Neurocognitive Disorders in HIV-positive Patients

Prateek S Padole¹, Rupal N Padhiyar², Dhirendra S Yadav³, Swati A Chavan⁴

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INTRODUCTION

Today, the widespread use of HAART has resulted in increased life expectancy of people living with HIV (PLHIV). This has led to rising concerns about the neurocognitive dysfunctions caused by the infection and its effect on the patient and the epidemic as a whole. Globally there were approximately 37.7 million PLHIV at the end of 2019.² HAND is the CNS manifestation due to the virus itself. It consists of a group of syndromes of varying degrees of impairment in cognition and its associated functioning in HIV-infected people. The clinical spectrum of HAND includes mild forms like asymptomatic neuropsychological impairment (ANI) and HIV-associated mild neurocognitive disorder (MND) to severe form of HAND. Although the prevalence of HAND has decreased, there is an increased number of affected individuals with milder forms of HAND. Neurocognitive dysfunction, even in the mild form, not only has profound effects on daily living of the patients, but also affects employability. This, in the long term, can hamper the efforts carried out by various agencies to limit this pandemic. These patients may not be adherent with taking medications or can miss their appointments, may suffer psychiatric manifestations, and may have difficulty in using preventive measures for viral transmission. Certainly, survival rate of patients with HAND is lower than that of HIV-positive individuals without HAND.³,⁴ With increase in age of HIV-positive population due to effective antiretroviral therapy, prevalence of cognitive disorders is likely to be on rise among older HIV-infected patients. HAND can also become the most common cause of dementia in these patients.

Although many studies addressing this issue were conducted in the Western and sub-Saharan countries, there are few such studies in India. This is a study on a multi-ethnic Indian population of Mumbai to find the prevalence of HAND in the local population. Our secondary objectives were to determine the pattern of neurocognitive involvement and the various factors affecting it. This can also have a clinical impact as to have a high suspicion of HAND in HIV-positive patients and early interventions against the same may improve the living quality of these patients.

AIMS AND OBJECTIVES

• To study the prevalence of HAND in HIV-affected individuals by using ACE-R and the IHDS.
• To compare and correlate the ACE-R score and the domain of ACE-R affected in subjects with HAND.
• To find the factors associated with HAND.

MATERIALS AND METHODS

Study

This study was a cross-sectional descriptive study done in the OPD of a tertiary care center, in Mumbai, Maharashtra, India, to find the prevalence of HIV-associated neurocognitive dysfunction in our local population. The study had 250 participants and was conducted over 12 months. The study protocol was approved by the local Institutional Ethics Committee (IEC) and the Review Board.

Inclusion Criteria

All HIV-positive (by enzyme-linked immunosorbent assay) patients attending OPD of our institution, with a formal education of 4 years (primary education) were included.

Objective

(1) To know the prevalence of HAND in HIV-infected patients of a multi-ethnic population. (2) To describe various types of neurocognitive impairment among patients of HAND and study the factors affecting HAND.

Study design

This study was a cross-sectional descriptive study conducted on 250 HIV-positive patients in outpatient department (OPD) of a tertiary care center in Mumbai, conducted over a period of 12 months. Patients with HIV-1 attending the OPD and having a minimal formal education of 4 years were included. Patients with concomitant delirium, any known central nervous system (CNS) disorder, any psychiatric disorder, and pregnant females were excluded. Outcome measures—the test batteries used were (1) International HIV Dementia Scale (IHDS) and (2) Addenbrookes cognitive examination-revised (ACE-R) scale.

Results

Of 250 subjects studied, 55.6% (139) were males and 44.4 % (111) were females. The mean age of study population was 39.42 years. The mean years of education were 8.32 years. The mean duration of infection (diagnosis of HIV-positive state) was 64.49 months and the mean duration of HAART intake in our patients was 52.30 months. The mean cluster of differentiation 4 (CD4) counts of our subjects were 527.13 per cumm [standard deviation (SD) of 234.13]. The mean nadir CD4 counts were 224.35 per cumm (SD of 115.09). Using the ACE-R scale, the prevalence of HAND was 71.60%, of which 37.20% had an asymptomatic neurological impairment, 29.60% had mild cognitive dysfunction, and 4.80% had HAD. Memory, verbal fluency and visuospatial abilities were the most affected domains on the ACE-R and memory recall and psychomotor speed were affected more on the IHDS. The prevalence of HAND was more with increasing age (p < 0.00), lesser education (p < 0.00) and lesser nadir CD4 counts (p < 0.00). However, it was not affected by the duration of the disease and the current CD4 counts (p > 0.05).

Conclusion

Human immunodeficiency viruses (HIV) associated neurocognitive disorders HAND is common in HIV-positive patients, most of whom are asymptomatic. Older patients with less education and severe disease, having lower nadir counts are at the highest risk of HAND. Memory, verbal fluency, and visuospatial abilities were the most commonly affected domains.

ARTICLE

Human immunodeficiency viruses (HIV) associated neurocognitive disorders (HAND) encompasses a group of syndromes of various degrees of impairment in cognition and daily functioning of HIV-positive individuals. Although the widespread use of highly active antiretroviral therapy (HAART) has drastically reduced the prevalence of severe form of HAND, like HIV associated dementia (HAD), the prevalence of HAND and associated morbidity remains high.

OBJECTIVES: (1) To know the prevalence of HAND in HIV-infected patients of a multi-ethnic population. (2) To describe various types of neurocognitive impairment among patients of HAND and study the factors affecting HAND.

Study design: This study was a cross-sectional descriptive study conducted on 250 HIV-positive patients in outpatient department (OPD) of a tertiary care center in Mumbai, conducted over a period of 12 months. Patients with HIV-1 attending the OPD and having a minimal formal education of 4 years were included. Patients with concomitant delirium, any known central nervous system (CNS) disorder, any psychiatric disorder, and pregnant females were excluded. Outcome measures—the test batteries used were (1) International HIV Dementia Scale (IHDS) and (2) Addenbrookes cognitive examination-revised (ACE-R) scale.

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Conclusion: Human immunodeficiency viruses (HIV) associated neurocognitive disorders HAND is common in HIV-positive patients, most of whom are asymptomatic. Older patients with less education and severe disease, having lower nadir counts are at the highest risk of HAND. Memory, verbal fluency, and visuospatial abilities were the most commonly affected domains.
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Exclusion Criteria
All those who did not consent to participation in the study. Patients having concomitant delirium, any known CNS disorder, use of psychoactive drugs, history of cerebrovascular accident, any psychiatric disorder, dementia with a known cause other than HIV, and pregnant females were excluded.

Participants
After applying the inclusion criteria, 250 patients were selected for the study. All these patients were assessed by the ART physician. HIV seropositive status was confirmed using the National AIDS Control Organization, Government of India guidelines and strategy. Demographic data like age, sex, address, education, and occupation were collected. Clinical information like other sexually transmitted infections, comorbidities like hypertension, diabetes, and dyslipidemia, and hepatitis B and C coinfection was also collected for the study purpose. Clinical data like other sexually transmitted infections, comorbidities like hypertension, diabetes, and dyslipidemia, and hepatitis B and C coinfection was obtained. Laboratory data included complete hemogram, liver and renal function tests, and electrolytes. Detailed information on current CD4 cell count, documented nadir CD4 cell count, length of time since diagnosis, and the antiretroviral therapy administered were also collected for the study purpose.

The participants were divided into three groups according to their CD4 cell counts (Centre for Disease Control and Prevention, 1992), that is, <200, 201–499, and >500 cells/mm³. Patients underwent a clinical and neurological evaluation before the study questionnaire.

Test Battery
Addenbrookes cognitive examination-revised (ACE-R)—the ACE-R is a cognitive test that assesses five domains of cognition, namely attention/orientation, memory, verbal fluency, language, and visuospatial abilities. Maximum score is 100, and higher the score, better is the cognitive functioning. At a cutoff score of 88, the sensitivity is 0.94 and the specificity is 0.89; while at a cutoff score of 82, the sensitivity is 0.84, and the specificity is 1.00. The Addenbrookes scale has been validated in various languages and has been effectively used as a screening tool for the early detection of dementia in various psychiatric clinics. We used the modified version of the ACE-R suiteing to the Indian standards and language as is been validated by Mathurananath et al. The various domain specific cutoffs were also defined for our study to know the proportion of affected individuals. They were—attention <15/18, memory <20/26, verbal fluency <11/14, language <24/26, and visuospatial <14/16.5.

Addenbrooke’s cognitive examination-revised (ACE-R) was used to screen the participants. The mean of the ACE-R score was found to be 71.60% (179/250) using the cutoff score of 89 and above as normal. The prevalence of HAND in our population using the ACE-R scale was found to be 71.60% (179/250) using the cutoff score of 89 and above as normal. The prevalence of HAND using the cutoff score of 10 in the IHDS Scale was 63.20% (158/250). ANI (score of 83–88 on ACE-R) was found in 37.20% (93/250). Mild cognitive dysfunction (score of 75–82) was found in 29.60% (74/250). HAD, as characterized by symptoms of dementia and ACE-R score <75 was found in 4.80% (12/250) of the subjects.

Definitions
- Asymptomatic neurocognitive impairment (ANI)—Addenbrookes score of 83–88, both inclusive. Scores above 88 were considered normal.
- Mild neurocognitive dysfunction (MCD)—Addenbrookes score of 75–82, both inclusive.
- HIV associated dementia (HAD)—Addenbrookes score of <75.

Results
Demography
After applying the inclusion and exclusion criteria, our sample size was 250 patients. Of which 139 (55.60%) were males, and 111 (44.40%) were females. It corresponded to the gender distribution of HIV affected individuals in the general population and also in our ART OPD. The mean age of our study population was 39.42 years (SD = 9). There were 14% subjects below 30 years of age, 76.40% between 30 and 50 years of age, and 9.60% above 50 years of age. The mean years of education were 8.32 years (SD = 2.81). There were 11.20% of subjects with a formal education of <5 years, 54% with 5–9 years, and 34.80% with >9 years of education. The mean duration of the infection (diagnosis of HIV-positive state) was 64.49 months (SD = 40.77). The duration of infection was <24 months in 19.20%, between 25 and 60 months in 32.40%, and >60 months in 48.40%. The mean duration of ART intake in our patients was 52.30 months (SD = 34.42). The duration of ART intake was <24 months in 26.80%, 25–60 months in 36.40%, and >60 months in 36.80%. The mean CD4 counts of our subjects were 527.13 per cumm (SD = 234.13). The current CD4 (per cumm) was below 200 in 3.60%, between 200 and 500 in 47.20%, and above 500 in 49.20% of subjects. The mean nadir CD4 counts were 224.35 per cumm (SD = 115.09). The nadir CD4 counts (in cumm) were below 200 in 41.60%, between 200 and 500 at 56.40%, and above 500 at 2% (Table 1).

Prevalence
The prevalence of HAND in our population using the ACE-R scale was found to be 71.60% (179/250) using the cutoff score of 89 and above as normal. The prevalence of HAND using the cutoff score of 10 in the IHDS Scale was 63.20% (158/250). ANI (score of 83–88 on ACE-R) was found in 37.20% (93/250). Mild cognitive dysfunction (score of 75–82) was found in 29.60% (74/250). HAD, as characterized by symptoms of dementia and ACE-R score <75 was found in 4.80% (12/250) of the subjects.

Domain Affected
Using the ACE-R, we found that domain of memory was affected in 47.20%, visuospatial ability was affected in 43.20%, and verbal fluency was affected in 42% of the subjects. Domain of language and attention was not affected much in our study population (around 10%) (Table 2 and Fig. 1).

When domains of the IHDS were studied, almost all domains were significantly affected in our population, with memory recall being maximally affected (76.40%), psychomotor speed was affected in 63.2%, and motor speed as affected in 40.8% of patients (Table 3 and Fig. 2). The scores in all domains were significantly different in the normal and affected groups (p-value <0.05). The difference in the mean scores of memory in both groups was the maximum.

Table 1: Demography and description of our population

<table>
<thead>
<tr>
<th>Study parameters</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>250</td>
<td>39.42</td>
<td>9.00</td>
</tr>
<tr>
<td>Years of education</td>
<td>250</td>
<td>8.32</td>
<td>2.81</td>
</tr>
<tr>
<td>Duration of infection (months)</td>
<td>250</td>
<td>64.49</td>
<td>40.77</td>
</tr>
<tr>
<td>On art since (months)</td>
<td>250</td>
<td>52.30</td>
<td>34.42</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study parameters</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 4 current (/cumm)</td>
<td>250</td>
<td>527.13</td>
<td>234.13</td>
</tr>
<tr>
<td>CD 4 nadir (/cumm)</td>
<td>250</td>
<td>224.35</td>
<td>115.09</td>
</tr>
</tbody>
</table>
The differences in the parameters of the IHDS scale were also significantly different in both groups (p-value < 0.05).

Factors affecting HAND and their correlation with ACE-R scores—age is significantly and inversely correlated to the ACE-R score (p-value < 0.05; correlation coefficient = −0.148). As the years of education increase, the ACE-R score also improves. This is positively and significantly related (p-value < 0.05; correlation coefficient = 0.558). The correlation between nadir CD4 and ACE-R score was significant and positive (p-value < 0.05; correlation coefficient = 0.344).

However, there seems to be no correlation between the duration of infection and the ACE-R scores, that is, the level of cognition (p-value > 0.05; correlation coefficient = −0.037) or between the current CD4 counts and the ACE-R scores (p-value > 0.05; correlation coefficient = 0.020) (Table 4 and Fig. 3).

**Discussion**

Prevalence of HAND—the prevalence of HAND in our study was 71.60% according to the ACE-R scale and 63.20% according to IHDS.

**Table 2: Domains of ACE-R**

<table>
<thead>
<tr>
<th>Addenbrookes domain</th>
<th>Affected*</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention (&lt;15/18)</td>
<td>27</td>
<td>10.80%</td>
</tr>
<tr>
<td>Memory (&lt;20/26)</td>
<td>118</td>
<td>47.20%</td>
</tr>
<tr>
<td>Verbal fluency (&lt;11/14)</td>
<td>105</td>
<td>42.00%</td>
</tr>
<tr>
<td>Language (&lt;24/26)</td>
<td>26</td>
<td>10.40%</td>
</tr>
<tr>
<td>Visuospatial (&lt;14/16)</td>
<td>108</td>
<td>43.20%</td>
</tr>
</tbody>
</table>

*Standard cut-offs

**Table 3: Domains of IHDS**

<table>
<thead>
<tr>
<th>IHDS domain</th>
<th>Affected (≤3)</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor speed (4)</td>
<td>102</td>
<td>40.80%</td>
</tr>
<tr>
<td>Psychomotor speed (4)</td>
<td>158</td>
<td>63.20%</td>
</tr>
<tr>
<td>Memory recall (4)</td>
<td>191</td>
<td>76.40%</td>
</tr>
</tbody>
</table>

**Table 4: Comparison of the various cognitive domains in normal and affected groups**

<table>
<thead>
<tr>
<th>Study parameters</th>
<th>Addenbrooke score ≤89 (normal) (N = 71)</th>
<th>Addenbrooke score &lt;89 (affected) (N = 179)</th>
<th>Unpaired t-test</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Attention (18)</td>
<td>71</td>
<td>17.21</td>
<td>0.72</td>
<td>179</td>
</tr>
<tr>
<td>Memory (26)</td>
<td>71</td>
<td>22.08</td>
<td>1.59</td>
<td>179</td>
</tr>
<tr>
<td>Verbal fluency (14)</td>
<td>71</td>
<td>11.93</td>
<td>0.78</td>
<td>179</td>
</tr>
<tr>
<td>Language (26)</td>
<td>71</td>
<td>25.65</td>
<td>0.48</td>
<td>179</td>
</tr>
<tr>
<td>Visuospatial (16)</td>
<td>71</td>
<td>13.83</td>
<td>0.38</td>
<td>179</td>
</tr>
</tbody>
</table>

Asymptomatic neurocognitive impairment was seen in 37.20%, mild cognitive dysfunction in 29.60%, and HAD in 4.80%. A study from Southern India in 30 HIV-positive individuals with advanced HIV-1 infection with (clade C virus variant) reported that 56% of patients had cognitive deficits in two cognitive domains. The sample consisted of individuals with severe levels of immune deficiency. In our sample we had 250 HIV-1-positive patients. The tests used in the study were standardized and validated in the Indian population (Mathuranath et al.). Other Indian studies showed a similar prevalence as in the study by Muniyandi et al. (78%). Our study was carried out in a multi-ethnic population of Mumbai, consisting of a large number of subjects and gave similar results. The prevalence of HAD was comparatively higher in the Western world as compared to the Indian data. This may reflect the less neurovirulence of HIV clade C virus variant, which is a causative virus in 95% of infections in India.

HIV and neurocognition Indian literature—Indian literature about the neurocognitive deficit in HIV is limited. Kamat et al., compared 69 HIV-positive and 67 HIV-negative patients, who were asymptomatic, attending clinic in Chennai. They used the international neuropsychological test battery. Prevalence of HAND was significantly higher (33 vs 13%) in HIV-positive patients. About 90% of asymptomatic HIV-positive patients had some psychiatric illness in a study by Satapathy et al. The common diagnosis was adjustment disorders and depression. None of the patients were found to have cognitive defects in this study. The above
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Studies were mostly clinical studies and neuropsychological tests were not carried out in all studies. It is impossible to recognize mild cognitive deficits with just clinical interview methods. A case-control study was conducted by Mandal et al., for cognitive impairment among 50 HIV-positive patients with stages I, II, and III in comparison to 50 control subjects utilizing digit span test, word association test, etc. They have shown that HIV-infected individuals had poor scores in all tests, and a statistically significant difference was noted in digit symbol substitution test, controlled word association test, and trail-making test.

Factors affecting—we found that age positively correlated with the prevalence of HAND, while nadir CD4 and years of education strongly and negatively correlated with the prevalence of HAND. Duration of illness, duration of ART, gender, and current CD4 counts did not affect the presence of HAND, as there was no significant correlation between them. We didn’t find any correlation between the duration of HAART intake and presence of HAND. This can point towards a finding that there is no significant neurotoxicity of HAART, though detailed studies considering these two parameters are required. Also, gender or the present immunological status (current CD4) did not correlate with HAND, as was confirmed by all other studies. An important observation was the strong correlation between the years of education and the presence of HAND. This could be due to the protective effect of education on particular domains of cognition. This could also reflect the sociodemographic characteristic of the population and can confound the results and other parameters. We did a multivariate analysis to nullify the compounding effect of years of education and found that nadir CD4 count still had a significant correlation with the presence of HAND. We propose that the nadir CD4 count represents the virulence of the organism and the correlation confirms that highly virulent organisms are more likely to cause HAND. It was also demonstrated in Indian study by Muniyandi et al.

Cognitive domains affected—the domains of cognition affected to determine the pattern of involvement in HAND. Domains studied were—attention and orientation, memory, verbal fluency, language, and visuospatial abilities (ACE-R Scale) and motor speed, psychomotor speed, and memory recall (IHDS Scale). We found that the domains most affected in HAND were—memory, verbal fluency, and visuospatial abilities, while attention and language domain were relatively spared. Domains of IHDS scale were almost equally and universally affected with less affection to motor speed than to memory recall and psychomotor speed. Current concepts indicate predominant subcortical pattern of involvement among HAND patients, with bradykinesia and bradyphrenia being the characteristic features. Most common domains affected in HIV patients as per general consensus are abstraction/executive functioning, learning, motor functioning, and attention/working memory, whereas there is sparing of language and verbal functioning. In contrast, in our study, both cortical and subcortical functions were found to be commonly affected, which is similar to a recent study demonstrating cortical and subcortical neurodegeneration. Our study, we could not comment whether these effects are due to HAART, as has been suggested by other studies. As a study done by Letendre et al., on CNS penetration-effectiveness of various ART drugs have observed that CNS penetration of different ART drugs varies in HAND patients and ART treatment strategies should include this aspect in their recommendations after validating it in clinical studies. Above study was a cross-sectional study and its interpretation was limited due to other confounding factors like duration and timing of ART initiation. Further studies should study the differences in the cognitive profile of HAND in patients on HAART and ART naïve patients. Some studies have reported similar deficits that support the involvement of subcortical and frontostriatal brain processes in clade B infection. The cognitive profile in the seropositive individuals in a study by Gupta et al., also suggest a frontostriatal pathology. The difference in cognitive functions of the healthy seronegative controls and the seropositive patients was in the domains of fluency, verbal working memory, and verbal learning and memory; thus cognitive deficits in these domains are associated with HIV1 infection. Earlier studies have shown evidence of working memory deficits in HIV-infected subjects supporting frontostriatal pathology in HIV infection. However, the type of cognitive dysfunction in South Asian patients with HAND does not fit into a discrete subcortical pattern, as shown in the study by Chan et al. Our study emphasize the importance of early diagnosis of neurological dysfunction among HIV patients to ensure that they are linked to comprehensive HIV care. Prior studies had used various neuropsychological assessment batteries for diagnosis of HAND. Our study has used a standardized mental assessment examination utilizing performance in various domain-specific parameters instead of total/recommended cutoff scores to provide a comprehensive cognitive assessment similar to the study done by Chan et al. Also, the IHDS scale was used as a study tool which allows comparisons with studies throughout the world. We hope that the results of this study will help to change the approach towards diagnosis, treatment, and management of HAND and sensitize physicians about this important topic.

Limitations of Study

Our study was a cross-sectional study, and thus, we could not keep follow-up subjects and could not study any intervention and its effects. The Neyman’s bias of selection could not be removed as not every HIV-affected individual visit the. We used the CD4 levels as the marker of immune suppression while HIV viral load was not done. We conducted the study only on the HIV-affected individuals and a control group was absent. However, we used cognitively normal HIV individuals as controls in our study to compare our results. Though the neurocognitive scales used are
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standardized and validated, there is a lack of published normative data on them. However, we have used demographically appropriate data wherever possible.

Future Directions
Future studies should concentrate on a follow-up cohort studying the effect of ART on the prevalence and manifestations of HAND. Also, studies on the effects of drugs on the molecular level should be conducted. There should be a consensus on the cognitive tools used to screen HAND and national guidelines for the same. Future studies should focus on the aspect of treatment as given by the providers, such that it can prevent the occurrence of HAND. This can affect the compliance to treatment, use of services, and decrease in morbidity of HIV-affected individuals.

Conclusion
The prevalence of HAND in our study is 71.6% using the ACE-R and standardized cut-offs. Asymptomatic neurocognitive impairment was seen in 37.20%, mild cognitive dysfunction in 29.60%, and HAD in 4.80%. Age has a significant correlation with the presence of HAND. As age increases, there is a decline in cognition, as evidenced by reduced scores on the neurocognitive scales. The years of education are also significantly and negatively correlated with HAND in our study. As the education level increases, the prevalence of HAND is less likely. Patients with lower nadir CD4 counts were more likely to be affected by HAND, showing a significant correlation. The neurocognitive domains most affected in HAND were memory, verbal fluency, and visuospatial abilities. This suggests both cortical and subcortical involvement in HAND. Attention and language domains were relatively spared in HAND. The duration of infection, duration of consumption of ART, gender, and the current immune status (current CD4) do not have an effect on the presence of HAND.

References