COGNITIVE DYSFUNCTION AMONG HIV-POSITIVE PATIENTS ATTENDING COMPREHENSIVE CARE CLINIC AT KENYATTA NATIONAL HOSPITAL

A dissertation in part fulfillment for the requirements of the degree of Masters of Medicine, Internal Medicine, University of Nairobi.

DR ZAHEER MOHAMED AFZAL BAGHA

M. B. Ch. B (UON, 2003)

DECLARATION

This dissertation is my original work and has not been presented for a degree at any other university.

Signed: ……... Date: ……

Dr. Zaheer M. A. Bagha

APPROVAL BY SUPERVISORS

This dissertation has been submitted with the approval of my supervisors, namely:

Signature: _____ Date: _____

Prof. E. O. Amayo

MBChB; MMed(Internal Medicine),

Associate Professor and Consultant Neurologist,

Department of Clinical Medicine and Therapeutics,

University of Nairobi.

Signature: _____ Date: _____

Prof. A. M. Adam

MBChB; DCPC (Lond.); MRCP (UK); FRCP (Edinburgh),

Professor and Consultant Neurologist,

Department of Clinical Medicine and Therapeutics,

University of Nairobi.

Signature: _____ Date: _____

Dr Jared O. Mecha

MBChB; MMed; MSc-RM (Lond.),

Consultant Physician / Lecturer,

Department of Clinical Medicine and Therapeutics,

University of Nairobi.

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ABBREVIATIONS

AAN	American Academy of Neurology
ADL	Activities of Daily Living
AIDS	Acquired ImmunoDeficiency Syndrome
ARV	AntiRetrovirals
CCC	Comprehensive Care Clinic
CDC	Centre for Disease Control
CCR3	Chemokine Receptor 3
CCR5	Chemokine Receptor 5
CD	Cluster of Differentiation
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CT	Computed Tomography
DSM	Diagnostic and Statistical Manual of Mental Disorders
HAART	Highly Active AntiRetroviral Therapy
HAD	HIV-Associated Dementia
HIV	Human Immunodeficiency Virus
HDS	HIV Dementia Scale
IADL	Instrumental Activities of Daily Living
IHDS	International HIV Dementia Scale
KNH	Kenyatta National Hospital
MCMD	Minor Cognitive/Motor Disorder
MCP-1	Monocyte Chemotactic Receptor 1
MRI	Magnetic Resonance Imaging

MSK	Memorial Sloan-Kettering
NEF	Negative Effector
PCR	Polymerase Chain Reaction
PHQ	Patient Health Questionnaire
PI	Principal Investigator
RAVLT	Rey Auditory Verbal Learning Test
SD	Standard Deviation
TAT	Transcriptional Activator
UCLA	University of California, Los Angeles
UON	University of Nairobi
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States
VDRL	Venereal Disease Research Laboratory
WHO	World Health Organisation

ABSTRACT

Objective: To determine the prevalence of cognitive dysfunction among HIV-positive patients attending the Comprehensive Care Clinic (CCC) at Kenyatta National Hospital.

Design: Cross-sectional study.

Setting: Comprehensive Care Clinic, Kenyatta National Hospital.

Subjects: HIV-positive patients.

Sampling, Data Collection and Analysis: Random sampling was done. Data was entered into a questionnaire, transferred to Excel and analysed using Stata version 11.0.

Results: The prevalence of cognitive dysfunction was 26%. The female: male ratio was 2.6:1. The peak age was 38-47 years with a mean age of 38.3 +/-7.9 yrs and a median of 38 years. For HIV-positive patients with cognitive dysfunction, the odds of having secondary and tertiary education were ×0.271and ×0.169 respectively that of having primary education (P=0.012). HIV-positive patients with cognitive dysfunction were more likely to be older (mean age was 40.7 +/- 7.6 years), have baseline and nadir CD4 counts ≤ 200/µl and duration of HIV infection and duration of HAART for ≥ 2 years compared to HIV-positive patients with no cognitive dysfunction. However, these differences were not statistically significant.

Conclusion and Recommendations: Cognitive dysfunction is quite prevalent (26%) among HIV-positive patients attending the CCC at KNH despite the fact that >75% of those with cognitive dysfunction were on HAART, and >50% were on HAART for ≥ 2 years. This could be explained by the "legacy effect" of HIV infection in the CNS. No statistically significant associations between cognitive dysfunction and sociodemographic and laboratory variables were found except for education. This could be due to the fact that education may be protective against dementia. HIV-positive patients should be routinely screened for cognitive dysfunction using the IHDS tool.

1.0 LITERATURE REVIEW

1.1 INTRODUCTION

Changes in memory, mood, attention, and motor skills are common in HIV-infected patients and present a diagnostic challenge to the clinician.HIV-associated dementia (HAD) produces a highly variable clinical course and a spectrum of signs and symptoms, ranging from subtle cognitive and motor impairments to profound dementia, as shown in Table 1.

Table 1: Clinical Manifestations of HIV-Associated Dementia

Type of Impairment	**Manifestations**
Affective	• Apathy (depression-like features) • Irritability • Mania, new-onset psychosis
Behavioral	• Psychomotor retardation (slowed speech or response time) • Personality changes • Social withdrawal
Cognitive	• Lack of visuospatial memory (misplacing things) • Lack of visuomotor coordination • Difficulty with complex sequencing (difficulty in performing previously learned complex tasks) • Impaired concentration and attention • Impaired verbal memory (word-finding ability) • Mental slowing
Motor	• Unsteady gait, loss of balance • Leg weakness • Dropping things • Tremors, poor handwriting • Decline in fine motor skills

Since these symptoms can represent a wide variety of disorders, accurate diagnosis is critical for patient treatment. [1]Locally, the burden of HAD is not known. However, in other settings the prevalence of HAD has been documented.The prevalence of HIV-minor cognitive/motor disorder and HIV-dementia in the Dana cohort in the pre-HAART era was 47.7% and 27.3% respectively. [2]In a study done in Uganda among HIV-positive individuals, dementia was diagnosed in 11% of the HIV-positive individuals (54% with CD4 cell count < 200/µl).[3]In another study done initially in a US clinic in John Hopkins Hospital (from July to November, 2002) andthen subsequently performed at an Infectious Disease Clinic in Kampala, Uganda (from August 2003 to March 2004), 31% of the HIV-positive individuals in the Uganda cohort were diagnosed with dementia. [4]In both these studies, the HAART status of the patients is not explicitly mentioned.

In the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, overall, 40% of HIV-positive individuals were found to have had neurocognitive impairment in the HAART era compared with 33% during the pre-HAART era, which was statistically significant (P = 0.004). [5]When this was analyzed by disease severity, only people with less advanced HIV disease (Centre for Disease Control, CDC stage A) in the past had a significantly higher rate of neurocognitive impairment since the advent of HAART [36% HAART era versus 29% pre-HAART era (P=0.004)], while those with more severe stages as well as HIV negative control participants, did not see significant increases in neurocognitive impairment.This was explained as probably having been due to negative CNS effects of longer survival in a pre-AIDS state during which the brain remainedrepeatedly exposed to HIV and/or chronic immune stimulation.

According to the CHARTER study, CD4 nadir (lowest-ever CD4 count) may represent a “legacy effect” that contributes substantially to HIV-related brain damage and neurocognitive impairment and may not be fully reversible. Prevention of severe immunosuppression by earlier HAART may lead to more favorable neurocognitive outcomes in HIV+ individuals.

In a cross-sectional study done in Botswana among 120 HIV-positive patients, 38% met the criteria for neurocognitive impairment using the International HIV Dementia Scale (IHDS) tool. [6]

Since the introduction of the antiretroviral therapy, the incidence of HIV-associated dementia has declined by 40% to 50%, whereas the prevalence has remained unchanged.[7]This is because patients with HIV-associated dementia live longer, which indirectly leads to a proportional increase in the number of patients diagnosed.[8]

1.2 PATHOPHYSIOLOGY

Much has been learned about the biology of HIV-1, the cells it infects and the mechanisms by which virus entry into cells occurs. However, just how HIV-1 exerts its effects on the CNS remains uncertain and continues to be the focus of ongoing research. HIV seeds the meninges and CSF early during the course of infection.[9] Viral load is distributed unequally in the brain, mostly concentrating in the hippocampus and basal ganglia (caudate and globuspallidus), correlating with the clinical symptoms of HIV-associated dementia.[10]Current knowledge indicates that HIV-1-infected macrophages/monocytes in blood are recruited to the brain by upregulation of chemoattractant-chemokines such as MCP-1[11] and adhesion molecules on endothelial cells. Upregulation enables transendothelial migration of activated macrophages/monocytes[12] and has been correlated with a high frequency of circulating activated monocytes expressing CD14/CD16 and CD14/CD9 in patients with HIV-associated dementia.

HIV-1 free viral particles, as well as infected monocytes, penetrate the brain tissue through the disrupted blood-brain barrier, most likely due to the dysfunction of endothelial cells and changes in the basal lamina proteins, such as laminin, entactin, and collagen.[13]In addition, some viral proteins may be transported to the brain even through the intact blood-brain barrier, as was shown for TAT.[14] Both CD4 receptors and chemokine receptors CCR5 and CCR3 have been implicated in viral entry of HIV-1 M-strains into the brain microglial cells,[15] which then undergo a productive infection, syncytial formation and cell death.In addition to the infection of microglia, HIV-1 infects astrocytes, mostly by T-tropic strains.[16] The mechanism is not known because astrocytes lack both CD4 and cytokine receptors.Interestingly, it seems that particular HIV-1 strains have specific affinity for specific cells types.For example, the V3 region of the HIV-1 envelope (ENV) gene sequences is different in astrocytes than in macrophages or multinucleated giant cells, indicating cell-specific compartmentalization. [17]The HIV-1 infection of astrocytes behaves differently

frominfection of microglial cells.Initially, the virus undergoes a productive infection, but then it enters a latent phase and does not cause cell death.[16] It practically stays in astrocytes indefinitely, escaping all antiretroviral agents.Hence, HIV-1 is neurotropic (increased propensity to invade the CNS) rather than neurovirulent (increased propensity to cause CNS damage).

In vitro studies of HIV-1 neurotoxicity indicate that changes in the envelope sequence might influence neuronal survival.[18] It has already been shown in in-vitro models of simian immunodeficiency virus (SIV) and feline immunodeficiency virus (FIV) that specific sequences of ENV or NEF genes confer neurovirulence.[19]In summary, pathogenetic mechanisms of HIV-associated dementia are complex and most likely multifactorial. Activated macrophages release multiple proinflammatory cytokines, as well as other factors that might impair the function of virtually all neural cell types and interfere with the release of neurotransmitters and, therefore, synaptic transmission.This process would then correlate with the neuropsychological findings in HIV-associated dementia.

1.3CLASSIFICATION OF HIV-ASSOCIATED NEUROCOGNITIVE DISORDERS

In 1991, the American Academy of Neurology defined two levels of neurologic impairment in patients with HIV: HIV-associated dementia (HAD) and minor cognitive/motor disorder (MCMD).A core difference between the two is the degree of functional impairment present; patients with HAD have more impairment than those with MCMD.The term *HIV-associated dementia or HIV dementia* incorporates the cognitive changes seen in HIV-1 infection as well as those occurring in the setting of AIDS. It is synonymous with the previously existing terms *AIDS dementia complex*[20] and *HIV encephalopathy*.[21]

AIDS dementia complex (ADC) describes the syndrome as a subcortical dementia with changes in memory, movement (motor) and mood.A six level staging system is used to describe the severity of symptoms. [22] Table 2 shows the staging of the AIDS Dementia Complex in comparison with WHO / AAN classification.

Table 2. Staging of the AIDS Dementia Complex (Memorial Sloan-Kettering staging) and comparison with the WHO/AAN classification

ADC Stage	**Clinical Features**	**WHO/AAN classification (comparative)**
0 (Normal)	Normal mental and motor function	No corresponding designation
0.5 (Equivocal/subclinical)	Either minimal or equivocal *symptoms* of cognitive or motor dysfunction characteristic of ADC, or mild signs (snout response, slowed extremity movements), but *without impairment of work or capacity to perform ADL*. Gait and strength are normal.	No corresponding designation
1 (Mild)	Unequivocal evidence (symptoms, signs, neuropsychological test performance) of functional intellectual or motor impairment characteristic of ADC, but able to perform *all but the more demanding aspects of work or ADL*.Can walk without assistance.	HIV-1-associated minor cognitive/motor disorder.

2 (Moderate)	Able to perform *basic activities of self-care* but cannot work or maintain the more demanding aspects of daily life. Ambulatory but may require single prop, e.g., cane)	Mild HIV-associated dementia and HIV-associated myelopathy.
3 (Severe)	*Major intellectual incapacity* (cannot follow news or personal events, cannot sustain complex conversation, considerable slowing of all output) or *motor disability* (cannot walk unassisted, requiring walker or personal support, usually with slowing and clumsiness of arms as well)	Moderate HIV-associated dementia and HIV-associated myelopathy.
4 (End stage)	Nearly vegetative, intellectual and social comprehension and output are at a rudimentary level, nearly or absolutely mute (paraparetic or paraplegic with urinary and fecal incontinence)	Severe HIV-associated dementia and HIV-associated myelopathy.

1.3.1HIV-Associated Dementia (HAD)

For an HIV-positive patient to be diagnosed with HAD, criteria for 1and 2 below must be met:

1. Scores 1 standard deviation (SD) below age- and education-adjusted norms on two of eight neuropsychological tests **or** 2 SDs below the norms on one of eight tests:

- Rey Auditory Verbal Learning Test – for assessing verbal memory.
- Rey Complex Figure Recall Test – for assessing visual memory.
- Rey Complex Figure Copy Test – for assessing constructional praxis.
- Digit Symbol Test - for assessing psychomotor skills.
- Grooved Pegboard and Timed Gait Tests - for assessing motor skills.
- Verbal Fluency and Odd-Man-Out Tests - for assessing frontal systems.

2. Requires assistance **or** has difficulty (due to either physical or cognitive deficit) in one of the following instrumental activities of daily living (IADL):

- Using the telephone
- Handling money
- Taking medication
- Performing light housekeeping
- Doing laundry
- Preparing meals
- Shopping for groceries
- Getting to places out of walking distance

and

Must meet either 1 **or** 2 of the following:

1. Any impairment in the following: lower extremity strength, coordination, finger tapping, alternating hand movements, leg agility, or performance on grooved pegboard 2 SDs below mean(dominant hand).

2. Self-reported frequent depression that interferes with function, loss of interest in usual

activities or emotional lability, **or** irritability.

1.3.2HIV-Associated Minor Cognitive/Motor Disorder (MCMD)

Does not meet criteria for HIV-1-associated dementia and meets 1 and 2of the

following:

1. Deficit in at least two of the following:

- Mental slowing: digit symbol at least 1 SD below age- and education-adjusted norms
- Memory: Rey Auditory Verbal learning test (total) at least **1** SD below norms
- Motor dysfunction: any impairment in finger tapping or pronation/supination
- Incoordination: mild impairment in gait or clumsiness
- Emotional lability or apathy/withdrawal

and

2. Deficit in at least one of the role function measures attributed in part to cognitive function:

- Need for frequent rests
- Cut down on amount of time in activities
- Accomplish less than desired
- Cannot perform activities as carefully as one would like
- Limited in work **or** activities
- Difficulty performing activities
- Requires special assistance to perform activities

1.4DIAGNOSIS

Comprehensive neuropsychological testing helps to determine the extent of the cognitive impairment and identifies other potential contributing factors, such as depression and anxiety. [23] However, such extensive testing is costly and requires highly skilled professionals for administration and interpretation.This has led to the development of bedside screening tools, for example the Mini Mental State Exam (MMSE).[24,25] However, the MMSE was designed to screen for cortical dementia such as Alzheimer's disease (sensitivity 72%), and it is, therefore, less sensitive for detecting subcortical dementia such as HIV dementia. [26]The HIV Dementia Scale (HDS) was designed as a brief but sensitive (sensitivity 80%) screening instrument to identify HIV+ patients at risk for dementia.[27]The HDS includes subtests that evaluate motor speed (timed written alphabet), memory (recall of four words at 5 min), constructional praxis (cube copy time), and executive functions (antisaccadic errors subtest).

The HDS has been validated as a sensitive and well-tolerated screening instrument for dementia in patients with HIV disease [28] and in patients with subcortical vascular ischemic disease.[29]The antisaccadic error subtest, however, has proven difficult for non-neurologists to administer.[30]Other components of the HDS such as alphabet writing and cube-copying tests, may be difficult for individuals with no formal educational background.

International HIV Dementia Scale (IHDS)

The IHDS eliminates the antisaccades subtest and replaces the timed written alphabet and cube copy time subtests with tests of motor speed and psychomotor speed which can easily be performed across different cultures.
It consists of three subtests: timed fingertapping, timed alternating hand sequence test, and recall of four items at 2 minutes.

The timed fingertapping test from the Unified Parkinson's Disease Rating Scale (UPDRS) is used. [29] The number of fingertaps of the first two fingers of the non-dominant hand is measured by instructing the participant to open and close the fingers as widely and as quickly

as possible over a 5-s period. The scale from the UPDRS is used with 4 points assigned for normal performance (i.e.≥ 15 taps/5 s).

The alternating hand sequence test is adapted from the Luria Motor test. [32] Individuals are asked to perform the following movement with the non-dominant hand as quickly as possible over a 10s period:

i. Clench the hand in a fist on a flat surface
ii. Put the hand flat on the surface with the palm down, and
iii. Put the hand perpendicular to the flat surface on the side of the fifth digit.

The three hand positions are demonstrated to the participant by the examiner, and the participant then performs the sequence correctly twice for practice before the 10-seconds subtest is performed. The number of sequences correctly performed within 10-seconds up to a maximum number of 4 is scored. A participant unable to perform the alternating hand sequence is assigned a score of 0.

The verbal recall subset of the IHDS is similar to the one for the HDS whereby registration (new learning) is measured by mentioning four words to the subject and then asking him/her to repeat them immediately. The words are repeated by the examiner until the subject can repeat all four words correctly. The subject is then asked to recall the four words after the timed fingertapping and alternating hand sequence tests are performed. The number of items recalled is scored out of 4. For words not recalled, the subject is prompted with a 'semantic' clue as follows: animal (dog), piece of clothing (hat), vegetable (bean), and color (red). A half-point is assigned for each correct word recalled after prompting.

A total score out of 12 is calculated for each participant, with each of the three subtests contributing 4 points to the total score.A patient with a score of ≤ 10 should be evaluated further for possible dementia.

The sensitivity of the IHDS for HIV dementia in the Uganda cohort was 80%, and the specificity for HIV dementia was 55% using a cut-off of ≤ 10 for abnormal performance.[4] If the cut-off of ≤ 10.5 for abnormal performance was used, the sensitivity of the IHDS for

HIVdementia in the Uganda cohort was increased to 88% with a mild decrease in the specificity to 48%.[4]

The sensitivity and specificity of the IHDS are comparable to the sensitivity (71%) and specificity (46%) of the Grooved Pegboard non-dominant hand test, an established test for HIV dementia (using a cut-off of 1.5 SD below the age- and education-adjusted mean). [30,33,34]

The IHDS does not require knowledge of the English language, is not time-consuming (can be performed briefly in 2-3 minutes by non-neurologists in an outpatient setting), and requires no special instrumentation other than a watch with a second hand. It is useful for HIV+ individuals with and without a complete high school education (US cohort mean education, 13 years; Uganda cohort mean education, 9 years).[4]

The limitations of IHDS include inabilityto detect mild cognitive impairment associated with HIV infection, as there was no difference between HIV+ individuals with normal neuropsychological testing (MSK stage 0) and HIV+ individuals with mild impairment on neuropsychological testing but not severe enough to meet criteria for dementia (MSK stage 0.5).[4] Italso cannot be used to distinguish between different stages of HIV dementia, although progressively lower mean IHDS scores did correspond to greater dementia severity in the US study.[4]

The IHDS should not be used as a replacement for a full neuropsychological test battery in the clinical diagnosis of HIV dementia. Most HIV+ individuals with HIV dementia will be identified and can be referred for subsequent full neuropsychological testing to confirm the diagnosis of dementia, since using the cut-off of ≤ 10, the false positive rate is notable, and HIV+ individuals with an abnormal IHDS score may upon further testing have normal neurocognitive functioning.

The neuropsychological testing battery used in the Uganda cohort covered the following cognitive domains:

- Verbal memory (WHO/UCLA Verbal Learning test)[35]

- Psychomotor performance (Digit Symbol test[36], ColorTrails test[35])
- Motor speed (Timed Gait and Grooved Pegboard tests)

The WHO/UCLA Verbal Learning test for verbal memory is similar to the Rey Auditory Verbal Learning test (RAVLT) in that it uses a list-learning task. However, all of its items have been carefully selected (from categories such as parts of the body, tools, household objects, and common transportation vehicles) to be familiar in a variety of cultures.

The Color Trails 1 and 2 are similar to the Trail Making test except that to minimize cultural bias, no letters or written instructions are used. Both Color Trails 1 and 2 consist of several numbered circles colored in pink or yellow; in Color Trails 1, each number is represented by only one color, whereas in Color Trails 2, each number is printed twice, once in pink and once in yellow. In Color Trails 1, the participant is instructed to draw a line between the numbered circles one after the other, following the number sequence. In Color Trails 2, the participant must maintain the sequence of numbers and alternate between pink and yellow.

Digit span forward and backward was used to assess attention. The functional assessment included the Karnofsky Performance Scale. [37]These assessments were used to assign a MSK dementia stage of 0, 0.5, or ≥ 1 by a consensus conference including the primary examiners, a neurologist, a neuropsychologist, and a psychiatrist.

1.5TREATMENT

Standard treatment for HIV-associated dementia is an optimal HAART regimen combined with aggressive treatment of associated psychiatric problems (such as mood, anxiety, or substance use disorders).

Regardless of the CNS penetration of HAART medications, patients improve clinically and have improvement of surrogate markers of HIV dementia.[38] Use of selegiline in HIV-infected subjects experiencing cognitive impairment is investigational.

2.0 RESEARCH QUESTION

What is the prevalence of cognitive dysfunction and its associated factors amongHIV-positive patients at the Comprehensive Care Clinic at Kenyatta National Hospital?

3.0 STUDY JUSTIFICATION

HIV-associated dementia is common (prevalence 11-31%) and continues to represent substantial personal, economic and societal burdens.[39,40] Local data for the prevalence of cognitive dysfunction in HIV-positive patients is not available.

HAD is an important complication to diagnose in patients with HIV infection because it is associated with an increased risk of mortality,[32,41] and contributes to an individual's inability to function effectively in the workplace and at home [42, 43] as well as adversely affect a patient's adherence to HAART. [44, 45]

The IHDS may have great value as a screening test for HIV dementia. The diagnosis of HIV dementia may then be an indication for further neuropsychological evaluation in addition to HAART which has been associated with an improvement in cognitive function. [46,47]

4.0 OBJECTIVES

4.1 BROAD OBJECTIVE

To determine the prevalenceof cognitive dysfunction and its associated factors among HIV-positive patients attending CCC at Kenyatta National Hospital.

4.2SPECIFIC OBJECTIVES

1. To determine the proportion of HIV-positive patients attending CCC at KNH with cognitive dysfunction.
2. To determine the sociodemographic factors of HIV-positive patients with cognitive dysfunction.
3. To determine the association between cognitive dysfunction and CD4 cell count, duration of diagnosis of HIV infection and duration of HAART.

5.0RESEARCH METHODOLOGY

5.1 STUDY SETTING

The study was carried out at the Comprehensive Care Clinic at the Kenyatta National Hospital.

5.2 STUDY DESIGN

This was a cross-sectional study.

5.3 STUDY POPULATION

HIV-positive patients attending CCC at KNH.

5.4INCLUSION CRITERIA

- Aged >18 years.
- HIV-positive (diagnosed using two of the three Rapid Diagnostic Tests – Determine®, Bioline® and Unigold®).
- Given informed consent.

5.5 EXCLUSION CRITERIA

- Clinical presumptive evidence of past or present CNS opportunistic infections.
- Patients with a positive Venereal Disease Research Laboratory (VDRL) test.
- Known psychiatric disorders (schizophrenia, major depressive disorder, bipolar disorder).
- Patients with active kidney / liver disease.
- Past or present substance abuse (alcohol, opioids, cannabis).
- Patients on medications such as anti-psychotics, sedative hypnotics and anti-depressants.
- Patients with known neurological deficit (motor, sensory or cognitive) such as those with vitamin B12 deficiency, niacin deficiency or thyroid disease.

5.6 SAMPLE SIZE

Sample size was 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 (the standard normal distribution value) at the selected level of significance

p = expected prevalence (40%)
d = the maximal acceptable difference of estimate from true value (10%)

$$N = \frac{(1.96)^2 \times 0.40 \times 0.60}{(0.1)^2}$$

N = 93 patients (This is the sample size needed to be 95% certain that the prevalence obtained in the study will be within 10% of the true prevalence).

A sample size of 100 (one hundred) patients was used in the study.

5.7SAMPLING METHOD

Random sampling of HIV-positive patients attending CCC at Kenyatta National Hospital using a table of random numbers (attached as Appendix 1) was done to obtain five patients per day until the desired sample size was achieved.

5.8 ETHICAL CONSIDERATIONS

Ethical approval was obtained from the Kenyatta National Hospital / University of Nairobi Scientific and Ethical Review Committee.

Informed written consent (attached as Appendix 2) was obtained.

All patients were offered standard of care whether or not they agreed to participate in the study.

All information was kept confidential.

Those patients found to have cognitive dysfunction were informed regarding their status and requested to involve their next-of-kin in their management if not already done so, since cognitive dysfunction can adversely affect their adherence to HAART and contribute to their inability to function effectively in the workplace and at home. Those who were not on HAART were recommended to start HAART.

5.9 STUDY MATERIALS

Study questionnaire for demographic, clinical and laboratory data (attached as Appendix 3).

IHDS tool (attached as Appendix 4) to assess cognitive dysfunction.

Patients' files at the CCC, KNH.

5.10 PATIENT RECRUITMENT

The Principal Investigator (PI) randomly went through the files brought to the CCC every morning and selected the patients based on the inclusion criteria until the desired sample size was achieved.

The objectives of the study were explained to the patients and those who gave written informed consent were included.

All patients received a structured demographic assessment, medical history and neurological examination. The IHDS tool to assess cognitive dysfunction was administered by the PI as part of the clinical evaluation of the patient.

Patients with a fever (axillary temperature > 37.2°C), focal neurological deficit, papilloedema and those with severe major depression (score of ≥ 20) as determined using the Patient Health Questionnaire (PHQ-9),were to be excluded.

The PHQ-9 (attached as Appendix 5) has been validated in mental health and primary care settings and is based on the diagnostic criteria for major depressive disorder in the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM IV).

Patients with alcohol abuse as determined using the CAGE questionnaire (attached as Appendix 6) were also to be excluded.

Laboratory results for VDRL tests and CD4 counts were obtained from the medical records in the patients' files. HIV viral loads were not included because they are not routinely done in the CCC, KNH. If the VDRL test had not been done for a study participant, the PI paid for the test to be undertaken at the KNH laboratory.

5.11 POTENTIAL PREDICTOR VARIABLES

5.11.1 Demographic

- Age
- Gender
- Level of education
- Duration of diagnosis of HIV infection
- Duration of HAART
- ARV drug classes used as HAART component

5.11.2Laboratory

- Baseline, nadir (lowest-ever) and current (most recent)CD4 cell counts (using CyFlowSL_3® software FloMax version 2.52).

5.12 DATA ANALYSIS

The data from the files and the patients were entered into the study questionnaire by the principal investigator.

Data input was done in Excel and analysis done using Stata version 11.0.

Categorical data such as presence/ absence of cognitive dysfunction, gender and level of education were summarized as proportions.

Associations between presence / absence of cognitive dysfunction and categorical variables were analyzed using the Chi-square test and logistic regression. For this analysis, the level of significance was set at $P<0.05$.

Results were presented as Odds Ratios (OR) with 95% Confidence Intervals (CI).

Continuous variables such as age, duration of diagnosis of HIV infection, duration of HAART and baseline and nadir CD4 counts were summarized as means, medians and standard deviations.

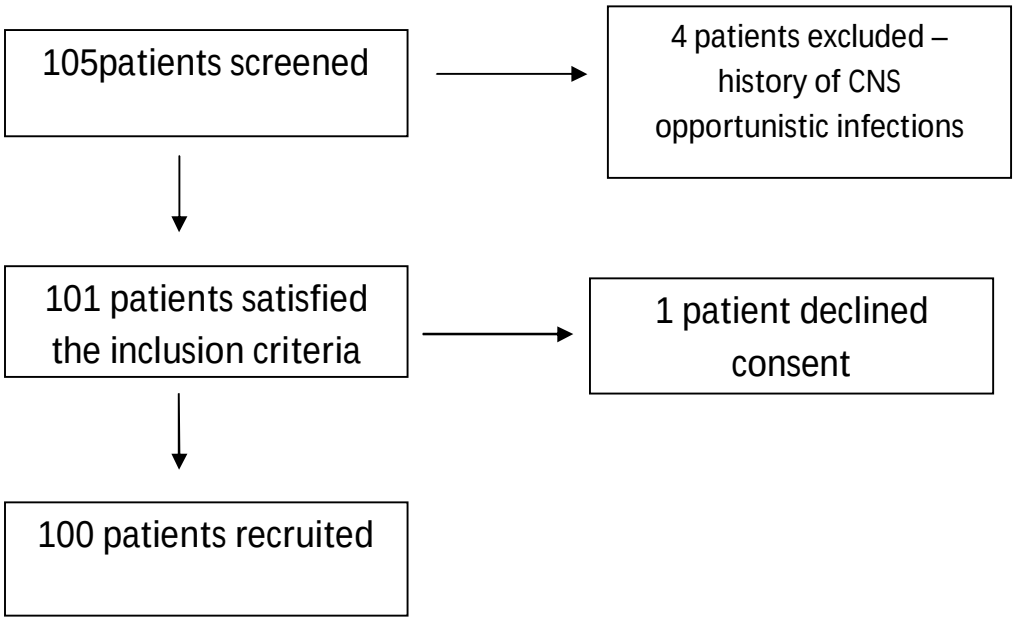
Data was presented in the form of tables, bar graphs and pie charts.

6.0 RESULTS

Between the period of January to April 2011, 105 patients were screened at the CCC, KNH. 101 patients satisfied the inclusion criteria but 100 patients were recruited into the study as 1 patient declined to give consent.

The 4 patients who were excluded had a history of being treated for CNS opportunistic infections in the past (3) and being VDRL positive (1).

The flow chart below summarises the patient recruitment.



The prevalence of cognitive dysfunction among HIV-positive patients attending CCC, KNH was 26%. The IHDS score for HIV-positive patients with cognitive dysfunction was ranging from a minimum of 8.0 to 10.0.

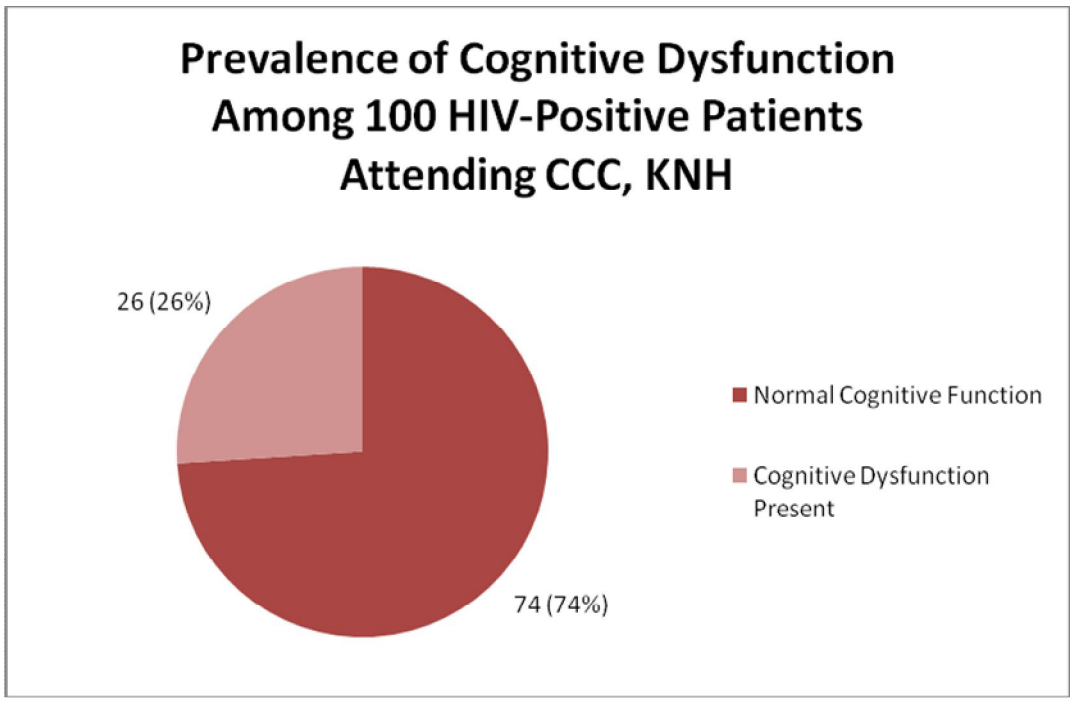


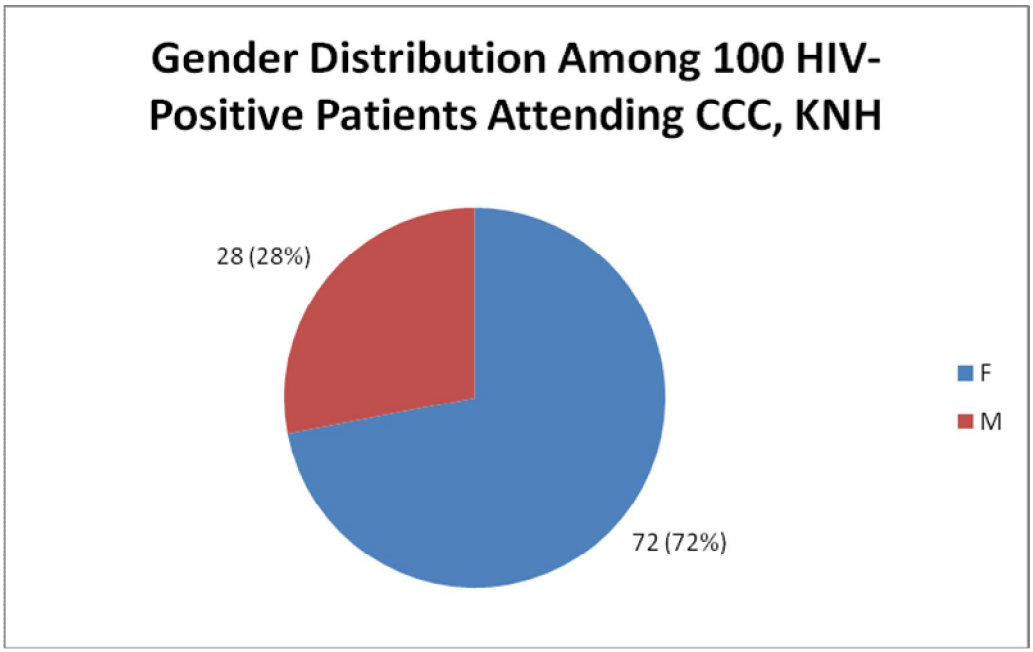
Table 3 below shows the characteristics of the study subjects by cognitive dysfunction status.

Table 3 : Characteristics of Study Subjects by Dysfunction Status

	No Cognitive Dysfunction		Cognitive Dysfunction		
	n	%	n	%	P-value
Age(mean(SD))	37.5(7.9)		40.7(7.6)		0.08
Education					
Primary	22	29.73	17	65.38	
Secondary	36	48.65	7	26.92	0.005
College	16	21.62	2	7.69	
Baseline CD4 Count (/μl)					
≤ 200	27	36.5	16	61.5	
201-350.	26	35.1	3	11.6	0.165
> 350	21	28.4	7	26.9	
Nadir CD4 Count (/μl)					
≤ 200	34	46.0	18	69.2	
201-350	28	37.8	4	15.4	0.159
> 350	12	16.2	4	15.4	
Duration of HAART					
≤ 2yrs	39	52.7	10	38.46	0.211
>2yrs	35	47.3	16	61.54	
Duration of HIV					
≤ 2yrs	30	40.54	7	26.92	0.216
>2yrs	44	59.46	19	73.08	
Gender					
Female	54	72.97	18	69.23	0.715
Male	20	27.03	8	30.77	
Employment Status					
Unemployed	10	13.51	4	15.38	0.813
Employed	64	86.49	22	84.62	

Generally, the characteristics were similar across the two groups. A significantly higher proportion of those with no cognitive dysfunction than those with cognitive dysfunction had more than primary education.

Demographic characteristics of the study cohort:

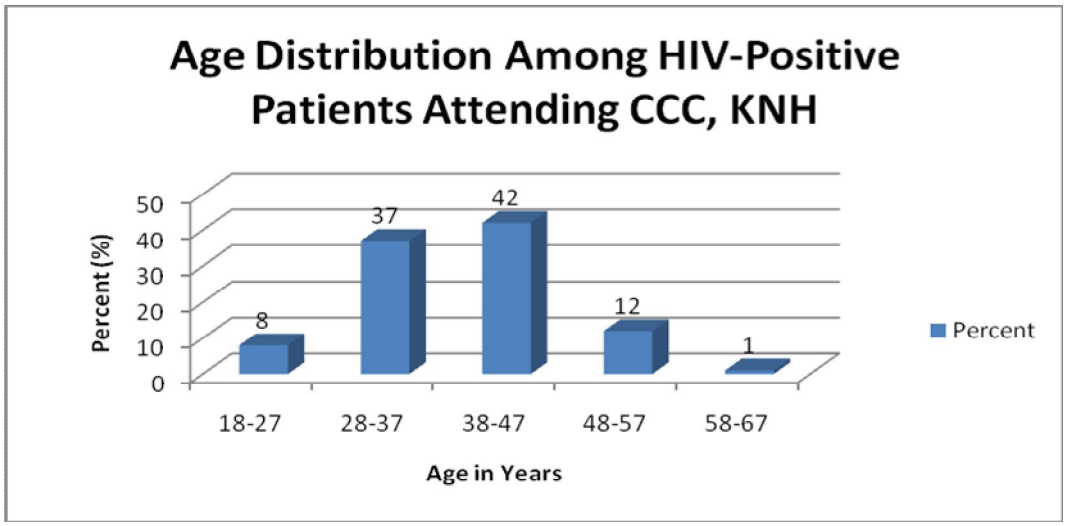


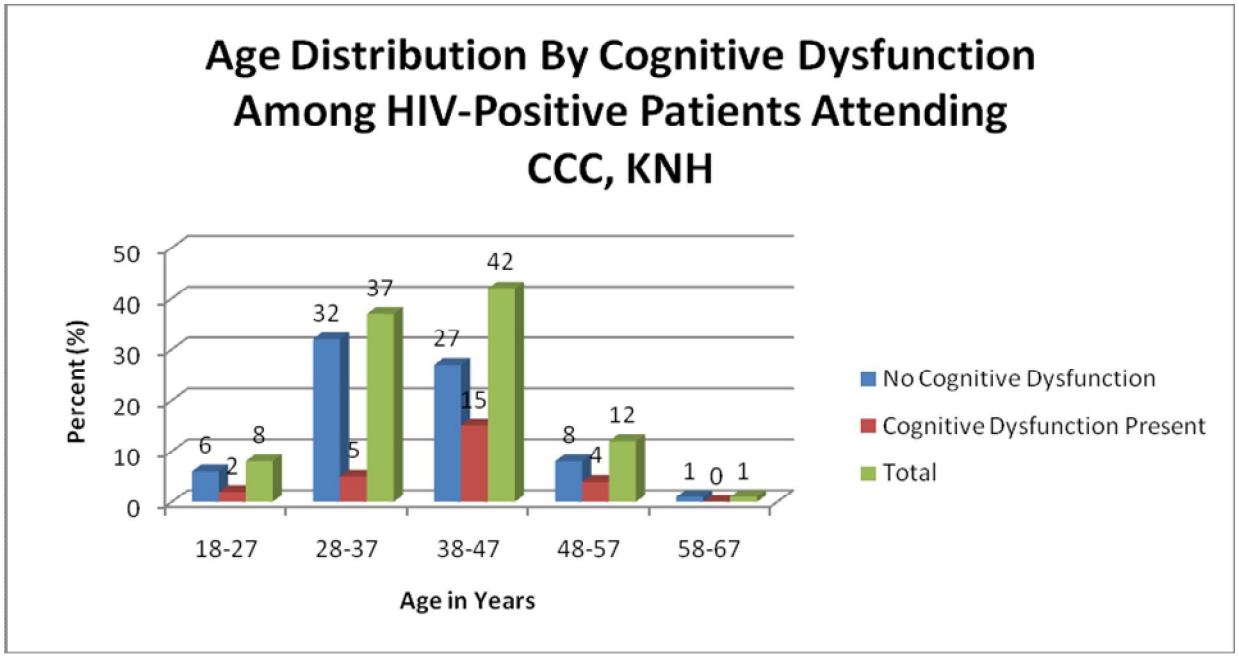
The female: male ratio was 2.6:1. For patients with cognitive dysfunction, 18 (69.23%) were female and 8 (30.77%) were male, while for those with normal cognitive function, 54 (72.97%) were female and 20 (27.03%) were male (P=0.715).

Relative to females, the odds of cognitive dysfunction was 1.2 for males (P=0.715).

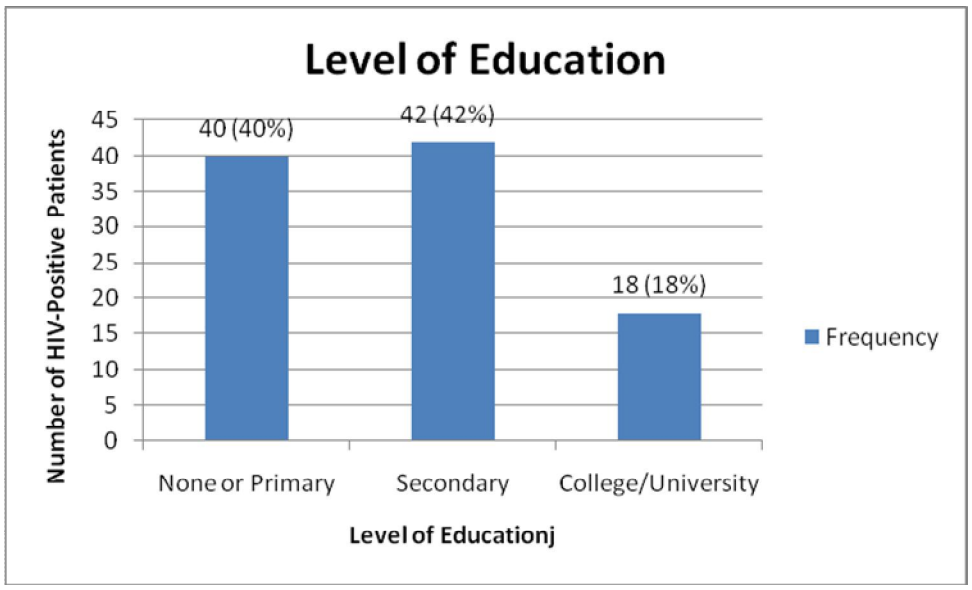
The peak age of the study patients was 38-47 years with a mean age of 38.3 +/-7.9 yrs and a median of 38 years. The youngest patient was 19 years of age and the oldest was 58 years of age.

When age was categorized as 18-27 years, 28-37 years, 38-47 years, 48-57 years, and 58-67 years, the age distribution is shown below:

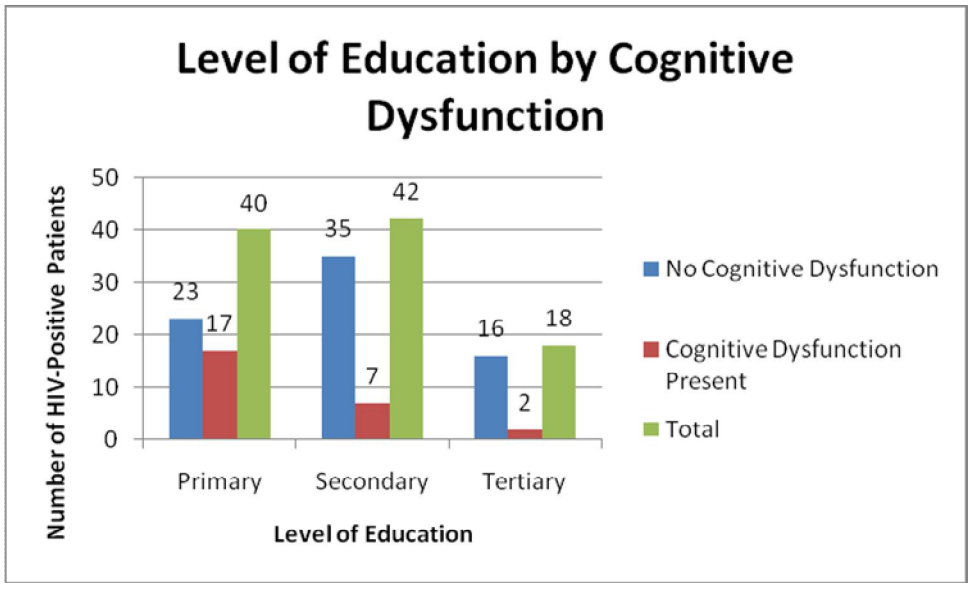




For patients with cognitive dysfunction, the mean age was 40.7 +/- 7.6 years, while for those with normal cognitive function, it was 37.5 +/- 7.9 years (P=0.08).



39 (39%) of the patients had primary education, 42 (42%) had secondary education, 18 (18%) had tertiary education while only 1 (1%) had no formal education (this was grouped with primary education for the purposes of analyses).



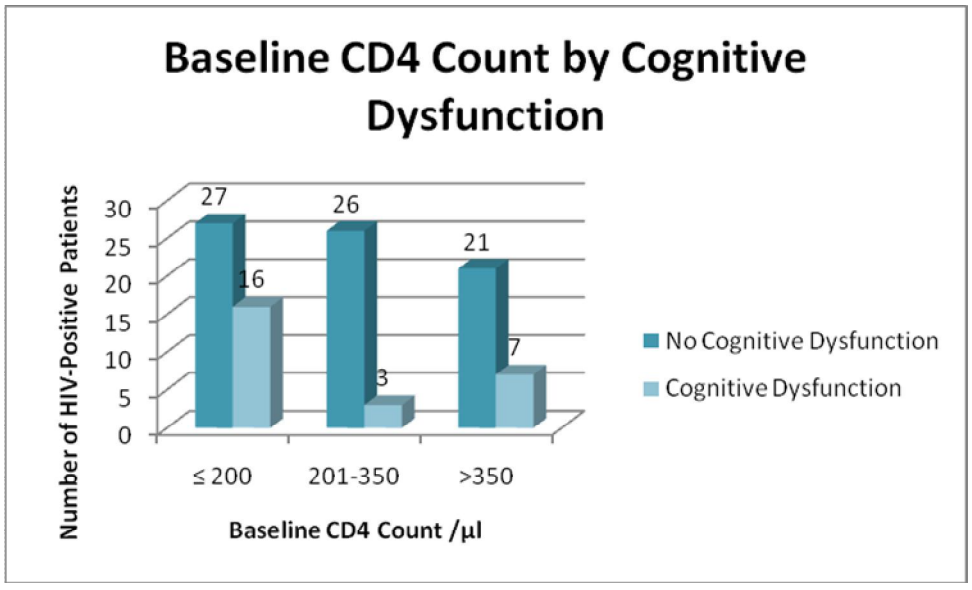
For those with normal cognitive function, 23 (31.08%) had primary education, 35 (47.30%) had secondary education and 16 (21.62%) had tertiary education, while for those with cognitive dysfunction, 17 (65.38%) had primary education, 7 (26.92%) had secondary education and 2 (7.69%) had tertiary education (P=0.005). When this was adjusted for

baseline CD4 count and nadir CD4 count, the P-value was still statistically significant (P=0.007)

Relative to those with primary education, the odds of cognitive dysfunction were 0.271, and 0.169 for those with secondary and tertiary education respectively (p=0.012).

The mean baseline CD4 count was 252+/-199/µl (median 236/µl and ranging from 2 to 850/µl). For those with cognitive dysfunction, the mean baseline CD4 count was 240+/-222/µl (median 146/µl and ranging from 11-700/µl), while those with normal cognitive function had a mean baseline CD4 count of 256+/-192/µl (median 250/µl and ranging from 2 to 850/µl) (P=0.719).

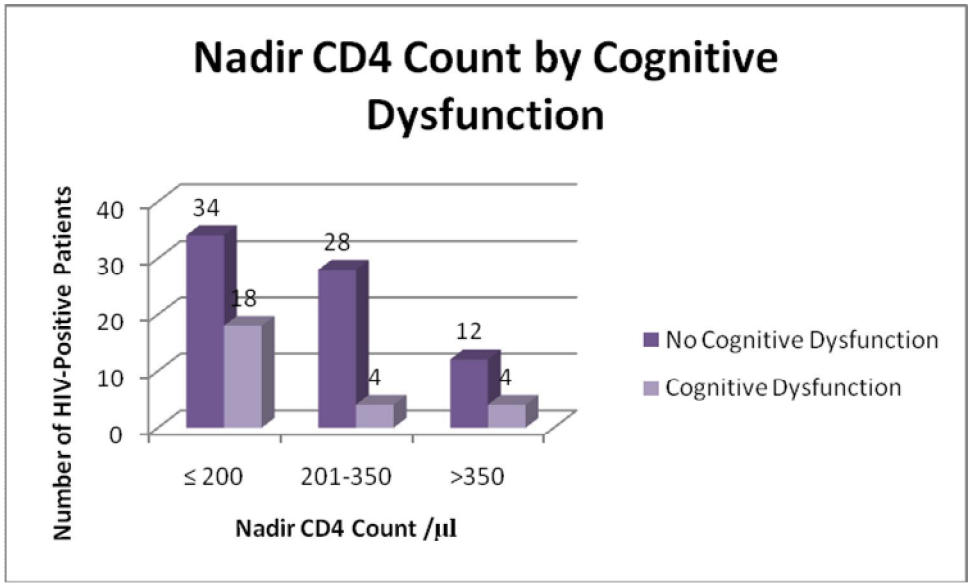
When the baseline CD4 count was categorized into ≤200, 201-350, and ≥350, for those with normal cognitive function, 27 (36.5%) had a baseline CD4 count of ≤200 /µl, 26 (35.1%) had 201-350 /µl and 21 (28.4%) had >350 /µl, while for those with cognitive dysfunction, 16 (61.5%) had a CD4 count of ≤200 /µl, 7 (11.5%) had 201-350 /µl and 3 (26.9%) had >350 /µl (P=0.165).



Relative to those with a baseline CD4 count of ≤200 /µl, the odds of cognitive dysfunction were 0.195 and 0.563for those with a baseline CD4 count of 201-350 /µl and >350 /µlrespectively (P=0.053).

The mean nadir CD4 count was 205+/-160/µl (median 195/µl and ranging from 2 to 680/µl). For those with cognitive dysfunction, the mean nadir CD4 count was 188+/-158/µl (median 146/µl and ranging from 11-584/µl), while those with normal cognitive function had a mean nadir CD4 count of 211+/-161/µl (median 207/µl and ranging from 2 to 680/µl) (P=0.531).

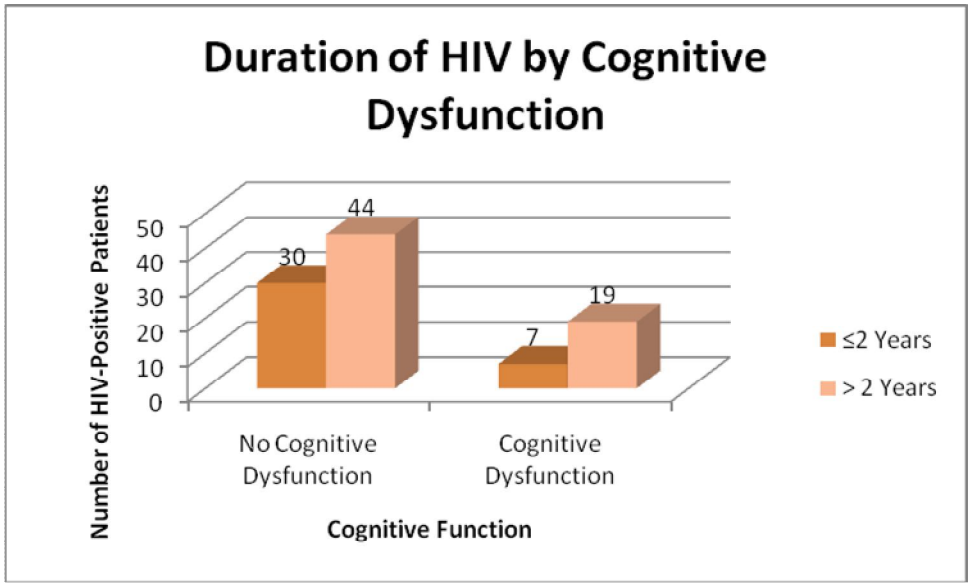
When the nadir CD4 count was categorized into ≤200, 201-350, and ≥350, for those with normal cognitive function, 34 (46.0%) had a nadir CD4 count of ≤200 /µl, 28 (37.8%) had 201-350 /µl and 12 (16.2%) had >350 /µl, while for those with cognitive dysfunction, 18 (69.2%) had a nadir CD4 count of ≤200 /µl, 4 (15.4%) had 201-350 /µl and 4 (15.4%) had >350 /µl (P=0.159).



Relative to those with a nadir CD4 count of ≤200 /µl, the odds of cognitive dysfunctionwere 0.27 and 0.63 for those with a nadir CD4 count of 201-350 /µl and >350 /µl respectively (P=0.096).

The mean duration of HIV infection from the time of diagnosis was 3.27 +/- 2.59 years. For patients with cognitive dysfunction, the mean duration of HIV infection from the time of diagnosis was 3.60 +/- 2.64 years, while for those with normal cognitive function, the duration was 3.15 +/- 2.58 years.

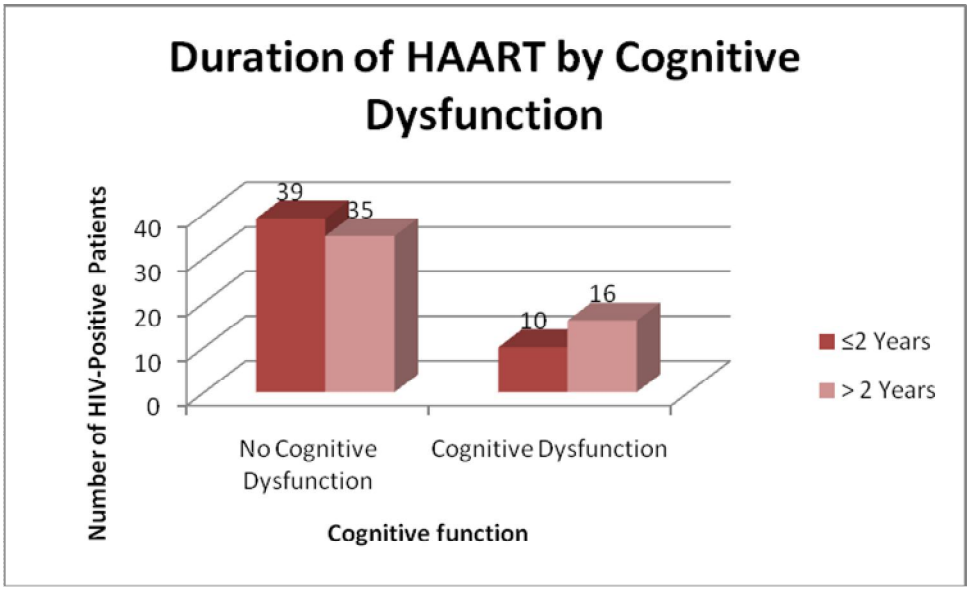
When the duration of HIV was categorized as ≤ 2 years and > 2 years, 30 (40.54%) patients with normal cognitive function were on HAART for ≤ 2 years while 44 (59.46%) patients were on HAART for > 2 years and for those with cognitive dysfunction, 7 (26.92%) were on HAART for ≤ 2 years while 19 (73.08%) were on HAART for > 2 years (P=0.216).



Relative to those having HIV infection for ≤ 2 years, the odds of cognitive dysfunctionwas 1.851 for those with HIV infection for more than 2 years (P=0.220).

The mean duration of HAART was 2.37 +/- 2.28 years. For patients with cognitive dysfunction, the mean duration of HAART was 2.59 +/- 2.23 years, while for those with normal cognitive function, the duration was 2.29 +/- 2.31 years.

When the duration of HAART was categorized as ≤ 2 years and > 2 years, 39 (52.7%) patients with normal cognitive function were on HAART for ≤ 2 years while 35 (47.3%) patients were on HAART for > 2 years and for those with cognitive dysfunction, 10 (38.46%) were on HAART for ≤ 2 years while 16 (61.54%) were on HAART for > 2 years (P=0.211).



Relative to those on HAART for ≤ 2 years, the odds of cognitive dysfunction was 1.783 for those on HAART for > 2 years (P=0.214).

The ARV regimens used were as follows:

ARV regimen	Frequency	Percent	Cumulative
AZT/3TC/EFV	14	14.00	14.00
AZT/3TC/NVP	10	10.00	24.00
TDF/3TC/EFV	14	14.00	38.00
TDF/3TC/NVP	4	4.00	42.00
TDF/3TC/SQV/r	1	1.00	43.00
d4T/3TC/EFV	15	15.00	58.00
d4T/3TC/NVP	20	20.00	78.00
HAART naive	22	22.00	100.00
Total	100	100.00	100.00

AZT = Zidovudine

3TC= Lamivudine

EFV = Efavirenz

NVP = Nevirapine

TDF = Tenofovir

SQV/r = Saquinavir/ritonavir

Only 3 patients had been changed to second-line HAART regimen [one was on TDF/ABC (Abacavir)/LPV/r (Lopinavir/ritonavir) and two were on TDF/3TC/LPV/r] and all 3 had normal cognitive function.

The table below summarises cognitive dysfunction as seen in HAART-naïve and HAART-experienced HIV-positive patients:

Table 5

HAART status	No Cognitive Dysfunction	Cognitive Dysfunction Present	Total
On HAART	58	20	78
Not on HAART	16	6	22
Total	74	26	100

Relative to those on HAART, the odds of cognitive dysfunction was 1.0875 for those not on HAART (P=0.878).

Table 4 below summarises the univariate analysis of cognitive dysfunction and selected covariates among HIV-positive patients attending CCC at KNH.

Table 4 : Univariate Association of Cognitive Dysfunction and Selected Covariates

		n	Freq (%)	OR	95%CI		p-value
Age		100	26(26)	1.054	0.994	1.117	0.079
Gender	Female	72	18(25)	1[Ref]			
	Male	28	8(29)	1.2	0.451	3.191	0.715
Level of Education	Primary	40	17(43)	1[Ref]			
	Secondary	42	7(17)	0.271	0.097	0.754	0.012
	Tertiary	18	2(11)	0.169	0.034	0.836	
Baseline CD4 Count (/µl)	≤200	43	16(37)	1[Ref]		.	
	201-350	29	3(10)	0.195	0.051	0.748	0.053
	>350	28	7(25)	0.563	0.196	1.616	
Nadir CD4 Count (/µl)	≤200	52	18(35)	1[Ref]			
	201-350	32	4(13)	0.270	0.082	0.890	0.096
	>350	16	4(25)	0.630	0.177	2.237	
Duration of HIV	≤2yr	37	7(19)	1[Ref]			
	>2yr	63	19(30)	1.851	0.692	4.946	0.220
Duration on HAART	≤2yr	49	10(20)	1[Ref]			
	>2yr	51	16(31)	1.783	0.716	4.44	0.214

In the univariate data analysis, only education was significantly associated with cognitive dysfunction. Specifically, the risk of cognitive dysfunction was lower among those with higher education levels. Relative to those with primary education, those with secondary education had a 73% reduced risk while those with tertiary education had 83% reduced risk.

7.0 DISCUSSION

Cognitive dysfunction remains one of the major threats to the management of HIV after opportunistic infections. The prevalence of cognitive dysfunction has varied depending on the population type and the method used. In our study using a sample of the HIV-positive patients attending CCC at KNH, the prevalence of HIV-associated dementia using the IHDS tool was 26%. This is comparable to the prevalences of 31%, 38% and 40% found in studies conducted by Sacktor et al[4] in 2005 in Uganda, Lawler et al[6] in 2010 in Botswana and in the CHARTER study[5] respectively.

The studies by Sacktor et al and Lawler et al had comparable populations and used the IHDS tool. The study by Sacktor et al was done on 81 HIV-positive patients at an Infectious Disease Clinic (which is part of a collaboration between HIV/AIDS care experts from North America and Makerere University Medical School) in Kampala, Uganda and they validated the IHDS tool using full standard neurological and neuropsychological assessments. The study by Lawler et al was a cross-sectional study on 120 HIV-positive patients done at the Infectious Disease Care Clinic at Princess Marina Hospital in Gaborone, Botswana. They used the IHDS tool in addition to utilizing other tools to assess verbal learning/memory and processing speed. The CHARTER study, done at 6 sites in the United States, included nearly 1800 participants (HIV-positive, HIV-negative and those with HIV/AIDS from the pre-ART and ART era). However, they did not use the IHDS tool but performed comprehensive neuropsychological evaluations for the participants.

Our study population was composed of young patients (mean age 38.3 +/- 7.9 years). This was comparable to the mean ages in the study done by Sacktor et al[4] in Uganda, where they found the mean age to be 37.0 +/- 9.4 years, and in the study by Lawler et al[6], where they found the mean age to be 37.5 +/- 6.5 years.

In the study by Lawler et al[6], increasing age was significantly associated with cognitive dysfunction (P=0.008). They used a cut-off IHDS score of ≤ 9.5 for neurocognitive impairment. Motor speed (finger tapping) and information processing speed (serial hand positions) were significantly affected with increasing age in that study.

Although, normally, age is associated with motor performance decline, this is more prominent in the fifth and sixth decades rather than the third and fourth decades of life. However, a report in the 16th Conference on Retroviruses and Opportunistic Infections (CROI) concluded that HIV infection was equivalent to approximately 15-20 years increase in brain aging, and HIV and aging produce similar additive effects i.e. reduce resting cerebral blood flow and decrease functional blood oxygen level dependent brain activity for visual stimuli;[48] consequently, cognitive dysfunction would be expected to occur in younger age groups.

HIV infection often strikes the population in the age group of 30 to 40 years; hence cognitive dysfunction in HIV-positive patients has profound socioeconomic implications since it causes an eventual decline in their work performance and diminished levels of income. Caregivers of patients with HIV dementia also often experience both physical and mental health problems.

Our study population comprised of more female patients (female: male ratio was 2.6: 1). This was similar to the findings by Ong'ondi et al in their study (MMed dissertation; unpublished data) on thrombocytopenia among HIV-positive patients attending CCC at KNH, where females were 61.6% of the study population. The 2007 Kenya AIDS Indicator Survey (KAIS) showed an estimated HIV prevalence of 7.4 percent among adults aged 15-49 years. These results indicated proportionately more women (8.8 %) than men (5.5 %) aged 15-49 are HIV-infected, which could explain the higher male to female ratio in this study.

The level of education was significantly associated with cognitive dysfunction as shown by patients with more than primary education having lower risks of cognitive dysfunction relative to those with primary education. This was statistically significant, even after adjusting for baseline and nadir CD4 counts.

This could be due to the fact that education may protect against dementia as shown in the studies by Bonaiuto et al and Zhang et al.[49,50] Bonaiuto et al found that the prevalence of Alzheimer's disease was 7.2% among illiterate people, 2.8% among those whose education had ceased at the fifth grade, and 0.5% among those who had studied in the fifth grade or over. Zhang et al studied 5,055 non-institutionalized persons aged ≥ 65 years in Shangai, China using a Chinese version of the Mini-Mental State Examination using 3 different cut-off points depending on the respondent's level of education. They found increasing age, female

gender and low education were each highly significant and independent risk factors for dementia. Education might in some way protect against neurodegeneration; or the onset of dementia might be delayed because education had improved neuronal networking so that when neurons died others could carry out similar functional tasks, so minimising signs of functional and cognitive impairment. Also, the IHDS tool may not be as robust to the effects of education as previously thought.

In the study by Lawler et al[6], fewer years of education were likewise significantly associated with cognitive dysfunction. Motor speed (finger tapping) was significantly slowed in those with fewer years of education. However, information processing speed (serial hand positions) was not significantly affected by level of education in that study.

Baseline and nadir CD4 counts would be expected to be associated with cognitive dysfunction and this was seen in the CHARTER study[5], where nadir CD4 count was strongly correlated with neurocognitive impairment even after adjusting for confounding variables. This association was attenuated with HAART but remained present when only those on HAART with an undetectable viral load were analyzed.

Our study did not find a significant association between cognitive dysfunction and nadir and baseline CD4 counts. This could possibly be due to discordance between CD4 count and HIV viral load whereby the CD4 count could be low yet the HIV viral load is suppressed. HIV viral loads were not included in the study because of financial constraints. The lack of significant association between baseline or nadir CD4 counts and cognitive dysfunction could also be due to categorization of the CD4 counts, which resulted in smaller numbers in each category.

Longer duration of HIV infection, not being on HAART or being on HAART for a longer period would be expected to correlate with cognitive dysfunction. Longer duration of HAART indicates longer exposure to HIV infection hence these patients would be more likely to have cognitive dysfunction as seen in the study by Lawler et al [6] i.e. the “legacy effect” of HIV infection in the CNS which results in aberrant and persistent immune activation and inflammation, thus establishing slow and irreversible brain damage and subsequently leading

to cognitive decline. Also, HIV-positive patients on HAART may have persistent cognitive dysfunction because of pre-treatment neurological damage, drug resistance or poor adherence.

Our study did not find a significant association between cognitive dysfunction and duration of HIV infection, HAART status or duration of HAART possibly because of dichotomization which resulted in smaller numbers in each category.

8.0 STUDY LIMITATIONS

The study population represents those HIV-positive patients who can access health care at the CCC, Kenyatta National Hospital and therefore results are not generalizable.

Laboratory and radiological procedures and investigations such as HIV viral load (which is a useful variable for assessing association with neurocognitive dysfunction),lumbar punctures, CT scans and MRIs to rule out CNS opportunistic infections were not done because of financial constraints.CD4 count was used as a surrogate marker for HIV viral load.

This was a cross-sectional study and therefore follow up of patients was not done, hence it is not possible to assess the impact of HAART on those patients found to have cognitive dysfunction.

9.0 CONCLUSION

HIV-associated neurocognitive dysfunction is quite prevalent (26%) among HIV-positive patients attending the CCC at KNH. No statistically significant associations between cognitive dysfunction and sociodemographic and laboratory variables were found except for education. This could be due to the fact that education may be protective against dementia and also, the IHDS tool might not be as robust to the effects of education as previously thought.

A high prevalence of cognitive dysfunction was seen despite the fact that more than 75% of the HIV-positive patients with cognitive dysfunction were on HAART, and more than 50% were on HAART for ≥ 2 years.

Hence HAART should be started earlier rather than waiting until the CD4 count drops to $\leq 200/\mu l$, and this is in line with the recent (March 2011) Kenyan Ministry of Medical Services directive that HAART should be initiated at a CD4 count of $\leq 350/\mu l$.

10.0 RECOMMENDATIONS

1. HIV-positive patients should be routinely screened for cognitive dysfunction using the IHDS tool.

2. Further validation of the IHDS tool to account for the effects of education on the cut-off scores used to indicate possible dementia may be needed (since it seems to be significantly affected by education).

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BUDGET

ITEMS	Unit Cost (KShs)	Quantity	Total (KShs)
1. Proposal preparation			
Typing & printing draft	30 per page	50 pages	1,500
Copies to supervisors	150 per copy	3 copies	450
Revision/correction of drafts	150 per copy	3 copies	450
Typing & printing final draft	30 per page	50 pages	1,500
Copies to ethical committee and supervisors: Photocopies Binding	 150 50	 6 6	 900 300
Ethical committee fees	1,000	1	1,000
Subtotal			***6,100***
2.Data collection			
Stationery & equipment e.g.questionnaires, flash disk, CD writing	3 200 2,000	100 questionnaires and consent forms (6 pages) Cd writing 1 flash disk	1,800 200 2,000
VDRL Test	300	100	30,000
Contracted services e.g. Statistician Research assistant	 20,000 5,000	 1 statistician 1 assistant	 20,000 5,000
Communication: e.g. Airtime	1,000	airtime	1,000
Sub total			***60,000***

3.Data Analysis&Reporting			
Typing & printing preliminary result	30	80pages	2,400
Copies to supervisors:	200 (black and white) per copy of book 600(coloured) per copy of book	3 copies 3 copies	600 1,800
Revision of Results:	30	80pages	2,400
Photocopies:- Black and white copies - Coloured copies	200 per copy of book 600 per copy of book	6 copies 6 copies	1,200 3,600
Binding of books	250	6 copies	1,500
Sub total			***13,500***
4. Contingencies (10%)			**7,960**
GRAND TOTAL			***87,560***

Source of funds: Self

APPENDIX 1: TABLE OF RANDOM NUMBERS

18 10 49 89 75	57 96 23 76 80	93 00 28 92 31	44 33 49 42 80
50 89 75 71 55	27 63 29 98 47	38 94 60 09 62	61 42 86 50 58
11 15 50 84 49	34 67 34 36 82	53 90 49 23 88	06 89 27 08 16
70 25 51 01 81	16 19 30 09 68	02 21 05 62 33	45 95 87 67 47
62 86 38 01 20	04 82 62 77 31	49 63 64 70 99	39 66 55 18 11
95 19 70 36 92	85 05 39 25 78	84 34 14 28 76	20 20 17 79 94
85 61 50 19 61	87 14 59 61 75	53 44 19 12 00	65 02 00 70 99
83 55 66 76 74	68 47 68 66 86	49 47 63 51 43	87 42 58 36 04
90 51 34 31 18	74 55 41 42 81	70 15 36 55 16	10 88 62 68 72
99 56 78 99 98	77 87 25 77 60	34 13 82 02 11	32 31 43 48 10
27 24 80 09 77	14 13 96 19 16	22 48 88 26 25	42 67 93 74 00
34 63 66 89 97	29 99 91 27 17	14 56 41 05 32	90 14 45 30 61
28 98 45 23 35	60 68 32 66 37	43 44 27 92 07	91 64 22 32 72
06 96 34 21 67	08 12 58 74 35	91 64 68 15 01	36 52 07 00 39
19 62 94 14 54	83 15 22 30 16	92 99 79 27 67	13 22 25 43 19
44 36 96 82 39	55 96 96 89 04	43 89 96 59 17	10 84 24 12 44
76 96 59 93 98	79 41 35 91 77	66 88 50 31 77	06 24 08 19 51
31 61 97 08 88	35 43 85 84 51	94 85 55 05 33	86 42 20 51 41
42 95 12 75 72	33 23 70 66 71	76 89 28 45 92	12 21 41 92 53
95 42 30 03 62	83 35 78 07 35	67 85 83 57 36	96 97 62 67 06
48 55 12 87 21	41 86 33 99 44	83 14 01 42 54	59 31 64 10 04
46 18 81 87 56	81 03 74 48 49	28 37 85 93 69	84 92 33 52 70
66 47 43 88 02	61 25 59 10 35	09 65 92 36 93	47 04 89 17 03
61 91 88 50 00	19 31 08 80 39	14 03 80 46 41	78 82 03 69 52
85 74 04 57 53	44 43 44 61 57	29 24 36 38 79	49 25 39 73 02
89 09 53 94 07	92 21 54 01 70	31 91 39 51 03	94 83 98 31 15
54 87 27 50 35	73 27 60 10 55	13 21 24 10 55	84 78 88 46 83
49 13 89 98 96	21 02 44 94 30	50 70 71 02 16	35 31 13 14 45
97 37 11 88 77	45 16 03 17 01	00 67 28 09 39	28 39 11 36 82
99 70 37 54 02	40 71 13 59 37	84 38 47 11 31	48 92 28 96 37
65 67 36 23 39	07 20 59 36 85	47 17 51 32 75	07 74 63 68 01
53 69 94 34 45	46 09 52 84 40	82 80 75 72 79	43 97 07 96 15
54 08 33 44 54	42 81 46 46 42	01 44 13 13 97	35 11 85 48 41
95 54 39 60 78	27 35 07 35 53	93 29 83 01 86	52 11 41 68 50
88 79 66 20 03	48 81 94 46 07	91 39 12 45 51	68 94 53 77 83
68 82 57 41 23	57 52 47 09 83	11 27 88 40 16	22 64 86 22 18
55 73 62 41 71	45 35 51 28 64	82 46 10 85 71	21 57 92 10 58
17 50 60 03 20	35 64 36 90 97	29 78 17 83 29	08 99 20 47 79
11 64 11 75 35	76 49 67 96 84	11 75 73 34 90	97 74 85 B8 37
78 32 11 34 33	55 30 20 68 10	68 96 94 82 04	94 10 52 73 51

APPENDIX 2: PATIENT INFORMATION AND CONSENT FORM

Investigators Introduction

My name is Dr. ZaheerBagha. I am a postgraduate student in the department of Internal Medicine and as part of the programme I am expected to carry out research. I have chosen to conduct a study on cognitive dysfunction in HIV- positive patients.

Purpose of the Study

To determine the prevalence of cognitive dysfunction in HIV-positive patients who are on HAART and who are HAART-naïve.

Procedures

If you agree to take part in the study, a medical history will be taken and a thorough physical examination will be done. The cognitive function will be assessed using the International HIV Dementia Scale (IHDS). If the VDRL test (a screening test for syphilis) has not been done, I will pay for it to be done at the Kenyatta National Hospital laboratory.

Study Population

I have chosen you as a potential candidate for the study because of your current clinical condition. You will be among the 93 patients who I will recruit for my study.

Risks

None involved.

Benefits

If an IHDS score of ≤ 10 is obtained, you will be informed and referred for appropriate care.

Confidentiality

The information obtained will remain with the Principal Investigator and a copy will be placed in the file.

Participation in the study is voluntary and denial to participate will in no way affect your further management at the hospital.

Participant's Consent

I declare that I have been explained to and have understood the purpose, the risks and benefits of the study and also that I can withdraw from the study at any point in time without losing any benefits that are due to me. I have been given an opportunity to ask questions and that my questions have been adequately answered. I also acknowledge that in case of any concerns during the period of the study or thereafter I can contact Dr. ZaheerBagha (0722865874).

I ……. of …….. declare that I have understood the above and I willingly and voluntarily agree to participate in the study.

Signed ……... Date …….

Investigators Statement

I declare that I have explained adequately to the patient about the purpose of the study, the risks and the benefits and have adequately answered all the queries.

Investigator…….. Date……..

IDHINI YA MGONJWA

Kuhusu Mchunguzi

Jina langu in Dr. Zaheer Bagha. Ninasomea udaktari Chuo Kikuu Cha Nairobi. Ninatakiwa kufanya uchunguzi fulani katika masomo yangu. Nimechagua kufanya uchunguzi juu ya madhara ya kiakili (kwa mafano kusahau mara kwa mara, kuwa na ugumu wa kuzingatia) kwa watu walio na Ukimwi.

Lengo la Uchunguzi

Kukagua kiwango cha madhara ya kiakili kwa watu walio na Ukimwi, ambao wanachukua dawa za ARVs na wale ambao hawajaanza dawa za ARVs.

Tutakayofanya

Ukikubali kushiriki katika huo uchunguzi, tutaongea na wewe na kukupima kimwili. Tutakagua madhara ya kiakili kwa kutumia “International HIV Dementia Scale (IHDS)”. Kama uchunguzi wa VDRL haujafanywa, nitaulipia ufanyike katika maabara ya Kenyatta National Hospital.

Watakao shiriki

Nimekuchagua ushiriki kwa uchunguzi wangu kwa sababu ya hali yako ya kuwa na Ukimwi. Utakuwa miongoni mwa watu 93 watakaoshiriki kwa uchunguzi.

Madhara

Hakuna madhara yoyote.

Faida ya Kushiriki

Kama utapatikana na madhara yoyote ya kiakili kulingana na IHDS, utaelezwa na kutumwa kupata matibabu zaidi.

Majibu

Majibu tutakayoyapata yatawekewa na mimi na nakala moja itawekwa kwa faili yako.

Kushiriki kwa huo uchunguzi ni kwa hiari yako na kutoshiriki haitakuletea shida yoyote upande wa matibabu yako.

Idhini ya Mgonjwa

Ninakubali kuwa nimeelezewa ya kutosha kuhusu uchunguzi huo, faida na madhara. Na pia kwamba ninaweza kukataa kushiriki kwa uchunguzi huo bila ya kukosa matibabu yangu ya kawaida. Maswali yangu yote yamejibiwa na ikiwa nitakuwa na swali lolote lingine nitaweza kumuuliza Dr. Zaheer Bagha (0722865874).

Mimi ……. wa …….. ninakubali kuwa ninaelewa haya yote na ninashiriki kwa huo uchunguzi kwa hiari yangu..

Sahihi ……... Tarehe …….

Ripoti / Taarifa ya Mchunguzi

Ninakubali kuwa nimemwelezea mgonjwa kuhusu uchunguzi huu, faida na madhara na nimeyajibu maswali yake yote.

Mchunguzi …….. Tarehe……..

APPENDIX 3: STUDY QUESTIONNAIRE

SUBJECT NO: ------

1. a) AGE: ------ years

b) GENDER: -------

c) LEVEL OF EDUCATION:

- NO FORMAL EDUCATION ----------
- PRIMARYSCHOOL ----------
- SECONDARY SCHOOL ----------
- COLLEGE / UNIVERSITY ----------

d) NUMBER OF YEARS OF COMPLETED FORMAL EDUCATION ---------- years

2. DURATION OF DIAGNOSIS OF HIV INFECTION ---------- years

3. DURATION OF HAART ---------- years

4. ARV DRUG CLASSES USED AS HAART COMPONENT

1ST LINE (INDICATE REGIMEN) ----------

2ND LINE (INDICATE REGIMEN) ----------

5. EMPLOYMENT / OCCUPATION ----------

6. HISTORY OF ALCOHOL USE PRESENT

YES ----- NO -----

7. IF YES (IN QUESTION 6), DOES PATIENT HAVE ALCOHOL USE DISORDER ACCORDING TO CAGE QUESTIONNAIRE

YES ----- NO -----

8. GENERAL PHYSICAL EXAMINATION (INDICATE ANY ABNORMALITIES DETECTED) ----------

9. FEVER PRESENT (AXILLARYTEMPERATURE > 37.2°C)

YES ----- NO -----

10. SEVERE MAJOR DEPRESSION PRESENT (SCORE OF ≥ 20 USING THE PATIENT HEALTH QUESTIONNAIRE PHQ-9)

YES ----- NO -----

11.NEUROLOGICAL EXAMINATION (INDICATE ANY ABNORMALITIES DETECTED)

- CRANIAL NERVES ----------
- MOTOR SYSTEM
  - ✓ MUSCLE BULK ----------
  - ✓ MUSCLE FASCICULATIONS ----------
  - ✓ MUSLE TONE ----------
  - ✓ MUSLE POWER ----------
  - ✓ DEEP TENDON REFLEXES ----------
  - ✓ GAIT ----------
  - ✓ INVOLUNTARY MOVEMENTS ----------
- SENSATION
  - ✓ PAIN ----------
  - ✓ TOUCH ----------
  - ✓ PROPRIOCEPTION ----------
- CO-ORDINATION
  - ✓ FINGER-NOSE TEST ----------
  - ✓ HEEL-SHIN TEST ----------
  - ✓ RAPID ALTERNATINGMOVEMENT OF SUPINATION AND PRONATION OF THE FOREARM ----------
- PRIMITIVE REFLEXES (GRASP, PALMOMENTAL, ROOTING, GLABELLAR) ----------
- PUPILLARY RELEXES ----------
- ARGYLL-ROBERTSON PUPIL PRESENT
  YES ----- NO -----

- FUNDOSOPY
  - PAPILLOEDEMA PRESENT ----------
  - PAPILLOEDEMA ABSENT ----------

12. INTERNATIONAL HIV DEMENTIA SCALE (IHDS) SCORE

- ≤ 10 ----------
- > 10 ----------

13. BASELINE CD4 COUNT ----------/µl

14. NADIR (LOWEST-EVER) CD4 COUNT ----------/µl

15. CURRENT (MOST RECENT) CD4 COUNT ----------/µl

APPENDIX 4: INTERNATIONAL HIV DEMENTIA SCALE (IHDS)

Memory-Registration – Give four words to recall (dog, hat, bean, red) – 1 second tosay 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.

APPENDIX 5: PATIENT HEALTH QUESTIONNAIRE (PHQ-9)

PATIENT HEALTH QUESTIONNAIRE-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? *(Use "✔" to indicate your answer)*	Not at all	Several days	More than half the days	Nearly every day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

FOR OFFICE CODING 0 + _____ + _____ + _____

=Total Score: _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from Pfizer Inc. No permission required to reproduce, translate, display or distribute.

PHQ-9 SCORE	PROVISIONAL DIAGNOSIS
5-9	Minimal symptoms
10-14	Minor Depression or Mild Major Depression
15-19	Moderately Severe Major Depression
≥20	Severe Major Depression

To make a tentative diagnosis of depression, functional impairment (the last question in the PHQ-9 questionnaire) should also be endorsed as “somewhat difficult” or greater.

APPENDIX 6: CAGE QUESTIONNAIRE

1. Have you felt you ought to **C**ut down on your drinking or drug use?

2. Have people **A**nnoyed you by criticizing your drinking or drug use?

3. Have you felt **G**uilty about your drinking or drug use?

4. Have you ever had a drink or used drugs first thing in the morning to steady your nerves or to get rid of a hangover or to get the day started? (**E**ye-opener)

Two or more "yes" answers indicates a need for a more in-depth assessment. Even one positive response should raise a red flag about problem drinking or drug use.