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Performance of Community Screening Instrument for Dementia in Screening for HIV-Associated Neurocognitive Disorders in Nigeria

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Abstract

Background: Cognitive function of HIV-infected patients in Nigeria has been studied using the community screening instrument for dementia (CSI-D) battery. However, its ability to detect HIV-associated neurocognitive disorders (HAND) is unclear. The study assessed the CSI-D battery in detecting HAND.

Methods: Age, sex and education matched 30 HIV-positive and 30 HIV-negative subjects were administered the CSI-D battery. An extensive multi-domain neuropsychological tests (MDNPT) battery was used as gold standard. Measures of functional status including personal assessment of own functioning inventory (PAOFI), instrumental activities of daily living (IADL) and Beck depression inventory (BDI) were also administered. Diagnostic accuracy indices of the CSI-D were determined from a receiver operator characteristic (ROC) curve. Linear associations were explored using correlation coefficient.

Results: HIV-positive subjects performed significantly worse than HIV-negative subjects in several domains across the 2 batteries. Large effect sizes were found in verbal fluency (COWAT), verbal learning, memory recall and language comprehension. Significant correlations between the two batteries were seen in all the domains except motor function. Subjects with HAND but normal on CSI-D scored poorly on motor function test. The area under the ROC curve was 0.79; 95 % confidence interval (CI) of 0.68-0.90, $p < 0.0001$. At cut-off score of ≤ 63, the CSI-D had sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 77%, 63%, 55% and 61% respectively.

Conclusion: CSI-D has good psychometric properties for use as a screening tool for HAND. The addition of test of motor function is advisable to complement it.

Keywords: HIV; Community Screening Instrument for Dementia (CSI-D); Comprehensive Multi-Domain Neuropsychological Tests (MDNPT); HIV-Associated Neurocognitive Disorders (HAND)

Abbreviations

AIDS-Acquired Immune Deficiency Syndrome; ANI-Asymptomatic Neurocognitive Impairment; ART-Antiretroviral Therapy; AUC-Area Under the Curve; BDI-Beck Depression Inventory; CDC-Centers for Disease Control and prevention; CI – Confidence Interval; CNS-Central Nervous System; COWAT-Controlled Oral Word Association Test; CSI-D-Community Screening Instrument for dementia; DH-Dominant Hand; HAD-HIV associated Dementia; HAND-HIV-associated neurocognitive disorders;; HCV-Hepatitis C Virus ; HIV-Human Immunodeficiency Virus; HNRC-UCS-HIV-Neurobehavioral Research Center University of California San Diego; HVLT-R-Hopkins Verbal Learning Test Revised; IADL-Instrumental Activities of Daily Living; IHDS-International HIV Dementia Scale; MDNPT-Multi-Domain Neuropsychological Tests; MND-Mild Neurocognitive Disorder; NDH-Non-Dominant Hand; NPV-Negative Predictive Value; PAOFI-Personal Assessment of Own Functioning Inventory; PPV-Positive Predictive Value; ROC-Receiver Operator Characteristic; SSA-Sub-Saharan Africa; WAIS-Weischler Adult Intelligence Scale; WMS-Weischler Memory Scale

Introduction

The burden of HAND in Sub-Saharan Africa (SSA) has been estimated to be >8 million in a recent meta-analysis [1]. Out of the 25 million people living with HIV/AIDS in SSA, about 3.1 million are in Nigeria making it the second country with the highest burden of HIV in the world [2,3]. Yet, majority of these patients pass through busy HIV clinics without basic neurocognitive evaluation. As described in the Frascati criteria, diagnosis of HAND required evidence of impairment in the neurocognitive domains commonly affected by HIV infection. These include psychomotor speed, memory, verbal fluency, executive function, motor, attention/working memory and learning [4]. Extensive MDNPT battery designed for use in the

industrialized countries is required to assess these subcortical functions before proper classification and rating of impairments. The MDNPT battery has been validated in Nigeria, Cameroon, South Africa and Uganda [5-8]. Despite demonstrating the ability to detect impairment across several domains in African HIV-positive patients, it has several limitations that may not allow its routine application in poor resource settings in SSA. It is expensive, complex, need expertise, requires several hours for administration and education-dependent [8]. Thus this ideal battery may not be suitable for Africans.

The CSI-D has proved reasonable (even among Africans with HIV) and lacks many of these limitations being independent of education and culture. It is a pencil and paper test that may even be administered by non-specialist. It mainly assess cortical function but had 2 of its tests that assess subcortical function; animal fluency and memory recall tests. Several studies in Nigeria have utilized this tool to assess neurocognitive dysfunction among HIV-positive patients [9-11]. The popularity of this instrument in neuro-screening of patients (including HIV-positive) in Nigeria stem from its simplicity, availability, ease of administration and required only 15 minutes to be administered. However, its ability to detect HAND is unclear as none of these studies in Nigeria used the battery on background extensive MDNPT battery. This highlighted the need for evaluating the performance of the CSI-D among patients with HAND and exploring ways of improving its efficiency in identifying patients at risk of HAND that might benefit from extensive neuropsychological testing.

Methods

It was a cross-sectional study conducted at the HIV clinic in Aminu Kano Teaching Hospital Kano, Northwestern Nigeria. Ethical approval was obtained from the ethical committee of the hospital. Each participant provided written consent before being enrolled in to the study. A total of 60 subjects participated in the study; 30 HIV-positive patients consecutively recruited from HIV clinic and 30 HIV-negative controls recruited from the voluntary counseling and testing clinic and blood donor clinic. All were matched for demographic variables that can influence test performance (age, sex and educational status).

Inclusion and exclusion criteria

To be included subjects should satisfy the following criteria: 1) Age ≥ 18 years; 2) Not diagnosed to have a psychiatric illness and no family history of psychiatric illness; 3) Absent history of current abuse or dependence on substance such as alcohol, hallucinogens, sedatives and stimulants; 4) Nil active Central Nervous System (CNS) infection; 5) No history of previous head injury; 6) Absence of physical deficit or impairment that will retard performance on neuropsychological testing or complicate interpretation of results obtained; 7) Not diagnosed to have hypertension, diabetes mellitus or cerebrovascular disease and 8) Free from encephalopathy-uremic, hepatic and hypertensive.

Subjects were excluded if they have any of the following: 1) Do not provide consent; 2) Had psychiatric illness of positive family history; 3) Met criteria for current abuse and/ or dependence on alcohol or other substances; 4) Positive Hepatitis C Virus (HCV) serology or serum cryptococcal antigen and 5) Could not satisfy any of the inclusion criteria.

Neuropsychological test batteries

Two batteries were administered to all the study participants. The first was an extensive MDNPT battery that assesses multiple domains and consists of the following tests; Speed of information processing [Weischler Adult Intelligence Scale (WAIS-III) symbol search], attention and working memory [Weischler Memory Scale (WMS-III) spatial span], Learning (HVLT-R immediate recall), memory [Hopkins Verbal Learning Test Revised (HVLT-R), delayed recall and trial recognition], motor [Grooved pegboard Dominant Hand (DH) and Non-Dominant Hand (NDH)], verbal fluency [Controlled Oral Word Association Test (COWAT-FAS)] and abstraction/executive function (color trails 2). The extensive MDNPT battery and measures of functional status such as Personal Assessment of Own Functioning Inventory (PAOFI), Instrumental Activities of Daily Living (IADL) and Beck Depression Inventory (BDI-II) were used to classify patients in to various grades of HAND as defined by the Frascati criteria; Asymptomatic Neurocognitive Impairment (ANI), Mild Neurocognitive Disorder (MND) and HIV-associated Dementia (HAD) [4]. About 2 hours is required for full administration of the battery. The various tests of the MDNPT battery were part of the battery employed by the HNRC-UCS and are sensitive to HAND as demonstrated in several studies [12-14]. One of the authors (AGH) received training at the HIV-Neurobehavioural Research Center University of California San Diego (HNRC-UCS) on extensive neuropsychological tests administration and had participated in earlier studies in Nigeria using these tests [5]. He trained AMY and MG who administered the tests. The second battery used was the CSI-D that comprised of the following tests; verbal fluency (animal fluency), language (naming, repetition and comprehension), memory, attention/calculation, orientation, registration and praxis (visuoconstruction skills).

Statistical analysis

Continuous variables were compared using student's t test while dichotomous variables were compared using Fishers exact test. Neuropsychological tests results of HIV-negative controls were used as the normative data. Effect sizes were interpreted using Cohen's method in which 0.2-0.49 denotes small effect size, 0.5-0.79 denotes medium effect size and ≥ 0.8 considered large effect size [15]. Pearson's correlation coefficient was employed to examine linear associations; r ≤ 0.35 indicates weak correlation, r=0.36-0.67 indicates moderate correlation and r=0.68-1.0 is considered strong correlation [16]. A ROC curve for the CSI-D was generated using MND and HAD grades of HAND as gold standard as done in a previous study [17]. Predictive value measures such as specificity, sensitivity, PPV and NPV were computed for the CSI-D. Statistical analyses were done with statistical package for social sciences (SPSS) version 18.

Results

Base line characteristics

Table 1 gives the summary of the demographic, clinical and laboratory characteristics of the study subjects. Both the cases and controls were matched in terms of age, sex and education. Among the HIV-positive subjects 15 (50%) were on Antiretroviral Therapy (ART). According to the Centers for Disease Control and prevention (CDC) staging, 21 (70%) of the 30 HIV-positive subjects were in stage A, 8 (27%) in stage B and 1 (3%) in stage C. 16 (53%) of these 30 HIV-

positive individuals have reached the Acquired Immune Deficiency Syndrome (AIDS) stage (having had an AIDS-defining illness), while 14 (47%) were non-AIDS. 14 (47%) of the 30 HIV-positive subjects have CD4 cells < 200/ml and 16 (53%) have CD4 cells > 200/ml. Viral load available for only 13 subjects was undetectable (< 400 copies/ml) in 7 (54%) of them, while detectable (≥ 400 copies/ml, range of 561-82156 copies/ml) among 6 (46%) of the 13 subjects.

Variables	HIV-positive (n=30)	HIV-negative (n=30)	p-value
Age (years)*	38.63 (8.70)	37.33 (8.29)	0.556
Education (years)*	11.90 (3.79)	12.30 (3.80)	0.681
Gender-female	13 (43)	12 (40)	0.793
BDI score (≥ 17)	5 (17)	2 (7)	0.228
PAOFI score (≥ 2)	6 (20)	2 (7)	0.129
IADL score (≥ 2)	4 (13)	1 (3)	0.161

Table 1: Demographic characteristics of study participants, Data are n (%). *mean (SD). HIV-Human Immunodeficiency Virus, BDI-Beck Depression Inventory, PAOFI-Personal Assessment of Own Functioning Inventory, IADL-Instrumental Activities of Daily Living.

Neuropsychological tests score

The extensive MDNPT battery scores are shown in Table 2. In all the seven (7) cognitive domains the HIV-positive subjects scored worse than the HIV-negative subjects. Three of the neuropsychological domains showed statistically significant difference between the two groups. These are verbal fluency (COWAT), learning (HVLT-R, immediate recall) and memory (HVLT-R, delayed recall). Domains of verbal fluency (COWAT) and verbal learning (HVLT-R, immediate recall) showed large effect sizes. Medium effect sizes were found in domain of memory (trial recognition and delayed recall tests). Small effect sizes were found in domains of attention/working memory, executive function and motor (DH and NDH).

Domain and NP test	**HIV-positive (n=30)**	**HIV-negative (n=30)**	**P-value**	**Cohen's d effect size**
Speed of information processing-WAIS-III symbol search	17.80 (6.34)	18.23 (5.96)	0.786	0.07
Attention/working memory-WMS-III Spatial span	10.73 (2.98)	11.77 (2.61)	0.159	0.37
Memory-HVLT-R (delayed recall)	6.60 (1.63)	7.77 (1.83)	0.012	0.68
Memory-Trial recognition	21.40 (2.18)	22.33 (1.49)	0.058	0.50
Verbal learning-HVLT-R (immediate recall)	18.43 (4.17)	22.10 (4.18)	0.001	0.88
Verbal fluency-COWAT	16.50 (8.61)	23.17 (7.11)	0.002	0.84
Motor-Grooved pegboard (DH)	88.30 (43.43)	75.87 (23.96)	0.175	0.35
Motor-Grooved pegboard (NDH)	108.17 (60.81)	90.13 (30.41)	0.152	0.38
Abstraction/executive function-Color trails 2	234.77 (120.34)	219.90 (85.88)	0.584	0.14

Table 2: Extensive MDNPT battery score of HIV-positive and HIV-negative subjects, Data are mean (SD). COWAT-Contrlled Oral Word Association Test, DH-Dominant Hand, HVLT-R-Hopkins Verbal Learning Test Revised, NDH-Non-Dominant Hand, NP-Neuropsychological, WAIS-Weischler Adult Intelligence Scale, WMS-Weischler Memory Scale

Table 3 showed the CSI-D battery scores. The total CSI-D score together with four (4) domains have statistically significant different scores between the cases and the controls. These are memory, motor, orientation to time and language expression (naming). Large effect sizes were found in domains of memory recall, language comprehension (motor response) and the total CSI-D score. Medium effect sizes were found in domains of verbal fluency (animal fluency), language expression (naming) and orientation to place and time. Small effect sizes were found in domains of registration, language expression (repetition), praxis and attention and calculation.

Among subjects with HAND from the extensive MDNPT battery, as expected those with abnormal CSI-D scores performed significantly worse than those with normal scores on the CSI-D in the domains of speed of information processing, executive function, verbal fluency and memory learning. However, in the motor domain (Grooved pegboard DH) the reverse is the case as those with normal CSI-D scores performed worse than those with abnormal CSI-D scores, though not statistically significant (Table 4).

Domain and NP test	HIV-positive (n=30)	HIV-negative (n=30)	P-value	Cohen"s d effect size
Verbal fluency (Animal fluency)	13.93 (4.52)	16.60 (4.93)	0.033	0.56
Language expression (Naming)	6.57 (0.73)	6.90 (0.31)	0.024	0.59
Memory recall	11.70 (1.95)	13.57 (1.10)	<0.0001	1.18
Orientation to place and time	11.37 (1.07)	11.97 (0.18)	0.040	0.78
Language comprehension (motor response)	4.37 (0.72)	4.87 (0.35)	0.001	0.88
Registration	3.33 (1.83)	3.00 (0.00)	0.321	0.26
Language expression (repetition)	0.97 (0.18)	1.00 (0.00)	0.321	0.24
Praxis (visuoconstruction skills)	1.50 (0.68)	1.73 (0.45)	0.123	0.40
Attention and calculation	4.80 (1.42)	5.30 (0.84)	0.103	0.43
Total CSID Score	58.33 (6.31)	64.80 (5.05)	<0.0001	1.13

Table 3: CSI-D test battery scores of HIV-positive and HIV-negative subjects, Data are mean (SD). CSI-D-Community Screening Instrument for dementia, NP-Neuropsychological.

	Subjects with HAND (ANI, MND and HAD) from extensive MDNPT battery		
Domain (test)	Impaired on CSI-D	unimpaired on CSI-D	P-value
Verbal fluency-COWAT	10.89 (6.79)	18.90 (8.29)	0.013
Executive function-Color trails 2	291.56 (162.28)	210.43 (91.60)	0.091
Motor-Grooved pegboard (DH)	84.67 (18.193)	89.86 (50.93)	0.77
Motor-Grooved pegboard (NDH)	117.11 (64.99)	104.33 (60.18)	0.607
Attention/working memory-WMS-III spatial span	9.89 (3.18)	11.10 (2.90)	0.318
Speed of information processing-WAIS-III symbol search	13.33 (5.96)	19.71 (5.60)	0.009
Memory-Trial recognition	20.44 (2.65)	21.81 (1.86)	0.117
Memory-HVLT-R, delayed recall	6.00 (1.66)	6.90 (1.59)	0.192
Verbal learning-HVLT-R, immediate recall	16.00 (2.78)	19.48 (4.29)	0.015

Table 4: Extensive MDNPT battery score of HIV-positive subjects with HAND based on the total CSI-D score, Data are mean (SD). CSI – D-Community Screening Instrument for dementia, COWAT-Controlled Oral Word Association Test, DH-Dominant Hand, HAND-HIV-associated neurocognitive disorders, HVLT-R-Hopkins Verbal Learning Test Revised, NDH-Non-Dominant Hand, NP-Neuropsychological, WAIS-Weischler Adult Intelligence Scale, WMS-Weischler Memory Scale.

The area under the curve (AUC) for the ROC curve generated for the CSI-D was 0.79, 95% confidence interval of 0.68-0.90 and p<0.001 (Figure 1).

The indices of diagnostic accuracy of the CSI-D at varying cut-off points derived from the ROC curve are shown in Table 5. At total CSI-D cut-off score of ≤ 63, 17 (56.7%) of the HIV-positive subjects and 11 (36.7%) of the HIV-negative subjects had neurocognitive impairment. This cut-off score has sensitivity of 76.7%, specificity of 63.3%, PPV of 54.8% and NPV of 61.1% for detecting HAND. Raising the cut-off score to ≤ 66 provided higher sensitivity of 93.3% but lower specificity of 33.3%. Lowering the cut-off score to ≤ 60 provided sensitivity of 66.7% and specificity of 73.3%.

The total CSI-D score significantly correlated with most of the tests of the extensive MDNPT battery as shown in Figure 2; COWAT (r=0.548, p <0.0001), WAIS-III symbol search (r=0.313, p=0.015), color trails 2 (r=0.257, p=0.024), WMS-III spatial span (r=0.269, p=0.037), HVLT-R, delayed recall (r=0.221, p=0.045), HVLT-R, immediate recall (r=0.331, p=0.010) and trial recognition (r=0.262, p=0.044). There was no correlation between the total CSI-D score and the grooved pegboard tests of motor function; DH (r=-0.109, p=0.409) and NDH (r=-0.152, p=0.247). The total CSI-D score showed statistically significant correlations with some of the CSI-D subsets scores; animal fluency (r=0.884, p < 0.001), memory (r=0.554, p < 0.001), orientation to place / time (r=0.512, p < 0.001), praxis (0.275, p=0.033), language comprehension (r=0.309, p=0.016) and language expression / naming (r=0.396, p=0.002).

Cut-off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
75.0	100	3.3	51.7	100
72.0	100	6.7	51.7	100
69.0	96.7	16.7	53.7	83.3
66.0	93.3	33.3	58.3	83.3
63.0	76.7	63.3	54.8	61.1
60.0	66.7	73.3	47.6	44.4
57.0	40.0	93.3	85.7	50.0
54.0	20.0	100	100	55.6
50.0	13.3	100	100	53.6
47.0	6.7	100	100	51.7

Table 5: Sensitivity, specificity, PPV and NPV of the CSI-D at varying cut-off values derived from the ROC curve, NPV – Negative Predictive Value, PPV – Positive Predictive Value.

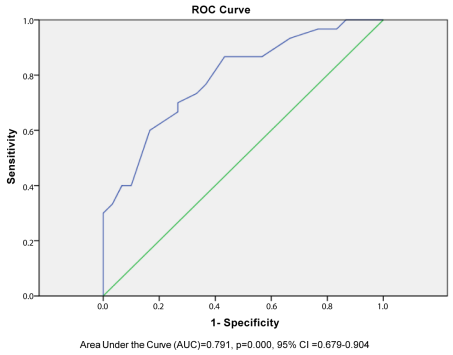

Figure 1: Receiver operator characteristic curve of the total CSI-D score compared to Frascati criteria defined MND and HAD categories of HAND as gold standard. At cut – off score of ≤ 63, the total CSI–D had sensitivity of 77% and specificity of 63% for detecting HAND.

Discussion

This is the first study in Nigeria that assessed the performance of the CSI-D battery in detecting HAND diagnosed with the ideal subcortical extensive MDNPT battery. Study participants were well matched in terms of demographic variables such as age, sex and education that could influence performance on neurocognitive evaluation tools. The extensive MDNPT battery applied in this study is sensitive to neurocognitive alterations associated with HIV infection in Nigeria [5]. The HIV-positive subjects performed worse than the HIV-negative subjects in all the domains tested with statistical significance in domains of verbal fluency, verbal learning and memory. Large effect sizes obtained in domains of verbal fluency (COWAT) and verbal learning in this study are similar to reports from previous studies in Nigeria using full neuropsychological tests battery and indicate a possible link between HIV infection and neurocognitive alterations in these domains in Nigeria [5].

Subcortical neurocognitive deficits in HIV infected patients commonly manifest with impairment in speed of information processing, memory, learning, verbal fluency, executive function, attention / working memory and motor functions [12-14]. The total CSI-D score significantly correlated with test score in all these domains with the exception of motor function. Also the total CSI-D score discriminated between subjects with HAND in all the domains except motor function (grooved pegboard-DH). The inclusion of ANI in the comparison of CSI-D score of subjects with HAND could have affected findings because its subtle features could only be detected with detailed NP testing and not by a screening instrument like CSI-D [4]. It is a good property for the CSI-D to correlate with the typical profile of neurocognitive deficit in HIV-infected patients and to properly identify subjects with HAND in most of the domains. However, addition of motor function test could greatly improve its accuracy. The strong correlation between the total CSI-D score and animal fluency and memory subsets of the CSI-D suggested the possibility of the CSI-D being heavily weighted on these domains when the test is applied to HIV-positive patients. This is not unexpected as animal fluency and memory are all subcortical functions.

The total CSID cut-off score of ≤ 63 maximizes the sensitivity, specificity, PPV and NPV for HAND (76.7%, 63.3% 54.8% and 61.1% respectively). Lower cut-off of ≤ 60 provided a mild reduction in the sensitivity (66.7%), a mild increment in specificity (73.3%) and a modest reduction in NPV (44.4%). A screening instrument should have high specificity and high NPV to avoid false negative results. Thus the cut-off score of ≤ 63 should be ideal for the CSI-D when screening for HAND as this value provided reasonable and acceptable indices of diagnostic accuracy. The prevalence of HAND at this cut-off was 57% while at ≤ 60 the prevalence was 66.7%. The higher prevalence may be related to the lower NPV of the CSI-D at cut-off score of ≤ 60. A previous study in Nigeria administered the CSI-D among patients with mild and moderate HIV infection. They found 61.6% and 56.6% prevalence of neurocognitive impairment by

applying a generous criterion and a conservative criterion respectively [9].

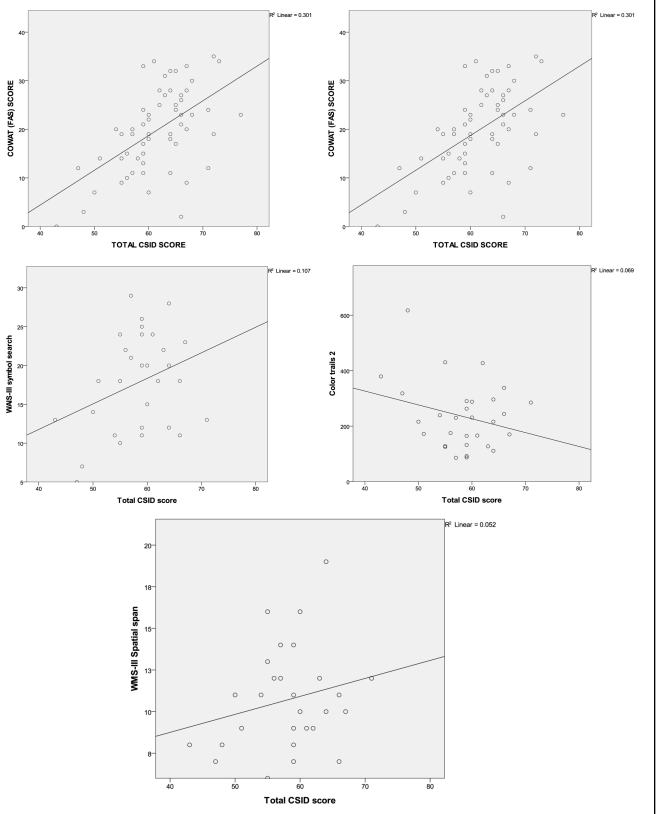

Figure 2: Correlations of the total CSI-D score with the extensive MDNPT battery; 2A-COWAT versus (vs) total CSI-D score (r=0.548, p=0.000); 2B – WAIS-III symbol search vs total CSI-D, r=0.313, p=0.015; 2C-Color trails 2 vs total CSI-D, r=-0.257, p=0.024; 2D-WMS-III spatial span vs total CSI-D, r=0.269, p=0.037.

One of the limitations of this study is the small sample size. This may be responsible for lack of significant difference between the cases and controls in some of the domains. Nevertheless, the effect of this is likely to be minimal as significant difference in tests results were found between the study groups in three domains examined. Moreover, as 50% of the cases were on ART neurological improvement could not be ruled out in some of the domains tested [18-21]. The strength of this study lies in the administration of an extensive MDNPT battery that assesses multiple domains that are sensitive to HIV infection. We explored the characteristics of the CSI-D battery on this background gold standard neuropsychological testing. We found it to be psychometrically good for use as a screening tool to detect patients at risk of HAND that may ultimately benefit from detailed neuropsychological evaluation. However, we recommended that test of motor function like grooved pegboard DH should be added to the CSI-D so as to increase its efficiency for use as a screening tool for HAND.

Application of culturally suitable and well standardized assessment tools in neuropsychology is always desired. It has the advantage of making neurocognitive evaluation simpler, more reliable, easier to administer and more tolerable to the patients. Extensive neuropsychological tests that are indexed to the industrialized countries are not readily available in most countries in SSA, they often require several hours for administration and expertise. Given the busy HIV clinics in Nigeria and across SSA, the CSI-D with the capacity for routine application to screen for patients at risk of developing HAND will be highly useful.

Conflicts of Interest

We declare that we have no conflicts of interest.

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