



Association of HIV Associated Neurocognitive Disorder with Mini-Mental State Examination Score – A Cross-Sectional Study

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Abstract: Even in the era of ART (Antiretroviral Therapy), HIV Associated Neurocognitive Disorder (HAND) is still prevalent. It may have been associated in some way with CD4 counts, disease duration, and the duration of treatments. This cross-sectional study was conducted at a tertiary care hospital in Raipur, Chhattisgarh, India. To determine the association of HIV-associated neurocognitive disorder with mini-mental state examination score (MMSES) and its correlation with CD4 counts, disease duration, and art regimen. Patients who meet the inclusion criteria are seen at the ART Centre, in the clinical OPD outpatient department, or hospitalized in the medical ward throughout the year from November 2021 to October 2022. People living with HIV (PLWH) underwent screening-validated methods to diagnose HIV-associated neurocognitive disorders (HAND) in central India. This study includes 92 HIV patients in total. The mean age of study subjects was 37.5 ± 12.76 years. 60.87% were male, and 39.13% were female study subjects. The mean mental score and CD4 counts among the study subjects were 23.29 ± 0.30 with [CI: 22.68-23.90] and 346.04 ± 22.29 with [301.75-390.33], respectively, and the prevalence of HAND was 52.17%. Between HAND, CD4 counts, and HIV disease duration, a significant correlation was found. This study concludes that the MMSES is a test for detecting HIV-associated neurocognitive disorder and the correlation between HAND and CD4 counts and HIV disease duration. Disease. However, the correlation between HAND and the duration of the ART regimen was insignificant.

Keywords: CD4 Counts, HIV-Associated Neurocognitive Disorders (HAND), art (Expand the abbreviation), Mild Neurocognitive Disorder (MND), HIV-Associated Dementia (HAD), Anti-Retroviral Therapy (ART)

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Date of Receiving	25 April, 2023
Date of Revision	14 August, 2023
Date of Acceptance	21 August, 2023
Date of Publishing	2 October, 2023

Funding This research did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors

Citation Dr. Gaurav Sharma, Dr. S. Chandrawanshi, Dr. D.P. Lakra, and Dr. Surbhi Dubey, Association of HIV Associated Neurocognitive Disorder with Mini-Mental State Examination Score – A Cross-Sectional Study. (2023). Int J Pharm Sci. 14(4), p18-24 <http://dx.doi.org/10.22376/ijpbs.2023.14.4.p18-24>

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Int J Pharma Bio Sci., Volume 14., No 4 (October) 2023, pp p18-24



1. INTRODUCTION

The pandemic of the human immunodeficiency virus (HIV), first recognized in 1981, has engulfed the entire planet in less than four decades. The number of infected individuals was as high as 37.9 million, by the end of 2018, according to the Joint United Nations Programme on HIV and AIDS (UNAIDS) [Reference]. Most (95%) of these people living with HIV (PLH) reside in low- and middle-income categories.¹ With the advent of modern medicine and combination antiretroviral therapy (cART), we see a constant decline in morbidity and mortality. According to the United Nations Programme on HIV and AIDS (UNAIDS) estimate, approximately 36.9 million people were living with HIV/AIDS (Acquired Immunodeficiency Virus) in 2015.² India has the third highest number of people living with HIV disease in the world.¹ There has been a steady decline in number since 2007, with numbers coming down from 2.23 million to 2.12 million in 2015.³ HIV virus has a direct effect on the cellular immune system through depletion of infected CD4 lymphocytes and has broad effects on the nervous system, including evidence for direct pathology in the brain, spinal cord, and peripheral nerves.⁴ Neurological involvement of HIV remains an important problem since antiretroviral therapy (ART) has not fully accomplished full protection of the nervous system. HIV-Associated Neurocognitive Disorders (HAND) are neurological disorders associated with HIV infection and AIDS. They have a highly variable clinical course and a spectrum of signs and symptoms, ranging from subtle cognitive and motor impairments to profound dementia.⁵ A consensus research definition of HIV-associated neurocognitive disorder includes the sub-classifications of Asymptomatic Neurocognitive Impairment (ANI), HIV-associated Mild Neurocognitive Disorder (MND), and HIV-Associated Dementia (HAD).⁶ HAND, even in its mild form, is associated with less ability to perform the most complex daily tasks, worse quality of life, difficulty obtaining employment, and shorter survival.⁷ In the study of individuals with longstanding a viremia, an overall prevalence of cognitive complaints was 27%. The prevalence of HAND was 84% among patients with cognitive complaints and 64% in those without. ANI was present in 24%, MND 52%, and HAD 8%.⁸ HAND confers an increased risk for early mortality, independent of medical predictors, and often interferes significantly with cognitively demanding activities of daily living such as employment, medication management, and driving.⁹ The gold standard for HAND assessment is a detailed battery of neuropsychological tests. However, they are seldom available to patients in busy settings.¹⁰ Various tools have been developed to help assess neurocognitive dysfunction. Various methods can test neurocognition, and the Mini-Mental State Examination (2S) and Modified Mini-Mental State Examination (3MS) are two methods.¹¹ Among Mini-Mental State Examination and Modified Mini-Mental State Examination, the Modified Mini-Mental State Examination is an expanded version, better at predicting functional outcomes in one study. Reference. Therefore, the study sought to determine the incidence of neurocognitive impairment using the Mini-Mental State Examination score and its correlation with CD4 counts, Duration of disease, and Duration of ART regimen. We aim to determine the Association of Neurocognitive disorder with the Mini-Mental State Examination Score and its correlation with CD4 counts, disease duration, and ART regimen in PLHA patients.

2. MATERIALS & METHODS

2.1 Study design

A hospital-based cross-sectional study was conducted in the Department of General Medicine at Tertiary Care Hospital from November 2021 to October 2022. Subjects enrolled in this study were patients attending ART Centre, Medicine OPD, and patients admitted in the medicine ward whose ages between 18 to 50 years were included after fulfilling the

2.2 Sample Size

The total sample size of 92 was calculated on HIV-associated neurocognitive dysfunction (HAND), and proportion (0.3904) was considered with a 95% confidence interval and 10% margin of error.

2.3 Ethical Statement

The study was conducted after approval by the institutional ethical committee (No./MC/Ethics/2022/49 dated 14/03/2022), and written informed consent was obtained from the participating patients.

2.4 Study population:

About 92 HIV-positive patients attending medicine OPD, ART center and admitted to medicine wards of Dr. Bhimrao Ambedkar Memorial Hospital, Raipur, Chhattisgarh, India, were screened for the study. Those who fulfilled the inclusion criteria were enrolled in this study. Major opportunistic infections in the past 3 years and neurological histories like hemorrhagic or ischemic stroke, tubercular meningitis, head injury, epilepsy, or seizure disorder were excluded. Also, mental retardation, depression, and other psychiatric illnesses were excluded.

2.5 Inclusion Criteria

Detailed demographic data were collected concerning age, sex, present complaints, associated symptoms, duration of HIV disease regimen of ART, and documented CD4 count were noted. History of alcoholism, comorbid conditions, and systemic disease were evaluated, and general examination was performed, like pallor, icterus, cyanosis clubbing, lymphadenopathy, and edema. Blood pressure, pulse, and temperature were recorded in all patients.

1. HIV-positive patients attending Medicine O.P.D, A.R.T Centre and admitted to medicine wards.

2. Patients of Age 18-50 years.

(Patients of more than 50 years would have a cognitive impairment, which would be difficult to differentiate from HIV Associated Neurocognitive disorder).

2.6 Exclusion criteria

1. Major Opportunistic infection in the past 3 years.
2. The patient is not giving consent for the study. Patients with a history of any Neurological insults like
 - a. Hemorrhagic / Ischemic stroke.
 - b. Tubercular Meningitis.
 - c. Head injury.
 - d. Epilepsy / Seizure disorder.
3. Age > 50 years and < 18 years.

4. Patients with Mental retardation.
5. Depression and other psychiatric illnesses like Generalised Anxiety Disorder, Mania, and Bipolar Disorder.

2.7 History

In all study subjects, detailed demographic data concerning name, age, sex, detailed address, contact number, present complaints, associated symptoms, duration of HIV disease, regimen of ART, and documented CD4 counts were noted. History of alcoholism, comorbid conditions, and systemic diseases was evaluated.

2.8 General Examination

A general examination was performed in all patients, and

2.11 HAND Classification⁷

- HIV – associated asymptomatic neurocognitive impairment (ANI)
- Acquired impairment in cognitive functioning involving at least two ability domains
- Cognitive impairment does not interfere with daily functioning
- Criteria for dementia or delirium are not present
- No evidence for an alternative etiology for the ANI
- HIV-associated mild neurocognitive disorder (MND)
- Acquired impairment in cognitive functioning involving at least two ability domains
- Cognitive impairment produces at least mild interference in functioning at work, at home, or in social activities.
- Criteria for dementia or delirium are not present
- No evidence for an alternative etiology for the ANI
- HIV-associated dementia (HAD)
- Acquired impairment in cognitive functioning involving at least two ability domains
- Marked interference in function (e.g., inability to work or manage affairs, etc.)
- Criteria for delirium are not present (clear sensorium)
- No evidence of another cause for the dementia

2.12 Neuropsychological evaluation

The Mini-mental state examination is used to measure cognitive impairment in older adults. According to Folstein et al.,¹² it can be used to screen for cognitive impairment, estimate the severity of cognitive impairment at a given time, follow the course of cognitive changes in an individual over time, and document an individual's response to treatment. The Mini-mental state examination is scored on a scale of 0-30, with scores > 25 interpreted as normal cognitive status.

- Severe cognitive impairment: 0-17
- Mild cognitive impairment: 18-23
- No cognitive impairment: 24-30

pallor, icterus, cyanosis, clubbing, lymphadenopathy, and edema were seen. Blood pressure, pulse, and temperature were recorded in all patients.

2.9 Systemic Examination:

The cardiovascular system and G gastrointestinal system were evaluated. Detailed C central nervous system was evaluated for consciousness and orientation to time, place, and person.

2.10 Laboratory Investigations

Routine blood investigations like blood sugar, Complete blood counts, Liver function tests, Renal function tests, and CD4 counts were done in all selected patients.

Interpretation of the mental status examination must consider the patient's native language, education level¹³, and culture, as these factors can affect performance.¹⁴

3. STATISTICAL ANALYSIS

Statistical analysis will be performed by the Graph pad software for Windows, version 10.0. Continuous variables will be presented as mean $\pm$ SD, and categorical variables will be absolute numbers and percentages. Data will be checked for normality before statistical analysis. Comparison of the mean for normally distributed continuous variables will be compared using the unpaired t-test. In contrast, the Mann-Whitney U test will be used for those variables that are not normally distributed. Categorical variables will be analyzed using the Chi-Square or Fisher's exact tests.

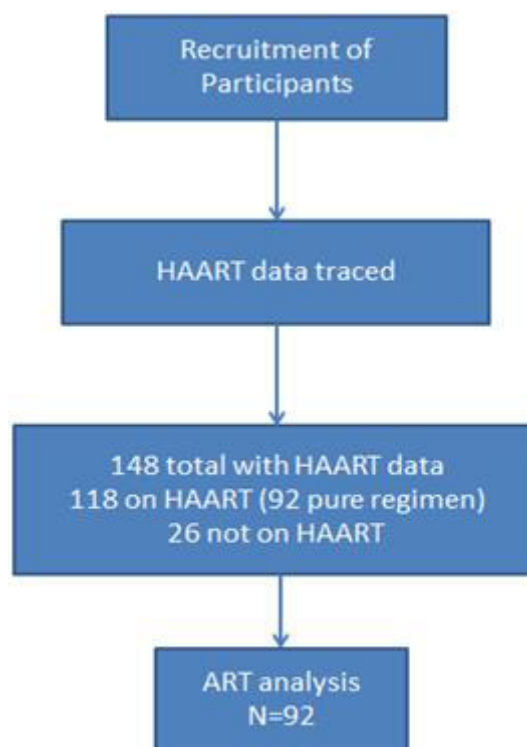


Fig. 1. Flow diagram of the study process.

4. RESULTS

The mean age of study subjects was 37.5 ± 12.76 years. Among the study subjects, 56 (60.87%) were male, and 36 (39.13 %) were females. Among study subjects 53 (57.61%) were on TLE-TLD (Tenofovir, lamivudine, efavirenz - Tenofovir, lamivudine, dolutegravir) regimen and 30 (42.39%) were on TLD (Tenofovir, lamivudine, dolutegravir) regimen.

The mean hemoglobin was 12.01 ± 0.14 (Mean $\pm$ SD), WBC count was 6.62 ± 0.18 , Urea was 19.08 ± 0.40 , Creatinine was 0.67 ± 0.02 . The majority of 42 (45.65%) had CD4 counts between 200-500, 29 (31.52%) had CD4 counts <200, and 21 (22.83%) had CD4 counts >500. Out of 92 patients, 1 had diabetes, 14 had HTN, and 13 had both diabetes & HTN. (Table I)

Table I: Baseline characteristics of the study subjects	
Characteristics	No. of patients (n=92)
Age (year)	37.5 ± 12.76
Gender (% male)	60.87%
ART regimen (TLD count)	39
ART regimen (TLE-TLD count)	53
Duration of ART regimen (4-6 years)	34
Haemoglobin (gm/dl)	12.01 ± 0.14
WBC Count ($\times 10^9/L$)	6.62 ± 0.18
Urea (mg/dl)	19.08 ± 0.40
Creatinine (mg/dl)	0.67 ± 0.02
CD4 Count	
<200	29
200-500	42
>500	21
Comorbidity	
DM	01
HTN	14
DM & HTN	13

Table 2: Association between CD4 counts and HAND grade in study subjects (N-92)					
CD4 counts	HAND grade			Total	P value
	Mild	Severe	Normal		
<200	23	6	0	29	p<0.01
	54.8%	100.0%	0.0%	31.5%	
200-500	19	0	23	42	
	45.2%	0.0%	52.3%	45.7%	
>500	0	0	21	21	
	0.0%	0.0%	47.7%	22.8%	
Total	42	6	44	92	
	100.0%	100.0%	100.0%	100.0%	

Among severe HAND grades (as per MMSE score) out of 6 cases, all 6 cases had CD4 count <200. Among mild HAND grades, out of 42 cases, 23 (54.8%) had a CD4 count <200, and 19 (45.2%) cases had a CD4 count between 200-500. Association was tested using the chi-square test, and it was found statistically significant ($P<0.1$). (Table 2)

Table 3: Association between MMSE and HAND grade in study subjects (N-92)						
Hand grade	No of cases	Mean MMSE score	Std. Deviation	95% Confidence Interval for Mean		P value
				Lower Bound	Upper Bound	
Mild	42	21.48	1.174	21.11	21.84	p<0.01
Severe	6	16.83	0.408	16.40	17.26	
Normal	44	25.91	1.030	25.60	26.22	
Total	92	23.29	2.952	22.68	23.90	

The mean difference of MMSE score per HAND grade was studied using the ANOVA test. The mean MMSE score in severe grade cases was 16.83; in mild cases, it was 21.48; and in normal cases was 25.91. The difference was found to be statistically significant ($p<0.01$). (Table 3)

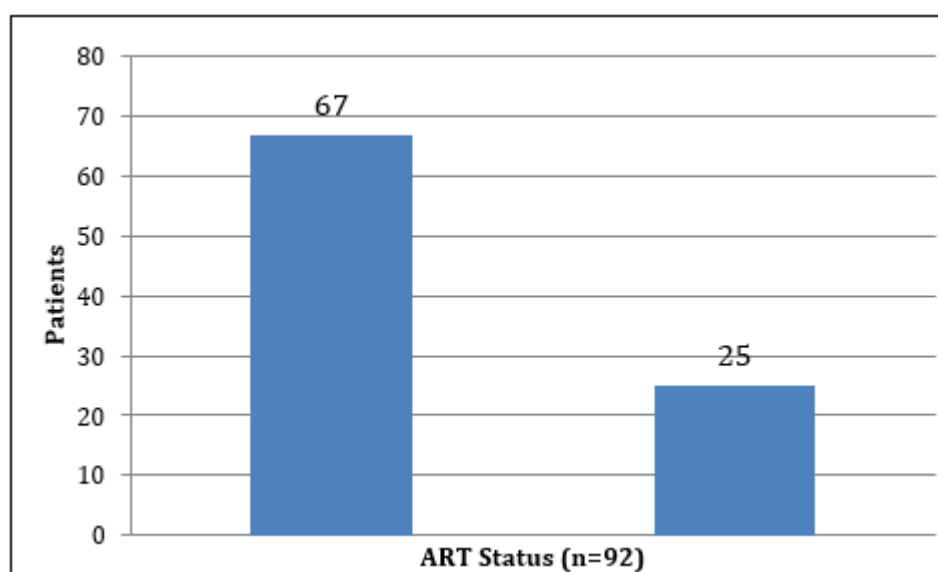


Fig.2. Cognitive response of antiretroviral therapy (ART) status.

The above figure shows that 67 (72.8%) maintained or improved cognitive function among the ART study participants, whereas 25 (27.7%) worsened.

5. DISCUSSION

The Pandemic of Human immunodeficiency virus (HIV), first recognized in 1981, has engulfed the entire planet in less than four decades. With the advent of modern medicine and combination antiretroviral therapy (cART), we see a constant decline in morbidity and mortality. However, HIV Associated Neurocognitive disorders (HAND) have a highly variable clinical course. There is a limited panel of investigations to

diagnose HAND. In the present study, the mean mental score among study subjects was 23.29 ± 0.30 , and the prevalence of HAND was 52.17%. Of that, 45.65% were in mild grade as per HAND criteria of MMSE, and 6.52% were in severe grade as per HAND criteria. Similarly, Chan LG et al. (2012)¹⁵ studied the HIV-associated neurocognitive disorders (HAND) in a South Asian population - contextual application of the 2007 criteria. The prevalence of HAND was 22.7%, of which 15.9% had an asymptomatic

neurocognitive impairment, 5.3% had mild neurocognitive disorder, and 1.5% had HIV-associated dementia. Also, Oshinaike OO et al. (2012)¹⁶ studied the comparison of the Mini-Mental State Examination Scale and the International HIV Dementia Scale in Assessing Cognitive Function in Nigerian HIV Patients on Antiretroviral Therapy. They reported that the Mean MMSE score of cases was 27.7 ± 1.8 . Achappa B et al. (2014)¹⁷ studied the Neurocognitive dysfunction among HIV-positive patients using the International HIV Dementia scale. Of the 101 patients studied, 91 (90.1%) had HAND. Kelly CM et al. (2014)¹⁸ studied HIV-associated neurocognitive disorders (HAND) in Malawian adults and the effect on adherence to combination antiretroviral therapy. They reported that symptomatic neurocognitive impairment was present in 15% (12% had mild neurocognitive disorder, and 3% had HIV-associated dementia. Balaini N et al. (2017)¹⁹ studied HIV-associated neurocognitive dysfunction and its association with CD4 count in HIV-positive patients in a hospital-based study. HIV-associated neurocognitive dysfunction (HAND) was found in 39.04% of patients. Mohamed, A.A. et al. (2020)²⁰ studied HIV-associated neurocognitive disorders at Moi Teaching and referral hospital, Eldoret, Kenya. The mean age of the study participants was 40.2 years. The overall prevalence of HAND was (81.1%), mild HAND was 78.6%, and severe HAND was 2.5%. The present study's mean CD4 count among study subjects was 346.04 ± 22.29 . The majority, 45.65%, had a CD4 count between 200-500, 31.52% had a CD4 count of less than 200, and 22.83% had a CD4 count >500. Similarly, Kelly CM et al. (2014)¹⁸ study the HIV-associated neurocognitive disorders (HAND) in Malawian adults and the effect on adherence to combination antiretroviral therapy. In this study, the median CD4 count was 323.5. Balaini N et al. (2017)¹⁹ studied HIV-associated neurocognitive dysfunction and its association with CD4 count in HIV positive patients-a hospital-based study. Out of 128 patients, the Mean CD4 cell count was 126.1/mm³. 68.3% of patients were having CD4 count less than 150. Kumar S et al. (2019)²¹ studied the prevalence of HIV Associated Neurocognitive Disorder using Modified Mini-Mental State Examination and its Correlation with CD4 Counts and Antiretroviral Therapy. In this study, mean scores of patients with CD4 counts<500(82.54 ± 5.58) were lesser than those of patients with CD4 counts>500. RA Shaik et al. (2021)²² studied the neurological manifestation with special reference to HIV-associated neurocognitive disorder (HAND) among people on antiretroviral treatment in India. The mean CD4 count was 427.45. In the present study, among severe HAND grades (as per MMSE score), out of 6 cases, all 6 cases had CD4 count <200. Among mild HAND grade out of 42 cases, 23 (54.8%) had a CD4 count

<200, and 19 (45.2%) cases had a CD4 count between 200-500. The association was statistically significant ($P < 0.01$). Similarly, Salahuddin M et al. (2020)²³ studied the prevalence and Predictors of Neurocognitive Impairment in the Ethiopian Population Living with HIV. They reported that those with a CD4 count >500 have 52.08% cognitive impairment compared to 47.92% who have a CD4 count <500. Kumar S et al. (2019)²¹ studied the prevalence of HIV Associated Neurocognitive Disorder using Modified Mini-Mental State Examination and its Correlation with CD4 Counts and Antiretroviral Therapy. In this study, they reported that the Mean scores of patients with CD4 counts<500(82.54 ± 5.58) were lesser in comparison to those of patients with CD4 counts>500 ($p < 0.001$).

6. CONCLUSION

The present study concludes that Mini-Mental State Examination Score can be used to find the presence of HIV-associated Neurocognitive disorder (HAND). MMSE score has a direct association with HAND. There was a significant correlation between HAND and CD4 counts. There was a significant correlation between HAND and Duration of HIV Disease. However, the correlation between HAND and the duration of the ART regimen was insignificant. The study shows MMSE as a tool to determine HIV-associated Neurocognitive disorder, and HAND correlates with CD4 counts and Duration of HIV disease.

7. LIMITATIONS OF THE STUDY

The sample size was limited to 92, and there was a difference between the Duration of the disease and the Duration of the ART regimen due to non-compliance with ART by some study subjects. So observations of this study can't be generalized. So further studies in a larger population group would yield better results.

8. AUTHORS CONTRIBUTION STATEMENT

Dr. Gaurav Sharma gathered the data for this study. Dr. D. P. Lakra and Dr. S. Chandravanshi conceptualized, and necessary inputs were given towards the study's design. Dr. S. Chandravanshi and Dr. Gaurav Sharma analyzed these data. All authors discussed the methodology and results and contributed to the final manuscript.

9. CONFLICT OF INTEREST

Conflict of interest declared none.

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