Neurocognitive Impairment in Patients with HIV and Depression in Nigeria

Abstract:

HIV has been associated with a neurocognitive impairment which may be due to the direct effect of the virus, indirect effect or due to medications side effects or due to a combination of factors. HIV and depression have been shown separately to have neurocognitive deficits.

Aim: Determine the prevalence of NCI and factors associated with it among depressed and non-depressed patients with HIV on combined antiretroviral treatment (cART)

Methodology. A descriptive comparative cross-sectional study was conducted among People living with HIV(PLHIV) at Aminu Kano Teaching Hospital in Kano State, northern Nigeria. Participants were grouped into HIV with depression and HIV without depression groups based on current diagnosis using the depression module of the MINI International Neuropsychiatric Interview (MINI)-7th edition. A multi-domain neuropsychological battery (MDNPT) of 5 tests (assessed 5 cognitive domains) was used to diagnose Neurocognitive impairment

Results: - Fifty-seven percent of the study sample were females, and the mean age of the participants was 37.54 (±10.04) years with an age range of 18-65 years.

The prevalence of NCI was 74% among the depressed 68.3% among the non-depressed group (p=0.484). Years of education and IHDS score were significantly associated with NCI in the depressed group ($p < 0.05$ respectively). While among the non-depressed group, Years of education, average monthly income and IHDS score were significantly associated with NCI ($p < 0.05$ respectively).

Conclusion: Neurocognitive impairment occurs in HIV-positive patients but is worsened by a depressive disorder. There is a need to adequately assess and treat HIV patients with depression. Treatment may improve neurocognitive impairment in depressed HIV patients.

Key Words: Neurocognitive impairment, HIV, Depression, Nigeria

Introduction

The terminologies and the criteria for the diagnosis of HIV-associated Neurocognitive impairment (NCI) have varied over the last two decades.[1] In 1991, The AIDS task force of the American Academy of Neurology (AAN) detailed criteria for diagnosing 2 degrees of NCI:

1) HIV-associated dementia (HAD) 2) minor motor cognitive disorder (MCMD).[2]

This was later revised in 1999 to include an asymptomatic neuropsychological impairment (ANI) making 3 degrees of severity. Due to the evolving epidemiology of the HAART-treated population in 2007 compared to those of untreated populations of the previous decades, a new revision known as the "Frascati criteria" ensued.[2] The Frascati criteria introduced the term HIV-associated Neurocognitive Disorder (HAND) which is determined by assessing at least 5 domains of neurocognitive functioning using objective measures. The Frascati criteria proposed a diagnosis of HAND can only be made when NCI is not attributable to a comorbid condition. Some studies suggest antiretrovirals are toxic to the CNS, impairing neurocognition and related functions. CNS toxicity of cART may occur through direct and indirect mechanisms.[3] Efavirenz (EFV), an NNRTI is the drug most implicated in causing neuropsychiatric adverse effects in a

dose-dependent fashion, both in the short and long term.[4] However a systematic review of 15 studies with single cohort treatment effect designs showed cART improves neurocognition generally, although it does not completely eradicate it.[5] Eleven of the studies reported improvement over 6 months period.

Aim: Determine the prevalence of NCI and factors associated with it among depressed and non-depressed patients with HIV on combined antiretroviral treatment (cART)

Methodology:

Study Area: The study was conducted at Aminu Kano Teaching Hospital (AKTH) a tertiary health facility in North-western Nigeria. The majority of the residents in Kano belong to the Hausa-Fulani tribe and the Islamic faith. The S.S. Wali Virology Centre is an outpatient clinic in AKTH that provides HIV care and treatment. All patients were selected from this clinic.

Study Design: The study was a comparative cross-sectional study.

Study Population: The study was conducted among adult HIV patients on combined antiretroviral treatment (cART). Participants were recruited into one of two groups based on their current diagnosis of MDD. The Criteria for inclusion and exclusion were as follows:

Inclusion Criteria for participants were; Adults, 18-65yrs, with positive antibodies to HIV1, HIV2 or both who were diagnosed within the last 2 years and have been receiving cART for at least 6 months. Had at least six years of education completed. Only Patients that granted informed consent. Those excluded were; Those with history of current substance abuse and/or dependence. Those with history of traumatic brain injury (TBI) with loss of consciousness of more than 30 minutes. Those with Previous or current neurological or major psychiatric disorder unrelated to HIV e.g., schizophrenia, stroke, dementia; Sensory disability like blindness, and

hearing defects; History of positive hepatitis C virus infection from the medical record; Documented history of Central Nervous System (CNS) opportunistic infections. The patient does not understand Hausa or English Language

Study Duration: The study was conducted over a period of 6 months.

Sample Size Determination was done based on the below level;

The sample size was determined using the standard formula for comparing two proportions.[6] n =

$$\frac{(Z\alpha + Z_1 - \beta)2\ [(P1q1) + (P2q2)]}{(P1-P2)2}$$

n = minimum sample size required in each group

= 117.5

A non-response rate of 10% (11.75) was added to this sample size making it 129.25 (rounded up to 130 in each group). Participants in both groups were matched for age, gender, level of education and duration of diagnosis of HIV infection.

Sampling Technique: Participants were selected using a two-stage systematic sampling technique. In the first stage, the Mini International Neuropsychiatric Interview (MINI) was administered to selected eligible participants to determine those with or without depression and then subsequently applied the instruments below;

The following instruments were used for data collection:

1. The Mini International Neuropsychiatric Interview (MINI)
2. Socio-demographic Questionnaire

3. HIV-related Clinical Questionnaire

4. Neuropsychological Instruments:

    i. International HIV Dementia Scale (IHDS)

    ii. Word List Learning and Word-List Delayed Recall – New learning

    iii. Stick Design Test – Constructional Praxis

    iv. Wechsler Adult Intelligence Scale III (WAIS-III) Symbol Search- Speed of information processing

    v. Colour Trails- Executive function domain

1. Socio-demographic Questionnaire: A questionnaire was used to collect socio-demographic information.

2. HIV-Related Clinical Questionnaire: A questionnaire was used to assess clinical history; information was retrieved from the patient's electronic medical record.

3. The MINI International Neuropsychiatric Interview (MINI)-7: The MINI International Neuropsychiatric Interview (MINI)-7th version is a brief structured diagnostic interview developed for clinical and research purposes.[7] It was designed for the International Classification of Diseases-tenth revision (ICD-10) and Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnoses.[8] The MINI has similar validity and reliability with the Structured Clinical Interview for DSM IV (SCID) and Composite International Diagnostic Interview for ICD 10 (CIDI).[8] The MINI can be administered within a shorter period than the SCID and CIDI.[8] The sensitivity and specificity for a diagnosis of a depressive episode were 0.94 and 0.79 respectively.[8] It has high inter-rater reliability, with kappa coefficients ranging from 0.88 to 1.0.[8]

For this study, the module for the diagnosis of major depressive disorder was administered to all participants. Screening questions in a grey box, corresponding to the cardinal symptoms of depression were administered to participants. The depressive module was administered to those with a positive screen. The participants were then grouped into those with current depression and those without. The MINI has been translated into the Hausa language, in a study conducted in Kano, with inter-rater reliability found to be 84%.[9] The MINI has been used widely in Nigeria among HIV patients.[10]

4. Neuropsychological Instruments (NPI)

A multi-domain neuropsychological battery (MDNPT) of 5 tests, each assessing different cognitive domains plus a screening instrument- the International HIV Dementia Scale (IHDS)- were used in this study. All instruments were simple to administer and easy to understand.[11] The tests independently assessed different cognitive domains including working memory and new learning, visuo-constructional ability, speed of information processing and executive functions mainly affected by depression.[12]

Due to a lack of demographically adjusted published normative data for rating and classification of impairments on neuropsychological function on these tests in Nigeria,[13] a group of 60 healthy HIV negative participants (HIVnp) were administered the NPI to establish normative data. For this study, NCI was defined as the performance of at least 1 standard deviation (SD) below the mean for norms of demographically matched (at least age and education) HIV-negative group on at least two domains; or at least 2 SD below the mean for norms on one test as reported in previous studies.[14]

i)international HIV Dementia Scale (IHDS): The International HIV Dementia Scale (IHDS) is an easy-to-administer (within 5 minutes) screening instrument free from the influence of language and culture that was modified by Sacktor et al from the original HIV dementia scale.[15] It was used in addition to the neuropsychological battery of 5 tests to determine if its sub-items will predict cognitive deficits measured by the neuropsychological battery of tests. IHDS has a maximum score of 12 points with a cut-off score of 10 having comparable sensitivities and specificities among participants. In Abuja, it was found to have a sensitivity of 100% and specificity of 79% for detecting impairment at a total score cut-off of 9, and 100% and 37% at a cut-off of 10.[16] It has been used widely in other populations in sub-Saharan Africa including Zaria, Nigeria. [17]

ii) Word List Learning and Word List Recall: The Word-List Learning (WLL) and recall test assess immediate and delayed recall respectively. They are part of the Consortium to Establish Registry for Alzheimer's Disease (CERAD).[18] This 10-word list test has been widely used and demonstrated to be valuable in detecting mild cognitive deficits.[19] It has been used previously in Nigeria by Guruje et al. and Yusuf et al [17]. An adapted version that replaced some of the original words was used for better cultural applicability.[20]

iii)Stick Design Test: The Stick Design Test (SDT) developed by Baiyewu *et al.* (2005) [21] is part of the World Health organisation (WHO) construction test that assesses the visuo-constructional ability of individuals, particularly those with little or no formal education as it eliminates the need for pen and paper.[21] It has shown significant convergent correlations (with the Clock Drawing Test), divergent correlations (with Digit Span Forward) and stable criterion-related validity across cultures.[22] The SDT measures constructional praxis. The SDT has a possible score of 0 to 12. A moderate sensitivity of 58% and specificity of 90% for detecting dementia (in the

elderly) at a cut-off score of 3 was reported in Nigeria by the inventors of the test.[21] It has previously been used among the HIV population in Nigeria by Yusuf *et al* in Zaria.[17]

iv) Wechsler Adult Intelligence Scale III (WAIS-III) Symbol Search: This test assesses the speed of information processing including psychomotor speed, attention and concentration.[23] The WAIS-III Symbol search has been used previously in studies in Nigeria.[11]

v) Colour Trails Test 2: Colour trail test 2 (CTT-2) was developed as an alternative to the trail-making test.[24] It is free from the influence of language and cultural bias as demonstrated by a WHO cross-cultural study. The CTT-2 tests executive function and requires visual scanning abilities, cognitive sequencing, mental double-tracking and alternation.[24] It has been used previously in studies in Sub-Saharan Africa and Nigeria.[11]

Study protocol:

Participants were divided into two groups to compare neurocognitive performance and medication adherence among depressed and non-depressed patients. Pre-test of Instruments

The study instruments were pre-tested at the ART clinic of Kumbotso Comprehensive Health Centre which is far away from Aminu Kano Teaching Hospital. Permission was obtained from the hospital management. The researchers carried out the pre-test after the translation of instruments and training exercises. The pre-test was carried out among 30 non-depressed patients with HIV.

Data Analysis: The data from all tools were checked at the end of each day for completeness, coded and entered in a fresh Microsoft Excel spreadsheet. It was then cleaned and sorted for any wrong entry or duplication. The clean data was exported into IBM Statistical Package for the Social Sciences (SPSS) version 23 for descriptive and inferential analysis.

Results:

A total of 260 HIV patients were enrolled in the study (130 with depression and 130 without depression). Fourteen participants (5.4%) were excluded from the analysis because of incomplete neuropsychological test results. Therefore, data from 123 HIV patients with depression and 123 HIV patients without depression were used for the analysis.

Data from a comparison group of 61 healthy HIV-negative individuals appropriately matched with the study population in terms of age, sex, and level of education were also analysed.

Socio-demographic features of the participants:

The age range of the study participants was 18 to 65 years, with mean age of 37.54 (SD±10.04) years. The mean years of education of participants was 11.85 (SD±2.74) years in the HIV-depressed group and 12.09 (SD±2.79) years in the HIV-non-depressed group, with a little more than two-thirds (69.5%) of the study participants having 12 or more years of education. The study participants did not significantly differ in gender, level of education, employment status and average monthly income ($p > 0.05$ respectively). This is reflected in Table 1.

Table 1: Sociodemographic Characteristics of HIV-Positive Participants.
[μ] McNemar's test. [∞] Kruskal-Wallis test. [Ψ] Mann Whitney U test.

Variable	HIV Depressed N=123 Frequency (%)	HIV non-Depressed N=123 Frequency (%)	χ^2	*p*-value
Gender n (%) ¶				
Male	54 (43.9)	58 (47.2)	0.148	0.359
Female	69 (56.1)	65 (52.8)		
Age group ∞				
18-30	36(29.3)	29(23.6)	1.764	0.623
31-40	50(40.7)	48 (39.0)		
41-50	24(19.5)	30 (24.4)		
>50	13(10.6)	16 (13.0)		
Employment status				
Employed	31 (25.2)	36 (29.3)	0.656	0.720
Unemployed	19 (15.4)	20 (16.3)		
Self-employed	73 (59.3)	67 (54.5)		
Level of education ∞				
Primary	12 (9.80)	7 (5.7)	1.434	0.488
Post-primary	27 (22.0)	29 (23.60)		
Post-secondary	84 (68.3)	87 (70.7)		
Marital status				
Single	20 (16.3)	26 (21.1)	2.966	0.227
Married	59 (48)	65 (52.8)		
Others	44 (35.8)	32 (26)		
Number of living Children				
No child	38 (30.9)	38 (30.90)		
1-4 children	66 (53.7)	56 (45.5)	2.903	0.234
>4 children	19 (15.4)	29 (23.6)		
Average monthly income ¥				
<₦30,000	45 (58.4)	56 (60.2)		
≥₦30,000	32 (41.6)	37 (39.8)		0.589

Clinical characteristics of participants:

Statistically significant associations were found between depression status and the following variables: ART regimen, CPE score and pill burden ($p < 0.05$ respectively). There was no statistically significant difference between depressed and non-depressed groups with regards to international HIV dementia scale (IHDS) ($p>0.05$ respectively). This is elucidated in Table 2.

Table 2: Clinical Characteristics of HIV Depressed and HIV Non-depressed Patients

Variable	HIV depressed N=123 Frequency (%)	HIV non-depressed N=123 Frequency (%)	χ^2	p-value
VAS				
Poor (<95%)	57(46.3)	43(35.0)	2.848	0.092
Good (≥95%)	66(53.7)	80(65.0)		
EFV-based regimen				
Yes	16(13.0)	31(25.2)	5.155	0.023*
No	107(87.0)	92(74.8)		
Regimen with NRTI backbone				
Yes	18(14.6)	21(17.1)	0.122	0.727
No	105(85.4)	102(82.9)		
ARV line				
1st line	114(92.7)	114(92.7)	0.000	1.000
2nd line	9(7.3)	9(7.3)		
CPE score, n (%)				
Poor (<7)	18(14.6)	35(28.5)	6.157	0.013*
Good (≥7)	105(85.4)	88(71.5)		
Pill burden [c]				
No	63(43.4)	82(56.6)	5.442	0.02*
Yes	60(59.4)	41(40.6)		
IHDS score				
Poor (< 10)	63(51.2)	67(54.5)	0.147	0.609
Good (≥10)	60(48.8)	56(45.5)		
Duration of diagnosis in months [d]				
< 24 months	63(51.2)	65(52.8)		0.811
>/= 24 months	60(48.8)	58(47.2)		
Viral load				
Undetectable (<20 copies/ml)	68(54)	58(46)		0.069
≥20 copies/ml	35(41.7)	49(58.3)		
Nadir CD4 count				
< 200 cells/ml	33(36.1)	45(44.6)	0.594	0.441
≥ 200 cells/ml	54(50.9)	56(55.4)		

[d] Mann Whitney U test. *Statistical significance.

ARVs, antiretroviral medications; CD4, a cluster of differentiation 4; CPE, CNS Penetration Effectiveness; EFV, efavirenz; IHDS, International HIV dementia scale; NRTI, nucleoside reverse transcriptase inhibitors; VAS, visual analogue scale; c=Septrin prophylaxis was the most prescribed additional medication 89% of the time.

Neuropsychological results of HIV patients compared with HIV-negative patients:

The neuropsychological scores of the HIV-negative participants were significantly different compared to the scores of the HIV-depressed and non-depressed patients across all the domains tested ($p < 0.05$), namely: verbal learning, memory, speed of information processing, executive function, and visuospatial skills (Tables 3 & 4 respectively).

The HIV-depressed participants performed worse than the HIV-non-depressed participants in verbal learning, executive function, visuospatial ability, and speed of information processing domains. A statistically significant difference was found only in the speed of information processing (SIP) domain (WAIS-III Symbol search) (t-test = 2.049; $p = 0.041$). On the other hand, the HIV-non-depressed participants performed slightly worse than the HIV-depressed participants in the memory domain. This difference was not statistically significant (t-test = 1.926; $p = 0.743$) (Table 5).

Table 3: Neuropsychological Test Score of Depressed Participants with HIV and Demographically Matched HIV Negative Individuals

NP Domain (NP test)	HIV depressed	HIV negative individuals	T	p-value
Verbal learning (Word list learning)	15.11 (3.12)	18.10 (3.03)	0.122	<0.001*
Memory (Word recall test)	5.02 (1.45)	6.07 (1.71)	3.23	<0.000*
Visuospatial ability (SDT)	8.15 (2.29)	9.3 (1.85)	4.331	<0.001*
SIP (WAIS-III Symbol search)	12.98 (5.00)	21.95 (7.08)	5.284	<0.001*
Abstraction / Executive functioning (Colour trails 2)	329.54 (134.01)	197.87 (94.79)	9.263	<0.001*

Data are mean (SD) from independent t-test. *Statistical significance.

NP; Neuropsychological, WAIS-III, Wechsler Adult Intelligence Scale; SDT, Stick Design Test; SIP, Speed of Information Processing.

Table 4: Neuropsychological Test Score of Non-depressed Participants with HIV and Demographically Matched HIV Negative Individuals

NP Domain (NP test)	**HIV non-depressed**	**HIV negative individuals**	**t**	***p*-value**
Verbal learning (Word list learning)	15.12 (3.48)	18.10 (3.04)	1.434	<0.001*
Memory (Word recall test)	4.95 (1.65)	6.07 (1.71)	0.36	<0.001*
Visuospatial ability (SDT)	8.41 (2.15)	9.3 (1.85)	1.654	0.006*
SIP (WAIS-III Symbol search)	14.43 (6.08)	21.95 (7.08)	0.353	<0.001*
Abstraction / Executive functioning (Colour trails 2)	307.38 (129.72)	197.87 (94.79)	10.363	<0.001*

Data are mean (SD) from independent t-test. *Statistical significance.

NP; Neuropsychological, WAIS-III Symbol, Wechsler Adult Intelligence Scale; SDT, Stick Design Test; SIP, Speed of Information Processing

Table 5: Neuropsychological Test Scores of Depressed and Non-depressed Participants with HIV

NP Domain (NP test)	HIV depressed	HIV non-depressed	*p*-value
Verbal learning (Word list learning)	15.11 (3.12)	15.12 (3.48)	0.985
Memory (Word recall test)	5.02 (1.45)	4.95 (1.65)	0.743
Visuospatial ability/constructional praxis (Stick design test)	8.15 (2.29)	8.41 (2.15)	0.374
SIP (WAIS-III Symbol search)	12.98 (5.00)	14.43 (6.08)	0.041*
Abstraction / Executive functioning (Colour trails 2)	329.54 (134.01)	307.38 (129.72)	0.189

Data are mean (SD) from independent t-test. *Statistical significance

NP; Neuropsychological, WAIS-III, Wechsler Adult Intelligence Scale; SDT, Stick Design Test; SIP, Speed of Information Processing.

Prevalence of Neurocognitive Impairment amongst Participants:

The prevalence of NCI was found to be 71.1% (175/246) for the entire HIV-positive patients. The prevalence of NCI was 74% (91/123) among HIV-depressed patients and 68.3% (84/123) among HIV-non-depressed patients (Figure 1). This difference was not statistically significant ($\chi^2 = 0.491$; $p = 0.484$).

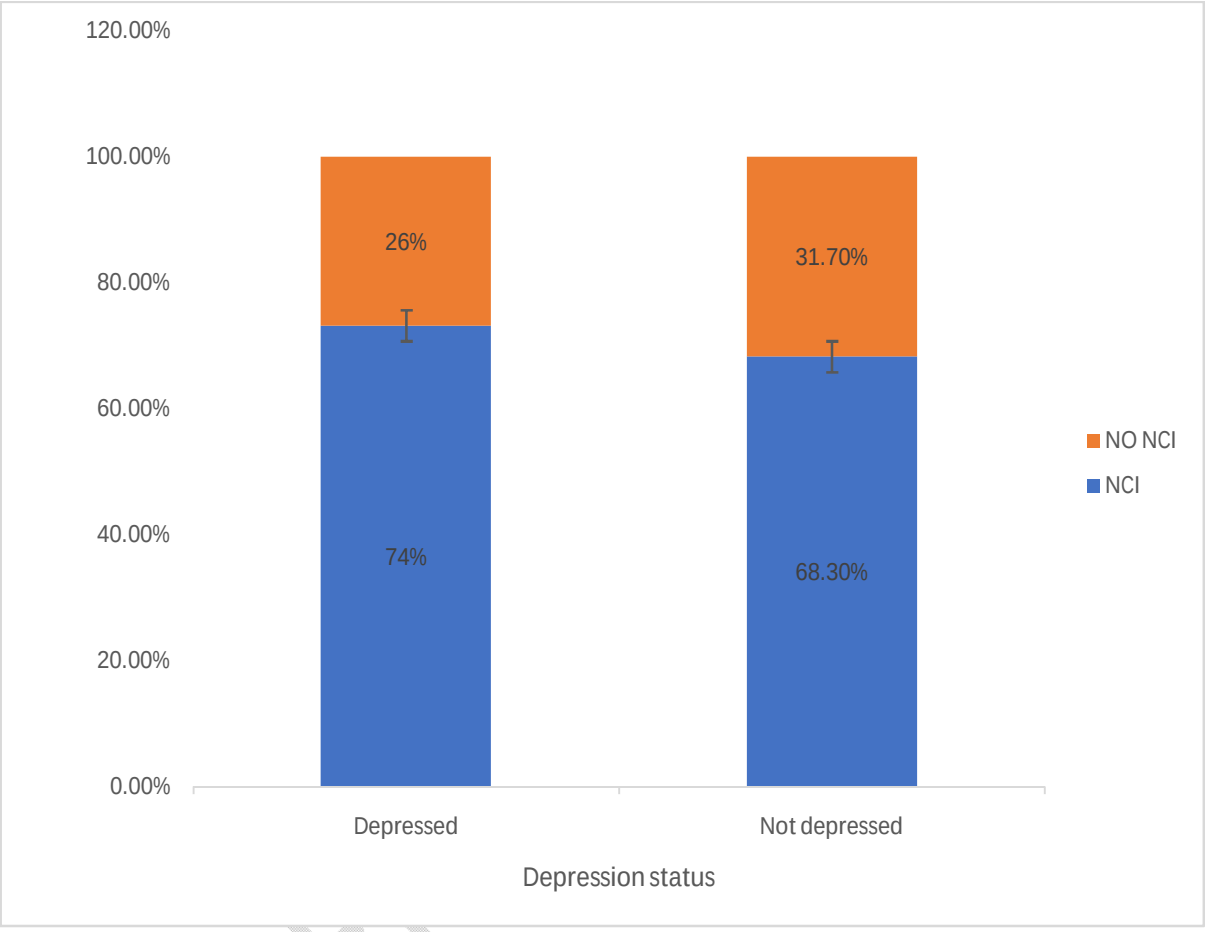

Figure 1: Prevalence of NCI among depressed and non-depressed patients with HIV.

Sociodemographic Factors Associated with NCI among Depressed and Non-depressed Patients

There was no statistically significant difference found between NCI and age, gender, employment, and marital status of the HIV-depressed and non-depressed patients ($p > 0.05$ respectively).

A statistically significant association was found between years of education and NCI in both depressed and non-depressed groups *(*p=0.03 and p=0.001, respectively). Also, a significant difference between average monthly income and NCI was found among the non-depressed group ($p = 0.033$).

Clinical Variables Associated with NCI among Depressed and Non-depressed Patients with HIV.

At an IHDS cut-off score of 10, 88.9% of depressed participants with a positive screen (score of <10) were found to have NCI while 56.7% of those with a good IHDS score had NCI. This difference was statistically significant ($\chi^2 = 14.654$; $p = <0.001$). A similar significant association was found among non-depressed patients ($\chi^2 = 4.163$; $p = 0.041$).

There was no significant association found between the following clinical variables and NCI in either the depressed or non-depressed group: duration of diagnosis, viral load, CPE score, CD-4 count, and pill burden (p= > 0.05, respectively)

Discussion:

Socio-demographic characteristics of the depressed compared to non-depressed patients with HIV:

The majority (57%) of the participants of the study were females. Previous studies in the region have also reported a predominantly female (77.8% and 68.4%) population.[17] More than two-thirds (69.5%) of the study participants had at least 12 years of education in clear contrast to another study that had a mean of 7.9 (SD± 6.2) years in Zaria.[17] The later study was conducted in a town that is surrounded by rural communities whose residents might have low education compared to the current study location sited in a major metropolitan city.

Neuropsychological performance of the participants compared with the healthy comparison group:

The HIV-positive participants (depressed and non-depressed) performed worse than the healthy HIV-negative comparison group in all 5 domains tested. A statistically significant difference was found in all the domains. This finding is consistent with a local study that found statistically significant differences in 5 of 7 domains tested.[11] Unlike in the current study, no significant difference was found in executive function and speed of information processing. Another study in Abuja found HIV patients performed worse than HIV-negative patients in 4 tests/domains, and better in one other test.[25] Importantly, there were no significant differences between the patient group and the healthy group in age, gender, education level, income, or other demographic traits. Thus, the difference in the neuropsychological assessment results between the HIV-positive study population and HIV-negative comparison groups was not confounded by demographics or culture and has greater scientific validity.

Although both the depressed and non-depressed HIV patients performed worse than the HIV-negative group, the neuropsychological raw scores of the non-depressed group were different compared to the depressed group in all domains, except the memory domain. A statistically significant difference was found only in the speed of information processing. This is in keeping with the findings of Lee et al in their meta-analysis that suggested impairment in other cognitive domains may be mediated by slowed information processing speed.[26]

Prevalence of NCI and its comparison among depressed and HIV-non-depressed patients:

This study found an overall prevalence of NCI among HIV patients in Kano to be 70.7%. The prevalence of NCI was 74% among HIV-depressed patients and 68.3% among non-depressed patients. The prevalence suggests that at least 2 out of 3 participants in this study had NCI. This is higher than what is mostly reported worldwide. The higher prevalence among non-depressed patients demonstrates the magnitude of cognitive deficits in PLHIV with no comorbidity. Although subjective cognitive complaints of patients were not assessed in the current study, the majority identified with NCI using an objective battery of tests likely had asymptomatic NCI. Subjects with asymptomatic NCI have been shown to progress over time to symptomatic illness and ultimately dementia compared to people without NCI.[27] The excess NCI seen among depressed patients may be a state-related effect of depression that has been reported previously.[28] If so, improvement in cognitive function should be expected in some patients when depression is treated. The criterion used in diagnosing NCI may also account for regional differences in reported prevalence. In sub-Saharan Africa, a systematic review found the prevalence of NCI pre-ART era at 42.37% and 30.39% among those on cART for > 6 months.[29,] Unlike the present study that utilised an NP battery of 5 tests to identify NCI, the review included studies that used IHDS to identify NCI. The IHDS is a screening instrument for detecting the risk of developing

NCI and its use to identify NCI may account for the discrepancy. Also, one of the studies was longitudinal with possible practice effects. Practice effects may occur when participants become familiar with tests and perform better following repeated exposure to the same tests. A significantly lower prevalence (21.5%) of NCI was reported in Zaria, Kaduna state.[17] The predominantly female (77.8%) participants were administered some of the instruments used in the present study. The present study did not include IHDS among the tests used in NCI diagnosis unlike in the Zaria study. The cut-off scores for two of the tests (stick design and word recall test) used among this population (mean age of 37.2 years) were normative scores for those over the age of 65 years.[17] This contrasts with scores obtained from the demographically matched HIV- negative group in the present study. These may explain the varied prevalence between the two studies. The prevalence of depression was not reported in the Zaria study. An NCI prevalence of 76% was reported among HIV patients in a study in Kano.[11] The participants of the study had similar sociodemographic characteristics to the present study but only half of the patients were on ART and 48% have attained advanced stage of HIV disease. These may account for the higher prevalence in this study (76% vs 71.1%) compared to the present study. Although depression was assessed using a screening instrument (BDI) and participants with severe NCI were found to have higher BDI scores, the prevalence of depression was not reported.

Sociodemographic Factors Associated with NCI among Depressed and Non-depressed Patients with HIV: All the sociodemographic factors were analysed for possible association with NCI among the HIV-depressed patients, only level of education was significantly associated with NCI. While among the non-depressed subjects, years of education and average monthly income were significantly associated with NCI. Studies in China,[30] and Kano[11] have also reported low levels of education as independent predictors of NCI. Although a significant

association was found between the level of education and NCI among depressed and non-depressed groups, an insignificant difference in the level of education was found between depressed and non-depressed respondents. This is possibly explained by the cognitive reserve theory which suggests that higher education confers high cognitive reserve through positive neuroplasticity.[31]

Interestingly, some of the studies also reported older age as an independent predictor of NCI.[32] This was not the case in the current study among both HIV groups, possibly because of the relatively younger population and age range of 18-65 years, compared to an older population and age range of 18-82 years in one of the previous studies.[32] Another reason may be a selection bias brought about by demographic matching of the depressed and non-depressed group, possibly deflating the NCI and age interaction.

There were more females with NCI compared to males in both depressed and non-depressed groups. Although the differences were not statistically significant, these could be due to the likelihood of men having more years of schooling compared to women who often marry early in Kano. The resultant low cognitive reserve in women may put them at higher risk of NCI. Low reading level, a measure of cognitive reserve was shown to account for higher prevalence of NCI in women compared to men in California, USA.[33] Additionally, more women recruited into the study may have contributed to this difference.

There was a statistically significant association between average monthly income of less than 30, 000 Naira, and NCI among HIV non-depressed subjects. This amount is the recommended minimum wage set by the government and amounts to approximately 64 Dollars. This is surprising considering the employment rate of 83.7% in the sample. A closer examination of those employed revealed that 65% were self-employed. The higher proportion of women with

NCI (54.8%) and less than 12 years of education (53.8%) compared to men in the non-depressed sample may explain this association. Women were less educated and less likely to have formal employment with reasonably good pay. Additionally, formal employment provides an avenue for social engagements and mental stimulation that may promote positive neuroplasticity.[34] Most women in Kano are self-employed petty traders working from home with minimal social interaction.

Clinical Factors Associated with NCI among Depressed and Non-depressed Patients with HIV: Almost all the clinical variables that were hitherto linked with NCI were not significantly associated in both depressed and non-depressed participants of the current study. This is in keeping with studies in the HAART era in sub-Saharan Africa[11] and globally.[35] For instance, viral load detection was not significantly associated with NCI in both depressed or non-depressed groups despite viral suppression (< 20 copies/ml) rates of 66% and 54%, respectively. The high NCI rates found in this study complement previous findings that NCI may persist despite cART treatment and plasma viral suppression. It is important to note that only 89% of participants' recent viral load results were retrieved from the electronic data, and this may have affected the results. Another possible explanation for high NCI prevalence despite a reasonable viral suppression rate may be a history of severe immunosuppression before the commencement of treatment, a risk factor for NCI. An important biomarker of severe immunosuppression is nadir CD4 count < 200.[36]

Nadir CD4 count was also not significantly associated with NCI in both groups. The non-association between Nadir CD4 count and NCI in the current study is consistent with studies in both resource-rich[37] and resource-limited settings.[11] This study's finding of high NCI rates in clinically asymptomatic patients on HAART, with sufficient viral suppression rate complements

the previous notion that advanced immunosuppression may cause neurotoxicity that persists despite treatment and immune restoration, a phenomenon known as "legacy effect".[2]

Other clinical variables that have been associated with NCI are duration of illness and duration of treatment.[37] No significant associations were found with these variables in this study. The relatively short duration of illness among study participants could have accounted for this finding. However, the higher prevalence of NCI seen in the depressed group may be due to a higher proportion of this group (45% Vs 37%) receiving treatment for less than a year compared to the non-depressed group. Hence, those without depression may have benefitted more from the cognitive-promoting effects of cART. Previous data show modest benefits in NP functioning, particularly in processing speed and executive function among patients that have taken cART for more than 1 year.[38]

Contrary to previous reports, no difference in CPE score was found between those with NCI and those without NCI in both depressed and non-depressed groups of the current study.[37] The former findings were from a longitudinal study while data reported here are from a single cross-sectional study. A possible reason for the observed lack of association may be because the study participants were neuro-asymptomatic and CNS penetration of drugs may be of limited benefit.

Similarly, no association was found between antiretroviral class and NCI, in both depressed and non-depressed groups. This finding should be interpreted with caution because some patients were recently (within the past year) switched from zidovudine and efavirenz-containing regimen to a regimen containing tenofovir (an NNRTI) and dolutegravir, an integrase strand transfer inhibitor (INSTI) as per revised national guideline. Thus, patients previously taking these medications were not included as part of the NRTI group even though they might have deficits from past exposure. Bonnet et al (2013) also found no significant association, although they

observed that those with NCI were less frequently treated with efavirenz.[39.] This is in contrast with other studies that found a significant association between different drugs of NNRTI and NRTI classes with NCI. [40.]

The findings of the current study that the IHDS score is significantly associated with NCI is not surprising since it is an instrument that was primarily designed to screen for NCI.[15] In fact, a sensitivity of 74.3% and specificity of 66.2% for the detection of NCI was found at a cut-off score of 10. This is comparable to a sensitivity of 80% and a sensitivity of 55% in a study by the inventors of the instrument.[15]

STRENGTHS

1. The use of comparison scores from demographically matched healthy persons recruited from the same locality as the study sample strengthens this study. Their shared language and culture avoided potential bias that may arise from culture and language differences.
2. A diagnostic instrument and objective multidomain neuropsychological battery of 5 tests were used to accurately diagnose depression and NCI, respectively

LIMITATIONS

1. The cross-sectional design precludes any hypothesis on a causal relationship between independent predictors and the dependent variables among PLHIV.
2. Restriction of the study to patients early in treatment makes the generalizability of the findings limited.

CONCLUSION

This study found the prevalence of NCI was higher among HIV patients with depression compared to those without depression. It is hereby recommended as follows; HIV patient management should compulsorily include the integration of HIV treatment and care. People diagnosed with HIV should be screened for psychiatric comorbidity at baseline. This should be followed with subsequent screening at periodic intervals particularly among at-risk groups. The Government should put in place policies that guarantee quality education to every citizen regardless of gender, origin, or social class. This should be made accessible and affordable.

Ethical Approval: Ethical approval for this study was obtained from the Health Research Ethics Committee of Aminu Kano Teaching Hospital.

Consent

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

REFERENCES:

1. Howard E. Gendelman, MD, Igor Grant, MD, Ian Paul Everall, MD, PhD, Howard S. Fox, MD, PhD, Harris A. Gelbard, MD, PhD et al. The Neurology of AIDS. Oxford University Press. 2011. p. 518–9.
2. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, LeBlanc S, et al. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: Differences in rates, nature, and predictors. J Neurovirol. 2011;17(1):3–16.

3. Underwood J, Robertson KR, Winston A. Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? Vol. 29, AIDS. 2014. p. 253–61.
4. Ma Q, Vaida F, Wong J, Sanders CA, Kao Y ting, Croteau D, et al. Long-term efavirenz use is associated with worse neurocognitive functioning in HIV-infected patients. J Neurovirol. 2016;22(2):170–8.
5. Joska JA, Gouse H, Paul RH, Stein DJ, Flisher AJ. Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. J Neurovirol. 2010;16(2):101–14.
6. Araoye M. Sample size determination. In: Araoye MO ed. Research methodology with statistics for health and social sciences. Ilorin: Nathadex Publishers; 2004. 115–30 p.
7. Sheehan D V., Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry. 1998;59(SUPPL. 20):22–33.
8. Lecrubier Y, Sheehan D V., Weiller E, Amorim P, Bonora I, Sheehan KH, et al. The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. Eur Psychiatry [Internet]. 1997;12(5):224–31. Available from: http://dx.doi.org/10.1016/S0924-9338(97)83296-8
9. Baguda AS. Mental ill-health of divorced women in urban Kano: psychosocial correlates. Diss Prep Fellowsh Award Natl Postgrad Med Coll Niger. 2015;

10. Bankole KO, Bakare MO, Edet BE, Igwe MN, Ewa AU, Bankole IA, et al. Psychological complications associated with HIV/AIDS infection among children in South-South Nigeria, sub-Saharan Africa. Cogent Med. 2017;4(1):1–16.
11. Yakasai AM, Gudaji MI, Muhammad H, Ibrahim A, Owolabi LF, Ibrahim DA, et al. Prevalence and Correlates of HIV-Associated Neurocognitive Disorders (HAND) in Northwestern Nigeria. Neurol Res Int. 2015;2015:1–9.
12. Rock PL, Roiser JP, Riedel WJ, Blackwell AD. Cognitive impairment in depression: A systematic review and meta-analysis. Psychol Med. 2014;44(10):2029–40.
13. Sillman B, Woldstad C, Mcmillan J, Gendelman HE. Neuropathogenesis of human immunodeficiency virus infection. In: Handbook of Clinical Neurology. 2018. p. 21–40.
14. Muñoz-Moreno JA, Pérez-Álvarez N, Muñoz-Murillo A, Prats A, Garolera M, Jurado MÀ, et al. Classification Models for Neurocognitive Impairment in HIV Infection Based on Demographic and Clinical Variables. Paraskevis D, editor. PLoS One. 2014;9(9):e107625.
15. Sacktor N, Wong M, Nakasujja N, Skolasky RL, Selnes OA, Musisi S, et al. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. AIDS. 2005;19(13):1367–74.
16. Royal W, Cherner M, Carr J, Habib AG, Akomolafe A, Abimiku A, et al. Clinical features and preliminary studies of virological correlates of neurocognitive impairment among HIV-infected individuals in Nigeria. J Neurovirol. 2012;18(3):191–9.
17. Yusuf AJ, Hassan A, Mamman AI, Muktar HM, Suleiman AM, Baiyewu O. Prevalence of HIV-Associated Neurocognitive Disorder (HAND) among Patients Attending a

Tertiary Health Facility in Northern Nigeria. J Int Assoc Provid AIDS Care. 2017;16(1):48–55.

18. Akiyama H. [CERAD (The Consortium to Establish a Registry for Alzheimer's Disease) criteria]. Nihon Rinsho. 2011;69(2):264–9.

19. Sosa AL, Albanese E, Prince M, Acosta D, Ferri CP, Guerra M, et al. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. BMC Neurol. 2009;9(1):48.

20. Guruje O, Unverzargt FW, Osuntokun BO, Hendrie HC, Baiyewu O, Ogunniyi A, et al. The CERAD Neuropsychological Test Battery: norms from a Yoruba-speaking Nigerian sample. West Afr J Med. 1995;14(1):29–33.

21. Baiyewu O, Unverzagt FW, Lane KA, Gureje O, Ogunniyi A, Musick B, et al. The Stick Design test: a new measure of visuoconstructional ability. JIntNeuropsycholSoc. 2005;11(5):598–605.

22. de Paula JJ, Costa MV, Bocardi MB, Cortezzi M, De Moraes EN, Malloy-Diniz LF. The Stick Design Test on the assessment of older adults with low formal education: evidence of construct, criterion-related and ecological validity. Int Psychogeriatr. 2013;25(12):2057–65

23. Underwood J, Robertson KR, Winston A. Could antiretroviral neurotoxicity play a role in the pathogenesis of cognitive impairment in treated HIV disease? Vol. 29, AIDS. 2014. p. 253–61.

24. Konstantopoulos K, Issidorides M, Spengos K. A normative study of the colour trails test in the greek population. Appl Neuropsychol. 2013;20(1):47–52.

25. Akolo C, Royal W, Cherner M, Okwuasaba K, Eyzaguirre L, Adebiyi R, et al. Neurocognitive impairment associated with predominantly early-stage HIV infection in Abuja, Nigeria. J Neurovirol. 2014;20(4):380–7.

26. Lee RSC, Hermens DF, Porter MA, Redoblado-Hodge MA. A meta-analysis of cognitive deficits in first-episode Major Depressive Disorder. J Affect Disord. 2012;140(2):113–24

27. Grant I, Franklin DR, Deutsch R, Woods SP, Vaida F, Ellis RJ, et al. Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline. Neurology. 2014;82(23):2055–62

28. McIntyre RS, Cha DS, Soczynska JK, Woldeyohannes HO, Gallaugher LA, Kudlow P, et al. Cognitive deficits and functional outcomes in major depressive disorder: Determinants, substrates, and treatment interventions. Depress Anxiety. 2013;30(6):515–27.

29. Habib AG, Yakasai AM, Owolabi LF, Ibrahim A, Habib ZG, Gudaji M, et al. Neurocognitive impairment in HIV-1-infected adults in Sub-Saharan Africa: A systematic review and meta-analysis. Int J Infect Dis. 2013;17(10):e820–31.

30. Zhao T, Wei B, Long J, Tang X, Zhou M, Dang C. Cognitive disorders in HIV-infected and AIDS patients in Guangxi, China. J Neurovirol. 2014;21(1):32–42.

31. Vance DE, Randazza J, Fogger S, Slater LZ, Humphrey SC, Keltner NL. An Overview of the Biological and Psychosocial Context Surrounding Neurocognition in HIV. J Am Psychiatr Nurses Assoc. 2014;20(2):117–24.

32. Pinheiro CAT, Souza LDM, Motta JVS, Kelbert EF, Souza MS, Martins CSR, et al. Depression and diagnosis of neurocognitive impairment in HIV-positive patients. Brazilian J Med Biol Res. 2016;49(10):e5344.

33. Sundermann EE, Heaton RK, Pasipanodya E, Moore RC, Paolillo EW, Rubin LH, et al. Sex differences in HIV-associated cognitive impairment. AIDS. 2018;32(18):2719–26.

34. Vance DE, Randazza J, Fogger S, Slater LZ, Humphrey SC, Keltner NL. An Overview of the Biological and Psychosocial Context Surrounding Neurocognition in HIV. J Am Psychiatr Nurses Assoc. 2014;20(2):117–24.

35. Milanini B, Ciccarelli N, Fabbiani M, Limiti S, Grima P, Rossetti B, et al. Cognitive reserve and neuropsychological functioning in older HIV-infected people. J Neurovirol. 2016;22(5):575–83.

36. Nightingale S, Winston A, Letendre S, Michael BD, McArthur JC, Khoo S, et al. Controversies in HIV-associated neurocognitive disorders. Vol. 13, The Lancet Neurology. 2014. p. 1139–51.

37. Ciccarelli N, Fabbiani M, Colaigli M, Trecarichi EM, Silveri MC, Cauda R, et al. Revised central nervous system neuro-penetration effectiveness score is associated with cognitive disorders in HIV-infected patients with controlled plasma viraemia. Antivir Ther. 2013;18(2):153–60.

38. Joska JA, Gouse H, Paul RH, Stein DJ, Flisher AJ. Does highly active antiretroviral therapy improve neurocognitive function? A systematic review. J Neurovirol. 2010;16(2):101–14.

39. Bonnet F, Amieva H, Marquant F, Bernard C, Bruyand M, Dauchy FA, et al. Cognitive disorders in HIV-infected patients: Are they HIV-related? Aids. 2013;27(3):391–400.

40. Sacktor N, Nakasujja N, Skolasky RL, Robertson K, Musisi S, Ronald A, et al. Benefits and risks of stavudine therapy for HIV-associated neurologic complications in Uganda. Neurology. 2009;72(2):165–70.