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Neurocognitive consequences of HIV in southern India: A preliminary study of clade C virus

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Abstract

The neurocognitive impact of the clade C viral strain of human immunodeficiency virus (HIV) has not been determined. The purpose of this study was to examine neurocognitive function in southern India among individuals with the clade C virus with advanced HIV. A battery of cognitive tasks sensitive to the effects of HIV on brain function was translated and administered in Tamil and Telegu, two widely spoken languages in southern India. A sample of 30 treatment-naïve HIV-positive individuals with a median CD4 cell count of 97, and 30 age and education matched healthy controls obtained from the same region of India, were included in the study. Results revealed significant differences on most cognitive tests, with lower performances obtained by the HIV-positive individuals. These results suggest that cognitive difficulties are present among individuals with the clade C virus in India, with as many as 56% of the patients with advanced HIV meeting the criterion for impairment in two cognitive domains. Additional study is needed to determine if clade C HIV infection is more or less prone to cause neurocognitive deficit than the clade B virus. Furthermore, the impact of antiretroviral therapy on neurocognitive dysfunction in clade C virual infection needs to be determined. (*JINS*, 2006, *12*, 424–430.)

Keywords: HIV, Clade C, Cognition, Dementia

INTRODUCTION

The predominant strain of HIV in India is clade C (also common in Africa), whereas clade B represents the predominant strain in the United States, Europe, and Australia. The two strains of the virus differ in terms of specific protein binding sites and binding characteristics, replicative capacity (Centlivre et al., 2005), and possibly in the development of treatment resistance (Grossman et al., 2001; Kantor et al., 2002). Together these findings suggest a potentially different outcome associated with the clade C viral strain.

One interesting clinical outcome associated with the clade C virus is the reportedly low prevalence of HIV-associated dementia (HAD) in India. Two studies (Satishchandra et al., 2000; Wadia et al., 2001) have reported that the prevalence of HAD prior to highly active antiretroviral therapy (HAART) was less than 3%, compared to 15–30% in the United States (Grant et al., 1995; Simpson, 1999). Most recently, Ranga et al. (2004) demonstrated an important natural variation in the dicysteine motif of the Tat protein (C31S) that was conserved only in the clade C virus. Furthermore, the authors demonstrated that the variation was functionally significant, as the mutation diminished monocyte chemokine migration properties. Since the Tat protein promotes viral replication directly and it reduces HIV-resistance in uninfected cells, a functional change in the Tat protein could have a significant impact on the virulence of the infection. Indeed, studies have demonstrated that Tat is selectively involved in the migration of monoctyes into the brain via up-regulation of inflammatory cytokines and adhesion molecules (Pu et al., 2003). The Tat protein also has been shown to disrupt the tight-junction proteins that support the blood-brain-barrier (Andras et al., 2003), possibly allowing for greater brain involvement via inflammatory

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processes. Given the important role that Tat plays in brain disruption secondary to HIV, Ranga et al. (2004) concluded that the Tat variation may in part explain the low prevalence of HAD in India.

As noted by Ranga et al. (2004), underdiagnosis of dementia may still be a factor associated with the low prevalence of HAD in India. Most commonly, previous studies have not employed standardized cognitive tests to determine the presence of impairment rates in India, and therefore the prevalence of significant impairment may be higher than previously reported. It is also possible that less severe, but still clinically meaningful, difficulties on cognitive tests are present among individuals with the clade C virus. Alternatively, the functional variation of the Tat protein may provide some protection from even subtle cognitive compromise in this population.

In the present study we examined the issue of cognitive compromise in a sample of treatment-naïve HIV-infected individuals with the clade C virus residing in southern India. A comparison sample of healthy control participants was also recruited. Both samples were administered a battery of cognitive tests, adapted from United States measures, that examined motor speed, executive function, information processing speed, and verbal and visual learning and memory. We predicted that HIV-positive individuals with advanced disease would exhibit lower performance on measures of cognitive function compared to healthy control participants.

METHODS

Research Participants and Setting

The study was conducted at the Y.R. Gaitonade Center for AIDS Research and Education (YRG CARE). YRG CARE is a tertiary HIV-referral center in southern India that provides voluntary counseling and testing, as well as outpatient and inpatient care for over 8,000 HIV-positive individuals.

Participants included males and females between the ages of 18 and 55 with documented HIV infection confirmed by either two different ELISA tests or an ELISA and Western Blot. Exclusionary criteria included: (1) confounding psychiatric illnesses such as major depression and schizophrenia, (2) confounding neurologic disorders such as multiple sclerosis, documented stroke, degenerative disease, chronic seizure disorder, or head injury, (3) unstable or active hematological, hepatic, or renal dysfunction, (4) active alcohol or drug abuse, and (5) presence of a neurological opportunistic infection (OI), or an acute and untreated OI.

The participants included 30 treatment-naïve HIV-positive individuals currently initiating HAART. A total of 30 healthy controls were recruited from family members of seropositive individuals, as well as individuals examined at YRG CARE who were seronegative. The healthy controls were matched to the HIV group according to sex, age, and education.

The patients were 87% male and averaged 36.4 (SD = 8.7) years of age and 8.7 (SD = 3.9) years of education. CD4 count was determined within one month of completion of the cognitive assessment. The median CD4 cell count was 97 (range = 14 to 209). The patient group was comprised of 8 individuals with a CD4 cell count less than or equal to 50, 20 individuals with a CD4 cell count between 51 and 200, and 2 with a CD4 cell count greater than 200. The 30 healthy controls were required to meet the same exclusion criteria as the HIV patients. The healthy control participants were 87% male and averaged 34 (SD = 10.4) years of age and 9.7 (SD = 4.4) years of education.

Procedure

At study entry, all participants underwent a clinical neurological evaluation during which medical and psychiatric symptoms were assessed. Demographic and employment data were obtained during patient interviews and medical history was obtained via chart review and neurological evaluation. Information on the most recent CD4 cell count, current medications, and past opportunistic infections was obtained from the patient's medical record. CD4 cell count had been obtained within one month of the cognitive assessments. All measures were administered and scored according to standard procedures described in more detail later.

Participants received no financial compensation for participation in the study. Written informed consent was obtained prior to enrollment. The protocol was approved by separate local institutional review boards in southern India and in the United States. The neuropsychological assessments were conducted in both Tamil and Telugu, two regional languages spoken in southern India. The distribution of language type for each group is provided in Table 1.

As evident from Table 1, most healthy control participants reported Telegu as their primary language compared to mainly Tamil speaking HIV-positive participants. The translation procedures for the neuropsychological tests are described later.

Neuropsychological measures

The cognitive test battery contained measures that tap cognitive domains vulnerable to the effects of HIV in United States populations (for a review see Paul et al., 2002). Tests were modified for administration in Tamil and Telegu, and efforts were made to facilitate cultural relevance specific to southern India. The development of the cognitive battery for administration in the two languages was based on a group consensus model that was generally consistent with the standards set by the International Test Commission (http://www.intestcom.org); the primary exception being that specific validity had not been formally determined prior to administration in the current study. The group consensus model included involvement with two clinical neuropsychologists based in the United States, a fourth-year medical student based in the United States and fluent in Telegu, a

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Table 1. Demographic and clinical data

Cognitive Measure	HIV-Positive	HIV-Negative
Age	36.4. (8.7)	34.0 (10.4)
Education	8.7 (3.9)	9.7 (4.4)
Primary language	*N* (%)	*N* (%)
Tamil	18 (60)	3 (10)
Telegu	11 (37)	26 (87)
Fluent in both languages	1 (3)	1 (3)
Employment	*N* (%)	*N* (%)
Currently employed	27 (90)	4 (13)
Physical labor/Driver	9 (30)	26 (87)
Business	14 (47)	9 (30)
Student	0 (0)	9 (30)
Other	4 (13)	4 (13)
Median CD4 cell count	97 (range 14–209)	NA
Frequency of CD4 classification		
0–50	8	
51–100	7	
101–150	6	
151–200	7	
> 200	2	

neurologist based in southern India and fluent in Tamil, and multiple staff members at YRG CARE fluent in Tamil, Telegu, and English. The investigative team met at YRG CARE prior to the start of the study to review the test materials for cultural relevancy, translate the materials, and collect pilot data on the battery. All instructions were forward-translated and multiple administrations were completed with YRG CARE staff prior to initiating data collection on the study participants.

For most tests (Trail Making, Pegboard, and Brief Visual Memory Test–Revised [BVMT-R]) no modifications were made to the test items, though the instructions were translated into the local languages. For the Stroop test, the words (Red, Green, Blue) on the stimulus pages were translated into local languages. The only test that was significantly modified for administration in southern India was the verbal list-learning test (Hopkins Verbal Learning Test–Revised [HVLT-R]; Brandt, 1991). In addition to translating the instructions to this test, we also modified one of the three semantic categories. Specifically, the category gemstones ("emerald," "sapphire," "opal," "pearl") was replaced with fruit names ("pineapple," "grapes," "mango," "banana"). A few modifications were also necessary on the recognition trial of this test in order to provide appropriate foils to the new category of fruit. For example, "jackfruit" and "sweet lime" were included as foils in the recognition trial. Determination of word frequency and difficulty level for this new category of words was determined informally by the collaborators based at YRG CARE. The individual measures are described in more detail later.

Our modified version of the HVLT-R (Brandt, 1991) was administered and scored according to standard methods (with the translation changes noted earlier). Specifically, participants were read a list of 12 culturally appropriate words belonging to several classes (animals, fruits, and dwellings) in their native language on three trials. They were required to recall as many words as possible on each trial. Following a delay of approximately 20 minutes, participants were required to recall as many words as possible from memory. At the end of the delay period, participants were also required to recognize the original 12 words from a distracter list read to them. The dependent measures were the total number of words recalled across the three learning trials, and the total number of words recalled on the delay trial. The recognition trial was not included as a dependent variable as this trial is likely to be less sensitive to cognitive difficulties associated with "subcortical" diseases such as HIV (Paul et al., 2002).

The BVMT-R (Benedict, 1997) was administered and scored according to the standard method. Participants were shown one sheet of paper with six geometric figures for ten seconds on three trials. They were required to replicate as many of the figures as possible in their correct location on the page for each trial. Following a delay of approximately 20 minutes, participants were required to draw the figures again from memory. They were also required to identify the original figures from a group of 12 target and foil figures. The dependent measure was the total number of correctly replicated images across the three learning trials and the total correct on the delayed trial.

Participants completed the Grooved Pegboard task (Matthews & Klove, 1964) using the dominant and nondominant hands on separate trials. All participants were instructed to place the pegs into the grooved holes one-at-a-time as quickly as possible using the designated hand. Time to completion for each hand was the dependent variable.

Participants were administered the Stroop Color Word Interference Test (Golden, 1978), which consisted of three trials administered on three cards. On the first trial, participants were instructed to read aloud color words (e.g., blue, red, green) printed in black ink in Tamil or Telugu. On the second trial, participants were presented with columns of blocks printed in colored ink, and they were required to name the colors that the blocks were printed in. On the final trial, participants were presented with color words printed in incongruent ink and they were instructed to name the color that the words were printed in. The dependent variable was the number of words/blocks identified in each 45-second trial.

Consistent with standard administration, participants completed Color Trail Making (Maj et al., 1993) Trails-1 and subsequently completed Color Trails-2. On the former task, participants were required to sequentially connect numbers in colored circles using a pencil (e.g., 1-2-3-4 to 25). On the latter task, participants were required to alternate back and forth between the two colors while keeping the numbers in the correct order (e.g., Pink 1 to Yellow 1, Pink 2 to

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Yellow 2, etc.). Time to completion was the dependent variable on each task.

Statistical analysis

Descriptive statistical analyses were conducted for each of the variables of interest. Between-group comparisons for each of the neurocognitive measures were conducted using independent sample *t* tests. The relationships between measures of CD4 cell count and cognitive performance were analyzed using a Spearman correlation method for the HIV-positive patients; nonparametric correlations were computed since the CD4 count was not normally distributed.

RESULTS

Descriptive data for demographic variables are presented in Table 1. There were no group differences for age, education, or gender. The descriptive statistics for the cognitive measures for each group are presented in Table 2.

The battery of tests was generally well tolerated, as the completion rate for most tests was 100%. The exceptions included Color Trails (93.3% for both HIV-positive and HIV-negative groups) and the Stroop test (73.3% for HIV-positive, 93.3% for HIV-negative groups). The observation that the HIV-negative cohort was capable of completing the Stroop test suggests that the lower completion percentage among the HIV-positive patients was not a straightforward reflection of poor translation procedures. There also was no difference in rate of completion of the Stroop test between HIV-positive patients fluent in Tamil *versus* Telegu, suggesting that the lower completion rate in this group was not a function of language subtype. Interviews with the study participants revealed that the primary reason for not completing the Stroop test was difficulty understanding the instructions.

Comparisons of HIV-positive patients with the seronegative controls demonstrated significant differences between the two groups for: verbal list learning total recall [t (58) = −2.4, p = .016], verbal list learning delayed recall [t (58) = −2.6, p = .012], BVMT-R total immediate recall [t (58) = −2.3, p = .023], BVMT-R delayed recall [t (58) = −2.2, p = .026], Grooved Pegboard Non-Dominant Time to completion [t (58) = 3.12, p = .003], Color Trails-1 [t (55) = 2.53, p = .014], and Color Trails-2 [t (55) = 2.6, p = .012]. Group contrasts on the Stroop Word Trial, Stroop Color Trial, Stroop Color/Word Trial, and Grooved Pegboard Dominant Hand Time were not statistically significant (ps > .12).

Table 2. Performances on the cognitive battery: Mean (*SD*)

Cognitive Measure	HIV-Positive	HIV-Negative
Pegs, Dominant	91.5 (42.6)	77.1 (22.5)
Pegs, Nondominant	96.6 (21.7)	81.9 (13.8)*
Stroop Trial 1	63.1 (21.7)	75.3 (20.0)
Stroop Trial 2	48.2 (43.7)	48.3 (14.2)
Stroop Trial 3	23.7 (8.1)	25.1 (8.9)
Color Trails, time 1	74.0 (21.7)	59.8 (20.5)*
Color Trails, time 2	180.1 (68.1)	138.5 (50.1)*
Verbal Learning total	18.6 (4.5)	21.7 (5.2)*
Verbal Memory total	6.8 (1.9)	8.2 (2.1)*
Visual Learning total	13.9 (9.3)	19.0 (7.4)*
Visual Memory total	5.7 (3.9)	7.8 (3.0)*

*p < .05.

We examined the percentage of patients impaired on the tests using the healthy control sample as the reference group. Performances worse than 1.5 standard deviations lower than the average performances for the healthy control sample were considered impaired. Figure 1 depicts the percentage of patients impaired on the individual tests.

The range of impairment was 4% to 40% (Stroop incongruent), with the largest percentages evident on the BVMT-R (total learning) and Color Trails 2. We also examined the frequency of impairment across domains of function. To accomplish this task we grouped the cognitive tests into one of five domains including: (1) motor speed (Pegs dominant and nondominant), (2) processing speed (Color Trails 1, Stroop trial 1), (3) executive function (Color Trails 2, Stroop trial 3), (4) learning (HVLT-R total learning, BVMT-R total learning), (5) memory (HVLT-R delayed recall, BVMT-R delayed recall). A domain was considered impaired if performance on one of the tests in the domain fell below 1.5 standard deviations from the healthy control group, or if performances on two tests in the domain fell 1.0 standard deviation below the performance of the healthy control group. Results of this analysis revealed that 56% of the HIV patients met the criterion for impairment in two domains. Since most individuals that met the criteria for impairment in the learning domain also met the criteria for impairment in the memory domain (likely due to the inherent relationship between the two variables), we also examined the percentage of patients who met criteria for impairment in two domains other than just learning and memory. Results from this analysis revealed that 30% of the patients were impaired in two domains, even when eliminating the dependence on learning and memory performances.

Given the differences in language distribution between the two groups of HIV patients, we examined neuropsychological performances between the two patient groups stratified by primary language. Mean scores and standard deviations are provided in Table 3. *T* tests revealed no significant differences between these groups on age or education (ps > .05). However, because the power to detect differences in these contrasts was limited, we repeated the contrasts between patients and control participants, including only those individuals whose primary language was Telegu. This most conservative approach revealed significant differences between patients and controls on Grooved Pegboard Non-Dominant Time to Completion [t (35) = 2.45, p = .019], Color Trails-1 [t (33) = 2.65, p = .012], Color

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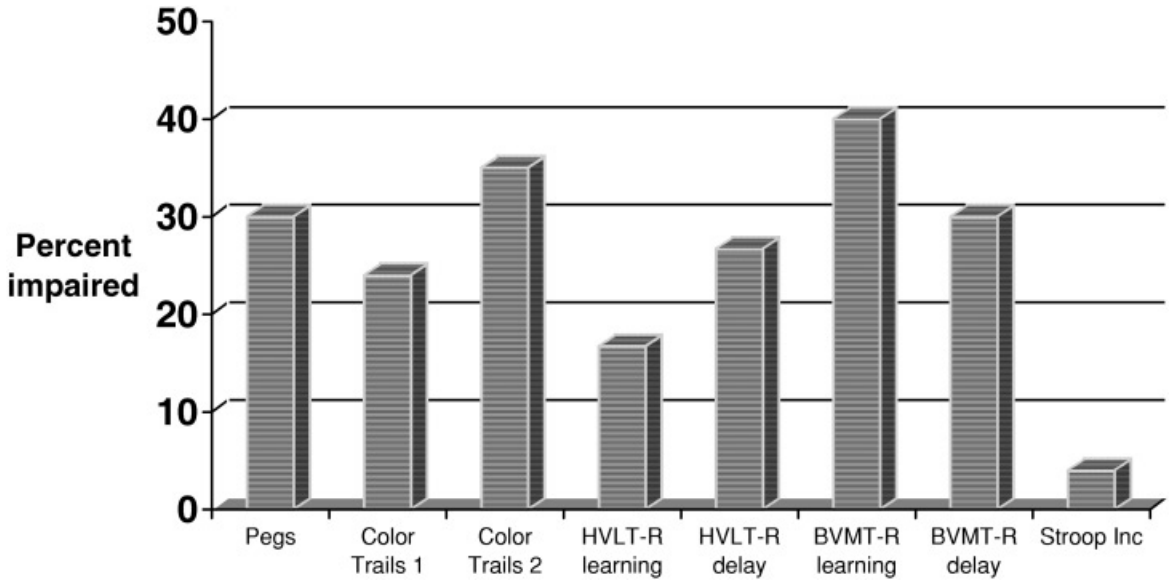

Fig. 1. Percentage of HIV patients impaired on the individual cognitive tests. Pegs: Grooved pegboard dominant hand, time to completion; Stroop Inc: number correct in 45 seconds on the incongruent trial.

Trails-2 [t (33) = 3.0, p = .004], and Stroop Word Trial [t (31) = −2.44, p = .020], with patients performing more poorly than controls on each measure. Group contrasts on the Stroop Color Trial, Stroop Color/Word Trial, Grooved Pegboard Dominant Hand Time, and the BVMT-R and HVLT-R learning and retention tests were not statistically significant (ps > .10).

There was no significant relationship between neurocognitive performance and CD4 count when examined using nonparametric correlation analyses. Generally, r-values for these relationships ranged from .001 to .197, demonstrating limited associations between these measures. It is of note, however, that the range of CD4 count was restricted to very low levels in the range of AIDS (in cells) and this may have limited the likelihood of identifying significant relationships between CD4 cell count and neuropsychological performance.

Table 3. Performances on the cognitive battery: Mean (*SD*)

Cognitive Measure	Tamil	Telegu
Pegs, Dominant	96.7 (53.3)	83.9 (17.8)
Pegs, Nondominant	99.0 (21.9)	94.9 (21.9)
Stroop Trial 1	65.4 (23.5)	54.7 (14.4)
Stroop Trial 2	54.1 (55.0)	37.6 (13.2)
Stroop Trial 3	24.5 (7.1)	21.3 (9.3)
Color Trails, time 1	71.2 (23.8)	80.3 (19.0)
Color Trails, time 2	171.3 (75.6)	200.4 (52.0)
Verbal Learning total	17.7 (5.4)	19.8 (3.4)
Verbal Memory total	6.5 (1.9)	7.4 (1.9)
Visual Learning total	12.3 (10.3)	16.1 (8.0)
Visual Memory total	5.7 (4.1)	6.6 (3.6)

DISCUSSION

Previous studies have suggested that the clade C strain of HIV is associated with a reduced risk of significant HIV-related cognitive impairment (HAD; Satishchandra et al., 2000; Wadia et al., 2001). However, few studies have examined cognitive function using standardized tests of cognitive function. In the present study we administered measures of cognitive function to HIV-positive individuals and comparison group of healthy control participants. Results of our study suggest that individuals infected with the clade C viral strain with advanced immunosuppression exhibit significant impairments in cognitive function. Since this preliminary study did not involve a detailed assessment of dementia, our study cannot directly address the prevalence of HAD in India. However, our findings do suggest that the clade C viral strain does not confer complete protection from cognitive compromise associated with HIV.

Results from our study revealed that HIV-positive individuals with low CD4 cell count performed significantly more poorly than healthy controls on verbal and visual measures of memory, fine motor speed and dexterity, and visual scanning/cognitive flexibility. This pattern is consistent with observations of HIV-related cognitive impairment in the United States (Lojek & Bornstein, 2005). The observation that HIV patients with clade C performed below expectations on multiple cognitive tests raises the possibility that the frequency of dementia associated with clade C remains higher than previously reported. We cannot address this issue directly since the test battery did not consist of sufficient breadth and depth to fully examine cognitive performances across domains (e.g., attention, visuospatial function, etc.) and we did not collect information related to activities of daily living.

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Although we conducted multiple analyses and possibly raised the risk of type 1 errors, it is important to note that our findings are remarkably similar to recent preliminary investigations from studies conducted in central India (Das Gupta et al., 2005). Das Gupta et al. (2005) examined 119 asymptomatic patients with higher CD4 counts than patients in the present study. Cognitive tests were administered to tap the domains of motor speed, fluency, working memory, planning, and verbal learning and memory. Remarkably, despite the recruitment of individuals with asymptomatic disease, 51% of the HIV patients exhibited impairments (performances below the 15th percentile of seronegative individuals) in two cognitive domains, yet none of the patients exhibited functional impairments. In our study, 56% of the patients exhibited deficits on two domains, a finding that is highly consistent with the results reported by Das Gupta et al. (2005). Considered together, the results of the studies suggest that neuropsychological difficulties are evident across the spectrum of clade C disease severity.

In the present study, we did not obtain a structured assessment of possible functional limitations associated with the observed cognitive difficulties, and this is an important next step for future studies. Assessing functional limitations in HIV is not a straightforward task, and this can be particularly difficult in cross-cultural studies and in developing parts of the world. Standard questionnaires to address activities of daily living frequently administered in studies conducted in the United States may not have cultural relevance in other parts of the world. For example, the ability to manage complex financial responsibilities may have less application in regions such as southern India.

Heaton et al. (2004) recently examined ecologically valid measures of functional impairments in HIV. In this study, participants were required to complete "real-world" performance-based measures of daily living, including ability to balance a fictitious checking account, follow the procedural steps of a recipe to prepare a simple meal, driving simulation, medication adherence, shopping, and ability to maintain gainful employment. As noted earlier, not all of these functional domains could be readily integrated into cross-cultural applications, however assessments of cooking, shopping, medication adherence, and money management would be appropriate and sensitive to cognitive difficulties in these populations. Nevertheless, culturally relevant approaches to measurement of ADLs will be a critical next step in international HIV research and care. In addition, the impact of cognitive function and treatment of HIV with HAART on the ability to maintain gainful employment represents an area for future study in southern India.

The process of developing standardized test batteries for cross-cultural applications is not trivial, particularly when verbal items require translation and significant modification. In our study we modified one category of the verbal memory test in order to maximize cultural relevance of the stimuli, based on the feedback of our Indian coinvestigators and collaborators. However, we did not establish the validity of this modification, and therefore this represents an important area of future work. At least one previous study also examined cognitive function associated with HIV in developing countries using a well-known verbal memory test developed in the United States (Maj et al., 1994a; 1994b). To our knowledge, the test was not modified for cultural relevance in this multinational study and this may explain the finding that verbal auditory learning and memory was less sensitive to cognitive difficulties associated with HIV among individuals in Zaire, Kenya, and Thailand compared to Germany and Brazil. Results of our study revealed greater utility for verbal learning and memory, and this may reflect the additional steps undertaken in our study to modify the targets and foils of the list-learning task for cultural relevance to the local culture. Nevertheless, additional studies are needed to define the cross-cultural utility of the tests administered in the present study, including procedures fully consistent with international guidelines for test development and administration.

Additional limitations that warrant some discussion include the limited information that we obtained on some key psychosocial variables. For example, although we collected personal histories of major psychiatric disease, we did not obtain a quantified measure of depression. Similarly, a more structured assessment of substance use history and alcohol history would have been helpful. At this point there is relatively limited information regarding these behaviors among HIV-infected individuals in southern India, though there is a clinical perception that both factors are less problematic in India than in the Western world. The differences in language between the patient group (37% Telegu-speaking) and the healthy control group (87% Telegu-speaking) warrant caution in interpreting the results of the current study. However, we do not believe the differences in cognitive function between the groups can be entirely attributed to language issues, since analyses restricted to Telegu-speaking individuals across groups revealed significant differences in most, but not all, measures that differentiated the overall samples. Nevertheless, it will be important for future studies to consider psychiatric factors, substance abuse issues, and primary language in defining cognitive abnormalities associated with clade C.

Individuals in our study were examined prior to beginning pharmacotherapy for HIV. It will be important to determine whether we can identify improvement in cognitive function associated with treatment, as has been described in previous studies conducted in western cultures (Cohen et al., 2001; Robertson et al., 2004). Given the evidence from the present study and an independently completed study in India (Das Gupta et al., 2005) that clade C may not provide protection from cognitive compromise associated with HIV, an important next question is whether this strain of the virus can be controlled within the central nervous system via HAART in a manner to support cognitive recovery. The answer to this question will significantly advance our understanding of HIV in a global context.

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