SCHOOL OF PUBLIC HEALTH,  
COLLEGE OF HEALTH SCIENCES  
UNIVERSITY OF GHANA  

PSYCHOBEHAVIOURAL FACTORS ASSOCIATED WITH NEUROCOGNITIVE TEST PERFORMANCE IN HIV-POSITIVE PERSONS ATTENDING A REGIONAL HOSPITAL IN ACCRA, GHANA

BY

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THIS DISSERTATION SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON IN PARTIAL FULFILLMENT FOR THE REQUIREMENT OF THE AWARD OF MASTER OF PUBLIC HEALTH DEGREE

JULY, 2017
DECLARATION

I, Nana Yaw Asiedu, do hereby declare that except for references made to other people’s work that have been duly acknowledged, this work is the result of my own original research done under supervision, and that this dissertation, either in whole or in part has not been presented elsewhere for another degree.

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DEDICATION

I dedicate this thesis to the men, women, and children living with HIV in the world today.
If my work can somehow make a difference for just one of over 36 million people who fight this disease, I am grateful.
ACKNOWLEDGEMENT

I do not feel I can ever finish counting the blessings I have received in this life. Far too many people have helped me get to where I am today, but I would be remiss if I did not make an effort naming as many as I can. Let me start by thanking my Aunty Akua Kwateng-Addo for inspiring me to pursue graduate education in the first place; it has truly been an honour to follow in her footsteps at the University of Ghana. After visiting the school, I understood the opportunity that presented itself for me to study in Ghana. From there, it was Professor Edwin Afari who really encouraged me to apply and saw some untapped potential in me that I couldn’t even see. Thank you Professor for your words of encouragement.

Thanks to my former supervisors Omarys Hersame and Irene Tseretopoulos who provided the necessary recommendations to receive admission. I will forever have fond memories of working with you at the Brain Trauma Foundation in New York. In fact, everyone at BTF helped me develop my professional skillset, and I am so happy to have obtained that job right after college. If it were not for the help of my former colleagues Umesh, Jun, Lisa, Phil, Nancy, and of course our brilliant president Dr. Jamshid Ghajar, I would not have had the platform in which to submit myself as a worthy candidate to the MPH programme.

Thanks goes to the faculty that guided me during my year in the school. Dr. Emmanuel “Bra Emma” Asampong was instrumental in pulling me into the Social and Behavioural Science department, and I will always appreciate his quick wit and even quicker helping hand. I had the pleasure to be taught by so many magnificent lecturers who were real masters of their field, including Doctors Abubakar Manu, Augustine Ankomah, Ernest
Kenu, Amos Laar, Aldophina Addo-Lartey, and Richard Adanu. So many obstacles came up during completion of my work, and the School of Public Health was always a support network for me. In particular, I need to thank those in the Academic Office (especially Eva and Irene,) Biostatistics Department (especially Tony,) and IT department (especially Solomon) because I could not have successfully submitted my work without your help at some point in the project.

I found a true mentor in the form of my academic supervisor Dr. Irene Kretchy. Doctor, your patience and diligence for perfection was always worth the trek to your office at the School of Pharmacy! This work could not have taken a tangible form without you helping me put the thoughts in my head into words on paper.

To the Ridge Regional Hospital staff, where I conducted the bulk of my field work: your cooperation was instrumental in the data collection. Thank you to Aunty Mercy, Julia, Dorcas, and Darlington for all the assistance you rendered me. I was so new to the workings of an ART clinic, and you graciously taught me all I needed to know to complete my work.

Finally, I have come to the most important people in all of this: my family. Grandma Lucy, you are a trailblazer and visionary; I feel all my creativity comes from you. Aunty Coup, Aunty Betty, Aunty Frema, and Uncle Opium: you made moving from the U.S. to Ghana so much easier because of your love and support. My siblings and cousins: thank you for just being yourselves and cheering me up when I needed it most. Of course the best comes last: my parents. Mom and Dad, you have been a pillar in my life since the beginning. The hardest part about all this has been being so far from you both, but to
know I was making you proud was worth it. I am so humbled to call myself your son.

Never forget that.
LIST OF ABBREVIATIONS

**AIDS**: Acquired immune deficiency syndrome

**ADC**: AIDS dementia complex

**ANI**: Asymptomatic Neurocognitive Impairment

**ART**: Antiretroviral Therapy

**AUC**: Area Under Curve

**BBB**: Blood Brain Barrier

**CNS**: Central Nervous System

**GAC**: Ghana AIDS Commission

**HAD**: HIV Associated Dementia

**HAND**: HIV Associated Neurocognitive Disorders

**HIV**: Human Immunodeficiency Virus

**IHDS**: International HIV Dementia Scale

**MND**: Mild Neurocognitive Disorder

**NACP**: National AIDS Control Programme

**NCI**: Neurocognitive Impairment

**ROC**: Receiver Operating Characteristic

**TMT**: Trail Making Test

**WHO**: World Health Organization
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ABSTRACT

Background: The Human Immunodeficiency Virus (HIV) can enter the brain and attack nerve cells, leading to problems of mental functioning collectively known as neurocognitive impairment (NCI). Globally, it is estimated that almost half of all treated HIV patients have some form of NCI. The primary method of diagnosing NCI is for an examiner to administer a battery of neuropsychological/neurocognitive assessments. There are very few studies of neuropsychological assessments in Ghana, due in part to limited resources for such testing. Therefore, the full burden of NCI in Ghana is unknown. HIV-positive Ghanaians may endorse certain psychological and behavioural traits that could contribute to mild or severe cases of NCI. The aim of the study was to explore neurocognitive performance in a group of HIV-positive adults in Ghana, and investigate the possible factors that contribute to their performance.

Method: This study investigated NCI in 104 HIV-positive Ghanaians attending an antiretroviral therapy clinic at Ridge Hospital in Accra, using a selection of brief non-invasive neuropsychological assessments as well as the International HIV Dementia Scale. Behavioural factors (alcohol use, depression, and medication adherence) as well as demographic factors were assessed to determine any association with performance on neurocognitive assessments and NCI risk. Linear regression and Receiver Operating Characteristic (ROC) analyses were used to determine which factors had a significant effect on neurocognitive performance.

Result: About 48% of the participants met the criteria for neurocognitive impairment risk, according to the International HIV Dementia Scale. Advanced age, low education, and risk of depression were significantly associated with neurocognitive impairment.
The Trail Making Test was highly accurate at identifying neurocognitive impairment in the group (area under curve = 0.7214).

**Conclusion:** HIV-positive Ghanaians may be at risk for some degree of neurocognitive impairment, even when on ART medication. Depression may be co-morbid with impairment. Certain neurocognitive tests like the Trail Making Test are best for measuring neurocognitive impairment. Further research is needed to map the extent of cognitive complications.
CHAPTER ONE: INTRODUCTION

1.1 Background

While it is not often addressed, the Human Immunodeficiency Virus (HIV), which may compromise the immune system enough to cause Acquired Immune Deficiency Syndrome (AIDS), also has the capability to infect the central nervous system, or CNS (Kaul, Zheng, Okamoto, Gendelman, & Lipton, 2005). Initially coming to prominence in the 1980’s as a rare cancer or lung infection, the evolution of HIV has come a long way, from the “gay man’s disease” to an epidemic capable of devastating communities (WHO, 2015). A major consequence of HIV infection in the brain is neurocognitive impairment (NCI) especially without medication (Habib et al., 2013). When this happens one may observe NCI worsening as the virus progress, with AIDS presenting the worst prognosis for cognition (Hardy et al., 2009). However, the severity of neurocognitive impairment varies, and patients with less virology may have reduced risk of cognitive impairment (Robertson et al., 2010). For clinicians to understand HIV’s effect on mental processes, it is important to discuss current terminology.

1.2 Clinical Manifestation of Cognitive Decline in HIV: HAND

When the Human Immunodeficiency Virus (HIV) enters the nervous system and attacks cells, some key functions of the brain may be disrupted, a mechanism yet to be fully understood (Clifford & Ances, 2013). Because these brain functions are part of what is cognition, clinicians classify this effect as HIV associated neurocognitive disorders, or HAND (Clifford & Ances, 2013). The cognitive deficits resulting from HAND can be global, but specific areas affected include psychomotor skills, speed of information processing, memory, attention, language, and perception (Vally, 2011). The relationship between HAND and viral load is at times ambiguous; for example a cross-sectional study done by Simioni and colleagues showed that HAND
prevalence was high even in aviremic (undetectable HIV RNA concentration) patients (Simioni et al., 2010). Much like the early studies of cognition, HAND is a mystery that has warranted extensive study worldwide. Indeed, the multi-site U.S.-based study CHARTER (CNS HIV Anti-Retroviral Therapy Effects Research) was commissioned in part to determine the frequency and severity of HAND, and factors that may contribute to it (Heaton et al., 2010). One way to facilitate HAND research is to categorize the neurocognitive impairment, since there is a range of deficits. Starting from a re-classification in 2007, most clinicians cite three distinct categories of HAND: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV Associated Dementia (HAD) (Rosca, Rosca, Simu, & Chirileanu, 2012). The most severe of the subtypes is HAD, which is a progressive disabling condition consisting of loss of attention, concentration, and motor function, usually culminating in death in less than a year (Clifford & Ances, 2013). This condition follows those who have a viral load indicative of AIDS, and at times the terms “AIDS Dementia Complex” (ADC) and HAD are used interchangeably in literature (Clifford & Ances, 2013).

With access to combination drugs used to stem the growth of the virus, known as anti-retroviral therapy, or ART drugs, HAD is the least common disorder of the three, and most expect that the prevalent HAND cases are asymptomatic neurocognitive impairment and mild neurocognitive disorder (Rosca et al., 2012). The shared feature in these two categories is memory loss (Chibanda, Benjamin, Weiss, & Abas, 2014). In the case of MND specifically, there is mild interference in everyday functioning, but caution must be applied in classifying the impairment as “mild” because the level of functional impairment is difficult to measure (Clifford & Ances, 2013). Although HAD has distinct viral load markers in addition to cognitive impairment, diagnosis of the other two categories of HAND rely almost exclusively on the outcome of neuropsychological
assessment (Gisslén, Price, & Nilsson, 2011). One study cites that almost half of all HIV patients have some form of cognitive impairment (Clifford & Ances, 2013), so it is necessary for assessments to be as robust as possible to identify the specific types of HAND.

1.3 Problem Statement

Although sub-Saharan Africa accounts for more than 66% of the world’s HIV population (Kanmogne et al., 2010), the implication of cognitive deficits due to HAND has not been extensively explored in this region. Figures cite that in low and middle income countries, the prevalence of HAND ranges from 6% to 64% in adults: this range has far too much uncertainty, and it should be noted that such figures do not take into account individuals on ART medication (Chibanda et al., 2014). It is also important to note that while most HAND studies in the developed world were performed on patients with the HIV-1 sub-type B, most HIV cases in Africa have the non-B HIV subtypes, and how this may affect the development of neurocognitive impairment is unclear (Kanmogne et al., 2010). In Ghana, there is a mission to have 85% of eligible patients on ART to limit the number of AIDS-specific fatalities (Ghana AIDS Commission, 2015). Where ART is limited, or where there is a lack of adherence, it is important to consider there could be severe cases of HAND in the country. This could very well mean a high prevalence of symptoms associated with HAD, in contrast to the low prevalence of these symptoms in high income countries. According to a report from UNAIDS in 2013, 24.7 million people in sub-Saharan Africa were living with HIV (Tobergte & Curtis, 2013). Only 39% percent of those people use anti-retroviral therapy, and the report specifically cited that in Ghana there has been a decrease in the number of pregnant women seeking ART (Tobergte & Curtis, 2013). Even with proper medication, milder forms of HAND may persist in high rates (Heaton et al., 2010) and any form of cognitive impairment has the potential to adversely affect daily life. To solve this problem, it is necessary to
understand the sort of cognitive impairment endorsed in HIV-positive Ghanaians, including factors that may independently contribute to cognitive impairment. This will be further illustrated in a conceptual framework.

*Figure 1: Conceptual Framework of relationship between HIV and Neurocognitive Impairment*
This framework explains the factors and effects of cognitive deficits in patients who are HIV-positive, regardless of their stage of disease. If more patients live longer with the disease in Ghana, it stands to reason they could develop one or more of the categories of HAND in their lifetime. Should this happen, it could directly lead to the decline of physical and mental well-being. Cognition encompasses the ability to sustain attention, keep information in memory, solve problems and make wholesome decisions for one’s life, thus its ties to all aspects of the physical, social, and mental health cannot be understated. For one example, while HIV associated dementia does not typically manifest itself in high resource settings (Chibanda et al., 2014), in a country without frequent access to ART, the threat should be assessed to know the prevalence of HIV associated dementia. A circular pathway develops now, because without drug treatments, impaired patients could lose frontal lobe function necessary for executive decision making (Chibanda et al., 2014; Dinesh Singh et al., 2010). Poor decision-making capability will in turn cause people to refuse or misuse drug treatments even if it does become accessible (Chibanda et al., 2014). Along with HIV, psychological/behavioural factors such as alcohol abuse and depression can be prevalent in low/middle-income countries and may lead to an increase in cognitive deficits, and possibly refusal to adhere to ART (Breuer, Myer, Struthers, & Joska, 2011; Chibanda et al., 2014). Depression and alcohol abuse are issues that not only create a low probability of ART adherence, but have no clear order of effect: depression and alcohol abuse can contribute to misuses/noncompliance of an ART regiment, and likewise poor ART adherence may lead to alcohol consumption and/or depression (Chibanda et al., 2014; Vance, Cody, Yoo-Jeong, Jones, & Nicholson, 2015). All these factors can occur in the HIV population independent of having a diagnosis of HAND. Still, these factors are in themselves potential by-products of HAND (Chibanda et al., 2014; Siakwa et al., 2015a), so the exact cause-and-effect pathway is not clear.
As of now, the “gold standard” for diagnosis of HAND is the use of neuropsychological assessments, compiled as a battery of tests (Dinesh Singh et al., 2010). Almost all studies done in the developed world utilize these tests, but in limited-resource settings there is the problem of time and expertise required to administer such assessments (Chibanda et al., 2014; Dinesh Singh et al., 2010). Quite recently, there has been a study in Ghana advocating for the use of neuropsychological assessment of cognitive decline in diabetic patients (Sarfo & Mate-Kole, 2014). This may highlight the need of assessment for cognitive impairment, and address issues of mental health in Ghana that often go unnoticed. The focus of this study then is to understand neurocognitive impairment with brief assessments that can feasibly administered to an HIV-positive population.

1.4 Justification

Ghana is an example of a country that has made successful strides in HIV care. The prevalence of HIV was estimated to be 1.6% in the general population in 2015, and a total of 9,248 AIDS deaths was recorded in 2014 (Ghana AIDS Commission, 2015). Ghana has made great effort to address the problem, particularly with the formation of the Ghana AIDS Commission in 2002 (Ghana AIDS Commission, 2013). But because more Ghanaians may be living with HIV, neurocognitive impairment may increasing in prevalence. It is a challenge to find specific studies about HAND in Ghana; virtually no such studies have been documented in the past five years. The most recent in-depth study of HAND done in sub-Saharan Africa was a meta-analysis of sixteen studies (Habib et al., 2013). The study compiled data on patients who were on and off anti-retroviral therapy living in Uganda, South Africa, Zambia, Malawi, Botswana, and Cameroon (Habib et al., 2013). While the study gave great insight into the burden of NCI in Africa, it was unfortunate that no literature could be found from Ghana. Indeed, many recent studies seem unable to capture data from
Ghanaians in their studies of NCI in HIV. Robertson and colleagues did a similar multi-country study on the neurology of AIDS in Africa; while HIV associated neurocognitive disorders was mentioned extensively, no data from Ghanaian participants was used to explain the disease burden (Robertson et al., 2010). Some studies have studied the psychological state of HIV patients in Ghana, such as Oppong Asante and colleagues (2012), in which it was suggested that social support was an important factor for the psychological well-being of people living with HIV/AIDS (PLHA). However, the profile of HIV-positive patients in Ghana rarely includes the cognitive aspect, which could be just as impactful to psychological well-being as the social aspect. In addition, a cross-sectional study of Mother-to-Child Transmission (MTCM) of HIV-positive Ghanaians women revealed that more than 90% of the women in the study had inadequate knowledge of illness and subsequently were more likely to default on their ART regiment (Boateng, Kwapong, & Agyei-Baffour, 2013). Educational level did not significantly influence knowledge or adherence to ART (Boateng et al., 2013); there is the possibility that neurocognitive impairment may have been a factor for adherence, had it been explored in that study.

This paucity of research calls for the need to investigate the profile of neurocognitive impairments among people living with HIV in Ghana. Although neuropsychological assessments are the most utilized method to understand these deficits, it is essential that researchers be sensitive to the restricted resources of testing in Ghana. Currently, a battery of quick-to-complete tests that are easy to administer would be the best method to administer assessments to an HIV-positive population in Ghana. Once assessments are done, performances can be analyzed to see whether they are indicative of neurocognitive impairment, and how the psychobehavioural components such as alcohol abuse, depression, and non-adherence to ART might have an impact. Such a study will be a preliminary step to appreciate the depths of the problem so that appropriate interventions can be instituted.
1.5 Research Question:

The research questions that this study seeks to answer are:

1. Is there a certain profile of neurocognitive performance in HIV-positive Ghanaians?
2. Does the neurocognitive performance of HIV-positive Ghanaians indicate a risk of neurocognitive impairment?
3. Is the performance on neurocognitive assessments associated with psychobehavioural and/or demographic characteristics?

1.6 General Objectives:

To examine neurocognitive impairment in HIV-positive Ghanaians, and factors associated with this impairment.

1.7 Specific Objectives:

- To create a profile of neurocognitive performance of HIV-positive persons on selected assessments.
- To determine whether the performance of HIV patients on neurocognitive assessments is associated with neurocognitive impairment risk (as measured by the International HIV Dementia Scale.)
- To examine how demographic and psychobehavioural factors are associated with risk of neurocognitive impairment.
CHAPTER 2: LITERATURE REVIEW

2.1 Cognition

As researchers try to understand the mysteries of mankind, cognition remains one of the most fascinating aspects of study. Aristotle was one of the earliest philosophers to speak about cognition in the fourth century B.C., stating that the heart was the seat of the mind and soul (Goldstein, 2009). In his work De Anima, Aristotle understood the soul to be the receptacle for thought and learning, and made a statement about the soul’s relation to humans:

“It is doubtless better to avoid saying that the soul pities or learns or thinks, and rather to say that it is the man who does this with his soul.” (Owens, 1976).

Here, Aristotle conceptualized the soul as a function of the human system—a function that is used to learn and to think, just as the mouth is used to eat or the eyes to see. This presented an essential point that future research developed on: higher-level cognition can be attributed to a part of the human body—in Aristotle’s case the soul—rather than the human as a whole.

What Aristotle described as a “soul” is now attributed to the brain’s executive function of coordinating thought and action towards a goal—the basic tenant of cognition (Miller & Wallis, 2010). To achieve goals, cognition encompasses activities such as attention, memory, language, problem solving, processing speed, and decision-making (Harvey, 2012). As the fields of psychology, philosophy, and biology intertwined, scientists became aware that cognitive activities can be attributed to structural and functional parts of the human anatomy: in particular, it was physician Thomas Willis who concluded from various dissections that the brain was the root of mental functioning (Goldstein, 2009). This link between cognition and the brain necessitated a special technique known as neurocognitive testing, or neuropsychological testing, in which cognitive status is measured through performance-based assessments, performance which then
determines what structural or functional areas of the brain have been compromised (Harvey, 2012). Such testing is derived from studies of neuropsychology that observed behavioural and cognitive changes in humans following brain damage (Goldstein, 2009). With the value that cognition has in human life, it is no doubt a serious and highly alarming prospect to be faced with cognitive loss or decline. The contribution of HIV to this decline has become a major concern for healthcare professionals and scientists.

2.2 HIV in the brain

Neurobiology now operates with the knowledge that the brain is the source of activities linked to cognition. Therefore, to understand the basis of neurocognitive impairment, it is important to understand the route of HIV to the central nervous system (CNS). The pathology of HIV/AIDS is that it infects and impairs the function of the body's organs, and it appears the virus has a predilection towards the brain because neurons (nerve cells) and microglia located in the brain produce the type of chemokine receptors that the virus needs to invade cells (Woods, Moore, Weber, & Grant, 2009). During the period when AIDS cases came to prominence, 390 AIDS autopsy cases were conducted at the University of California in the U.S. and the results showed that the brain was the second most frequently affected organ (Masliah, DeTeresa, Mallory, & Hansen, 2000). Normally the brain offers some resistance against infectious agents via the blood brain barrier (BBB). However HIV can infiltrate the brain by “hiding” within migrating monocytes and lymphocytes (white blood cells) that can cross the BBB (Lindl, Marks, Kolson, & Jordan-Sciutto, 2010; Valcour, Sithinamsuwan, Letendre, & Ances, 2011). In addition, CD4+ T lymphocytes can cross the barrier and use the brain as the reservoir for viral replication: this method of invading the brain is even characterized as the “Trojan horse” method and can occur just 1-2 weeks after the virus enters circulation (Lindl et al., 2010). Once within the barrier, HIV
manifests itself through perivascular macrophages that cause three main threats: producing HIV within the brain, releasing free virions, and facilitating the infection of microglial cells (Sanmarti et al., 2014). Some researchers believe that it is this uninhibited replication of the virus that is directly linked to the development of neurocognitive impairment (Crum-Cianflone et al., 2013). Specifically, the neurotoxic molecules created by HIV will activate astrocytes and these astrocytes themselves may produce HIV. The culmination of infectious agents will lead to neuronal death that may be manifest in infected persons as cognitive decline, indicative of HAND (Letendre, 2011). It should be noted that the cognitive impairment of HAND is indeed caused by neuronal death, but HIV almost never infects the neurons themselves (Lindl et al., 2010). A 2005 study by González-Scarano and Martín-García looked at the infection of macrophages and microglia and linked the genesis of HAND to two potential pathways: the direct mechanism and indirect (“bystander”) mechanism (González-Scarano & Martín-García, 2005). In the direct mechanism, the authors hypothesized that development of HAND begins with infected cells producing viral proteins, such as gp120, tat (transcriptional transactivator) or vpr (viral protein R); these proteins directly come into contact with neurons to cause death (González-Scarano & Martín-García, 2005; Lindl et al., 2010). Neurons maintain the integrity of human cognitive and motor function, so a loss of neurons explains cognitive impairment: the protein gp120 in particular seems to be evident in the neuropathy of severe impairment from HIV associated dementia (HAD), though whether gp120 directly damages neurons or rather stimulates infectious macrophages and microglia is unclear (González-Scarano & Martín-García, 2005). The other theory, the indirect mechanism theory, maintains that viral infections have a more limited role in neuronal damage and it is rather inflammatory processes that cause neurons to die (González-Scarano & Martín-García, 2005). Inflammation may lead to modification of macrophages and microglia to synthesize quinolinic and arachidonic acids, nitric oxide, inflammatory cytokines, and other products that may alter the
permeability of the BBB and allow more monocytes to enter the CNS (González-Scarano & Martín-García, 2005; Lindl et al., 2010). Accordingly, progression to HAD was shown to be correlated with an increase of these by-products (González-Scarano & Martín-García, 2005). The authors thus advocate for the indirect pathway to HAND, though other research maintains the direct and indirect methods are not mutually exclusive (González-Scarano & Martín-García, 2005; Lindl et al., 2010). However, the pathways illustrated only used evidence from studies of AIDS, which meant pathogenesis was associated to AIDS Demenita Complex/HIV associated dementia (González-Scarano & Martín-García, 2005). It is unclear how this pathway presents itself with the milder cases of HAND.

Most studies of neurocognitive impairment in HIV concentrate on the most severe form of HIV. In fact before 1991, HIV associated dementia (HAD), alternatively called AIDS Dementia Complex (ADC) was the only truly defined neurocognitive impairment in HIV (Sanmarti et al., 2014). As antiretroviral therapy (ART) became more accessible, a milder form of impairment of HAD and was given the term minor cognitive motor disorder (MCMD) (Woods et al., 2009). Though some like Kaul and colleagues (2005) operated under the belief that the mild form of MCMD derived from the same neuropathology as HAD, González-Scarano and Martín-García stressed that MCMD does not necessarily progress to HAD in all patients (2005). Ever since the revision of the classification in 2007 (set by what is known as the Frascati criteria), HAND is now divided into three categories: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV associated dementia (HAD) (Clifford & Ances, 2013; Heaton et al., 2011; Robertson, Liner, & Heaton, 2009). The pathogenesis of ANI and MND is not as well documented, and so far classification is only based neuropsychological assessment (Sanmarti et al., 2014). Despite this, it is known that when HIV enters the brain through monocytes, it targets specific pathways of the brain, such as the basal ganglia and other white matter tracts (Harezlak et al.,
2011). These pathways represent sub-cortical areas of the brain, and cognitive neuropsychology links these areas to impairments seen in executive functioning, motor skills, speed information processing, episodic memory, and more (Sanmarti et al., 2014). Because these are the components that are measured in neuropsychological assessment of HAND, it seems likely that milder classification on HAND stems from infection of sub-cortical areas of the brain.

There have been some human research studies done to confirm the link between neurotoxins and cognitive deficits. A study by Ernest and colleagues questioned whether an imbalance in glutamate, an excitatory neurotransmitter could cause neuronal injury (Ernst, Jiang, Nakama, Buchthal, & Chang, 2010). The study purported that an increase in extracellular glutamate could be due to HIV infecting the reuptake of astrocytes as well the increase of macrophages that produce said neurotransmitter (Ernst et al., 2010). At the same time, the authors explained that the decreased reuptake of astrocytes would lead to poor recycling of glutamate back into the cells: the result would be excess glutamate in the extracellular space, but a net loss in the neurons (Ernst et al., 2010). Ernest and colleagues took a group of 45 HIV-positive individuals and compared their glutamate concentration in the basal ganglia, grey and white frontal matter, and grey parietal matter to those of 46 controls; they also investigated the association of glutamate concentration in the HIV group and performance on neuropsychological tests (Ernst et al., 2010). The results proved insufficient to support the hypothesis that HIV patients had lower glutamate levels in the parietal and white matter regions compared to controls, but they did find that for both the HIV and control group, poor performance on neuropsychological testing was associated with lower glutamate (Ernst et al., 2010). In addition, HIV participants had glutamate levels in the parietal lobe that were equivalent to the levels of control subject ten years older; the study concluded that lower glutamate may contribute to cognitive deficits (Ernst et al., 2010). These findings corroborate a
recent Harvard study that found increased glutamate levels in the cerebrospinal fluid (CSF) of HIV-positive participants with neurocognitive impairments, as compared to those who did not show impairments (Cassol, Misra, Dutta, Morgello, & Gabuzda, 2014).

Further studies have assessed how antiretroviral therapy limits HIV’s effect on the brain. Clearly the severity of HAND is determined by the level of cognitive impairment; it is known that those on ART are at a decreased likelihood of HAD, but may still endorse other forms of HAND (Saylor et al., 2016). This can be attributed to the permeability of the BBB. A study by Letendre and colleagues in 2009 believed that the effectiveness of anti-retroviral viral (ARV) drugs to treating CNS infection was based on if the drugs could move through the blood-brain barrier, just as HIV monocytes are purported to do (Letendre et al., 2009). To this end, the researchers developed a rank system of different combinations of ARV drugs based on the reduction of viral load in the cerebral spinal fluid; this ranking system was labelled CNS Penetration Effectiveness, or CPE (Letendre et al., 2009). This was one the first studies undertaken to look at the effect of antiretroviral therapy on the brain: the researchers used a cohort group enrolled in the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER), a large prospective study of HIV patients receiving treatment (Letendre et al., 2009). The drugs used by patients were categorized into a CPE rank, with 0 = lowest penetration into the CNS, 0.5= intermediate penetration, and 1 = highest penetration. The final rank was calculated by averaging the individual penetration ranks (Letendre et al., 2009). The estimation of effectiveness proved conclusive: for the 467 participants analyzed, lower CPE ranks (i.e. drugs which had difficulty getting through the BBB to the brain) correlated with higher CSF viral loads, and when patients with a CPE a rank less than 2 were compared to those with a CPE rank of two or greater to assess detectable CSF viral load, the odds ratio was 1.88, meaning an 88% increase in the odds of having detectable CSF viral load in the former group.
(Letendre et al., 2009). In continuing with this work, Letendre applied the CPE rank to the
development of HAND and suggested a high CPE drug regiment would lead to better patient
performance on neuropsychological assessments, compared to low CPE regiment (Letendre, 2011).
Other studies, such as the one by Tozzi and colleagues, supported this association between CPE
and neuropsychological performance and concluded that anti-retroviral therapy with high CPE
ranking could in effect improve cognitive performance (Tozzi et al., 2009). There was however a
study that used magnetic resonance spectroscopy to measure HIV in the brain; no effect of CPE on
ART was found on cognitive impairment or CNS inflammation (Harezlak et al., 2011). In this
study it was found that there was a decrease in frontal white matter in the neuro-asymptomatic
group, which ties into previous discussion about the white matter decrease in milder forms of
HAND (Harezlak et al., 2011). These studies of HAND utilized biomarkers of the brain to come up
with conclusions for the pathology of HAND, and this is useful for understanding how
neurocognitive impairment develops. In terms of assessing HAND, the focus will be less on
biomarkers and more on the cognitive assessments of used in neuropsychology.

2.3 Neuropsychological Testing

One of the early uses of cognitive assessments was to evaluate brain injury at wartime, one specific
test was the Trail Making Test (TMT), which was original part of the Army Individual Test Battery
in 1944 (Harvey, 2012; Tombaugh, 2004). To complete TMT, a person is presented with a paper
with numbered dots, and using a pen/pencil the person draws a line starting from dot “1” to dot
“2,” and continues in sequential order until reaching the last numbered dot; the examiner assesses
performance based on time to completion (Periáñez et al., 2007). TMT has enjoyed popular use in
many test batteries, and it highlights common features of testing: objective, performance-based,
and structured to have participants use their skills in the presence of an examiner (Harvey, 2012).
In regards to HAND, neuropsychological assessment is the standard for a diagnosis, though its application to real-world impairment has been questioned by some (Ranka & Chapparo, 2010). One HAND study had 673 HIV-positive patients undergo a comprehensive battery, but considered two differing methods to assess functional (“real-world”) impairment: self-reported and performance-based. (Blackstone et al., 2012). 233 of the patients were diagnosed with HAND based on the comprehensive battery, and so the authors sought to identify which method of assessment would yield the highest proportion symptomatic HAND. Of interest, those classified with functional impairment through the performance-based method were more likely to be unemployed, more immunosuppressed, and have more hepatitis-C confection; those classified with just the self-report method were more depressed (Blackstone et al., 2012). In this way, researchers observed the different characteristics captured by performance-based characteristics compared to self-report: the former characterized a demographic-risk profile while the latter characterized a behaviour-risk profile. Ultimately, it was found that combining self-report measures with performance-based ones was the most effective way to capturing symptomatic HAND, with 53% of participants positively identified, rather than relying one method alone (Blackstone et al., 2012).

Although Blackstone and colleagues demonstrated the usefulness of self-report, some would still maintain that assessments based on self-reporting run the risk of being biased by the condition of interest, whereas performance-based reports have more value because conditions are standardized and compared with established norms (Harvey, 2012). The normative comparison is essential; individuals with suspected neurocognitive impairment must have their neuropsychological performance compared to a reference group, usually of the same age, race, sex, and educational attainment (Harvey, 2012). This comparison allows for the raw score of performance to be converted to a value on the normal distribution, though only if an appropriate reference group is
culturally tailored to the study population (Chibanda et al., 2014). When standardizing performance, a general rule that clinicians use to determine a meaningful difference between levels of impairment (non-impaired vs. impaired) is 0.5 standard deviations; while some severe conditions require a more substantial difference, this does appear to hold true for observable differences (Harvey, 2012). Dementia from Alzheimer’s Disease for example is diagnosed for patients if memory performance is below 3 standard deviations of the norm: the “standard deviation” assessment is relevant to previous studies of HIV/AIDS, because at a time clinicians operated under the assumption that HAD (or AIDS Dementia Complex) was the only type of neurocognitive impairment from HIV (Harvey, 2012; Sanmarti et al., 2014).

At the time when neurocognitive impairment was included only the HAD category, clinicians could use the classical criteria of dementia to obtain a clear diagnosis. From the neuropsychological perspective, the “classical criteria” for dementia requires memory impairments in addition to other cognitive and functional impairments; this would be a differential diagnosis from amnesia, which requires only memory deficits (Harvey, 2012). This means multiple tests must be used to measure performance in multiple cognitive domains. However, a comprehensive study of HAND by Grant and colleagues in 1987 showed patients could endorse objective neurocognitive impairment at all stages of HIV disease, starting from medically asymptomatic HIV to the AIDS stage (Grant et al., 1987; Woods et al., 2009). Starting in 1991, a new classification branched off from HAD: minor cognitive motor disorder (MCMD) which was described as impairment that slightly interfered with everyday functioning, but did not meet the classical criteria for dementia (Sanmarti et al., 2014).

Mild cognitive motor disorder is no longer heavily cited in literature of HAND. A revised criteria of HAND was created in 2007 in Italy, from a refinement done by the HIV Neurobehavioral
Research Center (Antinori, Arendt, Becker, Brew, Byrd, Cherner, Clifford, Cinque, Epstein, et al., 2007). This criterion, used almost globally, recognizes three types of HAND: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV Associated Dementia (HAD) (Antinori et al., 2007; Sanmarti et al., 2014; Woods, More, et al., 2009). Each of the three types has its own neuropsychological threshold for determination, as described below:

Asymptomatic Neurocognitive Impairment: Impairment in cognitive functioning, involving at least two ability domains, documented by performance at least 1 standard deviation below the mean for age and education norms on standardized neuropsychological assessments. (Antinori et al., 2007; Sanmarti et al., 2014)

Mild Neurocognitive Disorder: Impairment in cognitive functioning, involving at least two ability domains, documented by performance at least one standard deviation below the mean for age-education-appropriate norms on standardized neuropsychological test. To further distinguish this impairment from ANI, cognitive impairment must produce mild interference in daily functioning. (Antinori et al., 2007; Sanmarti et al., 2014).

HIV Associated Disorder: Impairment in cognitive functioning, involving at least two ability domains, usually more. Can be assessed in tests of learning of new information, information processing, and attention/concentration. Performance should be in at least two domains, with 2 standard deviations or greater than mean performance. (Antinori et al., 2007; Sanmarti et al., 2014).

A popular test battery for HAND evaluation in many international settings is the Memorial Sloan Kettering (MSK) staging for dementia (Robertson et al., 2009). Although meant for dementia, the MSK can generate a stage scale of 0.5-1 for MND and 2.0 or greater HAD (Antinori et al., 2007). However, a HAND diagnosis requires not just performance assessment, but an assessment of
functional or “real-world” impairment which cannot be directly assessed by neuropsychological tests (Antinori et al., 2007). HIV-positive patients would therefore need to complete neuropsychological assessments as well as functional assessment measures to receive a diagnosis of ANI, MND, or HAD; functional assessments may include: self-report, a questionnaire such as the Patient’s Assessment of Own Functioning Inventory, or reports from significant others and caregivers (Woods, Moore, Weber, & Grant, 2009). As previously mentioned, a mixed methods approach of self-report and performance based assessment seemed to best identify the symptomatic cases of HAND, although the former contains some bias (Blackstone et al., 2012; Harvey, 2012). The literature of HAND assessment remains quite divided on how much consideration to give self-report over neuropsychological assessment. Self-report assessment has been criticized as lengthy and thus impractical in low-resource clinics; also a psychiatric illness like depression may lead HIV-positive patients to over-report symptoms (Woods et al., 2009). This is actually consistent with the finding from Blackstone’s study, which found self-reported measures were associated with HAND patients who were depressed (Blackstone et al., 2012). Because ANI is distinguished from MND and HAD mainly by the lack of reported daily life impairment (Antinori et al., 2007), over-reporting symptoms could mislead clinicians to underdiagnose cases of ANI. This is the reason neuropsychological assessments with standardized scores remains an important requirement for HAND.

There are other controversies in terms of the validity of the current criteria. For example, Torti and colleagues questioned the incorporation of ANI into the HAND classification (Torti, Focà, Cesana, & Lescure, 2011). In their critique of ANI, the authors pointed out that ANI is categorized by performance below one standard deviation in at least two cognitive area; even in the general population of HIV-negative persons, a normal distribution of test performance would classify 16%
of the people —“abnormal” by this criteria; Torti based this assertion from a study from the *BMC Infectious Disease* journal which gave the actual overestimation as 20% (Gisslén et al., 2011; Torti et al., 2011). Furthermore Torti et al., (2011) argued that because ANI is characterized by a lack of functional deficits, the overestimation of ANI has no meaningful value, and may even lead to unnecessary anxiety and depression to patients who are given this diagnosis. Gisslén and colleagues proposed a solution to eliminating the overestimation of ANI burden is to have a cut-off of 1.5 standard deviations below the mean performance of the neuropsychological tests (Gisslén et al., 2011), though this viewpoint has yet to be readily adopted.

It seems that clinicians will need to reconcile the confusion about how to properly diagnose the milder categories of HAND, especially since use of ART appears to have reduced the prevalence of HAD (Rosca et al., 2012). While ANI still has its complexity in diagnosis, one study in Thailand by Chalermchai and colleagues attempted to better distinguish MND from HAD; this was done using the International HIV Dementia Scale or IHDS (Chalermchai et al., 2013). The IHDS was developed in 1995 to screen for HAND and has been used all across the globe because of its brevity and efficiency of assessment (Dang et al., 2015). However, there was concern that the effectiveness of IHDS was limited to only demented patients (those with HAD), and so Chalermchai considered how individual tests—not just full assessments—could increase the power of diagnosing the milder categories of HAND, namely MND (Chalermchai et al., 2013). From a study of 75 seropositive Thai participants, the study revealed illuminating results: IHDS alone was poor at predicting symptomatic HAND in the sample, but when combined with Trail Making Test (the task of connecting dots with a pencil) the net sensitivity and specificity of MND was calculated at 86% and 79% respectively (Chalermchai et al., 2013). This has promising application for the direction of neuocognitive testing of HAND: if a relatively short test like the Trail Making Test be
can be incorporated into a battery for effective MND diagnosis, then it can be used in settings that may not have the resources for lengthy assessments, and it can identify milder forms of impairment that plague everyday functioning.

Chalermchai’s findings may also promote the use of neuropsychological assessment where it is not as popular. While the ideal assessment should be done with a comprehensive battery of different tests, the reality for most healthcare workers is that consultation with patients may be time-limited (Cysique, Murray, Dunbar, Jeyakumar, & Brew, 2010; Rosca et al., 2012). Cysique and colleagues recognized the issue of detecting HAND in HIV patients and at the same time keeping the assessment brief, so they developed a screening algorithm (Cysique et al., 2010). The screening algorithm was created based on the risk factors the authors researched for HAND: this included age, educational achievement, plasma viral load, previous CNS infection, hemaglobin levels, HIV infection duration, CPE rank, and duration current ART regimen (Cysique et al., 2010). The authors applied their tool to screen 97 HIV-positive patients in the advanced stage, and it was met with an accuracy of 78%, when compared to the “gold standard” of neuropsychological testing. The authors were optimistic that their derived algorithm could be put on a web-based forum, in which a physician only needs to input the independent variables of the algorithm to compute a prediction of HAND (Cysique et al., 2010). This sort of study highlights the growing desire for assessments to be brief and concise, yet still maintain the accuracy of a long battery of neuropsychological tests. Should researchers choose to pursue this method of HAND diagnosis found by Chalermchai and others, it will be important to select neuropsychological assessments that will measure cognitive domains most often affected by HAND. Cognitive neuropsychology usually looks for at multiple domains in HAND assessments and these include motor skills, language, memory, attention, visuoperception, and executive functioning (Woods et al., 2009). On
careful consideration however, it has been shown that some domains may be less impacted by HAND, particularly the milder categories. For example language impairments seem to be a common feature in HIV-infected children as they develop, but generally unremarkable in an adult population (Woods et al., 2009). Similarly, motor skills seem to be evident only when HIV-infection reaches dementia levels (Woods et al., 2009), and therefore may be impractical for ANI and MND assessment. On the other hand, a cluster analysis by Dawes and colleagues demonstrated that impairments in the executive function are most prominent in all types of HAND profiles (Dawes et. al, 2008). This would explain Chalermchai’s results, because Trail Making Test is a test that taps into executive functioning components (Chalermchai et al., 2013). The Stroop Colour-Word Test, another test of executive functioning, has shown effectiveness as part of neuropsychological assessment; the performance of HIV-positive participants has shown to be significantly slower than controls (Woods et al., 2009). Similar to Trail Making Test, the Stroop Test is a relatively short test where performance is time-based: those completing the “Colour-Word” section are asked to read aloud the colour that a word is printed in, disregarding the actual word (Van der Elst, Van Boxtel, Van Breukelen, & Jolles, 2006). The words are “red” “blue” and “green,” however they are printed in a colour contrary to the word itself: for example the word “red” would be printed in blue ink, and so the reader should say “blue” aloud to earn a correct response (Dalrymple-Alford & Budayr, 1966). This introduces the concept of interference within executive functioning, as the subject must focus his/her concentration on the colour, ignoring the “interference” that is the colour-word discrepancy (Van der Elst et al., 2006). Use of such tests of executive functioning may be the key to better distinguishing the different categories.

Despite the fact that the issues of testing are far from resolved, information from this review is of great benefit, even in places where there less neuropsychological testing is implemented.
2.4 HAND in Sub-Saharan Africa

Understanding the burden HAND in Ghana requires appreciation of the research conducted in all Sub-Saharan Africa. The predominant sentiment is there is not enough use of neurocognitive assessment in many African countries; it would be ideal if ART clinics had the capacity to administer screenings, but this is not the norm in low-income countries (Chibanda et al., 2014). While it may seem counterintuitive that the continent with the highest burden of HIV does not have an abundance of HAND research, the limited focus is reflective of the lack of attention into mental health in Africa (Breuer et al., 2011; Lekoubou, Echouffo-Tcheugui, & Kengne, 2014). One study by Siakwa and colleagues highlights the need for this to be address mental health in Ghanaians HIV patients: 70% of the 206 HIV clients investigated had some kind of mental disorder, the most common being anxiety, depression, and manic episodes (Siakwa et al., 2015). Issues of mental health have strong ties into cognitive impairments in HIV-positive Africans, so it is important to study both concurrently. One study in Nigeria compared 149 HIV-positive patients to 58 HIV-negative participants: in addition to worse performance on cognitive tests, the HIV-positive patients also scored higher on depression scales (Royal et al., 2016). There is some possibly that the lack of attention to cognition and mental health in HIV-positive Africans is because currently the public health goal is to end HIV/AIDS, rather than addresses chronic symptoms from CNS infection. The World Health Organization (WHO) have concentrated on ending the AIDS epidemic by 2030, as part of the tasks set by the Sustainable Development Goals (SDG) (WHO, 2015). In its progress report the WHO lists three objectives to address this goal. The first objective is to have a seventy-five percent reduction in HIV incidence, with no new cases for children. The second objective is to reduce the annual number of people dying from HIV to less than 500,000. The third objective is to have ninety percent of HIV-infected people to be aware of their status (WHO, 2015).
The three main goals are essential to decreasing HIV-mortality, and explain why studying HAND may be given a lower priority, particularly in Africa. However while the lesser forms of HAND (ANI and MND) may not be deemed life-threatening, dementia from HAD is associated with reaching the AIDS stage of HIV infection (Clifford & Ances, 2013). The burden of dementia is not well-appreciated in the region, but a systematic review in 2014 indicated the prevalence of men with dementia ranged from 1 to 47.8% in hospital-based studies, coming from 11 African countries (Lekoubou et al., 2014). Because the proportion of elderly people is predicted to rise in the next years, many researchers expect dementia to become a major health concern in Africa; some studies have reported that already the prevalence rates are comparable to that of Western countries (Olayinka & Mbuyi, 2014). Another systematic review in Africa indicated in psychiatric consultations in hospitals in sub-Saharan Africa, 17% of referrals were from dementia, specifically due to HIV (Breuer et al., 2011).

Besides systematic reviews, insight can be gained from participant-based studies, like one done by Robertson and colleagues in Uganda (2007). 110 HIV-positive Ugandans in various stages of HIV were assessed on neurocognitive tests of attention, mental flexibility, memory, and motor functioning, with results compared to HIV-negative controls (Robertson et al., 2007). A diagnosis of AIDS dementia stage had to be based on a score of 1 or greater on the Memorial Sloan Kettering dementia scale, poor performance in two cognitive domains, and an endorsement of functional impairment. As expected, progression of HIV stage was associated with poorer performance on cognitive tests, with those reaching in the AIDS stage endorsing the most functional impairment. This study not only highlighted the characterization of performance in HIV-dementia, but also proved that the deficits in HIV were comparable to the developing world; this is despite the
prominent HIV clades in Uganda being A and C, and not clade B as in the developed world (Robertson et al., 2007).

Although dementia is a frightening outcome from HIV, the prevailing assertion from many investigators is HIV associated dementia has gone down with the introduction of ART in Africa (Heaton et al., 2011). However, when one considers the full range of cognitive disorders, there will likely be some manifestation, regardless of ART use. Meta-analysis of seven African countries showed that HIV is a major predisposing factor for NCI, potentially burdening 8.1 million people (Habib et al., 2013). However, the International HIV Dementia Scale (IHDS) does not access milder forms of NCI such as Mild Neurocognitive Disorder (MND) (Habib et al., 2013). This is the main disadvantage with the IHDS: it does not accurately estimate the burden of NCI, unless the impairment is severe enough to be categorized as dementia. And in both the U.S. and sub-Saharan Africa, use of ART has improved neuropsychological function such that dementia is less common with HIV (Saylor et al., 2016). In this regard, the problems discussed concerning appropriate HAND screening assessments are not unique to the developing world.

There remains the controversy as whether western norms can be assimilated into neuropsychological testing in Africa. Clinicians assert that no HAND screening tool is sufficient across all practice settings, and that limited resources and lack of trained clinicians should be considered before using neuropsychological assessments (The Mind Exchange Working Group, 2013). More pressing is the decision to use test batteries despite potential culture and language barriers (Chibanda et al., 2014). Kanmogne and colleagues were aware of these issues, but they chose to pilot a remarkable study in Cameroon to challenge the idea that Western neuropsychological norms could not be applicable in Africa (Kanmogne et al., 2010). To this end, the authors conducted a cross-sectional study with 44 HIV-positive Cameroonianians and matched
controls undergoing a neuropsychological battery of 19 tests; the test measures would not only measure the effect of viral load on different cognitive domains, but explore the validity of the test on Cameroonian. It is of note that once the tests were translated into French, participants had no trouble understanding examiner instructions. There were several important findings from the mean standardized-z score performance of participants: age and education were the two demographic variables with most influence on mean scores (with older age and lower education predicting low scores). Also, significantly lower performance was observed in the HIV-positive group on tests of executive function, speed of information processing, working memory, and psychomotor speed. Finally, patients in the AIDS subgroup performed significantly worse on the tests than those in less advanced stages. These findings are truly beneficial for Africa, because it brings more assurance that assessment of HAND can still be implemented in a cohort of Africa patients regardless of cultural and language differences; this would facilitate exploration of HAND in Ghana, particularly in a limited resource areas. The one limitation however is having a trained neuropsychologist who could properly administer the assessment and have the tests translated to the desirable language or dialect.

Other studies have supported Kanmogne’s findings, albeit with some limitation. The study in Nigeria done by Royal and colleagues (2016) used similar western tests to assess NCI in seven domains, and though they did find HIV-positive patients to exhibit impairment, they acknowledged that some of verbal tests needed adjustment to adapt to the cultural differences in Nigeria. Western test batteries may eventually become more applicable in sub-Saharan Africa, with some reasonable modification. However, it is far from being widely accepted as an international metric for HAND, and currently the gold standard appears to be the International HIV Dementia Scale, which is lauded for its easy use in an Africa setting (Dang et al., 2015). The problem, as discussed earlier, is
how to reconcile use of the IHDS with its lack of robustness for milder NCI, such as ANI and MND.

Although there is no definitive answer to this issue, the adoption of screening tools for HAND is a necessity for the progression of HAND research, and Ghana may take inspiration from what neighboring countries have accomplished. For example South Africa, home to one the largest HIV-positive populations, has made efforts to validate international screening tools for HAND. (Vally, 2011). One study used the IHDS for general HAND diagnosis in HIV-positive South Africans, and the results confirmed previous literature that incorporating brief executive functioning tests with the IHDS can improve the accuracy of HAND diagnosis (Joska et al., 2011). In corroboration, Singh and colleagues sought to use the Trail Making Test and the Digit Span test (a test in which an examiner reads out numbers and the participants must say them back in the correct order) in combination with the IHDS to diagnose the progression of HAND in South African patients; however it was imperative to produce normative scores for the two selected tests, based on age and gender (Dinesh Singh et al., 2010). These few studies haven’t been replicated on a continental scale to increase the frequency of incorporating brief screening tools for HAND assessments.

A study in 2016 by Dr. Samuel Adjourlolo from the City University of Hong Kong may help these assessments gain traction in Ghana; this study investigated whether socio-cultural difference between the Western world and Africa may make standardization of tests in Ghana difficult (Adjourlolo, 2016). There is a concern that the influence of setting/culture can affect neuropsychological performance (Robertson et al., 2010) and assessments that are not validated in the specific region of use have low generalizability (Breuer et al., 2011). However Adjourlolo believed that since the utility of western neuropsychological tests could be applied to certain minority groups (i.e. African-American), by extension it could apply to a Ghanaian cohort
Adjorlolo, 2016). His focus was on neuropsychological assessment of patients with traumatic brain injury, using the Trail Making Test, Stroop Test, and Controlled Oral Word Fluency (COWAT) in diagnosing injury; ROC analysis was used to determine how well the tests discriminated the brain injury patients from a similar group of uninjured controls (Adjorlolo, 2016). The area under the curve (AUC) values were all greater than 0.73, indicating very strong sensitivity for brain injury; this supported the author’s idea that neuropsychological tests used in the western world could still be a strong diagnostic tool for a Ghanaian population (Adjorlolo, 2016). Even though this study looked at brain injury, it is noteworthy that all three of tests Adjorlolo used were tests of the executive function domain, and Woods and colleagues made mention that HAND is primarily linked to deficits of this domain (Woods et al., 2009). This suggests that the tests could be reliable for HAND assessment in Ghana. However, other studies have been cautious with the approach of adopting western norms. Robertson and authors cited an on-going study in Zambia in which HIV-positive Zambians were tested with the HIV Neurobehavioral Research Center test battery, using African-American norms as a substitute for country-specific norms; even when adding a constant to the scaled scores to adjust for demographic effects, the authors still felt that there was demographic bias, and norms specific to Zambia should be have been used for more validity (Robertson et al., 2010). Nevertheless the use of these norms showed 33% of HIV-positive patients had cognitive impairment, compared to 15% of controls; this is more than double the proportion and is worth considering (Robertson et al., 2010).
CHAPTER THREE: METHODOLOGY

3.1 Study Area
The concern for this investigation was to have access to a population of HIV-positive Ghanaians who could undergo neuropsychological assessments as well as complete questionnaires regarding demographic and psychobehavioural characteristics of interest. One of the variables of interest was compliance to ART medication, because use of medication for HIV is strongly linked to lower risk of HIV-associated dementia. Because of this, the ideal site for the study would be place in which patients would go to receive ART drugs.

Ridge Hospital in Accra, Ghana is one of the leading hospitals in Accra. Within the hospital, there is an HIV clinic (otherwise known as an ART clinic) run by healthcare workers that provides services such as HIV/STI testing and provision of medication through the pharmacy. The clinic runs during the weekday, serving approximately 30 clients a week. The actual number of clients may vary depending on when the next prescription of medication is needed: for certain months, the clinic may have hundreds of clients come in to pick up medication. The client pool is mostly female, though of various socio-economic levels and ages. With all this in consideration, Ridge Hospital appeared to be an ideal place to recruit participants for an investigation, with the advantage that participants could be questioned on their adherence to medication.

3.2 Study Design
This was a cross-sectional exploratory study, using questionnaires and neurocognitive tests to collect quantitative data from HIV-positive patients recruited from the HIV clinic at Ridge Hospital. The data collected included neurocognitive test performance scores and behavioural scale ratings, in addition to demographic characteristics. The data were collected during the month June of 2017.
3.3 Study Population and Sampling

The current register of HIV-positive clients who attend the Ridge Hospital for counselling and ART medication was not known by the staff, but it was estimated that between 100 to 200 people presented themselves to the clinic each month (this included those coming in for HIV screening, and those coming in to pick up medication for a client.) Given the limited timeframe to collect data and the unpredictable nature of when clients came to the clinic, it appeared feasible to invite all clients who came into the clinic during the study period to participate in the study, rather than use a probability-based sampling method such as random sampling. This type of convenience sampling used would allow the maximum amount of people to be recruited into the study. In past studies of HIV, convenience sampling as well as snowball (‘respondent-driven”) sampling were frequently used to estimate hard-to-reach population variables (Beyrer et al., 2012). An HIV diagnosis in Ghana still carries some social stigma that make the population attending the HIV clinic hard to reach; for example, it was reported by Ridge staff that many clients (particularly wealthier men) do not present themselves in-person to obtain medicine, but rather have it delivered or picked up to avoid the risk of exposing their HIV status to the public. It would not be possible to sample from the list of clients that Ridge had in their registry: the study would only have access to those clients that presented themselves in-person during the study period. A 2005 review of sampling techniques in HIV surveillance showed that convenience sampling, while simple and effective for mass recruitment of hard-to-reach populations, is subject to large selection bias (Magnani, Sabin, Saidel, & Heckathorn, 2005). Another study in 2010 reviewed sampling methods used to estimate HIV prevalence rates among female sex workers; in studies using convenience sampling, the sample size was usually not enough to estimate prevalence (Pascom, Szwarcwald, & Júnior, 2010). With this current study however, the aim is not to use findings to estimate NCI prevalence or survey the HIV distribution of Ghana, as done in previous studies. Rather the study aimed to be the first
exploration undertaken in Ghana to look at trends in neurocognitive performance in a group of HIV-positive persons, with the hope of generating future studies of how to estimate the true prevalence of cognitive impairment. Given that this was ultimately an exploratory study with no set hypothesis, convenience sampling was deemed to be compatible with the research goals. Thus, all eligible patients were recruited into the study for the full month of data collection.

3.4 Inclusion/Exclusion Criteria

The inclusion criteria were adults (18 years and older) who had received a diagnosis of HIV. The inclusion was purposely broad to accommodate the convenience sampling that was done.

The exclusion criteria were clients younger than 18, as well as anyone with a prior diagnosis of major psychiatric disorder, or a history of severe head injury. This was to limit factors that could contribute to cognitive impairment, independent of HIV.

3.5 Study Tools

All the materials were in the form of paper-based questionnaires and performance measures. For the demographic profile, a questionnaire was given for patients to fill out. The questionnaire obtained the following patient characteristics: age, sex, current employment status, and education level. In addition, the years subject had been living with HIV (since the current year of 2017) and current drug regimen were verified from their health records for each patient completing this questionnaire.

The Psychobehavioural and Neurocognitive profile for the participants was obtained through six questionnaires and assessments.
3.5.1 Center for Epidemiologic Studies Short Scale Depression Scale (CES-D)

This is a 10-item depression scale. Each item prompts a participant to respond to a question about instances of certain behaviours or feelings, with available responses ranging from “rarely or none of the time” to “all of the time.” A certain number of points (ranging from 0-3) is assigned to each response and the score is the total number of points for all ten items. A score of ten or greater is considered depressed. This test by itself does not constitute a clinical diagnosis or healthcare recommendation (Radloff, 1977).

3.5.2 Alcohol Use Disorders Identification Test (AUDIT)

This is a 10-item screening tool used to assess alcohol consumption, drinking behaviours, and alcohol-related problems. This tool was invented by the World Health Organization (WHO) and has been well-validated across gender groups and a wide range of ethnic and racial groups. There are two versions of the test: a clinician-administered version and self-report, from which the study opted for the clinician-administered version. Participants endorse a response to each question about the frequency of certain drinking behaviours, and a certain number of points is assigned to each response. A score of 8 or more is generally considered indicative of harmful alcohol use.

3.5.3 Questionnaire on Taking Anti-retroviral Medication

This brief questionnaire was developed by Godin and colleagues (2003) and asks participants in non-accusatory language about any tendencies to forget to take medication, or opt not to take medication. The questionnaire comprises of 5 sections, first asking participants to name the medications being taken (if participants are unsure of names, medical records can confirm), and asks about specific instances in which medication was not taken and possible reasons attributed to not taking medication (i.e. visiting family, going out for a leisurely activity) (Godin, Gagné, & Naccache, 2003). Scores can be calculated based on number of pills missed during a certain period.
3.5.4 Trail Making Test (TMT) Part A

This neuropsychological test is a timed test in which participants use a pen. In Part –A,” the participant is to draw lines to connect circled numbers in a numerical sequence (i.e., 1-2-3, etc.) as rapidly in possible. They are first given a sample (“Sample A”) to practice before proceeding to the actual test, in which their time to completion is measured. This test is cited to reflect a wide variety of cognitive processes in addition to executive functioning: attention, visual search and scanning, sequencing and shifting, psychomotor speed, abstraction, flexibility, ability to execute and modify a plan of action, and ability to maintain two trains of thought simultaneously. The Trail Making Test is noted for good reliability, given by an inter-rater reliability coefficient of 0.99 for TMT A (Cangoz, Karakoc, & Selekler, 2009). It should be noted however, that this coefficient was generated from studies using Western norms; there has not been such reliability measures generated among a Ghanaian study population. However, a 2016 study from the City University of Hong Kong did look at the diagnostic accuracy of executive functioning (EF) tests in Ghana for traumatic brain injury patients; the Trail Making Test scores showed good accuracy in diagnosing brain injured Ghanaians from controls (area under curve values ranging from 0.746 to 0.902) (Adjorlolo, 2016). Though the impairment from traumatic brain injury may not be the same as that from HIV-associated neurocognitive disorders, the fact that the TMT could be used to identify neurocognitive dysfunction in Ghana holds promise in terms of its reliability for this study.

3.5.5 Stroop Colour-Word

The traditional Stroop test contains three components: The focus of the study is the Colour–Word task, in which the individual is shown the names of colours printed in conflicting ink colours (e.g., the word –blue” in red ink) and is asked to name the colour of the ink rather than the word as quickly as possible. The Colour–Word task is the component that is believed to measure both
mental flexibility and the ability to inhibit a dominant response, because of the interference that the word is printed in a conflicting colour (Homack & Riccio, 2004). The test-retest reliability coefficient for Colour Word has been cited to be 0.671 (Franzen, Tishelman, Sharp, & Friedman, 1987). Again, it should be noted that this coefficient was generated from studies using Western norms. The 2016 study from the City University of Hong Kong did show that, like with the Trail Making Test, the Stroop tests had high diagnostic accuracy for traumatic brain injury patients in Ghana (area under curve values ranging from 0.793 to 0.898) (Adjorlolo, 2016). This holds promise for the Stroop being a reliable tool for this study.

3.5.6 International HIV Dementia Scale

This is an internationally validated tool for diagnosing HAND in HIV-patients. The tool asks participants to perform memory and motor tasks, and should take no longer than 10 minutes to complete with participants. Some clinicians have a cut-off point of less than 10 as indicative of HIV-dementia, though it is by no means a conclusive test of dementia (functional impairment in daily life is required for diagnosis). Such patients would need further evaluation to determine whether a diagnosis of dementia is appropriate (Dang et al., 2015; Joska et al., 2011). Because there is no distinct measure to separate HIV-dementia from the milder forms of HAND, the IHDS cut-off point can be used to distinguish any form of neurocognitive impairment, not just dementia.

3.5.7 Katz Instrumental Activities of Daily Living (IADL)

Functional impairment (a key criterion to the assessment of HAND) was measured using the Katz Instrumental Activities of Daily Living (IADL) scale. This instrument assesses functional status as a measurement of the client’s ability to perform activities of daily living by himself or herself. The index ranks adequacy of performance in the six functions: bathing, dressing, toileting, transferring, continence, and feeding. Clients respond with a “yes” or “no” for their independence in each of the
six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment (Shelkey & Wallace, 2008).

3.5.8 Additional Notes on Assessments

Using neuropsychological assessments in this study area presented some challenge in the reliability in an African population. Two of the tests, TMT and Stroop Colour-Word, were selected for this study due to their relatively short time to administer and ease for an examiner.

Given the brevity of all assessments, it was estimated the time to completion should not exceed 20 minutes. This would put less burden on the time constraints the study participants who are only in the clinic to collect their medication. The assessments -only requiring a writing instrument, stopwatch, and a quiet space with a table with face-to face seating arrangement between subject and examiner. Although instructions should have been as standardized as possible to English, it was anticipated that there could be instances where instructions need to be reiterated in the local language for clarity. Due to this concern, we anticipated training the nurses on staff who were fluent in the local language (Twi) to aid with administration.

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Psychobehavioural</th>
<th>Neuropsychological</th>
<th>Functional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>CES-D Score</td>
<td>TMT Part A score</td>
<td>Katz IADL score</td>
</tr>
<tr>
<td>Sex</td>
<td>AUDIT score</td>
<td>Stroop score</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years living with HIV</td>
<td>ART pills missed</td>
<td></td>
<td>IHDS score</td>
</tr>
<tr>
<td>Employment Status</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1: List of Study Variables
The analysis was conducted with the purpose of achieving the research objectives listed for the study.

**Objective:** To create a profile summary of performance of HIV-positive persons on selected neuropsychological assessments.

**Analysis:** Summary statistics were performed on the data collected on participants and compiled to create a neurocognitive profile. Additionally, a demographic profile and psychobehavioural profile was used to further describe participant characteristics.

**Objective:** To determine whether the performance of HIV patients on tests of neurocognitive assessment is associated with neurocognitive impairment risk (as measured by the International HIV Dementia Scale.)

**Analysis:** Correlation test analysis was run to look at the relationship between neuropsychological test performance and scores on the International HIV Dementia Scale.

**Objective:** To examine how demographic and psychobehavioural factors are associated with risk of neurocognitive impairment.

**Analysis:** A linear regression analysis was used to assess the effect of demographic variables as well as factors for NCI (including neuropsychological and behavioural assessment) on patient IHDS score, currently considered a standard measure for NCI evaluation. Also, Receiver Operating Characteristic (ROC) analysis was used to assess how well various certain variables could distinguish that was a risk for neurocognitive impairment (based on the IHDS outcome). IHDS was designed to flag for HIV-associated dementia, but because the specific cut-offs for different types of HAND are not specified by the IHDS, this study classified NCI risk as a score below the IHDS threshold of 11.
3.7 Ethics

The safety, dignity, and privacy of the study group was taken extremely seriously. All tools used in study were non-invasive. The neurocognitive assessments required light physical activity (holding a pen, making hand gestures) that carried minimal to no risk of physical discomfort. However, the population in question was considered “high risk” due to the social stigma and marginalization often faced with HIV. In addition, because the assessments tools may indicate (but not conclusively diagnose) the presence of cognitive impairment, including dementia, resources needed be in place to ensure such patients had referrals for further clinical assessment. There may have been potential discomfort in answering questions and providing information of a personal nature. The study did all that was possible to minimize these concerns. Ethical issues were addressed as follows:

1. Ethical approval was sought from the Ghana Health Services, the National AIDS Control Programme (NACP), as well as permission from Ridge Hospital prior to study commencement.

2. Because assessments may indicate (but not diagnose) presence of dementia, the investigator utilized the services of Doctor Farida Abdulai (MD), medical officer at Ridge Hospital, such that any patient at risk for impairment was flagged and referred to the Dr. Farida Abdulai for follow-up.

3. Patient informed consent was obtained as pre-requisite to study enrolment.

4. During consent, patients was informed that all information being asked of them is voluntary.
5. During consent, patients were informed there are no benefits to be obtained from this study. In addition, refusal to complete assessments or questions was allowed, and had no consequence on a patient’s continued treatment or consultations at Ridge Hospital.

6. Upon data collection, all subject study forms (assessments and questionnaires) were de-identified. This was done by writing a unique alphanumerical ID on each subject’s completed form (–A4”). No other personal identification such as name or date of birth was written on the study forms. Only the consent form contained the subject’s full name as well as signature. The full name of the subject needed to be retained for the sole purpose of identifying those who may need to be referred for further NCI assessment. Consent and study forms were brought back from Ridge by the Principal Investigator after each day of data collection and stored in a locked cabinet.

7. Assessments and questionnaires were conducted by the Principal Investigator and/or the Ridge nursing staff to maintain confidentiality.

8. All study-related material (forms) have been slated to be destroyed after five years following end of study.

3.8 Procedure

The study was conducted at the ART clinic at Ridge Regional Hospital in June of 2017. The facility had tables and chairs for the examiner to conduct the consenting procedure and subsequent testing. A room was available (away from the other clients) to ensure privacy. During the study period, the clinic was undergoing a transition to a new facility in a building next door; while this presented some inconvenience for clients, it did not cause any major disruption for the study’s set up. Two nurses employed at the ART clinic were recruited to aid in data collection; a full two days
was spent training the nurses on how to collect consent and administer questionnaires and assessments. Only the Principle Investigator and the two nurses (always supervised) took part in the recruitment, consent, and administration of the study’s questionnaires and assessments. The main purpose of recruiting the nurses was to have assistance in verbally translating the consent form and questionnaires in Twi for the participants. Though all the participants had to have at least some grasp of the English language, it was ultimately necessary to communicate information in Twi to ensure the participant comprehended the study’s purpose, as well as the directions for completing the questionnaires and neurocognitive assessments. Translation to Twi was especially vital for clients who did not have a secondary school education. Recruiting nurses that were employed at Ridge (and thus familiar with the clients) proved to be beneficial, because clients were comfortable being approached for recruitment, and were more assured that their confidentiality would be maintained by the staff.

The procedure of study was to recruit as many HIV-positive clients as possible who came into the clinic to receive ART treatment or start their treatment. This was a type of convenience sampling, and it was done to allow data to be collected from as many clients as possible in the study timeframe; it was unknown how many people would present themselves at the clinic during the month of June. Generally, clients would be seated in a specific area as they waited for the pharmacist to call them for their medication; this was the period in which nurses and PI could approach them for recruitment. Persons who came into the clinic to undergo HIV/STI screenings were not approached, as their HIV status would be unknown at the time. As per ethical guidelines, the nurses assisting in the study were instructed to read the consent form in full to clients (translating in Twi, if necessary). It was emphasized during the consent process that there were no benefit to the client for enrolling, except the client would be providing valuable information for
research, and patients were free to decline participation or opt out at any time with no consequence to their treatment at Ridge Hospital. In addition, participants were told that while they needed to sign and print their full name on the consent form, their names and other personal identifiers would not appear on any other study forms; all participants would receive an alphanumeric ID that would be printed on their questionnaires and assessments; only this ID would be used in data entry and subsequent analysis. The printing of names with the signature was only necessary in the event the staff needed to follow-up with client after the study (specifically, referral to the Ridge doctor would be necessary if there was evidence of HIV dementia). Overall, the majority of clients were receptive to participating in the study once it was thoroughly explained to them. Only a few individuals declined participation, either due to limited time to stay and complete the study forms, or reluctance to print name on consent form.

Literacy was a major consideration for which clients to enroll. If clients were unable to read or write their name on consent form, they could not be considered for study. It was instructed to nurses that if participants declined to answer any question on the form, they should not be pressured, but rather reminded that everything in the study was voluntary and confidential. If participants still declined to provide responses, they were not pressed further, to avoid any confrontation or stress. Generally, most of the participants had no issue answering any of the questions, although there were a few who refused to answer the questions that they deemed too personal. In terms of the neurocognitive assessments, the participant’s ability to complete the tasks had to be considered. If a participant expressed strong frustration in completing a neurocognitive task, or if it was clear to examiner that the participant would not be able to either initiate or finish the task, the participant would be asked to stop and no response would be recorded for that item. Again, this was done to prevent any unnecessary distress for the clients or prolong their struggle.
For the two selected neurocognitive assessments used in the study Trail Making Test and Stroop Colour-Word, some participants expressed complete inability to correctly identify the printed numbers and colours respectively. As such, these assessments were skipped for them. All clients in the study were able to complete the International HIV Dementia Scale, to varying degrees of difficulty.

Although this study utilized convenience sampling, the study still adhered to the inclusion criteria (18 and older) and exclusion criteria (a prior diagnosis of major psychiatric disorder, or a history of severe head injury). It was confirmed by nurses that the clients met the criteria set forth in study, though no client needed to be turned away during the study period because of the exclusion criteria. As reported by nurses, all participants who came into the clinic were generally healthy, and were not in a terminal stage of HIV because they were on ART treatment. The Katz IADL questionnaire would serve to confirm that the participants were not so disabled to require assistance in daily functioning.
CHAPTER FOUR: RESULTS

4.1 Overview

After collection of data, all responses were imported to Stata (version 14.1) for summary and analysis. This will form the basis of the rest of this chapter. The demographic, psychobehavioural, and neurocognitive profile of the study group will be described in the next three sections. These will serve to address the first objective: to create a profile summary of performance of HIV-positive persons on selected neurocognitive assessments.

<p>| Table 2: Summary of Participant Characteristics |</p>
<table>
<thead>
<tr>
<th>N</th>
<th>Mean (S.D.)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>104</td>
<td>37.15 (10.06)</td>
</tr>
<tr>
<td><strong>Years living with HIV (years as of 2017)</strong></td>
<td>102</td>
<td>4.75 (3.84)</td>
</tr>
<tr>
<td><strong>CES-D Short Scale Score</strong></td>
<td>103</td>
<td>4.00 (4.47)</td>
</tr>
<tr>
<td><strong>AUDIT Score</strong></td>
<td>103</td>
<td>1.14 (3.21)</td>
</tr>
<tr>
<td><strong>ART pills missed in past week</strong></td>
<td>93</td>
<td>0.086 (0.318)</td>
</tr>
<tr>
<td><strong>TMT Score (seconds)</strong></td>
<td>102</td>
<td>69.77 (40.12)</td>
</tr>
<tr>
<td><strong>Stroop Colour-Word Score (# of words)</strong></td>
<td>93</td>
<td>21.08 (9.75)</td>
</tr>
<tr>
<td><strong>IHDS Total Score</strong></td>
<td>104</td>
<td>10.11 (1.58)</td>
</tr>
<tr>
<td><strong>Instrumental Activities of Daily Living</strong></td>
<td>104</td>
<td>6.00 (0)</td>
</tr>
</tbody>
</table>
4.2 Demographic Profile

Summary characteristics can be found in Table 2, and additional frequency calculations in Figure 2. A total of 104 participants were collected during the study period. The mean age of the group was 37.15 years (S.D. = 10.06). 22 (22.15%) of the participants were male, 82 (78.85%) were female. The education level (denoted as highest level of education completed) was distributed as follows: 42 of the participants had completed secondary school education (40.38%), 25 of the participants had some secondary school education, but had not graduated (24.04%), 16 of the participants had junior high school education (15.38%), 11 of the participants had university education (10.58%), 4 of the participants had primary school education, 3 had received some university education, 2 had never received a formal education, and 1 had completed graduate school.

Of the 104 participants, 87 (84.47%) were currently employed, although one subject opted not to disclose employment status. The average number of years living with HIV (as of 2017) was 4.75 years (SD = 3.84) for the 102 participants who disclosed this information. Of note, the nurses confirmed that the years of living with HIV coincided with the number of years participants had been receiving ART medication from the clinic.

4.3 Psychobehavioural Profile

Summary statistics can be found in Table 2, with additional frequencies in Figure 3. Depression risk was measured with the 10-item CES-D Short Scale. Higher scores indicate a higher risk of depression. Only one participant declined to undergo this questionnaire for personal reasons. The mean score for the remaining 103 participants who completed the CES-D Short Scale was 4.00 (S.D. = 4.46) with a range of scores 0 to 20.
Alcohol abuse was measured with the AUDIT questionnaire. Higher scores indicate a higher endorsement of alcohol use, with a score of 8 or more generally indicative of harmful alcohol use. The mean for the 103 participants who completed this questionnaire was 1.14 (S.D. = 3.21), which is a considerably low risk for alcohol abuse. It should be noted that 86 (83.5%) of the participants reported not taking any alcohol in the past year.
ART adherence was measured using Godin and colleagues’ questionnaire on antiretroviral adherence. ART adherence was noted to be exceptionally high in the group, with 86 participants (92.47%) having missed no pills in the past week, 6 participants (6.45%) having missed one pill, and only 1 participant (1.08%) missing two pills.

There were 11 participants who were recently diagnosed that did not complete this questionnaire, as they had yet to start ART regiment at the clinic. Clients who had missed pills attributed it to instances of forgetting. As this was a self-reported measure, there was no way to confirm the veracity of responses.

4.4 Neurocognitive Profile

A description of the Trail Making Test is in Figure 4. The score is measured by time to completion; thus a longer time indicates poorer performance. In this group two respondents had such difficulty
with the task that they could not complete it. For the remaining 102 participants, the mean score was 69.77 seconds (S.D. = 40.12). The range was from 18 seconds to 221.36 seconds.

A description of the Stroop Colour-Word is in Figure 5. The score is the number of colours (words) correctly named on the list in a 45-second time period, with more words named indicating better performance. This task was met with extremely difficulty for some participants, usually due to the inability to correctly identify the colour printed on the page. Some participants had to be excluded if they did not have sufficient literacy capacity to read out loud the words. In total, 93 of the participants were able to complete the task, with the mean performance being 21.07 words (S.D. = 9.75). The range for scores was from 5 words to 49 words.

A description of the International HIV Dementia Scale (IHDS) is in Figure 6. All 104 participants completed the IHDS scale and received a total score derived from the sum of the motor speed score, psychomotor speed score, and memory recall score. The range of scores is from 1 to 12, with lower scores indicating poorer performance. The IHDS indicates that a score below 11 should be flagged for risk of cognitive impairment. The mean score in the group was 10.11 (S.D. = 1.58). Given that a score below 11 is considered a flag for NCI risk, the mean score of 10.11 would suggest a large proportion of the group met the criteria for NCI risk. Table 3 shows the number of individuals who were either an NCI risk or not. It was shown that 50 of the 104 participants (48.08%) met the HIV dementia risk criteria based on their total score.
Participant is given a pen. First, he/she completes sample page (left). The actual test is timed to see how fast participant connects dots "1" to "25" (right).

Figure 4: Image of Trail Making Test.
Figure 5: Image of Stroop Colour-Word Test

Participant reads aloud the colours printed on the sample page (left). For the actual test (right), the words do not match the colour they are printed in. Participant has 45 seconds to read aloud the COLOUR the word is printed in.

Subject should say out loud: “blue”
Figure 6: Demonstration of the International HIV Dementia Scale Test.

For Motor Speed (left) participants must tap the two fingers together as quickly as possible for 5 seconds; points are awarded based on how many taps are done.

For Psychomotor Speed (centre) participants are shown a sequence of 3 hand movements, and must perform the same sequence of hand movements on the table as quickly as possible for 10 seconds. Points are awarded based on the number of correct sequences completed.

For Memory Recall (right) participants are asked to recall the four words they were given to memorise at the start of the test. Points are awarded based on how many words were correctly recalled. Total Score is the sum of the three tests.

Figure 7: Boxplot Summary of International HIV Dementia Scale (and subscales)
4.5 Statistical Analysis

Statistical analysis was conducted based on the last two objectives: to determine whether the performance of HIV patients on tests of neurocognitive assessment is associated with neurocognitive impairment risk (as measured by the International HIV Dementia Scale,) and to examine how demographic and psychobehavioural factors are associated with the risk of neurocognitive impairment.

A Pearson’s correlation test was generated between scores on the TMT (Trailing Making Test) and scores on the IHDS. For the TMT, the score is the time (number of seconds) to complete the task. A longer time indicates worse performance on the task. TMT was significantly correlated with HIV Dementia Score ($r = -0.3230$, $p<0.001$). The negative correlation indicated that the longer the time to complete the Trail Making Test, the worse the IHDS score.

A Pearson’s correlation test was generated between scores on the Stroop test and scores on the IHDS. For Stroop, the score is the number of words that the participant can correctly finishing reading in a 45 second time span. More words means better performance on the task. The Stroop score was significantly correlated with HIV Dementia Score ($r = 0.3572$, $p<0.001$). The positive correlation indicated that the more words completed, the better the IHDS score.
Table 3 shows a linear regression the outcome variable International HIV Dementia Score (IHDS Total) plotted against demographic variables (age, sex, education level, employment status, years living with HIV). Age and education level were the two demographic with a significant effect on IHDS score (age coefficient: -0.055, p < 0.001, education level coefficient: 0.413, p < 0.001).
To further investigate the relationship between education and IHDS score, a chi-square test was done to look at the association between educational level and the risk neurocognitive impairment, shown in Table 4. NCI risk was denoted by an IHDS total score below 11. There was a significant association between education level and HIV Dementia Risk ($X^2 = 15.32, p<0.05$).

Table 4: Association between NCI risk and Education.

<table>
<thead>
<tr>
<th>Education level</th>
<th>NCI Risk?</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No School</td>
<td>No: 0</td>
<td>Yes: 2</td>
</tr>
<tr>
<td>Primary School</td>
<td>No: 2</td>
<td>Yes: 2</td>
</tr>
<tr>
<td>JHS</td>
<td>No: 6</td>
<td>Yes: 10</td>
</tr>
<tr>
<td>Some Secondary School</td>
<td>No: 10</td>
<td>Yes: 15</td>
</tr>
<tr>
<td>Secondary School</td>
<td>No: 22</td>
<td>Yes: 20</td>
</tr>
<tr>
<td>Some University</td>
<td>No: 3</td>
<td>Yes: 0</td>
</tr>
<tr>
<td>University (first degree)</td>
<td>No: 10</td>
<td>Yes: 1</td>
</tr>
<tr>
<td>Graduate School</td>
<td>No: 1</td>
<td>Yes: 0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>No: 54</strong></td>
<td><strong>Yes: 50</strong></td>
</tr>
</tbody>
</table>

*Pearson $X^2$ (7) = 15.32, p value = 0.032*

Table 5 shows a linear regression plotting the outcome variable IHDS score against the psychobehavioural factors investigated (depression, alcohol use, ART.) Only depression (measured by the CES-D scale) had a significant effect on IHDS score in the regression equation (Coefficient: -0.082, p<0.05).
Table 5: Linear Regression Table for Psychobehavioural Factors Influencing IHDS total.

<table>
<thead>
<tr>
<th>IHDS Total</th>
<th>B Coefficient</th>
<th>S.E.</th>
<th>t</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CES-D Score</td>
<td>-0.082</td>
<td>0.038</td>
<td>-2.15</td>
<td>0.034</td>
<td>-0.158 – -0.006</td>
</tr>
<tr>
<td>AUDIT Score</td>
<td>0.045</td>
<td>0.054</td>
<td>0.84</td>
<td>0.402</td>
<td>-0.062 – 0.152</td>
</tr>
<tr>
<td>ART pills missed</td>
<td>0.387</td>
<td>0.527</td>
<td>0.74</td>
<td>0.464</td>
<td>-0.659 – 1.434</td>
</tr>
<tr>
<td>Constant</td>
<td>10.335</td>
<td>0.220</td>
<td>47.3</td>
<td>0.000</td>
<td>9.898 – 10.771</td>
</tr>
</tbody>
</table>

Adjusted $R^2 = 0.0304$

Table 6 shows a linear regression plotting the outcome variable IHDS score against the neurocognitive scores used (Trail Making Test and Stroop). Both tests had a significant effect on IHDS score in the regression (Trail Making coefficient: -.01, p<0.05; Coefficient: .046, p<0.01).

Table 6: Linear Regression Table for Neurocognitive Performance Factors Influencing IHDS.

<table>
<thead>
<tr>
<th>IHDS Total</th>
<th>B Coefficient</th>
<th>S.E.</th>
<th>t</th>
<th>P value</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMT Score</td>
<td>-0.0104</td>
<td>-0.004</td>
<td>-2.31</td>
<td>0.023</td>
<td>-0.019 – -0.001</td>
</tr>
<tr>
<td>Stroop Score</td>
<td>0.0461</td>
<td>0.016</td>
<td>2.88</td>
<td>0.005</td>
<td>0.014 – 0.078</td>
</tr>
<tr>
<td>Constant</td>
<td>9.85</td>
<td>0.531</td>
<td>18.55</td>
<td>0.000</td>
<td>8.80 – 10.91</td>
</tr>
</tbody>
</table>

Adjusted $R^2 = 0.1766$

Table 7 shows a Receiver Operating Characteristic (ROC) analysis to determine which variables are the most accurate in classifying a subject as NCI risk. Three variables (CES-D Score, TMT Score, Stroop Score) were selected for this analysis, based on their significant influence on IHDS scores from the regression analysis. Each variable was plotted as a curve of sensitivity (true positive) vs. 1 minus specificity (true negative), with the area under the curve representing the
CHAPTER FIVE: DISCUSSION

5.1 Demographics

This study only recruited adults as participants, limiting our sample to 18 years or older. The mean age of the group was approximately 37 years, but the range was quite considerable, with the youngest at 18 and oldest at 77 years. Age was not consolidated into age groups, but correlated with neurocognitive test scores. To this end, it was found that age had a significant relationship with performance on all neurocognitive assessments; specifically the trend was that performance on cognitive assessments got worse with increasing age, a finding that is supported by other neurocognitive studies. A 2014 paper that combined findings from imaging (diffuse tensor imaging) studies concluded that the brain’s white matter integrity declines in aging, and because cognitive ability is dependent on processes among brain regions, age plays a mediating role in cognitive decline (Bennett & Ilana, 2014). This trend appears to apply to HIV-positive persons as well. One study looked at a cohort of HIV-positive individuals who started long term ART medication, in follow-up assessments, the odds of neurocognitive impairment increased by nearly 20% with each decade of advancing age (Coban et al., 2017).

Education was also associated with performance, with higher education associated with better performance on the cognitive assessments. A study which recruited 3,435 adults to be assessed on various neuropsychological assessments showed that more years of education was associated with higher levels of cognitive impairment and slower cognitive decline (Zahodne, Stern, & Manly, 2015). This ties into the idea that educational attainment can increase what is known as cognitive reserve, where an individual has the ability to resist age-related brain changes or dementia-related
pathology (Stern, 2012). Had there been “standardized scores” available for a Ghanaians population, performance could have been assessed based on age and education.

The sample was predominantly female, which was confirmed by the Ridge staff to reflect the clients who attend clinic. The explanation for the high female proportion could be attributed to females in sub-Saharan having biological, socio-economic, cultural vulnerabilities to HIV (Ramjee et al., 2013). The staff also explained that a majority of the wealthier male clients do not come into clinic, rather have medications delivered to them. This could have been a factor in why more females presented themselves in the clinic. It should be noted that the psychobehavioural data and neurocognitive data did not vary by sex in our group.

Employment status was gathered as a means to learn about the socio-economic factors that could influence neurocognitive performance. The majority of the group had some form of employment, though it was not ascertained what type of employment or the income earned. Further exploration into the socio-economic status could have been obtained by asking about income, although it was feared that participants would be uncomfortable providing this information. One consideration is that the wealthier clients opt not to come to the clinic in-person. Nevertheless the high employment, coupled with the scores obtained on the Katz Instrumental Activities of Daily Living, would suggest that this group was generally independent and physically well enough to hold jobs.

Years living with HIV was obtained to see if there was any trend with performance of neurocognitive tests. All the participants in the study were clients who had received their HIV diagnosis and Ridge, and so years living with HIV coincided with the years of receiving ART medication at Ridge. The specific drugs the individual was using was collected through the ART adherence questionnaire, but it was not known how long participants had been taking a particular
drug, or if their regiment had changed over the years. Years living with HIV was not found to have any association with performance on the neurocognitive tests or psychobehavioural measures.

5.3 Psychobehavioural Factors

Three psychobehavioural factors were investigated in this study: depression (measured by the CES-D) alcohol use (measured by the AUDIT) and ART adherence (measured by Godin and colleagues’ questionnaire). Of the three, only depression seemed to have some significant association with neurocognitive performance. Higher scores on the depression scale was associated with worse neurocognitive performance in HIV-positive individuals, which supports previous studies looking at the interaction of depression and cognitive impairment in HIV. One Brazilian study by Pinheiro and colleagues looked at the association of depression and NCI in HIV-positive individuals, and the results showed that depression had the greatest evidence of association with neurocognitive loss (Pinheiro et al., 2016). Of note, Pinheiro and colleagues used IHDS as a measurement for NCI, just as was done in this study. Another Brazilian study using the IHDS as a measure for NCI found that of the 111 patients evaluated, 53.2% of them had a score indicative of NCI, with 26.3% of them having a depressive disorder (Troncoso & Conterno, 2015). A benefit to these studies is that depression was objectively assessed along with neurocognitive performance. It is believed that depression is frequently associated with HIV infection, and leads to an over-reporting of cognitive deficits (Thames et al., 2011). Indeed, because of the concern that participants would over-report cognitive deficits, this study opted for objectively-measured neurocognitive assessments to avoid the potential over-reporting of cognitive deficits. Though the trends for the correlation analysis showed depression endorsement significantly associated with poor neurocognitive performance, the correlation itself was weak (below 0.5). The mean score for the CES-D was quite low, an indication that overall depression was not strongly endorsed in the
study. There has been more evidence that mood and depression disorders should be screened in HIV-positive population (Robertson et al., 2014).

Alcohol and ART adherence did not have any significant association with neurocognitive impairment. It has been cited that alcohol has an additive effect on the cognitive dysfunction in HIV; specifically Persidsky and colleagues describe alcohol as creating a process of inflammation in the brain that would be seen in the neuropathology of HIV (Persidsky et al., 2011). In contrast, other research found that effects from HAND occur at same frequency between HIV-infected persons endorsing substance abuse (including alcohol) and those not endorsing substance abuse (Byrd et al., 2011). In the current study, the HIV-positive group recruited did not score particularly high on the AUDIT questionnaire, meaning there was generally low risk of alcohol abuse. Many of the participants reported not taking any alcohol at all in the past year. This can be attributed to two observations: clients at Ridge go through a period of counselling when initiating ART treatment in which they are advised by the nursing staff not to mix alcohol with their daily medication. Also there were some Muslim clients who abstained for alcohol as a religious practice.

Adherence to ARTs can also have an effect, according to another CHARTER study in which stronger neurocognitive performance was associated with better adherence, particularly for men that have lived longer HIV infection (Andrade et al., 2013). Rather than use a questionnaire, Andrade and colleagues measured ART adherence using pharmacy records. In the current study, ART adherence was noted to be extremely high, which made it difficult to determine whether lack of adherence contributed to neurocognitive impairment. 86% of the clients reported not missing any pills in the past week. The nursing staff at Ridge seemed assured that clients are thoroughly counselled about the importance of adhering to medication and therefore would not likely miss pills. However, self-reporting of this questionnaire can certainly be considered as a caution.
5.4 Neurocognitive Assessments

The study utilized two easy-to administer tests to accommodate the limited time clients could sit with the examiner. The two neurocognitive tests were Trail Making Test and Stroop Colour-Word, both tests of executive functioning (Homack & Riccio, 2004; Salthouse, 2011). It was found that scores on the two tests were correlated with the scores on the International HIV Dementia Scale, indicating that the two tests may be a good indicator of what performance on the IHDS would be. Of note, the Trail Making Test has an inter-rater reliability coefficient of 0.99, while the Stroop Colour-Word test has a test-retest coefficient of 0.671 (Cangoz et al., 2009; Franzen et al., 1987).

There is currently no objective way of assessing the range of neurocognitive impairment with neuropsychological testing. The revised criteria of HAND was created in 2007 (Antinori et al., 2007) creates three distinct categories of impairment: Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND), and HIV associated Dementia (HAD). Some studies have proposed categorizing individuals into these three categories based on if performance on neurocognitive assessment is at least one standard deviation below average (Antinori et al., 2007; Sanmarti et al., 2014). This evaluation is not universally accepted, and may not apply to seropositive individuals in sub-Saharan Africa.

This study chose not to adhere to the three category classification, but rather use two tests of executive functioning as a way to explore performance. Because this was an exploratory cross-sectional study, performance on the Trail Making Test and Stroop test was investigated for their association with the IHDS.

The correlation and linear regression analysis did show some significant trends. Age and education seemed to be related to performance, with longer time to completion on TMT and less words named on Stroop were associated with older age. It should be of note that some participants were
not able to complete these neurocognitive tasks, even though they were specifically selected due to their relative ease of administering. The problem that some participants had with Trail Making Test was the inability to identify numbers on the page, and with Stroop even more participants were unable to identify the colours or words on the page. From observation, it appears the difficulty was with older participants and less educated (especially those who did not have a proficient grasp of English.) HIV-positive Ghanaians could have their performance compared to control group matched by age and education in future; this would serve to properly assess whether performance was below average. In this study, we were only concerned with association of Trail Making Test Stroop Colour-Word performance, not whether the group performance was below the general population.

In terms of sex, there was no difference between males and females on performance. This is in contrast with a study in Zambia which indicated that NCI as measured by IHDS was more prominent in females, with 80% of HIV-positive woman scored at or below the cut-off point for the IHDS as opposed to just 42% in their male counterparts (Holguin et al., 2011).

Another aspect of the neurocognitive profile was performance on the International HIV Dementia Scale (IHDS). This is an internationally validated scale for assessing HIV-associated dementia and first used in Uganda in 1995 (Dang et al., 2015). Because the scale originated in another African country, it was believed its application would be well-suited for Ghanaian participants. It has been debated whether IHDS can be effective for diagnosing the milder categories of HAND, with some researchers advocating that the IHDS should be combined with other neurocognitive tests, such as Trail Making, to make it more sensitive to milder NCI (Chalermchai et al., 2013). With this ambiguity, it was decided that IHDS would be used in our study to flag for any NCI risk, not necessary dementia. Because the study group was made up of participants taking ART, we did not
anticipate that they would reach threshold for dementia risk (a score below 11). It was decided then that a score below 11 would constitute a “NCI risk” with subsequent follow-up with the Ridge medical doctor, as per ethical guidelines. The results obtained showed that the mean score of the group was 10.11, which is just at the threshold for HIV dementia risk. To query further, it was found that 48% of the group obtained a score to be flagged for dementia risk. This would imply the participants were all suffering from HIV-associated dementia (HAD), despite there being no other evidence of severe cognitive or physical impairment. All participants scored the maximum score on the Katz Instrumental Activities of Daily Living, which indicates full independence in daily functioning (bathing, dressing, toileting.) Further, since adherence to ART was so high, there is no reason to think that the low scores on the IHDS were attributed to lack of adherence, or that participants were in a terminal stage of the virus, which is when HIV-associated dementia usually occurs. It was for this reason that “NCI risk” was a better marker than dementia for this study. Indeed the proportion of NCI risk in our sample would support the paper by Clifford and Ances that cites almost half of all HIV patients have some form of cognitive impairment (2013).

This study utilized Receiver Operating Characteristic (ROC) analysis to evaluate the accuracy of assessments in classifying NCI risk. The ROC curve is a plot of true positive rate (sensitivity) as a function of false positive rate (1 minus specificity). “Classification variables” are plotted as curves, with each point on the curve representing a true positive/false positive pair corresponding with a particular decision threshold for the variable. Thus, the area under each ROC curve (AUC) is a measure of how well that variable can distinguish between a “disease” and “non-disease” case (Zweig & Campbell, 1993). In this study, “disease case” would represent individuals who had been classified as a NCI risk based on a score below 11 on the IHDS; “non-disease cases” would be those who scored an 11 or above. A classification variable with perfect discrimination would have
an AUC of 1, meaning 100% sensitivity (correctly classifying an individual as having NCI risk) and 100% specificity (correctly classifying an individual as non-NCI risk). Referring to Figure 11, three variables were selected to plot as curves: CES-D score, Trail Making Test (TMT) score, and Stroop Colour-Word score. These three were chosen because the linear regression analysis showed them to be most influential of the psychobehavioural and neurocognitive factors investigated. Of the three variables, TMT had the highest discriminability, with an area under curve .7214 (72.14% accuracy). This implicates the Trail Making Test as a strong diagnostic tool for NCI. This in fact was the same finding obtained by a 2013 of study in Thailand that sought to use TMT A to increase the IHDS’s sensitivity to milder forms of HAND (Chalermchai et al., 2013).

5.5 Limitations

The convenience sampling or "availability sampling" that was done in the study was intended to recruit as many participants as possible within the one-month study duration. This sampling method fit well with the exploratory nature of the study, and allowed the investigation to understand the overall profile of neurocognitive performance as well as any potential disadvantages with the assessments used. However, it must be cautioned that convenience sampling is highly susceptible to selection bias and sampling error. Despite this, studies of cognitive impairment in HIV have used convenience sampling or other non-probability sampling techniques to accommodate the hard-to-reach of subject recruitment (Beyrer et al., 2012; Cherner et al., 2005). Such techniques are often best when piloting new diagnostic tools: notably, a 2011 study in McGill University followed a similar design as this current one, using convenience sampling to recruit HIV-positive patients with no dementia in order to evaluate the effectiveness of a computerized screening tool for mild cognitive impairment (Koski et al., 2011). This study was the first to use a selection of neurocognitive tests for assessment of NCI in HIV. For this paper, it
is important to realise findings cannot be completely generalised because of selection bias; however, the findings in this study can lead to generating hypotheses on the relationship between neurocognitive impairment and HIV in Ghana. Although the results showed almost half of the participants had NCI, the risk of selection bias means this may not reflect the true prevalence of NCI in the HIV population of Ghana. It is hoped though that the results will encourage future researchers to do an actual prevalence estimate, based on probability-based sampling.

This study did not utilize a control group of HIV-negative individuals to compare data from the psychobehavioural and neurocognitive scales. This makes it difficult to state that performance or behavioural ratings were worse than average in the general (HIV-negative) population. Age and education played a large role in performance, and so a control group would need to be matched by those two factors to accurately assess performance. Though this study did not aim to make objective claims on the quality of performance, future studies however might want to do so.

There is concern that the neurocognitive scales used were not well-validated for use in a Ghanaian population, although the inter-rater reliability coefficients were very high for both the selected tests. Not all the participants in the study had a sufficient grasp of English needed to understand the directions of the study, and indeed it should not be assumed that English was the native language for all participants, despite it being the official language of the country. Despite the global application of IHDS, the memory recall sub-test may have proven to be too difficult, as participants had to memorise English words. Given that some participants scored particularly low on the memory recall subscale, this is a valid concern. Further investigation should be done to see if poor performance on the IHDS was truly due to NCI, or a language barrier. It should be concluded then that the results from the neurocognitive assessments should be interpreted with caution, particularly with the influence level of education could have contributed to performance.
The study was designed to be as brief as possible for the ease of the clients. This was because the Ridge staff had cautioned that clients would not be willing to stay for too long, leaving the facility when it was time to pick up their medication. Keeping the study forms brief allowed all participants to go through the questionnaires and assessments, however it created some limitations. A longer more comprehensive battery of neurocognitive assessments could have been utilized to gather more information, and test other cognitive domains (verbal fluency, working memory, etc.) Also, the brevity of some questionnaires may have not collected sufficient information. This is especially true of the demographic questions asked, since no socio-economic information or family information was collected. Also, the ART adherence questionnaire for this study only asked about pills missed in the past week; other studies gathered more information to ascertain adherence. In one example, a prospective study by Anderson and colleagues gathered adherence by a self-report of pills missed in the past week in addition to monthly electronic pill cap monitoring (Anderson, Higgins, Ownby, & Waldrop-Valverde, 2015). This would have been a much more objective resource to have for this study, to verify the veracity of the reports of the participants. If enough time with clients could be secured, a future study should take these limitations into consideration.
CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

Overall, the study group was physically functional and properly adhering to medication, yet nearly half (48%) of the group exhibited evidence of neurocognitive impairment based on an internationally-validated scale of measurement. Depression seems to have been a contributing factor to worsening performance. Mental health should not be ignored in HIV treatment, and as such this study advocates that HIV clinics like Ridge implement screening for depression. It is believed the use of a comprehensive neuropsychological battery will shed more light on the extent of cognitive impairment in Ghana.

This is of note, the first study that attempted to explore the neurocognitive profile of Ghanaians who are HIV-positive. The hope is that this study can bring this subject area into greater prominence for future investigators to continue studies.

6.2 Recommendations

This study could not objectively assess performance on the neuropsychological tests used, which could be done if there were reliable normed scores in the general Ghanaian population. Future research should attempt pilot studies that can establish average scores of neuropsychological assessments in the general Ghanaian population, based on both age, education, and gender. This will be of immense benefit to the study of cross-cultural neuropsychology.

The fact that this study was conducted as clinic where HIV-positive persons were receiving ART made it less likely that the sample would include people who had a low CD4 count. Although the years living with HIV was examined, it was confirmed by staff that all participants had received their diagnosis at the clinic (and therefore started treatment upon receiving diagnosis). This study
did not have access to CD4 counts of the participants, but future studies should consider this variable as an insightful dimension to the NCI assessment. A study in South Africa considered the utility of two tests used in this study: IHDS and CES-D; these were promoted as a rapid-screening tool for both depression and dementia in HIV, and concluded that for HIV-individuals with a low CD4 count, IHDS and CES-D was 88% sensitivity and 91% sensitivity respectively (Singh, Sunpath, John, Eastham, & Gouden, 2008). Taking from this study, future research could consider how psychobehavioural and neurocognitive factors could vary by CD4 count. It will behoove researchers to find a range of HIV-individuals, some who may not be on ART medication, to capture a wide range of CD4 count values.

This study had not considered the effects of anti-retroviral medication on cognitive impairment. From the literature it was presumed that NCI would be more likely to occur if participants were not adhering to antiretroviral medication. There was even some evidence to support that some drugs could stop the entry of HI entry into the brain based on the Central Nervous System Penetration Effectiveness (CPE) rank (Letendre et al., 2009). However, it was not considered that ART drugs could in fact have the exact opposite effect and cause cognitive impairment as side effect. This idea was gathered from a recent study of ART on cognitive impairment which looked at whether the ART drug efavirenz was associated with NCI when used long term; the results showed the efavirenz users had worse measures on speed of information processing, verbal fluency, and working memory compared to those on other drugs (Ma et al., 2016). Efavirenz was a drug many of the participants at Ridge were on, and given the poor performance on neurocognitive tests it certainly warrants future investigation. Perhaps it is the drugs-meant to treat the effects of HIV-that contribute to poor cognition more than anything else.
REFERENCES


APPENDICES

Appendix I: Ghana Health Service Ethical Review Committee Approval Letter
GHANA HEALTH SERVICE ETHICS REVIEW COMMITTEE

Research & Development Division
Ghana Health Service
P. O. Box MB 190
Accra
Tel: +233-302-681100
Fax: +233-302-685424
Email: ghserc@gmail.com

J. Yaw Asiedu
University of Ghana
School of Public Health
Legon, Accra

The Ghana Health Service Ethics Review Committee has reviewed and given approval for the implementation of your Study Protocol.

<table>
<thead>
<tr>
<th>GHS-ERC Number</th>
<th>GHS-ERC: 4872/16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Project Title</td>
<td>Psychobehavioural Factors Associated with Neurocognitive Test Performance in HIV-Positive Persons Attending a Regional Hospital in Accra, Ghana</td>
</tr>
<tr>
<td>Approval Date</td>
<td>15th May, 2017</td>
</tr>
<tr>
<td>Expiry Date</td>
<td>14th May, 2018</td>
</tr>
<tr>
<td>GHS-ERC Decision</td>
<td>Approved</td>
</tr>
</tbody>
</table>

This approval requires the following from the Principal Investigator:

- Submission of yearly progress report of the study to the Ethics Review Committee (ERC)
- Renewal of ethical approval if the study lasts for more than 12 months
- Reporting of all serious adverse events related to this study to the ERC within three days verbally and seven days in writing
- Submission of a final report after completion of the study
- Informing ERC if study cannot be implemented or is discontinued and reasons why
- Informing the ERC and your sponsor (where applicable) before any publication of the research findings.

Please note that any modification of the study without ERC approval of the amendment is invalid.

The ERC may observe or cause to be observed procedures and records of the study during and after implementation.

Kindly quote the protocol identification number in all future correspondence in relation to this approved protocol.

SIGNED................

DR. CYNTHIA BANNERMAN
(GHS-ERC CHAIRPERSON)

Cc: The Director, Research & Development Division, Ghana Health Service, Accra
Appendix 2: Informed Consent Form

PSYCHOBEHAVIOURAL FACTORS ASSOCIATED WITH NEUROCOGNITIVE TEST PERFORMANCE IN HIV-POSITIVE PERSONS ATTENDING A REGIONAL HOSPITAL IN ACCRA GHANA

You are being invited to take part in a research study of how the Human Immunodeficiency Virus (HIV), in addition to other factors may affect performance on tests of cognition. These tests of cognition will measure the ability to complete small physical tasks with the hand and say some words out loud. We are inviting you to take part as a person living with HIV who comes to Ridge Regional Hospital for treatment and other services. Please read the form carefully and ask any questions you may have before agreeing to take part of the study.

What this study is about: The purpose of this study is to learn how persons living with HIV perform on tests of cognition. We seek to understand how certain factors may influence test performance.

What we ask you do: Should you agree to be in this study, you will sit down with a researcher to complete a series of questionnaires and tests of cognition. The questionnaires will ask you to provide basic information about yourself, in addition to questions about your feelings, behaviour, use of medication and daily lifestyle. You will also complete some tests which can be described as ‘puzzles.’ Some of these tests will involve using a paper and pencil, some will involve performing light physical tasks, and some will involve reading out loud. Some of the tests may seem easy and some might seem more difficult. Please know that not every person doing these tests finishes, or gets everything right. We only ask that you give your best effort. The total time of questionnaires and tests should take no longer than 30 minutes.

Risks and benefits: There is a risk that you may find some of the questions about your personal life to be sensitive. However, we do not anticipate any risks to participating in this study other than those encountered in day-to-day life.
There are no benefits to you as a participant. Participating or declining to be in this study has no impact, positive or negative, on your continued treatment at Ridge Hospital or relationship with the staff.

**Your answers will be kept confidential:** The records of this study will be kept private. Your responses will not be shared with the healthcare staff of Ridge Hospital. In any sort of report made public, there will be no information that would make it possible to identify you by name. Research records will be kept in a locked file; only the researchers will have access to the records.

**Taking part is voluntary:** Taking part in this study is completely voluntary. You may skip any questions that you do not want to complete. If you decide not to take part or to skip some of the questions, it will not affect your current or future relationship with Ridge Hospital. If you decide to take part, you are free to withdraw at any time.

**If you have questions:** The researcher conducting this study Nana Yaw Asiedu, MPH candidate at School of Public Health, University of Ghana Legon. Please ask any questions you have now. If you have questions later, you may contact Nana Yaw Asiedu at nyasiedu@st.ug.edu.gh or at +233 505 699640. If you have any questions or concerns regarding your rights as a subject in this study, please contact the Ghana Health Services Ethical Review Committee Administrator, Ms. Hannah Frimpong at +233 302 681109 or Hannah.Frimpong@ghsmail.org.
Statement of Consent: I have read the above information (or the above information has been read to me,) and have received answers to any questions I asked. I consent to take part in the study.

Your Signature


Date ____________________________

Your Name (printed)


Signature of person obtaining consent


Name of person obtaining consent (printed)


Date ____________________________


Appendix 3: Demographic Questionnaire
Psychobehavioural Factors Associated with Neurocognitive Test Performance in HIV-positive Persons Attending a Regional Hospital in Accra, Ghana

The following questions are being asked to those who have consented to be part of a research study for the School of Public Health, University of Ghana. The answers to your questions will be collected for the purpose of producing original research, and for that purpose only. We understand these questions are sensitive in nature. Please know that all answers will be kept strictly confidential, and will not be shared with your healthcare provider or anyone in your family. If you are asked a question you don’t feel comfortable answering, you are not required to answer.

Demographic Information

1. Age _____

2. Sex _____

3. What is the highest level of education you have completed?
   - Primary School
   - Some Secondary School
   - Secondary School
   - Some University
   - University
   - 1-2 year Masters Programme (example: MBA, MPH)
   - Graduate Programme (example: MD, PhD, JD)

4. Are you currently employed? Y/N (Circle One)
Appendix 4: CES-D Questionnaire

Center for Epidemiologic Studies Short Depression Scale (CES-D 10)

Below is a list of some of the ways you may have felt or behaved. Please indicate how often you have felt this way during the past week by checking the appropriate box for each question.

<table>
<thead>
<tr>
<th>Items:</th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or a moderate amount of time (3-4 days)</th>
<th>All of the time (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I was bothered by things that usually don't bother me.</td>
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<tr>
<td>2. I had trouble keeping my mind on what I was doing</td>
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<tr>
<td>3. I felt depressed.</td>
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<tr>
<td>4. I felt that everything I did was an effort.</td>
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<tr>
<td>5. I felt hopeful about the future.</td>
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<tr>
<td>6. I felt fearful.</td>
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<tr>
<td>7. My sleep was restless.</td>
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<td></td>
</tr>
<tr>
<td>8. I was happy.</td>
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</tr>
<tr>
<td>9. I felt lonely.</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>10. I could not &quot;get going.&quot;</td>
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</table>
Scoring

<table>
<thead>
<tr>
<th></th>
<th>Rarely or none of the time (less than 1 day)</th>
<th>Some or a little of the time (1-2 days)</th>
<th>Occasionally or a moderate amount of the time (3-4 days)</th>
<th>All of the time (5-7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Items 5 &amp; 8</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>All other items</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Score is the sum of the points for all 10 items. If more than 2 items are missing, do not score. A score of 10 or greater is considered depressed.

This quiz is intended for educational purposes only and should not be understood to constitute any type of diagnosis or healthcare recommendation.

Please call your PCP or AMA Social Worker to report your score or any concerns. If you are having thoughts of hurting yourself or others, please call AMA immediately and tell the operator it is an emergency, or go to your local emergency room.

Allison Galbraith, LICSW Acton Medical Associates (978) 263-1131 ext. 310 321 Main Street Acton, MA 01720
Additional Information

This is the short version of the 20-item CES-D. The CES-D was developed in the 1970s by Lenore Radloff while she was a researcher at the National Institute of Mental Health.
Appendix 5: AUDIT Questionnaire

The Alcohol Use Disorders Identification Test: Interview Version

Read questions as written. Record answers carefully. Begin the AUDIT by saying “Now I am going to ask you some questions about your use of alcoholic beverages during this past year.” Explain what is meant by “alcoholic beverages” by using local examples of beer, wine, vodka, etc. Code answers in terms of “standard drinks.” Place the correct answer number in the box at the right.

1. How often do you have a drink containing alcohol?
   (0) Never [Skip to Qs 9-10]
   (1) Monthly or less
   (2) 2 to 4 times a month
   (3) 2 to 3 times a week
   (4) 4 or more times a week

2. How many drinks containing alcohol do you have on a typical day when you are drinking?
   (0) 1 or 2
   (1) 3 or 4
   (2) 5 or 6
   (3) 7, 8, or 9
   (4) 10 or more

3. How often do you have six or more drinks on one occasion?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

4. How often during the last year have you found that you were not able to stop drinking once you had started?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

5. How often during the last year have you needed a first drink in the morning to get yourself going after a heavy drinking session?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

6. How often during the last year have you had a feeling of guilt or remorse after drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

7. How often during the last year have you been unable to remember what happened the night before because you had been drinking?
   (0) Never
   (1) Less than monthly
   (2) Monthly
   (3) Weekly
   (4) Daily or almost daily

8. Have you or someone else been injured as a result of your drinking?
   (0) No
   (1) Yes, but not in the last year
   (2) Yes, during the last year

Total Score for Questions 2 and 3 = 0

Skip to Questions 9 and 10 if

University of Ghana  http://ugspace.ug.edu.gh
5. How often during the last year have you failed to do what was normally expected from you because of drinking?

| (0) | Never         |
| (1) | Less than monthly |
| (2) | Monthly       |
| (3) | Weekly        |
| (4) | Daily or almost daily |

10. Has a relative or friend or a doctor or another health worker been concerned about your drinking or suggested you cut down?

| (0) | No          |
| (2) | Yes, but not in the last year |
| (4) | Yes, during the last year |

Record total of specific items here

*If total is greater than recommended cut-off, consult User’s Manual.*
Appendix 6: Godin’s Questionnaire on Taking Anti-retroviral Medication

QUESTIONNAIRE ON TAKING ANTIRETROVIRAL MEDICATION

Like most people, it is likely that you have missed taking one or several pills at some point in time. In fact, even the most disciplined people may not always take all of their medication as they would wish to because of forgetfulness, unexpected situations, etc. The most difficult thing will no doubt be for you to remember the times that you have missed taking one or several pills. It is thus important for you to make an effort to remember so that your answers are as precise as possible. Take the time you need to answer.

We ask you to answer the questionnaire with only your ANTIRETROVIRAL medication in mind.

The word «pill» is used to mean tablets, caplets and capsules.

The expression «miss one or several pills» means NOT taking all your antiretroviral pills at a certain time.

Answer all the questions by entering a number or by checking one of the suggested answers.

Q1. Indicate the name of the antiretroviral medications you take. Next, enter the number of pills that you have to take each day for each of these medications. (please refer to the chart provided)

<table>
<thead>
<tr>
<th>Name of antiretroviral medication*</th>
<th>Number of antiretroviral pills</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Wake-up, breakfast, morning</td>
</tr>
<tr>
<td>Example: lamiduvine (3TC, Epivir)*</td>
<td>1</td>
</tr>
<tr>
<td>1.</td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td></td>
</tr>
</tbody>
</table>

*Indicate one of the names of the medication

Q2. How many antiretroviral pills have you missed during the last 2 days?

(If you haven’t missed any, write down the number "0")

<table>
<thead>
<tr>
<th>Number of antiretroviral pills that you have missed</th>
<th>Wake-up, breakfast, morning</th>
<th>Lunch, afternoon</th>
<th>Supper, evening, bed-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Example:</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Yesterdays</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day before yesterday</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Q3. During the last 7 days, did you ...

- Go out for a leisure activity? (movie, show, physical activity, etc.)? YES NO
- Go to a bar? YES NO
- Sleep away from home? YES NO
- Visit friend(s) or family member(s)? YES NO
- Go to a restaurant? YES NO
- Go to a party? YES NO
- Attend a meeting? YES NO
- Receive a visit from friend(s) or family member(s)? YES NO
Q4. **During the last 7 days**, did one of the situations listed in question Q3 prevent you from taking all your antiretroviral pills?

YES  |  NO

Q5a. **During the last 7 days**, how many times, in total, did you miss taking one or more of your antiretroviral pills? (If you haven’t missed any, write down the number “0”)

____ TIMES

Q5b. In total, this represents how many antiretroviral pills? ____ PILLS
Appendix 7: Trail Making Test (TMT) Part A

### Instructions:
Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper. Time the patient as he or she connects the "trail." If the patient makes an error, point it out immediately and allow the patient to correct it. Errors affect the patient's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the patient has not completed both parts after five minutes have elapsed.

**Step 1:** Give the patient a copy of the Trail Making Test Part A worksheet and a pen or pencil.

**Step 2:** Demonstrate the test to the patient using the sample sheet (Trail Making Part A – SAMPLE).

**Step 3:** Time the patient as he or she follows the “trail” made by the numbers on the test.

**Step 4:** Record the time.

**Step 5:** Repeat the procedure for Trail Making Test Part B.

### Scoring:
Results for both TMT A and B are reported as the number of seconds required to complete the task; therefore, higher scores reveal greater impairment.

<table>
<thead>
<tr>
<th></th>
<th>Average</th>
<th>Deficient</th>
<th>Rule of Thumb</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trail A</td>
<td>29 seconds</td>
<td>&gt; 78 seconds</td>
<td>Most in 90 seconds</td>
</tr>
<tr>
<td>Trail B</td>
<td>75 seconds</td>
<td>&gt; 273 seconds</td>
<td>Most in 3 minutes</td>
</tr>
</tbody>
</table>
Sources:

Trail Making Test Part A

Patient’s Name: __________________________  Date: ________________
Trail Making Test Part A – SAMPLE
Trail Making Test Part B

Patient’s Name: ____________________________  Date: ________________
Trail Making Test Part B – SAMPLE

Begin

End

1

2

3

4

A

B

C

D
Appendix 9: International HIV Dementia Scale

International HIV Dementia Scale (IHDS)

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

1. Motor Speed: Have the patient tap the first two fingers of the non-dominant hand as widely and as quickly as possible.
   - 4 = 15 in 5 seconds
   - 3 = 11-14 in 5 seconds
   - 2 = 7-10 in 5 seconds
   - 1 = 3-6 in 5 seconds
   - 0 = 0-2 in 5 seconds

2. Psychomotor Speed: Have the patient perform the following movements with the non-dominant hand as quickly as possible: 1) Clench hand in fist on flat surface. 2) Put hand flat on surface with palm down. 3) Put perpendicular to flat surface on the side of the 5th digit. Demonstrate and have the patient perform twice for practice.
   - 4 = 4 sequences in 10 seconds
   - 3 = 3 sequences in 10 seconds
   - 2 = 2 sequences in 10 seconds
   - 1 = 1 sequence in 10 seconds
   - 0 = unable to perform

3. Memory-Recall: Ask the patient to recall the four words. For words not recalled, prompt with a semantic clue as follows: animal (dog); piece of clothing (hat); vegetable (bean); color (red).
   - Give 1 point for each word spontaneously recalled
   - Give 0.5 point for each correct answer after prompting
   - Maximum – 4 points

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


New York State Department of Health AIDS Institute: www.hivguidelines.org
## Katz Index of Independence in Activities of Daily Living

<table>
<thead>
<tr>
<th>Activities</th>
<th>Independence</th>
<th>Dependence</th>
</tr>
</thead>
<tbody>
<tr>
<td>BATHING</td>
<td>(1 POINT) Bathes self completely or needs help in bathing only a single part of the body such as the back, genital area or disabled extremity.</td>
<td>(0 POINTS) Need help with bathing more than one part of the body, getting in or out of the tub or shower. Requires total bathing</td>
</tr>
<tr>
<td>Points: __________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRESSING</td>
<td>(1 POINT) Get clothes from closets and drawers and puts on clothes and outer garments complete with fasteners. May have help tying shoes.</td>
<td>(0 POINTS) Needs help with dressing self or needs to be completely dressed.</td>
</tr>
<tr>
<td>Points: __________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOILETING</td>
<td>(1 POINT) Goes to toilet, gets on and off, arranges clothes, cleans genital area without help.</td>
<td>(0 POINTS) Needs help transferring to the toilet, cleaning self or uses bedpan or commode.</td>
</tr>
<tr>
<td>Points: __________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TRANSFERRING</td>
<td>(1 POINT) Moves in and out of bed or chair unassisted. Mechanical transfer aids are acceptable</td>
<td>(0 POINTS) Needs help in moving from bed to chair or requires a complete transfer.</td>
</tr>
<tr>
<td>Points: __________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONTINENCE</td>
<td>(1 POINT) Exercises complete self control over urination and defecation.</td>
<td>(0 POINTS) Is partially or totally incontinent of bowel or bladder</td>
</tr>
<tr>
<td>Points: __________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEEDING</td>
<td>(1 POINT) Gets food from plate into mouth without help. Preparation of food may be done by another person.</td>
<td>(0 POINTS) Needs partial or total help with feeding or requires parenteral feeding.</td>
</tr>
<tr>
<td>Points: __________</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL POINTS: __________</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**SCORING:** 6 = High (*patient independent*) 0 = Low (*patient very dependent*)
### LAWTON - BRODY

**INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE (I.A.D.L.)**

**Scoring:** For each category, circle the item description that most closely resembles the client’s highest functional level (either 0 or 1).

<table>
<thead>
<tr>
<th>A. Ability to Use Telephone</th>
<th>E. Laundry</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Operates telephone on own initiative—looks up and dials numbers, etc.</td>
<td>1. Does personal laundry completely</td>
</tr>
<tr>
<td>2. Dials a few well-known numbers</td>
<td>2. Launders small items—rinses stockings, etc.</td>
</tr>
<tr>
<td>3. Answers telephone but does not dial</td>
<td>3. All laundry must be done by others</td>
</tr>
<tr>
<td>4. Does not use telephone at all</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>B. Shopping</th>
<th>F. Mode of Transportation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Takes care of all shopping needs independently</td>
<td>1. Travels independently on public transportation or drives own car</td>
</tr>
<tr>
<td>2. Shops independently for small purchases</td>
<td>2. Arranges own travel via taxi, but does not otherwise use public transportation</td>
</tr>
<tr>
<td>3. Needs to be accompanied on any shopping trip</td>
<td>3. Travels on public transportation when accompanied by another</td>
</tr>
<tr>
<td>4. Completely unable to shop</td>
<td>4. Travel limited to taxi or automobile with assistance of another</td>
</tr>
<tr>
<td></td>
<td>5. Does not travel at all</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C. Food Preparation</th>
<th>G. Responsibility for Own Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Plans, prepares and serves adequate meals independently</td>
<td>1. Is responsible for taking medication in correct dosages at correct time</td>
</tr>
<tr>
<td>2. Prepares adequate meals if supplied with ingredients</td>
<td>2. Takes responsibility if medication is prepared in advance in separate dosage</td>
</tr>
<tr>
<td>3. Heats, serves and prepares meals, or prepares meals but does not maintain adequate diet</td>
<td>3. Is not capable of dispensing own medication</td>
</tr>
<tr>
<td>4. Needs to have meals prepared and served</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>D. Housekeeping</th>
<th>H. Ability to Handle Finances</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Maintains house alone or with occasional assistance (e.g. &quot;heavy work domestic help&quot;)</td>
<td>1. Manages financial matters independently (budgets, writes checks, pays rent, bills, goes to bank), collects and keeps track of income</td>
</tr>
<tr>
<td>2. Performs light daily tasks such as dish washing, bed making</td>
<td>2. Manages day-to-day purchases, but needs help with banking, major purchases, etc.</td>
</tr>
<tr>
<td>3. Performs light daily tasks but cannot maintain acceptable level of cleanliness</td>
<td>3. Incapable of handling money</td>
</tr>
<tr>
<td>4. Needs help with all home maintenance tasks</td>
<td></td>
</tr>
<tr>
<td>5. Does not participate in any housekeeping tasks</td>
<td></td>
</tr>
<tr>
<td>Score</td>
<td>Score</td>
</tr>
<tr>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td></td>
<td><strong>Total score</strong></td>
</tr>
</tbody>
</table>

A summary score ranges from 0 (low function, dependent) to 8 (high function, independent) for women and 0 through 5 for men to avoid potential gender bias.