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Detecting HIV associated neurocognitive disorders (HAND) using neurocognitive assessment test in Uganda

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DETECTING HIV ASSOCIATED NEUROCOGNITIVE DISORDERS (HAND) USING NEUROCOGNITIVE ASSESSMENT TESTS IN UGANDA

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A research report submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology

August, 2017

DECLARATION

I declare that this research is my own work. It is being submitted in partial fulfilment of the requirements for the degree of Master of Science in Epidemiology at the University of Witwatersrand, Johannesburg. This research has not been submitted previously for any degree or examination to any other institution.

Ethics clearance certificate number: M161185

Name of candidate: LeeAnne Masilela



_____

(Signature of candidate)

Date: August, 2017

DEDICATION

I dedicate this work to my nephews Lwazi and Lwando and to my niece Hadassah. Thank you for always giving me a reason to smile.

ABSTRACT

Background:

HIV associated neurocognitive disorders (HAND), are a well-established consequence of HIV infection yet there is a lack of normative data required for diagnosis in Sub-Saharan Africa. Screening tools such as the International HIV dementia scale (IHDS) that are routinely used in the Sub-Saharan African region have questionable validity. This study investigates the use of the neuropsychological test battery in the detection of HAND in the absence of normative data. Further, the construct validity of the IHDS in the detection of HAND in the Ugandan context is examined.

Methods

Secondary data from a longitudinal Mental Health study carried out in Uganda were analysed. Information from a total of 1121 patients who underwent neuropsychological assessment in the main study qualified for the present study. A descriptive analysis of the neuropsychological performance of the study participants was conducted. To assess the relationship between demographic factors and the neurocognitive test scores of the neuropsychological test battery, multiple linear regression models were fitted. To determine how well the neuropsychological test battery predicted the IHDS score, a receiver-operating curve (ROC) analysis was conducted. The construct validity of the IHDS in detecting HAND in the Ugandan population was then assessed using ROC analysis and published normative data.

Results

The total study population was 1,121 participants, with the majority being female (66.3%) while almost 62% had only primary school education. The mean age of the study participants was 35.0±9.3 years. Using the IHDS, 73.3% of the HIV infected patients were identified to be at risk of developing HIV associated dementia (HAD). Using the Frascati criteria and published normative data, only 9.1% of the HIV infected patients had HAND. Ageing, being female, having a lower socio-economic score and having lower levels of education were identified as predictors for poor neurocognitive performance. Poor performance in the neurocognitive measures to assess gross and fine motor function was directly proportional to poor performance in the IHDS (score ≥10 points). Better performance in the neurocognitive measures to assess verbal leaning/working memory and attention/working memory was directly proportional to

poor performance in the IHDS (score ≥10 points). The neurocognitive tests discriminated modestly between patients at risk of developing HAD and those that were not at risk of developing HAD (sensitivity=64.62%; specificity=66.67%). At the recommended cut-off score of 10 points, the IHDS had poor ability to identify patients with HAND (sensitivity=34.54%) and a high ability to identify patients without HAND (specificity=90.74%). At a cut-off point of 7 points, the IHDS discriminated modestly between patients with HAND and those without (sensitivity=65.66%; specificity=58.52%).

Conclusion

The neuropsychological test battery used in the present study discriminated modestly among HIV patients at risk of developing HIV associated dementia and those that were not at risk of developing dementia. In the Ugandan population, the construct validity of the IHDS in the diagnosis of HAND was poor. Further work is required to produce an algorithm to detect HAND in the absence of normative data. This includes an inclusion of important clinical biomarkers, exploration of further demographic confounders as well strengthening of the HAND diagnostic criteria using the neuropsychological test battery.

ACKNOWLEDGEMENTS

My sincere gratitude goes to my supervisors Professor Jonathan Levin and Dr Sumaya Mall for their relentless support and guidance. I would also like to thank Professor Eugene Kinyanda and the Ugandan Medical Research Council for allowing me to use the ECTDP dataset. A special thanks to Ms Zodwa Ndlovu, research coordinator, Division of Epidemiology and Biostatistics, for her support in managing this research project and to all my lecturers for their knowledge and encouragement. Lastly, my gratitude goes to the patients from the Ugandan Masaka and Entebbe clinics that consented to participate in this study.

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ACRONYMS

AAN: American academy of Neurology

AIDS: Acquired immunodeficiency syndrome

ANI: Asymptomatic neurocognitive impairment

ART: Anti-retroviral therapy

CSF: Cerebrospinal fluid

EDCTP: European & developing countries clinical trials partnership

HAART: highly active antiretroviral therapy

HAD: HIV associated dementia

HAND: HIV associated neurocognitive disorders

HDS: HIV dementia scale

IHDS: International HIV dementia scale

MND: Mild neurocognitive disorder

MCMD: Mild cognitive motor disorder

PLWHA: People living with HIV/AIDS

SDS: Sheehan disability scale

SD: Standard deviation

SDA: Seventh day Adventist

SSA: Sub-Sahara-Africa

WHO-UCLA AVLT: World Health Organization-University of California-Los Angeles Auditory Verbal Learning Test

CHAPTER 1: INTRODUCTION

In this introductory chapter, the contextual background and literature review for the study are presented. The background section includes:

1.1.1. A global overview of the HIV/AIDS pandemic
1.1.2. A description of comorbid neurological complications associated with HIV
1.1.3. A classification of HIV associated neurocognitive disorders (HAND)
1.1.4. A description of the global epidemiology of HAND
1.1.5. An overview of the detection of HAND
1.1.6. A description of the epidemiology of HIV/AIDS in Uganda

The background precedes the literature review where a detailed discussion of the challenges with HAND diagnosis in Sub-Saharan Africa (SSA) will be given. The conclusion of the chapter will culminate in the justification, aims and objectives of the study.

1.1 Background

1.1.1 Global overview of HIV/AIDS

Since the emergence of the HIV/AIDS epidemic in 1981, approximately 70 million people have been diagnosed HIV positive, with the disease contributing substantially to the global burden of morbidity and mortality (1). Currently, the global prevalence of HIV is thought to be 0.8% with young adults (in the age bracket 15 -49 years) disproportionately infected. More than 70% (25 800 000 individuals) of global infections are found in the Sub-Saharan African region (See Figure 1 below).

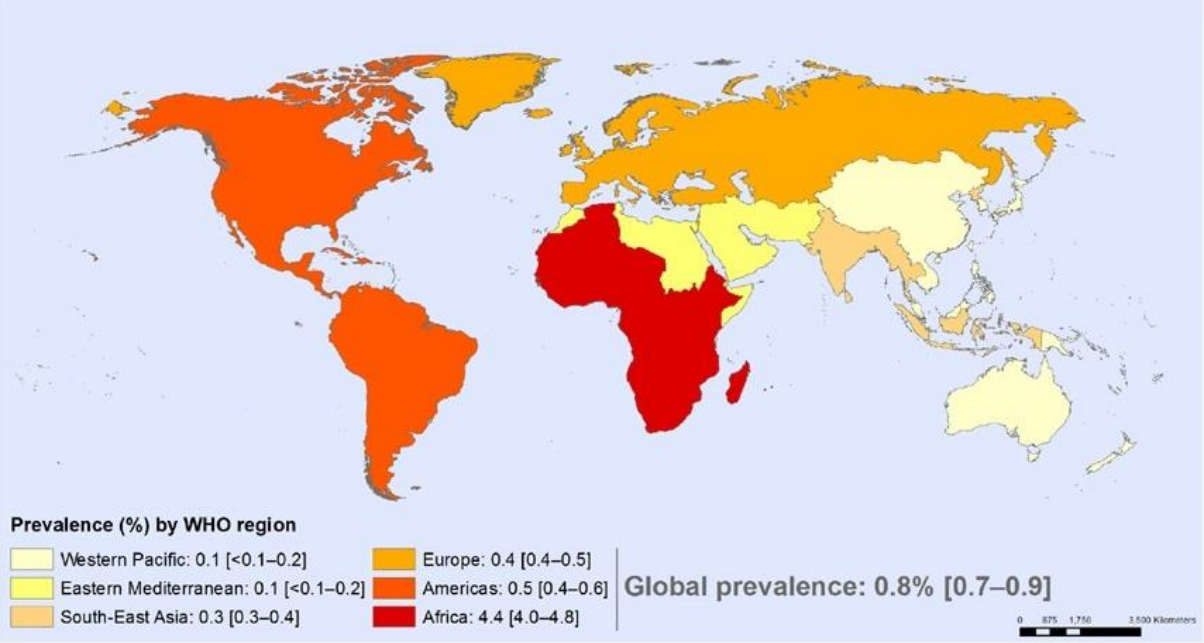


Figure 1: Global prevalence of the HIV/AIDS pandemic.

Adapted from: World Health Organization, 2016. Global Health Observatory (GHO) data. Available from: http://www.who.int/gho/hiv/en/. [03 March 2017].

1.1.2 HIV/AIDS and comorbid neurological conditions

People living with HIV/AIDS (PLWHA) are at risk of several comorbid illnesses including pneumonia, tuberculosis (TB), diarrhoea and HIV associated neurological disorders (1,2).

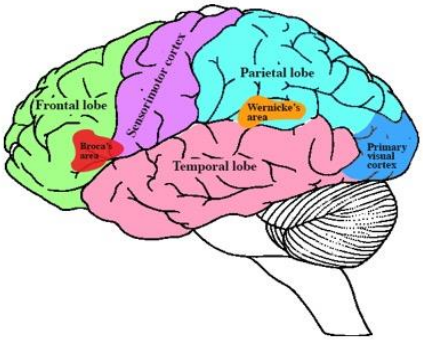
The HIV virus invades the brain during the early stages of infection where it replicates and mutates via migratory cells such as lymphoid cells (3). During this invasion, support cells in the brain known as microglia and astrocytes are infected (4). This in turn impairs nerve cells involved in cognitive control affecting one or more of the following cognitive domains: executive function, memory, attention, processing speed, visuospatial function, learning, reaction time and sensorimotor processes (5). A diagrammatic presentation of how HIV affects the neurocognitive domains of the brain is depicted in Figure 2 below.

The term HAND is used to describe the spectrum of neurocognitive dysfunction in patients infected with HIV (6). Neurocognitive disorders are often strong predictors of morbidity and mortality (3,5,7,8). In a systematic review of HIV associated neurocognitive disorders, Saylor

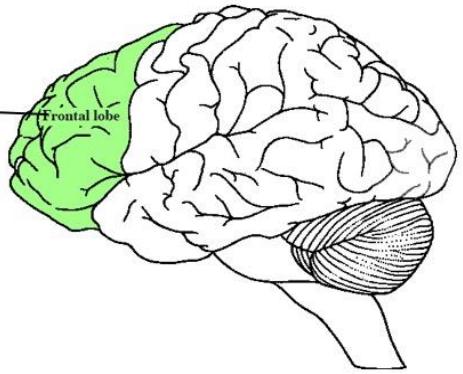
and colleagues elucidate the disabling nature of HAND by describing the mechanism of HIV in the human brain in the early stage of HIV infection characterized by cerebrospinal fluid (CSF) inflammation that triggers neurodegeneration (9).

1.1.3 Classification of HIV associated neurocognitive disorders

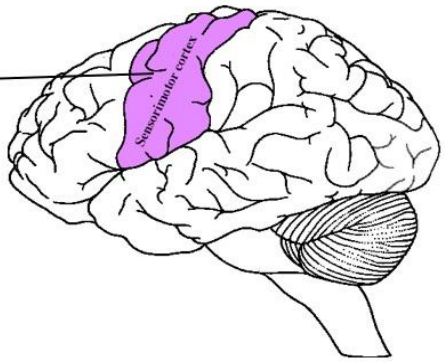
HIV associated neurocognitive disorders are classified into: Asymptomatic neurocognitive impairment (ANI), Mild neurocognitive disorder (MND) and the most severe, HIV associated dementia (HAD), (see Figure 2 below and Appendix A) (10).



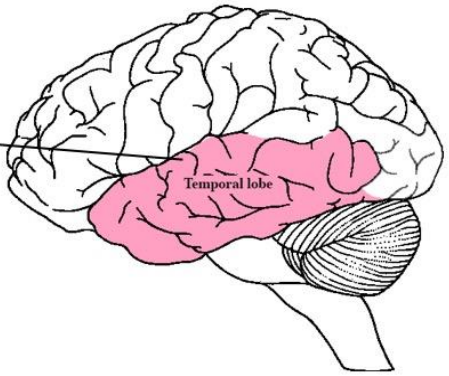
Brain regions implicated in HIV associated neurocognitive disorders



Domain 1: Executive function
Function: planning, conceptualizing, organizing.
Neurocognitive test: the colour trails 2 test (Arbuthnott and Frank, 2000).
ANI presentation: patient has no evidence of decline in everyday executive function, however scores 1 standard deviation (SD) below mean for demographic appropriate norms.
MND presentation: patient has mild interference in executive function evaluated by self report assessment such as the Sheehan Disability Scale and scores 1 SD below mean for demographic appropriate norms
HAD presentation: patient has marked interference with day to day ability to plan, organize and conceptualize and scores 2 SD below mean for demographic appropriate norms (Antinori et al., 2007).



Domain 2: Sensorimotor skills
Function: gross manual, fine and facial motor abilities.
Neurocognitive test: the timed gait test (Ng and Hui-Chan, 2005).
ANI presentation: patient has no evidence of decline in everyday sensorimotor ability, however scores 1 SD below mean for demographic appropriate norms.
MND presentation: patient has mild interference in sensorimotor ability evaluated by self-report assessment such as the Sheehan Disability Scale (SDS) and scores 1 SD below mean for demographic appropriate norms.
HAD presentation: patient has marked interference with day to day ability to perform motor functions such as walking, conceptualizing, making facial gestures and scores 2 SD below mean for demographic appropriate norms (Antinori et al., 2007).



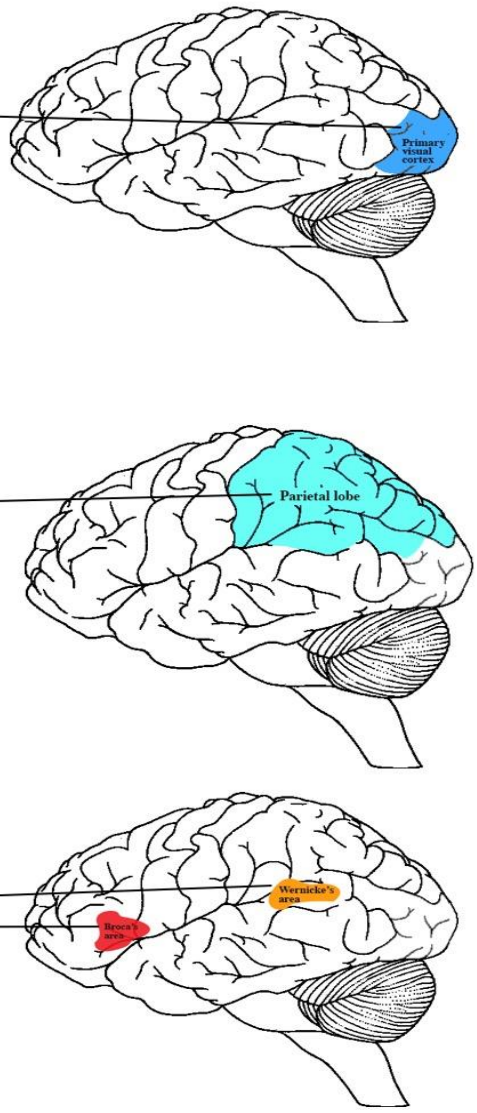
Domain 3: Attention
Function: ability to focus awareness on given task.
Neurocognitive test: the digit span forward and backward test (Reynolds, 1997).
ANI presentation: patient has no evidence of decline in everyday attention ability, however scores 1 SD below mean for demographic appropriate norms.
MND presentation: patient has mild interference in attention ability evaluated by self-report assessment such as the Sheehan Disability Scale and scores 1 SD below mean for demographic appropriate norms
HAD presentation: patient has marked interference with day to day ability to focus attention on task to the point of a formal attention deficit disorder and scores 2 SD below mean for demographic appropriate norms (Antinori et al., 2007).

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Domain 4: Visuospatial skills
Function: ability to make sense of the visual world, shapes and angles.
Neurocognitive test: the Hooper Visual Organisation Task (not commonly used in studies) (Moritz *et al.*, 2004).
ANI presentation: patient has no evidence of decline in everyday visuospatial ability, however scores 1 SD below mean for demographic appropriate norms.
MND presentation: patient has mild interference in visuospatial ability evaluated by self-report assessment such as the Sheehan Disability Scale and scores 1 SD below mean for demographic appropriate norms.
HAD presentation: patient has marked interference with day to day ability to conceptualize complex ideas and verbal expressions and scores 2 SD below mean for demographic appropriate norms (Antinori et al., 2007).

Domain 5: Memory
Function: foci are verbal visual and motor memory.
Neurocognitive test: the WHO-UCLA Auditory verbal learning test (Rosenberg, Ryan and Prifitera, 1984).
ANI presentation: patient has no evidence of decline in everyday memory ability, however scores 1 SD below mean for demographic appropriate norms.
MND presentation: patient has mild interference in memory ability evaluated by self-report assessment such as the Sheehan Disability Scale and scores 1 SD below mean for demographic appropriate norms.
HAD presentation: patient has marked interference with day to day ability to recall concepts and visual presentations and scores 2 SD below mean for demographic appropriate norms (Antinori et al., 2007).

Domain 6: Language
Function: ability to comprehend repeat express language.
Neurocognitive test: the WHO-UCLA Auditory verbal learning test (Rosenberg, Ryan and Prifitera, 1984).
ANI presentation: patient has no evidence of decline in everyday language ability, however scores 1 SD below mean for demographic appropriate norms
MND presentation: patient has mild interference in language ability evaluated by self-report assessment such as the Sheehan Disability Scale and scores 1 SD below mean for demographic appropriate norms.
HAD presentation: patient has marked interference with day to day ability to comprehend language and scores 2 SD below mean for demographic appropriate norms (Antinori et al., 2007).



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Figure 2: Brain regions implicated in HIV associated neurocognitive disorders

1.1.4 Global Epidemiology of HIV associated neurocognitive disorders

Milder forms of HAND such as ANI and MND are reported to occur in 30-60% of individuals infected with HIV (11). Since the introduction of highly active antiretroviral therapy (HAART), the incidence of severe forms of HAND such as HAD has declined by 40%. Today HAD is reported to occur in 10-15% of all HIV infected individuals (11,12). Physical and social factors such as age, cardiovascular disease, education and gender have been reported to be associated with the development of HAND (9). Studies in developed settings such as the United States of America have reported a HAND prevalence of 42% while studies in developing settings such as Uganda have reported a HAND prevalence of 31% (10,13).

1.1.5 Detection of HIV associated neurocognitive disorders

There are several considerations to make when developing strategies for assessing neurocognitive impairment in people living with HIV/AIDS (PLWHA). These considerations include: life circumstances and cultural context of the study population, ease of instrument/assessment administration and validity of assessment instrument (14). It is for these reasons that screening tools such as the brief International HIV dementia scale (IHDS) have been identified as sufficient for identifying the presence/absence of neurocognitive impairment for primary healthcare settings. On the other hand, the neurocognitive test batteries that sample a wider range of cognitive ability are reserved for characterization of impairment in research settings in resource limited counties (15,16).

In African countries, a battery of neurocognitive tests is commonly employed as the gold standard. The battery consists of the *timed gait test*- to assess gross motor function, the *colour trails 1 test* and the *symbol digit modalities test*- to assess speed of processing, the *colour trails 2 test*- to assess executive functioning, the *WHO-UCLA Auditory verbal learning test*-to assess verbal learning and memory ability and the *Digit span forward and backward test*-to assess verbal learning and memory ability (12,17).

The diagnostic criteria used in the classification of HAND are given in Figure 2 above. Administration of a battery of neurocognitive tests is often restricted to research settings due to the time-consuming and labour intensive nature of the tests as the tests can take up to four hours to administer (13). In addition, the use of neurocognitive tests to diagnose HAND

requires norms for the HIV seronegative population which are not readily available in resource limited settings such as Sub-Saharan-Africa (12,18).

In clinical settings, screening tools such as the HIV dementia scale (HDS) and the International HIV dementia scale (IHDS) are most common (15). The most common screening tool in resource limited settings is the IHDS (12,15,16,19,20). In a preliminary report on HIV associated dementia, Tross et al. identified neurocognitive tests of motor speed, concentration and memory to be prominently abnormal in patients with HIV dementia (21). This finding led to the development of an instrument designed to be rapid and sensitive in identifying dementia in HIV positive patients (19). Based on the findings by Tross et al, the IHDS was developed to identify deficits in the cognitive domains of motor function, concentration and memory (22).

The IHDS consists of the following set of tests: *the dominant finger tapping test* and *the non-dominant Lauria- hand sequence test-* to assess motor functioning as well as the *four-word recall test-* to assess memory and recall (19). These screening tools are effective in identifying participants at risk of developing the most debilitating form of HAND, HIV associated dementia (HAD), but are however not effective in identifying the category of cognitive impairment and moreover have questionable sensitivity and specificity as will be discussed later in the chapter (13,20).

1.1.6 Epidemiology of HIV/AIDS in Uganda

The Ugandan HIV/AIDS epidemic has had an interesting transition. Uganda was one of the earliest African countries to be affected by the HIV/AIDS epidemic in the early 1980's (23). By 2004, Uganda was considered a success in the arena of HIV/AIDS prevention particularly among younger cohorts and pregnant women attending antenatal surveillance sites. Several initiatives sought to encourage condom use and reduction in the number of sexual partners as well as increased access to anti-retroviral therapy (ART) (24). These efforts may have been associated with decline in HIV related mortality (24). In 2010, an estimated 67 000 Ugandans died from AIDS related illnesses. This declined in 2015 to 28 000 deaths.

Today, however, in the Sub Saharan African region, Uganda is reported to have the third highest number of HIV infections after South Africa and Nigeria (25). Currently, the HIV prevalence in Uganda is 7% with an estimated 1.5 million PLWHA. Annual infections are projected to rise to 340 000 by the year 2025. It is challenging to elucidate the reasons for the increase in incidence of HIV infection in Uganda. Research has suggested that HIV related stigma and discrimination against PLWHA might have consequences for both the general population and PLWHA (26). HIV related stigma results in decreased uptake of HIV testing services and increased sexual risk behaviour in the general population. In PLWHA, HIV related stigma might impede access and adherence to ARV therapy (26).

An increase in the incidence of HIV infection in Uganda may lead to an increase in the prevalence of comorbid neurological complications such as HAND (2). However, due to the absence of normative data and standardized HAND detection mechanisms in Sub Saharan Africa, it is difficult to elucidate the prevalence and incidence of HAND in Uganda. This prevents the development of appropriate medical interventions.

To address the problem, it is of public health importance to establish innovative accurate means to screen for HAND in resource-limited settings in order to understand the prevalence and incidence of HAND within Sub Saharan Africa. Such innovative means would entail an assessment of the performance of the neurocognitive tests in the absence of normative data and an investigation on the comparative utility of the neurocognitive assessment tests and rapid screening tools such as the IHDS which we aim to tackle in the present study (17).

Although Sub-Saharan Africa has been reported to account for more than half of the HIV infections globally, the data on HAND in the region are variable or poor. This paucity of data may be due to the lack of a comprehensive screening procedure, absence of normative data as well as variability in the validity of screening tools (15,27). Normative data is data obtained by administering a test to a reference population to establish norms. Norms are values that are representative of a certain population and are used as a baseline against which subsequently collected data is compared In the case of HAND, the reference population is an HIV negative population matched to the target HIV positive population for demographic factors such as age, education and gender (28). A detailed overview of studies aimed at attaining normative data in the Sub Saharan African region is presented in Table 1 below.

Table 1: Overview of HIV associated neurocognitive disorder normative data studies in sub Saharan Africa

Authors	Country	Population characteristics	Neurocognitive tests	Comments
Singh et al., 2010	South Africa	110 HIV seronegative participants, predominantly female, average 10 years of education	Digit span forward Digit span backward test Trail making test A Trail making test B	Sample size relatively small hence findings not generalizable to the entire population. A brief neuropsychological test battery was used.
Kelly et al., 2014	Malawi	103 HIV seronegative adults, median age 34.5 years, average 10.5 years of education	Hopkins verbal learning test WAIS digit symbol test Grooved pegboard dominant hand Grooved pegboard dominant hand Colour trails 1 test Colour trails 2 test Timed gait test	Relatively small sample size. Normative data was not stratified by important demographic factors such as age, education and gender
Robertson et al., 2016	Brazil India Malawi Peru South Africa Thailand Zimbabwe	2400 HIV seronegative adults were included in the multisite study. Mean age =35 years. 50% female, average 10 years education	Hopkins verbal learning test Semantic verbal learning test WAIS digit symbol test Grooved pegboard dominant hand Grooved pegboard dominant hand Colour trails 1 test Colour trails 2 test Timed gait test	There were substantial variations in neuropsychological performance across the different countries. This finding highlights the need for country based normative data. Cultural differences were suspected to account for variance in neuropsychological performance

1.2 Literature Review

1.2.1 Search Strategies

An extensive literature review was conducted in line with the study question of screening for HAND in the absence of normative data.

The following databases were searched in discussion with my thesis supervisors: PubMed, Global Health, Clinical key and Scopus. The following keywords and several permutations were employed for the search strategy: “HIV associated neurocognitive disorders”, “International HIV dementia scale”, “HIV neuropsychological test battery”. MeSH terms were used to search each database. A total of 9043 abstracts were identified and extracted into a Mendeley database. Abstracts were filtered according to the inclusion and exclusion criteria outlined in table 2. The literature search was limited to journal articles published between the year 1991 and 2016 as the first standardized approach to diagnose neurocognitive deficits in HIV positive populations was first published in 1991. A flow diagram of the search strategy for this literature review is presented in figure 3 below.

Table 2: Inclusion and exclusion criteria for search strategy

	Inclusion criteria	Exclusion criteria
Publication type	Journal article (published between 1991-2016) English language	Non-English journal article Pamphlets, editorials, guideline documents
Study design	Any study design in which the neuropsychological test battery and the International HIV dementia scale were used to detect HAND	
Study population	Adults (18 years and older)	
Condition of interest	HIV associated neurocognitive disorders	Substance/alcohol induced neurocognitive disorders

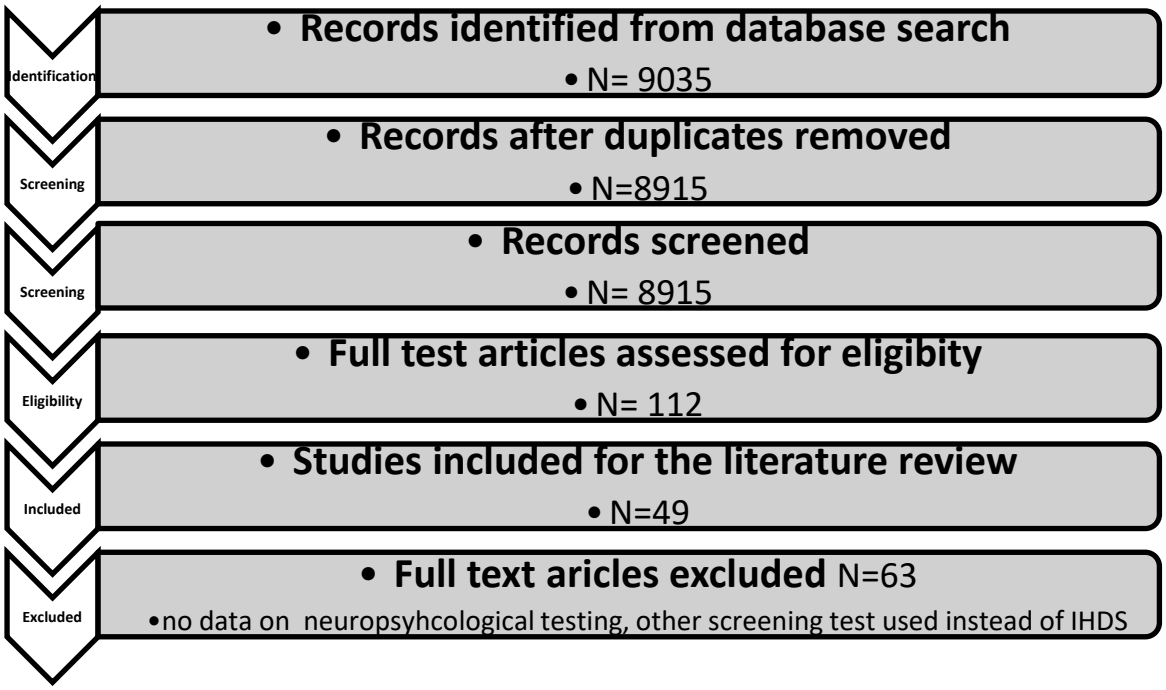


Figure 3: Flow diagram for literature review search strategy

The following themes emerged from the literature sourced:

- Challenges associated with the neuropsychological test battery
- Challenges associated with the IHDS

The themes will be described in detail below.

1.2.1.1 Challenges associated with the neuropsychological test battery

The most frequently used procedure for the diagnosis of HAND in research settings in Africa is that prescribed by the American Academy of Neurology (AAN) in the year 2007 (10) with the battery of neurocognitive tests described earlier in the thesis. There are several challenges that exist in interpreting these neurocognitive tests in the Sub-Saharan African context, including: confounding effects of demographic factors, loosely defined diagnostic criteria, ambiguity in ANI diagnosis and the lack of normative data (17,28,29).

The first challenge with the interpretation of neurocognitive tests is that it is suspected that demographic and cultural background could lead to the overestimation/underestimation of specific cognitive abilities (17). In a study conducted in the United States of America of a sample of 123 participants, ethnically diverse participants were compared with English speaking Anglo Americans. In this study English-speaking Anglo Americans were reported to outperform the ethnically diverse group (Boone et al., 2007). The study suggests that cultural familiarity with the testing format resulted in better performance in the *WASIII symbol digit* span and *color trails tests* for speed of information processing and attention abilities respectively (Boone et al., 2007). In addition, a study conducted in Australia revealed the following factors to contribute significantly to the proportion of variance in cognitive performance: age (13.8%), years of school (4.1%), culture (11.5%) and race (3%) (24). These findings lead us to strongly oppose the use of normative scores from Western settings to estimate HAND prevalence in Africa(28). In a conference for a review of the neuropsychological test battery, Anger et al. report that age and cultural differences affected the response time of adults in the neurocognitive assessment tests of the neuropsychological test battery which may affect estimation of HAND (Anger et al., 2000).

Similarly, in a South African HIV clinical disease cohort, Singh et al found age and gender to influence neurocognitive function, with older individuals performing worse while the effect of

gender varied across the different tests (12). These studies highlight the confounding effect of demographic factors such as age, education and gender in the diagnosis of HAND. However, to date, adjustment for demographic factors in HAND studies in Sub-Saharan Africa is still limited. In Sub-Saharan African studies where there has been an attempt to generate normative data for HAND diagnosis, the confounding effects of demographic factors have been largely ignored and sample sizes are often too small to generate conclusive data on neuropsychological performance in African cohorts (12,18,30). In addition, studies on the African continent suggest that cultural heterogeneity across the different African countries prevents any cross cultural use of normative data (12,18,28). It is important to explore the effect of demographic factors on the neurocognitive performance of HIV clinical disease cohorts across different cultural contexts.

The second challenge with the diagnosis of HAND using the neuropsychological test battery lies in the use of a broadly defined criteria to diagnose HAND which may lead to the rise of false positive results (29). The method of diagnosis proposed by the Frascati criteria (see Appendix A) is purely statistical and comes with recommendations that are not mandatory such as performing two tests per cognitive domain and at least 5 neurocognitive tests per individual (10). This loosely defined criterion has led to inconclusive prevalence reports in the region of Sub-Saharan Africa. For example, Lawler and colleagues conducted a cross sectional study of 60 HIV positive individuals demographically matched to 80 control subjects in Botswana and found 37% of the HIV positive patients to be cognitively impaired in the following domains: speed of information processing, executive function, fine motor skills, verbal learning and memory (31). These findings on areas of cognitive impairment in HIV positive Sub-Saharan Africans were consistent with a Ugandan study by Robertson and colleagues where 110 HIV positive individuals and 100 control subjects were compared and the prevalence of HIV dementia was found to be 31%. However, in this study by Robertson and colleagues, a brief test battery was used (only two neurocognitive tests) and patients were stratified by the Memorial Sloan Kettering dementia scale without adjustment for important demographic factors such as age, education and gender (30). In both studies, only single tests were performed per domain possibly due to the time-consuming nature of the tests. These studies raise the question on whether this generously defined criterion for HAND diagnosis has led to an overestimation of the burden of HAND. A standardized diagnostic procedure for HAND with mandatory guidelines is essential to rectify these problems (29).

The third challenge lies in the diagnosis of milder forms of HAND using neurocognitive tests. It seems ethically controversial to classify patients that do not have any symptoms as cognitively impaired. This is the case in the milder forms of HAND such as the Asymptomatic neurocognitive impairment (ANI) (10). In order to be diagnosed as an ANI case, patients need to have scored one standard deviation (1 SD) below the mean for demographically appropriate norms (10,17). This diagnostic criterion is questionable as there is currently no evidence to suggest that patients with ANI have an increased risk of developing more severe forms of HAND (29). The classification of patients as MND cases also needs to be taken with caution. This is due to the fact that there is a reliance on patients' self-reports as to whether there is a change in functioning on their daily life activities. It is important to note that self-reports are subjective to the emotional state of the patient as well as other external factors such as study setting at the time of questioning (Robertson et al., 2009). In a systematic review on cognitive dysfunction in HAND, it was revealed that self-reported functional abilities are often confounded by psychiatric and socio-economic factors. Depressed patients were reported to often over-report their functional impairment due to depressive symptoms while poor patients were likely to under-report their functional impairment to retain occupational responsibilities (8,32,33)

Lastly, the greatest challenge with the diagnosis of HAND in SSA is the lack of normative data from a control population that is matched to the target population for at least culture/ethnicity, age, education and gender in order to effectively estimate the prevalence of HIV associated neurocognitive impairments (18,31). Studies that have been aimed at obtaining normative data for HAND are often limited by small sample sizes (12,14,34,35).

Furthermore, the controversies that lie with attaining normative data include finding willing participants, considering the intense/time consuming nature of neuropsychological testing and the fact that it is difficult to match patients for all confounding factors that have been associated with HAND such as alcohol or drug abuse history (29). The absence of sophisticated technology such as neuroimaging techniques in resource limited settings to ascertain the absence/presence of neurocognitive impairment also poses as a limitation to finding the true prevalence of the disorders (36). In a recent study, Robertson and colleagues conducted a large scale multisite study to address the lack of normative data in resource limited settings. In this study 2400 HIV seronegative participants were enrolled from 7 resource limited countries including Brazil, Zimbabwe, Malawi, South Africa, India and Peru. However, there was a

marked variation in neuropsychological performance across different countries, which was suspected to be due to cultural diversity.

1.2.1.2 Challenges associated with the International HIV dementia scale (IHDS)

As described in the introduction above, the IHDS is widely used as a screening tool to identify patients at risk of developing HAD and patients who require further neuropsychological examination in resource limited settings (16). The instrument has also been increasingly used for the diagnosis of HAND in clinical settings despite the heterogeneity in accuracy reports (15,16). A great challenge in the detection of patients at risk of developing HAD using the IHDS is the uncertainty in the instrument validity for use in African cohorts. This is because literature on IHDS validity is limited by the lack of a standardized gold standard for HAND screening (13).

Another reason for the uncertainty in IHDS validity is due to varying reference standards in different studies (15). In a study to establish the validity of the IHDS as a screening test for HIV dementia, Sacktor et al assessed 81 HIV positive Ugandans using the IHDS and a neuropsychological test battery. They found the sensitivity and specificity of the IHDS in detecting HIV dementia to be 80% and 57% respectively at a cut-off score of ≤ 10 (19). In a study conducted in a similar setting, 96 HIV seropositive individuals in South Africa underwent a similar assessment procedure. In this study, the sensitivity and specificity of the IHDS in detecting HAD was found to be 45% and 79% respectively at a cut off score of ≤ 10 (20). In a recent study in a Southern Chinese population of similar socio-economic status as the Ugandan population, 230 HIV infected patients underwent neuropsychological assessment and IHDS screening. In this case, IHDS was found to be an economical and well performing screening tool with sensitivity and specificity of 74% and 71% respectively at a cut-off score of ≤ 7.25 (37). There is clear heterogeneity in validity reports on the IHDS emphasized in various papers (15,16,38).

The above-mentioned studies employed varying strategies to strengthen validity. In the first study by Sacktor et al, the reference standard for ascertaining IHDS validity was the neuropsychological test battery with normative data from an HIV negative cohort. This cohort was significantly younger (mean age 31 ± 7.3) than the HIV positive cohort (mean age 47 ± 9.4), raising the question of whether age confounded the performance in these assessments (14,19).

In the second study by Joska et al., (39) the reference standard for IHDS validity was the normative data adjusted for age, education and gender from neuropsychological tests. The adjustment for demographic factors highlighted these factors as independent determinants of neuropsychological performance. As this study by Joska et al. took the effect of confounding variables into account, the results may have been more accurate in detecting HAND (20). In the third study by Dang et al, which reported the IHDS to be an effective screening tool in resource limited settings, the reference population also underwent neuroimaging to rule out CNS opportunistic infections in addition to neuropsychological assessment with adjustment for demographic factors (37). This strengthened the diagnosis of neurocognitive impairment specific to HIV hence strengthening the validity ascertainment of the IHDS in detecting these disorders. However, in this study by Dang et al, the cut off was much lower than in the other studies, significantly improving the sensitivity and specificity of the IHDS (29).

Although the International recommendation for IHDS diagnosis is set at a cut off $\leq$10 points for participants at risk of developing HAD, this recommendation does not consider the influence of age, education level, gender, ethnicity and cultural differences reported in some studies (20,37). A cut off of $\leq$ 10 points may introduce false positive results (37). There is still much work to be done by the scientific community in ascertaining the validity of the IHDS. In undertaking this task, a range of diagnostic cut-offs need to be explored and demographic differences in the IHDS performance need to be considered. Furthermore, due to the fact that the IHDS only tests performance on limited domains of motor function and memory/recall, a question arises about whether this tool is sufficient on its own in the diagnosis of HAD. Studies have suggested participants who perform poorly on the IHDS may perform well on neurocognitive assessment tests. This leads to a questioning of the validity of the IHDS in HAND detection (19,20).The comparative utility of the IHDS as a diagnosis tool for HAND with the neuropsychological test battery needs to be further explored.

1.3 Problem Statement

The concerns above highlight a gap in knowledge on HIV related neurocognitive impairment that exists in Sub-Saharan Africa. The large scale multisite study to obtain normative comparison data in diverse international resource limited settings by Robertson and colleagues revealed the need for country based normative data due to the neurocognitive variation observed across different cultural contexts (Robertson et al., 2016). However, this may not

always be feasible in the Sub-Saharan context where sample sizes for cognitive impairment studies are often limited by the intensity of the neurocognitive assessment methods hence limiting the availability of a normative group for comparison. Population norms are typically required to have a sample size of at least 1000 individuals (40). There is a need to explore mechanisms for the diagnosis of HAND in the absence of normative controls.

1.4 Justification

The above literature review suggests a paucity of conclusive normative data on HIV associated neurocognitive disorders in Sub-Saharan Africa. This study will therefore investigate the use of neurocognitive assessment tests described above in the diagnosis of HAND in the absence of normative data in Uganda. This will serve as a baseline for further exploration of innovative methods to diagnose HAND in the absence of normative data. Finding efficient mechanisms for the screening and diagnosis of HAND will assist early detection of the condition and the initiation of antiretroviral therapy that has been reported to dramatically decrease the incidence of severe forms of neurocognitive impairment hence curbing detrimental HIV outcomes and lessening the HAND health care system burden in Sub-Saharan Africa (41).

1.5 Research question, aims and objectives

Research question: Can existing neurocognitive assessment tests be used in the diagnosis of HAND in the absence of normative data in Uganda in 2012?

Aim: To assess whether neurocognitive assessment tests can be used in the diagnosis of HAND in the absence of normative data in Uganda.

Objectives:

1. To describe the neurocognitive assessment test scores (i.e. scores for the *timed gait test*, the *WHO-UCLA verbal learning test*, the *grooved pegboard test*, the *colour trails 1 & 2 test*, the *Auditory verbal learning test,* the *digit span backward and forward test* and the *symbol digit modalities test*) for each age, gender and education category among HIV-infected Ugandans using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda.
2. To investigate how each of the six neurocognitive test scores is related to age, gender and education, and to calculate age, gender and education adjusted scores among HIV-infected Ugandans using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda.
3. To determine the relationship between the seven neurocognitive assessment test scores and the International HIV Dementia Scale (IHDS) test score and to see how well the six scores predict the IHDS using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda adjusting for age, education and gender.

CHAPTER 2: METHODS

2.1. Study design

The study is a cross sectional study design of baseline data nested within a longitudinal European & Developing Countries Clinical Trials Partnership (*EDCTP*) Mental Health study.

2.2. Data source

Data were provided by the Ugandan Medical Research Council/Uganda Virus Research Institute (MRC/UVRI). Professor Eugene Kinyanda is the Principal Investigator for the mental health study under which the baseline data for the present study is nested. The Ugandan MRC/UVRI Research Unit has been involved in several clinical studies on psychiatric and psychosocial complications of HIV/AIDS over the past 6 years, which have culminated in over 40 publications in peer-reviewed journals.

2.3 Study site

The data were collected at the Aids Support Organization (TASO) Masaka and Entebbe clinics in Uganda by the MRC/UVRI Research Unit on AIDS in 2012.

2.4 Study population

The study population included consenting HIV positive participants (18 years and older) that were ART naïve and were registered as outpatients at the TASO Entebbe (semi-urban site) and TASO Masaka (rural site) clinics in Uganda in 2012.

At the Entebbe study site, a random sample of 555 ART naïve HIV positive persons was recruited and at the Masaka study site, a random sample of 568 ART naïve HIV positive persons was recruited. The combined study sample size was 1127 participants; six observations were dropped due to the large amount of missing data resulting in an effective sample size of 1121 participants. The study participants were identified by a unique study number that could not be linked to any personal identifiers.

2.5 Study sample

All participants (18 years and older) who underwent neurocognitive evaluation in the TASO Entebbe and Masaka clinics were included in the present study. The exclusion criteria for the study included: participantswho had severe health problems that could prevent them from understanding the study instruments such as bed ridden cardiovascular disease participants and those who were unable to provide informed consent.

2.6 Measuring instruments

Data were collected using the *EDCTP* Mental Health study baseline questionnaire. The baseline questionnaire consisted of ten sections. The current study employed two sections from the baseline questionnaire i.e. the socio-demographics section and the HIV associated neurocognitive impairment section.

Questionnaires were administered in the local language (Luganda). The data collection tools were back translated to meet a threshold reliability (42). The following socio-demographic data were collected: study site, sex, marital status, religion, education level, occupation, date of birth and socio-economic index.

Standardised locally translated neurocognitive assessment tools administered by psychiatric nurses were used to collect data on HIV associated neurocognitive impairment. For neurocognitive assessment, the following neurocognitive domains were measured: gross motor functioning (using the *timed gait test*), fine motor functioning (using the *grooved pegboard test*), speed of processing (using the *colour trails 1 test* and the *symbol digit modalities test*), executive functioning (using the *colour trails 2 test*), verbal learning and memory ability (using the *WHO-UCLA Auditory verbal learning test*) and attention/working memory (using the *Digit span forward and backward test*).

A brief dementia screening tool known as the International HIV dementia scale (IHDS) was administered to identify participants at risk of developing HIV associated dementia (HAD), the

most severe form of HAND. The IHDS screening tool is made up of three tests used to assess motor functioning (using the *dominant finger tapping test* and *the non-dominant alternating hand sequence test*) and memory/recall (using the *four-word recall test*). (12,17). Data collected by the psychiatric nurses was entered into an MS ACCESS database (42). The data collection variables will be described in detail below.

2.7 Measurement of variables

The study variables used in the present study were grouped into four categories namely: demographic variables, neurocognitive assessment variables, dementia screening test variables and the Sheehan disability scale variables. The variables are described in detail below.

2.7.1 Demographic variables

- **Study site:** The study site was defined as either Entebbe or Masaka clinic.
- **Sex:** This variable was defined as either 'female' or 'male'.
- **Marital status:** This is a nominal categorical variable with the following categories: 'married', 'widowed', 'separated/divorced' and 'single'.
- **Religion:** This is a nominal categorical variable with the following categories: 'Born again (converted to a personal faith in Jesus Christ)', 'Catholic', 'Muslim', 'Protestant (follower of any of the Western Christian churches that are separate from the Roman Catholic Church)', 'Seventh Day Adventist (SDA)' (protestant Christian religion distinguished by its observation of Saturday as the day of worship) and 'other'.
- **Education:** This is an ordinal categorical variable with the following categories: 'none', 'primary' and 'secondary and above'.
- **Employment:** This is a nominal categorical variable with the following categories: 'farmer or fisher', 'professional or clerical', 'trader or artisan or transport' and 'unemployed or retired or housewife'.
- **Age:** The age of the participant was calculated from the date of birth to the interview date. Age was recorded as a continuous variable
- **Socioeconomic score:** This variable was derived from binary (yes/no) variables for ownership of the following consumer items: electricity, car, bicycle, radio, telephone, refrigerator, cupboard and flask. A principal components analysis was carried out to

recode the socioeconomic index as a variable taking values from 0 (for those who had no consumer items to 2.33 (for those who had all consumer items) (43).

2.7.2 Neurocognitive assessment variables

- **The timed gait test score:** The timed gait test was used to assess gross motor functioning. Participants were asked to walk a distance of 10 yards (9.14 meters) and return for a total of 20 yards (18.29 meters) as fast as possible. The time (in seconds) it took the participants to walk this distance was recorded and the score was rounded to the nearest full second. The timed gait test was administered for three trials. The total timed gait test score was the average of the three trials in seconds accurate to $1/10^{th}$ of a second. If the participant required more than 45 seconds to complete trial, this trial was not considered and the mean time to complete test was calculated as the average of time for the completed trials (44).

- **The grooved pegboard test score:** The grooved pegboard test was used to assess fine motor functioning. The pegboard consists of 25 slotted holes oriented in different directions. Participants were tested by how quickly they could slot the pegs into the holes. The pegs consisted of a square and rounded side. These pegs were to be rotated to match the hole on the pegboard before being inserted. The grooved pegboard test consisted of two subtests: the grooved pegboard dominant hand test and the grooved pegboard non-dominant hand test. Each subtest was dependant on whether a participant was left or right handed. For the right hand trial, pegs were required to be placed from participants left to right and the opposite applied for the left hand trial. Only one peg could be picked at a time. The score for each hand was the total time that the participant took to complete the entire board. If the participant took longer than 240 seconds to complete the entire board, the test was stopped. A total grooved pegboard score was calculated by adding the number of seconds it took to complete the dominant hand trial and the non-dominant hand trial (45).

- **The colour trails 1 test score:** The colour trails 1 test was used to assess speed of processing. Participants were asked to make pencil line connections in numerical order between 25 encircled numbers which were randomly arranged (odd numbers were in

pink and even numbers were in yellow). The colour trails 1 test score was defined as the total time it took the participant to complete the test.

- **The colour trails 2 test score:** The colour trails 2 test was administered to assess executive functioning. For this test, all numbers (1-25) were shown twice, once in pink and once in yellow. Participants were asked to connect in the numbers in sequential order alternating between colours. The colour trails 2 test score was defined as the total time it took the participant to complete the test.

- **The WHO_UCLA auditory verbal learning test (AVLT) score**: The AVLT was used to assess verbal learning and memory recall. A list of 15 words was presented to the participant and the participant was required to recall as many items as possible from the list in any order. The test was repeated for a total of five trials. The list is read at a rate of one word per two seconds. For each word repeated correctly, a participant scored 1 point. A total AVLT score was calculated by adding the total points from each of the five trials. The maximum score for the auditory verbal learning test is 75 points (46).

- **The Digit span test scores:** The Digit span forward and backward tests were used to assess attention and working memory. The digit span forward test was administered separately from the digit span backward test. For the digit span forward test, participants were asked to repeat digits that the examiner recited to them. The digits were given at the rate of one per second with the pitch of the voice dropping on the last digit. The test was administered for a total of two trials. The test was discontinued after failure on both trials of any item. Each item was scored 2 points if the subject passed both trials, 1 point if the subject passed only one trial, 0 points if the subject failed both trials. The maximum score on the digit span forward test is 14 points.

  For the digit span backward test participants were asked to repeat digits that the examiner recited to them, however the participants had to repeat the digits backwards. Digits were read at a rate of one per second. The test was discontinued after failure on both trials of any item. Scoring of the digit span backward test is similar to the digit span forward test scoring. A total digit span score was generated by adding the score of

the digit span forward and the digit span backward test making a total maximum score of 28 points (46).

- **Symbol digit modalities test score:** The symbol digit modalities test was used to assess speed of processing. Using a reference, each participant was given 90 seconds to pair specific numbers with specific symbols on a sheet of paper with empty boxes next to the numbers for the participant to fill in the symbol. The score of the symbol digit modalities test was the total number of correctly identified symbols. For this test, the maximum score a participant could get is 110 points (46).

2.7.3 The dementia screening variables

- **IHDS scale score:** The IHDS was used as a brief screening test for HIV dementia that provides information about verbal memory (using the *four-word recall test*), motor, and psychomotor speed performance (using the *finger-tapping test* and *alternating hand sequence test* respectively). The scale consisted of three components namely a four-word memory recall test, a finger tapping hand test and an alternating hand sequence test with the non-dominant hand.

  To assess verbal memory, the four-word recall test was used. For this test, four words were recited to the participant and the participant was asked to repeat them immediately. The words were repeated by the examiner until the participant could repeat all four words correctly. The participant was then asked to recall the four words after the timed finger tapping and alternating hand sequence tests were performed. If the participant could not repeat the word, the examiner prompted semantic clues. Participants scored 1 point for each word repeated correctly and 0.5 points for a word recalled after prompting making a total maximum score of 4 points for the verbal memory test.

  For the finger-tapping test, the number of finger taps of the first two fingers of the non-dominant hand were measured by instructing the participant to open and close the fingers as widely and as quickly as possible over a 5-second period. The participants were scored as follows; 4points for 15 taps in 5 seconds, 3 points for 11-14taps in 5 seconds, 2 points for 7-10 taps in 5 seconds, 1 point for 3-6 taps in 5 seconds and 0

points for =0-2 taps in 5 seconds. The total maximum score for the finger-tapping test is 4 points.

For the alternating hand sequence test, individuals were asked to perform the following movements with the non-dominant hand as quickly as possible over a 10-second period: (i) clench the hand in a fist on a flat surface; (ii) place the hand flat on the surface with the palm down; and (iii) place the hand perpendicular to the flat surface on the side of the fifth digit. The three hand positions were demonstrated by the examiner. The participants were scored as follows: 4 points for 4 sequences in 10 seconds, 3 points for 3 sequences in 10 seconds, 2 points for 2 sequences in 10 seconds, 1 point for 1 sequence in 10 seconds, 0 points if unable to perform test.
A total IHDS score out of 12 was calculated for each participant, with each of the three tests contributing 4 points to the total score (19).

2.7.4 Sheehan disability scale (SDS) variables

- **SDS score:** The Sheehan disability scale is a brief self-report tool that was administered to participants to assess general functional impairment in the following interrelated fields: work life, family life and social life. Participants were asked to rate the extent to which their work, social and family life was impaired on a 10-point visual analogue scale. The general functional impairment SDS score was calculated by adding the three scores on work, social and family life to make a maximum total score of 30 points. A higher score indicated greater functional impairment. The instructions of the scale indicate that a patient who scores greater than five for any of the three scales has significant functional impairment (47).

2.8 Main outcomes, exposures and potential confounders for each study objective

Objective 1: To describe the neurocognitive assessment test scores (i.e. for the *timed gait test*, the *grooved pegboard test*, the *color trails 1 test*, the *color trails 2 test*, the *WHO_UCLA test, auditory verbal learning test*, the *digit span test* and the *symbol digit modalities test* for each age, gender and education category among HIV-infected Ugandans using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda.

- Outcome variables: Neurocognitive assessment test scores
- Exposure variables: Age, education, gender.

Objective 2: To investigate how each of the seven neurocognitive assessment test scores is related to age, gender and education, and to calculate age, gender and education adjusted scores among HIV-infected Ugandans using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda.

- Outcome variables: the *timed gait test*, the *grooved pegboard test*, the *color trails 1 test*, the *color trails 2 test*, the *WHO_UCLA auditory verbal learning test*, the *digit span test* and the *symbol digit modalities test.*
- Exposure variables: age, education and gender
- Potential confounders: study site, marital status, religion, socioeconomic index, Sheehan disability score.

Objective 3a: To determine the relationship between the seven neurocognitive assessment test scores and the International HIV Dementia Scale (IHDS) test score using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda adjusting for age, education and gender.

- Outcome variables: IHDS test score as an ordinal variable
- Exposure variables: the following neurocognitive test scores adjusted for age, gender and education: the *timed gait test*, the *grooved pegboard test*, the *color trails 1 test*, the *color trails 2 test*, the *WHO_UCLA auditory verbal learning test*, the *digit span test* and the *symbol digit modalities test.*

Objective 3b: To determine how well the seven neurocognitive assessment test scores predict the IHDS outcome using data collected from January 2012 to November 2012 in Masaka and Entebbe, Uganda adjusting for age, education and gender.

- Outcome variables: IHDS outcome as a binary variable
- Exposure variables: the *timed gait test*, the *grooved pegboard test*, the *color trails 1 test*, the *color trails 2 test, the WHO_UCLA auditory verbal learning test*, the *digit span test* and the *symbol digit modalities test* adjusted for age, education and gender.

2.9 Data management and analysis

The data were managed and analysed using STATA version 14 (Stata Corp, LP Texas USA).

2.9.1 Data management

To ensure that the statistical analysis programme operated on clean data, the data were taken through a process of data checking and data reduction.

The data checking process included checking the data for any missing and miscoded data. For categorical variables, frequency tables were computed to assess if all the observations were related to the allowed category. For example, the allowed score range for each of the IHDS scores is 0-4, observations with values outside of this range were considered errors in recording. For numeric/ continuous variables, normal probability plots were used to check for the distribution of the data. Six observations were dropped since more than 98% of the data were missing for these observations. Variables were labelled for ease of analysis and ease of result interpretation.

The data reduction process included deriving categorical variables from continuous variables. For example, recoding the discrete variable, IHDS score into 3 categories. This step was done to create an ordinal outcome to fulfil objective 3a of the study, noting the variation in responses for certain answer choices on the IHDS scale, for example there were only two participants with an IHDS score of 2 points while there were 273 participants with an IHDS score of 10 points.

Following the process of data checking, the data was re-examined to check for errors and to gain an understanding of the study population characteristics. The initial sample size of 1127 observations was reduced to 1121 following the data management process (observations that were dropped had no other data other than study site). Table 3 below shows a detailed description of the data management process for each study variable for the present study.

Table 3: Data management table

No.	Variable	Data management procedure	Comment
1	Study site	Cross tabulation	No missing observations (total 1127)
2	Sex	Cross tabulation	2 missing observations (both from Masaka)
3	Marital status	Cross tabulation	4 missing observations (1 from Entebbe, 3 from Masaka)
4	Religion	Cross tabulation	2 missing observations (both from Masaka)
5	Education	Cross tabulation	5 missing observations (1 from Entebbe, 4 from Masaka)
6	Employment	Cross tabulation	12 missing observations (7 from Entebbe, 5 from Masaka)
7	Age	Probability distribution curve, variable summary	Age range was 18-82, no outliers identified, normal distribution, 2 missing observations (both from Masaka)
8	Socio-economic score	Probability distribution curve, variable summary	Range 0-2.33, no outliers identified, normal distribution, 3 missing observations (all from Masaka)
9	Timed gait score	Generated from the average of 3 trials. Probability distribution curve, variable summary	As per test instructions, observations> 45 seconds must be dropped. One observation was dropped from trial 2 as it was identified as an outlier (>45 seconds), an average of 2 trials was taken to generate timed gait score. Range 5.7-18, normal distribution,10 missing observations (4 from Entebbe, 6 from Masaka)
10	Grooved pegboard total score	Generated from the sum of the gpd and gpnd	As per test instructions, observations > 240 seconds must be dropped. There were 3 such observations for the gpnd, and they were dropped Range

No.	Variable	Data management procedure	Comment
		Probability distribution curve, variable summary	67-505, normal distribution, 19 missing observations (5 from Entebbe, 14 from Masaka)
11	Grooved pegboard dominant (gpd) hand score	Probability distribution curve, variable summary	Range 25-240, , no outliers identified, normal distribution, 14 missing observations (4 from Entebbe, 10 from Masaka)
12	Grooved pegboard (gpnd) non-dominant hand score	Probability distribution curve, variable summary	Range 25-240, 5 outliers identified (two of these took 2 seconds to complete the board (highly unlikely), 3 of these spend more than 240 seconds and they were set as missing values, normal distribution,12 missing observations (2 from Entebbe, 10 from Masaka)
13	Colour trails 1 score	Probability distribution curve, variable summary	Range 28-320, no outliers identified, normal distribution, 25 missing observations (10 from Entebbe, 15 from Masaka)
14	Colour trails 2 score	Probability distribution curve, variable summary	Range 60-360, no outliers identified, normal distribution, 32 missing observations (13 from Entebbe, 19 from Masaka)
15	Auditory verbal learning test total score	Probability distribution curve, variable summary	Range 14-64, no outliers identified, normal distribution, 32 missing observations (13 from Entebbe, 19 from Masaka)
16	Digit span total score	Generated from the sum of the dgspnf and dgspnb. Probability distribution curve, variable summary	Range 1-22, no outliers identified, normal distribution, 12 missing observations (10 from Entebbe, 2 from Masaka)

No.	Variable	Data management procedure	Comment
17	Digit span forward (dgspnf)score	Probability distribution curve, variable summary	Range 1-15, no outliers identified, skewed normal distribution, 11 missing observations (9 from Entebbe, 2 from Masaka)
18	Digit span backward (dgspnb)score	Probability distribution curve, variable summary	Range 0-12, no outliers identified, normal distribution, 12 missing observations (10 from Entebbe, 2 from Masaka)
19	Symbol digit modalities score	Probability distribution curve, variable summary	Range 1-90, no outliers identified, skewed normal distribution, 63 missing observations (32 from Entebbe, 31 from Masaka)
20	IHDS score	Generated from the average of four-word recall+finger tapping test+non-dominant hand alternating sequence test Probability distribution curve, variable summary Score was categorized into an ordinal variable for use in objective 3a	Range 3.3-12, As per the scoring instructions each of the 3 subtests is scored out of 4 (see section 2.6.3). One observation had a score of 9 for the four-word recall test; this value was set as missing. skewed (p-0.0000), 12 missing observations (6 from Entebbe, 6 from Masaka) IHDS score (ordinal outcome) categories were selected based in-order to meet the proportional odds assumption for the ordinal regression. Categories were selected ensuring that there were balanced proportions in the 3 categories (Category 1: score 3-8, Category 2: score >8-≤10, Category 3: >10-≤12
21	IHDS_outcome	Binary outcome: 1= 'at risk of developing HAD and 0= 'not at risk of developing HAD'	Study participants were grouped into 2 categories i.e. those at risk of developing HAD (using prescribed criterion: IHDS score ≤10) and those not at risk of developing HAD (using prescribed criterion: IHDS score>10) (Sacktor et al., 2005)

No.	Variable	Data management procedure	Comment
22	SDS score	Generated from the average of sdswork+sdsfamily+sdsscocial scales Probability distribution curve, variable summary	Range 0-30, no outliers, normal distribution, 2 missing observations (both from Masaka)
23	HAND_outcome	Binary variable generated using Frascati criteria specifications (See Appendix A) and published normative data (28)	Study participants were grouped into 2 categories i.e. HAND cases (score of above 1 SD above the mean for age appropriate norms on two or more neurocognitive tests) and non-HAND cases (score within SD of specified appropriate norms)

2.9.2 Data analysis

2.9.2.1 Descriptive analysis

2.9.2.1a Socio-demographic characteristics of study participants by study site

The data consisted of eight demographic variables. The categorical demographic variables are study site, sex, marital status, religion, education and employment. The continuous demographic variables are age and socioeconomic index. To gain an understanding on the characteristics of the study population, cross tabulations (for the categorical variables) were computed to determine the proportion of the study population per demographic category. Central tendency measures were computed for the continuous variables. The results of the descriptive analysis for the study participants are presented in table 4. The data analysis plan for each objective is outlined below.

2.9.2.1b Objective 1: Neuropsychological characteristics of the study participants

The continuous variables included the seven neurocognitive tests, the IHDS score and the SDS score. To assess if the continuous variables approximately followed a normal probability distribution, a normal probability plot was plotted for each continuous variable (48). The normal probability plot was used to assess the normality of the data as the plot allows for large sample sizes as opposed to other statistical tests for normality that allow for limited ranges of sample sizes (Filliben, 2017; Shapiro, Wilk and Chen, 2017).The plots suggested that all continuous variables followed a normal distribution hence the mean±SD of the distribution of continuous variables were reported. To further assess the distribution of the data, the skewness and kurtosis tests were used. The results are presented in table 5. In accordance with the STROBE guidelines, inferential measures such as statistical tests of comparison e.g. t-test were not incorporated into the descriptive statistical analysis for this study (50).

2.9.2.2 Analytical analysis

2.9.2.2a Objective 2: Relationship between demographic factors (age, gender and education) and neurocognitive test scores

A multiple linear regression model was fitted to assess the association between demographic factors (exposure variables) and each of the neurocognitive tests (continuous outcome) using the equation below:

$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \ldots \beta_n x_n + \varepsilon$

Where: Y is the neurocognitive test scores for a given test

β_0 is the intercept

β_1 β_2…. B_n are the regression coefficients for the explanatory variables

x_1 x_1…. x_n are the explanatory variables i.e. age, gender, education etc.

This model was fitted to assess how much variance in the neurocognitive test scores was explained by the demographic predictors. The linear regression analysis included a two-fold process of a multiple linear regression analysis with age, gender and education only and a multiple linear regression analysis with age, gender and education, adjusting for all other demographic factors. The reason for models with age, gender and education only was informed by previous studies in which these demographic factors were reported to be associated with neurocognitive performance (13). In the present study we aimed to explore this relationship. Multiple linear regression models were fitted to obtain age, gender and education adjusted scores. Age was treated as a continuous variable and centered for ease of intercept interpretation (51). The raw residuals for each test were then calculated by subtracting the fitted values from the observed values. The results of the multiple linear regression models to assess the relationship between age, gender, education and the neurocognitive test scores are presented in section 3.3.1 of the report.

For the multiple linear regression analysis that incorporated all demographic factors, an interactive backward selection method which entailed a backward elimination process to reduce the predictors to those that can account for most of the variance in the dependent variable was used while forcing age, gender and education into the model. In this model, non-

significant predictors were removed one at a time, starting with the factor that had the largest p-value, until all remaining factors had a two-sided p-value of less than 0.10 (52). The interactive backward selection method was used in order to avoid the omission of negatively confounded sets of variables (i.e. two or more variables which must be included in the model as a set to control for confounding) which is a risk when using the forward and stepwise selection methods. All continuous variables were centered for ease of intercept interpretation (51).

Prior to fitting the models, the assumptions for fitting a linear regression model were checked. These assumptions included: evidence of a linear relationship between the outcome variable and independent variable, response variable normality, no multicollinearity and homoscedasticity. To test the assumption of linearity between outcome and independent variable, a plot of standardized residuals versus the predicted Y values was computed. To assess the assumption of response variable normality, a normal probability plot was used. To test the assumption of no multicollinearity i.e. that independent variables are not correlated with each other, the VIF statistic was used. To test the assumption of homoscedasticity i.e. that the variance of error terms are similar across the independent variable, the Cook-Weisberg test for homogeneity was used. In instances where the linear regression assumptions were not met, the data was transformed. The Ramsey test was used to check if there was evidence of non-linearity in the models assessing the relationship between the demographic factors and the neurocognitive tests. In instances where there was evidence of non-linearity, Multiple fractional polynomials were fitted to find the best power transformation (53). The results for the multi-linear regression models are presented in section 3.3.2.

2.9.2.2b Objective 3a: Association between the six neurocognitive assessment tests and the IHDS test scores

The outcome variable for this objective was the IHDS score as an ordinal outcome variable as described in Table 2.1 (variable 20). The explanatory variables were the neurocognitive test scores. For each neurocognitive score measured in seconds (i.e. grooved peg, colour trails 1 &2), each score was divided by 20 for ease of interpretation. Univariable ordinal logistic regression models were fitted to assess the relationship between the scores of each independent neurocognitive test and the IHDS score. The raw residual test scores calculated removing the effect of age gender and education from the observed test scores were used for this section. A

multiple ordinal logistic regression model was fitted to assess the collective effect of the all the neurocognitive assessment tests (age, gender and education adjusted) on the IHDS score. The Brant test was used to check the proportional odds assumption (54). The odds of neurocognitive scores for the different IHDS score levels were found to be proportional (p=0.589). The results for this objective are presented in section 3.3.3 of the report.

2.9.2.2c Objective 3b: Determining how well the neurocognitive assessment test scores predict the IHDS outcome

To fulfill this objective, the variable 'IHDS_outcome' described in table 2 (variable 21) was used as the outcome (Sacktor et al., 2005). This variable classifies the study participants into two categories namely: participants at risk of developing HIV associated dementia (HAD) and participants that are not at risk of developing HAD. To determine how well the neurocognitive test scores, predict the IHDS outcome, univariable logistic regression models were fitted and a receiver operating curve (ROC) analysis was conducted. The logistic regression models were fitted to estimate the predicted probabilities to use as the classification variable in the ROC analysis. The ROC curve was used to estimate the area under the curve (AUC) and the optimum cut off points for the best tradeoff between sensitivity and specificity using the IHDS outcome as the reference variable. A parametric ROC curve was computed to estimate the AUC. The AUC was used to measure the ability of the neurocognitive tests to discriminate between individuals at risk of developing HAD and those that were not. A post estimation graph plot of the sensitivity/specificity versus probability cut-off was then plotted to obtain the optimal cut-off point. The distribution of the neurocognitive tests did not follow a normal distribution hence a non-parametric estimation of the ROC curve was computed. The purpose of the non-parametric estimation of the ROC curve was to tabulate the calculate sensitivities and specificities for each IHDS cut-off point. To evaluate the predictive accuracy of the models, with the highest AUC, and best trade-off between sensitivity and specificity were chosen (55).

A multiple logistic regression model was then fitted to explore the combined predictive power of all the neurocognitive tests (age, gender and education adjusted) on the IHDS outcome. The ROC curve for this model was also computed following the steps used for the univariable models. The results of the ROC analysis are presented in section 3.4 of the report.

The high prevalence of HAD (i.e. participants identified to be at risk of developing HAD=73%) led to the questioning of the validity of the IHDS in this study population. Published normative data for HAND diagnosis in resource limited settings was then used to calibrate the cut-off scores for the neurocognitive test scores based on the Frascati criteria (see Appendix A) (28). Study participants were classified as either having HAND or not. The different categories of HAND were not specified however any participant with a score of 1 SD below the mean for age and education appropriate norms on two or more neurocognitive tests fit the description of a HAND diagnosis. For tests such as the timed gait score where a lower score meant better functioning, a score of above 1 SD above the mean for age appropriate norms on two or more neurocognitive tests was considered a HAND case. The selection of the normative data to use for the present study was justified by the similarity in study settings and similarity in age distribution (Age range for normative data study =18-85 years; mean age 35±12, age range for current study 18-82 years; mean age 35±9.32) (28). A ROC analysis to determine the validity of the IHDS in identifying HAND participantswas computed using the neurocognitive battery (HAND outcome) as the gold standard. A non-parametric and parametric ROC method was used. The parametric method included a graphical presentation of the sensitivity, specificity and probability cut-off. The non-parametric method tabulated calculated sensitivity and specificity for each cut-off point, this method was used allow for cut-off adjustment (55). The results are presented in section 3.5 of the report.

CHAPTER 3: RESULTS

In this chapter, the results corresponding to each of the study objectives are presented.

3.1 Socio-demographic characteristics of study participants by study site

Table 4 presents the socio-demographic characteristics of the sample by study site. A total sample of 1127 HIV infected ART naïve participants were enrolled in the study. Participants with missing data on neurocognitive performance were excluded reducing the study sample to 1121 participants. The TASO Masaka clinic had a higher number of participants (n=563) in comparison to the TASO Entebbe clinic (n=558).

Socio demographic variables were compared across sites. Of the total study population, the majority of the participants were female (77.3%), a trend seen in both study sites. Slightly more than half of the study participants were married (51.4%). More than half of the participants were Catholic (52.9%). The distribution of participants by religious affiliation per study site showed that the TASO Masaka clinic had more Catholics (62.8%) in comparison to the TASO Entebbe clinic (43.2%). Almost 62% of the study participants had primary school education only. The proportion of primary school educated participants (i.e. had only primary school education) was higher in Masaka (69%) than in Entebbe (54.1%). In both study sites, i.e. most the participants were employed either as a farmer/fisher (29.4%) or as a trader/artisan/transporter (36.5%).

The distribution of all the continuous variables was approximately normal. Therefore, the mean (SD) of the variables was reported. The mean age of the study participants in Masaka (37.1±9.3 years) was higher than the mean age of the study participants in Entebbe (32.9±8.9 years). The overall mean age of all the study participants was 35.0±9.3 years and the mean socio-economic score was 1.2±0.6.

The participants from the Masaka region which is predominantly rural were poorer than the participants from the Entebbe region as measured by the mean socio-economic score. The socio-economic score was based on the possession of a fixed number of assets (see section 2.7.1), higher scores correspond to owning more assets with a minimum score of 0 and a maximum score of 2.33. The mean socio-economic score of the Masaka region was lower

(0.9±0.5) than the mean socio-economic index of the Entebbe region which had a mean socio-economic index of 1.4±0.6.

Table 4: Descriptive statistics of the socio-demographic characteristics of study participants by study site

Characteristic	Entebbe (N=558) N (%)	Masaka (N=563) N (%)	Total (N=1121) N (%)
Sex			
Female	433 (77.6)	432 (77.0))	865 (77.3)
Male	125 (22.4)	129 (23.0)	254 (22.7)
Marital status			
Married	298 (53.4)	276 (49.0)	574 (51.4)
widowed	50 (9.0)	114 (20.3)	164 (14.7)
Separated/divorced	134 (24.0)	136 (24.2)	270 (24.2)
Single	75 (13.4)	34 (6.0)	109 (9.8)
Religion			
Born again	66 (11.8)	30 (5.3)	96 (8.6)
Catholic	241 (43.2)	351 (62.8)	592 (52.9)
Muslim	71 (12.7)	96 (17.1)	167 (14.9)
Protestant	163 (29.2)	81 (14.4)	244 (21.8)
SDA	14 (2.5)	2 (0.4)	16 (1.4)
Other	3 (0.5)	1 (0.2)	4 (0.4)
Education			
None	53 (9.5)	70 (12.4)	123 (11.0)
Primary	302 (54.1)	389 (69.1)	691 (62.0)
Secondary +	201 (36.2)	100 (17.8)	302 (27.1)
Employment			
Farmer/fisher	75 (13.4)	251 (44.6)	326 (29.4)
Professional/clerical	23 (4.1)	20 (3.6)	43 (3.9)
Trader/artisan/transport	233 (41.8)	172 (30.6)	406 (36.5)
Unemployment/retired/housewife	87 (15.6)	59 (10.5)	146 (13.2)
Student/other	133 (23.8)	56 (10.0)	189 (17.0)
	Mean±SD	**Mean±SD**	**Mean±SD**
Age	32.9±8.9	37.1±9.2	35.0±9.3
Socio-economic score	1.41±3.6	0.92±0.5	1.2±0.6

3.2 Neurocognitive characteristics of the study participants

In table 5 below, a description of the distribution of the neurocognitive, dementia screening and global functional impairment test scores of the study population is given. The neurocognitive scores of the study participants were not symmetrical as suggested by the skewness values (skewness ≠0) and the difference in mean and median values (mean ≠median). A similar trend of asymmetry in the test scores can be seen for the dementia-screening test and the global functional impairment test.

In comparison to the maximum possible score (45 seconds), the study participants seem to have scored fairly well in the timed gait test that assesses motor function (mean=11.9 ± 1.7).

With regard to the grooved pegboard test to assess fine motor function, the overall average score for the study sample was fairly low (174.5 ± 49.9) in comparison to the maximum possible score (480 seconds) that the participants could potentially obtain.

For the colour trails 1 & 2 tests to assess speed of processing and executive function respectively, the maximum possible score is not specified. However, a lower score suggests better function.

The data from the colour trails 1 & 2 tests suggests that there was a positive skew for the distribution of both tests (skewness >0), hence there were a few individuals who obtained much higher scores than the remainder of the participants. The data on the digit symbol test to assess attention/working memory, suggests that the participants of the study had a fairly low attention/working memory rating when comparing the mean digit span total score (10.0 ± 3.3) to the maximum possible score (28 points). The overall speed of processing mean score for the study participants (18.1 ± 9.1) as assessed by the symbol digit modalities test was low in comparison to the maximum possible score (110 points).

For the IHDS, a score of ≤10 indicates that participant is at risk of developing HIV associated dementia (HAD), the most severe form of HAND. The data on the IHDS score of the study participants show a mean score of 9.4 ± 1.5 and a median score of 10 (IQR=8.5-10.5) showing half of the study participants to be at borderline risk of developing HIV associated dementia

(HAD). There was an overall poor performance in the mean global functional impairment score of the study participants (4.56 ± 6.75) showing the study participants to have a decline in function in their work, social and family life.

Table 5: Descriptive statistics of the neurocognitive characteristics of the study participants

Characteristic	Mean ± SD	Median (IQR)	Skewness	Kurtosis	Possible maximum score
Neurocognitive tests					
Timed gait *	11.9 ± 1.7	12 (10-13)	0.2	3.4	45
Grooved peg total*	174.5 ± 49.9	162 (144-188)	2.3	10.5	480
grooved peg dominant hand*	77.8 ± 23.1	72 (64-86)	2.4	12.8	240
grooved peg non-dominant hand*	96.9 ± 31.0	90 (78-105)	2.2	12.2	240
Colour trails 1*	84.1 ± 34.8	77 (61-99)	2.1	10.6	ns
Colour trails 2*	142.7 ± 51.8	128 (107-170)	1.3	5.0	n/a
Auditory verbal learning	39.1 ± 7.7	39 (34-44)	0.2	3.0	75
Digit span total	10.0 ± 3.3	10 (8-12)	0.5	3.4	28
digit span forward	6.2 ± 2.2	6 (5-8)	0.4	3.2	14
digit span backward	3.8 ± 1.6	4 (3-5)	0.5	4.0	14
Symbol digit modalities*	18.1 ± 9.1	17 (12-22)	2.0	13.0	110
Dementia screening test					
IHDS	9.4 ± 1.5	10 (8.5-10.5)	0.8	3.9	12
Global functional impairment test					
SDS	4.56 ± 6.75	2 (0-6)	2.0	6.3	30

For the tests marked with an asterisk*, a lower score indicates better function.
n/a= not applicable
The following test scores were recorded in **seconds**: timed gait, grooved pegboard dominant &non-dominant hand, colour trails 1&2
The following test scores were recorded as **points**: digit span forward and backward, symbol digit modalities, IHDS and the SDS

3.2.1 Neurocognitive characteristics of the study participants by age

Age was associated with neurocognitive performance as seen in the variation in neurocognitive performance across the different participant ages shown in figure 4-12. However, the results suggest considerable residual variation. The distribution of the timed gait scores shows that an increase in age corresponded with an increase in the time taken for the timed gait test and hence motor function declined with increasing age.

A similar trend of direct proportionality in the age of participants and neurocognitive tests is seen for the grooved pegboard test. This suggests that older participants had poorer fine motor function compared to younger participants.

Further, the data suggest that older participants also had poor speed of processing (shown in figure 6 and figure 10) and executive function (shown in figure 7) in comparison to younger participants. There was an inverse relationship between age and Auditory verbal learning score. This suggests that as participants' age, there was a decline in verbal learning/memory. As the age of the study participants increased, there was a gradual decline in the IHDS score, showing older participants to be more susceptible to developing HIV associated dementia. There was little to no variation in general functional impairment from ages 18-40 years, however, from age 50-80 years there was a slight variation in functional performance in the participant's work, social and family lives.

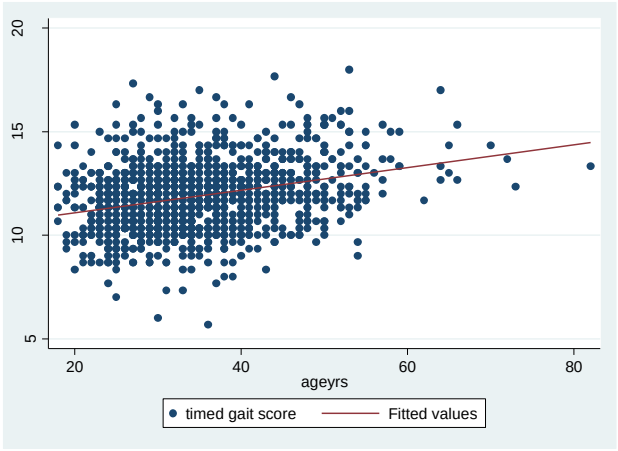


Figure 4: Distribution of the timed gait score by age

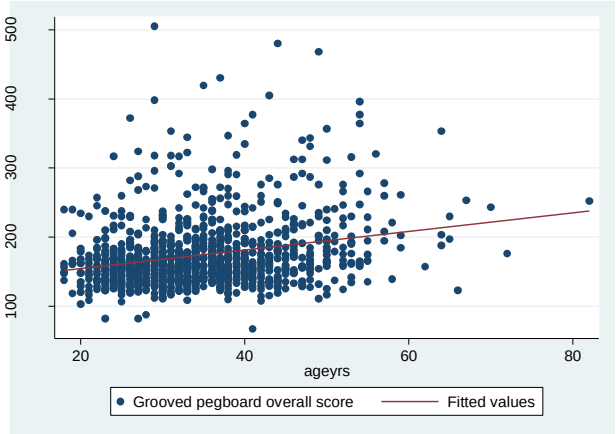


Figure 5: Distribution of the grooved pegboard overall score by age

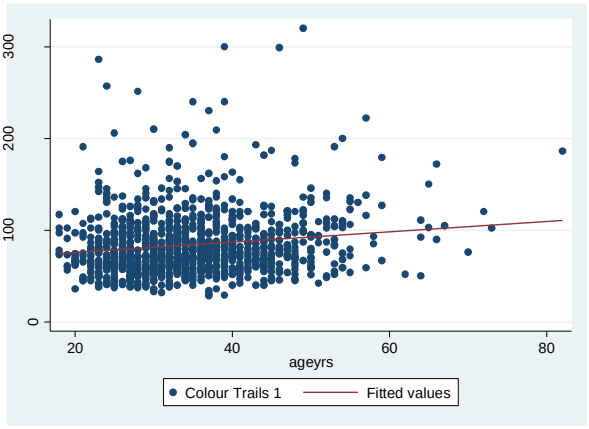


Figure 6: Distribution of the colour trails 1 score by age

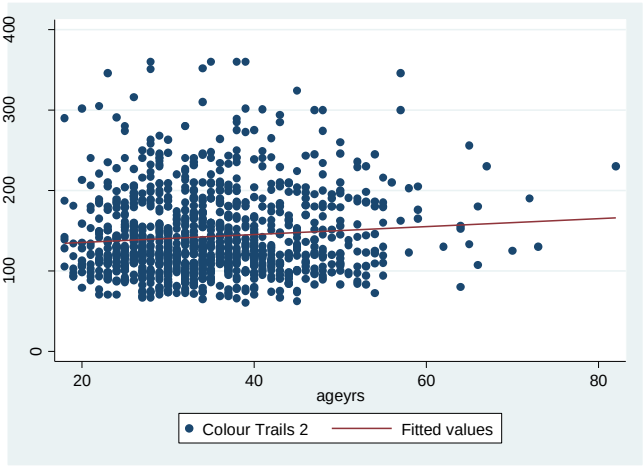


Figure 7: Distribution of the colour trails 2 score by age

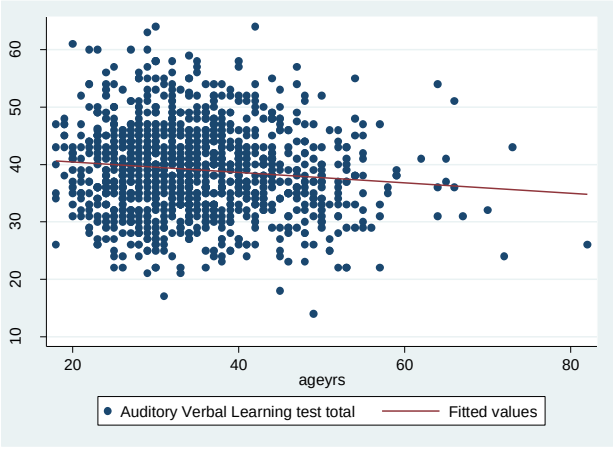


Figure 8: Distribution of the Auditory verbal learning test score by age

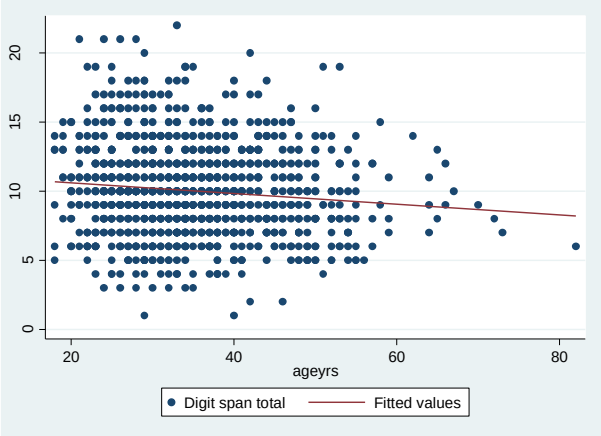


Figure 9: Distribution of the digit span score by age

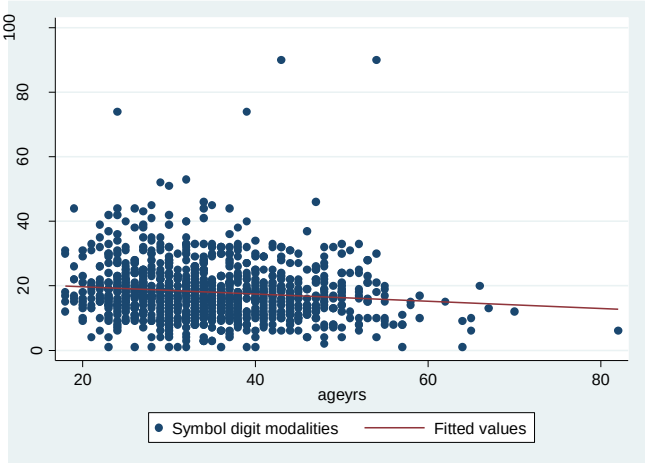


Figure 10: Distribution of the symbol digit modalities score by age

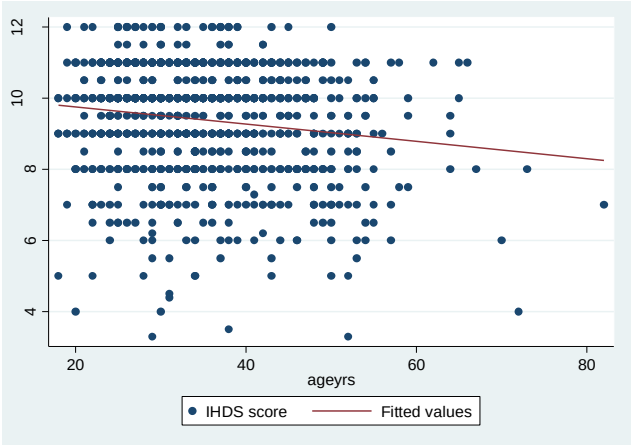


Figure 11: Distribution of the IHDS score by age

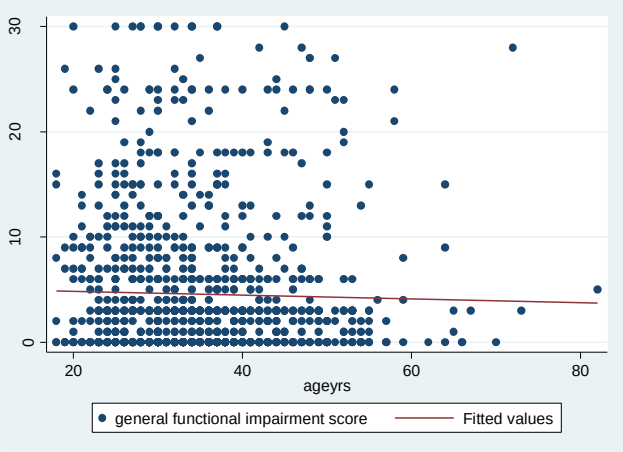


Figure 12: Distribution of the general functional impairment score by age

3.2.2 Neurocognitive characteristics of the study participants by gender

Table 6 below, presents the distribution of the neurocognitive test scores by participant's gender. Female participants' performance was not as strong as male participants in the tests that assessed the following cognitive domains: gross motor function (timed gait test), fine motor function (grooved pegboard test), speed of processing (colour trails 1 test), executive function (colour trails 2 test) and verbal learning/memory (digit span, forward and backward) as shown by the difference in the neurocognitive mean scores. Although male participants were shown to outperform female participants in the colour trails 1 test to assess speed of processing, this finding was contradicted by the results of the symbol digit modalities test which assesses the same cognitive function.

From the symbol digit modalities mean test scores where a higher score indicated poorer cognitive function, female participants showed poorer verbal learning/memory function (18.2 ± 9.3) in comparison to male participants 17.8 ± 8.3. There was no difference in the mean test scores between the two genders for the digit span tests to assess attention/working memory. The mean score of the IHDS shows that both males and females were at similar risk of developing HAD. Male participants had a slightly higher score on general functioning in their work, social and family lives.

Table 6: Descriptive statistics of the neurocognitive characteristics of the study participants by gender

	Female Mean±SD	Male Mean±SD
Neurocognitive tests		
Timed gait *	12.07 ± 1.7	11.3 ± 1,6
Grooved peg total *	176.4 ± 52.0	168.1 ± 41.1
grooved peg dominant hand *	78.7 ± 23.7	75.2 ± 20.5
grooved peg non-dominant hand *	98.0 ± 32.3	93.4 ± 25.7
Colour trails 1 *	85.7 ± 36.1	78.9 ± 29.6
Colour trails 2*	145.3 ± 53.0	134.1 ± 46.5
Auditory verbal learning	39.4 ± 7.7	38.1 ± 7.7
Digit span total	10.0 ± 3.3	10.0 ± 3.0
digit span forward	6.2 ± 2.3	6.2 ± 2.0
digit span backward	3.9 ± 1.6	3.8 ± 1.5
Symbol digit modalities*	18.2 ± 9.3	17.8 ± 8.3
Dementia screening test		
IHDS	9.4 ± 1.5	9.4 ± 1.6
Global functional impairment test		
SDS	4.4 ± 6.6	5.0 ± 7.3

*a lower test score indicates better function

3.2.3 Neurocognitive characteristics of the study participants by education level

The means and standard deviations of the study participants by education category are presented in table 7 below. There was a variation in the digit span test to assess attention/working memory, participants with a primary school education had a higher mean score (9.8 ± 3.0) showing poorer performance in comparison to participants with no education (mean score= 8.1 ± 3.3) and secondary+ educated participants (mean score= 8.0 ± 1.0). There was slight variation in the mean scores for the IHDS screening test across the different education levels, the mean IHDS test scores ranged between 9.1-9.4 points. As education level increased, the general functional impairment score decreased.

Table 7: Descriptive statistics of the neurocognitive characteristics of the study participants by education

	None Mean ±SD	Primary Mean ±SD	Secondary + Mean ±SD
Timed gait *	12.5 ± 1.6	12.0 ± 1.6	10.67 ± 1.5
Grooved peg total *	193.5 ± 59.4	177.1 ± 50.5	138.7 ± 67.5
grooved peg dominant hand *	87.6 ± 30.8	78.5 ± 22.7	78.7 ± 19.5
grooved peg non-dominant hand*	107.4 ± 35.4	98.9 ± 31.4	60 ± 51.4
Colour trails 1 *	115.5 ± 53.8	85.6 ± 31.5	52 ± 8.7
Colour trails 2*	175.7 ± 65.2	143.6 ± 50.4	95.3 ± 5.5
Auditory verbal learning	37.1 ± 7.6	38.8 ± 7.4	41.3 ± 1.5
Digit span total	8.12 ± 3.3	9.8 ± 3.0	8.0 ± 1.0
digit span forward	5.2 ± 2.1	6.0 ± 2.1	3.7 ± 0.6
digit span backward	3.0 ± 1.8	3.7 ± 1.5	4.3 ± 0.6
Symbol digit modalities*	10.8 ± 5.6	16.8 ± 8.4	26 ± 8.0
IHDS	9.0 ± 1.8	9.3 ± 1.4	9.1 ± 1.6
SDS	4.7 ± 7.0	4.6 ± 7.0	1 ± 1.7

*a lower test score indicates better function

3.3 Association between age, gender, education and the neurocognitive test scores

3.3.1 Multiple linear regression analysis for the association between age, gender, education and the neurocognitive test scores

Table 8 shows the results of the multiple linear regression models fitted to examine the association between the factors: age, education and gender for each of the seven neurocognitive tests used in the study**.** For test scores with missing values (see table 3), observations were automatically dropped when the multiple regression model was fitted (56). Age was treated as a continuous variable and centred at the mean age of 35 years for ease of intercept interpretation. The results of the multiple regression model for each test are examined below.

3.3.1.1 Association between age, gender, education and the timed gait test score

The relationship between age, education and gender and each of the seven neurocognitive test scores was modelled by the equations below:

- ***Timed gait test score (seconds)*** *= 12.20 + 0.05*age + 0.86*female_gender + 0.29*no_education - 0.48*secondary_education*
- ***Grooved pegboard test score (seconds)*** *= 178.71 + 1.27*age - 9.63*male+ 14.41*no_education - 12.20*secondary_education*
- ***Colour trails 1 test score (seconds)*** *= 86.81 + 0.43*age³ - 6.17*male + 28.92*no_education - 15.10*secondary_education*
- ***Colour trails 2 test score (seconds)*** *= 145.88 + 0.40*age - 10.53*male + 30.83*no_education - 13.28*secondary_education*
- ***Auditory verbal learning test score (points)*** *= 39.18 - 0.07*age - 1.21*male - 1.77*no_education + 3.35*secondary_education*
- ***Digit span test score (points)*** *= 9.73 - 0.02*age - 0.08*male -1.63*no_education + 1.59*secondary_education*
- ***Symbol digit modalities (points)*** *= 16.52 - 0.07*age - 0.46*male- 6.13*no_education + 6.03*secondary_education*

Age, gender and education influenced the participant scores on gross motor function, fine motor function, speed of processing, executive function, verbal learning and attention as shown in the equations above and table 8 below.

Aging, being female and lower education levels were identified as important predictors for neurocognitive impairment across all domains. The constants displayed in table 8 below indicate the average time taken to complete the test or average points scored by a 35-year-old male with a primary school education. Across all cognitive domains except for attention/working memory as measured by the digit span test and speed of processing as measured by the symbol digit modalities test, older participants displayed poorer cognitive function in comparison to younger participants. Speed of processing as measured by the colour trails 1 test shows older participants to perform better in this domain which is different from the results of the symbol digit modalities test which shows younger participants perform better than older participants in this domain (note the two tests measure the same cognitive domain). Male participants had better cognitive function in all cognitive domains as shown by the time taken for male participants to complete the timed gait, grooved pegboard, colour trails tests and

points scored in the auditory verbal learning, digit span and symbol digit modalities tests in comparison to female participants. An increase in the education level of the participants was associated with better cognitive function across all domains. The overall variation in each of the neurocognitive test scores that can be explained by the test scores linear relationship with age, gender and education ranged from 2.9%-16.0%.

Table 8: Multiple linear regression analysis for the association between age, education and gender and the neurocognitive tests scores

The timed gait test* (cons=12.20 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	0.05 (0.04-0.06)	0.01	0.000
Gender:			
male compared to female	-0.86 (-1.07--0.64)	0.11	0.000
Education:			
None compared to primary	0.29 (-0.01-0.59)	0.15	0.056
secondary compared to primary	-0.48 (-0.69--0.26)	0.11	0.000
*a lower test score indicates better function			
test score in seconds			
F=52.44; p=0.000; R^2=15.98%			
The grooved pegboard test* (cons=178.71 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	1.27 (0.96-1.57)	0.16	0.000
Gender:			
male compared to female	-9.63 (-16.40--2.87)	3.44	0.005
Education:			
none compared to primary	14.41 (5.16-23.67)	4.72	0.002
secondary compared to primary	-12.20 (-18.74--5.65)	3.34	0.000
*a lower test score indicates better function			
test score in seconds			
F=28.16; p=0.000; R^2=9.34%			
The colour trails 1 test* (cons=86.81 seconds)			
	Unadjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	0.43 (0.22-0.64)	0.11	0.000
Gender:			
male compared to female	6.17 (-10.76--1.58)	2.34	0.008
Education:			
None compared to primary	28.92 (22.50-35.34)	3.27	0.000
secondary+ compared to primary	-15.10 (-19.50--10.69)	2.24	0.000
*a lower test score indicates better function			
test scores in seconds			
F=48.53; p=0.000; R^2=15.14%			

The colour trails 2 test* (cons=145.88 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	0.40 (0.07-0.72)	0.17	0.016
Gender:			
male compared to female	-10.53 (-17.68--3.37)	3.65	0.004
Education:			
none compared to primary	30.83 (20.72-40.95)	5.16	0.000
secondary compared to primary	-13.28 (-20.14--6.41)	3.50	0.000
*a lower test score indicates better function			
test scores in seconds			
F=20.57; p=0.000; R^2=7.07%			

The Auditory verbal learning test (cons=39.18 points)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age	-0.07 (-0.12--0.02)	0.02	0.004
Gender:			
male compared to female	-1.21 (-2.29--0.14)	0.55	0.027
Education:			
none compared to primary	-1.77 (-3.24--0.30)	0.75	0.018
secondary compared to primary	3.35 (1.74-4.96)	0.82	0.009
test scores in points			
F=8.37; p=0.000; R^2=2.93%			

The digit span test (cons=9.73 points)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	-0.02 (-0.04--0.00)	0.10	0.018
Gender:			
male compared to female	0.08 (-0.36-0.52)	0.22	0.711
Education:			
none compared to primary	-1.63 (-2.2--1.04)	0.30	0.000
secondary compared to primary	1.59 (1.16-2.01)	0.22	0.000
test scores in points			
F=29.58; p=0.000; R^2=9.67%			

The symbol digit modalities test* (cons=16.52 points)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age	-0.07 (-0.17--0.05)	0.03	0.017
Gender:			
male compared to female	0.46 (-7.98--4.29)	0.61	0454
Education:			

none compared to primary	-6.13 (-7.98--4.29)	0.94	0.000
secondary compared to primary	6.03 (4.89-7.19)	0.59	0.000

*a lower test score indicates better function

test scores in points

F=49.27; p=0.000; R^2=15.74%

3.3.2 Multiple linear regression analysis for the association between demographic factors and the neurocognitive test scores

The following demographic variables were considered as potential explanatory variables in the multiple linear regression models for the neurocognitive test scores: socio-economic index, Sheehan disability score, marital status, religion and study site. All models included age, education and gender as previous work has shown these factors to be associated with neurocognitive performance (18,20,37). Initially all potential explanatory variables were included in the model. Those that were not significant at the 10% level were removed in a backward elimination algorithm. The results for each regression model are presented below.

3.3.2.1 Association between demographic factors and the timed gait test score

The overall regression model was highly significant (F=57.82; p<0.001) with 30% of the variation in the timed gait test score accounted for by its linear relationship with the demographic factors listed in table 3.3.2.i below. Individuals from Masaka were likely to take 1.25 seconds longer (showing worse gross motor function) to complete the timed gait test in comparison to individuals from the Entebbe study site. Widowed and single participants took longer to complete to timed gait test in comparison to married participants.

Table 9: Multiple linear regression analysis for the association between demographic factors and the timed gait test score

The timed gait test * (cons=11.43 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	0.04 (0.03-0.05)	0.01	0.000
Gender:			
male compared to female	-0.82 (-1.02--0.61)	0.10	0.000

Education:			
None compared to primary	0.31 (0.04-0.57)	0.14	0.031
secondary compared to primary	-0.24 (-0.44--0.04)	0.10	0.025
Study site:			
Masaka compared to Entebbe	1.25 (1.07-1.43)	0.09	0.000
Sheehan disability score (centred)	0.01 (0.00-0.03)	0.01	0.033
Marital status:			
Divorced compared to married	-0.07 (0.25-0.14)	3.59	0.490
Single compared to married	0.26 (-0.03--0.55)	0.15	0.041
Widowed compared to married	0.32 (0.05-0.58)	0.13	0.118

*a lower test score indicates better function

F=57.82; p=0.000; R^2=30.16%

3.3.2.2 Association between demographic factors and the grooved pegboard test score

Keeping all other demographic factors in the model constant, a unit increase in the socio-economic score on average led to a 6.24 second decrease in the grooved pegboard score (p=0.001). Single participants on average took 12.72 seconds longer to complete the grooved pegboard test in comparison to married participants. The total variation in the grooved pegboard test score explained by its linear relationship with the demographic factors listed in table 10 below is 10.6%. The overall model was highly significant (F=17.61; p<0.001).

Table 10: Multiple linear regression analysis for the association between demographic factors and the grooved pegboard test score

The grooved pegboard test * (cons=177.38 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	1.34 (1.02-1.65)	0.16	0.000
Gender:			

male compared to female	-9.96 (-16.77--3.20)	3.44	0.004
Education:			
None compared to primary	13.27 (4.00-22.54)	4.73	0.005
secondary compared to primary	-10.88 (-17.53--4.24)	3.39	0.001
Socio-economic score (centred)	-6.24 (-11.11--1.38)	2.47	0.012
Marital status:			
Divorced compared to married	5.78 (-1.26-12.82)	3.59	0.107
Single compared to married	12.72 (2.80-22.65)	5.06	0.012
Widowed compared to married	3.41 (-5.76-12.60)	4.68	0.465

*a lower test score indicates better function

F=21.04; p=0.000; R^2=10.61%

3.3.2.3 Association between demographic factors and the colour trails 1 test score

The overall variation in the colour trails test score explained by its linear relationship with the demographic factors in table 11 below is 16.0% hence 84.0% of the variation in the colour trails 1 test remains unexplained. Participants from the Masaka study site on average took 4.78 seconds less (showing better speed of processing) to complete the colour trails 1 test in comparison to participants from the Entebbe region.

Table 11: Multiple linear regression analysis for the association between demographic factors and the colour trails 1 test score

The colour trails 1 test* (cons=89.17 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	0.47 (0.26-0.69)	0.11	0.000
Gender:			
male compared to female	-6.17 (-10.76--1.88)	2.33	0.009
Education:			

None compared to primary	28.72 (22.25-35.19)	3.26	0.000
secondary+ compared to primary	-14.34 (-18.84--9.83)	2.31	0.000
Socio-economic score (centred)	-4.86 (-8.46--1.26)	1.83	0.001
Study site			
Masaka compared to Entebbe	-4.78 (-89.11--0.45)	2.21	0.024

*a lower test score indicates better function

F=28.86; p=0.000; R^2=16.03%

3.3.2.4 Association between demographic factors and the colour trails 2 test score

For every unit increase in the socio-economic score, the colour trails 2 test score decreased by 6.51 seconds suggesting improved executive function when adjusting for the demographic factors listed in table 12 below. A Sheehan disability scale score of 1 point higher on average resulted in a 0.67 second longer to complete the colour trails 2 test. The total variation in the colour trails 2 test score explained by its linear relationship with the demographic factors listed in the table below is 9.2%, much of the variation in the colour trails 2 test (90.8%) remains unexplained. Adjusting for the participants' study site and religion did not significantly improve the fit of the colour trails 2 score model (p>0.10).

Table 12: Multi-linear regression analysis for the association between demographic factors and the colour trails 2 test score

The colour trails 2 test * (cons=143.56 seconds)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	0.28 (-0.07-0.64)	0.18	0.118
Gender:			
male compared to female	-10.18 (-17.49--2.86)	3.72	0.006
Education:			
none compared to primary	30.91 (20.70-41.11)	5.19	0.000
secondary compared to primary	-10.89 (-17.88--3.91)	3.55	0.002

Socio-economic score (centred)	-6.51 (-11.70 --1.33)	0.43	0.014
Sheehan disability scale (centred)	0.67 (0.23-1.12)	2.64	0.003

*a lower test score indicates better functioning

F=15.16; p=0.000; R^2=9.18%

3.3.2.5 Association between demographic factors and the auditory verbal learning test

The total variation in the auditory verbal learning test score explained by its linear relationship with the demographic factors listed in the equation above is 4.5%. Most of the variation (95.5%) in the auditory verbal learning test score remains unexplained. Individuals who had a point score higher for general functional impairment in the Sheehan disability score, on average scored 0.11 points less in the auditory verbal learning test. Divorced participants were likely to have better verbal learning and memory function (Coef=1.44; 95% CI=0.30-2.57) than married participants.

Table 13: Multi-linear regression analysis for the association between demographic factors and the auditory verbal learning test score

The Auditory verbal learning test (cons=36.59 points)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	-0.08 (-0.13--0.03)	0.03	0.002
Gender:			
male compared to female	-1.14 (-2.23--0.05)	0.56	0.041
Education:			
none compared to primary	-1.80 (-3.29--0.31)	0.76	0.018
secondary compared to primary	1.42 (0.36-2.47)	0.54	0.009
Marital status			
Divorced compared to married	1.44 (0.30-2.57)	0.58	0.013

Single compared to married	0.66 (-0.95-2.27)	0.82	0.421
Widowed compared to married	-0.61 (-2.09-0.87)	0.75	0.419
Sheehan disability score (centred)	-0.11 (-0.18--0.05)	0.35	0.001
F=8.52; p=0.000; R^2=4.52%			

3.3.2.6 Association between demographic factors and the digit span test score

The results from the multiple linear regression model show that participants from Masaka region on average scored 0.61 points lower in the digit span test in comparison to participants from Entebbe region.

Table 14: Multi-linear regression analysis for the association between demographic factors and the digit span test score

The digit span test (cons=7.47 points)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	-0.02 (-0.04--0.00)	0.01	0.043
Gender:			
male compared to female	-0.05 (-0.48-0.39)	0.19	0.830
Education:			
none compared to primary	-1.59 (-2.19--1.00)	0.30	0.000
secondary compared to primary	1.49 (0.94-1.81)	0.22	0.000
Study site:			
Masaka compared to Entebbe	-0.61 (-0.98--0.23)	0.09	0.002
F=21.67; p=0.000; R^2=10.77%			

3.3.2.7 Association between demographic factors and the symbol digit modalities test score

The overall model to predict the symbol digit modalities test score was highly significant (F=39.51; p=0.000). However only 16.1% of the variation in the symbol digit modalities test score was explained by its linear relationship to age, gender, education and marital status. The study site, Sheehan disability score and socio-economic index explanatory variables did not improve the fit of the symbol digit modalities test score model, hence they were omitted (p>0.10). Divorced individuals were likely to have poorer speed of processing (coef 1.75; 95% CI=0.49-3.02) in comparison to married individuals.

Table 15: Multi-linear regression analysis for the association between demographic factors and the symbol digit modalities test score

The symbol digit modalities test* (cons=16.54 points)			
	Adjusted Coef (95% CI)	**Std error**	**p-value**
Age (centred)	-0.07 (-0.13--0.02)	0.03	0.009
Gender:			
male compared to female	-0.24 (-0.13-0.02)	0.62	0.694
Education:			
none compared to primary	-6.00 (-0.62--15.72)	0.95	0.000
secondary compared to primary	6.10 (4.93-7.27)	0.60	0.000
Marital status:			
Divorced compared to married	1.75 (0.49-3.02)	0.65	0.007
Single compared to married	1.40 (-0.39-3.18)	0.91	0.126
Widowed compared to married	0.05 (-1.58-1.67)	0.84	0.953

*a lower test score indicates better function

F=39.51; p=0.000; R^2=16.12%

3.3.3. Relationship between the neurocognitive assessment test scores and the IHDS score

A sensitivity analysis was conducted to determine the most suitable model to describe the relationship between the neurocognitive assessment test scores and the IHDS score. In the first model, the IHDS score was treated as a continuous variable, in the second model the IHDS was treated as a binary variable as described in table 3 (variable 21) and the third model, the IHDS score was treated as an ordinal outcome variable as described in table 3 (variable 20). The results of the sensitivity analysis are presented in Appendix C of the report. Due to the distribution of the IHDS score the model that best described the relationship between the neurocognitive assessment test scores and the IHDS scores was the one with the IHDS as an ordinal outcome variable. For each neurocognitive score measured in seconds (i.e. grooved peg, colour trails 1 &2), the score was divided by 20 for ease of interpretation. The results from the univariable and multivariable ordinal regression models to assess the relationship between the neurocognitive assessment test scores (adjusted for age, gender and education) and the IHDS score are presented in table 16 below.

For the univariable models, there was a significant relationship between all the neurocognitive test scores and the IHDS score, except for the timed gait test scores. The multivariable model was found to be highly significant ($F=179.87$; $p<0.001$). In the multivariable model there was no significant relationship between the following neurocognitive tests: timed gait, colour trails 1, colour trails 2, symbol digit modalities and the variation in the IHDS scores ($p>0.05$).

The odds of performing better in the IHDS decreased by 0.92 for each 20-second increase in time taken to complete the grooved pegboard test. For every 1-point increase in the auditory verbal learning test score, the odds of performing better in the IHDS test increased by 1.05 participants. Participants who scored higher in the digit span test were more likely (OR=1.18, 95%CI= 1.13-1.24) to score higher in the IHDS test when adjusting for all the neurocognitive test scores listed in the model below.

Table 16: Univariable and Multiple ordinal logistic regression models to assess the relationship between the neurocognitive assessment test scores and the IHDS score

	Univariable analysis		Multivariable analysis	
	OR 95%CI	**p-value**	**OR 95%CI**	**p-value**
Timed gait *	0.79 (0.41-1.55)	0.497	0.55 (0.26-1.15)	0.114
Grooved peg total *	0.87 (0.83-0.91)	0.000	0.92 (0.86-0.97)	0.002
Colour trails 1 *	0.89 (0.83-0.96)	0.001	1.05 (0.94-1.17)	0.419
Colour trails 2*	0.91 (0.87-0.96)	0.000	0.97 (0.91-1.03)	0.329
Auditory verbal learning	1.07 (1.05-1.08)	0.000	1.05 (1.03-1.07)	0.000
Digit span total	1.23 (1.19-1.29)	0.000	1.18 (1.13-1.23)	0.000
Symbol digit modalities*	1.03 (1.02-1.05)	0.000	1.01 (0.99-1.02)	0.292

*a lower test score indicates better functioning

3.4 Determining how well the neurocognitive assessment test scores predict the IHDS outcome

Out of the 1115 participants that underwent HIV dementia screening using the International HIV dementia scale, 73.25% of the study participants were identified to be at risk of developing HAD.

3.4.1 Determining how well the neurocognitive tests predict the IHDS outcome (univariable analysis)

Table 17 shows the ability of each of the neurocognitive tests to predict participants at risk of developing HAD. A post estimation graph plot of the sensitivity/specificity versus probability cut-off was the plotted to obtain the optimal cut-off point The digit span test was identified to have the highest predictive capacity among all the tests (AUC=66.40), however the test's ability to identify participants at risk of developing HAD was one of the lowest (sensitivity=55.50%). The colour trails test to assess executive function showed the highest ability to identify participants at risk of developing HAD (sensitivity =82.42%), however the

test showed very low ability to identify participants that were not at risk of developing HAD (specificity=22.34%).

Table 17: Univariable ROC analysis to determine how well the neurocognitive tests predict the IHDS outcome

	TGT	GPD	CT1	CT2	AVLT	DIGTSP	SYMDIG
Optimal cut-off	0.73	0.71	0.72	0.70	0.74	0.76	0.74
Area under the curve	56.37%	55.92%	53.55%	56.44%	63.34%	66.40%	58.38%
Sensitivity	56.58%	46.58%	72.11%	82.42%	55.30%	55.50%	49.16%
Specificity	55.89%	61.77%	31.16%	22.34%	64.09%	69.02%	61.05%

TGT-timed gait, GPD-grooved pegboard, CT1-colour trails1, CT2-colour trails 2, AVLT-auditory verbal learning, DIGTSP-digit span, SYMDIG-symbol digit modalities

3.4.2 Determining how well the neurocognitive tests predict the IHDS outcome (Multivariable analysis)

Table 18 shows the combined ability of each the neurocognitive tests to predict participants at risk of developing HAD. A multivariable logistic regression model containing all the seven neurocognitive tests (adjusted for age, education and gender) was fitted to estimate the predicted probabilities to use as the classification variable in the ROC analysis. The predictive power of the neurocognitive tests was high (71%). The neurocognitive tests had a specificity ~65% showing fair ability to identify participants that were not at risk of developing HAD and fairly adequate capacity to identify participants that were at risk of developing HAD (sensitivity ~65%).

Table 18: Multiple ROC analysis to determine how well the neurocognitive tests predict the IHDS outcome

	Neurocognitive battery
Optimal cut-off	0.73

Area under the curve	70.25%
Sensitivity	64.62%
Specificity	66.67%

Neurocognitive battery comprised of all seven tests

3.5 Performance of the IHDS in the Ugandan population

Using the neurocognitive battery and the Frascati criteria (See appendix A and appendix B), the prevalence of HAND in this study population was 9.10% whereas the IHDS had identified 73.25% of the study population to be at risk of developing HAD. Using the parametric method (see table 19 and figure 13-14), the IHDS was found to have very high specificity (91%) hence high ability to identify participants without HAND however the scale was found to have a very low ability to identify participants with HAND (sensitivity=35%). Using the non-parametric method, at a cut-off point of 10 points, the sensitivity and specificity results were similar to those obtained in the parametric method. When the cut-off point was adjusted to 7 points, the IHDS validity was as follows: sensitivity=65.66%; specificity=58.52%.

Table 19: ROC analysis (parametric method) for the validity of the IHDS detecting HAND

	IHDS
Optimal cut-off	0.15
Area under the curve	67.45%
Sensitivity	34.54%
Specificity	90.74%

Neurocognitive battery comprised of all seven tests

Table 20: ROC analysis (non-parametric method) for the validity of the IHDS detecting HAND

	IHDS (non-parametric 1)	**IHDS (non-parametric 2)**
Cut point	10	7
Sensitivity	34.54%	65.66%
Specificity	90.74%	58.52%

Neurocognitive battery comprised of all seven tests

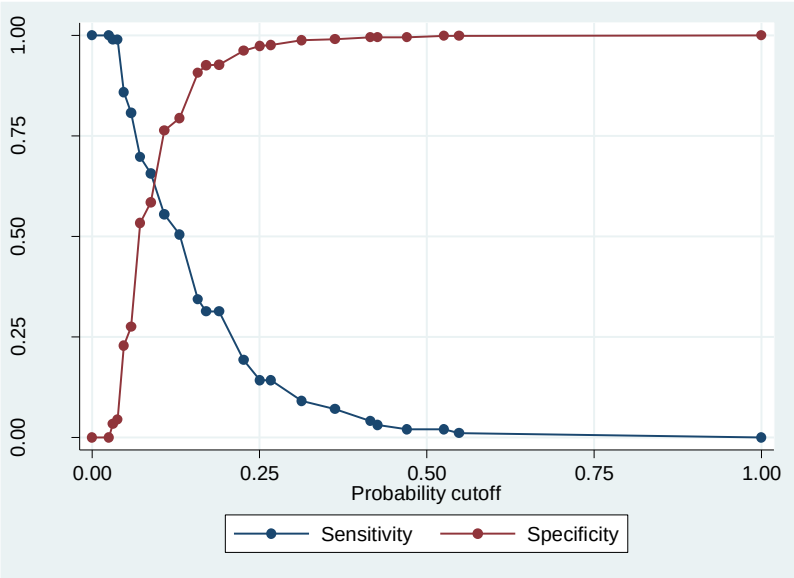


Figure 13: Sensitivity/specificity probability cut-off plot for validity of the IHDS in detecting HAND

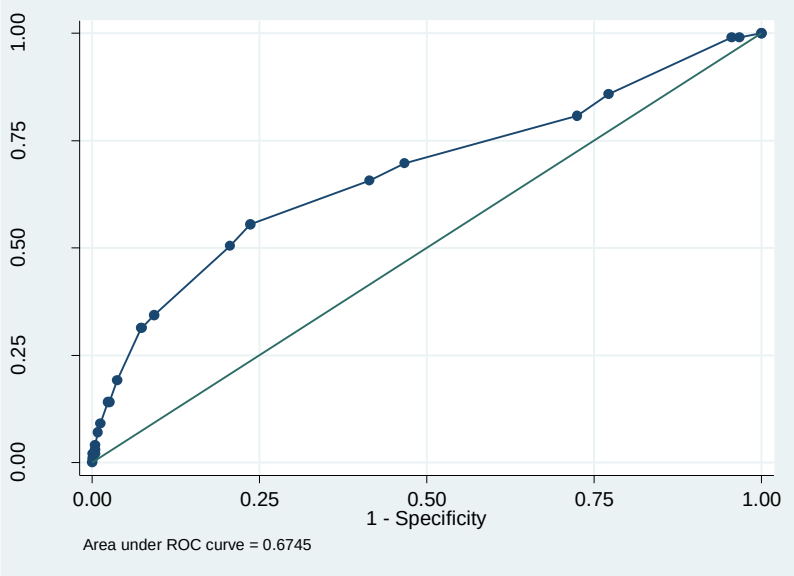


Figure 14: Sensitivity-specificity plot for validity of the IHDS in detecting HAND

CHAPTER 4: DISCUSSION

In this discussion chapter, a brief overview of the results will be provided. The chapter will further discuss the association between demographic factors and neurocognitive test scores. Following this, the relationship between the neurocognitive test scores and the IHDS as well as the performance of the IHDS in the Ugandan population will be discussed. To conclude the report, the strengths and limitations of the study as well the conclusions and recommendations drawn from the study will be outlined.

4.1 Overview of the study findings

In this study, the primary objective was to investigate whether the neurocognitive test battery (made up of the following neurocognitive assessment tests: *the timed gait test*, *the WHO-UCLA verbal learning test*, *the grooved pegboard test*, *the colour trails 1 & 2 test*, *the Auditory verbal learning test*, *the digit span backward and forward test* and the *symbol digit modalities test*) would be appropriate to detect HAND in the absence of normative data in a Ugandan cohort. The study has revealed several useful findings including:

- Demographic variables: ageing, being female, having a lower socio-economic score and having lower levels of education were associations for poor neurocognitive performance in PLWHA.
- The neurocognitive test battery discriminated moderately between PLWHA who were at risk of HAD and those who were not at risk.
- The recommended IHDS to screen for HAND demonstrated poor validity in the Ugandan context.

Each of these findings will be discussed in detail below.

4.2 Association between demographic factors and the neurocognitive test scores\

Increasing age, lower education levels, the female, and being from the Masaka region were identified as important predictors of neurocognitive impairment across all domains. However, the results of the study suggest that not all neurocognitive measures in the administered neurocognitive battery were as strongly associated with these demographic factors. Advanced age and low education were associated with poorer neurocognitive performance across nearly all neurocognitive measures. Education in particular, affected neurocognitive performance on tests of gross motor function, fine motor function, speed of processing and attention/working memory. Executive function while sensitive to education was not affected by age but age was significantly associated with a decline in all other neurocognitive domains.

4.2.1 Association between age and the neurocognitive test scores

Previous studies have revealed similar trends of the effect of age and education on neurocognitive performance (9,12). Valcour et al. reported a threefold increase in neurocognitive impairment in participants older than 50 years to participants who were aged between 20-39 years independent of other demographic factors. The confounding effect of age on neurocognitive impairment has however not been consistent in all studies. Cysique and colleagues assessed cognitive function in 146 patients in Australia and found no significant neurocognitive impairment differences based on age differences (57). The authors of the study suggested participants who were infected with HIV at a higher age to have more rapid neurocognitive decline and advised future studies to explore the neurocognitive effect of HIV

and age on a larger sample. In the present study, a larger sample size was employed to address this recommendation.

4.2.2 Association between gender and the neurocognitive test scores

An interesting finding is that being female was significantly associated with poor performance in the following neurocognitive domains: gross motor function, fine motor function, speed of processing, executive function however; there was no significant association between gender and the verbal learning/working memory cognitive domain. This finding is different to findings from previous studies where gender was found to not affect neurocognitive performance in PLWHA (57,58). In a study by Welsh-Bohmer and colleagues, the investigators examined neurocognitive performance of participants without illness and the results revealed gender to have negligible effects on neurocognitive performance when adjusting for age and education (58). In the present study, it is not clear why there a variation in neurocognitive performance was observed between the two genders even after controlling for age and education, we suspect a possibility of females having comorbidities such as depression as revealed in a study on the same cohort (42). The difference in findings could be attributed to variation in testing standards, cultural context as well as differing demographic distribution based on sample size or chance.

4.2.3 Association between education and the neurocognitive test scores

Participants with lower education levels were found to have poorer cognitive function across all neurocognitive measures. Our results were consistent with several studies which explored the effect of education on neurocognitive performance in PLWHA (12,28,37,46). We suspect familiarity with testing formats in educated individuals to contribute to their ability to follow instructions and complete tasks (Boone, 2007). It is important to note that in the present study the 'education' variable was categorised. Previous studies have reported the need to consider quality as well as years of schooling when investigating the effects of education on neurocognitive performance. In an Australian study on an HIV positive cohort, Manly et al. compared the effect of education as a categorical variable and 'reading level' as a measure of quality of education on neurocognitive performance (24,59). The study revealed quality of

education to account for the most variance in neurocognitive performance in comparison to education category, HIV status and age (24).

4.2.4 Association between place of residence/socio-economic index and the neurocognitive test scores

Our results also suggest variation in neurocognitive performance between the two study sites. Participants from the Masaka region (mean socio-economic index=0.92±0.5) had poorer performance in neurocognitive measures of gross motor function, speed of processing and attention/working memory in comparison to participants from Entebbe region (mean socio-economic index=1.41±3.6).

It is worth emphasizing that to accentuate that participants from the Masaka area had a lower socio-economic index in comparison to participants from the Entebbe area, hence our study reveals that low socio-economic status to be associated with poor neurocognitive performance in PLWHA. These findings are similar to that of da Rosa and colleagues who conducted a systematic review of investigations that examined the relationship between socio-economic status and neurocognitive performance (60). In this systematic review low socio-economic status was associated with poor performance in neurocognitive measures of visio-spatial function, executive function and attention/memory and stress was found to mediate the relationship between socio-economic status and neurocognitive performance (60). However, the studies reviewed by da Rosa and colleagues consisted of HIV negative cohorts, the relationship between socio-economic status, stress and neurocognitive performance ought to be explored in an HIV infected population. We also suspect socio-economic status to be a surrogate marker for access to education which has been found to be associated with neurocognitive performance (28,37).

These findings on the association between demographic factors and neurocognitive performance have biological plausibility. In a review on the pathogenesis of HIV associated neurocognitive disorders, Saylor and colleagues pooled the results of several HAND studies and suggested, the HIV virus triggers inflammation of the cerebrospinal fluid which triggers the neuronal cells of the brain that transmit and receive signals to execute tasks to undergo a decline in dendritic arborisation (41,61). Dendritic arborisation is the organization of the cell body of the neuron and its dendritic processes that enable cognitive tasks to be performed (62).

Cerebrospinal inflammation is also reported to occur in the aging brain, which could explain the results of the study concerning the patterns of neurocognitive performance in aging participants (35).

4.3 Association between the neurocognitive test scores and the IHDS

The third of objective of the study was to investigate the relationship between neurocognitive test scores and the IHDS and to determine how well the neurocognitive test scores predict the IHDS score/outcome.

Our results suggest a significant association between the IIHDS and the following neurocognitive measures: *timed gait test*-to assess gross motor function, *grooved pegboard test*-to assess fine motor function, *auditory verbal learning test*-to assess verbal learning and memory ability, and the *digit span test* to assess attention/working memory. There was no association between the IHDS and the *colour trails 1 test/symbol digit modalities test*-to assess speed of processing and the *colour trails 2* test-to assess executive function. To the best of our knowledge, there are no studies that have explored how well the neurocognitive battery predicts the IHDS outcome. Previous studies have used the neurocognitive battery as the gold standard to investigate the validity of the IHDS but have however not reported how each of the tests of the neurocognitive battery relate to the IHDS outcome (19,20,37,63)

The IHDS assesses the memory and motor function domains, hence we hypothesized a direct correlation between the IHDS scores and neurocognitive measures for the memory domain (i.e. auditory verbal learning and digit span tests) and neurocognitive measures for the motor function domain (i.e. the timed gait and grooved pegboard tests). Our results support this hypothesis for neurocognitive measures of motor function (i.e. timed gait and grooved pegboard test) however there was an inverse relationship between the neurocognitive measures that assess the memory domain (i.e. auditory verbal learning and digit span tests) and the IHDS. We suspect this inverse relationship to be attributed to the difference in the quantity of questions assessing the memory domain between the IHDS and the neurocognitive tests. While a participant is required to recall 15 words in the auditory verbal leaning test, a participant is only required to recall four words for the IHDS to assess memory. There is a possibility of participants being able to perform better in a brief word recall test as opposed to a longer word

recall tests, which could explain the results found in the present study. Variation in neurocognitive performance using different tests ought to be explored further.

4.4 Performance of IHDS in the Ugandan population

The high prevalence of HAD (73.25%) led to us to question the validity of the IHDS in this study population. Using the gold standard for HAND diagnosis (neurocognitive battery and published normative scores) we found the prevalence of HAND in the study population to be 9.10% yet the results from the IHDS revealed 73.25% of the study population to be at risk of developing HIV associated dementia, the most severe form of HAND. The IHDS was found to discriminate poorly among participants with HAND and those without even after adjusting cut-offs. Our findings differ from previous findings on the validity of the IHDS in similar populations (19,20,37). In 2005, Sacktor and colleagues investigated the validity of the IHDS in the Ugandan context and found the IHDS to discriminate satisfactorily among participants with HAND and those without with a sensitivity of 80% and a specificity of 55% at a cut-point of 10 points. However the study sample in the study by Sacktor et al. was small and neurocognitive scores were not adjusted for demographic factors which may have led to the overestimation of the prevalence of HAND and in turn the validity of the IHDS (19).

Our study differs from previous studies on the validity of the IHDS in similar contexts. However, our findings do however support the suggestion made by Dang et al of exploring different diagnostic cut-off points for the IHDS to take into account the variation of the IHDS accounted for by demographic differences reported in several studies and also seen in the present study (37,63,64). It is worth noting that the current recommendation by the international community of a diagnostic cut-off of 10 points on the IHDS does not include the influence of educational level, age, ethnicity, and other sociocultural factors in its definition. We suspect the cut-off score of 10 points to lead to the emergence of false positives when applied to HAND diagnoses in underdeveloped regions as seen in the present study.

4.5 Strengths and limitations

The strength of this study lies in the fact that the information gathered is derived from a large carefully examined sample where rigorous data collection methods were employed to ensure

little missing data. It is our belief that the study contributes to our knowledge about HAND diagnosis in Sub Saharan Africa.

There are several epidemiological, technical and statistical limitations to the study, which are described below:

- As this study was a cross sectional study, the cause for poor neurocognitive performance cannot be determined from the associations identified.
- The neurocognitive assessment tools in the present study were not taken through a formal validation process, however the tools were taken through forward and backward translation process to meet a threshold reliability (42).
- Based on previous studies on neurocognitive performance in resource-limited settings, cultural contexts were found to contribute to substantial variation in neurocognitive performance (Robertson et al., 2016). Therefore, generalizability of the current study results may be limited due to the cultural context of the study participants.
- The use of the IHDS to screen for HAND posed a limitation in answering the study question as the IHDS was found to have poor validity in detecting HAND in the Ugandan context. Using the IHDS as the reference test to determine whether neurocognitive test scores could be used to detect HAND in the absence of normative data could have led to an overestimation or underestimation of the ability of neurocognitive assessment tests to screen for HAND in the absence of normative data.
- The HAND outcome of participants was determined using solely statistical means without the expertise of a psychiatrist to confirm diagnosis; hence, there is a possibility of misdiagnosis.
- The amount of variation in the neurocognitive test scores accounted for by the demographic factors recorded in this study was minimal; inclusion of clinical biomarkers such as CD4 count, comorbid conditions and HIV clade would have strengthened the neurocognitive test score models.
- There is a possibility that the HIV infected participants may have had undetected aetiologies that have the potential to impair cognitive ability such as syphilis or malaria (65–67).

- The inability to rule out opportunistic central nervous system infections using neuroimaging technology may have led us to overestimate the prevalence of HAND (36).
- Normative data to assess the construct validity of the IHDS in the Ugandan population was obtained from a published study on neuropsychological normative scores for resource limited populations (28). This study highlights the need for country based normative data shown by the cross-cultural variation in neuropsychological performance in the participants of this study. The use of data from this study in which a Ugandan population was not included could have led to false estimates of the validity of the IHDS in the Ugandan population.

4.6 Conclusion and recommendations

In conclusion, the present study shows an overall poor performance in the cognitive domains of speed of processing, executive function, attention/working memory among HIV infected participants. Low education and advanced age were associated with poorer neurocognitive performance. The present study also underscores the importance of age, gender, education marital status, religion and place of residence as important markers for neurocognitive performance. The neurocognitive test battery used in the present study discriminated modestly among HIV participants at risk of developing HIV associated dementia and those that were not at risk of developing dementia. In the Ugandan population, the construct validity of the IHDS in the diagnosis of HAND was poor.

While there needs to be further work done to obtain country based normative data, comprehensive neurocognitive testing that involves normative data is not feasible for routine HAND screening. Further work is required to produce an algorithm to detect HAND in the absence of normative data. This includes an inclusion of important clinical biomarkers, exploration of further demographic confounders as well strengthening of the HAND diagnostic criteria using the neuropsychological test battery. Development of algorithms to detect HAND in resource-limited settings is essential in order to understand the HAND burden in the face of a high prevalence of HIV seen in these settings.

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Appendix A: The Frascati Criteria for the classification of HIV associated neurocognitive disorders

HIV Associated Asymptomatic Neurocognitive Impairment (ANI)	1. Acquired impairment in cognitive functioning must involve at least two ability domains, documented by performance of at least 1.0 standard deviation below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language, attention/working memory, abstraction/executive, memory (learning/ recall), speed of information processing, sensory-perceptual, motor skills. 2. The cognitive impairment does not interfere with everyday functioning. 3. The cognitive impairment does not meet criteria for delirium or dementia. 4. There is no evidence of another pre-existing cause (like depression or substance abuse) for the ANI.
HIV-1 Associated Mild Neurocognitive Disorder (MND)	1. Acquired impairment in cognitive functioning must involve at least two ability domains, documented by performance of at least 1.0 standard deviation below the mean for age-education-appropriate norms on standardized neuropsychological tests. The neuropsychological assessment must survey at least the following abilities: verbal/language; attention/working memory; abstraction/executive; memory (learning; recall), speed of

	information processing, sensory-perceptual, motor skills. *Typically, this would correspond to a Memorial Sloan Kettering (MSK) scale stage of 0.5 – 1.0* 2. The cognitive impairment produces at least mild interference in daily functioning (at least one of the following): i. Self-report of reduced mental acuity, inefficiency in work, homemaking, or social functioning. ii. Observation by knowledgeable others that the individual has undergone at least mild decline in mental acuity with resultant inefficiency in work, homemaking, or social functioning. 3. The cognitive impairment does not meet criteria for delirium or dementia. 4. There is no evidence of another pre-existing cause for the MND.

HIV-1 Associated Dementia (HAD)	1. There is marked acquired impairment in cognitive functioning, involving at least two ability domains; typically, the impairment is in multiple domains, especially in learning of new information, slowed information processing, and defective attention/concentration. 2. The cognitive impairment must be ascertained by neuropsychological testing with at least two domains 2 SD or greater than demographically corrected means. (If neuropsychological testing is not available, standard neurological evaluation and simple bedside testing may be used, but this should be indicated in algorithm ~ see below). 3. The cognitive impairment produces marked interference with day-to-day functioning (work, home life, social activities). 4. The marked cognitive impairment has been present for at least one month. 5. The pattern of cognitive impairment does not meet criteria for delirium (e.g., clouding of consciousness is not a prominent feature); or, if delirium is present, criteria for dementia need to have been met on a prior examination when delirium was not present. 6. There is no evidence of another, pre-existing cause for the dementia (e.g., other CNS infection, CNS neoplasm, cerebrovascular disease, pre-existing neurological disease, or severe substance abuse compatible with CNS disorder).

Appendix B: Ethics clearance certificate

R14/49 Miss Leeanne Masilela

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M161185

NAME: (Principal Investigator)	Miss Leeanne Masilela
DEPARTMENT:	Epidemiology and Biostatistics School of Public Health University of the Witwatersrand
PROJECT TITLE:	Detecting HIV Associated Neurocognitive Disorders using Neurocognitive Assessment Tests in Uganda
DATE CONSIDERED:	25/11/2016
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof Jonathan Levin and Dr Sumaya Mall
APPROVED BY:	Professor P Cleaton-Jones, Chairperson, HREC (Medical)
DATE OF APPROVAL:	13/01/2017

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

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary in Room 30', Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown 2193, University of the Witwatersrand. I/We fully understand the conditions under which I am/we are authorized to carry out the above mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated from the research protocol as approved, I/we undertake to resubmit the application to the Committee. **I agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in November and will therefore be due in the month of November each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator's Signature — Date: 01/12/2016

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

Appendix C: Sensitivity analysis for the association between neurocognitive test scores and the IHDS score

Table 1: Univariable and Multiple linear regression models to assess the relationship between the neurocognitive assessment test scores and the IHDS score

	Univariable analysis		Multivariable analysis	
	Coef (95%CI)	**p-value**	**Coef (95%CI)**	**p-value**
Timed gait *	-0.01 (-0.27-0.01)	0.214	0.01 (-0.00-0.03)	0.081
Grooved peg total *	-0.01 (-0.01--0.01)	0.000	0.00 (0.00-0.01)	0.000
Colour trails 1 *	-0.01 (-0.01--0.01)	0.000	0.00 (-0.00-0.00)	0.610
Colour trails 2*	-0.01 (-0.01--0.00)	0.000	-0.00 (-0.00-0.00)	0.023
Auditory verbal learning	0.06 (0.05-0.07)	0.000	0.03 (0.02-0.05)	0.000
Digit span total	0.17 (0.14-0.19)	0.000	0.11 (0.08-0.14)	0.000
Symbol digit modalities*	0.02 (0.01-03)	0.000	0.00 (-0.01-0.01)	0.896

*a lower test score indicates better functioning

Table 2: Univariable and multivariable binary logistic regression models to assess the relationship between the neurocognitive assessment test scores and the IHDS score

	Univariable analysis		Multivariable analysis	
	OR (95%CI)	**p-value**	**OR (95%CI)**	**p-value**
Timed gait *	-0.02 (-0.04-0.01)	0.326	-0.03 (-0.06--0.00)	0.027
Grooved peg total *	0.01 (0.00-0.01)	0.000	0.00 (0.00-0.01)	0.049
Colour trails 1 *	0.01 (0.01-0.01)	0.015	-0.00 (0.01-0.00)	0.414
Colour trails 2*	0.00 (0.01-0.01)	0.002	0.00 (-0.00-0.01)	0.518
Auditory verbal learning	-0.06 (-0.08--0.04)	0.000	-0.04 (-0.06--0.02)	0.000
Digit span total	-0.19 (-0.24--0.14)	0.000	-0.16 (-0.21--0.11)	0.000
Symbol digit modalities*	-0.03 (-0.04--0.02)	0.000	-0.11 (-0.03-0.01)	0.217

*a lower test score indicates better functioning

Table 3: Univariable and Multiple ordinal logistic regression models to assess the relationship between the neurocognitive assessment test scores and the IHDS score

	Univariable analysis		Multivariable analysis	
	OR 95%CI	**p-value**	**OR 95%CI**	**p-value**
Timed gait *	0.79 (0.41-1.55)	0.497	0.55 (0.26-1.15)	0.114
Grooved peg total *	0.87 (0.83-0.91)	0.000	0.92 (0.86-0.97)	0.002
Colour trails 1 *	0.89 (0.83-0.96)	0.001	1.05 (0.94-1.17)	0.419
Colour trails 2*	0.91 (0.87-0.96)	0.000	0.97 (0.91-1.03)	0.329
Auditory verbal learning	1.07 (1.05-1.08)	0.000	1.05 (1.03-1.07)	0.000
Digit span total	1.23 (1.19-1.29)	0.000	1.18 (1.13-1.23)	0.000
Symbol digit modalities*	1.03 (1.02-1.05)	0.000	1.01 (0.99-1.02)	0.292

*a lower test score indicates better functioning

Appendix D: Graphical plots showing optimal cut-offs for how well neurocognitive test scores predicted the IHDS outcome

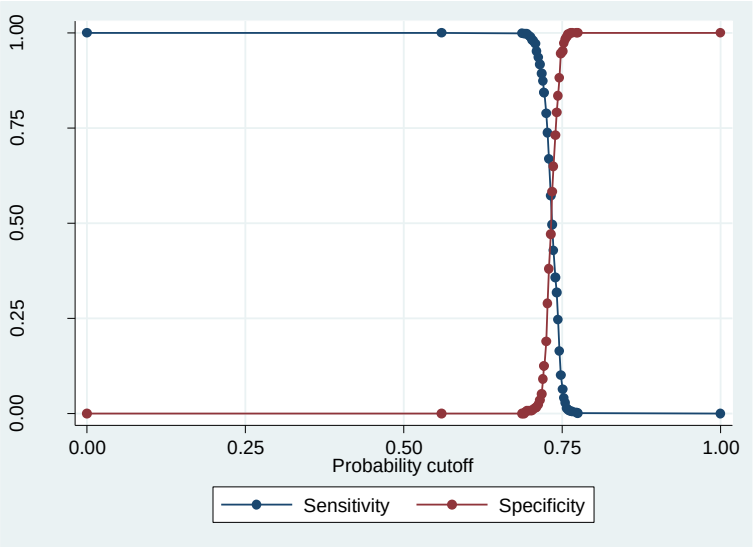


Figure 1: Optimal cut-off for the timed gait score in predicting IHDS outcome

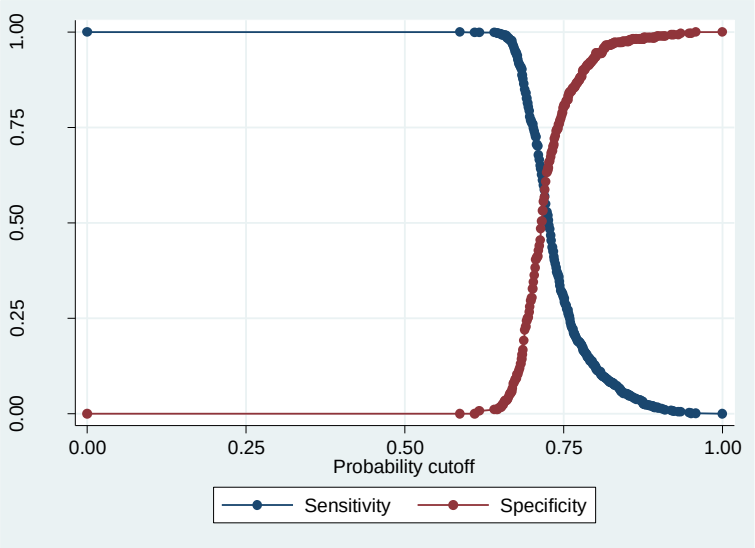


Figure 2: Optimal cut-off for the grooved-peg score in predicting IHDS outcome

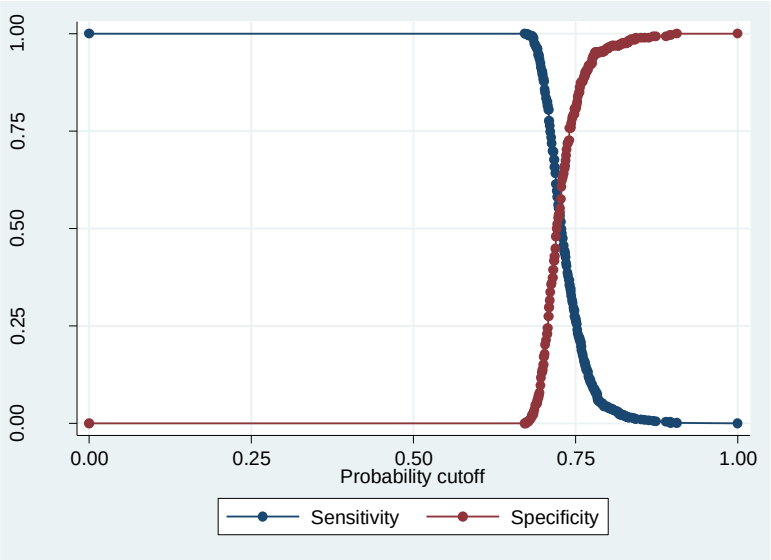


Figure 3: Optimal cut-off for the colour trails 1 score in predicting IHDS outcome

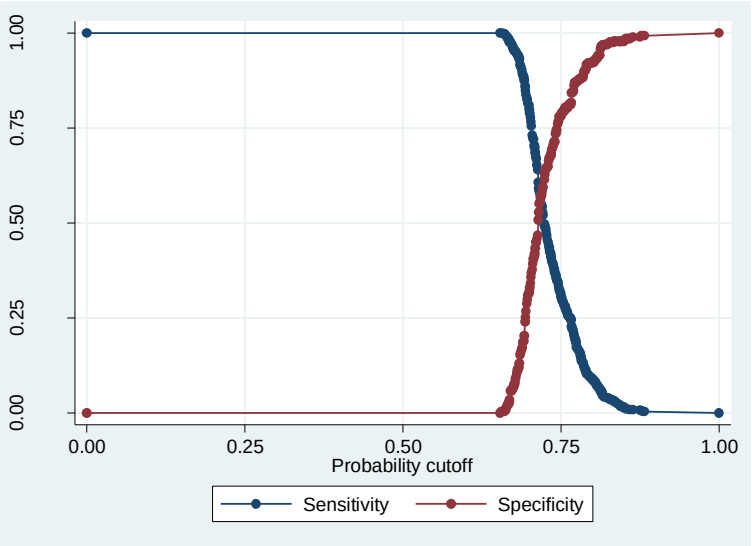


Figure 4: Optimal cut-off for the colour trails 2 score in predicting IHDS outcome

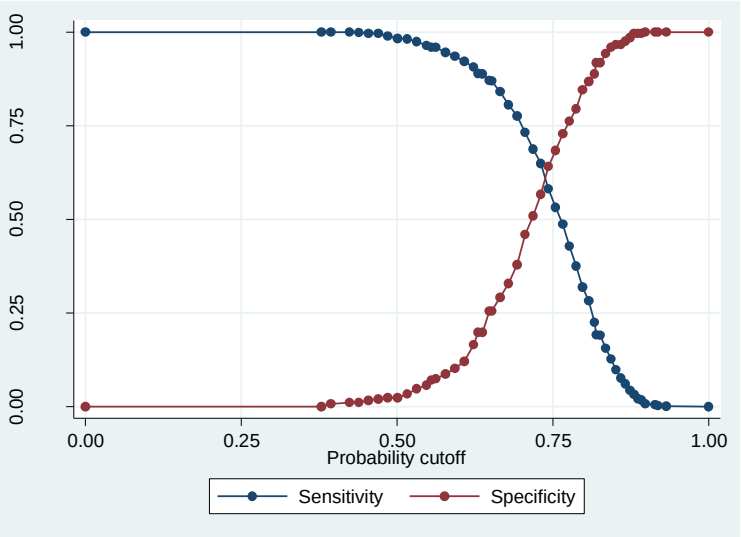


Figure 5: Optimal cut-off for the auditory verbal learning score in predicting IHDS outcome

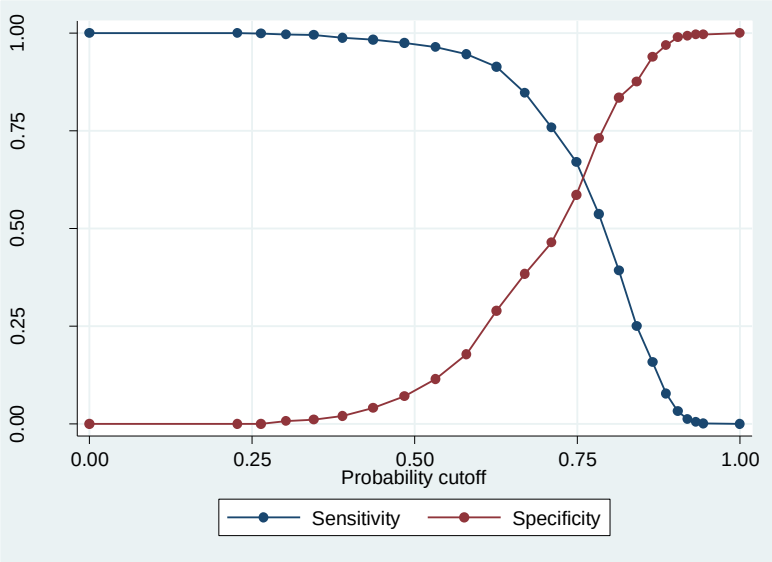


Figure 6: Optimal cut-off for the digit span score in predicting IHDS outcome

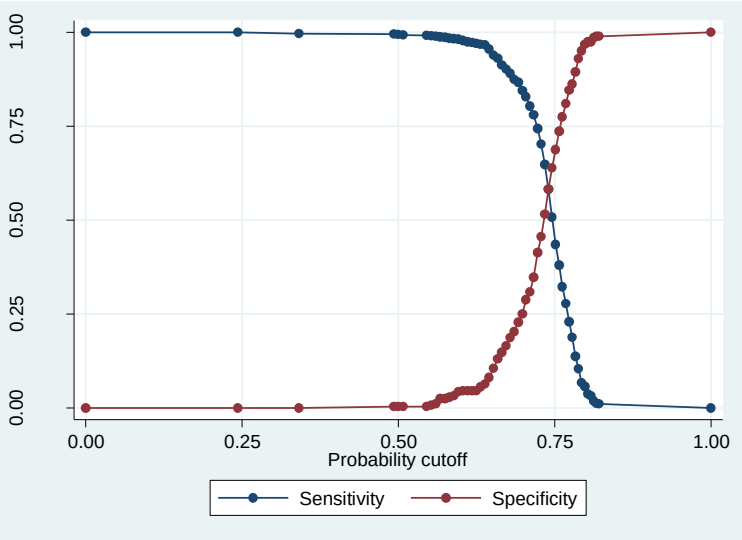


Figure 7: Optimal cut-off for the symbol digit modalities score in predicting IHDS outcome