Prevalence and predictors of HIV-associated Neurocognitive Disorder in Ethiopians

Mohammed Salahuddin (msalahuddin.mohammed@gmail.com)
Mizan-Tepi University
Md Dilshad Manzar
Majmaah University
Hamid Yimam Hassen
Mizan Tepi University
Mihretu Ashuro
Mizan-Tepi University
Aleem Unissa
Malla Reddy College of Pharmacy
Mohammed Aziz Mohammed
Shadan College of Pharmacy
Unaise Abdul Hameed
Monash University
David Warren Spence
Independent researcher
Seithikurippu R. Pandi-Perumal
Somnogen Canada Inc.

Research

Keywords: cART, HIV, IHDS, Africa, Dementia, Ethiopia, Social drugs

Posted Date: May 29th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-29666/v1

Abstract

Background

Modern antiretroviral therapy has extended the life expectancies of people living with HIV; the prevention and treatment of their associated neurocognitive decline has remained a challenge. Consequently, it is desirable to investigate the prevalence and predictors of HIV-associated Neurocognitive Disorder (HAND) to help in targeted screening and disease prevention.

Methods:

Two hundred and forty-four people living with HIV were interviewed in a study using a cross-sectional design and International HIV Dementia scale (IHDS). Additionally, the sociodemographic, clinical and psychosocial characteristics of the patients were recorded. Chi-square and binary logistic regression analysis were used to determine the level of significance among the independent risk factors and probable HAND.

Results

The point prevalence of HAND was found to be 39.3%. Participants' characteristics of being older than 40 years (AOR = 2.81 (95% CI; 1.11–7.15)), having a history of recreational drug use (AOR = 13.67 (95% CI; 6.42–29.13)), and being non-compliant with prescribed medications (AOR = 2.99 (95% CI; 1.01–8.87)) were independent risk factors for HAND.

Conclusion

The identification of predictors, some of which may be more closely related to the Ethiopian people living with HIV, may help in targeted screening of vulnerable groups during cART follow-up visits. This may greatly help in strategizing and implementation of the prevention program, more so, because: (i) HAND is an asymptomatic condition for considerable durations, and (ii) clinical trials of HAND therapies have been unsuccessful.

Background

In recent decades, the successful development and widespread implementation of anti-retroviral therapies have seen an associated increase in the longevity of HIV-infected patients. However, this important public health achievement has presented new challenges of clinically maintaining the health and quality of life of these patients. One of the major health deficits afflicting HIV-infected individuals is the development of neurocognitive disorders, including progressive symptoms of dementia. The successful implementation of cART regimens has considerably reduced the prevalence of the most severe form of dementia, i.e., HIV-associated dementia (HAD) (1,2). However, milder forms of this condition, namely, mild neurocognitive disorder (MND) and asymptomatic neurocognitive impairment (ANI), are commonly prevalent and may reduce the quality of life of HIV-infected patients. These clinical manifestations have been an important concern, especially for patients belonging to special clinical categories, including those with a late diagnosis of HIV, untreated adults, pregnant women,

patients with low medication adherence, and pediatric patients, associated diagnoses which make affected patients particularly vulnerable to severe forms of dementia (HAD; 3,4).

Some of the milder and severe forms of associated co-morbid symptomology include, but are not limited to, attention deficits, depression, mood swings, psychomotor disturbances, and spasticity. An additional symptom is an increase in the alteration in extrapyramidal movements, which in turn is associated with major signs of neurological deterioration, including astrocytosis, microgliosis, demyelination of axons, breaks in the dendritic processes, neuro-degeneration, increased infiltration of inflammatory mediators and lymphocytes, and a chronic increase in markers of oxidative stress (5-8). HIV-infected individuals diagnosed with HIV-associated neurocognitive disorder (HAND) remain asymptomatic for long durations (9). The neurocognitive impairment could potentially interfere with daily life functioning such as work ineptitude, increased driving errors, and poorer adherence to treatment, which may indirectly influence the viral load and CD4 lymphocyte status. A lower CD4 count is the hallmark of a weaker immune system and compromises the ability to fight infections, thus increasing the degree of neurodegenerative insult by attacking the microglia and macrophages in the central nervous system. Additionally, HIV-infected persons frequently present with comorbidities such as Hepatitis-C co-infection, drug abuse, or prior head injuries, which can further exacerbate HIV-related effects on the brain. Thus, early diagnosis of the neuroHIV symptoms is important for improved CD4 count and reduced viral load. In support of this public health objective, the UNAIDS, an HIV education, and prevention program of the United Nations, has strategically supported to improve the quality of life of patients with existing sexual and reproductive health services (10).

Post cART era there has been decrease in the prevalence of HAD but up to 40% still suffer from HAND (11,12). Additional study by Heaton et al group in 2011 revealed greater than 50% of HIV^+ patients showed HAND symptomology (13). Nevertheless it is prudent to mention that unavailability of sophisticated tools to parse the asymptomatic neurocognitive disorder (ANI) from mild neurocognitive disorder (MND) in the present population, IHDS was used as a screening tool for those individuals who are at high risk of dementia only. However, no studies have investigated the prevalence of HAND and its associated conditions in a population of Ethiopians living with HIV in the present facility setting. Therefore, the present study sought to determine the prevalence and predictors of HIV-associated neurocognitive disorder (HAND) using International HIV dementia scale (IHDS).

Materials And Methods

Participants and procedures

The target population was people living with HIV, who were residents of Mizan-Aman, Ethiopia. The accessible population consisted of people living with HIV who were attending the HIV/ART clinic of Mizan-Tepi University Teaching Hospital (MTUTH), Aman, Ethiopia. The study was carried out for a period over two months from February 2018 to April 2018. Out of the total of 384 patients attending the HIV/ART clinic of MTUTH during these months, 300 eligible patients initially agreed and signed an informed consent form. Of the 300 eligible patients, 250 were finally selected using a simple random sampling method. Inclusion criteria were (i) age greater than 18 years and (ii) mentally stable, as determined by the attending clinicians. Finally, after removing the construct-level missing data, 244 samples were finally used for quantitative analysis (See Supplementary File attached). Three trained psychiatric nurses from the HIV/ART clinic of MTUTH performed the structured

interview. The four words used as a part of recall memory test were translated into Amharic by a native Amharic language expert. These four words were native to local Ethiopian community and are used commonly in the Ethiopian cultural context.

The dementia task comprised 3 tasks which assessed memory recall, motor speed, and psychomotor speed. The first task involved a short-term memory task in which the participants were given four words to recall (dog, hat, bean, red) (translated into Amharic as wusha, kofiya, bakele, keyi) and were provided one second to say each word. Amharic translations of these four words are native to the local Ethiopian community and are used commonly (i.e. High-frequency words) in the Ethiopian cultural context. Though, it is plausible to think that the word length and number of syllables might play some role in recall memory, because the Amharic translation of these words are slightly longer and have slightly higher number of syllables. However, the associative retrieval mechanism facilitated by the high-frequency nature of these four words in both English and Amharic versions would have somewhat compensated the effect caused by the variation in the word lengths and number of syllables. The participants were then asked to remember the 4 words and told that they would be asked to recall the words again a bit later. This was followed by a motor speed task in which the patient was asked to tap the first two fingers of the non-dominant hand as quickly and as rapidly as possible. The maximum score for the motor task was 4 points, with specific performance levels being scored as follows: 4 = ≥ 15 taps in 5 seconds; 3 = 11-14 taps in 5 seconds; 2 = 7-10 taps in 5 seconds, 1 = 3-6 taps in 5 seconds; and 0 = 0-2 taps in 5 seconds with the maximum 4 points for motor speed task. Psychomotor speed was further assessed by asking the patient to perform several movements with the non-dominant hand as quickly as possible. Primarily the patients needed to clench their hand into a fist on a flat surface. They were then asked to put their hand flat on the surface with their palm down. Finally, they were asked to place their hand perpendicular to the flat surface while displaying the 5th digit. The whole task was demonstrated once to the patients who were then allowed to practice twice before starting the test. A maximum of 4 points was possible for the psychomotor task, with patient performance being 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 = unable to perform the task. Finally, the patients were given the follow-up to the memory recall in which they were asked to recall the four words. For the words that were not recalled correctly the patients were prompted with a semantic clue as follows: animal (dog); a piece of clothing (hat); vegetable (bean); color (red). A maximum 4 points was possible for the memory recall task, with the scoring as follows: one point for each word spontaneously recalled, and 0.5 points for each correct answer after prompting. The final score was a sum of the three tasks, the maximum being 12. Patients who scored 10 points or less were referred for further dementia testing.

Measures

Sociodemographic measures

A questionnaire was used to gather sociodemographic information regarding the participants' age, gender, marital status, religion, ethnicity, and occupation. The questionnaire also recorded information related to substance use: this included information about participants' habitual use of commercial and indigenous alcoholic drinks such as tej, tella, areki, shamita, borde, and korefe, as well as about habits such as tobacco smoking, consumption of caffeinated drinks, and khat chewing (14)

Clinical measures

Data regarding participants' clinical symptoms were also recorded. These included the patients' current CD4 count, baseline CD4 count, viral load, duration on combination antiretroviral therapy regimen (cART), side effects from cART, opportunistic infections, duration since HIV diagnosis, other neuropsychiatric diagnosis, and duration of hospital stay.

Psychosocial measures

Information related to psychosocial factors such as support from family, perceived stigma accruing from HIV status, and discrimination from society was collected. Further, questions about perceived memory deficits in the past month which might have interfered with daily functioning were assessed by questions such as "Do you experience frequent memory loss?", "Do you feel you are slower when reasoning or solving problems?", and "Do you have difficulties in paying attention?" (15).

The International HIV dementia scale (IHDS)

The International HIV dementia scale (IHDS) (16) was used to screen for HIV-associated neurocognitive disorder or HIV dementia. This tool has been validated in different African and Caucasian populations and has been shown to have a sensitivity of 88% and 80% and specificity scores of 50% and 55% respectively (16-17). The tool measures three essential components of neurological impairments: these include cognition, motor, and psychomotor deficits. Each component has a maximum score of 4, with a total score of three components summing to 12 (16). Any value of less than 10 is indicative of neurocognitive deficits, and patients receiving such a score are referred for further psychiatric follow-up by higher referral hospital (16). The IHDS does not require proficiency in the English language and is ideal for measuring probable HAND in people living with HIV.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 21 (SPSS Inc., Chicago, IL). Bivariate correlation and Chi-square tests were used to determine the correlation between the independent variables and probable HAND status; those sociodemographic, clinical and psychosocial risk factors with a p-value of less than 0.25 were selected for the multivariate association analysis with the outcome measure. Binary logistic regression was used to assess the multivariate association between the dependent variable, i.e., HAND status and independent variables. Models were adjusted for age, gender, education, marital status, severity of illness (hospital stay) and stigma (indirectly related to increased anxiety and depression) towards people living with HIV. A Mann Whitney test was performed to assess the difference between the mean scores of participants in the probable HIV dementia group and the non-demented group.

Logistic regression was applied after verifying all its assumptions in the study data. In general, the dependent variable, namely, HAND status was measured as a dichotomous variable. Second, there was independence of observations as assessed by the Durbin Watson test. No outlier was found, as assessed by Mahalanobis Distances for multivariate outliers and box plot analysis for univariate outliers. Independent variables (continuous) were linearly related to log odds as determined by the absence of significance for the interaction effect. Additionally, the study data also satisfied the minimum sample size requirement. Based on the present prevalence of 41% for HAND, the sample size calculation for 9 independent variables included in the model and the expected probability of the least frequent outcome being .10, it was determined that a minimum sample size of (10*9/.4) =90/.4=225 was needed.

Results

Sociodemographic characteristics of the study population

Table 1 presents the patients' characteristics. Most of the patients were under 40 years of age (85%). The majority of the patients (64%) were female and approximately three-fourths (69%) were married. Most of the patients (70%) reported having completed less than eight years of primary school or had no formal education. One-fourth of the patients admitted that they used recreational drugs (25%). Nearly 65% of the patients belonged to the low and very low-income groups. Most of the patients lived in urban locations (86%). No significant association between education level and gender groups was found; $\chi 2(3) = 4.985$, $p = .173$.

Clinical characteristics of the study population

Table 2 shows the clinical characteristics of the study participants. Approximately 96% (235, 96.4%) of patients had been diagnosed with HIV for greater than 6 months of which 94 (40%) showed symptoms of HAND. The current CD4 count is a good marker for dementia as per the WHO recommended criteria; patients with current CD4 count < 500 cells/mm^3 could potentially show signs of cognitive impairment. In the present study, approximately 44% of the HIV diagnosed patients had a current CD4 count <500 cells/mm^3. Most of the patients reported that they did not adhere to their prescribed medication regimen (88%). About one-third of the patients were diagnosed with opportunistic infections at the time of participation in the study. None of the clinical characteristics showed any significant statistical association with HAND in the bivariate analysis.

Psychosocial characteristics of the study population

Table 3 shows the psychosocial characteristics of the patients enrolled in the study. Most of the patients (87%) reported no social support for medical adherence from their family or friends. Most (about three fourths) of the participants reported that they did not experience any stigma and discrimination from society.

Bivariate associations: HAND status with sociodemographic, clinical and psychosocial covariates

Age was significantly associated with HAND, i.e., participants aged 40 years of age or older were more likely than younger participants to show neurocognitive symptoms [$\chi^2(1) = 2.635$, $p<0.05$; Table 1]. Social drug use also significantly predicted HAND [$\chi^2(1) = 57.245$, $p<0.05$; Table 1].

Differences in HAND component scores between demented and non-demented groups

The prevalence of HAND identified by IHDS was 39.34% with the IHDS total score of 9.57±1.57. Independent mean IHDS recall score was revealed as 3.36±0.80, motor score as 3.32±0.66 and psychomotor score as 2.90±0.72 (Table 4). The difference between those who had HAND and those who didn't was evident in all the three components of IHDS, i.e., recall [$U = 2732$, $p = p<.001$], motor performance [$U = 2704.500$, $p<.001$] and psychomotor abilities [$U = 1930.500$, $p<.001$; see Figure 1].

Factors associated with the neurocognitive deficit: a multivariate analysis

Binary logistic regression was performed to measure the effects of age, gender, current CD4 count, medication adherence status, stigma, marital status, hospital stay, social drug use and education on the HAND status.

Gender, education, marital status, current CD4 count and hospital stay were included in the model based on previous studies showing them to be consistent predictors for HAND (18-25). The logistic regression model was statistically significant, $\chi 2(9) = 72.91$. The model explained 35.0% (Nagelkerke R^2) of the variance in dementia status and correctly classified 75.8% of cases. Participants who were older than 40 years of age were 2.8 times more likely than younger subjects to exhibit HAND ($p<.05$, Table 5). Those who admitted to that they did not adhere to their medication regimens were 2.9 times more likely to have symptoms of HAND ($p<.05$, Table 5). Study subjects who stated that they used recreational drugs were 13.6 more likely than non-recreational drug users to have symptoms of HAND ($p<.001$, Table 5

Discussion

The present study determined the prevalence, and identified predictors for HIV dementia (HAND) in Ethiopians living with HIV. People living with HIV were found to have a high prevalence of neurocognitive, motor and psychomotor deficits. The present findings confirmed the hypothesis that some of the patient-associated socio-demographics and clinical factors can serve as predictors of HAND. The identification of predictors, some of which may be more closely related to the Ethiopians living with HIV, may help in targeted screening of vulnerable groups during cART follow-up visits. This may greatly help in strategizing and implementation of the prevention program, more so, because: (i) HAND is an asymptomatic condition for considerable durations, and (ii) clinical trials of HAND therapies have been unsuccessful (9).

The point prevalence of the neurocognitive deficit in this study was 41%. The present prevalence findings were similar to those of a study from Canada (39.4%)(26) but higher when compared to other studies from Ethiopia (33.3%,67.1%) (21,27), sub-Saharan Africa (30.9%) (28). However, the present findings were less than some of the studies conducted in Nigeria (54.3%, 2012; 66.2%, 2013) (29,30), Cameroon (85%) (31), Asia (85%) (32) and Uganda (64.4%, 2013) (33).

The majority of the present study sample (96%) had been diagnosed as having had HIV for more than 6 months and thus most of the patients (99%) were already on the cART regimen. Despite being treated with cART medication, some of the patients still showed symptoms of cognitive impairment. The possible explanation for this would be that many patients reported having poor medication adherence (88%) or inability of cART to achieve optimum therapeutic concentration in the CNS due to its poor penetration beyond the blood-brain barrier (34).

Similar to previous studies, being older than 40 years was found to have a positive association with HAND status in the people living with HIV (35-39). Generally, cognitive performance deteriorates with increasing age, and some studies have shown that being in the 40 plus age group is a significant predictor of HAND. One study in Uganda did not show any association between advanced age and HAND (33). This might be because of some moderator variables in their study (33), because consistency in association is suggested by multiple reports (35-39).

Recreational drug use has been shown to be a strong predictor of HAND in the present study. The present study assessed self-reported use of social drugs such as khat, alcohol, cigarette, coffee and other caffeinated drinks in people living with HIV. Drinking indigenous varieties of alcohol and khat chewing is among the most prevalent social habits in Ethiopia (40). There has been a growing body of evidence which points towards

cognitive decline due to drug misuse (41-43). Social drug misuse frequently involves drug takers in various risk-taking behaviors (44). Some studies have shown that low to moderate alcohol consumption may actually facilitate cognition (45-46); others have shown that it impairs cognition (47) or produces no change (48). Another recreational drug called Khat is abused widely in Ethiopia and has been associated with short-term memory deficits and loss of cognitive flexibility in adults (49-51). Additionally, the deleterious effects of khat on cognitive performance have been similarly demonstrated in people living with HIV (52). Nevertheless, the association between khat and cognition is complex. Khat has a biphasic response on cognition, wherein low doses may enhance cognition until reaching a peak, at which progressively higher doses begin to produce adverse cognitive effects, and, additionally, are associated with classic signs of addiction similar to psychostimulants (53). Other lines of evidence have tended to suggest the presence of an adverse additive effect, in as much as, drug users without HIV are more vulnerable to cognitive impairment than patients who are HIV positive (54-57). It's worth mentioning that since Khat is a social drug being extensively used in the present Ethiopian community setting and clinical and preclinical evidences show that it produces spatial memory, working memory and cognitive flexibility deficits (49). Delineating khat neurocognitive effects from other social drugs like coffee, tobacco, alcohol and soft beverages may need a longitudinal follow-up of the HIV+ patients which was out of the scope of the present study. Furthermore. social drug abuse has led to a synergistic interaction with HIV which may need future longitudinal follow up trials and experiments for its confirmation. Nevertheless, this is consistent to a study in the preclinical population which demonstrated the combined exposure of HIV-1 Tat protein and clinical opioid namely Oxycodone to promote the psychomotor behavioral effects, thus making the drug more rewarding, with the initial perceived potency of the drug being an important predictor of whether the patient would enter into the addiction cycle (58,59)

The study sought to identify which clinical factors might be most important for predicting HAND. The candidate predictors included the current CD4 count, duration of time since HIV diagnosed, presence of opportunistic infections, and WHO clinical staging. These factors, however, did not show any significant association with HAND status in our study. Inconsistent results have been reported between different clinical correlates of HAND (60,61). One of the possible associations, i.e., between self-reported lapses in medication adherence and HAND, was of interest inasmuch as patients frequently reported that being on multiple drug regimens made it particularly burdensome for them to reliably take their medicines (62). However, this potential association failed to reach statistical significance. The study subjects positive to have HAND symptomology should further be confirmed by more robust cognitive neuropsychological test batteries, computerized testing, Mini-Mental State Examination (MMSE), and grooved pegboard action fluency (63).

There was an apparent contradiction in the findings of bivariate and multivariate analysis with regards to the association of medication adherence with HAND. Poor medication adherence did not show a significant relationship with HAND in the bivariate analysis, but it did have a significant positive association in the multivariate analysis. This is most plausibly explained by statistical consideration that some of the covariates in the multivariate analysis in this study might have mediated the relationship (64).

The limitations of assessing the cellular and molecular changes in the brain morphology in clinical population makes it pressing need for identifying these aspects in preclinical population for further understanding the repercussions of combined expression of the HIV+ proteins and other factors which predict cognitive impairment.

Limitations of the study

The study failed to include any psychosocial correlates such as depression, stress, and anxiety, which could potentially influence the outcome variable. The study also could not include patients belonging to special clinical categories, those with a late diagnosis of HIV, untreated adults, and pediatric patients, associated diagnoses which make these HIV patients particularly vulnerable to severe forms of dementia (HAD) (3-4).

Moreover IHDS tool comes with limitations. Previous studies signify the use of IHDS to be suboptimal in screening cognitive impairment among HIV^{+} individuals (65). However, in present limited resource setting where full neuropsychological testing was not possible, IHDS was used as a screening tool for those individuals who are at high risk of dementia only. Any patients showing probable neurocognitive symptoms would then be referred to a neurological facility for further diagnosis.. However, IHDS is not the gold standard and further follow-up of patients by robust neuropsychological test batteries who report memory issues is needed. Moreover, future studies may need to explore the psychometric properties of the IHDS scale to determine the sensitivity and specificity scores in the Ethiopian demographics. Moreover, future assessments of the sensitivity and specificity for recall, motor and psychomotor which are the independent components of the IHDS tool is the need of the hour.

Conclusion

This study showed the point prevalence of probable HIV associated neurocognitive disorder in an Ethiopian population living with HIV as 39.3%. The use of social/recreational drugs, poor medication adherence, and 40 years of age or older were significant predictors of cognitive impairment in people living with HIV. Additional strategies to curb this epidemic would emphasize early screening for the diagnosis of dementia in the resource-poor sections of the Ethiopian community. This would further help to direct the targeted patients for further follow-up in higher psychiatric referral hospitals for assessment and management, given the positive association between people living with HIV and HAND. Furthermore, awareness campaigns about the deleterious effects of khat chewing and drinking excess alcohol on the functional effects of the brain need to be investigated.

Declarations

Ethics approval and consent to participate

This cross-sectional study was approved by the Institutional review board of the College of Medicine and Health Sciences, Mizan-Tepi University, Ethiopia. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed written consent was obtained from all participants prior to the commencement of the study.

Consent for publication

Not applicable.

Availability of data and material

The de-identified dataset used and/or analyzed during the current study is available as supplementary file.

Competing interests

The authors have read the journal's policy and have the following potential conflicts: This study was not an industry-supported study. S.R. Pandi-Perumal is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. This does not alter his adherence to all of the journal policies. Pandi-Perumal has edited several academic volumes for which he receives occasional annual royalties. He declares that he has no competing interests that might be perceived to influence the content of this article. Other remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.
The views expressed in this article are those of the authors and do not necessarily represent the official views of their affiliated institutions.

Funding

The Deanship of Scientific Research at Majmaah University funded this work under Project Number No (RGP-2019-40). There was no formal research funding received, however, later on, one of the authors received funds from through a publication support program. "The funder provided support in the form of salaries for authors to cover cost of statistical software, consultation with statistical experts, access to subscribed referencing software, access to subscribed scientific literature, and access to subscribed English editing services and software, but did not have any additional role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. The specific roles of these authors are articulated in the 'author contributions' section."

Author's Contributions

Conceived and designed the experiments: Mohammed Salahuddin, Aleem Unissa and Md Dilshad Manzar, Hamid Yimam Hassen. Performed the experiments: Mihretu Ashuro. Analyzed the data: Mohammed Salahuddin and Md Dilshad Manzar. Contributed reagents/materials/analysis tools: Majmah University. Wrote the paper: Mohammed Salahuddin, Md Dilshad Manzar, Aleem Unissa, Mohammed Aziz Mohammed, Unaise Abdul Hameed, David Warren Spence, Seithikurippu R. Pandi-Perumal. Obtained permission from institutional ethics committee: Mohammed Salahuddin. All authors reviewed and accepted the final version of the paper prior to the submission. No writing assistance was utilized in the production of this manuscript.

Acknowledgments

We are grateful to the participants of the study and the Mizan-Tepi University. The authors extend their appreciation to the Deanship of Scientific Research at Majmaah University for funding this work under Project Number No (RGP-2019-40).

Role of the Sponsor

The Somnogen Canada, Mizan Tepi University and Majmaah University had no role in the design and conduct

of the study: collection; management, analysis, and interpretation of the data, preparation, review, or approval of the manuscript, and decision to submit the manuscript for publication.

Bibliography

1. Maschke M, Kastrup O, Esser S, Ross B, Hengge U, Hufnagel A. Incidence and prevalence of neurological disorders associated with HIV since the introduction of highly active antiretroviral therapy (HAART). J Neurol Neurosurg Psychiatry. 2000;69(3):376–80.
2. Sacktor N, McDermott MP, Marder K, Schifitto G, Selnes OA, McArthur JC, et al. HIV-associated cognitive impairment before and after the advent of combination therapy. J Neurovirol. 2002;8(2):136–42.
3. McArthur, J.C; Hoover, D.R; Hoover, D.R; Bacellar, H; Miller, E.N; Cohen, B.A; Becker, J.T; Graham, N.M.H; McArthur, J.H; Selnes, O.A; Jacobson, L A. Dementia in AIDS patients: incidence and risk factors. Multicenter AIDS Cohort Study. Neurology. 1993;43(11):2245–51.
4. Zhang YL, Ouyang YB, Liu LG, Chen DX. Blood-brain barrier and neuro-AIDS. Eur Rev Med Pharmacol Sci. 2015;19(24):4927–39.
5. Paul Shapshaka, Pandjassarame Kangueane, Robert K. Fujimurae, Deborah Commins, Francesco Chiappelli, Elyse Singerh, Andrew J. Levineh, Alireza Minagari FJ, Novembrej, Charurut Somboonwita, k AN and JTS. Editorial NeuroAIDS review. spAIDS. 2011;25(2):123–41.
6. Spudich S, Gisslen M, Hagberg L, Lee E, Liegler T, Brew B, et al. Central nervous system immune activation characterizes primary human immunodeficiency virus 1 infection even in participants with minimal cerebrospinal fluid viral burden. J Infect Dis. 2011;204(5):753–60.
7. Klunder AD, Chiang MC, Dutton RA, Lee SE, Toga AW, Lopez OL, et al. Mapping cerebellar degeneration in HIV/AIDS. Neuroreport. 2008;19(17):1655–9.
8. Cole MA, Castellon SA, Perkins AC, Ureno OS, Robinet B, Reinhard MJ, et al. Relationship between psychiatric status and frontal–subcortical systems in HIV-infected individuals. J Int Neuropsychol Soc 2007. 2007;13(3):549–54.
9. Saylor D, Dickens AM, Sacktor N, Haughey N, Slusher B, Pletnikov M, et al. HIV-associated neurocognitive disorder - Pathogenesis and prospects for treatment. Nat Rev Neurol. 2016;12(4):234–48.
10. UNAIDS. UNAIDS DATA 2017 [Internet]. 2017. p. 1–248. Available from: https://www.unaids.org/sites/default/files/media_asset/20170720_Data_book_2017_en.pdf
11. Nabha L, Duong L, Timpone J. HIV-associated neurocognitive disorders: Perspective on management strategies. Drugs. 2013;73(9):893–905.
12. Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, et al. Updated research nosology for HIV-associated neurocognitive disorders. Neurology. 2007;69(18):1789–99.
13. Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: Charter Study. Neurology. 2010;75(23):2087–96.
14. Manzar MD, , Mohammed Salahuddin , Peter Sony , Tarekegn Tesfaye Maru , Seithikurippu R. Pandi-Perumal , Adam Moscovitch ASB. Sleep disturbances and memory impairment among pregnant women consuming khat: An under-recognized problem. Ann Thorac Med. 2017;12(4):247–51.

15. Simioni, Samanta; Cavassini, Matthias; Annoni, Jean-Marie; Rimbault Abraham, Aline; Bourquin, Isabelle; Schiffer, Véronique; Calmy, Alexandra; Chave, Jean-Philippe; Giacobini, Ezio; Hirschel, Bernard; Du Pasquier RA. Cognitive dysfunction in HIV patients despite long-standing suppression of viremia. AIDS. 2010;24(9):1243–50.
16. Sacktor NC, 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.
17. Singh D, Sunpath H, John S, Eastham L GR. The utility of a rapid screening tool for depression and HIV dementia amongst patients with low CD4 counts- a preliminary report. Afr J Psychiatry. 2008;11(4):282–6.
18. Bhaskaran K, Mussini C, Antinori A, Walker AS, Dorrucci M, Sabin C, et al. Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy. Ann Neurol. 2008;63(2):213–21.
19. 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.
20. Alford K, Banerjee S, Nixon E, O'brien C, Pounds O, Butler A, et al. Assessment and management of HIV-associated cognitive impairment: Experience from a multidisciplinary memory service for people living with HIV. Brain Sci. 2019;9(2):1–13.
21. Animut MD, Sorrie MB, Birhanu YW, Teshale MY. High prevalence of neurocognitive disorders observed among adult people living with HIV/ AIDS in Southern Ethiopia: A cross-sectional study. PLoS One [Internet]. 2019;14(3):1–15. Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L2001727802%0Ahttp://dx.doi.org/10.1371/journal.pone.0204636
22. 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.
23. Thai TT, Jones MK, Harris LM, Heard RC. Prevalence and Correlates of Probable HIV-Associated Dementia in HIV Outpatients in Ho Chi Minh City, Vietnam. J Int Assoc Provid AIDS Care. 2017;16(4):366–75.
24. Kinai E, Komatsu K, Sakamoto M, Taniguchi T, Nakao A, Igari H, et al. Association of age and time of disease with HIV-associated neurocognitive disorders: a Japanese nationwide multicenter study. J Neurovirol. 2017;23(6):864–74.
25. Gandhi NS, Moxley RT, Creighton J, Roosa HV, Skolasky RL, Selnes OA, et al. Comparison of scales to evaluate the progression of HIV-associated neurocognitive disorder. HIV Ther. 2010;4(3):371–9.
26. Skinner S, Adewale AJ, Deblock L, Gill MJ, Power C. Neurocognitive screening tools in HIV/AIDS: Comparative performance among patients exposed to antiretroviral therapy. HIV Med. 2009;10(4):246–52.
27. Belete T, Medfu G, Yemiyamrew E. Prevalence of HIV Associated Neurocognitive Deficit among HIV Positive People in Ethiopia: A Cross Sectional Study at Ayder Referral Hospital. Ethiop J Health Sci. 2017;27(1):67–76.
28. 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 [Internet]. 2013;17(10):e820–31. Available from: http://dx.doi.org/10.1016/j.ijid.2013.06.011
29. Oshinaike OO, Akinbami AA, Ojo OO, Ojini IF, Okubadejo UN, Danesi AM. Comparison of the minimental state examination scale and the international hiv dementia scale in assessing cognitive function in nigerian

HIV patients on antiretroviral therapy. AIDS Res Treat. 2012;2012.

30. Ogunrin. The Burden of HIV-Associated Dementia in Acquired Immunodeficiency Syndrome: A Case-Control Study. J Neurol Epidemiol. 2013;(September 2014).
31. Atashili J, Gaynes BN, Pence BW, Tayong G, Kats D, O'donnell JK, et al. Prevalence, characteristics and correlates of a positive-dementia screen in patients on antiretroviral therapy in Bamenda, Cameroon: A cross-sectional study. BMC Neurol [Internet]. 2013;13(1):1. Available from: BMC Neurology
32. Achappa B, Priyadarshni S, Madi D, Bhaskaran U, Ramapuram JT, Rao S, et al. Neurocognitive dysfunction among HIV positive patients using International HIV dementia scale. Asian J Med Sci. 2014;5(4):61–4.
33. Nakku J, Kinyanda E, Hoskins S. Prevalence and factors associated with probable HIV dementia in an African population: A cross-sectional study of an HIV/AIDS clinic population. BMC Psychiatry. 2013;13(126).
34. G M. Breaking down barriers. Science (80-). 2002;297(5584):1116–8.
35. Childs, EA, Lyles RH, Selnes EA, Chen, B, Miller EN, Cohen BA, Becker JT, Mellors J MJ. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. Neurology. 1999;52(3):607.
36. Wong MH, Robertson K, Nakasujja N, Skolasky R, Musisi S, Katabira E, et al. Frequency of and risk factors for HIV dementia in an HIV clinic in sub-Saharan Africa. Neurology. 2007;68(5):350–5.
37. Becker JT, Lopez OL, Dew MA AH. Prevalence of cognitive disorders differs as a function of age in HIV virus infection. AIDS. 2004;18(1):S11–8.
38. Nakasujja N, L Skolasky R, Musisi S, Allebeck P, Robertson K, Ronald A, et al. Depression symptoms and cognitive function among individuals with advanced HIV infection initiating HAART in Uganda. BMC Psychiatry. 2010;10.
39. Tozzi V, Balestra P, Lorenzini P, Bellagamba R, Galgani S, Corpolongo A, et al. Prevalence and risk factors for human immunodeficiency virus-associated neurocognitive impairment, 1996 to 2002: Results from an urban observational cohort. J Neurovirol. 2005;11(3):265–73.
40. Manzar MD, Salahuddin M, Maru TT, Dadi TL, Abiche MG, Abateneh DD, et al. Sleep correlates of substance use in community-dwelling Ethiopian adults. Sleep Breath. 2017;21(4):1005–11.
41. Juárez-Portilla, C, Molina-Jiménez, T, Morin J, Roldán-Roldán G, Zepeda R. Influence of Drugs on Cognitive Function. Intech. 2016;
42. Gould TJ. Addiction and cognition. Addict Sci Clin Pract. 2010;5(2):4–14.
43. Hulse GK, Lautenschlager NT, Tait RJ AO. Dementia associated with alcohol and other drug use. Int Psychogeriatr. 2005;17(Suppl 1):109–27.
44. Bigdeli I, Haft Asia MN, Miladi-Gorji H, Fadaei A. The spatial learning and memory performance in methamphetamine???sensitized and withdrawn rats. Iran J Basic Med Sci. 2015;18(3):234–9.
45. Sklar AL, Gilbertson R, Boissoneault, J, Prather R NS. DIFFERENTIAL EFFECTS OF MODERATE ALCOHOL CONSUMPTION ON PERFORMANCE AMONG OLDER AND YOUNGER ADULTS. Alcohol Clin Exp Res. 2012;36(12):2150–6.
46. Gilbertson R, Ceballos NA, Prather R, Nixon SJ. Effects of acute alcohol consumption in older and younger adults: Perceived impairment versus psychomotor performance. J Stud Alcohol Drugs. 2009;70(2):242–52.

47. Friedman TW, Robinson SR, Yelland GW. Impaired perceptual judgment at low blood alcohol concentrations. Alcohol [Internet]. 2011;45(7):711–8. Available from: http://dx.doi.org/10.1016/j.alcohol.2010.10.007
48. Dry MJ, Burns NR, Nettelbeck T, Farquharson AL, White JM. Dose-Related Effects of Alcohol on Cognitive Functioning. PLoS One. 2012;7(11):1–8.
49. Berihu BA, Asfeha GG, Welderufael AL, Debeb YG, Zelelow YB BH. Toxic effect of khat (Catha edulis) on memory: Systematic review and meta-analysis. J Neurosci Rural Pr. 2017;8(1):30–7.
50. Colzato LS, Ruiz MJ, van den Wildenberg WPM, Hommel B. Khat use is associated with impaired working memory and cognitive flexibility. PLoS One. 2011;6(6):1–6.
51. Hoffman R, Al'Absi M. Working memory and speed of information processing in chronic khat users: Preliminary findings. Eur Addict Res. 2013;19(1):1–6.
52. Yideg Yitbarek G, Mossie Ayana A, Bariso Gare M, Garedew Woldeamanuel G. Prevalence of Cognitive Impairment and Its Predictors among HIV/AIDS Patients on Antiretroviral Therapy in Jimma University Medical Center, Southwest Ethiopia. Psychiatry J. 2018;2018:1–7.
53. Wood S, Sage JR, Shuman T, Anagnostaras SG. Psychostimulants and cognition: A continuum of behavioral and cognitive activation. Pharmacol Rev. 2014;66(1):193–221.
54. Chiesi, A.; Vella, S.; Dally, LG; Pedersen, C; Danner, S.; Johnson, A. M.; Schwander, S.; Goebel, F. D.; Glauser, M.; Antunes F. Epidemiology of AIDS Dementia Complex in Europe. J Acquir Immune Defic Syndr Hum Retrovirol. 1996;11(1):39–44.
55. Goodkin K, Shapshak P, Metsch LR, McCoy CB, Crandall KA, Kumar M, et al. Cocaine abuse and HIV-1 infection: Epidemiology and neuropathogenesis. J Neuroimmunol. 1998;83(1–2):88–101.
56. Tyor WR, Middaugh LD. Do alcohol and cocaine abuse alter the course of HIV-associated dementia complex? J Leukoc Biol. 1999;65(4):475–81.
57. Nath A, Hauser KF, Wojna V, Booze RM, Maragos W, Prendergast M, Cass W TJ. Molecular basis for interactions of HIV and drugs of abuse. J Acquir Immune Defic Syndr. 2002;31(Suppl 2):S62-69.
58. Koob GF, Schulkin J. Addiction and stress: An allostatic view. Neurosci Biobehav Rev. 2019;106(September 2018):245–62.
59. Salahuddin MF, Qrareya AN, Mahdi F, Jackson D, Foster M, Vujanovic T, et al. Combined HIV-1 Tat and oxycodone activate the hypothalamic-pituitary-adrenal and -gonadal axes and promote psychomotor, affective, and cognitive dysfunction in female mice. Horm Behav [Internet]. 2019;119(November 2019):104649. Available from: https://doi.org/10.1016/j.yhbeh.2019.104649
60. Clifford DB, Ances BM. HIV-Associated Neurocognitive Disorder (HAND). Lancet Infect Dis. 2013;13(11):976–86.
61. Nightingale S, Winston A, Letendre S, Michael BD, McArthur JC, Khoo S, et al. Controversies in HIV-associated neurocognitive disorders. Lancet Neurol. 2014;13(11):1139–51.
62. Ettenhofer ML, Foley J, Castellon SA, Hinkin CH. Reciprocal prediction of medication adherence and neurocognition in HIV/AIDS. Neurology. 2010;74(15):1217–22.
63. Bloch M, Kamminga J, Jayewardene A, Bailey M, Carberry A, Vincent T, et al. A Screening Strategy for HIV-Associated Neurocognitive Disorders That Accurately Identifies Patients Requiring Neurological Review. Clin Infect Dis. 2016;63(5):687–93.

64. Baron, RM and Kenny D. The Moderator-Mediator Variable Distinction in Social Psychological Research: Conceptual, Strategic, and Statistical Considerations. J Perosnality Soc Psychol. 1986;51(6):1173–82.
65. Milanini B., Paul R., Bahemana E., Adamu Y., Kiweewa F., Owuoth J., Allen E., Polyak C., Ake J., Valcour V. AST. Limitations of the International HIV Dementia Scale in the Current Era. AIDS. 2018;32(17):2477–83.

Tables

Table 1 Participants' characteristics and their relationship with HAND in Mizan Tepi University Teaching hospital (MTUTH)

Characteristics	Mean±SD/ Frequency (percentage)	Normal (n=148) Mean±SD/ Frequency (percentage)	Cognitive Impairment (n=96) Mean±SD/ Frequency (percentage)	Chi-Square (χ2) Statistics	P-value
Age (yr)				2.64	<.05
Up to 40	207(84.84)	130(87.84)	77(80.21)		
40 and above	37(15.16)	18(12.16)	19(19.79)		
Gender				1.20	.17
Male	89(36.48)	58(39.19)	31(32.29)		
Female	155(63.52)	90(60.81)	65(67.71)		
Education				.99	.20
Primary education and lower	169(69.26)	99(66.89)	70(72.92)		
Secondary education and higher	75(30.74)	49(33.11)	26(27.08)		
Marital Status				.18	.39
Single	75(30.74)	44(29.73)	31(32.29)		
Married	169(69.26)	104(70.27)	65(67.71)		
Income				1.04	.66
Very Low	57(23.36)	33(22.30)	24(25.00)		
Low	99(40.57)	59(39.86)	40(41.67)		
Average	38(15.57)	25(16.89)	13(13.54)		
Above average	29(11.89)	19(12.84)	10(10.42)		
High	21(8.61)	12(8.11)	9(9.37)		
Residence				.38	.33
Urban	210(86.07)	129(87.16)	81(84.38)		
Rural	34(13.93)	19(12.84)	15(15.62)		
Social Drugs				57.25	<.05
No	183(75.00)	136(91.90)	47(48.96)		
Yes	61(25.00)	12(8.10)	49(51.04)		

SD: Standard deviation; Statistics: Chi-square test/ Fisher's exact test for categorical variables

Table 2 Clinical characteristics and their relationship with HAND in Mizan Tepi University Teaching hospital (MTUTH)

Characteristics	Mean±SD/ Frequency (percentage)	Normal (n=148) Mean±SD/ Frequency (percentage)	Cognitive Impairment (n=96) Mean±SD/ Frequency (percentage)	Chi-Square ($\chi 2$) Statistics	P-value
HIV Diagnosis < 6 months > 6 months	9(3.69) 235(96.31)	7(4.73) 141(95.27)	2(2.08) 94(97.92)	1.15	.24
WHO Clinical Stage Stage I Stage II Stage III Stage IV	125(51.23) 67(27.46) 46(18.85) 6(2.46)	75(50.68) 45(30.41) 24(16.22) 4(2.69)	50(52.08) 22(22.92) 22(22.92) 2(2.08)	2.69	.44
Current CD4 (cells/mm^3) <500 >500	108(44.26) 136(55.74)	62(41.90) 86(58.10)	46(47.92) 50(52.08)	.86	.21
Presence of chronic conditions/diseases* No Yes	155(63.52) 89(36.48)	95(64.19) 53(35.81)	60(62.50) 36(37.50)	.07	.45
Medication Adherence No Yes	214(87.70) 30(12.30)	126(85.14) 22(14.86)	88(91.67) 8(8.33)	2.30	.09

SD:standard deviation; Statistics: Chi-square test/ Fisher's exact test for categorical variables
*Presence of chronic conditions: Diagnosis of AIDS, Hepatitis A, Hepatitis B, Hepatitis C, Diabetes typel/II, Epilepsy, hypertension, tuberculosis, cardiovascular complications and any other chronic diseases

Table 3 Psychosocial characteristics and their relationship with HAND in Mizan Tepi University Teaching hospital (MTUTH)

Characteristics	Mean±SD/ Frequency (percentage)	Normal (n=148) Mean±SD/ Frequency (percentage)	Cognitive Impairment (n=96) Mean±SD/ Frequency (percentage)	Chi-Square (χ2) Statistics	P-value
Adherence support from family No Yes	213(87.30) 31(12.70)	128(86.49) 20(13.51)	85(88.54) 11(11.46)	.22	.40
Stigma & Discrimination No Yes	186(76.23) 58(23.77)	115(77.70) 33(22.30)	71(73.96) 25(26.04)	.45	.30

SD: standard deviation; Statistics: Chi-square test/ Fisher's exact test for categorical variables

Table 4 IHDS scores and their relationship with HAND in Mizan-Tepi University Teaching hospital (MTUTH)

Characteristics	Mean±SD/ Frequency (percentage)	Normal (n=148) Mean±SD/ Frequency (percentage)	Cognitive Impairment (n=96) Mean±SD/ Frequency (percentage)	Chi-Square (χ2) Statistics	P-value
IHDS Recall Score 1 2 3 4	3.36±0.80 8(3.28) 26 (10.66) 79(32.38) 131(53.68)	 0(0) 2(1.35) 35(23.65) 111(75.00)	 8(8.33) 24(25.00) 44(45.83) 20(20.84)	83.57	<.05
IHDS Motor Score 2 3 4	3.32±0.66 27(11.07) 113(46.31) 104 (42.62)	 3(2.03) 50(33.78) 95(64.19)	 24(25.00) 63(65.63) 9(9.37)	81.57	<.05
IHDS Psychomotor Score 2 3 4	2.90±0.72 77(31.56) 115(47.13) 52 (21.31)	 8(5.41) 91(61.49) 49 (33.10)	 69(71.88) 24(25.00) 3 (3.12)	122.54	<.05

SD: standard deviation; Statistics: Chi-square test/ Fisher's exact test for categorical variables

Table 5 Multivariate logistic regression analysis: association between dementia and predictors in HIV positive patients in Mizan Tepi University Teaching hospital (MTUTH)

Predictors	AOR(95% CI)	P-value
Age ≥ 40 years	2.82 (1.11-7.14)	<.05*
Gender Female	1.61 (0.77-3.38)	0.21
Education Primary education and lower	1.72 (0.85-3.47)	0.13
Marital Status Single	0.75 (0.38-1.49)	0.42
Social drugs Yes	13.67 (6.42-29.13)	<.01*
Medication Adherence Status Non adherent	2.99 (1.01-8.87)	<.05*
Current CD4 (<500 cells/mm^3)	0.74 (0.40-1.37)	0.34
Hospital Stay > 6 months	1.00 (1.00-1.01)	0.36
Stigma Yes	1.36 (0.63-2.93)	0.44

Figures

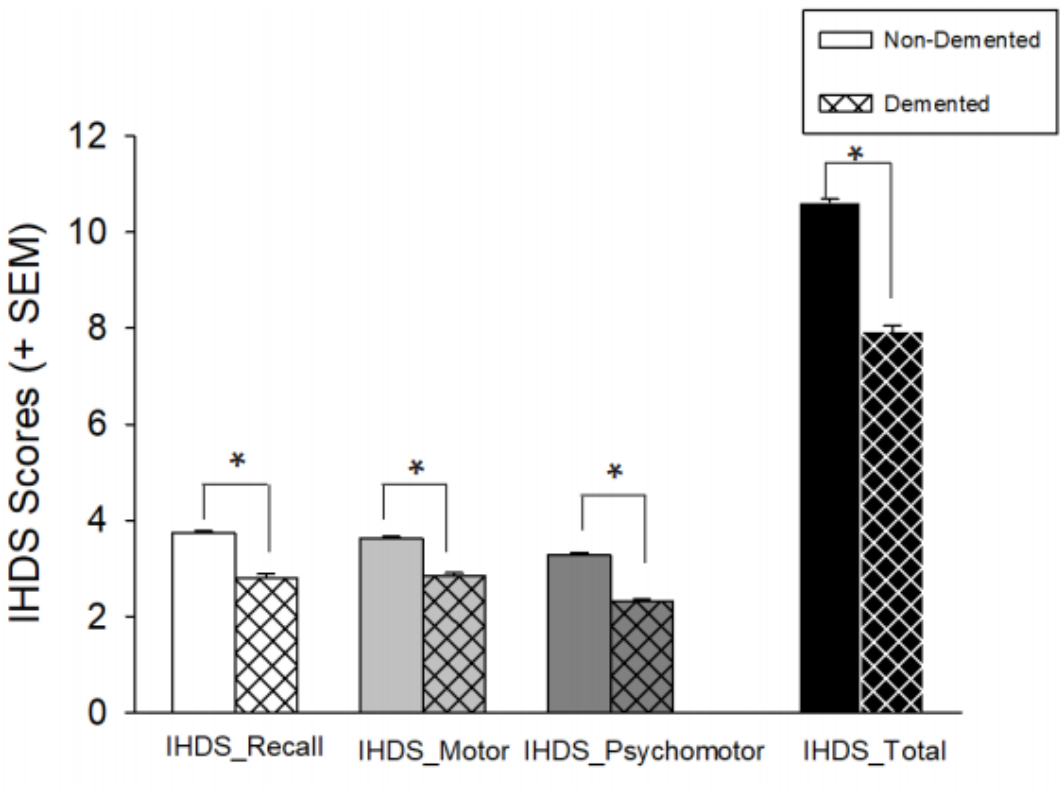

Figure 1

Independent components of IHDS scores like recall, motor and psychomotor were calculated. * indicates a main effect wherein probable HIV dementia patients differ from respective non-dementia patients. $p<0.05$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- IHDSDataSupplementary.xls
- FlowChartSampling.doc