HIV Clade-C Infection and Cognitive Impairment, Fatigue, Depression, and Quality of Life in Early-Stage Infection in Northern Indians

R. Cook, BA1, D. L. Jones, PhD1, R. Nehra, MD2, A. M. Kumar, PhD1, S. Prabhakar, MD2, D. Waldrop-Valverde, PhD3, S. Sharma, PhD2, and M. Kumar, PhD1
1Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL, USA
2Postgraduate Institute of Medical Education and Research, Chandigarh, Punjab, India
3Nell Hodgson Woodruff School of Nursing, Emory University, Atlanta, GA, USA

Abstract

HIV disease progression is associated with declining quality of life and overall health status, although most research in this domain has been conducted among Western populations where B is the infecting clade. This study sought to determine the effects of early-stage clade-C HIV infection (CD4 count ≥400 cells/mm³) on neurocognitive functioning, cognitive depression, and fatigue by comparing a matched sample of HIV-positive and HIV-negative Northern Indians. This study also examined the impact of these factors on quality of life within the HIV-positive individuals. HIV-positive participants demonstrated reduced cognitive functioning, increased fatigue, and lower quality of life. Fatigue and cognitive impairment interacted to negatively impact quality of life. Results suggest that early-stage HIV clade-C-infected individuals may experience subclinical symptoms, and further research is needed to explore the benefit of therapeutic interventions to ensure optimal clinical outcomes and maintain quality of life in this vulnerable population.

Keywords

early-stage HIV; cognitive impairment; fatigue; quality of life; India; clade C

Introduction

The availability of combination antiretroviral therapy (cART) for HIV has shifted the disease management to a chronic, rather than life-threatening, status. India, where most HIV infections are of clade-C strain, is home to the third largest HIV/AIDS population worldwide; approximately 2.4 million people live with HIV/AIDS.1 HIV clade-C differs from clade-B that is commonly found in the United States and most Western countries and is
a CCR5 tropic virus that may predominately infect macrophages, which are likely to affect the brain. Additionally, the structure of transactivating protein (Tat), which is highly neurotoxic in patients with clade-B infection, differs in clade C. At amino acid sequence 31, cystein is replaced by serine, which may render Tat nonneurotoxic in clade C. However, there are various other pathways such as gp 120 and high levels of tumor necrosis factor-α, which may result in neurocognitive deficits among clade-C-infected patients. Studies among southern Indian populations have examined the prevalence and severity of HIV-associated neurocognitive disorders (HAND) and quality of life among clade-C, HIV-positive individuals. However, research in this domain has rarely described northern Indian populations and has not described early-stage patients (here defined as those with CD4 count >400) prior to antiretro-viral (ARV) medication initiation.

A recently published profile of new HIV infections in northern India found that a substantial proportion of newly diagnosed patients entered care in the advanced stage of disease (CD4 count <200 cells/mm³). Untreated, HIV disease progression is associated with declining health and reduced quality of life, including increased depression, fatigue, and disrupted sleep. Quality of life has been associated with improved treatment outcomes, for example, high CD4 count and low viral load, and thus, is important to maintain. Quality of life is negatively impacted by depression, fatigue, and sleep disruption as well as by one of the most common but least understood complications of HIV, HIV-associated neurocognitive impairment.

The cART has nearly eliminated the most severe HIV-associated dementia, but the prevalence of milder forms of HIV-associated neurocognitive impairment, despite treatment with cART, has been the subject of ongoing research. Studies estimate cognitive impairment to affect 15% to 50% of all HIV clade-B-infected patients. Most recently, less severe cognitive impairment has been found to affect HIV-infected patients who were considered “normal” by previously existing neuropsychological measures. In addition, detection of HAND may be confounded by other factors, for example, education and depression. Finally, there is a lack of research describing the neuropsychological effects of HIV clade-C infection. Therefore, neurocognitive disorders in HIV-positive individuals may continue to be misdiagnosed or undiagnosed, especially in low- and middle-income countries where HIV clade-C is predominant. Delayed diagnosis and treatment onset may result in increasing cognitive impairment, which may thereby impact medication management behavior, reduce appointment adherence, and increase morbidity and mortality associated with HIV.

Depression and increased fatigue are among the most common symptoms of HIV. HIV-related fatigue has been associated with disability, reduced quality of life, and decreased ability to perform daily activities. Disrupted sleep has been associated with diminished treatment outcomes, that is, lower CD4 count, and may contribute to reduced cognitive functioning.

One of the most frequently utilized conceptual models of health-related quality of life, published by Wilson and Cleary, links physiological variables (eg, CD4 count) with symptoms of illness, functional status, perception of health, and overall quality of life along
a causal pathway, thus providing a framework for improving quality of life in the health care setting. Following this model, evaluation of individual symptoms of HIV, for example, depression and fatigue, and functional status, for example, cognitive impairment, may guide targeted strategies to improve quality of life among HIV clade-C-infected individuals. Thus, this study sought 2 primary aims: to determine the impact of early-stage clade-C HIV infection on neurocognitive functioning, depression, fatigue, and quality of life by comparing a matched sample of HIV-positive and HIV-negative Northern Indians and to evaluate the individual impact of these factors on quality of life in the HIV-positive sample. It was theorized that cognitive impairment, depression, and increased fatigue would be more prevalent in HIV-positive participants than HIV-negative participants and would negatively impact quality of life among HIV-positive patients.

Methods

Prior to study initiation, approval was obtained from the institutional review board, University of Miami, and the Ethical Review Committee, Postgraduate Institute of Medical Education & Research (PGIMER; Chandigarh, India).

Recruitment and Eligibility

This report presents baseline data from an ongoing prospective study on HIV and cognition in northern India. HIV-1 sero-positive participants were recruited from the clinics in the PGIMER, and HIV-negative control participants were recruited from nonspousal family and friends of HIV-positive patients. All participants were aged 18 to 45, with no history of head trauma, substance abuse, or opportunistic infections affecting the central nervous system. All sero-positive participants were early-stage HIV-1-infected patients with a confirmed CD4 count ≥400 cells/mm$^3$ and were not on ART. Prior to enrollment, confirmation of HIV-1 infection was obtained by enzyme-linked immunosorbent assay and Western Blot. Among studies carried out in India, sequence analysis showed that nearly all patients had C-clade infection and a few had recombinant-type clade infection. Although sequence studies were not carried out in the present investigation, it can be assumed that all participants had C-clade infection.

Measures

Demographics—The demographic questionnaire assessed age, employment status, religion, education, income, and ethnicity. Marital status, children, living situation, and time since diagnosis were also assessed.

Beck Depression Inventory

The Beck Depression Inventory II$^{34}$ is a 21-item Likert-type scale assessing depression, including somatic and cognitive subscales. Participants rate items from 0 to 3; total scores range from 0 to 63. Higher scores indicate higher depression; a score of 14 or higher may be indicative of moderate to severe depression. Since symptoms of somatic depression are very similar to those of HIV-related fatigue, only the cognitive depression subscale was examined in this study.
International HIV-Dementia Scale

The International HIV-Dementia Scale (IHDS) is a 31-item measure of quality of life, adapted from the WHOQOL-BREF with the addition of 6 questions specific to people living with HIV/AIDS. The WHOQOL-HIV BREF measures quality of life and satisfaction with health with 2 general questions as well as within 6 domains (physical, psychological, independence, social, environmental, and spiritual) and an overall score, with higher scores indicating higher quality of life. The WHOQOL-HIV BREF has demonstrated high internal consistency (Cronbach's α = .93).

Fatigue Visual Analog Scale—Fatigue was assessed using seven 100-mm visual analog scales, assessing different domains of fatigue-related symptoms (eg, feeling tired, feeling sleepy, having trouble concentrating). Participants indicated the severity of symptoms they were experiencing at the time of assessment by making a mark somewhere between the left (eg, feeling no fatigue) and right (eg, feeling extreme fatigue) ends of the scale. Because of the skew, each subscale was dichotomized into those endorsing symptoms (severity > 0) and those not endorsing symptoms (severity = 0). Added to the fatigue score were 2 items addressing sleep disruption. The first assessed whether participants’ previous night’s sleep was fewer hours than normal, and the second whether it was restful or not. Participants endorsing less sleep than normal or nonrestful sleep were considered to have disrupted sleep. Subscales were then summed to create a fatigue score, ranging from 0 (endorsed no symptoms) to 9 (endorsed all symptoms).

Statistical Analyses—Recruitment of controls from nonspousal family and friends of enrolled patients was conducted to minimize potential confounds in this sample; however, substantial differences in characteristics may still be present. Propensity score matching (PSM) was used to adjust for differences in covariates, allowing for a more accurate estimate of the effect of clade-C HIV infection on cognitive functioning, depression, fatigue, and quality of life. Propensity scores, the likelihood of being HIV infected given a set of covariates, were estimated for each participant using multivariable logistic regression. Cases were then matched, without replacement, with controls one to one based on the closest possible value of the propensity score (“nearest neighbor” matching), starting from the highest. A matching “caliper” of 0.2 standard deviations of the logit of the estimated propensity score was enforced in order to ensure that matches of poor fit were excluded. The PSM with a caliper results in a reduced sample that is similar with respect to the covariates included, allowing for estimates of the effects of interest to be measured with less bias. The PSM was conducted using a Statistical Package for the Social Sciences (SPSS v. 19.0, 2010,
Bivariate analyses (t tests, chi-square \( \chi^2 \) tests of independence) were conducted before and after matching to determine whether the differences in confounding variables were reduced or eliminated by PSM. Additional bivariate analyses were conducted in order to estimate the effect of early-stage HIV on depression, cognitive impairment, fatigue, and quality of life among the matched sample. Finally, multivariable regression was conducted to estimate the relative effects of cognitive impairment, depression, and fatigue on quality of life among HIV-positive participants. SPSS was utilized for all analyses; all statistical tests are presented at a 2-tailed significance level of \( P = .05 \).

**Results**

**Participant Demographics**

A total of 102 HIV-negative control individuals were enrolled; of the 258 HIV-positive individuals screened for eligibility, 58 were excluded from enrollment due to low CD4 count, and the remainder were enrolled (n = 200). In total, 158 men and 144 women were enrolled (N = 302), between 18 and 44 years of age (mean age = 29 ± 3). Most were married (64%), working (60%), and had a high school-level education or higher (62%). The majority were of the Hindu (61%) or Sikh (38%) faiths. All participants, but 1, identified Hindi as their first language, and 57% considered themselves bilingual (Hindi and English). Participants reported an average monthly income of 2993 Indian rupees (~ US$54) and were split according to the region of residence (50% urban or semiurban and 50% rural).

**Matching**

Propensity score matching, enforcing a 0.2 matching caliper, resulted in 75 HIV-positive and 75 HIV-negative participants in the analytical sample. The variables used to estimate propensity scores were age, gender, employment status, marital status, income, education, and living area as well as all interaction terms between these variables. After matching, there were no significant differences between HIV-positive and HIV-negative individuals in any matched variables (see Table 1). The overall balance test was nonsignificant, indicating good balance between groups, \( \chi^2 \) (7 degrees of freedom) = 2.8, \( P = .91 \). Table 1 presents the demographic information and results of tests of group differences after matching; matched sample n = 75 HIV-positive cases and n = 75 HIV-negative controls.

**Cognitive Functioning**

In the matched sample, mean total scores for cognitive functioning were 10.0 for HIV-positive participants and 10.7 for HIV-negative control participants. HIV-positive participants had lower scores on psychomotor speed (\( t_{148} = 3.36, P = .001 \)) and overall cognitive functioning (\( t = 3.46, P = .001 \)) than the control participants. Of the HIV-positive participants (n = 27), 36% had a total score of less than 10, suggesting potential HIV-associated neurocognitive dysfunction among this group. In contrast, 12% (n = 9) of HIV-negative control participants had a score of less than 10, \( \chi^2 \) (n = 150) = 11.2, \( P = .001 \).
**Fatigue and Cognitive Depression**

Mean fatigue scores were 1.4 for HIV-positive participants and 0.8 and for HIV-negative participants. HIV-positive participants reported more fatigue than those who were HIV-negative ($t_{48} = 2.4, p = .02$). Generally, participants did not report high levels of cognitive depression (mean [HIV-positive] = 3.8 ± 4.3, mean [HIV-negative] = 3.1 ± 3.3). HIV-positive and HIV-negative participants did not differ in cognitive symptoms of depression ($t = 1.2, P = .25$).

**Quality of Life**

Overall, HIV-positive participants reported lower quality of life than HIV-negative participants (mean [HIV-positive] = 90.1, mean [HIV-negative] = 96.5, $t_{48} = 2.7, P = .01$). Specifically, HIV-positive participants scored lower on physical functioning (mean [positive] = 15.3, mean [negative] = 17.1, $t = 4.1, P < .001$) and spiritual functioning (mean [positive] = 14.9, mean [negative] = 16.6, $t = 3.6, P < .001$) and had a trend toward lower scores on social functioning (mean [positive] = 15.4, mean [negative] = 16.4, $t = 1.76, P = .08$). In addition, HIV-positive participants reported less satisfaction with their health ($t = 2.5, P = .01$).

Regression analyses were conducted to evaluate the effects of depression, cognitive impairment, and fatigue on quality of life among HIV-positive individuals ($n = 75$). The results are presented in Table 2. In summary, fatigue negatively impacted quality of life, and there was an interaction between fatigue and cognitive impairment. For an HIV-positive person, each 1-point increase in fatigue predicted a 3.3-point decrease in quality of life, holding cognitive impairment constant. The interaction between fatigue and impairment demonstrates that as fatigue increased, cognitive impairment had a stronger negative impact on quality of life. Similarly, as cognitive impairment increased, fatigue had a stronger negative impact on quality of life.

The model, including all parameters, was significant and explained 29% of the variance in total quality of life ($F_{3,71} = 9.58, P < .001$, $R^2 = .29$). Because the predictors in this model are highly related to one another, multicollinearity statistics are also reported in Table 2 (variance inflation factor $\leq 1.1$ for all the predictors).

**Discussion**

This study sought to evaluate the impact of early-stage clade-C HIV infection on cognitive functioning, depression, fatigue, and quality of life by comparing a matched sample of HIV-positive and HIV-negative participants and to evaluate the impact of these factors on quality of life among HIV-positive participants. Reduced cognitive functioning and higher fatigue were observed in HIV-positive participants compared to HIV-negative control participants; however, there were no differences in depression. Reduced quality of life was observed in HIV-positive participants, even in the early stages of illness. Differences were identified in physical and spiritual functioning, suggesting that participants may have been negatively impacted by the symptoms of illness and worried about the consequences of their health even during the early stages of infection. Additionally, among HIV-positive participants,
while fatigue was associated with lower quality of life, the interactive effect of increased cognitive impairment and fatigue compounded their overall negative impact on quality of life. As cognitive impairment increased, the negative effect of fatigue on quality of life was enhanced.

Consistent with the previous research\textsuperscript{40}, early-stage HIV infection had a negative impact on cognitive functioning. This finding supports earlier research encouraging early identification and treatment of cognitive impairment, as impairment may persist despite viral suppression and has been linked with nadir CD4 count.\textsuperscript{15} More importantly, cognitive impairment may result in challenges to adherence to treatment, appointments, and engagement in care, resulting in increased HIV morbidity.\textsuperscript{26} Although recent recommendations support the initiation of ART for all the HIV-infected patients, regardless of the CD4 count,\textsuperscript{11} low- and middle-income countries, such as India, may initiate medication provision later in the disease progression and, as such, may encounter greater treatment-related challenges in provision of care to more cognitively impaired patients. Finally, in order to manage cognitive impairment, the patient's neuropsychological functioning should be considered by providers when selecting an ARV regimen, particularly since efavirenz has been associated with increased HIV-associated neurocognitive disorders.\textsuperscript{41}

Increased depression was not observed among HIV-positive participants in this sample; however, HIV-positive participants reported more fatigue. As HIV progresses, fatigue has been associated with the development of physical impairment, increased pain, and greater psychological distress.\textsuperscript{42} Additionally, fatigue and cognitive impairment interacted to jointly reduce the quality of life in this sample. Among individuals with increased cognitive challenges, fatigue may be experienced as a greater burden and compound the negative effect of HIV on quality of life.

This study was limited primarily by its relatively small sample size. Additionally, although PSM was employed to minimize bias, potential limitations have been raised regarding accurate evaluation of cognitive impairment using the IHDS in this population.\textsuperscript{20} Data on sleep disruption and fatigue only assessed the previous day, and while recall is likely accurate, it may not represent the participants’ typical experience of those symptoms. Finally, there may be other unmeasured covariates (eg, stigma, disclosure of HIV status, undiagnosed comorbidities) negatively impacting quality of life in HIV-positive participants.

In support of previous research among clade-C-infected Indian populations,\textsuperscript{2-4} neurocognitive impairment was detected in early-stage clade-C HIV-infected northern Indians. In addition, this study demonstrated the negative impact of cognitive impairment and fatigue on quality of life. Fatigue and cognitive impairment were found to have a synergistic role in the reduction in quality of life. This suggests that although physiological variables (ie, CD4 count) are still in the normal range, subclinical symptoms may still occur and quality of life may be negatively impacted, demonstrating the need for early evaluation of cognitive functioning and fatigue. Diagnosis of cognitive impairment during early-stage HIV infection is especially important, given the recent support for the use of highly active ART to prevent transmission and the associated potential for reduced adherence.\textsuperscript{43} Finally, although faced with constraints due to limited resources for large populations, research in
India has demonstrated that increased quality of life is achievable following initiation of ART. Further research is needed to explore the benefit of therapeutic interventions provided early in the disease progression to ensure optimal clinical outcomes and maintain quality of life in this vulnerable population.

Acknowledgments

Funding: The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was made possible by a grant from the National Institutes of Health, R01NS055653.

References


### Table 1

Demographics\(^{a}\)(Matched Sample).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV Positive, n = 75</th>
<th>HIV Negative, n = 75</th>
<th>(t)/(\chi^2), (P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>29 (6)</td>
<td>29 (6)</td>
<td>.26, .79</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td>.00, 1.0</td>
</tr>
<tr>
<td>Male</td>
<td>47 (63%)</td>
<td>47 (63%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>28 (37%)</td>
<td>28 (37%)</td>
<td></td>
</tr>
<tr>
<td>Employment status, n (%)</td>
<td></td>
<td></td>
<td>1.1, .29</td>
</tr>
<tr>
<td>Employed</td>
<td>48 (64%)</td>
<td>54 (72%)</td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>27 (36%)</td>
<td>21 (28%)</td>
<td></td>
</tr>
<tr>
<td>Monthly income (INR), M (SD)</td>
<td>3301.3 (4553.3)</td>
<td>3444.5 (4707.1)</td>
<td>.19, .85</td>
</tr>
<tr>
<td>Marital status, n (%)</td>
<td></td>
<td></td>
<td>1.9, .17</td>
</tr>
<tr>
<td>Single</td>
<td>30 (40%)</td>
<td>22 (30%)</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>45 (60%)</td>
<td>53 (71%)</td>
<td></td>
</tr>
<tr>
<td>Education level, n (%)</td>
<td></td>
<td></td>
<td>.46, .50</td>
</tr>
<tr>
<td>≤High school</td>
<td>50 (67%)</td>
<td>46 (61%)</td>
<td></td>
</tr>
<tr>
<td>&gt;High school</td>
<td>25 (33%)</td>
<td>29 (39%)</td>
<td></td>
</tr>
<tr>
<td>Living area, n (%)</td>
<td></td>
<td></td>
<td>1.9, .17</td>
</tr>
<tr>
<td>Urban</td>
<td>44 (59%)</td>
<td>52 (69%)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>31 (41%)</td>
<td>23 (31%)</td>
<td></td>
</tr>
<tr>
<td>CD4 count, M (SD)</td>
<td>586.9 (158.8)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: INR, Indian rupee; SD, standard deviation.

\(^{a}\) Matched sample.
Table 2

Quality of Life.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Outcome = Quality of Life</th>
<th>B (SE)</th>
<th>t</th>
<th>P</th>
<th>VIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intercept</td>
<td>90.22</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>−3.26 (.06)</td>
<td>5.04</td>
<td>&lt;.001</td>
<td>1.08</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>−0.49 (1.02)</td>
<td>0.48</td>
<td>.632</td>
<td>1.02</td>
</tr>
<tr>
<td>Fatigue × cognitive impairment</td>
<td>1.24 (.50)</td>
<td>2.49</td>
<td>.015</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Abbreviations: SE, standard error; VIF = Variance inflation factor.

\textsuperscript{a}HIV positive only, n = 75.