the participant's medical records was sought from the clinic manager.
- The above-mentioned preliminary permission letter along with accompany documents were submitted to the University of Pretoria's Postgraduate Committee and Research Ethics Committee. Clearance was obtained on the 25th of June 2013.
- This information was then relayed to the Tshwane Research Committee. Written permission was obtained on the 2nd July 2013 which provided approval for data collection to commence at the selected hospital.
- The research study and aims were discussed with the clinic manager and nursing staff. They approved the research and assisted in the participant recruitment procedure.
- Suitable participants were contacted, and written informed consent was obtained before any data was collected. Also, permission was obtained from the participants to utilise their hospital information/medical records once they agreed to participate in the study.
- The privacy of each participant was respected, and all data gathered remained confidential.
- The anonymity of each participant was respected as far as possible, and no names were used in the study; each participant was identified by a number only.
- Participants were allowed the right to withdraw from the study at any time.
- Participants were treated with the utmost consideration, and care was taken that no one would suffer any foreseeable harm. However, if any discomfort was identified by the researcher or participant after having completing the test, the participant was referred to a

relevant medical or psychological professional at the clinic for debriefing or further intervention.

In summary, this chapter provided an outline of the research design and methodological endeavours used in conducting this research. A correlational research design strategy was used in aiding the researcher to examine and describe the natural-occurring relationships and/or associations between the variables identified in this study. The outcome of using the chosen research design and methodological procedures will be documented in chapter 4.

Chapter 4: Results

4.1 Introduction

This chapter provides a summary of the results of this study, based on the chosen research design and methodological procedures outlined in chapter 3. Descriptive statistics are reported first; this is followed by the correlational statistics; and in conclusion, the exploratory cluster analysis findings are reported.

4.2 Descriptive Data

4.2.1 Demographic data of the sample

A total of 83 subjects participated in this study of whom 46 were HIV positive according to medical records; 29 were of a nonreactive (negative HIV) status according to medical records; and eight were of unknown status due to the unavailability of their medical records. Of the 46 HIV-positive individuals identified via their medical records, 12 did not meet the inclusion/exclusion criteria required for the study (five had a past medical/psychiatric history; five had poor basic literacy skills; and two had to discontinue due to a lack of transportation and other obligations).

Therefore, a total of 34 suitable subjects participated in this study. The average age of the participants was 49.41 years (*SD* = 4.66). As mentioned in the literature review, HIV samples generally classify ‘older’ as 50 years of age. However, given the sampling procedures of this study and access to one clinic site, the age range was restricted to this group and not older. From the 34 protocols reviewed, the majority were female (65%), black (68%), single (44%), with secondary education (77 %), and currently employed (50%).

4.2.2 Clinical data of the sample

The mean duration over a period of months since participants had their first HIV tests done (chronicity of the illness) is 40.67 (n = 27; SD = 36.98). The mean duration over a period of months for initiation of ART treatment is 35.88 and (n = 34; SD = 41.70). The mean of the latest absolute CD4 count (degree of immunosuppression) is 407.25 cell/µL (n = 32; SD = 232.19).

4.2.3 Neuropsychological performance of the sample

Statistics describing the sample's performance on the various neuropsychological tests are summarised in table 3.

Table 3: *Performance on the Neuropsychological Measures*

Neuropsychological Measures	*n*	*M*	*SD*	Range
DRS 2 Attention	34	33.88	2.50	25-37
DRS 2 Initiation	34	30.85	5.22	21-37
DRS 2 Construction	34	5.85	0.36	5-6
DRS 2 Conceptual	34	31.15	4.58	20-39
DRS 2 Memory	34	22.59	2.44	17-28
DRS 2 Total	34	124.24	11.28	101-142
SDMT Primary Task	32	25.97	9.34	8-50
Stroop CW	31	23.13	8.85	4-42
D-KEFS TMT 1 (s)*	32	42.66	17.47	25-91
D-KEFS TMT 4 (s)*	31	196.35	57.66	68-240
D-KEFS TMT 5 (s)*	31	66.45	27.74	33-137

Note. n = *34*; DRS 2 = Dementia Rating Scale 2; SDMT = Symbol Digit Modalities Test; CW = Colour-Word; D-KEFS TMT = Delis-Kaplan Executive Function System Trail Making Test; * indicates time in seconds to complete the test.

4.2.4 Health-related quality of life of the sample

Statistics describing the sample performance on the health-related quality of life measure (EQ-5D 5L) are summarised in table 4.

Table 4: *Characteristics of Health-Related Quality of Life*

EQ-5D 5L (HRQoL) Variable	*n*	*M*	*SD*	Range
Mobility	34	1.47	1.05	1-5
Self-care	34	1.26	0.86	1-5
Usual activity	34	1.35	1.01	1-5
Pain/Discomfort	34	1.85	0.86	1-4
Anxiety/Depression	34	1.62	0.99	1-5
State	34	16126	10824	1111-54524
EQ-5D VAS	34	84.24	18.29	30-100

Note. n = 34; EQ-5D VAS = EuroQuol-5D Visual Analogue Scale.

4.2.5 Preliminary analyses and distribution of the sample

The assumptions of normality and independence of the variables were evaluated before further analyses were conducted. The distribution of a number of variables, and the assumptions of normality were not fully met for all the variables. This is likely the result of a small sample size and the nature of some of the neuropsychological tests. It can be argued that complications with data, such as the above-mentioned (non-normality of data and incomplete data records from participants) are commonly encountered in neuropsychological research (Cross, 2013). This was taken into account for further analyses. Correlational analyses were performed on the data, and a discussion follows below.

4.3 Correlational Analysis

As previously discussed, the main aim of this study was to determine if there is a relationship between health-related quality of life, and neuropsychological performance in older participants with HIV.

Spearman's rank order correlation was chosen as the appropriate method to construct a correlational matrix. This is because it is considered a more appropriate procedure, considering the distribution of data for this sample (Hauke & Kossowski, 2011).

The tables that follow summarise Spearman's coefficients of correlation *(r_s)* which provide an indication of the degree of correlation between the variables.

4.3.1 Correlation between neuropsychological performance and clinical variables

As indicated in table 5, the number of months on ART (duration) is significantly associated with three neuropsychological measures: DRS-2 Conceptual index (r_s = -.30, $p \leq .10$), SDMT Primary task (r_s = -.33, $p < .05$) and the D-KEFS TMT 4 (r_s = .40, $p \leq .10$).

The results suggest that a participant's performance, as measured on the DRS-2 Conceptual index, increases with fewer number of months on ART. The DRS-2 Conceptual index measures abstract reasoning, an aspect of executive functioning. It is therefore plausible that despite ongoing ART treatment, deficits on measures of abstract executive functioning are continually being detected, or longer duration on ART's may indicate longer duration of HIV infection.

Similarly, participant's performance on the SDMT Primary Task also reflect an inverse correlation; participant's performance increase with fewer months on ARTs. The SDMT Primary Task measures attention, visual attention and sustained attention, information

processing speed, and psychomotor performance (Spreen & Strauss, 1998; Lezak et al., 2012).

Time to complete the D-KEFS TMT 4 increased as the months on ART increased. The D-KEFS TMT 4 measures attention and complex attention, speed of information processing, sequencing, mental flexibility (executive functioning), visual search, and motor function (Spreen & Strauss, 1998). This corroborates the findings from the SDMT and DRS-2 Conceptual index.

Therefore, these findings show that performance on neuropsychological domains of attention, visual and sustained attention, executive functioning (abstract reasoning, mental flexibility), processing speed, and psychomotor performance are significantly associated with the number of months on ART treatment.

Furthermore, the participant's performance on the DRS-2 Construction index (r_s = .31, $p \leq .10$) increased as their CD4 count increased. DRS-2 Construction index is considered a measure of visuo-spatial, visuo-constructional, and motor abilities. This indicates that participants with a higher CD 4 count (degree of immunosuppression) display better performance on tasks measuring visuo-spatial, visuo-constructional, and motor abilities. It is important to note that visuo-constructional abilities are subserved by the executive functioning system which may be less compromised with a higher degree of immunosuppression.

Table 5: *Significant Associations between Neuropsychological Measures and Clinical Characteristics*

	Clinical Variables	
Neuropsychological Measures	ART Duration	CD4 count cell/µL
DRS 2 Construction	-	.31
n	-	32
p	-	.08
DRS 2 Conceptual	-.30	-
n	34	-
p	.08	-
SDMT Primary	-.33	-
n	32	-
p	.06	-
D-KEFS TMT 4	.40	-
n	31	-
p	.02	-

Note: ART = antiretroviral therapy; SDMT = Symbol Digit Modalities Test; CW = Colour-Word; D-KEFS TMT = Delis-Kaplan Executive Function System Trail Making Test.

4.3.2 Correlations between HRQoL variables and clinical variables

As indicated in table 6, the number of months since a first HIV test (chronicity of the illness) was significantly associated with two of the health-related quality-of-life variables: mobility (r_s = -.33, $p \leq .10$) and anxiety/depression (r_s = -.46, $p \leq .01$).

Mobility and self-reported anxiety/depression symptom scores were inversely correlated with the number of months since the first HIV test (chronicity of the illness) respectively. These results may demonstrate that there are more reported problems with mobility and anxiety/depression symptoms during the initial diagnosis phase (least number of months since the first HIV test). Also, as the disease progresses, fewer problems are reported on these same HRQoL items.

Table 6: *Significant Associations between HRQoL Variables and Clinical Variables*

	Clinical Variables		
EQ-5D 5L (HRQoL) Variables	Illness Chronicity	ART Duration	CD 4 count cell/µL
Mobility	-.33	-	-
n	27	-	-
p	.09	-	-
Anxiety/Depression	-.46	-	-
n	27	-	-
p	.01	-	-

Note: ART = antiretroviral therapy; HRQoL = health-related quality of life.

4.3.3 Correlation between neuropsychological performance and HRQoL variables

An interesting finding was that the self-reported anxiety/depression correlated with five of the neuropsychological tests: Total DRS-2 (r_s = -.38, $p \leq .05$), DRS-2 Conceptual index (r_s = - .29, $p \leq .10$), DRS-2 Memory index (r_s = -.29, $p \leq .10$), D-KEFS TMT 4 (r_s = .34, $p \leq .10$) and SDMT (r_s = -.33, $p \leq .10$). These findings are indicated in table 7.

The Total DRS-2 score is considered a global indicator of a participant's neuropsychological performance. This score was inversely correlated with the anxiety/depression item. This may indicate that a better global neuropsychological performance is associated with fewer self-reported anxiety/depression symptoms.

An inverse relationship was noted between the DRS-2 Conceptual index and anxiety/depression, indicating that better performance in executive function (abstraction reasoning ability) was associated with fewer self-reported anxiety/depression symptoms.

Furthermore, an inverse relationship was noted between the DRS-2 Memory index and anxiety/depression, indicating that better performance in aspects of memory was associated with fewer self-reported anxiety/depression symptoms.

Time taken to complete the D-KEFS TMT 4 was associated with more reported problems on anxiety/depression. This indicates that better performance in attention, speed of information processing, sequencing, executive function (mental flexibility), visual search, and motor function is associated with fewer self-reported anxiety/depression symptoms.

The SDMT results confirm similar findings, namely that better performance in the domains of visual attention and sustained attention, processing speed, and psychomotor performance is associated with fewer self-reported anxiety/depression symptoms.

Table 7 also indicates that the SDMT strongly correlated with two other HRQoL variables: self-care (r_s = -.31, $p \leq .10$) and pain/discomfort (r_s = -.30, $p \leq .10$). This implies that better performance in domains of attention, visual attention and sustained attention, processing speed, and psychomotor function is associated with fewer self-reported problems of self-care and pain/discomfort.

Table 7: *Significant Associations between Neuropsychological Performance and HRQoL Variables*

Neuropsychological Measures	EQ-5D 5L (HRQoL) Variables		
	Self-Care	Pain/Discomfort	Anxiety/Depression
DRS 2 Conceptual	-	-	-.29
n	-	-	34
p	-	-	.09
DRS 2 Memory	-	-	-.29
n	-	-	34
p	-	-	.09
DRS 2 Total	-	-	-.38
n	-	-	34
p	-	-	.02
SDMT Primary	-.31	-.30	-.33
n	32	32	32
p	.08	.09	.06
D-KEFS TMT 4	-	-	.34
n	-	-	31
p	-	-	.06

Note. DRS 2 = Dementia Rating Scale 2; SDMT = Symbol Digit Modalities Test; CW = Colour-Word; D-KEFS TMT = Delis-Kaplan Executive Function System Trail Making Test.

4.4 Exploring multivariate relationships through Cluster Analysis

Following the above-mentioned correlational analyses, moderation may be tested in various ways, one of which is by using interaction terms in a regression setting. Spearman's correlations, however, indicate the presence of multicollinearity within the three groups of variables. The appropriate technique for testing for moderation under these conditions will lie

within structural equation modelling (SEM). Partial least squares (PLS) were considered as a statistical procedure, however, given the size of the sample *(n = 34)*, an exploratory cluster analysis was performed. This was used to determine the appropriate number of clusters or patterns in the cohort.

4.4.1 Discussing the cluster formation

The cluster procedure was carried out iteratively until no cluster had a second principal component greater than 1. This is illustrated in a dendogram where each cluster contained a grouping of variables, which is more closely correlated with each other than with variables in other clusters. The horizontal axis of the dendogram represented the proportion of variance explained. The dendogram, presented in figure 1, revealed that five clusters were formed at a proportion of variance explained by the cluster at 0.617.

Cluster 1 included the clinical variable of the number of months since the first HIV test (chronicity of the illness), and neuropsychological tests that appeared more specific and do not require a motor component in the domains that they measure, namely simple attention (DRS-2 Attention index), memory (DRS-2 Memory index), and executive function (DRS-2 Initiation/Perseveration index).

Cluster 2 included HRQoL variables of EQ-5D VAS and the item of pain/discomfort only.

Cluster 3 included the demographic variable of age, and tests predominantly related to speed of information processing (SDMT; D-KEFS TMT 4), complex attention and working memory (D-KEFS TMT 4; Stroop Colour-Word), executive functioning (abstract reasoning and mental flexibility: DRS- 2 Conceptual index; D-KEFS TMT 4; Stroop Colour-Word), motor function (D-KEFS TMT 1, TMT 4, TMT 5; SDMT), psychomotor speed (D-KEFS

TMT 4; SDMT), and visual search (D-KEFS TMT 1, TMT 4; SDMT).

Cluster 4 included only clinical variables pertaining to the CD4 count (degree of immune suppression), and the number of months since initiation of ART treatment.

Cluster 5 included only HRQoL variables of anxiety/depression, usual activities, self-care, and mobility.

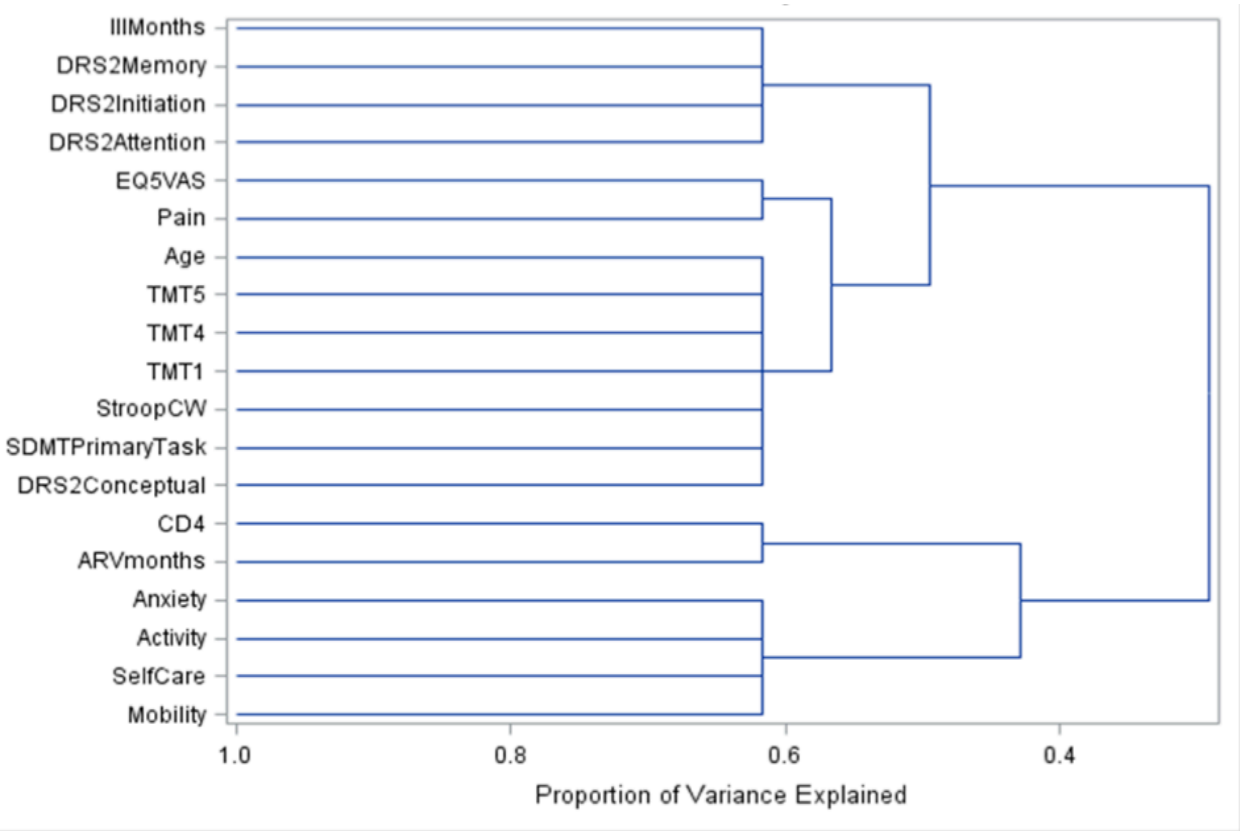

Figure 1. Dendogram of the cluster analysis.

4.4.2 Testing for moderation

The demographic and clinical variables were tested for possible moderating effects on the relationship between HRQoL and neuropsychological performance. This was done by examining the intracluster correlations coefficient (ICC) which provided data on the degree of similarity between variables, possibly indicating moderating effects. Positive correlations indicate similarity, whilst negative correlations are indicative of dissimilarity (opposite patterns of relative strengths and weaknesses) between clusters.

The only significant ($p \leq .10$) correlated clusters were clusters 1 and 4, and clusters 2 and 3, both of which were negatively correlated (r = -.51 and r = -.30 respectively) indicating variation between these pairs of clusters. Hence these findings, although modest, may indicate that age might be a possible moderating variable between neuropsychological domains of speed of information processing, complex attention and working memory, executive functioning, motor function, psychomotor speed, visual search (cluster 2), and HRQoL (cluster 3). Also, the association noted between cluster 1 and cluster 4 may indicate that the clinical variables have moderating effects on neuropsychological domains of simple attention, memory, and executive function (initiation/perseveration).

Clusters 2 and 5 indicated a positive correlation (r = .34, $p \leq .05$) indicating similarity between these cluster pairs. This similarity is likely due to these clusters comprising HRQoL variables only.

Table 8: *Intracluster Correlation Coefficient for five Clusters*

Number of clusters	1	2	3	4	5
1	1	-	-	-0.51	-
2	-	1	-0.30	-	0.34
3	-	-0.30	1	-	-
4	-0.51	-	-	1	-
5	-	0.34	-	-	1

In summary, the exploratory analyses revealed a five-cluster formation. Intracluster correlation coefficient findings may be indicative of possible moderating effects of the clinical variables of the number of months since the first HIV test (chronicity of illness), duration of months for initiation of ART, CD4 count (degree of immunosuppression), and age.

4.5 Chapter Conclusion

The overall findings indicate that there are significant correlations between some of the items of HRQoL, neuropsychological test performance, and the clinical variables as proposed in the study. Cluster analyses revealed that certain variables were clustered together, and may be indicative of moderation. These findings are discussed in more detail in chapter 5.

Chapter 5: Discussion and Conclusion

5.1 Introduction

The purpose of this preliminary study was to investigate the associations between HRQoL and neuropsychological performance in older individuals with HIV. In order to explore these associations, the following objectives were addressed: firstly, the relationship between neuropsychological performance and clinical variables in older individuals with HIV; secondly, the relationship between HRQoL and clinical variables in older individuals with HIV; thirdly, the relationship between HRQoL and neuropsychological performance in older individuals with HIV; and lastly, the moderating influences of clinical and socio-demographic variables on the relationship between HRQoL and neuropsychological performance. The latter was determined through exploratory cluster analysis used to determine the appropriate number of clusters or patterns in the cohort.

Furthermore, in order to answer the research question the following, more specific, hypotheses were formulated and examined through the use of Spearman's correlational coefficient:

1. There is a significant positive association between neuropsychological performance and clinical variables.
2. There is a significant positive association between HRQoL and clinical variables.
3. There is a significant positive association between neuropsychological performance and HRQoL.

In essence, this chapter aims to corroborate and integrate the significant findings of this study with the relevant literature. This chapter begins by discussing the findings of the correlational analysis presented in chapter 4. The discussion that follows explores the

preliminary cluster analyses findings, and the possible moderating effects of clinical and socio-demographic variables on the relationship between HRQoL and neuropsychological performance. Finally, the chapter concludes with a section on the limitations of the study and future recommendations for prospective research.

5.2 Relationship between Neuropsychological Performance and Clinical Variables

The first objective of this study aimed at exploring the relationship between neuropsychological performance and clinical variables in older individuals with HIV. It was hypothesised that there would be a significant positive association between neuropsychological performance and the clinical variables in an older HIV population. As hypothesised, associations were observed in some neuropsychological tests, whilst others showed no significant associations. In this current study, the number of months on ART (duration) was associated with domains of executive functioning (abstraction, mental flexibility), attention and working memory, divided and complex attention, visual attention and sustained attention, processing speed, and psychomotor performance as measured by the DRS-Conceptual index, D-KEFS TMT 4, and SDMT.

Moreover, the findings suggest that participants' performance in these domains decline despite ongoing treatment. These findings seem unusual, as one would expect neuropsychological performance to improve with treatment, especially since all the participants ($N = 34$) in this study were receiving ART at the time of data collection. However, mixed findings are noted in the literature, with some studies reporting beneficial outcomes in an individual's general cognitive functioning whilst on ART and HAART (Al-Khindi, Zakzanis, & Van Gorp, 2011; Cohen et al., 2001; Ferrando et al., 1998; Price et al., 1999; Suarez et al., 2001), whilst other authors document no noticeable changes in cognitive

functioning, despite long-term treatment (Robertson, Smurzynski et al., 2007; Tozzi et al., 2007).

The latter confirms the findings in this study, namely that declining neuropsychological performance continues despite more than several weeks' treatment (Robertson, Smurzynski et al., 2007; Tozzi et al., 2007). One explanation might be that the current treatment regimen is not sufficiently adequate to treat HIV-associated neurocognitive disorders. This could be because the current drugs do not penetrate through the CNS properly, therefore resulting in poor control of viral replication in the CNS (Groothuis & Levy, 1997; Robertson, Smurzynski et al., 2007). The data obtained in this study does not account for viral load as much of that information was absent from participants' files, and could therefore not be included in analysis. Alternatively, the bidirectional relationship between medication adherence and cognitive impairment itself, often reported in the literature, might be another explanation for the current findings. Specifically, deficits in executive function, memory, and attention have been associated with poor adherence to HAART regimens in infected adults (Hinkin et al., 2002). Although this study found poor performance in these cognitive domains, medication adherence was not measured. In addition, the moderating effects of age may also explain the findings noted. However, this premise will be discussed later in the chapter.

Marcotte, Deutsch, McCutchan et al. (2003) suggest that findings are mixed with regard to the relationship between immunological and virological indicators and HIV-associated neuropsychological impairment. They indicate that some studies have been unsuccessful in finding a relationship between levels of CD4 count (degree of immunosuppression) and cognitive functioning (Bornstein et al., 1993; Stern et al., 2001), whilst others have reported modest associations (Bornstein et al., 1991). This study demonstrated a relationship between the immunological indicator of CD4 count and domains of cognitive functioning, including

visuo-spatial/visuo-construction and motor function (as measured by the DRS-2 Construction index). Although associations were modest and included only a few neuropsychological domains, it is possible that the small sample size of this study resulted in inadequate statistical power to reveal further correlations between CD4 count and cognitive functioning. Future studies should investigate a larger sample in order to clarify these associations.

Also, literature seems to suggest that when significant relationships between CD4 count and cognitive performance are found, it often occurs when comparing the most immunocompromised participants (CD4 count < 200 cell/µL) with the most immunocompetent participant groups (eg., CD4 count > 400 or > 500 cells/µl) (Marcotte, Deutsch, McCutchan et al., 2003). However, this study was not of a comparative nature.

5.3 Relationship between HRQoL and the Clinical Variables

The second objective of this study aimed at exploring the relationship between HRQoL and clinical variables in older individuals with HIV. It was hypothesised that there would be a significant positive association between variables of HRQoL and the clinical variables in an older HIV population. As hypothesised, associations were observed in some items of theEQ-5D 5L, whilst others showed no significant associations.

In this study, the only clinical variable found to be associated with mobility and self-reported anxiety/depression symptoms was the number of months since the participant's first HIV test (chronicity of illness). The results indicated that more problems, relating to these aspects of HRQoL, were being reported during the initial diagnostic phase, and fewer problems as the disease advanced. Several possibilities might explain these findings. Firstly, the initial impact of being diagnosed with a chronic disease and disease progression could have an effect on participants' subjective experience of their health. Although the researcher was not in a position to monitor disease symptoms or stages of the disease, literature

indicates that the diagnosis of HIV, disease-related symptoms, and disease stage (Hays et al., 2000; Parsons et al., 2006; Tsevat et al., 1996) have all been associated with lower quality-of-life scores. Secondly, self-esteem has been shown to positively correlate with QoL (Manhas, 2014). It is plausible that receiving an initial diagnosis of HIV may be seen as a change in the way a person sees him- or herself. Low self-esteem may lead to more problems in self-reported anxiety/depression symptoms, possibly explaining the findings of this study. Thirdly, sampling techniques may have influenced the research findings. The sample was not randomly chosen; therefore, participants with physical ailments and other disease-related symptoms were not included in the study. Lastly, it is possible that participants may have developed ways to cope with and manage their illness, and that receiving treatment improved HRQoL. This may have included medical treatment and other interventions that have been administered for a prolonged length of time to manage the disease and curb symptom progression.

Although the findings of this research suggest that infected patients receiving treatment may demonstrate improvement in some aspects of their HRQoL profiles, physicians/ clinicians should not underestimate HRQoL as a subjective construct, subject to change with disease evolution and neuropsychological outcomes.

5.4 Relationship between Neuropsychological Performance and HRQoL

The third objective of this study aimed at exploring the relationship between health-related quality of life, and neuropsychological performance in older individuals with HIV. It was hypothesised that there would be a significant positive association between neuropsychological performance and HRQoL in an older HIV population. As hypothesised, associations were observed amongst some aspects of neuropsychological performance and HRQoL, whilst others showed no significant associations.

In particular, the findings of this study confirm an association between more self-reported anxiety/depression symptoms, reduced global neuropsychological performance (as measured by the DRS-2 Total score), deficiencies in specific aspects of speed of information processing, attention, divided and complex attention, memory, sequencing, executive function (mental flexibility, abstract reasoning), visual search, and motor function (as measured by the DRS-2 Conceptual index, DRS-2 Memory index, D-KEFS TMT 4, and SDMT).

A plausible explanation for these findings is that participants with limited available cognitive resources are less likely to employ appropriate methods to cope with stress associated with their health, and therefore experience a loss of independent behaviour. In turn, this loss of functioning might impact an individual's perceived quality of life, and result in an increase in the reporting of symptoms of depression and anxiety (Osowiecki et al., 2000; Parsons et al., 2006).

The above-mentioned findings are interesting since the researcher purposefully excluded individuals with a past psychiatric history because of the reported impact affective disorders have on neurocognitive performance (Gallego, Barreiro & Lopéz-Ibor, 2011). Yet, it is evident from the current findings that neurocognitive and self-reported affective symptoms appear to be directly correlated. In other words, patients exhibiting decreased performance on neuropsychological measures also report increased levels of depression and/or anxiety on self-reported measures. These findings confirm prior outcomes investigating neuropsychological performance and quality of life in infected populations (Osowiecki et al., 2000; Parsons et al., 2006; Tozzi et al., 2003).

However, factors such as the cultural and ethnic influence of words like 'anxiety' and 'depression' used in the EQ-5D should be considered. Jelsma, Mkoka et al. (2004) argue that

although words like ‘anxiety’ and ‘depression’ are easily translated, the views or meanings associated with the words may differ between African and Western cultures. For example, the word ‘depression’, to a Xhosa-speaker, is temporary and requires a source. Therefore, anxiety/depression symptoms may be over-reported in our sample population due to misinterpretation of these words and their meaning. This also pertains to the subjective nature of the HRQoL measure used in this study. If an objective measure were to be used, findings may differ. Moreover, one cannot ignore that these findings might be influenced by test anxiety. It is possible that individuals, who are not familiar with the traditional testing environment, may become anxious in a standardised test setting. Furthermore, literature suggests the influence of anxiety as particularly pertinent in tests of psychomotor performance (Van Wijk, 2012).

Therefore, the overall anxiety/depression HRQoL profile and its association with some domains of neuropsychological performance in this study should be interpreted with caution. Further research, especially the utilisation of an objective measure of depression/anxiety, in addition to a subjective measure, should be included in the battery in order to clarify the above possibilities.

This study also highlighted that specific attention should be given to the SDMT, despite the number of neuropsychological tests used. The SDMT, amongst other domains, is considered a measure of psychomotor performance (Smith, 1982). This test was found to correlate with three of the HRQoL items: pain/discomfort, self-care, and anxiety/depression. A study conducted by Tozzi et al. (2003) found the Digit Symbol Test to be the best predictor of quality of life, after entering various variables into a multivariable analysis. Osowiecki et al. (2000) confirm these findings. The Digit Symbol Test assesses neuropsychological domains similar to the SDMT. Furthermore, these two tests are said to be highly correlated (Spreen & Strauss, 1998). Therefore, these findings might indicate that the SDMT can be a

good indicator for HRQoL outcomes, although further research would need to confirm these findings. Furthermore, it highlights the importance of sustained attention, speed of mental processing, and visuo-motor coordination in a participant's quality of life (Tozzi et al. 2003). This is particularly valid with regard to aspects of self-care, anxiety/depression, and pain/discomfort

5.5 Moderating Effects of Clinical and Socio-demographic Variables

The fourth objective of this study aimed at exploring the moderating influences of clinical and socio-demographic variables on the relationship between HRQoL and neuropsychological performance.

It is well documented that gender and education are obvious predictors of cognitive performance, with those individuals who have more years of education performing better in cognitive measures (Grant, 2008; Joska et al., 2011). Therefore, the moderating effects of sample characteristics such as gender and education on cognitive functioning could potentially explain the relationship between HRQoL and neuropsychological performance, as noted in section 5.4. Education and gender, however, were not included in the additional exploratory cluster analysis, as these variables are not considered measurement-type data, and only represented two categories in the final analysis. Therefore, one cannot make conclusive remarks regarding their impact on the results presented.

The intracluster correlation coefficient, however modest, between neuropsychological domains of speed of information processing, complex attention and working memory, executive functioning, motor function, psychomotor speed, visual search (cluster 2), and HRQoL (cluster 3) might be an indication that age is a possible moderator variable. Age may thus influence the strength of the relationship between HRQoL and neuropsychological performance. Literature confirms that normal aging is independently thought to have an

influence on neuropsychological functioning (Cherner et al., 2004; Gonzalez & Cherner, 2008; Valcour et al., 2011; Hardy et al., 1999).

In addition, the possible moderating effects of age may explain the associations observed between individuals' neuropsychological performance and ongoing treatment, as noted in section 5.2. The age at which treatment is introduced is said to be an important predictor of neuropsychological outcome (Smith, Adnams & Eley, 2008). If older infected adults were to receive a latent or missed diagnosis, it is plausible that the virus may have caused debilitating brain injury, and that ART can no longer improve cognitive functioning (Al-Khindi et al., 2011). Older individuals are known to have less capacity for immune recovery, and may not respond as well to treatment as their younger counterparts (Gebo, 2006). Therefore, age may moderate treatment outcomes, and this can have implications for neuropsychological performance and quality of life.

Alternatively, clinical variables such as the number of months since a first HIV test (chronicity of illness), CD4 count (degree of immunosuppression), and the number of months since initiation on ART treatment may also moderate the strength of the relationship between HRQoL and neuropsychological performance. The intracluster correlation coefficient findings revealed a significant difference between neuropsychological domains of attention, memory, executive functioning, and clinical variables (cluster 1 and cluster 4). Recent literature confirms that the latest CD4 and viral load history are important predictors of current cognitive function across several cognitive domains. This was evident in a study conducted by Tate et al. (2011), who investigated the association between recent trends in CD4, viral loads, and cognitive test performance with the probability that this information could predict cognitive performance.

In essence, these findings allude to age and clinical variables (number of months since first HIV test – chronicity, CD4 count, and the number of months since initiation of ART treatment) as possible moderator variables. These speculations, however, are exploratory in nature and require further investigation.

5.6 Conclusion

The primary aim of this study was to investigate the associations between neuropsychological performance and HRQoL in an older population with HIV. To achieve the aim of the study, four objectives were determined and three hypotheses explored. The study arrived at the following conclusions regarding the cohort of older participants with HIV:

- Significant associations were found between HRQoL and neuropsychological performance. In particular, the findings suggested that reduced global neuropsychological performance and poor performance in domains of speed of information processing, attention, working memory, memory, sequencing, executive function (mental flexibility, abstract reasoning), visual search, and motor function are significantly associated with more self-reported anxiety/depression symptoms.
- Better performance in domains of attention, visual attention and sustained attention, processing speed, and psychomotor performance is associated with fewer self-reported problems of self-care and pain/discomfort.
- A significant association was found between neuropsychological performance and the clinical variables relating to the date of initiation on ART treatment and the CD4 count (degree of immunosuppression). Specifically, a decline in performance in domains of executive functioning (abstraction, mental flexibility), attention and working memory, complex attention, processing speed, and psychomotor function was associated with a

longer period of ART treatment. Also, decreased performance in domains of visuo-spatial/visuo-construction and motor function was associated with a lower CD4 count. These findings from the sample indicate that neuropsychological difficulties may persist, despite ongoing treatment.

- A significant association was found between HRQoL variables of mobility and self-reported anxiety/depression and the number of months since a participant's first HIV test (illness chronicity). These results indicated that, on these aspects of HRQoL, more problems were being reported during the initial diagnostic phase, and fewer problems as the disease advanced.
- The exploratory cluster analysis revealed that age and clinical variables relating to the date of the first HIV test (illness chronicity), date of initiation of ART treatment, and the latest CD4 count (degree of immunosuppression) may act as possible moderator variables, influencing the strength of the relationship between neuropsychological performance and HRQoL.

5.7 Limitations and Recommendation

1. A convenience sampling rather than a random sampling method was used. Thus, results cannot be generalised to an entire population of persons living with HIV/AIDS. It is therefore recommended that future studies incorporate a larger, more representative sample, utilising comprehensive, neuropsychological, and quality-of-life measures.
2. Future studies should incorporate longitudinal designs to further investigate the moderating effects of specific variables and the age-related nature of this study.
3. Not all the neurocognitive domains sensitive to HIV infection were included in the neuropsychological battery (e.g., speech and language). This was due to time constraints and language barriers.

4. The use of a self-report measure of HRQoL lends itself to scores that are not objective, as they are based on self-perceptions which may result in socially desirable responses.
5. Anxiety/depression was measured subjectively through the EQ-5D 5L anxiety/depression item. Instead, future studies should consider the use of an objective measure of depression. This may assist in controlling for the moderating effects/ elimination of the influence of depression from a sample.

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Appendix A: Medical Records Cover Page

University of Pretoria – Department of Psychology

UNIVERSITEIT VAN PRETORIA
UNIVERSITY OF PRETORIA
YUNIBESITHI YA PRETORIA

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 CD4 count: _____

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?

_____

_____

_____

Appendix B: Socio-demographic Questionnaire

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