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Research article

Assessment of neurocognitive disorders in HIV infected patients receiving combination of anti-retroviral therapy at a tertiary care hospital - An observational study

Shwetha S[1], Rebecca Elizabeth Chacko[*1], Dr. Blessy K George[2], Dr. Balakeshwa Ramaiah[3], Dr. Shirley James[4]

[1]*Intern, Doctor of Pharmacy (Pharm D intern), Karnataka College of Pharmacy.*
[2] *Pharm D, Assistant Professor at Karnataka College of Pharmacy.*
[3]*Head of Department of Pharmacy Practice, Karnataka College of Pharmacy.*
[4]*Specialist in General Medicine and HIV medicine, Bangalore Baptist Hospital.*

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***Corresponding Author:** Rebecca Elizabeth Chacko, Karnataka College of Pharmacy, Bangalore, Karnataka, India.
Phone No: +91-9741320460.
Email id: eliza.rebu@gmail.com

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Abstract

cART Therapy (combination antiretroviral therapy) has improved the live expectancy of people living with HIV (PLHIV). But HIV associated neurocognitive disorders (HAND) are still prevalent. One of the factors associated could be the cART therapy itself. The study aims to calculate the prevalence of HAND and associated risk factors in PLHIV who are on Cart therapy and to compare the efficiency of MMSE and IHDS scales in the assessment of HAND. A case-control study involving 54 PLHIV on cART therapy and 27 HIV negative controls were screened for their neurocognition by two neuropsychological tests such as MMSE and IHDS, followed by staging into Asymptomatic Neurological Impairment (ANI), Mild Neurocognitive Impairment (MND), HIV Associated Dementia (HAD) in PLHIV. Statistical analysis was done using suitable software. The overall prevalence of HAND in our study was found to be 70.37%. Prevalence estimates for specific HAND diagnoses were 57.89% ANI, 28.9% MND, and 13.1 % HAD. IHDS demonstrated good screening ability for HAND with an optimal cut-off score of 10, high sensitivity of 70% and minimal specificity. Age, male gender, low literacy, presence of comorbidities, severity of the disease, cART regimen with low CPE (CNS penetration effectiveness) score were strongly correlated. Study findings suggest that IHDS serves as a better screening tool for HAND with greater sensitivity and can facilitate further cognitive evaluation. The overall prevalence was found to be equivalent to that of the recently reported studies.

Introduction

The central nervous system (CNS) can act as a compartment for replication of HIV (Human Immunodeficiency Syndrome) independently from plasma and continuous replication can contribute to neurocognitive impairment. Therefore, it is essential that adequate concentration of antiretrovirals reach the CNS to provide neuroprotection and improve neurocognition [1].

The CNS is surrounded by the Blood - Brain Barrier (BBB), the Blood - Cerebrospinal Fluid (CSF) Barrier, and the CSF Brain Barrier [2]. HIV associated neurocognitive disorder (HAND) is neurocognitive impairment associated with HIV infection. It is an important consideration during an HIV examination as it can lead to many challenges such as employment issues and medication adherence.

In patients with HIV viral load managed by combination anti-retroviral therapy (cART), it was reported that HAND

has a 20-74% prevalence rate. A simple screening tests can be used to evaluate cognition. The Mini Mental State Examination (MMSE) is one of the most widely used dementia screening test, also for HAND screening. The international HIV dementia scale (IHDS) was published as a tool to screen patients at a high risk for HAND, without being affected by language and culture [3].

Recent publications estimate the prevalence of HAND exceeds 50%, and this rate is likely higher among older patient [4]. The use of cART therapy has significantly improved the quality of life for people living with HIV (PLHIV), however HAND continues to be encountered [5]. Anti-retroviral therapy (ART) have changed the patterns of AIDS dementia complex and have significantly reduced the incidence of a severe form of HAND [6].

The clinical severity of HAND can range from asymptomatic neurocognitive impairment (ANI) to full blown HIV-associated dementia (HAD) [7]. HAND have been shown to interfere with cART adherence, social factors, other opportunistic infections (OI) associated with HIV. The study aimed at comparing IHDS and MMSE in assessing neurocognitive impairment among PLHIV. The hypothesis is that IHDS will detect more people with HAND compared to MMSE [8].

Many factors are associated with the risk of developing HAD rather than progression through various levels of neurocognitive dysfunction [9]. Long-term cART regimens with a high degree of CPE (CNS penetration effectiveness) were not associated with significantly improved neuropsychological or neuroimaging outcomes in HIV+ adults [10]. The extent to which ART leads to a reduction in the incidence and prevalence of HIV-related cognitive impairment remains unclear [11].

This study focused on the complications that are prevalent despite the use of ART, and complications of cART attributable to medication side effects [12].

Methods

Study design and settings

A case-control study was conducted at a tertiary care hospital, with NABH accreditation and is a teaching hospital with more than 340 beds. The hospital also runs a RV clinic every Friday with at least 10 patients a day.

Sample size and sampling procedure

PLHIV visiting the RV clinic during a 3 months period (December to February 2020) were included in the study. 81 subjects were included in the study of which 54 were HIV positives (cases) and 27 were HIV negatives (control).

Inclusion/Exclusion criteria

PLHIV who were 18 years or older and able to give informed consent were included. Control group was matched against cases for age, sex, level of education, presence or absence of chronic illness and who are able to give informed consent. Those with hearing or visual impairments, impaired articulation or limb disabilities unable to perform neurocognitive tasks were excluded.

Data collection and analysis

Socio-demographics including age, gender, education qualifications, and duration of illness were noted in a predefined form. Clinical profile including WHO HIV clinical staging, presence of other chronic illnesses, patient's recent CD4 count and current therapy regimen were documented. They were administered MMSE and IHDS, followed by staging of HAND. Prevalence of HAND was calculated by using IHDS, a more accurate scale. Medication adherence of the patient was checked using the Morisky-4 item scale (MMAS). Association between HAND and CD4 counts, ART therapy, medication compliance was established and the risk factors associated with the development of HAND were assessed. The data was stored confidentially and subjected to further analysis using appropriate statistics.

Description of study instruments

The MMSE scale was originally developed to screen for dementia and delirium but is now widely used to screen cognition. It assesses five domains of cognition such as orientation, memory registration, attention and calculation, memory recall, and language. The maximum possible score is 30 on which the cut-off point for defining cognitive impairment was set at 24 [13]. In the pre-ART era, the HIV dementia scale (HDS) was evolved which was then adapted for its use in the international settings as the IHDS. It assesses memory recall, motor speed, and psychomotor speed as domains of neurocognitive functions. It consists of fixed finger tapping (measures motor speed), fixed alternating hand sequence (psychomotor speed), and remembrance of 4 items in 2 minutes (memory registration and recall). Each of these subsets are rated on a scale of 0–4 [14].

Results

Socio-demographics and clinical profile of the study participants

During a period of 6 months, 81 participants were included in the study of which 54 were PLHIV and 27 in the control group. Of the total, 31 were males and 50 were females. As for 54 participants in the PLHIV, 23 (42.59%) were males and 31 (57.40%) were female.

Table 1. Socio-demographics and clinical profile of PLHIV.

Variable	Category	Count	Percentage (%)
Age of patients (in years)	18-25	5	9.25
	26-35	3	5.55
	36-45	19	35.18
	46-55	13	24.07
	>55	14	25.92
Duration of HIV since diagnosis (in years)	<1	1	1.85
	1-5	10	18.51
	6-10	11	20.37
	>10	32	59.25
Presence of other comorbid conditions	Yes	40	74.07
	No	14	25.92
Presence of opportunistic infections	Yes	21	38.88
	No	33	61.11
Clinical staging of the disease	Stage 1	16	29.62
	Stage 2	14	25.92
	Stage 3	12	22.22
	Stage 4	12	22.22
CPE score category	</=7	35	64.81
	>7	19	35.18
Medication adherence (MMAS score)	0-2	5	9.25%
	3	8	14.81%
	4	41	75.92%

Comparison of neurocognitive performance of study participants by IHDS and the MMSE scales

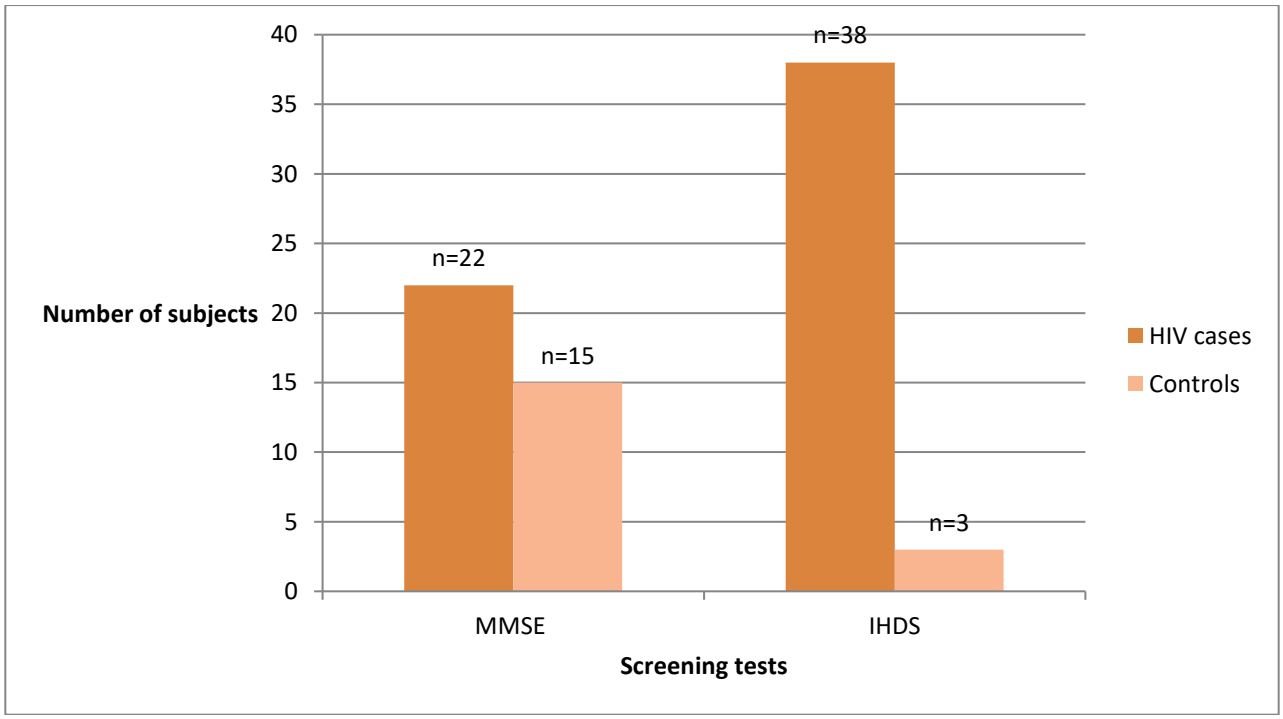

Figure 1. Frequency of neurocognitive impairment based on the MMSE and IHDS scores of cases (PLHIV) and controls (HIV negative).

Calculation of sensitivity, specificity, and accuracy of the assessment scales

Table 2. Distribution of MMSE and IHDS scores in HIV+ positive cases and HIV- negative controls.

MMSE		Diseased, N (%)		Not disease, N (%)	Total
Positives	True positive (a)	22 (40.74%)	False positive (b)	15 (55.55%)	37
Negatives	False negative (c)	32 (59.25%)	True negative (d)	12 (44.44%)	44
	Total	54	Total	27	
IHDS		Diseased, N (%)		Not disease, N (%)	Total
Positives	True positive (a)	38 (70.37%)	False positive (b)	24 (88.8%)	62
Negatives	False negative (c)	16 (29.62%)	True negative (d)	3 (11.11%)	19
	Total	54	Total	27	

Assessment of the frequency of association of HAND with other factors

Out of the 54 participants, 38 (70.37%) screened positive for HIV associated neurocognitive deficits.

Table 3. Socio - demographics and clinical characteristics of HAND subjects.

Variable	Category	HIV associated neurocognitive disorder			
		Positive screening		Negative screening	
		N	%	N	%
Age of patients (in years)	18-25	3	60	2	40
	26-35	1	33.33	2	66.66
	36-45	11	57.89	8	42.10
	46-55	9	69.23	4	30.76
	>55	14	100	0	0
Duration of HIV since diagnosis (in years)	1-5	8	80	2	20
	6-10	9	81.81	2	18.18
	>10	21	65.62	11	34.37
Presence of other comorbid conditions	Yes	29	72.5	11	27.5
	No	9	64.28	5	35.71
Presence of opportunistic infections	Yes	14	66.66	7	33.33
	No	24	72.72	9	27.27
Clinical staging of the disease	Stage 1	10	62.5	6	37.5
	Stage 2	11	78.57	3	21.42
	Stage 3	6	50	6	50
	Stage 4	11	91.66	1	8.33
CPE score category	</=7	25	71.4	10	28.57
	>7	7	36.84	12	63.15
Medication adherence (MMAS score)	0-2	5	100	0	0
	3	6	75	2	25
	4	27	65.85	14	34.14

Age, male gender, low literacy level, longer duration of illness, presence of other comorbidities and opportunistic infections, severe stage of HIV (stage 4), medication non-adherence were positively associated with HAND and thus older HIV patients are at high risk of developing neurocognitive impairment.

The association of an individual ARV drug within a particular combination was analyzed. The single most common ART used was Lamivudine (3TC) with 34 (89.47%) of HAND cases being on a 3TC containing combination. So, Lamivudine was significantly associated with neurocognitive impairment then followed by Efavirenz and Tenofovir.

The most common cART regimen used included TDF/3TC/EFV (50%) and AZT/3TC/NVP (13.15%). Use of TDF/3TC/EFV was strongly associated with HAND, because of its low CPE score and the majority of patients out on this regimen.

Table 4. Association between CPE score category of ARV drugs and HAND.

CPE score category	ART type	HIV associated neurocognitive disorder			
		Positive screening		Negative screening	
		N	%	N	%
1	TDF	23	67.64	11	32.35
	Ritonavir	1	100	0	0
2	3TC	34	69.56	14	30.43
	D4T	5	50	5	50
	ATV	1	100	0	0
3	ABC	3	100	0	0
	FTC	3	50	3	50
	Darunavir	1	100	0	0
	EFV	25	75.75	8	24.24
4	AZT or ZDV	5	83.33	1	16.66
	NVP	6	54.54	5	45.45

Table 5. Association between the cART regimen and HAND.

ART regimen	CPE score	CPE score category	Number of HAND patients on this regimen (N)	Percentage (%)
3TC + D4T + NVP	8	Medium	3	7.89
TDF + 3TC + EFV	6	Low	19	50
TDF + FTC + EFV	7	Low	3	7.89
AZT + 3TC + NVP	10	High	5	13.15
Darunavir-r + DOL	6	Low	1	2.63
ABC+ 3TC + DOL	8	Medium	3	7.89
TDF + 3TC + D4T	5	Low	1	2.63
AZT + 3TC + EFV	9	Medium	1	2.63
3TC + D4T + EFV	7	Low	2	5.26

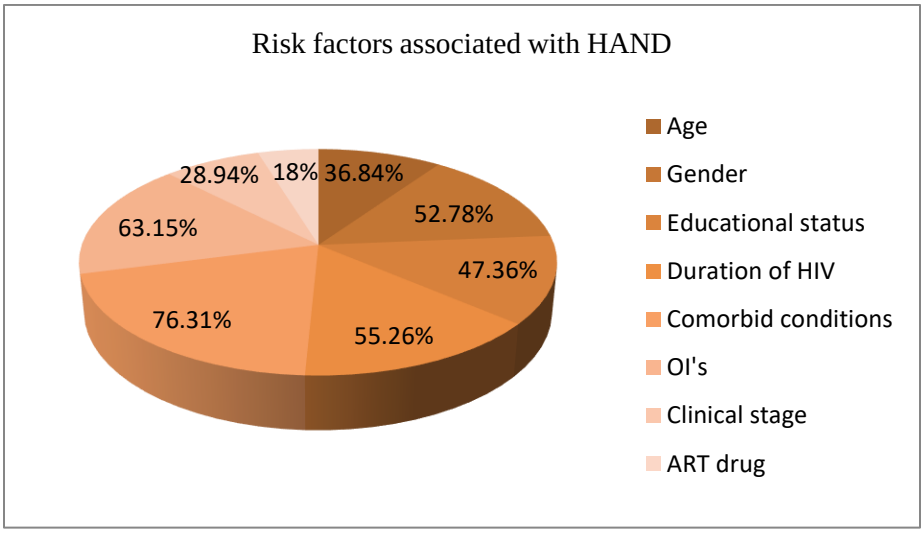

Figure 2. Figure showing the association between HAND and other possible risk factors.

Discussion

The main aim of the study was to calculate the period prevalence of HAND by assessing the neurocognition in PLHIV using MMSE and IHDS scales at a tertiary care hospital, Bangalore. Knowing the prevalence of HAND is important as it is associated with medication non-adherence, decreased quality of life, and increased risk of mortality in PLHIV. This helps to facilitate a better understanding of the CPE of all the available ARV drugs and thus the management of HAND would be easier. Use of ART regimens with a high CPE score may be effective against CNS complications including HAND by direct inhibition virus replication in CNS and thus improve overall survival

and reduce the incidence of CNS disease that may manifest as HAND [15-17].

Though the introduction of cART therapy has significantly improved the survival rate of HIV subjects by lowering the viral burden, raising CD4 cell counts, reducing OIs or improving the overall health-related quality of life, HAND is still prevalent in cART era and hence remains the major public health concern [3, 6].

Many factors were found to contribute to the disease severity such as age, gender, socio-economic status, duration of illness, presence of comorbidities, OIs, medication non-compliance, and cART therapy. Of all, direct neurotoxic effects of cART are an important consideration, which can further lead to challenges in performing the activities of daily living [6, 18]. Hence here comes the role of a clinical pharmacist to intervene the therapy and prevent adverse effects related to ART drugs. HAND causes sub-cortical dementia and the MMSE is most useful in detecting cortical dementia [19].

Our study revealed that IHDS at a cut-off value of </=10 was a better tool for screening of HAND compared to MMSE, but with less specificity. Consequently, the main finding of our study is that IHDS significantly detects a greater portion of HAND when compared to MMSE.The overall period prevalence of HAND in our study was found to be 70.3% of which 57.89% representing ANI, 28.9% MND, and 13.1% HAD. The incidence of ANI was found to be higher and it is characterized by mild impairment in two or more of the domains with diminished everyday functioning. HAD, being the chronic cognitive deterioration was found to be rare in the cART era.

IHDS was found to have better sensitivity with less specificity compared to MMSE and thus is an accurate tool for the screening of HAND. Thus, the prevalence of HAND is calculated using the number of patients who screened positive for neurocognitive impairment with the IHDS scale.

In determining the frequency of association between HAND and many other factors, the following findings were suggested:

Studies have not found gender to be a significant predictor of cognitive impairment in PLHIV [20], in contrast to other studies, a larger number of men were found to be abnormal in our study. Greater age was found to be consistently associated with declining cognitive performance. The most important intervention in managing cognitive impairment remains to verify that patients are on ART therapy and are adherent to treatment [21]. Low literacy rate was found to be associated with worsened neurocognitive performance, however, higher education may be protective [22, 23, 15]. Existence of HIV associated OIs and other comorbidities such as diabetes, obesity, anxiety, depression, other psychiatric and cardiovascular disorders, co-infection with the hepatitis C virus would increase the risk of HAND [24]. Greater proportions of HAND was associated with increased severity of HIV/AIDS based on the WHO clinical staging. It is important to focus on the importance of CNS-penetrating ARV regimens to target active replication of the virus and thus improve cognitive outcomes [25]. It is thus important to be cautious about the utility of the CPE score in predicting outcomes or modifying approaches to ART therapy [21]. The use of cART regimens with high CPE scores may be protective against HAND, other CNS complications and thereby tend to improve the overall survival by directly inhibiting viral replication in the CNS [17, 18]. Considering individual ARV drugs, Lamivudine was found to have a stronger association with HAND then followed by Efavirenz and Tenofovir [15]. However, the use of the Tenofovir/Lamivudine/Efavirenz regimen, which has a low CPE score 6, was greatly linked with HAND.

Limitations

The study has several limitations: it was a single-center study with a relatively small sample size, which resulted in limited power to determine prevalence rate and also a statistically significant association of HAND with various factors. The initial sample size was 50 subjects, which was reduced due to the Covid pandemic and the subsequent lockdown in India. Lack of powerful comprehensive gold standard tools such as a neuropsychological battery to compare with other screening tools such as MMSE and IHDS limits the study from ascertaining the exact sensitivity and specificity of our screening tools. Few factors such as economic status, substance abuse was not correlated with the neurocognitive performance from the used screening tools.

Conclusion

Our study reports that neurocognitive disorders are highly prevalent among PLHIV, even while having a larger number of management strategies including cART therapy. Hence, regular screening for HAND would be an interesting approach to detect early asymptomatic neurological infection and thus prevent a decline in neurocognition trend or development of HIV associated dementia.

IHDS has been demonstrated to be an inexpensive, rapid, easy to administer and more accurate tool for the screening of HAND.

The study also highlights the link between multiple factors such as age, gender, literacy level, duration of illness, other comorbidities, opportunistic infections, medication adherence, ART regimen, and their association with HAND. However, the optimization of individual ART regimen would be a better approach for the prevention of HAND.

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Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this research article.

Authors Contribution

All the authors have contributed equally in designing, drafting the manuscript as per the journal submission format. All authors read and approved the final manuscript.

References

1. Ene L, Duiculescu D, Ruta SM. How much do antiretroviral drugs penetrate into the central nervous system? Journal of medicine and life. 2011; 4(4):432.
2. Gisslen M, Hagberg L. Antiretroviral treatment of central nervous system HIV-1 infection: a review. HIV medicine. 2001; 2(2):97-104.
3. Kami-Onaga K, Tateyama M, Kinjo T, Parrott G, Tominaga D, Takahashi-Nakazato A, Nakamura H, Tasato D, Miyagi K, Maeda S, Arae H. Comparison of two screening tests for HIV-Associated Neurocognitive Disorder suspected Japanese patients with respect to cART usage. 2018; 13(6):e0199106.
4. Valcour V, Paul R, Chiao S, Wendelken LA, Miller B. Screening for cognitive impairment in human immunodeficiency virus. Clinical Infectious Diseases. 2011; 53(8):836-42.
5. Wagner GA, Chaillon A, Siqi LI, Franklin Jr DR, Caballero G, Pond SL, Vaida F, Heaton RK, Letendre SL, Grant I, Richman DD. HIV-associated neurocognitive disorder is associated with HIV-1 dual infection. AIDS (London, England). 2016; 30(17):2591.
6. Heaton RK, Clifford DB, Franklin DR, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. Neurology. 2010; 75(23):2087-96.
7. McRae M. HIV and viral protein effects on the blood brain barrier. Tissue barriers. 2016; 4(1):e1143543.
8. Nyundo AA, Ndetei DM, Othieno CJ, Mathai AM. The performance of International HIV dementia Scale (IHDS) versus Mini Mental Status Examition Scale (MMSE) in assessment of HIV-associated Neurocognitive Disorders (HAND) among HIV-Infected Tanzanian adults: a Case-Control Study.
9. Gandhi NS, Moxley RT, Creighton J, Roosa HV, Skolasky RL, Selnes OA, McArthur J, Sacktor N. Comparison of scales to evaluate the progression of HIV-associated neurocognitive disorder. HIV therapy. 2010; 4(3):371-9.
10. Baker LM, Paul RH, Heaps-Woodruff JM, Chang JY, Ortega M, Margolin Z et al. The effect of central nervous system penetration effectiveness of highly active antiretroviral therapy on neuropsychological performance and neuroimaging in HIV infected individuals. Journal of Neuroimmune Pharmacology. 2015; 10(3):487-92.
11. Robertson KR, Smurzynski M, Parsons TD, Wu K, Bosch RJ, Wu J, McArthur JC, Collier AC, Evans SR, Ellis RJ. The prevalence and incidence of neurocognitive impairment in the HAART era. Aids. 2007; 21(14):1915-21.
12. Kranick SM, Nath A. Neurologic complications of HIV-1 infection and its treatment in the era of antiretroviral therapy. CONTINUUM: Lifelong Learning in Neurology. 2012; 18(6 Infectious Disease):1319.
13. Comparison of the Minimental State Examination Scale and the International HIV Dementia Scale in Assessing Cognitive Function in Nigerian HIV Patients on Antiretroviral Therapy. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3463159/
14. Hu X, Zhou Y, Long J, Feng Q, Wang R, Su L, *et al.* Diagnostic accuracy of the International HIV Dementia Scale and HIV Dementia Scale: A meta-analysis. Exp Ther Med. 2012; 4(4):665–8.
15. Nyundo AA, Ndetei DM, Othieno CJ, Mathai AM. Neurocognitive correlates of the use of combined Antiretroviral Therapy among HIV-infected adults attending care and treatment center at Muhimbili National Hospital, Dar es Salaam, Tanzania: An analytical cross-sectional study. Tanzania Med J. 2016; 27(1):114–32. Available from: http://tmj.or.tz/index.php/tmj/article/view/201
16. Liner KJ, Ro MJ, Robertson KR. HIV, antiretroviral therapies, and the brain. Vol. 7, Current HIV/AIDS Reports. Curr HIV/AIDS Rep; 2010; 85–91.
17. Garvey L, Winston A, Walsh J, Post F, Porter K, Gazzard B, *et al.* Antiretroviral therapy CNS penetration and HIV-1-associated CNS disease. Neurology. 2011; 76(8):693–700.
18. Mupawose A. The effects of highly active antiretroviral therapy on the cognitive-linguistic abilities of adults living with HIV and AIDS in south africa a thesis submitted in fulfilment of the requirements for the degree of doctor of philosophy, in the faculty of humanities, university of the witwatersrand. 2012.
19. Valcour VG. Evaluating cognitive impairment in the clinical setting: Practical screening and Assessment tools. Top Antivir Med. 2011;19(5):175–80.
20. Pereda M, Ayuso-Mateos JL, Gómez Del Barrio A, Echevarria S, Farinas MC, García Palomo D, *et al.* Factors associated with neuropsychological performance in HIV-seropositive subjects without AIDS. Psychol Med. 2000; 30(1):205–17.
21. Valcour VG. HIV, aging, and cognition: Emerging issues. Top Antivir Med. 2013; 21(3):119–23.
22. Kabuba N, Anitha Menon J, Franklin DR, Lydersen S, Heaton RK, Hestad KA. Effect of age and level of education on neurocognitive impairment in HIV Positive Zambian adults. Neuropsychology. 2018; 32(5):519–28.
23. Ritchie SJ, Bates TC, Deary IJ. Is education associated with improvements in general cognitive ability, or in specific skills? Dev Psychol. 2015; 51(5):573–82.
24. Sanmarti M, Ibáñez L, Huertas S, Badenes D, Dalmau D, Slevin M, *et al.* HIV-associated neurocognitive disorders. J Mol Psychiatry. 2014; 2(1):2.
25. Liner KJ, Hall CD, Robertson KR. Effects of antiretroviral therapy on cognitive impairment. Vol. 5, Current HIV/AIDS Reports. Curr HIV/AIDS Rep; 2008; 64–71.