HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS AT MOI TEACHING AND REFERRAL HOSPITAL, ELDORET, KENYA.

AMINA ALI MOHAMED

A thesis submitted in partial fulfillment of the requirement for the award of the degree of Master of Medicine in Internal Medicine, Moi University.

DECLARATION

Student's Declaration:

I declare that this research thesis is my original work and that it has never been presented for a degree in any other university. No part may be reproduced without prior permission of the author or Moi University.

Amina Ali Mohamed **MBChB**

SM/PGM/12/15

Sign …… Date ……

Supervisors' Declaration:

This research thesis has been submitted for examination with our approval as Moi University supervisors.

Dr. Chrispine Oduor, **MBChB, MMed.**

Senior Lecturer, Department of Medicine

Moi University School of Medicine

Sign…….. Date**....**…….

Dr. W.D.C Kinyanjui, **MBChB, MMed.**

Senior Lecturer, Department of Mental Health

Moi University School of Medicine

Sign …… Date ……

DEDICATION

I would like to dedicate this dissertation to my loving parents Mr. Ali Mohamed Hassan and Mrs. Mariyam Khamis Mohamed who have really encouraged and fully supported me in each step of the way.

ABSTRACT

Background: Human Immunodeficiency Virus (HIV) infection causes a myriad of neurological complications including cognitive deficits referred to as HIV-Associated Neurocognitive Disorders (HAND). With the introduction of combination antiretroviral therapy, there has been an epidemiological shift in cognitive disorders with a decline in the more severe HIV-Associated Dementia (HAD) to an increase in the less severe HAND: Asymptomatic Neurocognitive Impairment (ANI) and HIV-associated Mild Neurocognitive disorder (MND). Central Nervous System (CNS) involvement in HIV interferes with cognitively demanding activities of daily living and hence a worse quality of life. Tools have been developed to help assess the degree of neurocognitive dysfunction; however, early diagnosis is delayed until symptoms are overt.

Objective: To determine the prevalence and the factors associated with HIV-Associated Neurocognitive Disorders (HAND) at Moi Teaching and Referral Hospital (MTRH) at Eldoret, Kenya.

Methods: A cross sectional analytical study of HIV infected patients on antiretroviral therapy attending HIV clinic. A systematic random sampling was done to select 360 patients calculated using the fisher's exact formula. An interviewer administered structured questionnaire was used to collect socio-demographic data and the CD4 count and viral load collected from the Academic Model Providing Access to Healthcare (AMPATH) database. Pearson's Chi Square test was used to compare proportions and independent sample t- test was used to compare continuous variables between the patients diagnosed with HAND and those without HAND. Logistic regression model was used to assess the factors associated with HAND.

Results: The mean age of the study participants was 40.2 years with a standard deviation of 11.5. The overall prevalence of HAND was found in 292 patients (81.1%). Mild HAND (ANI and MND) was found in 283 patients (78.6%). Severe HAND (HAD) was in 9 patients (2.5%). The factors associated with HAND were older age OR: 1.06 (95% CI: 1.03, 1.10), male gender OR: 0.48 (95% CI: 0.24, 0.97), Advanced WHO clinical staging OR: 2.45 (95% CI: 1.20, 5.01) and a higher level of education; secondary/tertiary OR: 0.16 (95% CI: 0.07, 0.38); 0.11 (95% CI: 0.04, 0.35).

Conclusion: The prevalence of HAND in this population was found to be (81.1%) which is high. HAND was more frequently associated with patients of older age and advanced WHO clinical staging.

Recommendation: There is need for regular cognitive screening for early identification of HAND and appropriate intervention in HIV infected patients.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ACKNOWLEDGEMENT

First and foremost, I would like to thank the Almighty God who gave me the ability to develop and accomplish this dissertation.

I would like to convey my sincere gratitude to my supervisors, Dr. Chrispine Oduor and Dr. Daniel Kinyanjui who were actively involved in the successful completion of the thesis. I appreciate their invaluable guidance and support throughout the entire course.

I wish to express special thanks to the Department of Medicine for helping me shape the document to its final form and the Academic Model Providing Access to Healthcare (AMPATH) HIV clinic and the reference lab for helping me with laboratory work and facilitation.

I would also like to extend my gratitude to my research assistant Eunice Jeptanui for her hard work in data collection and Alfred Keter who analysed the data in a timely and organized manner and the National Research Fund for funding the work.

Finally, I would also like to thank my entire family particularly my older sister Halima Ali Mohamed, for their unconditional support and encouragement throughout the entire course.

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
AMPATH	Academic Model Providing Access to Healthcare
ANI	Asymptomatic Neurocognitive Impairment
ABC	Abacavir
ART	Antiretroviral therapy
ARV	Antiretroviral drugs
AZT	Zidovudine
BMI	Body Mass Index
cART	Combined Antiretroviral Therapy
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CD4	Cluster of differentiation 4
CPE	Central nervous system Penetration Effectiveness
ETR	Etravirine
EFV	Efavirenz
HAD	HIV-Associated Dementia
HAND	HIV-Associated Neurocognitive Disorders
HAART	Highly Active Antiretroviral Therapy
IADL	Lawton Instrumental Activities of Daily Living
IHDS	International HIV Dementia Scale
IREC	Institutional Research and Ethics Committee
MND	HIV-associated Mild Neurocognitive Disorder
MoCA	Montreal Cognitive Assessment tool
MTRH	Moi Teaching and Referral Hospital

NCI	Neurocognitive Impairment
NVP	Nevirapine
NRTI	Nucleoside reverse transcriptase inhibitors
NNRTI	Non-nucleoside reverse transcriptase inhibitors
RNA	Ribonucleic Acid
TDF	Tenofovir
PLHIV	People living with HIV
PI	Protease Inhibitors
WHO	World Health Organization

DEFINITION OF TERMS:

HIV- Associated Neurocognitive Disorders (HAND): Umbrella definition comprising of mild HAND (ANI, MND) and severe HAND (HAD)

Asymptomatic Neurocognitive Impairment (ANI): Cognitive impairment involving at least 2 cognitive domains with no interference in daily functioning. Assessed by MoCA< 26 and IHDS >10

HIV-associated Mild Neurocognitive Disorder (MND): Cognitive impairment involving at least 2 cognitive domains with mild interference in daily functioning. Assessed by MoCA< 26 and IHDS >10

HIV-Associated Dementia (HAD): Cognitive impairment involving at least 2 cognitive domains with marked interference in daily functioning. Assessed by MoCA< 26 and IHDS < 10

No HAND: No cognitive impairment, MoCA ≥ 26 and IHDS ≥ 10

CHAPTER ONE: INTRODUCTION

1.1 Background

HIV emerged as a major threat to world health over 30 years ago; it has challenged scientists and clinicians to combat its vast and devastating effects. Despite the virus being recognized for its direct effect on the cellular immune system through depletion of infected CD4 lymphocytes, it also has broad effects on the nervous system, including evidence for direct pathology in the brain, spinal cord, and peripheral nerves(Harrison MJG, 1995).

HIV-Associated Neurocognitive Disorders (HAND) are neurological disorders associated with HIV infection and AIDS. They have a highly variable clinical course and a spectrum of signs and symptoms, ranging from subtle cognitive and motor impairments to profound dementia. This primary HIV-associated neurocognitive disorder, together with a unique range of opportunistic infections and malignant disease, constitutes neuroAIDS (Clifford & Ances, 2013).

Since the introduction of highly active antiretroviral therapy (ART) in 1996, mortality, AIDS, AIDS- defining diagnoses, and hospitalizations have all decreased.

Despite the above achievement, neurological involvement of HIV remains an important problem since ART has not fully accomplished full protection of the nervous system.

Cross-sectional studies show that about half of all treated patients with HIV have cognitive impairment, with the more severe forms of neurocognitive impairment being rare, although milder forms remain. Establishment of the associated risk factors, prognosis, and optimum cART regimen for patients with HIV-associated neurocognitive disorder remains a major goal.

A consensus research definition of HIV-associated neurocognitive disorder includes the sub classifications of; Asymptomatic Neurocognitive Impairment (ANI), HIV-associated Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD)(Antinori et al., 2007).

The gold standard for assessment of HAND is a detailed battery of neuropsychological tests, however; they are seldom available to patients in busy settings (Antinori et al., 2007; Ridha & Rossor, 2005).

Various tools have been developed to help assess the neurocognitive dysfunction. They have been used in several studies in Africa including Kenya. These include the Montreal cognitive assessment (MoCA), which is more sensitive to the milder forms of HAND (ANI/MND) and the International HIV dementia scale (IHDS), which is more sensitive to the severe form of HAND (HAD). The Lawton Instrumental activity of daily living (IADL) has been used to assess the functional status of the patients, which are mostly impaired in patients diagnosed with HAND.

The Montreal Cognitive Assessment (MoCA) tool consists of 30 items measuring eight cognitive domains. It takes approximately 10-15 minutes to complete. The MoCA is sensitive in differentiating milder forms of cognitive impairments and has been validated in non- HIV infected patients (Cross, Onen, Gase, Overton, & Ances, 2013; Koski et al., 2011; Milanini et al., 2014). The eight cognitive domains measured include: visuospatial/executive, memory, attention, language, abstraction, delayed recall, and orientation. A total score was calculated by summing scores of the 13 tasks. The maximum score possible is 30 points, with a cutoff score of $\leq$26 indicative of cognitive impairment. One point was added for each participant with 12 or fewer years of formal education.

The International HIV Dementia scale (IHDS) consists of three subsets: timed finger taping, timed alternating hand sequence, and recall of four items at 2 minutes. A total score out of 12 was calculated for each participant, with each of the three subsets contributing 4 points to the total score. It takes 2-3 minutes to administer. IHDS is a useful screening test for detecting the severe form of HAND with a cutoff ≤ 10 indicative of HIV dementia.

The Lawton Instrumental Activities of Daily Living (IADL) assesses the eight domains of functions and is most useful for identifying the functional status. The domains include: Ability to use telephone, Laundry, shopping, Mode of transportation, Food preparation, responsibility for own medication, housekeeping and ability to handle finances. A score of 0 depicted low functioning and a score of 8; high functioning.

1.2 Problem Statement

Changes in memory, concentration, attention and motor skills are common in HIV patients and present a diagnostic challenge to the clinician.

Being diagnosed with HAND increases one's risk of mortality (Vivithanaporn et al., 2010), and often leads to poor functional outcomes, such as suboptimal antiretroviral therapy (ART) adherence, employment difficulties, driving problems, and impaired activities of daily living (Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009; Heaton et al., 2004; Hinkin et al., 2004; van Gorp et al., 2007).

Early diagnosis of HAND in our setting is delayed until symptoms are overt. Neurocognitive dysfunction leads to poor adherence to ART (Chibanda, Benjamin, Weiss, & Abas, 2014; Heaps et al., 2013; Zhang et al., 2012), which in turn leads to increased viral resistance and treatment failure (Gifford et al., 2000; Liu et al., 2001).

Recent estimates in South Africa suggest HAND may be present in as many as 70% of ART- naive adults with late stage HIV under 40 years of age(Joska et al., 2011), and may have a prevalence of as high as 80% among adults with documented ART adherence difficulties and low CD4 counts (Robbins et al., 2013).

The presence of cognitive dysfunction can contribute to an individual's inability to function effectively in the workplace and at home, as well as adversely affects a patient's adherence to HAART (Hinkin et al., 2004).

HAND confers an increased risk for early mortality, independent of medical predictors (Ellis, Jones, & Mosdell, 1997; Mayeux et al., 1993) and often interferes significantly with cognitively demanding activities of daily living. e.g. employment, medication management, driving (Heaton et al., 2004; Hinkin et al., 2004).

HAND even in its mild form is associated with less ability to perform the most complex daily tasks, worse quality of life, difficulty obtaining employment, and shorter survival.

In a study of individuals with longstanding aviremia (Simioni et al., 2010) found cognitive complaints overall prevalence was 27%. The prevalence of HAND was 84% among patients with cognitive complaints and 64% in those without. ANI was present in 24%, MND in 52%, and HAD in 8% (McArthur & Brew, 2010).

Individuals with the less severe forms of HAND are likely to develop the severe forms hence early diagnosis and treatment is critical. People with HAND have a significantly increased risk of death. In a Canadian cohort, the survival of individuals with HAND was only one-third of those without (Vivithanaporn et al., 2010), worse antiretroviral adherence maybe a contributing factor(McArthur & Brew, 2010).

The prevalence of HAND continues at very high rates, in the cohort; CNS HIV Anti-retroviral Therapy Effects Research (CHARTER), 53% of the total sample had neurocognitive impairment, with increasing rates in those with more comorbid illness. Prevalence estimates were 33% for ANI, 12% for MND, and 2% for HAD (McArthur & Brew, 2010).

This sheds new light on the question and the adequacy of current screening techniques for HAND. We have less information about the performance of tests in the HAART era. HAND can develop at almost any stage of HIV infection, although it is more common as immunosuppression advances. In resource-limited areas, HAND is probably as prevalent as in developed countries (McArthur & Brew, 2010).

1.3 Study Justification

Despite HAND being an important cause of morbidity and mortality among people with HIV, the prevalence and the factors associated with HAND in our set up have not been established. There is paucity of data in Kenya.

Additionally, early screening of HAND will improve diagnosis and this will help institute the necessary interventions to prevent further cognitive decline. Worsening neurocognitive dysfunction may trigger consideration of antiretroviral modification where other causes have been excluded.

Drugs with high central nervous system penetration effectiveness (CPE score) can be prioritized as first line drugs while neurotoxic drugs be completely avoided in such patients.

Central Nervous System penetration effectiveness (CPE) rank is helpful as it demonstrates that antiretroviral agents that penetrate CNS better have a higher CPE rank and thus more effective to treat the HIV CNS infection.

ART regimen that have higher CPE score are associated with better scores on neuropsychological testing. Drugs with high CPE score of 4 include zidovudine, nevirapine and dolutegravir.

Antiretroviral agents to use with caution include efavirenz, which not only is confirmed to have an association with Central Nervous System toxicity, especially in early treatment but also has emerging evidence of increased suicidality. Furthermore its low barrier to resistance could be problematic in the setting of poor adherence.

Integration of the above data into treatment guidelines is crucial as the brain is a potential sanctuary for persistent infection and ongoing inflammatory damage (McArthur & Brew, 2010).

The clinical importance of HAND is receiving increasing attention as patients are surviving longer and neurocognitive health has become an issue of importance in the HIV and general community.

1.4 Research Questions

Is HAND common in patients on ART and what are the factors associated with HAND?

1.5 Research Objectives

1.5.1 Broad Objective

To determine the prevalence and the factors associated with HIV-associated neurocognitive disorders (HAND) in Moi Teaching and Referral hospital (MTRH), Eldoret, Kenya

1.5.2 Specific Objectives

1. To determine the prevalence of HAND among HIV infected patients on ARVs at MTRH
2. To determine the factors associated with HAND among HIV infected patients at MTRH. (Age, gender, level of education, WHO clinical staging, CD4 count, viral load, duration of HIV, ART regimen, CPE score)

CHAPTER TWO: LITERATURE REVIEW

2.1 Epidemiology of HIV

2.2.1 Worldwide:

In its fourth decade, it is evident that the global HIV epidemic is quite different from that first recognized among a small number of homosexual men in 1981.

The epidemic has reached every country and nearly all populations throughout the world.

Spread of the disease has been particularly alarming in resource- limited countries, especially sub- Saharan Africa and south East Asia, but continues to threaten other populations in Eastern Europe, Latin America, and the Caribbean (UNAIDS, 2013).

By the end of 2013, the reported statistics on the global burden of HIV were the following:

35 million adults and children were living with HIV/AIDS, 2.1 million people, including 240,000 children, had been newly infected with HIV in that year and 1.5 million people died of AIDS in that year.

The overall prevalence of HIV appears to have stabilized, or increased in some countries, likely due to increased survival of infected people because of antiretroviral treatment.

2.2.2 Sub- Saharan Africa:

Nearly three quarters of the world's HIV infected population are in sub- Saharan Africa. Countries in sub- Saharan Africa and the Caribbean have the highest national rates of adult HIV prevalence. As an example, in 2013, the adult HIV prevalence ranged from <0.1 percent in the Middle East and North Africa to 4.7 percent in sub-Saharan Africa overall, and it exceeded 20 percent in some sub- Saharan countries,

such as Botswana, Lesotho, and Swaziland. Part of the disparity can be attributed to the maturity of the epidemics in Africa and the more recent introduction of HIV into some other areas of the world.

2.2.3 Kenya

In 2014, the Kenya National AIDS and Sexually Transmitted Infections Control Program (NASCOP) estimates showed the adult national HIV infection prevalence to be 6.0% (*HIV Estimates report Kenya*, 2014). HIV prevalence rates vary throughout the country depending on the social, cultural and economic circumstances. Uasin Gishu County had an adult prevalence of 4.9% (2012). The number of PLHIV is estimated to have increased from about 1.4 million in 2009 to 1.6 million in 2013. Women constitute about 57% of the PLHIV, while men account for 43%. About 80% to 90% of the PLHIV are adults. ("Kenya Aids Progress report," 2014)

2.2 HIV and HAND

HIV disseminates to the central nervous system during the initial days of systemic infection and can be detected in the cerebrospinal fluid (CSF) of most untreated patients thereafter (McCutchan et al., 2007; Price et al., 2014; Valcour et al., 2012).

HAND is as a result of direct infection by the virus, due to its predilection to invade and cause disease in the CNS. HIV enters the brain during the initial viremia following infection. It occurs through infected macrophages/monocyte lineage cells crossing the blood-brain barrier. In the brain parenchyma, mainly monocyte derived cells (microglia and macrophages), and to lesser extent astrocytes, can be infected by HIV. This ultimately leads to cell death. Once the virus is within the brain parenchyma, it distributes selectively with the highest concentrations being found in the basal ganglia, subcortical frontal white matter and frontal cortex. This regionally

preferential distribution within the brain may relate to viral entry through the CSF pathways.

However, the character of CSF infection changes over the course of infection and disease evolution. Initially, CSF viruses are genetically identical to those in blood and likely originate from trafficking CD4 cells. Later, CNS infection can become "compartmentalized," with the virus evolving independently from the virus found in blood. Additionally, the cell tropism of the CNS virus may change to become largely macrophage-tropic (M-tropic), in contrast to blood virus, which characteristically maintains tropism for T-lymphocytes.

CNS injury prior to initiation of ART is likely to lower the threshold for symptomatic neurocognitive impairment, by decreasing the physiological reserve.

A Consensus Report of the Mind Exchange Program recommended that, all HIV patients should be screened for HAND early in disease using standardized tools. Follow up frequency depends on whether HAND is already present or whether clinical data suggest risk for developing HAND. Worsening neurocognitive impairment may trigger consideration of antiretroviral modification when other causes have been excluded.
The program provides practical guidance in the diagnosis, monitoring and treatment of HAND (2013).

It is appropriate to assess neurocognitive functioning in all patients with HIV as there is limited rationale for screening only symptomatic patients (Gandhi et al., 2011; Rourke, Halman, & Bassel, 1999; Tozzi et al., 2007; Woods, Moore, Weber, & Grant, 2009), or only those recognized risk factors for HAND (e.g. nadir $CD4^{+}$T -cell counts <200 cells/ul). Furthermore, because the CNS is commonly one of the first targets of

HIV infection, good practice suggests that a patient's neurocognitive profile should be assessed early (within 6 months of diagnosis, as soon as clinically appropriate) using a sensitive screening tool (Valcour et al., 2012).

If possible, screening should take place before the initiation of cART, as this will establish accurate baseline data, and allow for subsequent changes to be more accurately assessed.

Although there are insufficient data to establish the best time for follow-up assessments, the consensus group agreed that screening for HAND should occur every 6-12 months in higher risk patients or every 12-24 months in lower risk patients.

When treated patients have persistent NCI despite effective cART, the possibility of cART neurotoxicity should be considered. Evidence for the development of neuropsychiatric symptoms (e.g. sleep disturbance, dizziness, anxiety, depression) is greatest for efavirenz; however, the effects typically occur early in therapy and in many cases resolve spontaneously. If symptoms continue to persist, switching to an alternative treatment should be considered.

Prevalence in the ART era — The widespread use of suppressive combination antiretroviral therapy (ART) has been associated with a marked decrease in the incidence of more severe neurocognitive deficits (i.e., HIV-associated dementia [HAD])(d'Arminio Monforte et al., 2004). Data from 15,380 HIV-infected patients followed in the CASCADE cohort (Concerted Action on Sero-conversion to AIDS and Death in Europe) demonstrated a decrease in the incidence of HAD from 6.49 per 1000 person- years in the pre-ART era to 0.66 per 1000 person-years by 2003 to 2006 (Bhaskaran et al., 2008). Similarly, a Danish population study reported that the

incidence of severe neurological deficits in those with HIV infection was approaching that of the uninfected population (Lescure et al., 2011).

In contrast to the major impact of ART on the incidence of HAD, a number of reports document a continued, substantial prevalence of milder impairment on testing in the setting of HIV infection (ranging from 20 to 69 percent in various series), even among patients with viral suppression (Bonnet et al., 2013; Crum-Cianflone et al., 2013; Heaton et al., 2010; Heaton et al., 2015; Pumpradit et al., 2010; Robertson et al., 2007; Simioni et al., 2010). In a study of 1521 HIV infected patients from the eras before and after combination ART, neurocognitive impairment of any type was seen slightly more frequently in the post-ART compared with pre-ART cohorts (40 versus 33 percent, respectively) (Heaton RK, 2011). In a separate analysis of the same post-ART cohort, the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study, asymptomatic neurocognitive impairment (ANI) was most common, occurring in 33 percent, with mild neurocognitive disorder in 12 percent and HAD in only 2 percent of 1316 HIV-infected patients (the majority were on ART) (Heaton et al., 2010).

In a smaller study of HIV infected patients, the prevalence of neurocognitive deficits was similar among 51 patients treated with single-drug ART and 90 patients treated with combination ART (Cysique, Maruff, & Brew, 2004). However, the patterns of deficits differed: the use of combination ART specifically was associated with improvement in attention, verbal fluency, and visuoconstruction defects, but deterioration in learning efficiency and complex attention.

The Australian Society of HIV (ASHM) guidelines recommend the use of specific antiretroviral in patients diagnosed with HIV-associated CI with suspected favourable CNS pharmacokinetics, such as zidovudine (AZT) (ASFH, 2009). The U.S Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents (DHHS ART Guidelines) recommend the avoidance of efavirenz in those with HAD, favouring darunavir-or dolutegravir- based regimens (AIDSInfo, 2016).

In the United States, three regimes are among the recommended regimens for initial treatment of HIV infection including patients with HAD provided there is no documented or expected resistance to the regimens or other contraindications. The drugs have theoretical benefit to their CNS pharmacokinetics. These include; Tenofovir-emtricitabine plus darunavir, Abacavir-lamivudine plus dolutegravir (if HLA-B*5701 is negative) and Tenofovir-emtricitabine plus ritonavir-boosted darunavir (Caniglia et al., 2014).

Observational studies have suggested that ART regimens that have higher CPE scores are associated with better scores on neuropsychological testing. In one study of 185 HIV infected patients, initiation of an ART regimen with a high CPE score was associated with greater improvements in tests of concentration, speed of mental processing, and mental flexibility (Cysique et al., 2009).

In South Africa, a study was done on; Exploring the utility of the Montreal Cognitive Assessment to Detect HIV- Associated Neurocognitive Disorder: The challenge and need for culturally valid screening tests in South Africa by (Robbins et al., 2013).

HIV infected participants performed significantly worse overall and specifically in the domains of visuospatial, executive, attention, and language (confrontation naming).

Regression analysis indicated that HIV status and education were the strongest predictors of total scores.

The Montreal Cognitive Assessment (Nasreddine et al., 2005), a screening tool designed to detect mild neurocognitive impairment, may hold promise to assist in the detection of HAND, including its less severe forms, in South Africa. The MoCA, which takes only approximately 10 minutes to administer, assesses many of the neurocognitive domains most affected by HIV, including executive functioning, attention/concentration, and memory. Although originally developed for use in North America with older adults at risk for Alzheimer's disease, it has been validated for use as a screening tool for mild neurocognitive impairment related to other disease processes e.g., Parkinson's and Huntington's Diseases (Bourdeau et al., 2005; Videnovic et al., 2010; Zadikoff et al., 2008).

A recent study published in 2016 compared HAND in USA and South Africa using the screening tools including IHDS and MoCA. MoCA had a sensitivity of 89% and specificity of 23% (Joska et al., 2016).

The IHDS was validated in Uganda with a sensitivity of 80% and specificity of 55% (Sacktor et al., 2005).

The validity of the Lawton IADL was tested by determining the correlation of the Lawton IADL with four scales that measured domains of functional status, the Physical Classification (6-point rating of physical health), Mental Status Questionnaire (10-point test of orientation and memory), Behavior and Adjustment rating scales (4-6-point measure of intellectual, person, behavioral and social adjustment), and the PSMS (6-item ADLs). All correlations were found to be significant at the 0.01 or 0.05 level (Lawton & Brody, 1969).

CHAPTER THREE: RESEARCH METHODOLOGY

3.1 Study Setting

MTRH serves as the teaching hospital for Moi University School of Medicine and is the second largest tertiary referral centre in Kenya.

It serves a population of 16 million people (40% of Kenya's population) in western Kenya and is the primary care site for the 300,000 urban populations in Eldoret town.

There are four AMPATH (Academic Model Providing Access To Healthcare) HIV clinics, modules, one of which is for paediatric patients.

AMPATH centre at MTRH has over 30,000 HIV infected patients actively enrolled into care with almost half of them (14,000) on ART.

3.2 Study Population

Adult HIV infected patients on ART enrolled into care in the AMPATH clinic. Approximately 80 adult patients are seen daily in each module at AMPATH.

3.3 Eligibility

3.3.1. Inclusion Criteria

- HIV infected patients on ART receiving care in the AMPATH HIV clinic
- Age between18and 65 years

3.3.2. Exclusion Criteria

- Active or known past CNS opportunistic infection.
- Fever of $> 38^0C$
- History of chronic neurological disorder such as stroke, epilepsy and traumatic disorders of nervous system due to head trauma
- Active psychiatric disorder
- Alcoholism (CAGE score >2) and drug abuse
- Severe medical illness that would interfere with the ability to perform study evaluation

3.4 Study Design

This was a cross-sectional analytical study.

3.5 Sample Size Calculation

Objective 1:Fisher's exact formula to calculate the prevalence.

The Sample size is calculated as shown below:

$$N = \frac{(Z\alpha/2)^2 \times p(1-p)}{d^2}$$

Where:

N = minimum sample size required

α = the level of significance (5%)

$Z\alpha/2$ = the value of Z at the selected level of significance

p = likely prevalence (31%)- Ugandan study- N.Sacktor

d = P value (0.05)

$$N = \frac{(1.96^2)*0.31*0.69}{(0.05)^2}$$

N= 328 patients

10% adjusted for non-response and missing data = 360 patients

Objective 2:Pedduzi et al formula to determine the associated factors.

$$n = \frac{10K}{P}$$

n= required sample size

K= No of independent variables 9

$$n = \frac{10*9}{0.31}$$

290 patients

The sample size of 360 patients was selected since it was large and fulfilled both objectives.

3.6 Sampling Technique

Systematic random sampling technique was used to sample the participants meeting the inclusion criteria.

Simple random sampling was used to identify the first study participants in any randomly selected module out of the first eight patients who arrived at the clinic on any given day.

Every eighth patient who will report to the clinic (nurse station) was approached and requested to take part in the study.

If the eighth patient was not eligible to participate in the study, the next patient was approached until an eligible participant was recruited.

Every eighth interval was arrived by considering that an average of eighty patients are seen on daily basis in each module and the study target was to recruit ten participants each day. Eighty divided by 10 gives an interval of eight.

3.7 Data Variables

3.7.1 Primary Outcome Variables

- Asymptomatic neurocognitive impairment (ANI) – Based on low scores <26 in MoCA (Montreal cognitive assessment tool) and good performance in IHDS (International HIV dementia scale tool)>10
- Mild neurocognitive disorder (MND) – Based on low scores <26 in MoCA (Montreal cognitive assessment tool) and good performance in IHDS (International HIV dementia scale tool) >10
- HIV- Associated Dementia (HAD)- Based on low scores <26 in MoCA (Montreal cognitive assessment tool) and poor performance in IHDS (International HIV dementia scale tool) <10

3.7.2 Predictor Variables

- Age
- Gender
- Level of education
- WHO clinical staging
- CD4 count
- Viral load
- Duration of HIV (length of time since diagnosis)
- Type of regimen of ARV'S
- CPE score

3.7.3 Other data variables that were collected

- BMI
- Level of Income
- Duration of HAART
- Co -morbidities

3.8 Study Procedure

The study was conducted within the HIV clinic at the AMPATH centre. Recruitment of participants into the study was done in the triage room and at the waiting bay as they waited to see the clinicians. The purpose of the study and potential benefits was explained to the participants. Those who met eligibility criteria and consented participated in the study after signing informed consent form. The participants were then recruited until the desired sample size was achieved.

Participants had their anthropometric measurements; height and body weight measured. They were then taken through the interviewer administered structured questionnaire (Appendix I) then the tools starting with the MoCA, IHDS then the IADL were administered. Subsequently, they were sent for the CD4 count at the AMPATH reference lab and the baseline CD4 count and viral load collected from the Academic Model Providing Access to Healthcare (AMPATH) database.

Measures were taken to ensure safety and confidentiality of the participant's data.

3.8.1 Recruitment Schema and Study procedure

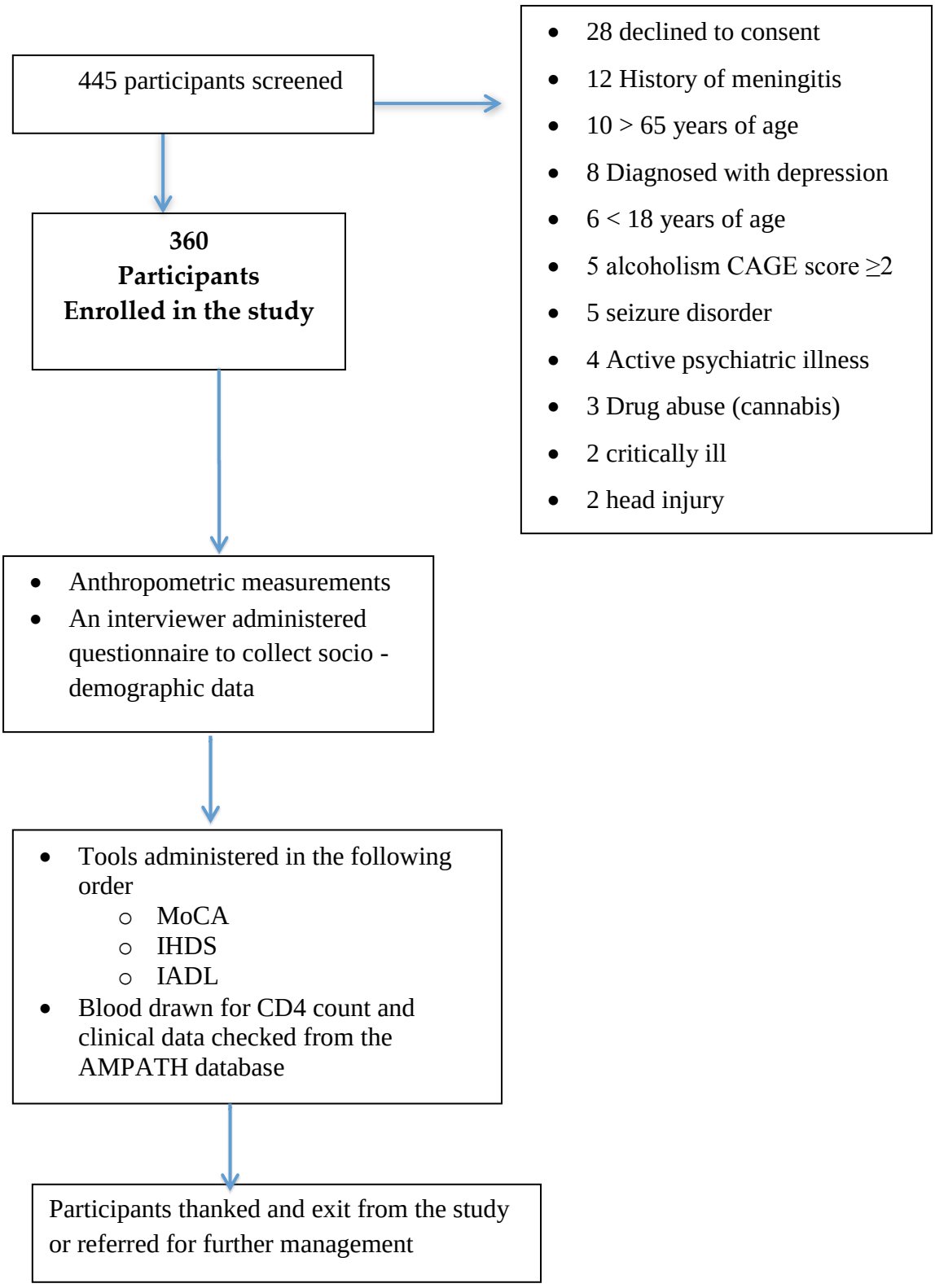


Figure 1: Recruitment Schema and Study procedure

3.9 Data Collection and Management

3.9.1 Data Collection

Anthropometric measurements were recorded. An interviewer administered structured questionnaire was used to collect socio-demographic data. The tools MoCA, IHDS, Lawton instrumental activities of daily living were administered. Blood was drawn for the CD4 count and the baseline CD4 count and viral load collected from the Academic Model Providing Access to Healthcare (AMPATH) database.

The completed questionnaires were coded and entered into an excel sheet and later exported into STATA version 13.

3.9.2 Data Analysis

Data analysis was done using STATA version 13.

Descriptive statistics for measures of central tendency such as the mean and median were used to summarize continuous variables. The mean and the corresponding standard deviation were used to summarize continuous variables that assumed the Gaussian distribution. Such variables include age and years of education among others. Variables such as CD4, body mass index (BMI), duration of living with HIV, and duration of using HAART among others violated the Gaussian assumptions hence were summarized using the median and the corresponding inter quartile range (IQR). Gaussian assumptions were assessed using Shapiro-Wilk test and histograms. Frequencies and the corresponding percentages were used to summarize categorical variables such as gender, marital status, and education level, WHO clinical stage among others.

The outcome, HIV-Associated Neurocognitive Disorder (HAND), was defined using the indices, MoCA and IHDS. Participants with MoCA ≥ 26 and IHDS ≥ 10 were considered normal. A participant who had a MoCA score < 26 and IHDS >10 had mild HAND (ANI/MND), a participant who had MoCA score < 26 and IHDS score < 10 had severe HAND. Hence the outcome had three levels: normal, mild HAND and severe HAND. In the latter analysis the mild and the severe cases of HAND were combined to give two levels: with and without HAND.

Pearson's Chi Square test was used to compare proportions between the participants diagnosed with HAND and those without HAND while Independent samples t-test was used to compare continuous variables between the participants diagnosed with HAND and those without HAND.

Logistic regression model was used to assess the determinants of HAND. Odds ratios (OR) and the corresponding 95% confidence intervals (95% CI) were reported. Factors associated with the diagnosis of HAND were determined using backward selection method. Under this approach, a model with all the variables of interest (following the initial screening) was fit. Then the least significant variable was dropped, so long as it had the largest p-value that was greater than 5%. This process was repeated by successively re-fitting reduced models and applying the same rule until the remaining variables were statistically significant. In the model clinically meaningful variables that were not statistically significant were retained. Such variables include viral load suppression, duration of being on HAART, use of second line HAART, and CPE score.

3.12 Ethical Considerations

Ethics review and approval was acquired from the department of Internal medicine and IREC (Institutional Research and Ethics Committee).

Permission to conduct study was obtained from management of MTRH and AMPATH. Written informed consent was obtained from the study participants.

Data storage and protection was kept strictly confidential and anonymity was maintained.

Study participants who were found to have HAND had their attending clinicians informed to facilitate close follow-up and assessment of their cognitive decline.

CHAPTER FOUR: RESULTS

A total of 360 participants with mean age 40.2 (SD: 11.5) years, Range: 18.0 – 65.0 years were included in the study.

4.1: Socio-demographic characteristics

Table 1: Socio-demographic characteristics

Variable	N	Mean (SD) or n (%)
Age (Years)	360	40.2 (11.5)
Range (Min. – Max.)		18.0 – 65.0
Male	360	126 (35.0%)
Marital status		
Single		89 (24.9%)
Married	358	161 (45.0%)
Divorced/Separated		38 (10.6%)
Widowed		70 (19.6%)
Education level		
Primary		159 (44.2%)
Secondary	360	155 (43.1%)
Tertiary		46 (12.8%)
Years of education	360	9.9 (3.1)
Range (Min. – Max.)		2.0 – 18.0
Occupation		
Employed		82 (22.8%)
Self employed	359	89 (24.8%)
Unemployed		188 (52.4%)
Level of income (Kenya Shillings/Month)		
<10000		302 (86.5%)
10000 – 50000	349	41 (11.8%)
50000 – 100000		5 (1.4%)
>100000		1 (0.3%)

SD – Standard Deviation

One third, 126 (35%), were male and 45% were married. Three hundred and fourteen (87.3%) had primary and secondary level of education, and the mean years of education was 9.9 (SD: 3.1) with a range of 2.0 – 18.0 years.

Slightly more than half of the participants were unemployed (52.4%), and the majority 86.5% earned less than Kenya Shillings 10000 per month.

4.2: Clinical Characteristics

Table 2: Clinical characteristics

Variable	N	Median (IQR) or n (%)
Body Mass Index (Kg/m^2)	360	22.9 (20.3, 25.5)
Range (Min. – Max.)		14.8 – 54.0
< 18.5		34 (9.4%)
18.5 – 25.0	360	221 (61.4%)
25.0 – 30.0		86 (23.9%)
> 30.0		19 (5.3%)
Have comorbidities	360	28 (7.8%)
Comorbidities		
Asthma		1 (3.6%)
Diabetes mellitus		1 (3.6%)
Hypertension	28	23 (82.1%)
Hypertension / Diabetes mellitus		2 (7.1%)
Rheumatic Heart disease		1 (3.6%)

IQR – Inter Quartile Range

The median BMI was 22.9 (IQR: 20.3, 25.5) kg/m^2 with 29.2% who were overweight or obese. Twenty-eight (7.8%) of the participants had comorbidities. Hypertension was the predominant comorbidity affecting 6.3% of the total participants.

4.3: HIV treatment and markers of immunity
Table 3: HIV treatment and markers of immunity

Variable	N	Median (IQR) or n (%)
Duration since diagnosis of HIV (Months)	360	107.0 (71.5, 132.0)
Range (Min. – Max.)		1.0 – 181.0
Duration before ART initiation (Months)	360	44.0 (4.5, 78.5)
Range (Min. – Max.)		0.0 – 166.0
Duration of ART use (Months)	360	88.0 (51.0, 122.5)
Range (Min. – Max.)		1.0 – 141.0
Duration of current ART (Months)	360	51.0 (17.0, 76.0)
Range (Min. – Max.)		0.0 – 147.0
ART Line		
First line (NRTI + NNRTI)	360	286 (79.4%)
Second line (NRTI + PI)		74 (20.6%)
Others		
Dapsone		5 (1.4%)
Septrin	359	353 (98.3%)
Septrin/Isoniazid		1 (0.3%)
Suppressed viral load (<1000 copies/ml)	358	303 (84.6%)
Baseline CD4 cell count per mm^3	304	243.0 (10.8.0, 399.0)
Range (Min. – Max.)		1.0 – 1459.0
<200.0		122 (40.1%)
200.0 – 499.0	304	132 (43.4%)
≥500.0		50 (16.4%)
Current CD4 cell count per mm^3	360	491.0 (336.5, 701.0)
Range (Min. – Max.)		1.0 – 1845.0
<200.0		33 (9.2%)
200.0 – 499.0	360	153 (42.5%)
≥500.0		174 (48.3%)
WHO Clinical stage		
Stage 1		122 (35.6%)
Stage 2	343	61 (17.8%)
Stage 3		132 (38.5%)
Stage 4		28 (8.2%)

IQR – Inter Quartile Range

**N is less than 360 in other variables due to missing data*

Participants have been living with HIV for median duration of 107.0 (IQR: 71.5, 132.0) months with a minimum and a maximum of 1.0 and 181.0 respectively. They stayed for a median duration of 44.0 (IQR: 4.5, 78.5) months before initiating ART, Range: 0.0 – 166.0.

The median duration on the current regimen was 51.0 (IQR: 17.0, 76.0) months. One fifth of the participants were on second line regimen, a combination of NRTI and PI based regimen. And 98.6% were on septrin.

There were 84.6% of the participants who had suppressed viral load.

The median baseline and current CD4 were 243.0 (10.8.0, 399.0) cells per mm^3 and 491.0 (336.5, 701.0) cells per mm^3 respectively. Fifty (16.4%), and 48.3% had at least 500 cells per mm^3 at baseline CD4 and current CD4 respectively. And 160 (46.7%) of the participants were in WHO clinical stages 3 or 4.

4.4: Montreal cognitive assessment (MoCA), International HIV dementia scale (IHDS), and the Lawton Instrumental Activities of Daily Living Scale (IADL)

Table 4: **Montreal cognitive assessment (MoCA), International HIV dementia scale (IHDS), and the Lawton Instrumental Activities of Daily Living Scale (IADL)**

Item	N	Mean (SD) or n (%)
MoCA	360	21.2 (4.2)
Range (Min. – Max.)		12.0 – 30.0
Mild ANI/MND (MoCA < 26)	360	292 (81.1%)
Normal (MoCA ≥ 26)		68 (18.9%)
IHDS	360	9.8 (1.7)
Range (Min. – Max.)		5.0 – 12.0
HAD (IHDS < 10)		9 (2.5%)
No HAD (IHDS ≥ 10)	360	351 (97.5%)
IADL	360	8.0 (0.3)
Range (Min. – Max.)		5.0 – 8.0
Experienced functional impairment	360	13 (3.6%)
Activity		
Food preparation/Housekeeping/Laundry		1 (7.7%)
Food preparation/Laundry	13	2 (15.4%)
Responsibility for own medication		6 (46.2%)
Laundry		3 (23.1%)
Shopping		1 (7.7%)
CPE score	360	7.4 (1.8)
Range (Min. – Max.)		5.0 – 10.0

SD – Standard Deviation

Subsets of HAND from the results were: 9 (2.5%) had severe HAND, 283 (78.6%) had mild HAND, and 68 (18.9%) were normal. There were 13 (3.6%) who had functional impairment.

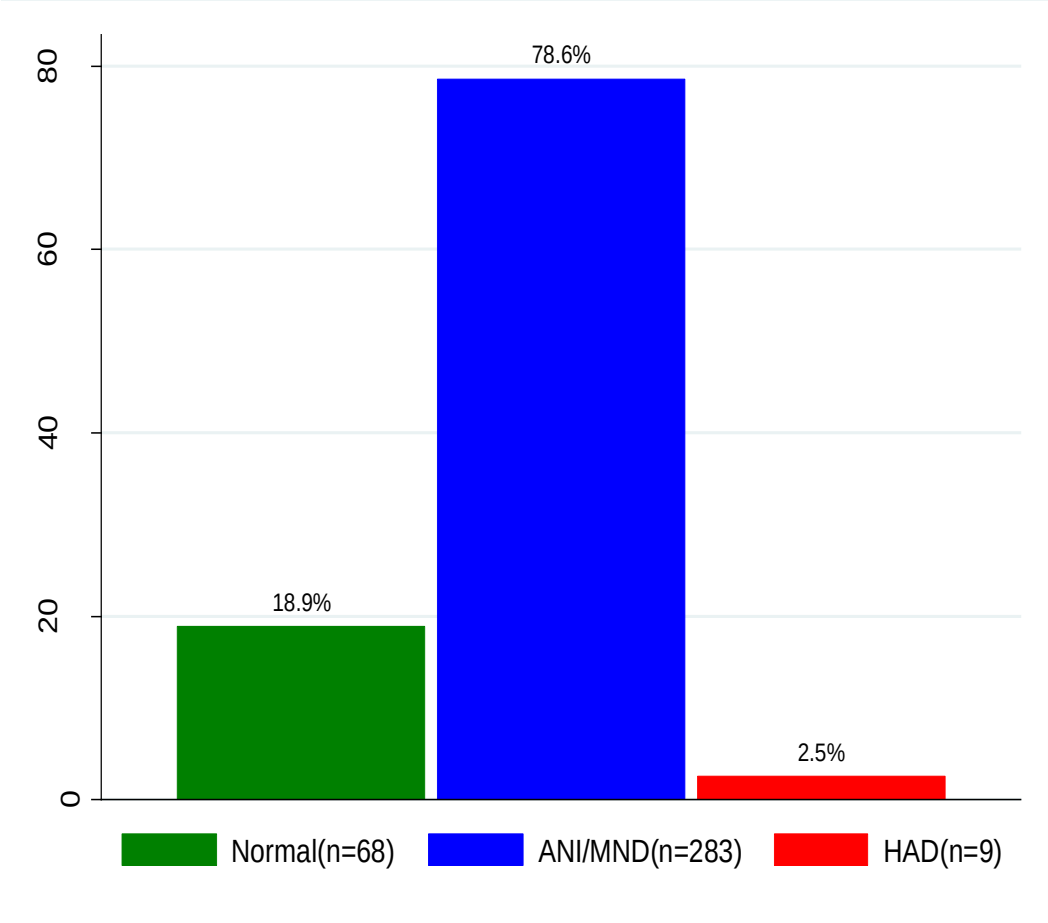


Figure 2: HIV Associated Neurocognitive disorder

4.5: Montreal cognitive assessment (MoCA), and International HIV dementia scale (IHDS) cognitive domains

The cognitive domains of MoCA and IHDS were analyzed to understand which items contributed mainly to the MoCA and IHDS scores. The results were as presented in Table 5.

Table 5: Montreal cognitive assessment (MoCA), and International HIV dementia scale (IHDS) cognitive domains

Domains	N	Mean (SD)	Range (Min. – Max.)
MoCA			
Executive		1.4 (1.9)	0.0 – 5.0
Naming		2.8 (0.5)	1.0 – 3.0
Attention		4.4 (1.6)	0.0 – 6.0
Language		1.3 (0.7)	0.0 – 3.0
Abstraction		1.1 (0.7)	0.0 – 2.0
Memory		2.7 (1.8)	0.0 – 5.0
Orientation		6.0 (0.2)	4.0 – 6.0
Total		21.2 (4.2)	12.0 – 30.0
IHDS			
Motor speed		3.6 (0.5)	2.0 – 4.0
Psychomotor speed		3.1 (0.7)	0.0 – 4.0
Memory-recall		3.0 (1.1)	0.0 – 4.0
Total		9.8 (1.7)	5.0 – 12.0

IHDS – International HIV Dementia; MoCA – Montreal Cognitive Assessment

Analysis of the cognitive domains showed that MoCA was mainly driven by the orientation, mean: 6.0 (SD: 0.2) with a minimum and a maximum of 4.0 and 6.0 respectively. Abstraction and language contributed the least to MoCA, mean: 1.1 (SD: 0.7), and 1.3 (SD: 0.7) respectively. The total MoCA score was 21.2 (SD: 4.2) with a range of 12.0 – 30.0.

The motor speed, psychomotor speed, and memory-recall domains contributed equally to IHDS. Motor speed ranked highest, mean: 3.6 (SD: 0.5) then psychomotor speed, mean: 3.1 (SD: 0.7), and lastly memory-recall, mean: 3.0 (SD: 1.1). The total mean score was 9.8 (SD: 1.7) with a range of 5.0 – 12.0.

4.6: The associations between socio-demographic characteristics and diagnosis of HAND.

Table 6: Association between socio-demographic characteristics and diagnosis of HAND

Variable	Presence of HAND			
	Yes (n=292, 81.1%) Mean (SD) or n (%)	**No (n=68, 18.9%)** Mean (SD) or n (%)	**P-value**	**UOR (95% CI)**
Age (Years)	41.9 (10.6)	33.0 (12.5)	<0.001	1.07(1.05,1.10)
Male vs. Female	95 (32.5%)	31 (45.6%)	0.042	0.58(0.34,0.98)
Married vs. Single/Widowed/separated/ divorced	138 (47.6%)	23 (33.8%)	0.040	1.78(1.02,3.09)
Education				
Primary	150 (51.4%)	9 (13.2%)	<0.001	Reference
Secondary	113 (38.7%)	42 (61.8%)	0.001	0.16(0.08,0.35)
College	29 (9.9%)	17 (25.0%)	0.001	0.10(0.04,0.25)
Occupation				
Unemployed	153 (52.6%)	35 (51.5%)	0.869	Reference
Self employed	71 (24.4%)	18 (26.5%)	0.722	0.90(0.48,1.70)
Employed	67 (23.0%)	15 (22.1%)	0.864	1.02(0.52,2.00)
Income (Ksh.per Month)				
> 10000	39 (13.6%)	8 (12.7%)		Reference
≤ 10000	247 (86.4%)	55 (87.3%)	0.843	0.92(0.41,2.08)

UOR - Unadjusted Odds Ratio; 95% CI – 95% Confidence Interval.

Participants who were diagnosed with HAND were significantly older than those without HAND; 41.9 (SD: 10.6) vs. 33.0 (SD: 12.5) years, p <0.001. This demonstrates a 7% increased chance/risk of diagnosis of HAND among the older participants compared to the younger; OR: 1.07 (95% CI: 1.05, 1.10).

Significantly lower proportion of male participants, and significantly higher proportion of the married participants were diagnosed with HAND compared to those without HAND; 32.5% vs. 45.6%, $p = 0.042$, and 47.6% vs. 33.8%, $p = 0.040$ respectively. These findings show that there was a 42% reduced odds of diagnosis of HAND among the male participants compared to the female, OR: 0.58 (95% CI: 0.34, 0.98), and a 78% increased odds of diagnosis of HAND among the married participants compared to the single/separated/widowed/divorced, OR: 1.78 (95% CI: 1.02, 3.09).

Compared to the participants without HAND, a significantly lower proportion of participants with secondary and tertiary level of education were diagnosed with HAND, 38.7% vs. 61.8%, $p < 0.001$, and 9.9% vs. 25.0%, $p = 0.001$ respectively. Compared to those with primary level of education, the participants with secondary and tertiary level of education had 84%, and 90% reduced odds of diagnosis of HAND; OR: 0.16 (95% CI: 0.08, 0.35), and 0.10 (95% CI: 0.04, 0.25) respectively.

There was no evidence of a difference in employment status between those who were diagnosed with HAND and those who did not have HAND, $p > 0.05$.

4.7: The associations between clinical characteristics and diagnosis of HAND.

Table 7: Association between clinical characteristics and diagnosis of HAND

Variable	Presence of HAND		P-value	UOR (95% CI)
	Yes (n=292, 81.1%) Mean (SD) or n (%)	**No (n=68, 18.9%)** Mean (SD) or n (%)		
BMI (Kg/m^2)				
<18.5	24 (8.2%)	10 (14.7%)	0.099	0.56 (0.25, 1.27)
18.5 – 25.0	179 (61.3%)	42 (61.8%)	0.944	Reference
25.0 – 30.0	73 (25.0%)	13 (19.1%)	0.306	1.32 (0.67, 2.60)
>30.0	16 (5.5%)	3 (4.4%)	0.723	1.25 (0.35, 4.49)
Baseline CD4 (cells per mm^3)				
<200	103 (42.0%)	19 (32.2%)	0.166	Reference
200 – 500	105 (42.9%)	27 (45.8%)	0.686	0.72 (0.38, 1.37)
> 500	37 (15.1%)	13 (22.0%)	0.197	0.53 (0.24, 1.17)
Current CD4 (cells per mm^3)				
<200	27 (9.3%)	6 (8.8%)	0.913	Reference
200 – 500	121 (41.4%)	32 (47.1%)	0.398	0.84 (0.32, 2.21)
> 500	144 (49.3%)	30 (44.1%)	0.440	1.07 (0.41, 2.81)
WHO Clinical stage				
Stage 1	95 (34.4%)	27 (40.3%)	0.367	Reference
Stage 2	47 (17.0%)	14 (20.9%)	0.458	0.95 (0.46, 1.99)
Stage 3	110 (39.9%)	22 (32.8%)	0.289	1.42 (0.76, 2.66)
Stage 4	24 (8.7%)	4 (6.0%)	0.465	1.71 (0.54, 5.34)
Have comorbidities	23 (7.9%)	5 (7.4%)	0.879	1.08 (0.40, 2.96)
Regimen				
First line (NRTI + NNRTI)	241 (82.5%)	45 (66.2%)		Reference
Second line (NRTI + PI)	51 (17.5%)	23 (33.8%)	0.003	0.41 (0.23, 0.74)
Years on current HAART	4.4 (3.0)	3.2 (2.8)	0.002	1.16 (1.05, 1.28)
Individual HAART drugs				
EFV/ETR/ABC	139 (47.6%)	35 (51.5%)	0.565	Reference
AZT	127 (43.5%)	18 (26.5%)	0.010	2.99 (0.49, 18.01)
TDF	161 (55.1%)	48 (70.6%)	0.020	1.93 (0.33, 11.15)
NVP	108 (37.0%)	12 (17.7%)	0.002	2.28 (1.11, 4.67)
Years since HIV diagnosis	8.1 (3.7)	8.4 (3.7)	0.620	0.98 (0.91, 1.06)
Viral load < 1000 copies/ml	248 (85.5%)	55 (80.9%)	0.340	1.40 (0.70, 2.77)
CPE score	7.6 (1.8)	6.8 (1.7)	<0.001	1.30 (1.11, 1.53)

UOR - Unadjusted Odds Ratio; 95% CI – 95% Confidence Interval.

There was no evidence of a difference in BMI, baseline CD4 levels, current CD4 levels, WHO clinical stage, and presence of comorbidities between those who were diagnosed with HAND and those who did not have HAND, $p > 0.05$.

Significantly lower proportion of participants who were diagnosed with HAND were on second line regimen which comprised of NRTI and PI, 17.5% vs. 33.8%, $p = 0.003$. This represented a 59% reduced odds of diagnosis of HAND among those who were in second line compared to those who were in first line; OR: 0.41 (95% CI: 0.23, 0.74).

There was no difference in the average duration of living with HIV among the participants who were diagnosed with HAND compared to those without HAND; 8.1 (SD: 3.7) vs. 8.4 (SD: 3.7) years, $p = 0.620$. Compared to the participants without HAND, the participants who were diagnosed with HAND had been on their current HAART for a significantly longer average duration; 4.4 (SD: 3.0) vs. 3.2 (SD: 2.8) years, $p = 0.003$.

The proportion of participants with suppressed viral load were similar for those who were diagnosed with HAND, and those who were normal, 85.5% vs. 80.9%, $p = 0.340$ respectively.

The average CPE score was significantly higher among those who were diagnosed with HAND compared to those without HAND; 7.6 (SD: 1.8) vs. 6.8 (SD: 1.7), $p <0.001$. The crude estimates show that the participants who had higher CPE score were associated with 30% increased odds of being diagnosed with HAND; OR: 1.30 (95% CI: 1.11, 1.53)**.**

4.8: The adjusted model of the determinants of diagnosis of HAND.

Table 8: Logistic regression model assessing the determinants of diagnosis of HAND

Variable	**Unadjusted Estimates**		**Adjusted Estimates**	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age (Years)	1.07 (1.05, 1.10)	<0.001	**1.06 (1.03, 1.10)**	**<0.001**
Male	0.58 (0.34, 0.98)	0.042	**0.48 (0.24, 0.97)**	**<0.001**
Education level				
Secondary vs. primary	0.16 (0.08, 0.35)	0.001	**0.16 (0.07 0.38)**	**<0.001**
Tertiary vs. Primary	0.10 (0.04, 0.25)	0.001	**0.11 (0.04, 0.35)**	**<0.001**
Income ≤ Ksh/Month10000	0.92 (0.41, 2.08)	0.843	0.54 (0.19, 1.54)	0.252
Years on current HAART	1.16 (1.05, 1.28)	0.002	1.04 (0.90, 1.19)	0.627
On Second line regimen	0.41 (0.23, 0.74)	0.003	0.66 (0.30, 1.43)	0.288
WHO stage 3/4 vs. 1/2	1.49 (0.86, 2.57)	0.152	**2.45 (1.20, 5.01)**	**0.014**
Viral load < 1000 copies/ml	1.40 (0.70, 2.77)	0.340	0.70 (0.28, 1.73)	0.439
CPE score	1.30 (1.11, 1.53)	<0.001	1.13 (0.89, 1.42)	0.312
Sample Size			**331**	

OR – Odds Ratio CI – Confidence Interval

The findings demonstrate that older participants were associated with 6% increased odds of diagnosis of HAND compared to the younger participants, OR: 1.06 (95% CI: 1.03, 1.10). And male participants were associated with 52% reduced odds of being diagnosed with HAND, OR: 0.48 (95% CI: 0.24, 0.97).

Education level was associated with diagnosis of HAND. The findings show that participants who had secondary level of education and those who had tertiary level of education were associated with 84% and 89% reduced odds of being diagnosed with HAND, OR: 0.16 (95% CI: 0.07, 0.38) and 0.11 (95% CI: 0.04, 0.35) respectively.

Compared to low WHO clinical stage (stage 1 or 2), the advanced WHO clinical stage (stage 3 or 4) was associated with more than twice increased odds of being diagnosed with HAND, OR: 2.45 (95% CI: 1.20, 5.01).

After adjusting for age, gender, education level, income, years on the current HAART, use of second line regimen, WHO clinical stage, and viral load level, the effect of CPE score was removed, AOR: 1.13 (95% CI: 0.89, 1.42).

4.9: Comparison of Montreal cognitive assessment (MoCA), and International HIV dementia scale (IHDS) cognitive domains by presence or absence of HAND.

Table 9: Comparison of Montreal cognitive assessment (MoCA), and International HIV dementia scale (IHDS) cognitive domains by presence or absence of HAND

Domains	**N**	**HAND (N=292)**	**No HAND (N=68)**	**P-value**
		Mean (SD)		
MoCA				
Executive		2.0 (1.8)	4.3 (1.0)	<0.001
Naming		2.7 (0.5)	3.0 (0.0)	<0.001
Attention		4.0 (1.6)	5.8 (0.5)	<0.001
Language		1.1 (0.6)	1.8 (0.7)	<0.001
Abstraction		1.0 (0.6)	1.5 (0.6)	<0.001
Memory		2.4 (1.8)	4.3 (1.0)	<0.001
Orientation		5.9 (0.2)	6.0 (0.2)	0.415
Total		19.8 (3.4)	27.0 (1.0)	<0.001
IHDS				
Motor speed		3.6 (0.6)	4.0 (0.2)	<0.001
Psychomotor speed		3.0 (0.7)	3.7 (0.5)	<0.001
Memory-recall		2.8 (1.1)	3.8 (0.6)	<0.001
Total		9.4 (1.6)	11.5 (0.9)	<0.001

IHDS – International HIV Dementia; MoCA – Montreal Cognitive Assessment

The participants who were diagnosed with HAND performed consistently and significantly worse than the cognitively normal group across all domains, except for the domain of orientation (Table 9).

4.10: Logistic regression showing the predictive power of domain specific impairment

Table 10: Logistic regression results showing the predictive power of domain specific impairment

Cognitive domain	Unadjusted Regression coefficient (95% Confidence Interval)	P-value	Adjusted Regression coefficient (95% Confidence Interval)	P-value
MoCA				
Executive	-0.91 (-1.16, -0.66)	<0.001	-2.49 (-3.56, -1.42)	<0.001
Attention	-1.66 (-2.18, -1.15)	<0.001	-2.73 (-4.13, -1.32)	<0.001
Language	-1.31 (-1.72, -0.90)	<0.001	-2.19 (-3.44, -0.93)	0.001
Abstraction	-1.15 (-1.61, -0.69)	<0.001	-2.15 (-3.42, -0.88)	0.001
Memory	-0.91 (-1.17, -0.65)	<0.001	-2.52 (-3.54, -1.49)	<0.001
IHDS				
Motor speed	-2.66 (-3.83, -1.48)	<0.001	0.52 (-1.60, 2.64)	0.632
Psychomotor speed	-2.16 (-2.74, -1.58)	<0.001	-0.10 (-1.47, 1.28)	0.891
Memory-recall	-1.66 (-2.22, -1.10)	<0.001	0.00 (-0.94, 0.93)	0.994

IHDS – International HIV Dementia; MoCA – Montreal Cognitive Assessment

The logistic regression model results show that all the cognitive domains were independently predictive of the presence of HAND. The logistic regression model with all the cognitive domain elements in the model (adjusted model) show that the MoCA cognitive domain elements were the only domains that were strongly associated with the presence of HAND.

CHAPTER FIVE: DISCUSSION

5.1 Prevalence of HAND

The prevalence of HAND in the study was high (81.1%). The prevalence of mild HAND (ANI/MND) was (78.6%) and the severe HAND (HAD) (2.5%). The current literature depicts rising prevalence of the milder forms of HAND and decrease in severe form of HAND (Cross et al., 2013; Nabha, Duong, & Timpone, 2013; Woods et al., 2009).

The findings are closely similar to a study in Nairobi, Kenya (Awori, Mativo, Yonga, & Shah, 2018). In the study, the prevalence of the mild HAND was 69%. She used the MoCA tool for assessment with a cut- off of <26 for mild HAND.

A study in Ethiopia (Tsegaw, Andargie, Alem, & Tareke, 2017)found the prevalence of severe HAND to be 36.4%. This was higher compared to the present study and this was because they used a lower cut-off of IHDS of <9.5 as opposed to <10.

The prevalence of HAND was lower in a Ugandan study, 31% (Wong et al., 2007) and this could be due to the fact that in their study ANI, the mild form of HAND was not accounted for as it was done before the current sub classification by (Antinori et al., 2007).

Different viral clades may also account for the variation in HAND as certain clades maybe more or less neuropathogenic (Lovejoy & Suhr, 2009; Nabha et al., 2013; Tedaldi, Minniti, & Fischer, 2015). Neurocognitive deficit is more prevalent in regions where subtype C HIV predominates and this subtype is predominant in Sub-Saharan Africa. However, the viral clades were not studied in the present study.

5.2 Socio-demographic and Clinical Characteristics

Socio-demographic characteristics are important health features that affect the prevalence of HAND. Various studies on HAND in Africa included a relatively similar population with a mean age ranging from 29.75 to 40 years (Meta-analysis of studies in sub- Saharan Africa).

Older age was associated with HAND. This was similar to a study done by(Chibanda et al., 2014) in Zimbabwe, (Heaps et al., 2013)in Thailand and (Zhang et al., 2012) in china. This is thought to be due to the neurocognitive decline that comes with aging.

Men were less likely to have HAND. This was comparable to studies (Hestad et al., 2012)in Zambia and (Royal et al., 2016) in Nigeria. This is because of genetic and social factors. In the pathogenesis of HAND men have less immune activation of the macrophages, astrocytes and microglia hence less toxin signaling pathways that underlie the brain dysfunction in HAND. Most men in our African society are privileged to go to school and get educated while female play a role of doing house chores hence they have better cognitive reserve than women hence better cognitive performance(Kabuba, Menon, Franklin, Heaton, & Hestad, 2016).

Majority of the participants were married, unemployed with low level of income and this represents a low socio-economic status of the patients. This was a predictor of poor neurocognitive performance as seen in a study in Cameroon (Atashili et al., 2013).

There was no evidence of a difference in BMI between participants diagnosed with HAND and those without HAND. Hypertension was the predominant comorbidity affecting 6.3% of the total participants. Comorbid conditions are vascular risk factors

contributing to HAND and they include diabetes mellitus, hypertension and abdominal obesity.

Higher level of education was associated with less HAND. This was in line with findings (Breuer, Myer, Struthers, & Joska, 2011) from a systematic review in sub Saharan Africa, (Cross et al., 2013) in USA and (Joska, Fincham, Stein, Paul, & Seedat, 2010)in South Africa. Participants with higher level of education have better scoring in the screening tests, better awareness about the chronicity of HIV and good follow up resulting in good ART adherence and a reduced risk of HAND. This also highlights the need to take the education factor into account when determining local normative cut offs scores for the screening tests for HAND.

The above findings give key information about the impact of HAND on socio-demographic and clinical variables.

5.3 HAND and markers of Immunity

Assessment of the stage of HIV infection with WHO clinical staging, CD4 cell count and viral load is an important element in the evaluation of HAND.

Majority of the participants were in WHO clinical stages 3 and 4. Advanced WHO clinical stage 3 or 4 was associated with more than twice increased odds of being diagnosed with HAND.

This was similar to other studies which showed increased rate of HAND with advanced stages of HIV infection (Odiase, Ogunrin, & Ogunniyi, 2007) in Nigeria, (Wong et al., 2007) in Uganda and (Heaton et al., 1995).

There is evidence of advanced immunosuppression leading to a higher incidence of HIV associated brain injury and also most patients present to the hospitals with late stage of HIV infection and advanced neurocognitive impairment.

There was no evidence of a difference in baseline and current CD4 levels between those participants who were diagnosed with HAND and those who did not have HAND.

Studies in the HAART era have shown that the current CD4 counts have no correlation and are not predictive of HAND (Tozzi et al., 2007). Current CD4 count was relevant in the Pre HAART era. In the above study it did not appear as an important marker.

The baseline CD4 cell count informs the likelihood that progressive cognitive impairment is due to HAD, which occurs at counts of <200 cells per mm^3in untreated patients. From the study, the Prevalence of HAD was very low and could explain the lack of association.

The proportion of participants with suppressed viral loads <1000 copies per ml were similar in both those with HAND and the normal participants. The findings were similar to those found by(Brew, 2004; Brew, Crowe, Landay, Cysique, & Guillemin, 2009; Tozzi et al., 2007) and (Simioni et al., 2010) which revealed that markers such as plasma viral load are not associated with HAND. This shows that normalization of immune indices that reflect peripheral immune function does not adequately reflect the environment that continues to exist in the CNS.CSF viral load has shown promise as a predictor of HAND but more studies need to establish the association.

In the study, CPE score was not associated with HAND after adjusting for the other variables. This was similar to(Marra et al., 2009) and (Cysique et al., 2009) findings.

The cross sectional study design limited meaningful interpretation of the relationship between CPE scores and the presence of HAND since the timing of treatment initiation and duration of treatment need to be considered. Besides, the national ART

treatment guidelines determine the initial ART regimen choice and thereby the CPE scores.

There was no difference in the average duration of living with HIV among the participants who were diagnosed with HAND compared to those without HAND. This was similar to a study done in Botswana(Lawler et al., 2010). This is because the clinical course of HAND is variable and could occur at any time.

5.4 Strengths and Limitations of the study

- Strengths of the study is that various validated and recommended tools were used
- Due to limited neuroimaging among study participants, active CNS pathologies could not be ruled out
- The cross sectional study design limited meaningful interpretation of the relationship between CPE scores and the presence of HAND since the timing of treatment initiation and duration of treatment need to be considered

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

The prevalence of HAND remains high in this HAART error with a higher prevalence of mild HAND (78.6%) and low prevalence of severe HAND (2.5%).

The independent factors associated with HAND are age, gender, level of education and WHO clinical stage.

6.2 Recommendations

- Early screening for HAND in HIV patients.
- A future prospective study to help understand the true association between HAND and the CPE score of ART regimen.

REFERENCES

AIDSInfo. (2016). Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents (2016).

Antinori, A., Arendt, G., Becker, J. T., Brew, B. J., Byrd, D. A., Cherner, M., ... & Gisslen, M. (2007). Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*, *69*(18), 1789-1799.

ASFH. (2009). Medicine ASFH. HIV Management in Australasia [Internet]. ashm.org.au. 2009 [cited 2016 Jan 11].

Atashili, J., Gaynes, B. N., Pence, B. W., Tayong, G., Kats, D., O'Donnell J, K., . . . Njamnshi, A. K. (2013). Prevalence, characteristics and correlates of a positive-dementia screen in patients on antiretroviral therapy in Bamenda, Cameroon: a cross-sectional study. *BMC Neurol*, *13*, 86. doi:10.1186/1471-2377-13-86

Awori, V., Mativo, P., Yonga, G., & Shah, R. (2018). The association between asymptomatic and mild neurocognitive impairment and adherence to antiretroviral therapy among people living with human immunodeficiency virus. *Southern African journal of HIV medicine*, *19*(1).

Bhaskaran, K., Mussini, C., Antinori, A., Walker, A. S., Dorrucci, M., Sabin, C., ... & Cascade Collaboration. (2008). Changes in the incidence and predictors of human immunodeficiency virus–associated dementia in the era of highly active antiretroviral therapy. *Annals of neurology*, *63*(2), 213-221.

Bonnet, F., Amieva, H., Marquant, F., Bernard, C., Bruyand, M., Dauchy, F. A., ... & Catheline, G. (2013). Cognitive disorders in HIV-infected patients: are they HIV-related?. *Aids*, *27*(3), 391-400.

Bourdeau, I., Bard, C., Forget, H., Boulanger, Y., Cohen, H., & Lacroix, A. (2005). Cognitive function and cerebral assessment in patients who have Cushing's syndrome. *Endocrinology and Metabolism Clinics*, *34*(2), 357-369.

Breuer, E., Myer, L., Struthers, H., & Joska, J. A. (2011). HIV/AIDS and mental health research in sub-Saharan Africa: a systematic review. *African Journal of AIDS Research*, *10*(2), 101-122.

Brew, B. J. (2004). Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. *Aids*, *18*, 75-78.

Brew, B. J., Crowe, S. M., Landay, A., Cysique, L. A., & Guillemin, G. (2009). Neurodegeneration and ageing in the HAART era. *Journal of Neuroimmune Pharmacology*, *4*(2), 163.

Caniglia, E. C., Cain, L. E., Justice, A., Tate, J., Logan, R., Sabin, C., ... & Olson, A. (2014). Antiretroviral penetration into the CNS and incidence of AIDS-defining neurologic conditions. *Neurology*, *83*(2), 134-141.

Chibanda, D., Benjamin, L., Weiss, H. A., & Abas, M. (2014). Mental, neurological, and substance use disorders in people living with HIV/AIDS in low-and middle-income countries. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *67*, S54-S67.

Clifford, D. B., & Ances, B. M. (2013). HIV-associated neurocognitive disorder. *The Lancet infectious diseases*, *13*(11), 976-986.

Cross, S., Önen, N., Gase, A., Overton, E. T., & Ances, B. M. (2013). Identifying risk factors for HIV-associated neurocognitive disorders using the international HIV dementia scale. *Journal of Neuroimmune Pharmacology*, *8*(5), 1114-1122.

Crum-Cianflone, N. F., Moore, D. J., Letendre, S., Roediger, M. P., Eberly, L., Weintrob, A., ... & Hale, B. R. (2013). Low prevalence of neurocognitive impairment in early diagnosed and managed HIV-infected persons. *Neurology*, *80*(4), 371-379.

Cysique, L. A., Maruff, P., & Brew, B. J. (2004). Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus-infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre-and post-highly active antiretroviral therapy eras: a combined study of two cohorts. *Journal of neurovirology*, *10*(6), 350-357.

Cysique, L. A., Vaida, F., Letendre, S., Gibson, S., Cherner, M., Woods, S. P., . . . Ellis, R. J. (2009). Dynamics of cognitive change in impaired HIV-positive patients initiating antiretroviral therapy. *Neurology*, *73*(5), 342-348. doi:10.1212/WNL.0b013e3181ab2b3b

d'Arminio Monforte, A., Cinque, P., Mocroft, A., Goebel, F. D., Antunes, F., Katlama, C., . . . Lundgren, J. (2004). Changing incidence of central nervous system diseases in the EuroSIDA cohort. *Ann Neurol*, *55*(3), 320-328.

Ellis, H. D., Jones, D. M., & Mosdell, N. (1997). Intra-and inter-modal repetition priming of familiar faces and voices. *British Journal of Psychology*, *88*(1), 143-156.

Gandhi, N. S., Skolasky, R. L., Peters, K. B., Moxley, R. T., Creighton, J., Roosa, H. V., ... & Sacktor, N. (2011). A comparison of performance-based measures of function in HIV-associated neurocognitive disorders. *Journal of neurovirology*, *17*(2), 159-165.

Gifford, A. L., Bormann, J. E., Shively, M. J., Wright, B. C., Richman, D. D., & Bozzette, S. A. (2000). Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *Journal of acquired immune deficiency syndromes (1999)*, *23*(5), 386-395.

Gorman, A. A., Foley, J. M., Ettenhofer, M. L., Hinkin, C. H., & van Gorp, W. G. (2009). Functional consequences of HIV-associated neuropsychological impairment. *Neuropsychology review*, *19*(2), 186-203.

Group, M. E. W. (2013). Assessment, diagnosis, and treatment of HIV-associated neurocognitive disorder: a consensus report of the mind exchange program. *Clinical Infectious Diseases*, *56*(7), 1004-1017. doi:10.1093/cid/cis975

Harrison, M. J. G., & Mc Arthur, J. C. (1995). Opportunistic Infections Virus in AIDS and Neurology. *Tokio: Churchill-Livingstone*, 141-50.

Heaps, J., Valcour, V., Chalermchai, T., Paul, R., Rattanamanee, S., Siangphoe, U., ... & Suttichom, D. (2013). Development of normative neuropsychological performance in Thailand for the assessment of HIV-associated neurocognitive disorders. *Journal of clinical and experimental neuropsychology*, *35*(1), 1-8.

Heaton, R. K., Clifford, D. B., Franklin, D. R., Woods, S. P., Ake, C., Vaida, F., ... & Rivera-Mindt, M. (2010). HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*, *75*(23), 2087-2096.

Heaton, R. K., Franklin Jr, D. R., Deutsch, R., Letendre, S., Ellis, R. J., Casaletto, K., ... & Marcotte, T. D. (2014). Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clinical Infectious Diseases*, *60*(3), 473-480.

Heaton, R. K., Franklin, D. R., Ellis, R. J., McCutchan, J. A., Letendre, S. L., LeBlanc, S., ... & Collier, A. C. (2011). HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *Journal of neurovirology*, *17*(1), 3-16.

Heaton, R. K., Grant, I., Butters, N., White, D. A., Kirson, D., Atkinson, J. H., ... & Wolfson, T. (1995). The HNRC 500-Neuropsychology of HIV infection at different disease stages. *Journal of the International Neuropsychological Society*, *1*(3), 231-251.

Heaton, R. K., Marcotte, T. D., Mindt, M. R., Sadek, J., Moore, D. J., Bentley, H., ... & HNRC GROUP. (2004). The impact of HIV-associated neuropsychological impairment on everyday functioning. *Journal of the international neuropsychological society*, *10*(3), 317-331.

Hestad, K. A., Menon, J. A., Silalukey-Ngoma, M., Franklin Jr, D. R., Imasiku, M. L., Kalima, K., & Heaton, R. K. (2012). Sex differences in neuropsychological performance as an effect of human immunodeficiency virus infection: a pilot study in Zambia, Africa. *The Journal of nervous and mental disease*, *200*(4).

Hinkin, C. H., Hardy, D. J., Mason, K. I., Castellon, S. A., Durvasula, R. S., Lam, M. N., & Stefaniak, M. (2004). Medication adherence in HIV-infected adults: effect of patient age, cognitive status, and substance abuse. *AIDS (London, England)*, *18*(Suppl 1), S19.

HIV Estimates report Kenya. (2014).

HIV, A. (2013). JUNPo,(UNAIDS). 2013 UNAIDS Report on the global AIDS epidemic. *Geneva: Joint United Nations Programme on HIV/AIDS (UNAIDS)*.

Joska, J. A., Fincham, D. S., Stein, D. J., Paul, R. H., & Seedat, S. (2010). Clinical correlates of HIV-associated neurocognitive disorders in South Africa. *AIDS and Behavior*, *14*(2), 371-378.

Joska, J. A., Fincham, D. S., Stein, D. J., Paul, R. H., & Seedat, S. (2010). Clinical correlates of HIV-associated neurocognitive disorders in South Africa. *AIDS and Behavior*, *14*(2), 371-378.

Joska, J. A., Westgarth-Taylor, J., Myer, L., Hoare, J., Thomas, K. G., Combrinck, M., ... & Flisher, A. J. (2011). Characterization of HIV-associated neurocognitive disorders among individuals starting antiretroviral therapy in South Africa. *AIDS and Behavior*, *15*(6), 1197-1203.

Joska, J. A., Witten, J., Thomas, K. G., Robertson, C., Casson-Crook, M., Roosa, H., ... & Sacktor, N. C. (2016). A comparison of five brief screening tools for HIV-associated neurocognitive disorders in the USA and South Africa. *AIDS and Behavior*, *20*(8), 1621-1631.

Kabuba, N., Menon, J. A., Franklin Jr, D. R., Heaton, R. K., & Hestad, K. A. (2016). HIV-and AIDS-associated neurocognitive functioning in Zambia–a perspective based on differences between the genders. *Neuropsychiatric disease and treatment*, *12*, 2021.

Kenya, A. I. D. S., & Kenya, A. I. D. S. (2014). Response Progress Report. *Kenya National AIDS Control Council*.

Koski, L., Brouillette, M. J., Lalonde, R., Hello, B., Wong, E., Tsuchida, A., & Fellows, L. K. (2011). Computerized testing augments pencil-and-paper tasks in measuring HIV-associated mild cognitive impairment. *HIV medicine*, *12*(8), 472-480.

Lawler, K., Mosepele, M., Ratcliffe, S., Seloilwe, E., Steele, K., Nthobatsang, R., & Steenhoff, A. (2010). Neurocognitive impairment among HIV-positive individuals in Botswana: a pilot study. *Journal of the international AIDS society*, *13*(1), 15.

Lawton, M. P., & Brody, E. M. (1969). Assessment of older people: self-maintaining and instrumental activities of daily living. *Gerontologist*, *9*(3), 179-186.

Lescure, F. X., Omland, L. H., Engsig, F. N., Roed, C., Gerstoft, J., Pialoux, G., ... & Obel, N. (2011). Incidence and impact on mortality of severe neurocognitive disorders in persons with and without HIV infection: a Danish nationwide cohort study. *Clinical Infectious Diseases*, *52*(2), 235-243.

Liu, H., Golin, C. E., Miller, L. G., Hays, R. D., Beck, C. K., Sanandaji, S., . . . Wenger, N. S. (2001). A comparison study of multiple measures of adherence to HIV protease inhibitors. *Ann Intern Med, 134*(10), 968-977.

Lovejoy, T. I., & Suhr, J. A. (2009). The relationship between neuropsychological functioning and HAART adherence in HIV-positive adults: a systematic review. *Journal of Behavioral Medicine, 32*(5), 389-405.

Marra, C. M., Zhao, Y., Clifford, D. B., Letendre, S., Evans, S., Henry, K., ... & McArthur, J. C. (2009). Impact of combination antiretroviral therapy on cerebrospinal fluid HIV RNA and neurocognitive performance. *AIDS (London, England), 23*(11), 1359.

Mayeux, R., Stern, Y., Ottman, R., Tatemichi, T. K., Tang, M. X., Maestre, G., . . . Ginsberg, H. (1993). The apolipoprotein epsilon 4 allele in patients with Alzheimer's disease. *Ann Neurol, 34*(5), 752-754.

McArthur, J. C., & Brew, B. J. (2010). HIV-associated neurocognitive disorders: is there a hidden epidemic? *Aids, 24*(9), 1367-1370.

McCutchan, J. A., Wu, J. W., Robertson, K., Koletar, S. L., Ellis, R. J., Cohn, S., ... & Williams, P. L. (2007). HIV suppression by HAART preserves cognitive function in advanced, immune-reconstituted AIDS patients. *Aids*, *21*(9), 1109-1117.

Milanini, B., Wendelken, L. A., Esmaeili-Firidouni, P., Chartier, M., Crouch, P. C., & Valcour, V. (2014). The Montreal Cognitive Assessment (MoCA) to screen for cognitive impairment in HIV over age 60. *Journal of acquired immune deficiency syndromes (1999)*, *67*(1), 67.

Nabha, L., Duong, L., & Timpone, J. (2013). HIV-associated neurocognitive disorders: perspective on management strategies. *Drugs*, *73*(9), 893-905.

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., ... & Chertkow, H. (2005). The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *Journal of the American Geriatrics Society*, *53*(4), 695-699.

Odiase, F. E., Ogunrin, O. A., & Ogunniyi, A. A. (2007). Memory performance in HIV/AIDS-a prospective case control study. *Canadian journal of neurological sciences*, *34*(2), 154-159.

Price, R. W., Spudich, S. S., Peterson, J., Joseph, S., Fuchs, D., Zetterberg, H., ... & Swanstrom, R. (2014, February). Evolving character of chronic central nervous system HIV infection. In *Seminars in neurology* (Vol. 34, No. 01, pp. 007-013). Thieme Medical Publishers.

Pumpradit, W., Ananworanich, J., Lolak, S., Shikuma, C., Paul, R., Siangphoe, U., ... & Valcour, V. (2010). Neurocognitive impairment and psychiatric comorbidity in well-controlled human immunodeficiency virus—infected Thais from the 2NN Cohort Study. *Journal of neurovirology*, *16*(1), 76-82.

Ridha, B., & Rossor, M. (2005). The Mini Mental State Examination. *Practical Neurology*, *5*(5), 298-303.

Robbins, R. N., Joska, J. A., Thomas, K. G., Stein, D. J., Linda, T., Mellins, C. A., & Remien, R. H. (2013). Exploring the utility of the Montreal Cognitive Assessment to detect HIV-associated neurocognitive disorder: the challenge and need for culturally valid screening tests in South Africa. *The clinical neuropsychologist*, *27*(3), 437-454.

Robertson, K. R., Smurzynski, M., Parsons, T. D., Wu, K., Bosch, R. J., Wu, J., ... & Ellis, R. J. (2007). The prevalence and incidence of neurocognitive impairment in the HAART era. *Aids*, *21*(14), 1915-1921.

Rourke, S. B., Halman, M. H., & Bassel, C. (1999). Neurocognitive complaints in HIV-infection and their relationship to depressive symptoms and neuropsychological functioning. *Journal of Clinical and Experimental Neuropsychology*, *21*(6), 737-756.

Royal, W., 3rd, Cherner, M., Burdo, T. H., Umlauf, A., Letendre, S. L., Jumare, J., . . . Blattner, W. A. (2016). Associations between Cognition, Gender and Monocyte Activation among HIV Infected Individuals in Nigeria. *PLoS One*, *11*(2), e0147182. doi:10.1371/journal.pone.0147182

Sacktor, N. C., Wong, M., Nakasujja, N., Skolasky, R. L., Selnes, O. A., Musisi, S., . . . Katabira, E. (2005). The International HIV Dementia Scale: a new rapid screening test for HIV dementia. *Aids*, *19*(13), 1367-1374.

Simioni, S., Cavassini, M., Annoni, J. M., Abraham, A. R., Bourquin, I., Schiffer, V., ... & Du Pasquier, R. A. (2010). Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. *Aids*, *24*(9), 1243-1250.

Tedaldi, E. M., Minniti, N. L., & Fischer, T. (2015). HIV-associated neurocognitive disorders: the relationship of HIV infection with physical and social comorbidities. *BioMed research international*, *2015*.

Tozzi, V., Balestra, P., Bellagamba, R., Corpolongo, A., Salvatori, M. F., Visco-Comandini, U., ... & Narciso, P. (2007). Persistence of neuropsychologic deficits despite long-term highly active antiretroviral therapy in patients with HIV-related neurocognitive impairment: prevalence and risk factors. *JAIDS Journal of Acquired Immune Deficiency Syndromes*, *45*(2), 174-182.

Tsegaw, M., Andargie, G., Alem, G., & Tareke, M. (2017). Screening HIV-associated neurocognitive disorders (HAND) among HIV positive patients attending antiretroviral therapy in South Wollo, Ethiopia. *Journal of psychiatric research*, *85*, 37-41.

Valcour, V., Chalermchai, T., Sailasuta, N., Marovich, M., Lerdlum, S., Suttichom, D., ... & van Griensven, F. (2012). Central nervous system viral invasion and inflammation during acute HIV infection. *The Journal of infectious diseases*, *206*(2), 275-282.

Van Gorp, W. G., Rabkin, J. G., Ferrando, S. J., Mintz, J., Ryan, E., Borkowski, T., & Mcelhiney, M. (2007). Neuropsychiatric predictors of return to work in HIV/AIDS. *Journal of the International Neuropsychological Society*, *13*(1), 80-89.

Videnovic, A., Bernard, B., Fan, W., Jaglin, J., Leurgans, S., & Shannon, K. M. (2010). The Montreal Cognitive Assessment as a screening tool for cognitive dysfunction in Huntington's disease. *Movement disorders*, *25*(3), 401-404.

Vivithanaporn, P., Heo, G., Gamble, J., Krentz, H. B., Hoke, A., Gill, M. J., & Power, C. (2010). Neurologic disease burden in treated HIV/AIDS predicts survival: a population-based study. *Neurology*, *75*(13), 1150-1158.

Wong, M. H., Robertson, K., Nakasujja, N., Skolasky, R., Musisi, S., Katabira, E., . . . Sacktor, N. (2007). Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. *Neurology*, *68*(5), 350-355.

Woods, S. P., Moore, D. J., Weber, E., & Grant, I. (2009). Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev*, *19*(2), 152-168.

Zhang, Y., Qiao, L., Ding, W., Wei, F., Zhao, Q., Wang, X., ... & Chen, D. (2012). An initial screening for HIV-associated neurocognitive disorders of HIV-1 infected patients in China. *Journal of neurovirology*, *18*(2), 120-126.

APPENDICES

Appendix 1: Study Questionnaire –Demographic Data

1. PID ☐ AMRS ☐ HT(cm) ☐ WT(kg) ☐ BMI ☐

2. GENDER MALE ☐ FEMALE ☐

3. DOB (DMY) ...../...../.....AGE ----------

4. EDUCATION LEVEL ACHIEVED
   - Primary ☐
   - Secondary ☐
   - Tertiary ☐

Specify level(University-(Diploma,Bachelors,Masters,PHd),College, Technical Institute)----------

5. WHO Clinical Staging
   - I ☐
   - II ☐
   - III ☐
   - IV ☐

6. | BASELINE CD4 COUNT | DATE (DMY) | CURRENT CD4 COUNT | DATE (DMY) |
   |---|---|---|---|
   | ---------- | ---------- | ---------- | ---------- |

7. | CURRENT VIRAL LOAD COPIES/ML | DATE DMY |
   |---|---|
   | ---------- | ---------- |

8. DRUG REGIMEN 1^{ST}LINE 2^{ND} LINE 3^{RD} LINE

   _____ _____

   Other-Specify_____

9. Which date of first diagnosis of HIV ----------Duration of HIV infection .....

10. Year of initiation of ART _____Duration of HAART_____

Current ARV regimen start date _____ Duration_____

11. Marital Status:

Married ☐
Widowed ☐
Divorced/Separated ☐
Single ☐

12. Do you live alone

YES ☐

NO ☐
(If NO please specify----------)

13. Employment Status Employed ☐

Self Employed ☐

Unemployed ☐

14. Level of Income(KSHS per month)

0 to 10,000 ☐

10,000 to 50,000 ☐

50,000 to 100,000 ☐

Above 100,000 ☐

15 .Have you Suffered from Any Infectious illness in the Last 1 year and got admitted?If Yes,please specify the illness and whether you are still on medication.

YES ☐----------
NO ☐

16 .Do you suffer from any other chronic illness for which you take medication such as High Blood Pressure,Diabetes?If Yes,please specify,with duration of taking those drugs

YES ☐ ----------

NO ☐

17.Do you consume Alcohol or any Substance of Abuse such as Bhang,Cocaine,Heroine?If Yes,please specify

YES ☐ ----------

NO ☐

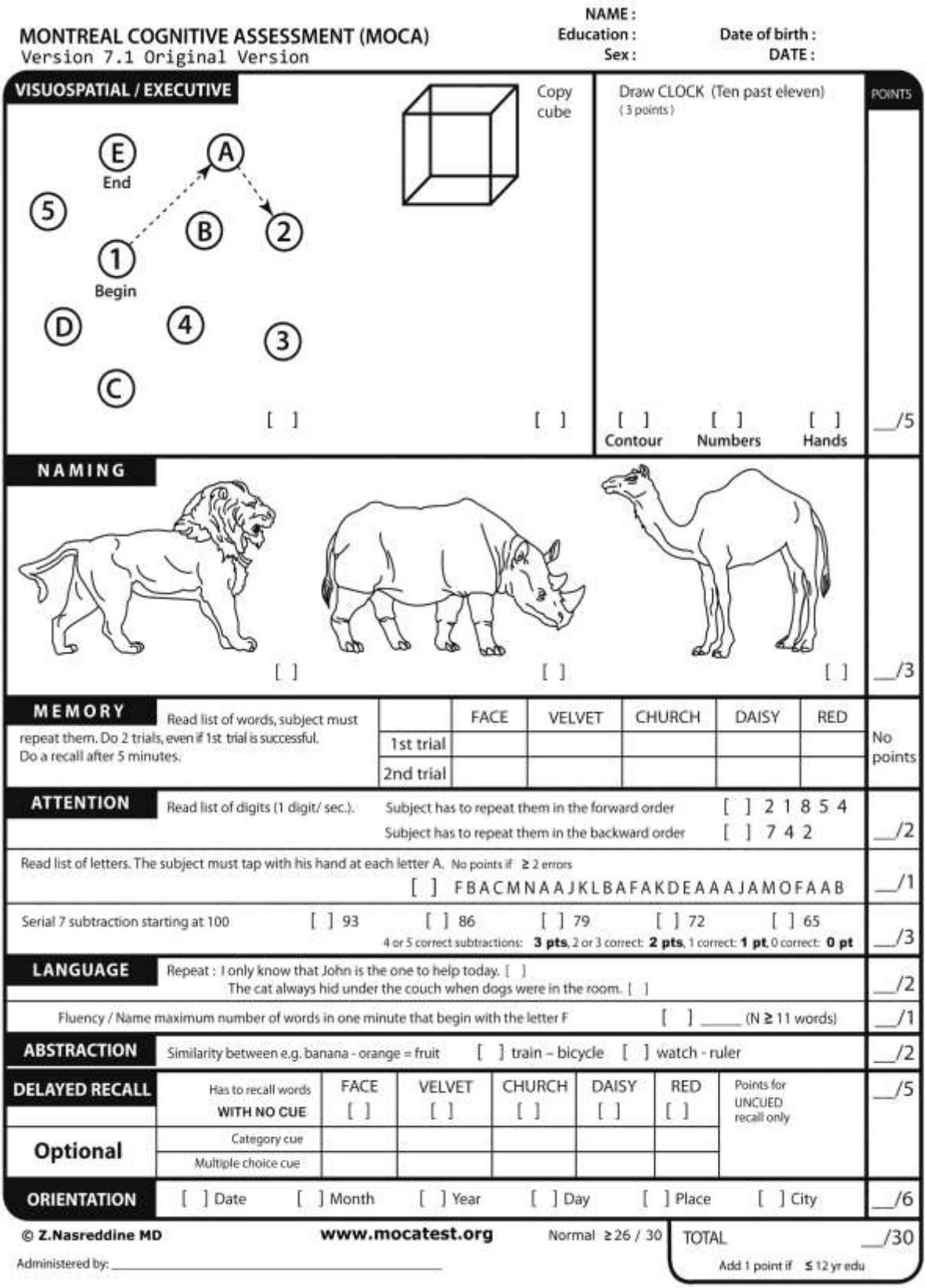
18.When did you last take alcohol? ---------- How much of alcohol do you take per sitting?---------- CAGE score--------

19.Have you ever suffered injury on the head with loss of consciousness for more than 30 minutes?

YES ☐

NO ☐

Appendix 2: MoCA Tool- English version



MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE — Copy cube — Draw CLOCK (Ten past eleven) (3 points) — POINTS

E End, A, 5, B, 2, 1 Begin, D, 4, 3, C

[ ] [ ]

[ ] Contour [ ] Numbers [ ] Hands — /5

NAMING — /3

[ ] [ ] [ ]

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes. — No points

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

ATTENTION Read list of digits (1 digit/ sec.). — /2

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

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

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors — /1

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

Serial 7 subtraction starting at 100 — /3

[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

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

LANGUAGE Repeat : I only know that John is the one to help today. [ ] — /2

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

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) — /1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler — /2

DELAYED RECALL — /5

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

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City — /6

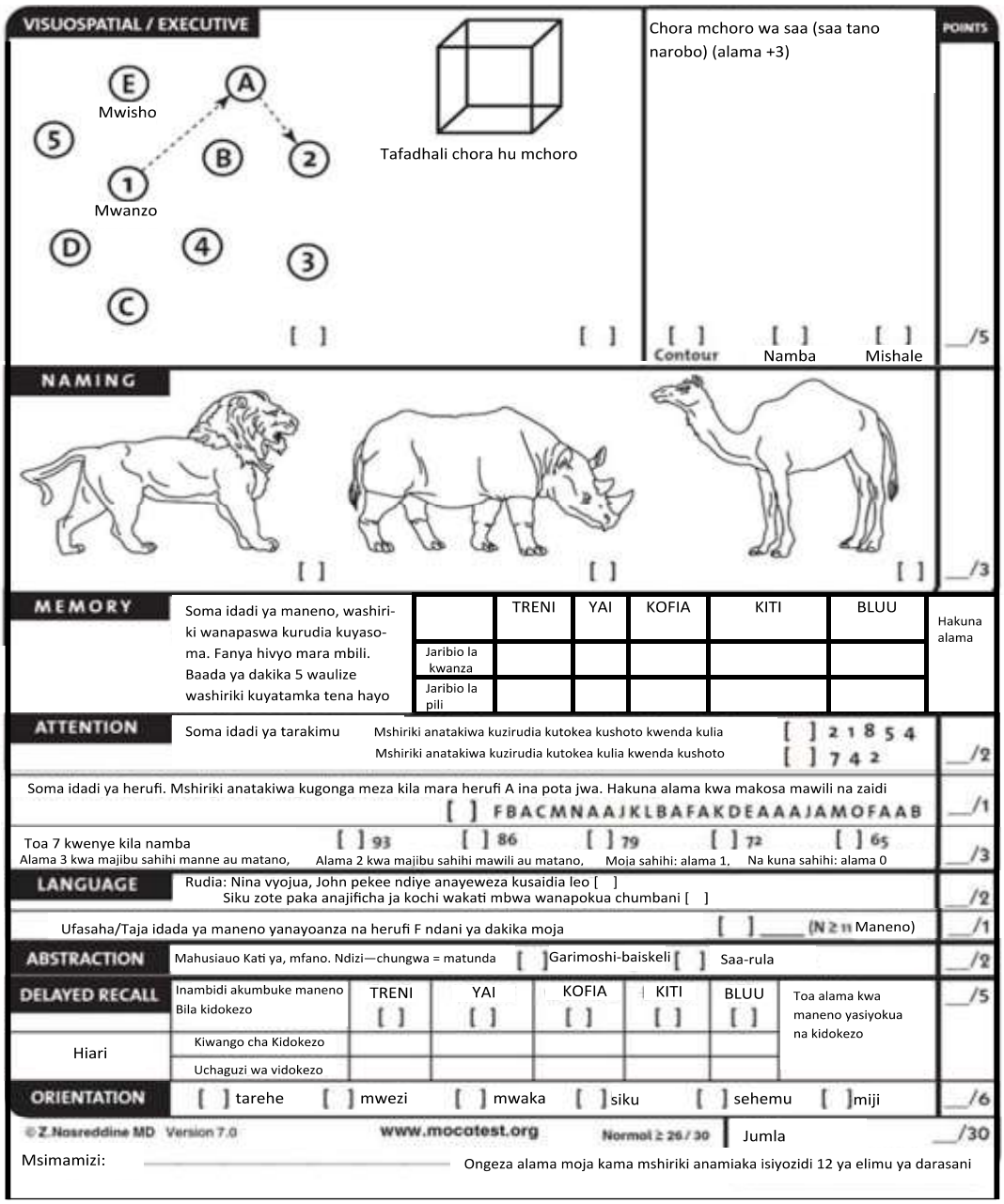
© Z.Nasreddine MD — www.mocatest.org — Normal ≥ 26 / 30

TOTAL /30

Add 1 point if ≤ 12 yr edu

Administered by: _____

Appendix 3 :MoCA tool-Swahili version



VISUOSPATIAL / EXECUTIVE

E Mwisho
A
5
B
2
1 Mwanzo
D
4
3
C

Tafadhali chora hu mchoro

[ ] [ ]

Chora mchoro wa saa (saa tano narobo) (alama +3)

[ ] Contour [ ] Namba [ ] Mishale

POINTS __/5

NAMING

[ ] [ ] [ ]

__/3

MEMORY

Soma idadi ya maneno, washiriki wanapaswa kurudia kuyasoma. Fanya hivyo mara mbili. Baada ya dakika 5 waulize washiriki kuyatamka tena hayo

	TRENI	YAI	KOFIA	KITI	BLUU
Jaribio la kwanza					
Jaribio la pili					

Hakuna alama

ATTENTION

Soma idadi ya tarakimu

Mshiriki anatakiwa kuzirudia kutokea kushoto kwenda kulia [ ] 2 1 8 5 4

Mshiriki anatakiwa kuzirudia kutokea kulia kwenda kushoto [ ] 7 4 2

__/2

Soma idadi ya herufi. Mshiriki anatakiwa kugonga meza kila mara herufi A ina pota jwa. Hakuna alama kwa makosa mawili na zaidi

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

__/1

Toa 7 kwenye kila namba

[ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65

Alama 3 kwa majibu sahihi manne au matano, Alama 2 kwa majibu sahihi mawili au matano, Moja sahihi: alama 1. Na kuna sahihi: alama 0

__/3

LANGUAGE

Rudia: Nina vyojua, John pekee ndiye anayeweza kusaidia leo [ ]

Siku zote paka anajificha ja kochi wakati mbwa wanapokua chumbani [ ]

__/2

Ufasaha/Taja idada ya maneno yanayoanza na herufi F ndani ya dakika moja [ ] ____ (N ≥ 11 Maneno)

__/1

ABSTRACTION

Mahusiauo Kati ya, mfano. Ndizi—chungwa = matunda [ ] Garimoshi-baiskeli [ ] Saa-rula

__/2

DELAYED RECALL

	Inambidi akumbuke maneno Bila kidokezo	TRENI	YAI	KOFIA	KITI	BLUU	Toa alama kwa maneno yasiyokua na kidokezo
		[ ]	[ ]	[ ]	[ ]	[ ]	
Hiari	Kiwango cha Kidokezo						
	Uchaguzi wa vidokezo						

__/5

ORIENTATION

[ ] tarehe [ ] mwezi [ ] mwaka [ ] siku [ ] sehemu [ ] miji

__/6

© Z.Nasreddine MD Version 7.0 www.mocatest.org Normal ≥ 26 / 30 Jumla __/30

Msimamizi: Ongeza alama moja kama mshiriki anamiaka isiyozidi 12 ya elimu ya darasani

Appendix 4: Instrumental activities of daily living (IADL)

THE LAWTON INSTRUMENTAL ACTIVITIES OF DAILY LIVING SCALE

Ability to Use Telephone

1. Operates telephone on own initiative; looks up and dials numbers 1
2. Dials a few well-known numbers 1
3. Answers telephone, but does not dial 1
4. Does not use telephone at al 0

Shopping

1. Takes care of all shopping needs independently 1
2. Shops independently for small purchases 0
3. Needs to be accompanied on any shopping trip 0
4. Completely unable to shop 0

Food Preparation

1. Plans, prepares, and serves adequate meals independently 1
2. Prepares adequate meals if supplied with ingredients 0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet 0
4. Needs to have meals prepared and served 0

Housekeeping

1. Maintains house alone with occasion assistance (heavy work) 1
2. Performs light daily tasks such as dishwashing, bed making 1
3. Performs light daily tasks, but cannot maintain acceptable level of cleanliness 1
4. Needs help with all home maintenance tasks 1
5. Does not participate in any housekeeping tasks 0

Laundry

1. Does personal laundry completely 1
2. Launders small items, rinses socks, stockings, etc 1
3. All laundry must be done by others 0

Mode of Transportation

1. Travels independently on public transportation or drives own car 1
2. Arranges own travel via taxi, but does not otherwise use public transportation 1
3. Travels on public transportation when assisted or accompanied by another 1
4. Travel limited to taxi or automobile with assistance of another 0
5. Does not travel at all 0

Responsibility for Own Medications

1. Is responsible for taking medication in correct dosages at correct time 1
2. Takes responsibility if medication is prepared in advance in separate dosages 0
3. Is not capable of dispensing own medication 0

Ability to Handle Finances

1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank); collects and keeps track of income 1
2. Manages day-to-day purchases, but needs help with banking, major purchases, etc 1
3. Incapable of handling money 0

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

Appendix 5: 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 words if the patient does not recall them all immediately. Tell the patient you will ask for recall of the words again a bit later.

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

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

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

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

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

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

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

From Sacktor NC, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, Robertson K, McArthur JC, Ronald A, KatabiraE.The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS. 2005 Sep 2;19(13):1367-74

Appendix 6: Consent for participation (English)

My name is Dr. Amina Ali Mohamed. I am a qualified doctor, registered by the Kenya Medical Practitioners and Dentists Board. I am currently pursuing a Masters degree in Internal Medicine at Moi University. I would like to recruit you into my research which is to study whether HIV-infected adults, who are HAART, attending the AMPATH clinics, could have a condition called HIV-associated neurocognitive disorders (HAND).

HIV AND HAND

HIV infection causes a myriad of neurological complications including cognitive deficits referred to as HIV associated Neurocognitive Disorders (HAND).

HAND is a significant burden to people living with HIV, caregivers and the healthcare system. The consequences of HAND include poor medication adherence, unemployment, difficulty with interpersonal functioning and overall poor quality of life.

Early diagnosis of HAND will enable us to know it's a problem in our patients with HIV infection and early screening will be essential to all patients and drugs with high central nervous system effectiveness score will be advocated. There are no costs to you for participating in the study.

If you have any questions about the study, please contact Dr. Amina Ali Mohamed at Moi Teaching and Referral Hospital.

YOUR CONSENT:

I have been adequately informed that I am being recruited in a study to find out if I have HIV-associated neurocognitive disorders. The investigator has also informed me that my participation in this study is voluntary and will not exclude me from my routine care even if I were to opt out. She has also informed me that I'll not be required to pay for the tests done for the purposes of this study.

Sign: ……

Name

(Initials):……

Date: ……

Appendix 7: Consent for Participation (Swahili)

Jina langu ni Dk. Amina Ali Mohamed. Mimi ni daktari niliyohitimu, kusajiliwa na Kenya Medical Practitioners na Madaktari wa Bodi. Sasa natafuta shahada ya uzamili katika Tiba ya Ndani katika Chuo Kikuu cha Moi. Napenda kukuajiri katika utafiti wangu ambao ni kujifunza kama watu wazima walioambukizwa HIV, ambao wanatumia HAART, wanaohudhuria kliniki ya Ampath, wanaweza kuwa nahali inayoitwa HIV-associated neurocognitive disorders (HAND)

HIV NA HAND

Aambukizi la HIV husababisha Matatizo yamishipa ya Fahamui kiwani Pamoja na hali ya utambuzi inajulikana Kama HIV-associated neurocognitive disorders (HAND) HAND ni mzigo Mkubwa kwa Watu wanaoishi na HIV, walezi na mfumo waAfya. Matokeo ya HAND ni Pamoja na kutozingatia dawa, ukosefu waajira, ugumu wautendaji Kazi Kati yaWatu na kwaujumla maisha ya umaskini.

Utambuzi wa mapema wa HAND inatuwezesha kujua ni tatizo kwa wagonjwa wetu namaambukizi ya HIV nauchunguzi wa mapema itakuwamuhimu kwa wagonjwa wote na madawa yawezekutumika. Hakuna gharama kwako wewe kwaajili ya kushiriki katika utafiti huu.

Kama una maswali yoyote kuhusu utafiti, tafadhali wasiliana na Dk. Amina Ali Mohamed katika Moi Teaching and Referral Hospital.

IDHINI YAKO

Nimeelezwa vya kutosha yakwamba mimi nasajiliwa katika utafiti ili kujua kama nina matatizo ya HIV-associated neurocognitive disorders. Mpelelezi pia alinieleza kwamba ushiriki wangu katika utafiti huu ni wa hiari na sikunitenga mimi kutoka huduma yangu ya kawaida hata kama ningekuwa nimeamua kuwacha. Yeye pia alinieleza kwamba mimi sitahitajika kulipia kwa ajili yavipimo vitakavyofanyika kwa madhumuni yautafiti huu.

Sahihi.……

Jina (awali)……

Tarehe:……

Appendix 8: CPE Score

Central nervous system penetration effectiveness ranking of antiretroviral agents

Drug class	CPE score			
	1	2	3	4
NRTI	Tenofovir* Didanosine ¶	Lamivudine* Stavudine ¶	Emtricitabine* Abacavir*	Zidovudine ¶
INSTI		Elvitegravir/cobicistat*	Raltegravir*	Dolutegravir*
PI	Saquinavir-ritonavir ¶ Nelfinavir-ritonavir ¶ Tipranavir-ritonavir ¶	Boosted atazanavir Δ	Boosted darunavir* *Boosted lopinavir* ◊ Indinavir-ritonavir ¶ Fosamprenavir-ritonavir ¶	
NNRTI		Etravirine ¶	Efavirenz Δ Rilpivirine Δ Delavirdine ¶	Nevirapine ¶
Entry/fusion inhibitor	Enfuvirtide ¶		Maraviroc ¶	

Appendix 9: Procedure for drawing venous blood

Venous blood will be drawn for CD4 count. The procedure will be explained to the participant and verbal consent obtained. Universal safety procedures will be observed. Venous blood draw will be from the median cubital vein in the antecubital fossa of the less dominant upper limb.

An overview of the steps that will be followed:

1. Arm is selected and a tourniquet is placed on the arm above the draw site. The median cubital vein is selected.
2. The site is cleansed with a sterile alcohol or methylated spirit preparation pad.
3. A needle is inserted into the vein and the collection tube is engaged.
4. Two milliliters of blood is collected into a blood collection bottle.
5. Tourniquet is removed once the quantity of blood desired has been obtained.
6. A small gauze pad and a Band-Aid are placed on the venous blood draw site.
7. The blood collection tube is labeled with the patient's information.
8. Blood collection tubes batched and taken to AMPATH reference lab.

Appendix 10: Procedure for measuring CD4 count

Flow cytometry will be done using the following Lyse No-Wash Staining Procedure:

1. A Proper labeling of the 12*75mm Trucount tubes with specimen accessioning numbers will be done.
2. 20ul AB reagent will be added (BDIS Multitest CD3/CD8/CD45/CD4) just above the steel retainer.
3. The specimen vacutainer tube will be gently inverted 5 times to mix and then carefully removing the stopper.
4. 50ul of blood will be added to each tube just above the retainer using a pipette. The reverse pipetting method will be used to ensure the correct volume is added.
5. The tube will be capped and vortex gently to mix.
6. It will be incubated at Room Temperature (RT)- (20 to 25^{o}c) in the dark for 15 minutes.
7. 450ul of 1*FACSLyse will be added to each tube and vortex after each addition
8. Incubation will be done at RT for 15minutes in the dark to lyse the red blood cells.
9. FACSCalibur will be analysed on flow cytometry immediately. Samples will be stored in the dark at RT until ready to analyze; however, they should be run on the flow cytometer within 4 hours of staining. Each tube will be vortex gently before placing on the FACSCalibur.

Appendix 11: Procedure for measuring height

The height of participants will be taken to help calculate the body mass index (BMI), which is the weight relative to the height. The height will be measured with a mechanical roll- up tape (Seca 260) with wall attachment in the nursing station.

The steps that will be followed in measuring height:

1. The participant will be asked to remove their footwear (shoes, slippers, sandals etc.) and head gear (hat, cap, hair brows etc.). Those with a scarf or veil will not be asked to remove them as the measurement may be taken over light fabric.
2. The Participant will be asked to stand next to the measuring board or wall facing the research assistant or investigator.
3. The Participant will be asked to stand with feet together, heals against the measuring board or wall and the knees to be straight.
4. The Participant will be asked to look straight ahead and not tilt their head up.
5. The measure arm will be moved gently down onto the head of the participant and the participant asked to breath in and stays tall.
6. The height will be read in centimeters at the exact point.
7. The participant will be asked to step away from the measuring board or wall.
8. The height measurement in centimeters will be recorded in the participant's questionnaire.

Appendix 12: Procedure for measuring body weight

The weight of participants will be taken to help calculate the body mass index (BMI), which is the weight relative to the height. The weight will be measured with a 762 Dial Bathroom Floor scale at the nursing station.

The steps that will be followed in measuring weight:

1. The scale will be placed on a firm, flat surface.
2. The Participants will be asked to remove their footwear (shoes, slippers, sandals etc.)
3. The participant will be asked to step onto scale with one foot on each side of the scale.
4. The participant will be asked to stand still, face forward, place arms on the side and wait until they will be asked to step off.
5. The weight in kilograms will be recorded on the participant's questionnaire.
6. The participant will be asked to step off the scale

Appendix 13: WHO clinical staging of HIV/AIDS in adults and adolescents

WHO clinical stage 1

1. Asymptomatic
2. Persistent generalized lymphadenopathy

WHO clinical stage 2

1. Moderate unexplained weight (< 10% of presumed or measured body weight)
2. Minor mucocutaneous manifestation (seborrheic dermatitis, popular pruritic eruptions, fungal nail infections, recurrent oral ulcerations, angular cheilitis)
3. Herpes zoster
4. Recurrent upper respiratory tract infections (sinusitis, tonsillitis, bronchitis, otitis media, pharyngitis)

WHO clinical stage 3

Conditions where presumptive diagnosis can be made using clinical signs or simple investigations:

1. Unexplained severe weight loss (over 10% of presumed or measured body weight)
2. Unexplained chronic diarrhea for longer than one month
3. Unexplained persistent fever (Intermittent or constant for longer than one month)
4. Persistent oral candidiasis
5. Oral hairy leukoplakia
6. Pulmonary tuberculosis
7. Severe bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia)
8. Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis
9. Unexplained anemia (below 8 g/dl), neutropenia (below $0.5*10^9$/l) and / or chronic thrombocytopenia (below $50*10^9$/l)

WHO clinical stage 4

1. HIV wasting syndrome
2. Pneumocystis jiroveci pneumonia (PCP)
3. Recurrent severe bacterial pneumonia (>2episodes within 1 year)
4. Cryptococcal meningitis
5. Toxoplasmosis of the brain
6. Chronic orolabial, genital or ano-rectal herpes simplex for > 1 month
7. Kaposi sarcoma (KS)
8. HIV encephalopathy
9. Extra pulmonary tuberculosis (EPTB)

Conditions where confirmatory diagnostic testing is necessary:

1. Cryptosporidiosis with diarrhea > 1 month
2. Isosporiasis
3. Cryptococcosis (extra pulmonary)
4. Disseminated non-tuberculous mycobacterial infection
5. Cytomegalovirus (CMV) retinitis or infection of the organs (other than liver, spleen, or lymph nodes)
6. Progressive multifocal Leucoencephalopathy (PML)
7. Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis)
8. Candidiasis of the oesophagus or airways
9. Non-typhoid salmonella (NTS) septicaemia
10. Lymphoma cerebral or B cell Non Hodgkin’s Lymphoma
11. Invasive cervical cancer
12. Visceral Leishmaniasis
13. Symptomatic HIV-associated nephropathy or HIV-associated cardiomyopathy

Appendix 14: MU-MTRH IREC Approval

INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE (IREC)

MOI TEACHING AND REFERRAL HOSPITAL
P.O. BOX 3
ELDORET
Tel: 33471//2/3

MOI UNIVERSITY
SCHOOL OF MEDICINE
P.O. BOX 4606
ELDORET

Reference: IREC/2016/130
Approval Number: 0001720

1st September, 2016

Dr. Amina Ali Mohamed,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

INSTITUTIONAL RESEARCH & ETHICS COMMITTEE
01 SEP 2016
APPROVED
P. O. Box 4606-30100 ELDORET

Dear Dr. Mohamed,

RE: FORMAL APPROVAL

The Institutional Research and Ethics Committee has reviewed your research proposal titled:-

"HIV Associated Neurocognitive Disorders (HAND) at Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya".

Your proposal has been granted a Formal Approval Number: ***FAN: IREC 1720*** on 1st September, 2016. You are therefore permitted to begin your investigations.

Note that this approval is for 1 year; it will thus expire on 31st August, 2017. If it is necessary to continue with this research beyond the expiry date, a request for continuation should be made in writing to IREC Secretariat two months prior to the expiry date.

You are required to submit progress report(s) regularly as dictated by your proposal. Furthermore, you must notify the Committee of any proposal change (s) or amendment (s), serious or unexpected outcomes related to the conduct of the study, or study termination for any reason. The Committee expects to receive a final report at the end of the study.

Sincerely,

PROF. E. WERE
CHAIRMAN
INSTITUTIONAL RESEARCH AND ETHICS COMMITTEE

cc CEO - MTRH Dean - SOP Dean - SOM
Principal - CHS Dean - SON Dean - SOD

Appendix 15: MTRH permission to conduct study

IREC/2016/130

MOI TEACHING AND REFERRAL HOSPITAL

Telephone: 2033471/2/3/4
Fax: 61749
Email: director@mtrh.or.ke
P. O. Box 3
ELDORET

Ref: ELD/MTRH/R.6/VOL.II/2008

7th September, 2016

Dr. Amina Ali Mohamed,
Moi University,
School of Medicine,
P.O. Box 4606-30100,
ELDORET-KENYA.

RE: APPROVAL TO CONDUCT RESEARCH AT MTRH

Upon obtaining approval from the Institutional Research and Ethics Committee (IREC) to conduct your research proposal titled:-

"HIV Associated Neurocognitive Disorders (HAND) at Moi Teaching and Referral Hospital (MTRH), Eldoret, Kenya".

You are hereby permitted to commence your investigation at Moi Teaching and Referral Hospital.

7/09/2016

DR. WILSON ARUASA
CHIEF EXECUTIVE OFFICER
MOI TEACHING AND REFERRAL HOSPITAL

CC - Deputy Director (CS)
- Chief Nurse
- HOD, HRISM

Appendix 16: AMPATH permission to conduct study

ampath
Leading With Care

Academic Model Providing Access To Healthcare

Telephone: 254 53 2033471/2P.O. BOX 4606, ELDORET Fax: 254 53 2060727

RESEARCH

Ref: RES/STUD/14/2016

November 17, 2016

Dr. Amina Ali Mohamed
Moi University
P.O Box 4606-30100
Eldoret

Dr. Mohamed,

RE: PERMISSION TO CONDUCT RESEARCH AT AMPATH

This is to kindly inform you that your study *"HIV Associated Neurocognitive Disorders (HAND) AT Moi Teaching and Referral Hospital (MTRH) Eldoret, Kenya.""* has been reviewed by the AMPATH Research Program Office. Permission is therefore granted to begin collecting your data at AMPATH.

Please note that your research activities should not in any way interfere with the care of patients. This approval does not support access to AMRS data at AMPATH.

You are required to submit a final report of your findings to the AMPATH Research Program Office.

Should you wish to publish your research findings, permission has to be sort from AMPATH Publications Committee. Please contact the AMPATH Research Office in case of any enquiry regarding this matter.

Thank you,

AMPATH CENTRE RESEARCH 1 NOV 2016 P.O. Box 4606-30100, Eldoret

Prof. Winstone Nyandiko
AMPATH Executive Director, Research