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The International HIV Dementia Scale, a valuable screening instrument for HIV-Associated Neurocognitive Disorder (HAND) in HIV-Infected adults in North Central Nigeria

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Abstract

Background: The study sought to determine the usefulness of the International HIV Dementia Scale (IHDS) as a screening tool for HIV-Associated Neurocognitive Disorder (HAND) in HIV-positive adults in Jos, North Central Nigeria.

Design: The frequency of HAND is largely unknown in resource-limited settings. In Nigeria, there is paucity of data on the prevalence of HAND because very little research has previously being carried out in this area. We therefore studied HIV-positive adults as cases and HIV-negative individuals as controls to determine the usefulness of the IHDS as a screening instrument.

Methods: HIV-positive adults in an HIV outpatient clinic were matched to HIV-negative subjects for age, sex and education. Screening for HAND was carried out using IHDS. The study participants were further subjected to full neuropsychological assessment to confirm or exclude HAND

Results: Overall, 87 HIV-positive individuals and 87 HIV-negative subjects were screened. The HIV-positive subjects had a significantly lower IHDS mean total score of 8.4±0.2 compared with the HIV-negative subjects with a mean score of 11.1±0.7 ($p < 0.001$). Abnormal scores (≤10) on the IHDS were found in 67.8% of the HIV-positive subjects and in 0% of the HIV-negative subjects ($p < 0.001$).

Conclusions: The results suggest that the frequency of HAND may be higher than the previous estimates in North Central Nigeria and demonstrates that the IHDS can be used as a screening tool for HAND in Nigeria. We therefore advocate that all studies on HAND in Nigeria should strategically start with the IHDS as a screening tool.

Keywords: *HIV/AIDS, neurocognitive impairment, IHDS, HAND.*

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Résumé

Contexte : L'étude visait à déterminer l'utilité de l'Echelle Internationale de Démence VIH (IHDS) en tant qu'outil de dépistage du Trouble Neurocognitif Associé au VIH (HAND) chez les adultes séropositifs à Jos, Nord Central du Nigéria.

Conception: La fréquence de HAND est largement inconnue dans les environnements à ressources limitées. Au Nigéria, il y a peu de données sur la prévalence de l'HAND car très peu de recherches ont déjà été menées dans ce domaine. Nous avons donc étudié les adultes séropositifs en tant que cas et les personnes séronégatives comme témoins afin de déterminer l'utilité de l'IHDS en tant qu'instrument de dépistage.

Méthodes: Des adultes séropositifs dans une clinique VIH pour patients externes ont été appariés à des sujets séronégatifs pour l'âge, le sexe et l'éducation. Le dépistage de l'HAND a été effectué à l'aide de l'IHDS. Les participants à l'étude ont été soumis à une évaluation neuropsychologique complète pour confirmer ou exclure l'HAND.

Résultats: Dans l'ensemble, 87 personnes séropositives et 87 sujets séronégatifs ont été dépistés. Les sujets séropositifs avaient un score total moyen inférieur de 8,4 ± 0,2 à l'IHDS par rapport aux sujets séronégatifs avec un score moyen de 11,1 ± 0,7 ($p < 0,001$). Des scores anormaux (≤ 10) sur l'IHDS ont été trouvés chez 67,8% des sujets séropositifs et chez 0% des sujets séronégatifs ($p < 0,001$).

Conclusions: Les résultats suggèrent que la fréquence de l'HAND peut être plus élevée que les estimations précédentes dans le centre nord du Nigeria et démontre que l'IHDS peut être utilisé comme un outil de dépistage pour l'HAND au Nigeria. Nous préconisons donc que toutes les études sur l'HAND au Nigeria devraient commencer stratégiquement avec l'IHDS en tant qu'outil de dépistage.

Mots-clés: *VIH / SIDA, déficience neurocognitive, IHDS, HAND.*

Introduction

HIV-associated neurocognitive disorder (HAND) is an important spectrum of neurological complication of HIV infection. The frequency of this disorder is

largely underreported in resource-limited countries although preliminary surveys in Uganda [1] and India [2] suggest a relatively high frequency of cognitive dysfunction. A study done in Cameroun found that 6.6% of 108 subjects with HIV had HIV-Associated Dementia (ADC) [3], this suggested that HIV Associated Neurocognitive Dementia (HAND) was frequent in sub-Saharan Africa in the pre-HAART era. With improved access to HAART in our setting, this picture is expected to have changed remarkably for the better. However, because of the paucity of data in Nigeria on HAND, this study was carried out using a simple screening tool: the International HIV Dementia Scale (IHDS) to assess the current trend of HAND in the post HAART era.

With the advent of HAART, the incidence of HIV-Associated Dementia (HAD), the most severe form of HAND has been decreasing in the United States [4] but with continued survival, the prevalence of this disorder has actually increased [5]. Given the increased prevalence of HAD and its negative impact on quality of life [6], the morbidity of HAD is potentially significant especially in developing countries like Nigeria where large numbers of people are infected with HIV. HAD is associated with an increased morbidity and mortality [7,8].

HAND is treatable with highly active antiretroviral therapy [9,10]. It can affect patients' ability to work, adhere to medication instructions and carry out instrumental and basic activities of daily living [11]. However, improvements in function and prognosis have been achieved in such patients by the use of HAART [12]. The presence of HAND can thus be used as a clinical indicator to facilitate the commencement of antiretroviral therapy hence the need to screen these patients for this condition.

The diagnosis of HAND requires subjecting suspected persons to a time consuming battery of neuropsychological tests that usually requires experts. Therefore, it is important to have a simple screening tool that can be used to identify subjects who are at risk and would need to undergo a battery of neuropsychological testing for confirmation so that appropriate management can be instituted.

Objectives

The specific objectives of this study were (1) to validate IHDS as a screening tool for HAND in HIV patients, (2) to determine the prevalence of HAND and assess the value of the IHDS as a screening tool in our context, and (3) to propose a strategy for future studies on HAND in Nigeria.

Methods

Study setting

The site of this study was the AIDS Prevention Initiative in Nigeria (APIN) supported HIV clinic at the Jos University Teaching Hospital (JUTH), Jos. This clinic provides comprehensive HIV care services for the city of Jos, which is located in the Jos North Local Government Area (LGA) of Plateau State. The clinic serves as a referral centre for both health facilities in the other LGAs of the state and some neighboring states in the country. Plateau State has a population of about 3,206,531 with the state capital having a population of approximately 900,000 [13]. Plateau state has an HIV seroprevalence of 2.3% [14]. On regional basis, the North Central zone has a seroprevalence rate of 3.4% [14] in the country.

Study design

We used a case-control study design involving HIV positive adults as cases and an equal number of HIV-negative individuals as controls to determine the usefulness of the IHDS as a screening tool, having complied with the standard requirements of the ethics committee of the Jos University Teaching Hospital, Jos.

Patients and data collection

This study was conducted using a questionnaire developed by the AIDS Clinical Trial Group (ACTG A5199 team) which was translated into Hausa, a language generally spoken in Jos, North Central Nigeria to assess demographic parameters, medical history, depression history and neurological symptoms. Assessment of functional impairment was done with the Karnofsky Performance Scale. All recruited patients and controls were screened for HAND using the International HIV dementia scale (IHDS) and a 5-test neuropsychological battery comprising; Grooved Pegboard, Finger Tapping test, Timed Gait, Semantic Verbal Fluency and Digit Span. A detailed general, systemic and neurological examination was performed on each subject. All the HIV-positive subjects had their full blood count, serum biochemistry, CD4 cell counts, viral loads and serological tests for hepatitis B surface antigen and anti-hepatitis C antibody performed.

The IHDS and adaptation

The IHDS is an adjustment to that proposed by Power *et al* (1995)[15] which was later adapted by Sacktor *et al* [16] (2005). The IHDS if validated could be used to screen and identify patients at risk of HAND without the need for the laborious and expensive neuropsychological tests that are not readily available in Nigeria.

The IHDS consists of 3 subsets: Motor speed, assessed by timed finger tapping; timed alternating hand sequence for psychomotor speed and recall of 4 items to assess registration and recall. The subtests above were rated on a scale of 4 each. Memory was assessed with the 4-word recall at 2 minutes, which assesses memory, registration and recall. This was done by reciting 4 words to the subject (rat, chair, orange, and blue) saying each of these words one per second. The subject was then asked to repeat the words. If the subject failed to repeat all the words immediately, the examiner repeated all the words until the subject could repeat all the 4 words correctly. The subject was then asked to recall the 4 words after performing the other 2 subtests. For words not recalled, the subject was prompted with a semantic clue as follows: animal (rat), furniture (chair), fruit (orange), color (blue).

One point was given for each word recalled spontaneously and 0.5 points for each word recalled with prompting. For the assessment of motor speed, the number of finger-taps of the first 2 fingers of the non-dominant hand was measured by instructing the participant to open and close the fingers as widely and as quickly as possible over a 5-second period. Points were assigned as follows: 4 = ≥15 taps/5s; 3 = 11–14 taps/5s; 2 = 7–10 taps/5s; 1 = 3–6 taps/5s; and 0 =0–2 taps/5s. In the alternating hand sequence for assessing the psychomotor speed, the subject was asked to perform the following movement in succession with the non-dominant hand as quickly as possible over a 10-second period: (1) clench the hand in a fist on a flat surface, (2) put the hand flat on the surface with the palm down, and (3) put the hand perpendicular to the flat surface on the side of the fifth digit. The 3 hand positions were demonstrated to the participant by the examiner, and the participant was then asked to perform the sequence correctly twice for practice before the 10-second subtest was performed.

The task was scored as follows: 4 = 4 sequences in 10 seconds; 3 = 3 sequences in 10 seconds; 2 = 2 sequences in 10 seconds; 1 = 1 sequence in 10 seconds; and 0 = 0 sequence in 10 seconds. Timing was done using a Professional Quartz Timer. The total score out of 12 was calculated for each participant, with each of the 3 subtests contributing 4 points maximum to the total score. For our study, an IHDS score of ≤10 was considered abnormal. The sensitivity and specificity for the detection of HAND for a score of ≤10 have been shown to be 80% and 55%, respectively in a Ugandan cohort and 80% and 57% in a US cohort [16]

Data analysis

The mean scores of the neuropsychological parameters of the control subjects provided the normative data against which the neuropsychological test scores of each HIV+ve subjects were compared and classified as either neurocognitively impaired or unimpaired in each cognitive test based on standard definitions ; HIV+ve subjects that scored one standard deviation below mean for age and education appropriate norm in at least 2 of the 5 tested domains was diagnostic of Asymptomatic cognitive impairment (ANI), those that had Mild neurocognitive disorder (MND) met the criteria for ANI but also had impairment of activities of daily living and HIV-associated dementia (HAD) scored 2-SD below the normative mean in at least 2 cognitive domains with marked impairment in activities of daily living.

The data was entered and analyzed using Epi-info 3.5.4, Atlanta, Georgia, USA. HAND was the dependent variable and all other variables were independent variables. Standardized- z- scores of the neuropsychological test scores were calculated for the HIV negatives group. The HIV positive subjects then had their neuropsychological scores converted to z scores using the demographically adjusted means of the normative sample.

Neurocognitive impairment was stratified based on IHDS as normal or abnormal. Group comparison was made on demographic, medical history, neurologic symptoms and current functional and immune status. Categorical variables were compared using the chi square test and continuous variables compared using ANOVA. The sensitivity and positive predictive values of the neuropsychological assessment were also determined. In all tests of associations, critical p value of < 0.05 was regarded as statistically significant. A logistic regression model was developed to determine significant predictors and their strength of association with HAND. Subjects gave a written informed consent to participate in the study and this research was approved by the Ethics committee of the Jos University Teaching Hospital, Jos, Nigeria.

Results

Eighty seven HIV-positive subjects were matched for age, gender and educational attainment with 87 HIV-negative controls. The sociodemographic characteristics of the HIV+ve subjects are shown in Table 1. There were no statistically significant differences with respect to age, sex and educational status between the HIV-positive and HIV-negative

Table 1. Sociodemographic and Clinical Characteristics of the study subjects

Variable	HIV Positive	HIV Negative	Total	P-Value
Sex				
Male	28(32.2%)	28(32.2%)	56(32.2%)	-
Female	59(67.8%)	59(67.8%)	118(67.8%)	
Mean Age in Years	35.9±8.2	35.6±7.9	35.6±8.1	0.77
Male	42.0±6.8	41.9±5.8	42.0±6.3	0.95
Female	33.1±7.2	32.6±7.0	32.8±7.1	0.72
Mean Education(Year)	12.1±4.7	12.8±4.5	12.4±0.4	0.37
Mean CD4 Count	338.5±183.9	NA		NA

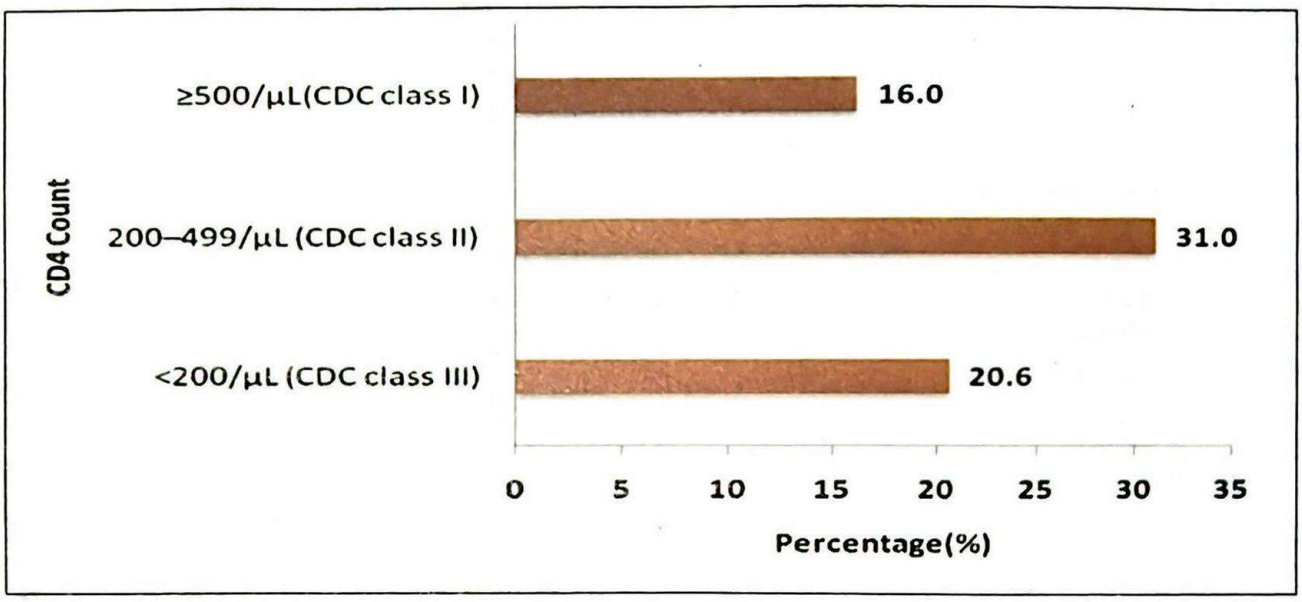

Fig 1: CD4 Levels and CDC Class among HIV-Positive Subjects

Table 2: Comparison of the IHDS scores between the HIV-positive and HIV-negative subjects

Variable	HIV Positive Controls (n = 87)	HIV Negative Cases (n = 87)	Total	P-Value
IHDS total score	8.4±1.8	11.1±0.7	9.7±1.9	<0.001
Finger-tapping Test (Non Dominant)	34.3±9.2	42.5±5.9	40.0±9.6	<0.001
Finger-tapping Test (Dominant)	34.6±9.5	45.5±5.8	38.4±8.8	<0.001
Time Gait	13.3±3.2	10.7±1.2	12.0±2.7	<0.001
Semantic Verbal Fluency	9.3±3.3	10.6±3.3	10.0±3.4	0.01
Digit Span Forward	5.0±1.1	5.8±0.9	5.4±1.1	<0.001
Digit Span Backward	3.1±1.7	4.7±0.8	3.9±1.5	<0.001
IHDS 4-word recall	2.1±0.9	2.7±0.5	2.4±0.8	<0.001

Values are given as mean values (± SD).

subjects. The mean ages of the HIV-positive and HIV-negative subjects are as shown in table 1, likewise their sex distribution, mean education years as well as the mean CD4 cell count of the HIV-positive subjects.

The HIV-positive subjects had a mean of IHDS score of 8.4±1.8 while the HIV-negative subjects scored 11.1±0.7 ($p < 0.001$). Fifty nine (67.8%) of HIV-positive subjects had IHDS score ≤10 (abnormal) and thus had possible

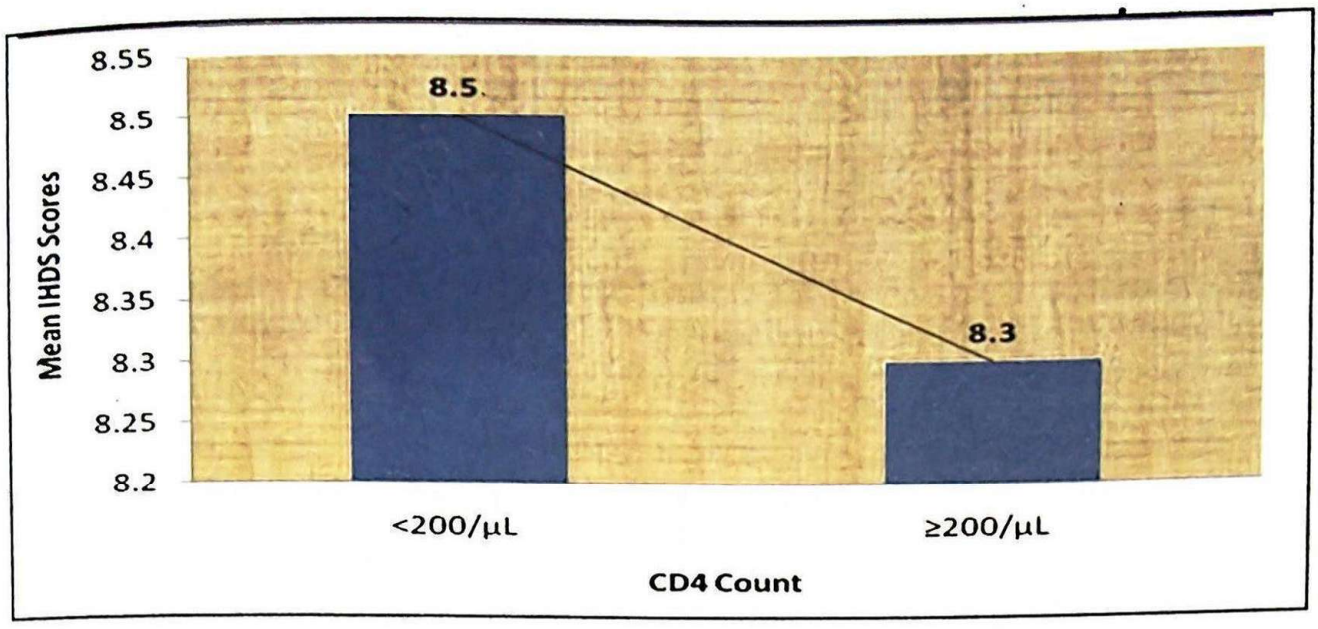

Fig. 2: Mean IHDS scores by CD4 count cut-offs

Table 3: Comparing HIV years and ARV weeks by IHDS score of HIV+ subjects

Variables	Normal(>10)	Abnormal(10 and Below)	t	95% Confidence Intervals	P-Value
HIV Years (Mean±SD)	2.7±1.4	3.5±1.7	2.2	(-1.6, -0.08)	0.03
ARV Weeks (Mean±SD)	151.3±71.0	170.95	0.8	(-71.8, 32.5)	0.5

Table 4: Comparing mean IHDS score across ARV regimen category for HIV+ subjects

ARV Regimen Category	Mean±SD	95% Confidence Interval for Mean	
		Lower Bound	Upper Bound
None	8.7±2.0	7.9	9.5
1st Line	8.3±1.5	8.0	8.8
2nd Line	6.3±3.4	0.8	11.7
Total	8.4±1.8	8.0	8.7

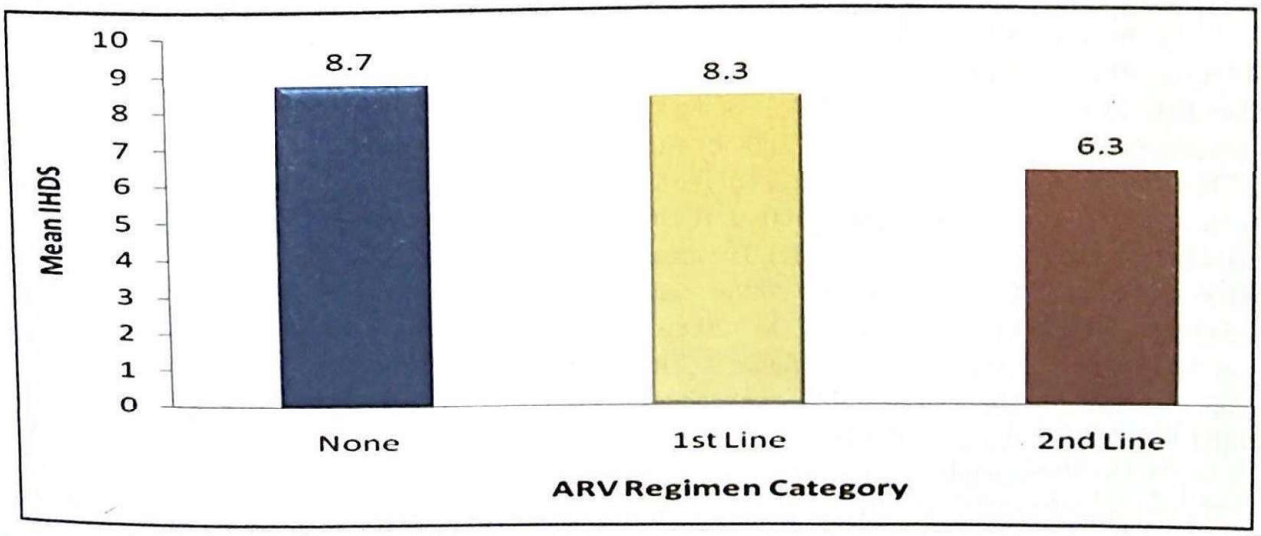

Fig. 3 Comparing Mean IHDS Score across ARV Regimen Category for HIV+ Subjects

neurocognitive impairment whereas there were no HIV-negative subject (0.0%) who had an IHDS score of ≤10 (95% confidence interval: 56.9% to 77.4%) p <0.001.

However, after neuropsychological assessment, the proportion of HIV-positive subjects that had HAND was 33 (37.9%). Using the neuropsychological assessment test as gold standard, the sensitivity and specificity of the IHDS screening tool were found to be 72.7% and 75.2% respectively. The overall accuracy of the test was 74.7%. The mean total IHDS score of HIV-positive subjects with abnormal scores was 7.6 ±1.6, and that of the HIV-negative subjects was 11.1±0.7 (p <0.001). Table 2 shows the comparison between the 2 groups with respect to the mean IHDS scores on the 8 components of the neuropsychological test. In the Finger-tapping test (Non Dominant), the HIV-positive subjects scored an average of 34.3±9.2 as compared to the HIV-negative group which recorded a mean of 42.5±5.9 (p <0.001). The Finger-tapping test (Dominant) recorded a mean of 34.6±9 among the HIV- positive subjects whereas the HIV-negative had a mean of 45.5±5.8 (p <0.001). The Time Gait test (TG), revealed that the HIV-positive subjects recorded a mean of 13.3±3.2sec whereas the HIV-negative group had a mean of 10.7±1.2sec to cover a distance of 60 meters with marked significant differences (p <0.001). The Semantic Verbal Fluency (SVF) test scores revealed that the HIV-positive subjects recorded an average of 9.3±3.3 while their HIV-negative counterparts had a mean of 10.6±3.3 (p <0.001). Digit span forward test showed that the HIV-positive subjects scored a mean of 5.0±1.1 when compared with the HIV-negative group that had a mean of 5.8±0.9 (p <0.001). Observation with the Digit Span Backward revealed same trend where the HIV-positive recorded an average of 3.1±1.7 as compared to the HIV-negative arm that had a mean of 4.7±0.8 (p <0.001)

In the HIV-positive group, 18 of the 87 subjects (20.6%) with CD4 counts <200/μL (CDC class III) had an IHDS score ≤10, while 27 of the 87 subjects (31.0%) with CD4 counts 200–499/μL (CDC class II) had a score <10, and only14 of the 87 subjects (16.0%) with CD4 counts ≥500/μL (CDC class I) had an abnormal score (p < 0.001). The mean IHDS score of subjects with CD4 ≥200/μL was 8.5±1.5 while that of patients with CD4 <200/μL was 8.3±1.9 (p = 0.67) as shown in figure 2. The proportion of cases with abnormal IHDS for subjects with CD4 ≥200/uL was 69.5.0% (49/59), confidence limits: 24.2%–70.5% while that of patients with CD4 <200/μL was 5/28 (17.9%) with confidence limits of 15.5%–40.3%.

Discussion

This study reveals the usefulness of the IHDS in evaluating patients with HIV/AIDS. The study established that IHDS can be successfully used for screening of cases of HAND. It was identified that the mean total IHDS score of the HIV-positive subjects was significantly lower than that of HIV-negative controls (p <0.001). This marked differences in the IHDS score between both groups (Cases and Control) is not very different from the figure obtained in a similar study in Yaoundé, Cameroun [17]. In this study, the HIV-positive subjects had a mean of IHDS score of 8.4±1.8, as compared with the HIV-negative subject's score of 11.1±0.7 (p <0.001), which is much lower than 10.87± 0.91 for cases and 11.28 ± 0.56 for controls obtained from the Cameroonian study and 9.9±1.6 for cases and 11.0±1 for controls in a study done in Uganda. These differences may be due to differences in disease stage of subjects as well as the age differences between the study populations in the three studies. Another possibility is the age difference between the HIV positive subjects and the HIV-controls in the case of the Ugandan study as well as differences in methodologies.

The sub-tests of the IHDS which include Finger-tapping Test (Non Dominant), Finger-tapping Test (Dominant), Time Gait, Semantic Verbal Fluency, Digit Span Forward and Digit Span Backward revealed statistically significant differences between the HIV-positive and HIV negative subjects. For instance the Finger-tapping Test (Non Dominant) scores of HIV positive subjects differed significantly from that of the HIV negative subjects.(P<0.001). Similar differences were observed in the scores of Finger-tapping Test (Dominant), Time Gait, Semantic Verbal Fluency, Digit Span Forward and Digit Span Backward. These research findings are very different from the studies conducted in Yaoundé, United states, Uganda and India where differences in performance were found only in memory recall and psychomotor speed and it was thought that these subtests were the surrogate markers for picking up the early changes associated with HAD. Furthermore, in contrast to our finding, there was no difference in the finger tapping subtest between the HIV- positive and HIV-negative controls in the Yaoundé and Indian studies. However, our finding was similar to the finding in the Ugandan study where there was a statistically significant difference in the finger tapping subtest between the HIV-positive and HIV-negative controls, although this was attributed to the fact that the HIV-positive cohort was significantly older than the HIV-

negative cohort and age is associated with motor performance decline, especially in the fifth and sixth decades of life. In our study cases and controls were matched for age so the influence of the age factor was excluded.

This study showed that HIV-positive subjects were as high as 67.8% at risk of HAND using IHDS tool. However, upon subjecting these subjects to extensive neuropsychological tests battery, only 37.9% of them had HAND demonstrating that using a cut off of IHDS ≤ 10 is associated with false positive result. Interestingly, there were no subjects among the HIV-negative subjects that were found to have an IHDS score ≤ 10. This observation differs from reports from other studies where up to 2.5% and 15% of HIV negative controls had abnormal IHDS scores [17,18].

In our study as in the Ugandan study a cut off value of IHDS of ≤ 10 was used because of its sensitivity of 80% at this point. In the Cameroonian and Indian studies a cut off of >10 was used, the differences in this cut off may be responsible the differences in the prevalence of HAND in the different studies and the high false positive rate noted in our study using the IHDS. In contrast to the Cameroonian study, full neuropsychological screening was done on the HIV-positive subjects and HIV-negative control making it possible to identify false positive subjects.

We identified the population of HIV-positive subjects at risk for potential HAND; they were subsequently subjected to full neuropsychological assessment for confirmation. We do recognize that the IHDS does not replace the neuropsychological tests for diagnosing HAND, but it is useful in directing limited resources for the diagnosis of HAND to those at risk of developing this complication and therefore seems to be quite suitable for resource-limited countries like Nigeria. We therefore suggest that future studies investigating HAND in Nigeria and other limited settings in Africa should utilize this tool for screening before employing subsequent neuropsychological assessment for those at risk for good surveillance and HIV management and control.

Conclusion

In this study we have successfully screened for the risk of HAND using the IHDS and subsequently confirmed HAND using a 5-test neuropsychological battery in Jos, North Central Nigeria. The performance scales was found to be a good method for identifying HIV patients at risk of HAND and normal healthy subjects. It is therefore suggested that neurological clinical care in Nigeria adopts this method of screening for the identification of those as risk of HAND in clinical care and practice. HAND seems to be an important complication of HIV infection in North Central Nigeria with a potential risk prevalence of 67.8% with IHDS screening tool, however neuropsychological assessment is necessary to confirm the diagnosis.

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