STUDY OF SOME NEUROCOGNITIVE FEATURES WITH RESPECT TO CD4 CELL COUNT AND DURATION OF HAART IN HIV/AIDS PATIENTS OF ART CENTRE OF A TERTIARY CARE HOSPITAL IN WEST RAJASTHAN

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ABSTRACT
The HIV infection is associated with neurocognitive deficits in attention/working memory, motor abilities and executive functioning, which are often attributed to disruption in fronto-striatal circuitry. These conditions, however, remain largely unrecognized. The primary objective of this study was to delineate the factors affecting the neurocognitive functions in HIV/AIDS patients undergoing Highly Active Antiretroviral Therapy (HAART). This prospective cohort study was carried out between October 2011 to September 2012 in '80' HIV positive individuals, randomly selected from ART Centre of PBM and AG Hospital, Bikaner, India. The neurocognitive features were assessed using International HIV Dementia Scale (IHDS). The lower baseline CD4 cell count and duration of HAART for less than one year, both were found to be significantly associated with cognitive impairment. However, the patients receiving Stavudine, Lamivudine and Nevirapine combination regimen had better status of cognitive functions in comparison to patients receiving other regimens.

Key words: HIV/AIDS; HAART; neurocognitive features; IHDS; CD4 cell count.

INTRODUCTION
The Central Nervous System (CNS) is one of the major targets of HIV-1 infection showing much of HIV associated neurocognitive impairment depending on various parameters. According to Antinori et al., HIV related neurocognitive impairment occurs on a spectrum ranging from asymptomatic neurocognitive impairment to mild neurocognitive disorder (cognitive impairment with mild functional impairment) to frank HIV associated dementia (marked cognitive impairment and marked functional impairment). Several studies reported that CD4 cell count is inversely related with neurocognitive impairment. It is now established that low education level is an independent risk factor for HIV related cognitive impairment. Stern et al. found that well educated people have less HIV associated cognitive impairment than poorly educated people.

Both age and HIV status have been established as independent risk factors for the development of cognitive impairment. Valcour et al. identified a greater incidence of cognitive impairment in older people relative to their younger counterparts. A preliminary study addressing the effect of HAART on neurological function in Uganda found that HIV dementia improved from 61% at baseline to only 4% after six months of HAART.

To date, the data regarding the factors affecting the neurocognitive functions in HIV patients are still limited in India. We, therefore, conducted this prospective cohort study to delineate these factors in HIV/AIDS patients undergoing HAART.

MATERIAL AND METHODS
Study Design
This prospective cohort study was conducted among '80' HIV- positive patients receiving NACO- based HAART regimen between October 2011 to September 2012 in ART Centre of PBM and AG Hospital, Bikaner, Rajasthan (India). To calculate the sample size, '85' patients were recruited on the basis that they passed the inclusion criteria. Five patients were withdrawn due to non-compliance. The rest of '80' patients were followed for six months.

Patients were being treated with NACO supplied antiretroviral drugs, which does not include any protease inhibitors. The treatment strategy for all patients was the inclusion of two nucleoside reverse transcriptase inhibitors and one non-nucleoside reverse transcriptase inhibitor (2 NRTI + 1 NNRTI).

Any one of the following regimens was chosen according to the requirement of the patient and availability of the drugs:-
1. Stavudine (30mg) + Lamivudine (150mg) + Nevirapine (200mg)
2. Stavudine (30mg) + Lamivudine (150mg) + Efavirenz (600mg)
3. Zidovudine(300mg) + Lamivudine (150mg) + Nevirapine (200mg)
4. Zidovudine(300mg) + Lamivudine (150mg) + Efavirenz (600mg)

Ethical considerations
The study was approved by the Ethical Committee of S.P. Medical College, Bikaner. In this cohort study, each patient was given full information of the purpose and procedure of the study and then only written informed consent was taken.

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Inclusion criteria: (1) HIV positive patients on stabilized HAART for more than 6 weeks, (2) HIV infected individuals between the age 21-50 years, (3) Ambulatory patients with CD4 count above 200 cells/mm$^3$ and (4) Ability to comprehend study procedures.

Exclusion criteria: (1) Serious ill/ moribund patients, (2) Addiction or any substance abuse, (3) Severe psychiatric disorder or any other illness (TB, Epilepsy, Cancer etc.), (4) Pregnancy and (5) Lactating women

**Data collection Tools**
All eligible patients underwent socio-demographic, medical history and neurocognitive assessment using International HIV Dementia Scale (IHDS)$^2$. It is a bedside screening tool for detecting HIV dementia. It can be used in a clinic setting and requires only 2-3 minutes to administer. Cut-off score of ≤10 was taken to screen dementia cases. This tool that assesses for memory impairment, motor and psychomotor speed does not require one to be proficient in English, is brief & inexpensive. It is one of the best tools for use across cultures for screening of neurocognitive impairment in HIV. Baseline CD4 count was estimated by CyFlow Counter (Partec).

IHDS consist of three subtests: - (i) Timed finger tapping, (ii) Timed alternating hand sequence test and (iii) Recall of four items in 2 minutes.

**INTERNATIONAL ‘HIV’ DEMENTIA SCALE (IHDS)**

(A) MEMORY REGISTRATION AND RECALL of 4 common objects

SCORE = _______ 4 (1 point for each word spontaneously recalled and 0.5 point if correct answer after prompting)

(B) MOTOR SPEED - Rapid tapping of thumb with first Digit of non-dominant hand

SCORE =

4 = 15 in 5 Sec.
3 = 11-14 in 5 sec.
2 = 7-10 in 5 sec.
1 = 3-6 in 5 sec.
0 = 0-2 in 5 sec.

(C) PSYCHOMOTOR SPEED - Repetition of three position alternating hand sequence-

(1) Clench hand in fist on flat surface
(2) Put hand flat on surface with palm down
(3) Put hand perpendicular to flat surface on the side of 5th digit.

4 = 4 sequences in 10 sec.
3 = 3 sequences in 10 sec.
2 = 2 sequences in 10 sec.
1 = 1 sequence in 10 sec.
0 = unable to perform

SCORE = ____________

Total Score = ____________ Maximum Score = 12

If Score 10, Patient should be evaluated further for DEMENTIA

**Statistical analysis**
Means and Standard Deviations (SD) were calculated for continuous variables. To analyse the association between the various factors and cognitive dysfunction, chi square test was employed. The p value of less than 0.05 (p<0.05) was considered as statistically significant. All statistical analysis was done by using ‘indostat software’.

**RESULTS**
A total of ‘80’ HIV-positive patients were followed up monthly for 6 months. The initial CD4 count between 200-349 cells/mm$^3$ was significantly associated with cognitive dysfunction (p<0.05), whereas initial CD4 count above 500 cells/mm$^3$ was significantly associated with normal cognitive function (p<0.05) (Fig.1)

The patients receiving STV + LMV + NVP regimen were more likely to have normal cognitive function (P<0.05)(Fig.2)

The duration of being on ART for less than one year was significantly associated with cognitive dysfunction (p<0.05), whereas duration of more than two years was significantly associated with normal cognition. (p<0.05) (Fig.3)
NEUROCOGNITIVE FEATURES and CD4 CELL COUNT

DISCUSSION
In present study, significant association was found between initial CD4 count between 200-349 cells/mm³ and cognitive dysfunction whereas CD4 count above 500 cells/mm³ was significantly associated with normal cognitive function (p<0.05). This finding is in concordance with several previous studies.[6,7] However, in contrast to this, Honni & Bornstein et al. observed no relationship between neuropsychological performance and CD4 cell count.

In present study, the patients receiving STV+LMV+NVP regimen were more likely to have normal cognitive function (p<0.05). This finding is in concordance with the study by Letendre et al. who found that HAART schemes with higher CNS-Penetration-effectiveness (CPE) ranks were associated with greater reductions of HIV RNA level in CSF.

In contrast, Marra et al. showed that ARV with good CNS penetration was more effective in reducing CSF viral load. However, these ARV regimen were associated with poor neurocognitive performance.[8]

In support of the previous studies, the present study showed significant association (p<0.05) between the duration of being on ART for less than one year and cognitive dysfunction. Duration of ART of more than two years was found to be significantly associated with normal cognitive function (p<0.05). However, in contrast to this Lawler K et al. observed that longer duration of HAART was associated with neurocognitive impairment.

Many researchers demonstrated the enhancement of cognitive functioning after initiation of HAART regimen. Cysique et al. found enhanced neurocognitive function following HAART therapy in 13% of subjects at week 12 but reported more gains at week 24 and 36.[9]

The routine use of HAART has changed the epidemiology of HIV dementia. Multiple studies have shown that patients on HAART show partial reversal of cognitive deficits and significant improvement, whereas patients not on HAART steadily decline.[10,11]

Limitation of the study- As the study was conducted on a small sample, the results cannot be generalized to the population.

CONCLUSION
Neurocognitive impairment is likely to be an important component in patients suffering from HIV infection in developing countries and may be more likely to occur with the low baseline CD4 cell count. Hence HAART should be started earlier rather than waiting until the CD4 count drops to 200 cells/mm³ and HIV positive patients should be routinely screened to recognize the cognitive deficits at an early stage. This will improve quality of life and arrest further deterioration of brain function.

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