



Cognitive function in patients with newly diagnosed HIV infection in a tertiary health facility in south – west Nigeria: Assessment using computer-assisted neuropsychological test battery



Taofiki A. Sunmonu ^{a,*}, Olubunmi A. Ogunrin ^b, Frank A. Imarhiagbe ^b, Lukman F. Owolabi ^c, Morenikeji A. Komolafe ^d, Olayinka S. Ilesanmi ^e

^a Neurology Unit, Department of Medicine, Federal Medical Centre, Owo, Ondo State, Nigeria

^b Neurology Unit, Department of Medicine, University of Benin Teaching Hospital, Benin City, Edo State, Nigeria

^c Neurology Unit, Department of Medicine, Aminu Kano University teaching Hospital, Kano, Nigeria

^d Neurology Unit, Department of Medicine, Obafemi Awolowo University Teaching Hospital, Ile-ife, Osun State, Nigeria

^e Department of Community Health, Federal Medical Centre, Owo, Ondo State, Nigeria

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ABSTRACT

Introduction: Cognitive dysfunction is common among patients with human immunodeficiency virus (HIV) infection however there are few reports from sub-Saharan Africa.

Methods: We studied fifty seropositive patients with human immunodeficiency virus (HIV) infection along with fifty matched seronegative control. Medical history taking and general physical and neurological examinations were done for all study participants. Laboratory evaluations and chest X-ray were done for all the patients. The cognitive function was done with the aid of 'Fepsy' automated test battery for all the study participants. The data was analyzed with statistical package for social sciences software version 21.0 (SPSS Chicago IL).

Result: About 70% of the HIV patients were in advanced disease stage. The auditory and visual reaction times, binary choice reaction times, and computerized visual scanning task time were more prolonged in the HIV group ($p < 0.05$). There were also increased memory accuracy and binary choice task accuracy in the HIV group ($p < 0.05$). However the vigilance task performance was similar between the two groups ($p > 0.05$). Among the patients with HIV infection, the presence of anemia and central nervous system toxoplasmosis infection was associated with prolonged auditory and visual reaction times.

Conclusion: There was a high rate of cognitive dysfunction in patients with HIV infection in this study.

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1. Introduction

Human immunodeficiency virus (HIV) infection is a major cause of morbidity and mortality in the sub-Saharan Africa. As at the end of 2014, about 36.9 million people in the world were infected with HIV infection and 70% of these were living in sub-Saharan Africa. The annual mortality from HIV infection was 1.4 million [15].

Cognitive impairment may be a major manifestation of central nervous system (CNS) HIV infection. The cognitive deficits that have been described in people living with HIV/AIDS include impairment of attention/concentration, memory and psychomotor speed [20,36]. Several workers have documented that cognitive deficits seen in HIV infected patients affected those people with advanced HIV infection [42]. There are evidences that showed that HIV associated neurocognitive disorders

occur through the infiltration of HIV infected monocytes, macrophages and CD4 T cells into the brain by crossing the blood–brain barrier [4,17].

Neurocognitive impairment (NCI) could lead to impairment of activities of daily living, quality of life and poor medication adherence in patients with HIV infection [1,2,8,21,40]. Neurocognitive impairment could predict mortality in patients with HIV infection [30,47]. Various report showed that socio-demographic and some clinical variables affected cognitive functions in patients with HIV infection [10,23,38].

Evaluation of NCI in HIV-infected patients have been done with both traditional and computerized testing in the past but most studies [16,29,31] agreed that computerized assessment of cognitive function offers a standardized assessment in which timing of responses from the patients were very accurate (e.g. reaction times are measured in milliseconds). Also most of the cognitive domains that are affected in early stages of HIV infection such as psychomotor speed, executive functions amongst others were readily assessed by computerized test batteries. In this study, we assessed the burden and pattern of NCI in patients with newly diagnosed HIV infection as well as the influence of socio-

* Corresponding author.

E-mail address: taosunmonu@yahoo.com (T.A. Sunmonu).

demographic and some clinical variables on cognitive function in patients with HIV infection since there is paucity of literature on this topic in Nigeria Africans.

2. Methods

This is a cross-sectional study in which fifty patients with HIV infection and fifty age, sex and educationally matched controls were studied. The study was carried out at the Federal Medical Centre, Owo, Nigeria which is one of the tertiary health facilities appointed by the Federal Government of Nigeria as an HIV treatment centre with the major aim of providing free access to medical care including anti-retroviral therapy (ART) to patients with HIV infections.

The inclusion criteria for the patients were age greater than 18 years, seropositivity for HIV infection, minimum education of 6 years (as the test items require the study participants to be able to read English Language) and patients must not be on ART. The exclusion criteria were the presence of co-morbidities that could cause cognitive dysfunction (such as diabetes mellitus, hypertension, epilepsy, other metabolic diseases, cerebrovascular disease, Parkinson's disease, brain tumor among others) and subject must not be a known psychiatric patient. Other exclusion criteria include drug abuse, current use of psychoactive drugs, history of previous head injuries with loss of consciousness, severe functional impairment (Karnofsky performance less than 50%), alcohol intake greater than 13 units/week, presence of cardiac failure, use of anti-cholinergic medication and severe anemia (PCV < 20%). The same exclusion criteria were also applied to controls who were HIV seronegative individuals recruited from the general out-patient clinic and healthy members of staff of the hospital.

The study participants had general physical and neurological examinations. The patients were staged clinically for HIV infection using the World Health Organization (WHO) staging system. The presence of opportunistic infections in the patients were sought with the aid of chest X-ray and sputum examination (pulmonary tuberculosis) and empirical clinical response to anti toxoplasmosis drug was taken as evidence of toxoplasmosis infection. All the patients had laboratory testing which included serum electrolytes, urea and creatinine, full blood count, and liver function test and HIV serological testing with ELISA and CD4 cell count was estimated with automated flow cytometry.

3. Cognitive test assessment

The cognitive testing was done with the aid of a computer assisted neuropsychological test battery called 'iron psychology' with the acronym 'Fepsy' [32]. This instrument had been utilized in the study of cognitive function in various patients groups in Nigeria [35,44]. The 'Fepsy' consists of reaction times tasks, recognition memory tests, visual scanning task, seashore rhythm test, abstraction task and Corsi block task. In this study, we used the reaction time tasks, recognized memory test, computerized visual scanning task, recognition memory test and vigilance task only. Seashore task rhythm task and Corsiblock task were not utilized because they assess for brain damage which could also be done with computerized visual scanning task.

The study participants need not be computer literate to perform the tests as they only need to carry out instruction as they relate to each test. Language does not affect the performance on the test. The test was administered in a reasonably quiet and well lit room at a room temperature between 20 °C to 25 °C. The subject sat at a distance of 40 cm to 60 cm from the visual display screen of the computer. Effort was also made to ensure adequate brightness and contrast of the screen with adequate sound of the computer speakers. One of the authors (S.T.A.), a neurologist with experience in administration of Fepsy was always around to guide the patient during the cognitive assessment of all the study participants. The Fepsy test had been used in several institutions worldwide (www.fepsy.com). It took an average of 90 min to administer Fepsy to a subject.

4. Memory function

The memory function was assessed using the recognition memory test (RMT). The test involved the use of a study item consisting of three or four figures for the visual (non-verbal) memory and four to six words for the verbal memory test which were presented simultaneously. Details of this test were described elsewhere [35].

5. Mental or psychomotor speed

This was assessed using the simple reaction time test. The auditory version involved the presentation of a sound stimulus of 800Hz generated by the computer and the subject was asked to react by pressing the space bar as quickly as possible. For the visual version, the subject reacted as quickly as possible on seeing a white square in the middle of the computer by pressing the space bar. Thirty stimuli each were presented for the auditory and visual version.

6. Attention & concentration

Focused attention was assessed with continuous performance test (CPT) which involved the display of a string of eight characters either 'XXXXXXXX' or 'XAXXXXXX'. The subject had to decide on the appearance of a character 'A'. The task was a continuous performance test that lasted 10–20 min. The result yielded two parameters (d and β) d (perceptual sensitivity) ≥ 2 points to a good discriminating ability while β (response bias) value < 1 reflected impulsive behaviour while β value > 1 indicated a conservative way of responding.

Binary choice task is a complex form of continuous performance test. It has two components; binary choice reaction time which assesses psychomotor speed and binary choice reaction accuracy which assesses attention/concentration. Details of the binary choice task were described elsewhere [34,35]. The binary choice reaction time is weakly and positively correlated with binary choice accuracy.

7. Assessment of brain damage

The assessment of brain damage was done with the aid of computerized visual scanning task (CVST). The task involved finding a grid pattern out of 24 which matches the one in the centre. The grid patterns were displayed in the checker board fashion and were numbered 1 to 24. Twenty four patterns were presented and each subject had a total of 24 trials. Results showed accuracy and speed of response and were evaluated within the context of complex visual information processing and perceptual mental changes.

8. Statistical analysis

Data were analyzed using SPSS version 21. The mean scores of these tests were compared between patients with HIV infection and controls using student t-test. Student t-test and analysis of variance (ANOVA) were also utilized to evaluate the influence of the socio-demographic and clinical variables on cognitive function in the patients with HIV. The effect sizes were calculated with Cohen's d ; d value less or equal to 0.2 was taken as small effect size. Cohen's d of 0.5–0.7 as medium effect size while $d \geq 0.8$ was taken to be large effect size. p value was set at 0.5 and $p < 0.5$ was taken as being significant.

9. Results

One hundred and thirty-one participants were initially recruited for the study but 31 participants (20 patients with HIV infection and 11 controls) were excluded from the study because of incomplete data and unwillingness to continue with the study). The results of the cognitive assessment of the participants were automatically displayed on the screen of the computer after a session of administration of Fepsy

neuropsychological test. There were 31 males and 19 females in the HIV positive group while the HIV negative controls had 32 males and 18 females ($p > 0.5$). The mean age of the HIV positive group was 36.44 ± 8.22 years while that of the HIV negative controls was 35.40 ± 11.53 years ($p > 0.5$). The other details of the socio-demographic characteristics of the study participant were as shown in Table 1. The frequency distribution of the clinical and laboratory variables in the patients with HIV infection was highlighted in Table 2.

Table 3 compared the cognitive performance of patients with HIV and that of the controls. The results revealed prolonged auditory and visual reaction times, prolonged binary choice reaction time, computerized visual scanning times reduced recognition memory test (both word & figures) and binary choice reaction accuracies in patients with HIV when compared to controls ($p < 0.05$). The effect sizes calculated were large for the analyses. However, there was no difference in performance on vigilance task between the patients with HIV infection and controls ($p > 0.05$). The effect sizes calculated were small.

The prevalence of severe neurocognitive impairment as defined according to AAN updated criteria [5] to be impairment in neurocognitive function by at least 2 standard deviations below the mean of HIV matched seronegative controls on at least two ability cognitive domains was calculated for the HIV positive patients and HIV negative controls in this study. Twenty six out of 50 patients with HIV infection (52%) had severe neurocognitive impairment while 4 out of 50 controls (8%) had severe neurocognitive impairment. Seventeen males and nine females had severe NCI while only 4 females had severe NCI.

9.1. Socio-demographic variables and cognitive performance in patients with HIV infection

9.1.1. Sex

There were no differences in the mean auditory, reaction time (ART), visual reaction time (VRT), binary choice reaction time (BCRT), binary choice accuracy (BCR accuracy), recognition memory tests accuracy (RMT accuracy) and vigilance tasks between men and women with HIV infection ($p > 0.05$). The effect sizes were small for all the analyses. Details were as shown in Supplement 1A.

9.1.2. Age

The median age for the HIV patients in this study was 36 years (range 19–58 years). There were no significant differences in the ARTs, VRTs, BCRT, BCR accuracy, CVST, RMTs accuracy (both verbal/visual) and vigilance tasks between the HIV patients below and above

Table 1
socio-demographic characteristic of study participants

Variables	Cases N (%)	Controls N(%)	Statistics	p
Sex				
Male	31(62.0)	32(64.0)	$\chi^2 =$	0.500
Female	19(38.0)	18(36.0)		
Mean age (year)	36.44 ± 8.22	35.40 ± 11.53	$t =$	0.605
			0.519	
Level of education completed				
Primary	7(14.0)	2(4.0)	$\chi^2 =$	0.180
Secondary	26(52.0)	32(64.0)		
Tertiary	17(34.0)	16(32.0)		
Primary	- At least 1–6 years of education			
Secondary	7–12 years of education	t-Student t-test value		
Tertiary	- Greater than 12 years of education			
$p < 0.05$	- Significant			
χ^2	- Chi-square value			

Table 2
Frequency distribution of clinical/laboratory variables in patients with HIV infection

Variable	N	%
1. PCV (%)		
20–29	25	(52.1)
<30	23	(47.9)
2. CD_4 cell count (cells/ μ l)		
<200	33	(66.0)
200–499	15	(30.0)
≥ 500	2	(4.0)
3. Presence of opportunistic infections		
PTB	12	(24.0)
Oral cand.	3	(6.0)
OTB + oral cand.	4	(8.0)
PTB = skin herpes	1	(2.0)
CNS toxoplasmosis	2	(4.0)
None	28	(56.0)
4. WHO stage		
1	5	(10.2)
2	9	(18.4)
3	30	(61.2)
4	5	(10.2)
5. Weight (kg)		
30–39	5	(10.9)
40–49	12	(26.1)
50–59	21	(45.7)
60–69	6	(13.0)
≥ 70	2	(4.3)

the median age ($p > 0.05$). The effect sizes were also small for all the analyses. Details were as shown in Supplement 1A.

9.1.3. Education

The mean duration of education for the patients with HIV in this study was 13 years. There were no statistical differences in the ARTs, VRTs, BCRT, BCR accuracy, CVST, RMTs and vigilance tasks between the HIV patients who have duration of education below or above 13 years ($p > 0.05$). The effect sizes calculated were medium sizes for RMT (words) and CVST, otherwise the effect sizes for the rest of the analyses were small. Details were as shown in Supplement 1B.

9.2. Clinical variables and cognitive performance in patients with HIV infection

9.2.1. Weight

The effect of weight on cognitive function in the patients with HIV infection was analyzed separately for males and females. The median weight for the male and female patients with HIV infection was 54 years (range: 43–102 kg) and 45 years (range = 134–65 kg) respectively. There were no significant differences in ARTs, VRTs, BCRT, BCR accuracy, RMTs accuracy and vigilance between male patients below or above 54 years ($p > 0.05$). The effect sizes for the analyses were small with the exception of RMT (word) that was of medium size. For the females with HIV infection, there were no statistical differences in all cognitive domains assessed between women with HIV infection that were below or above 45 years ($p > 0.05$) but the effect sizes were medium for the statistical analyzes of VRT, BCRT, CVST, RMTs between the two age groups. Details were as shown in Supplement 2A.

9.2.2. Anaemia

HIV infected patients with packed cell volume of 20–29% had significant prolonged ARTs, VRTs and BCRT when compared to those with $PCV \geq 30\%$ ($p < 0.05$) and the effect sizes calculated were large for this analyzes. There was no statistical difference in the CVST, BCR accuracy, RMTs and vigilance tasks between the two groups ($p > 0.05$) and the effect sizes for these analyzes were small. Details were as shown in Supplement 2B.

Table 3
Comparison of cognitive function between patients with HIV infection and controls using Fepsy.

Tests	Patients with HIV infections N = 50 Mean ± SD	Controls N = 50 Mean ± SD	t	d	p
ART mean (ms)					
Dominant	530.41 ± 166.99	363.98 ± 140.05	5.255	1.09	<0.001
Non-dominant	432.93 ± 171.52	307.48 ± 116.18	4.196	1.40	<0.001
VRT mean (ms)					
Dominant	561.75 ± 211.88	92.78 ± 131.88	4.700	0.98	<0.001
Non-dominant	524.91 ± 231.92	363.94 ± 126.10	4.248	0.87	<0.001
BCRT mean					
Mean time	679.70 ± 327.91	495.64 ± 88.09	3.818	0.77	<0.001
Accuracy	81.90 ± 19.33	95.52 ± 5.69	4.996	0.97	<0.001
CVST					
Mean time (ms)	22.18 ± 8.04	18.49 ± 5.83	2.570	0.53	0.012
RMT (word)					
Accuracy	40.63 ± 19.85	54.08 ± 26.26	2.753	0.58	0.007
RMT (figures)					
Accuracy	38.68 ± 13.60	46.10 ± 13.46	2.627	0.55	0.010
Vigilance					
Δ (perceptual sen.)	0.77 ± 0.82	0.64 ± 0.69	0.794	0.02	0.429
β (response bias)	0.94 ± 0.45	1.04 ± 0.39	1.226	0.24	0.1223
ART	Auditory reaction time	t	Student	t test	
VRT	Visual reaction time		Value		
BCRT	Binary choice reaction time	d-	Cohen's d value		
CVST	Computerized visual scanning task	P -	Level of significance		
RMT	Recognition Memory test				
MSEC	Milliseconds	p < 0.005	Significance		
SEC	Seconds				

9.2.3. WHO stage

The patients with HIV infection that were in stage III & IV (late stages) had statistically prolonged ART than those in stage I & II (early stage), $p < 0.05$ and the effect sizes for the analyzes were large. There were no statistical differences in VRTs, BCRT, BCR accuracy, RMTs accuracy and vigilance between the patients in early and late clinical stages ($p > 0.05$). The effect sizes for these analyzes were small sizes. Details were as shown in Supplement 2B.

9.2.4. CD4 cell count

There were no statistical differences on the assessment of ARTs, VRTs, BCRT, BCR accuracy, RMTs and vigilance tasks between HIV infected patients that had CD4 cell count below or above 200 cells/ μ l. The effect sizes for the analyzes were small. Details were as shown in Supplement 2C.

9.3. Opportunistic infection (OIs)

There were no statistical difference between HIV infected patients that had OIs and those who did not have OIs on ARTs, VRTs, BCRT, BCR accuracy, CVST, RMTs accuracy and vigilance tasks ($p > 0.05$). The effect sizes were medium size for the analyses of vigilance task perceptual sensitivity and small sizes for the other analyzes.

The HIV infected patient with CNS toxoplasmosis had significantly prolonged auditory reaction time (dominant hand) and visual reaction times and reduced perceptual sensitivity when compared into HIV infected patients with pulmonary tuberculosis and oral candidiasis ($p < 0.05$). Details were as shown in Supplement 2C and 2D.

10. Discussion

Most of the fatal causes of HIV infection remain in the context of late diagnosis and delayed initiation of ART [3,6]. An especially important

public aspect is the impact of HIV infection on the occurrence of cognitive disturbance. A large number of HIV infected adults demonstrated HIV associated neurocognitive disorder [11]. These ranged from asymptomatic HIV infection to mild neurocognitive disorder and HIV associated dementia.

Commonly used instruments for the assessment of NCI in patients with HIV infection included the HIV dementia scale and mini mental state examination (MMSE). Computer assisted cognitive assessment instruments that were previously employed in the evaluation of cognitive function in patients with HIV infection included California computerized assessment package cal-CAP [16,31], Covert orienting of visuospatial attention – COVAT [28], Cogstate [12]. In Nigeria, 'Fepsy' Neuro psychological test battery had been utilized in several studies including those on HIV-infected patients [34–36,44].

It has been shown that the prevalence of NCI in HIV infected patients differ among studies due to different methodological approaches, study population and choice of normative data [18]. In this study, the prevalence rate of severe NCI obtained using 'Fepsy' test battery in the HIV-infected patients was 52% which is similar to that of a study in Nigeria (54%) that used IHDS [37]. Studies in Uganda, USA and India found prevalence rates of severe NCI of 27%, 47% and 51 % respectively in patients with HIV infection [41,48]. The high rate of severe NCI observed in the current study might be because the majority of the patients were in advanced stages of HIV infection.

The neuropsychological domains assessed in this study were psychomotor speed (auditory/visual reaction times, binary choice reaction times), memory (recognition memory tests – words/figures), attention and concentration (binary choice reaction accuracy and vigilance). Previous studies showed that cognitive impairments were not present in asymptomatic HIV infected patients when compared to controls [31,34,36] while other workers reported poorer neurocognitive performance in patients with advanced HIV infection when compared to controls [14,20]. The findings from this current study are in agreement with the latter studies in which the patients with HIV infection performed

poorly on measures of psychomotor speed, attention/concentration and memory relative to control subjects.

Previous works have shown that various factors were associated with neuropsychological impairment in patients with HIV infection which included alcohol/substance abuse, cardiovascular/metabolic diseases, psychiatric disorders hepatitis virus co-infection host genetic factors virus subtype, anemia, opportunistic infections CD4 cell counts, virus load and so on [12]. The influence of gender on neurocognitive functioning is unclear. Chiesi and the AIDS in Europe study groups reported that rate of cognitive impairment in patients were higher for women with HIV infection while another study [23] found cognitive impairment to be more in men with HIV infection. However, another study found no difference between the neuropsychological performance of HIV-seropositive men and women [38]. Our findings agreed with the latter in which there were no significant differences in psychomotor speeds, attention concentration and memory between the men and the women with HIV infection.

The impact of age on neuropsychological performance in HIV infection is well established [38]. In addition, age at the time of seroconversion is significantly associated with extent of neurocognitive impairment in patients with HIV infection [33]. Studies have shown the deleterious effects of increasing age on neurocognitive functioning in HIV infected patients [19,23,25,38]. The findings from this study revealed that there were no differences on measures of psychomotor speed, memory and attention /concentration among the two age groups in the HIV infected cohort; the reason for this discrepancy could be because the majority of the patients (69%) were in the middle age group (30–44 years).

It has been established that low level of education is an independent risk factor for the HIV associated neurocognitive disorder in a HIV seropositive individual [23]. In this study visual memory was better in HIV infected patients with tertiary education when compared to patients with primary or secondary education. However, non-verbal memory, psychomotor speed and attention/concentration were similar among the HIV infected patients irrespective of their educational level. The reason for this finding could be that majority (68%) of the patients with the HIV infection had equal or lesser than 12 years of education.

Weight loss continues to be a common problem in the era of highly active anti-retroviral therapy (HAART) and is associated with the reduced quality of life. Notably, weight loss has also been associated with deteriorated neurocognitive functions even in non-HIV-infected person [26]. A longitudinal study of treatment studies of AIDS wasting [13] indicated that HIV infected women at low weight demonstrated significantly reduced verbal learning, memory and motor function while HIV infected men at low weight demonstrated moderate impairment in verbal learning and visual construction but normal executive functioning. In this study, there were no differences on measures of psychomotor speed, memory and attention /concentrations between HIV infected patients with low weight and those with normal weight. The reasons for these findings were unclear from the current study.

An increased rate of neurocognitive impairment is found in patients with advanced stage of HIV infection. Low CD4 cell count, increased viral RNA load and advanced WHO stage (stages 3 and 4) usually characterize the late stage of HIV infection. Low CD4 cell count has been associated with impaired neurocognitive functioning in HIV infected patients as reported by several authors [9]. Previous works [36,43,46] have shown that impaired psychomotor speed, impaired memory, impaired attention /concentration were associated with low CD4 cell count. Majority of these studies showed that patients in (WHO stage 4 and CDC stages 3 and 4) had significantly slowed psychomotor speed while there was no difference between patients with clinically asymptomatic HIV infection and normal control subjects. [27,43]. Despite these findings, another investigator reported no relationship between immune suppression and neurocognitive functioning in HIV infected individuals [39]. The current study showed that there was no relationship between CD4 cell count and performance on measure of psychomotor speed, memory,

attention concentration and vigilance tasks; this finding may be explained by the fact that majority (66%) the HIV infected patients in our study were in low CD4 cell count group (<200 cell/ μ l). In analogy the WHO clinical stage was not associated with neurocognitive performance of the patient, most likely related to the fact that majority (70%) of the patients were in advanced WHO HIV disease stages.

There is paucity of literature on the role of opportunistic infections in the development of neurocognitive impairment in patients with HIV infection. A study showed that it is only the combined effects of immune suppression and the presence of opportunistic infections that could lead to neurocognitive impairment in HIV infected patients [42]. Some studies showed that HIV infected patient with AIDS defining illness with CD4 cell count less than 200 cells/ μ l performed worse on neurocognitive test than HIV infected patients with CD4 cells counts < 200 cells/ μ l without AIDS defining illness [7,9]. It was thought that opportunistic infection may exacerbate production of cytokines during immune suppression and because cytokines (such as tumor necrosis factors, interleukin-1 interleukin-6) tend to be toxic to neurons of the central nervous system, these may lead to a greater NCI in patients with AIDS defining illness. In this study, there was no difference in the performance of HIV infected patient with OIs when compared to those without OIs on measures of psychomotor speed, verbal memory and attention concentration. The reasons for these findings may be due to small sample size studied and the fact that only few opportunistic infections were sought for.

A patient with CNS toxoplasmosis performed significantly worse on measures of psychomotor speed and vigilance when compared to the other patients with pulmonary tuberculosis and oral candidiasis. This finding is in keeping with a report [45] where CNS toxoplasmosis and cryptococcal meningitis were associated with HIV dementia. The effects of opportunistic infection on neurocognitive functioning in HIV infected patient need to be confirmed in a future large scale study.

Anaemia was shown to be associated with impaired cognitive function and activities of daily living in elderly people [22]. Among HIV infected patient, cognitive impairment, low CD4 cell count and low haematocrit predicted cognitive dysfunction and mortality [47]. In the current study, HIV infected patients with moderate anemia performed poorly on measure of psychomotor speed when compared to non-anemic HIV infected patients. This is in concordance with a study among healthy adolescent girls where iron deficiency anemia was associated with impaired psychomotor speed [24].

11. Conclusion

This current study demonstrated that most HIV infected patients presented late for medical treatment and subsequent high rate of neurocognitive impairment and co-morbidities were found in these patients.

12. Limitations

There were several limitations in this study which include not studying the impact of psychiatric symptoms in detail as patients with only minor psychiatric symptoms were included in the study. The study is also limited by small sample size as a result of poor hospital attendance among HIV infected patients because of high level of stigma that is associated with the illness in sub-Saharan Africa. Additional causes for structural brain damage and central nervous system infection could have been present in the cohort but was not evaluated due to lack of resources for brain imaging and laboratory testing.

Conflict of interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <http://dx.doi.org/10.1016/j.ensci.2016.02.005>.

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