# The Burden of HIV-Associated Dementia in Acquired Immunodeficiency Syndrome: A Case-Control Study

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**Abstract:** *Objectives*: The prevalence of HIV dementia in West Africa is poorly defined. Hence we sought to determine the frequency of HIV-associated dementia in advanced HIV-1 infection and assess the contributory role of HIV-2 co-infection and other risk factors in a Nigerian population.

*Subjects and Methods*: A total of 130 HIV seropositive patients with CD4+ T lymphocytes count <200 cells/µl were compared with 130 age- and sex-matched healthy controls. Detailed clinical evaluation and cognitive assessment for dementia using the International HIV Dementia Scale (IHDS) were carried out on all participants.

*Results*: The life-time prevalence of dementia in HIV- positive patients was 66.2%. The HIV-positive patients had lower scores in all cognitive domains of the IHDS ($p<0.05$). Reduced mean score of Karnofsky performance scale, reduced body mass index, reduced total lymphocyte count and CD4+ T-lymphocyte cell count increased risk of dementia but HIV-2 co-infection was not associated with development of dementia.

*Conclusion*: There is a high burden of dementia among Nigerian adults with HIV/AIDS. This underscores the need for regular cognitive assessment for early detection and institution of appropriate intervention.

**Keywords:** AIDS, cognition, dementia, HIV, IHDS, Nigeria, prevalence.

## INTRODUCTION

Human Immunodeficiency Virus (HIV) not only causes immune depletion but, like all lentiviruses, also invades the central nervous system (CNS) [1, 2]. Following the initial systemic infection, HIV-1 can penetrate the central nervous system presumably persisting in the CNS for decades [3]. The terms AIDS dementia complex (ADC), HIV-associated dementia (HAD) and HIV encephalopathy, are used to describe the neurological and psychiatric symptoms caused by CNS HIV-1 infection [4, 5]. Case reports indicate that HIV-2 can cause similar neurological symptoms as HIV-1 [6-9]. The essential feature of dementia is a loss of intellectual abilities of sufficient severity to interfere with social or occupational functioning, in the presence of clear consciousness [10]. HIV-1 is responsible for the great majority of infections globally, HIV-2 being very rare outside of West Africa. Most people with HIV-2 infection have some epidemiological link to West Africa [11]. There have been reports of similar or even higher frequencies of HIV encephalitis in HIV-2 than in HIV-1 infected individuals [12, 13]. There is currently no explanation for this observation. Whether this portend a higher prevalence of HAD in West Africa which is the epicenter of HIV 2 infection remains unclear.

The prevalence of HIV dementia is 10–15 % in HIV positive individuals with advanced infection in the United States [16]. HIV dementia may be the most common cause of dementia worldwide in patients under the age of 40 years [17]. Nigeria is the only African country which has reported a substantial amount of research on the subject of the prevalence of dementia [14]. Estimates of dementia prevalence and incidence for the African region (primarily sub-Saharan Africa) are considerably lower than most of the other world geographical regions [15]. There are few studies that have reported the prevalence of HIV dementia in Nigeria and other sub- Saharan African countries [16 - 19]. In previous studies done in Africa, frequencies of AIDS dementia complex (ADC) varied widely; 8.7% in the Democratic Republic of Congo, 16% in rural Uganda, 21.1% in Cameroon and as high as 54% in Tanzania [18 - 20,21 - 23]. A relatively high frequency of cognitive dysfunction in patients with HIV infection has been reported in Nigerians. This frequency increases with progression of disease [21, 24]. The prevalence of HIV infection in Nigeria is 5.8%, affecting about 5 million persons [22, 25]. The previous studies conducted among Nigerians have focused on cognitive functioning at various stages of HIV infection (18, 19, 26). Little is known however of the contribution of the HIV 1 and 2 dual infections on the frequency of HIV-dementia in West Africa.

This study was designed to determine the prevalence of HIV dementia among anti-retroviral

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therapy naïve adult Nigerians with advanced HIV infection. The International HIV Dementia Scale (IHDS) was used to screen for HIV dementia. The effect of HIV- 2 co-infection and other risk factors on the frequency of dementia among the HIV seropositive patients was evaluated.

## SUBJECTS AND METHODS

One hundred and thirty antiretroviral therapy naïve adults with advanced HIV infection (CD4+ T lymphocyte counts less than 200cells/ul) were randomly selected from all those who met the inclusion criteria for participation in the study. The control group comprised age- and sex- matched HIV seronegative individuals recruited from among blood donors, patient's relations and patients seen in the medical out-patient department. The exclusion criteria included severe medical illness that would interfere with the ability to perform the cognitive test, age less than 18 years of age, an active or previous CNS opportunistic infection, a history of a chronic neurological disorder, current or past history of psychiatric disorder (major depression or psychosis), active alcoholism; physical deficit (e.g., amputation), history of head injury with loss of consciousness greater than 1 hour and use of recreational or psychoactive drugs.

The study site was the HIV/AIDS Outpatients' Clinic of the University of Port Harcourt Teaching Hospital (UPTH), a major tertiary health facility situated in cosmopolitan Southern Nigeria. Informed written consent was obtained from each patient before participation in the study. Ethical approval for the study was given by the Hospital Ethics Committee before commencement of the study.

The study participants were assessed using standardized questionnaires to obtain demographic information including age, sex, primary language used and reading abilities, level of education, medical history, psychiatric history (anxiety and depression assessment), history of use of alcohol or substances and neurological symptoms. Detailed general and systemic (including neurological) examinations were performed on each patient. The body mass index (BMI) was calculated as the ratio of weight to the square of height ($Kg/m^2$). Blood samples were obtained for complete blood counts, renal and liver function tests. Assessment of functional impairment was done with the Karnofsky Performance Scale [23, 27]. All study participants were screened for HIV associated dementia using the International HIV Dementia Scale (IHDS).

### Test Instrument

The International HIV Dementia Scale (IHDS) consists of three subtests, namely: timed finger tapping, timed alternating hand sequence test, and recall of four items at 2 minutes. It was administered in keeping with the protocol of its developers [24]. A total score of 12 is achievable on this scale, i.e. a maximum score of 4 on each of the three subtests. A pilot study was conducted to determine the optimal cut-off score for this study. A cut-off score of <10 indicates HIV dementia [24].

### Statistical Analysis

Data was analyzed using Statistical Package for Social Sciences (SPSS) version 11. Continuous variables were analyzed with the Students t-test. Proportions or categorical parameters were analyzed with the 2-tailed Fisher's exact test. Strength of association between occurrence of dementia and risk factors was determined with a 2 x 2 contingency table. A p-value of 0.05 or less was considered statistically significant.

## RESULTS

### Results of the Pilot Study

To determine the optimal cut-off value for the IHDS to maximize sensitivity and specificity, a receiver–operator characteristic (ROC) curve analysis was performed. The cut-off value of 9.5 for the IHDS maximized the sensitivity (60.9%) and specificity (64.6%) for HIV dementia. The cut-off value of 10.0 however increased the sensitivity to 92.2% with fewer false negative results (specificity of 62.6%). The area under the curve was 0.873 and was statistically significant ($p<0.05$). The ROC curve plot for patients' IHDS scores is shown in Figure **1**.

### Results of Main Study

Of the 130 patients recruited for the study, 73 (56.2%) were HIV 1 positive while 57(43.8%) were positive for both HIV-1 and HIV- 2 ($z = 1.985$ $p = 0.05$). There was no patient with seropositivity for only HIV-2. The age distribution of the patients ranged from 18 years to 65 years with a mean age of 34.7 (SD 9.3) years. The mean age of the control group was 34.5 (SD 9.4) years and was not significantly different from that of the patients ($t = 0.220$, $p = 0.41$). The mean ages of the male and female patients were 39.9 (SD 8.9) years and 30.5 (SD 7.3) years respectively ($p <$

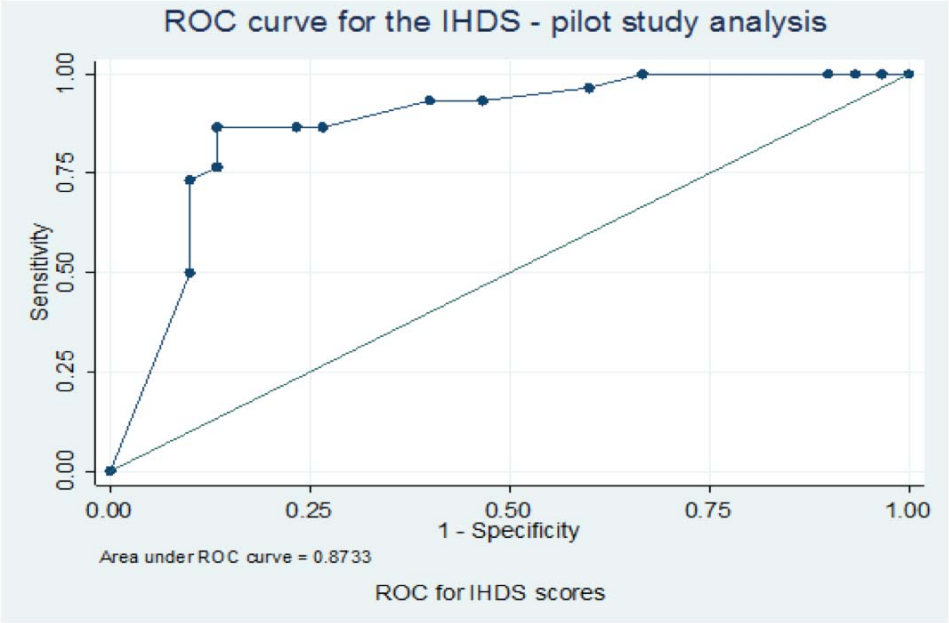


**Figure 1:** Receiver operating characteristics curve for IHDS pilot study.

0.0001). There were 58 (44.6%) males and 72 (55.4%) females among patients while the control group consisted of 57 (43.8%) males and 73 (54.2%) females ($\chi^2$ 0.016; p=0.91) refer Table **1**. The mean number of years of education attained by the patients was 10.45 (SD 4.28) years while that of the controls was 14.05 (SD 3.79) (p < 0.0001).

The range of IHDS total scores among patients was from 3.5 to 12 with a mean score of 9.57 (SD 1.57) while the mean score of the controls was 11.01 (SD 1.13); t=8.48, p=0.001. The HIV-seropositive patients had significantly lower scores than controls in all the domains of the IHDS (refer Table **2**). Using the diagnostic criteria of the IHDS, patients were classified into those with an IHDS score >10, considered to be normal, and those with an IHDS score <10 considered to have HAD. Forty four (33.8%) of the patients had a total score above 10.0 on the IHDS, while the other 86 (66.2%) scored <10. Among the control group, 98(75.4%) had a score >10 while the other 32(24.6%)

**Table 1: Age and Sex Distribution of the HIV+ Patients and Controls**

| Age groups | Male | | Female | |
|---|---|---|---|---|
| | HIV+ patients | Controls | HIV+ patients | Controls |
| 18-25 | 1 | 2 | 18 | 16 |
| 26-35 | 16 | 17 | 39 | 37 |
| 36-45 | 24 | 25 | 12 | 15 |
| 46-55 | 13 | 10 | 3 | 5 |
| 56-65 | 4 | 3 | 0 | 0 |
| Total | 58 | 57 | 72 | 73 |

**Table 2: Comparison of the IHDS Subtests Scores Between HIV- Positive Patients and HIV- Negative Controls**

| Parameter | Patients | Controls | t | P |
|---|---|---|---|---|
| Motor | 2.55±0.85 | 3.38±0.69 | 8.57 | P<0.001 |
| Psychomotor | 3.54±0.77 | 3.81±0.47 | 3.41 | P<0.001 |
| Memory | 3.47±0.77 | 3.79±0.37 | 4.39 | P<0.001 |
| Total | 9.57±1.57 | 11.01±1.13 | 8.49 | P<0.001 |

**Table 3: Comparison of Demographic, Clinical and Laboratory Parameters Between HIV+ Patients with and without Dementia**

| Parameter | Patients with HAD Means (SD) | Patients without HAD Means (SD) | P values |
|---|---|---|---|
| Age (years) | 34.2 (9.6) | 35.7 (8.5) | 0.39 |
| School years attained (years) | 10.3 (4.8) | 10.8 (3.2) | 0.49 |
| Body Mass Index (BMI) | 21.0 (3.2) | 22.27 (3.7) | 0.05 |
| Karnofsky performance score | 81.4 (10.8) | 85.7 (7.0) | 0.007 |
| CD4 T-cell count (cells/µl) | 89.7 (50.5) | 125.2 (41.7) | <0.0001 |
| Total lymphocyte count (cells/µl) | 2232 (925.8) | 3441.7 (2301) | 0.002 |
| Total white cell count (cells/µl) | 6630.2 (3194.2) | 6965.9 (3142.4) | 0.57 |
| Hemoglobin level (g/dl) | 9.7 (1.9) | 10.8 (1.0) | <0.0001 |

scored <10.0. The prevalence of dementia in HIV-positive patients was 66.2%. There was no statistically significant difference in the mean age and years of education attained between patients with and without dementia as determined by the IHDS scores (refer Table **3**). Patients with dementia had a lower mean Karnofsky performance score, body mass index, CD4 positive T- lymphocyte cell counts and other laboratory parameters as shown in Table **3**. A higher proportion of patients with CD4+ T- lymphocyte cell count less than 100 cells/ µl had HAD compared with those with counts above 100cells/µl. Table **4** showed the association between age, gender, HIV type, years of education, CD4+ cells count and the presence of HIV associated dementia. Infection with HIV type 1 and very low CD4+ cell count of less than 100 conferred a two and four fold risk of developing HAD.

The CD4 positive T- lymphocyte cell count distribution of the patients ranged from 11 to 192 cells/ µl with a mean of 101.7 (SD 50.43)cells/µl. The distribution of the CD4 positive lymphocytes was such that 59 (45.4%) had counts under 100 cells/ µl while the other 71 (54.6%) of the patients had counts between 100- 199 cells/µl. The range of total lymphocyte count among the patients was 1530 to 7474 cells/ml while the mean was 2641.38 (SD 1624.22)cells/ml. The mean hemoglobin concentration

**Table 4: Test of Association Between Various Parameters and IHDS Diagnosed Dementia in HIV- Positive Patients with and without Dementia**

| Parameter | IHDS diagnosis | | $X^2$ | P value | OR (95% CI) |
|---|---|---|---|---|---|
| | Dementia n (%) | No dementia n (%) | | | |
| *Gender* | | | | | |
| Male | 38 (65.5) | 20 (34.5) | 0.02 | 0.89 | 0.95 (0.458 – 1.972) |
| Female | 48 (66.7%) | 24 (33.3) | | | |
| *HIV type* | | | | | |
| HIV 1 | 52 (71.2) | 21 (28.8) | 1.44 | 0.23 | 1.68 (0.805 – 3.486) |
| HIV 1 & 2 | 34 (59.6) | 23 (40.4) | | | |
| *Age (years)* | | | | | |
| <50 | 79 (65.3) | 42 (34.7) | | 0.72* | 0.54 (0.107 – 2.704) |
| >50 | 7 (77.8) | 2 (22.2) | | | |
| *CD4+ count (cells/ml)* | | | | | |
| 0-99 | 48 (81.4) | 11 (18.6) | 9.94 | 0.002 | 3.79 (1.695 – 8.471) |
| 100-199 | 38 (53.5) | 33 (46.5) | | | |
| *Years of education* | | | | | |
| 0-12 years | 71 (65.7) | 36 (34.3) | 0.01 | 0.92 | 1.05 (0.408 -2.713) |
| >12 years | 15 (65.2) | 8 (34.8) | | | |

$X^2$ chi-square, OR odds ratio, CI confidence interval *Fisher's exact test.

was 10.07 (SD 1.73) with a range of 6g/dl to 13g/dl. Fifty eight (44.6%) had heamoglobin level less than or equal to 10 g/dl while 72 (55.4%) had hemoglobin level above 10g/dl (t = -1.74, p = 0.08). The range of Karnofsky performance was 60 to 100 with a mean of 82.85 (SD 9.82) compared to 95.92 (SD6.90) for controls with a range of 70 to 100 (t= -12.42, p = 0.000).

## DISCUSSION

This study, being the first to determine the frequency of HAD in Nigerians with advanced HIV infection using the IHDS as a screening tool, identified significant differences in performance on all domains of the IHDS among patients when compared with age and sex-matched controls. The mean IHDS total score obtained in this study is comparable to that obtained by Sacktor *et al.* [16] in Uganda. It is however lower than the mean total score reported in a recent study from Cameroon [36]. This disparity in mean scores may be attributed to the variations in stages of disease among the cohorts of patients studied.

Furthermore, the frequency of HIV- associated dementia obtained in this study was higher than figures reported from earlier studies in Nigeria. Since progression of HIV disease is characterized by worsening cognitive impairment [21], it is expected that patients with advanced HIV infection would have a higher dementia frequency compared to other unselected cohorts reported earlier. An earlier study among Nigerians, using the Mini Mental Scale Examination (MMSE), documented a prevalence of 12.3% among 202 patients [25]. Another study from South-West Nigeria detected an HIV dementia prevalence of 12% among 154 HIV seropositive patients with neurological diseases [26]. Aside from differences of stages of HIV infection, disparities in the results obtained from these studies may not be unrelated to differences in diagnostic criteria, diversity of screening tools, sample size and methodology employed by the different researchers. Ndjamshi *et al.* [36] using a similar methodology and screening tool reported a HAD frequency of 21.1% in Cameroon [19]. Other studies have however corroborated our finding of a higher prevalence of HAD in hospitalized patients with advanced disease [27,37,38]. For purpose of comparison, the various prevalence rates from studies conducted in Africa are presented in Table **5**.

The high rate of (apparently false positive) dementia diagnosed using the IHDS in an apparently healthy control group seen in this study suggested that some of the patients diagnosed with HIV dementia could be false positive. This is due to the low specificity of the IHDS at a cut off score of 10. Hence the IHDS like other screening instruments for cognitive impairment cannot be used alone for diagnosing HIV dementia. They may however help to narrow the antiretroviral therapy (ART) access gap for a subset of patients with HAD that would not otherwise qualify for ART initiation especially in resource limited settings [28].

HAD is the initial AIDS defining illness for 3–4% of antiretroviral naïve patients in the United States and Australia [4, 29]. Identification of HAD would also benefit patients who do not qualify for ART on the basis of laboratory criteria and patients in areas with limited laboratory diagnostic resources. The main factors associated with HAD in this study were lower hemoglobin level, CD4 positive T-lymphocyte and total lymphocyte count, Karnofsky performance score and body mass index. There was no association between socio-demographic parameters and dementia in the patient population studied. The differences in proportion of patients with HIV dementia in patients with only HIV 1 infection and those with dual infection (i.e. with HIV 1 and 2) did not reach statistical significance. In agreement with results of other studies [30-33], individuals who had severe immuno-suppression (with CD4 positive T- lymphocytes count less than 100 cells/µl) had a higher risk for HAD compared to those with CD4 positive T lymphocytes between 100-199 cells/µl. Bouman *et al.* [34] has suggested that a low CD4 positive T lymphocyte count may be a reliable marker of rapid ADC progression as it indicates high viral CNS seeding. The date of onset of HIV is often difficult to tell for most patients. Adjustment for CD4 positive T- lymphocyte count partially adjusts for the duration of infection [35]. The implication is that a higher frequency of HAD in a setting of lower CD4 positive T- lymphocyte count may mean longer duration of infection.

Patients who had dementia also had a statistically significant lower hemoglobin level compared with those without dementia. The association between low hemoglobin and HAD has been reported in Africans [36]. McArthur *et al.* in the Multicenter AIDS Cohort Study also reported lower pre-AIDS hemoglobin as the most significant predictor of dementia [17], and also demonstrated an increased risk of dementia among patients with more constitutional symptoms and weight loss (reduced body mass index) 7-12 months before development of AIDS. The association between increasing age and HIV dementia has being reported

**Table 5: Comparison of Prevalence Rates of HIV-Associated Cognitive Impairments in Africans**

| Authors' name | Country | Scope of Cognitive impairments studied | Prevalence rates | Cognitive tool | Study design |
|---|---|---|---|---|---|
| Lawler *et al.* [50] (2010) | Botswana | HAD | 38% (n=120) | IHDS (cut off score of 9.5) | Cross-sectional, randomized sample of HIV patients on therapy attending a hospital HIV clinic |
| Holguin *et al.* [51] (2012) | Zambia | HAD | 22% (n=141) | IHDS (cut off score of 10); Color Trail tests 1 &2; Grooved Pegboard; Timed Gait test | Patients recruited through referral system to the teaching hospital |
| Joska *et al.* [52] (2010) | South Africa | HAD | 24% (n=536) | HDS (cut off score of 10) | Cohort of HIV+ patients attending HIV clinics |
| Kanmogue *et al.* [53] (2010) | Cameroon | HANDs | 21.1% (n=44) | HNRC test battery | Cross-sectional case control study of patients attending the HIV voluntary counseling and testing centers |
| Ogunrin *et al.* [37] (2009) | Nigeria (south) | HANDs | 68.1% (n=160) | Modified HDS | Cross-sectional case control study of HIV+ patients attending HIV clinics |
| Ogun *et al.* [26] (2005) | Nigeria (west) | HAD | 12% (n=154) | Clinical criteria | Cross sectional study of HIV+ patients attending neurology clinics |
| Odiase *et al.* [21] (2006) | Nigeria (south) | HANDs | 32.6% (n=192) | CSID | Randomly selected asymptomatic HIV+ patients attending HIV clinics |
| Salawu *et al.* [46] (2008) | Nigeria (north) | HANDs | 61.6% (n=60) | CSID | Randomly selected asymptomatic HIV+ patients attending HIV clinics |
| Imam [25] (2007) | Nigeria (central) | HANDs | 12.3% (n=89) | MMSE | HIV+ patients referred to a specialist clinic |
| Wong *et al.* [54] (2007) | Uganda (Kampala) | HAD | 31% (n=78) | Digit Span forward & Backward; Grooved Pegboard; WHO AVLT; Color Trail tests 1 & 2; Symbol Digit Modalities test; Timed Gait test | Systematic sampling of patients attending HIV clinics |
| Nakku *et al.* [38] (2013) | Uganda (Entebbe) | Probable HAD | 64.4% (n=618) | IHDS (cut off score of 10) | Cross sectional study of HIV+ patients attending 2 clinics |
| Nwanza *et al.* [55] (2004) | DR Congo | HAD | 8.7% (n=166) | Clinical | HIV+ patients attending neurology and infectious disease clinics |

HAD – HIV associated dementia; HANDs – HIV associated neurocognitive disorders; HNRC – HIV Neurobehavioral Research Center; HDS – HIV dementia scale; IHDS – International HIV dementia scale; WHO AVLT– World Health Organization Auditory Verbal Learning Test; MMSE – Mini Mental state examination.

by some investigators [39-41]. However, consistent with other studies [17, 42], we did not observe increasing age as a risk factor for dementia. Notwithstanding, the frequency of dementia was higher (though not statistically significant) among patients aged fifty years and above. The lack of association between increasing age and risk of developing HIV dementia in this cohort may not be unrelated to the fact that the data was skewed age wise as current demographic characteristics of the HIV epidemic in Nigeria revealed that the bulk of the patients living with HIV/AIDS (PLWHIV) were in the younger age group

[43]. There may be a need for a larger study that will specifically test this relationship by recruiting a larger pool of older patients.

Though both types of HIV have been documented in Nigeria, the reported proportions of HIV-1 and HIV-2 infections in Nigeria vary but in agreement with our study, most studies showed that HIV-1 infection is still the predominant subtype [26, 44-46]. We observed that patients with HIV 1 infection tended to have a higher frequency of dementia compared to those with dual infection. This difference however did not reach statistical significance. HIV- 2 exhibits a longer latency period, slower progression towards AIDS, lower viral burden, and decreased transmissibility than HIV 1. However, in the advance stage of infection when the immune system is severely affected, the rate of mortality is the same irrespective of HIV type [47]. There is a dearth of literature on the comparative frequency of HIV dementia in patients with HIV-1 compared with those with a dual infection of HIV-1 and 2. The slightly lower frequency of HIV dementia among patients with dual HIV-1 and 2 infections observed may have resulted from alteration of the natural course of HIV-1 infection by co-infection with HIV-2. HIV-2 has been shown to inhibit HIV-1 *in vitro* [48, 49].

## CONCLUSION

This study has demonstrated a high burden of HIV dementia among adults with advanced HIV infection presenting to our specialized clinics and the utility of the International HIV Dementia Scale in the detection of this complication. A lower hemoglobin level, lower total lymphocyte count and reduced BMI also characterized individuals with HIV dementia in this population. We recommend early screening of HIV-positive patients in the clinics using the IHDS as a screening test for HIV dementia.

## LIMITATIONS OF STUDY

The fact that the IHDS is a screening tool that demonstrated a relatively low specificity in this study further emphasizes the need for development of cheap and accessible neurocognitive diagnostic batteries for diagnosing HIV dementia in resource limited settings. The lack of laboratory facility to perform cerebrospinal fluid examination to rule out CNS opportunistic meningoencephalitis is worth mentioning. However, none of the HIV subjects in this study had either a fever or focal signs on neurological examination to suggest a focal CNS lesion or meningoencephalitis.

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