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# The effects of antiretroviral treatment initiation on cognition in HIV-infected individuals with advanced disease in Pune, India

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**Abstract** There has been a reduction in the most severe cases of HIV-associated neurocognitive disorders (HAND) with advances in antiretroviral treatment (ART). But the prevalence of milder forms of HAND still remains high. Data from systematically conducted studies on the effects of ART on cognition are scanty in India, where HIV-1 clade C is prevalent. The purpose of the present study was to assess the effect of antiretroviral therapy in HIV-seropositive (HIV+) individuals ($n$=92) with CD4 cell counts <200 cells/mm$^3$. The overall and domain-specific levels of cognitive functioning were determined using a locally recruited normative sample, and a change in neurocognitive functioning at the 1-year follow-up visit was analyzed. Results revealed cognitive impairment in 44.6 % of the HIV+ group at baseline. At the 1-year follow-up, the group showed significant improvement in the Learning domain ($p$<0.05). HIV+ individuals showing improvement in the global cognitive scores had a significantly lower baseline CD4 cell count compared to others. Overall, the degree of improvement associated with the magnitude of rise in CD4 suggests the possibility that early, mild subclinical deficits may also benefit from treatment.

**Keywords** HIV · Neurocognitive impairment · Antiretroviral therapy · CD4 count · HIV RNA

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## Introduction

With the introduction of combination antiretroviral therapy (cART), HIV has become a chronic manageable disease, resulting in increased longevity of infected individuals. While the severity of HIV-related cognitive impairment is less in the cART era, mild impairments remain prevalent (Heaton et al. 2010). Symptoms of neurocognitive dysfunction may include poor concentration or attention, confusion, impaired short-term or long-term memory, decreased problem-solving ability or ability to calculate, difficulty in learning new things, psychomotor slowing, decreased fine motor skills, problems in coordination, mood and personality changes, and altered behavior (Becker et al. 1997; Highleyman 2009). Neurocognitive impairment can range from mild to severe, and can sometimes occur in the early, asymptomatic stages of HIV disease (Grant and Atkinson 2000).

Most large studies have examined HIV-related impairment rates and the impact of ART initiation on cognition in HIV-1 clade B virus, a prevalent HIV variant in Europe and the United States (US) (Heaton et al. 1995, 2010; Sacktor et al. 2001; Marra et al. 2003; Robertson et al. 2004; Cysique et al. 2009). However, HIV-1 clade C is the most commonly observed clade globally (Buonaguro et al. 2007), and it has been reported that the rate of primary brain disease seen in clade C may be lower than that seen in clade B. It may be possibly linked to a defect in clade C Tat gene, which might be acting as a monocytic chemotactic chemokine (C31S) (Ranga et al. 2004). Since the Tat protein promotes viral replication directly, a functional change in the Tat protein could have a significant impact on the virulence of the infection monocytic chemotactic chemokine (C31S) (Ranga et al. 2004).

In India, where clade C is most prevalent, the studies in ART naïve populations have examined impairment rates within relatively small cohorts or with limited neuropsychological tests. Reports on the prevalence of HIV-associated dementia from southern and western India range from 3 to 7 % among untreated individuals (Satishchandra et al. 2000; Wadia et al. 2001). But a high prevalence of neurocognitive impairment (56 and 60.5 %) using standardized test batteries in ART naïve populations has been reported (Yepthomi et al. 2006; Gupta et al. 2007). In South Africa, with clade C as a predominant subtype, using a brief screening instrument (the HIV Dementia Scale), HAND was identified in 23.5 % of patients attending HIV clinics (Joska et al. 2010). In a later report, using a more comprehensive neuropsychological battery, 76 % of untreated HIV patients were classified as impaired (Joska et al. 2011). A recent study of ART naïve HIV+ patients in South Africa (Cross et al. 2013) found significant preservation or improvement in cognition following ART initiation, although the study was limited by the small number of participants available to adjust for practice effects.

A meta-analytic review of 23 studies indicated that ART was associated with modest improvements in attention, as well as executive and motor function. It was also reported that the NP performance of patients on and not on ART did not differ significantly (Al-Khindi et al. 2011). It has been recommended that development of pharmaceutical treatments and rehabilitation strategies targeting the cognitive effects of HIV infection is necessary. Similarly, a review (Cysique and Brew 2009) emphasized the need to address methodological limitations of published studies and the need for large and representative cross-disciplinary longitudinal investigations to explore the types and depth of neurocognitive impairment across the span of HIV illness.

To date, there are no reports in India of ART initiation on neurocognition in advanced cases of AIDS among individuals infected with HIV-1 clade C. The aim of the current study was to examine the impact of ART on cognition among HIV-infected individuals with advanced disease (CD <200 cells/$mm^3$) at the end of a 1-year follow-up.

## Methods

*Ethics statement* All data from the human subjects were collected in accordance and compliance with the standards outlined by the University of California at San Diego (UCSD) Human Research Protections Program and the Ethics Committee of the National AIDS Research Institute (NARI).

*Study population* A total of 92 HIV-1-infected and ARV-naïve individuals, with CD4 counts less than 200 cells/$mm^3$ and with more than or equal to 4 years of education, were recruited between October 2008 and August 2010. Eighty-nine age-, education-, and gender-matched HIV-uninfected individuals referred from the general community through the outreach program of the institute were recruited as controls to adjust for expected practice effects on the outcomes of cognitive tests.

At study entry, clinical, neurological, neurocognitive and laboratory evaluations were performed after collecting data on demographic characteristics. HIV-1-infected participants were initiated on ART as per the national guidelines (National guidelines 2007). All the participants completed 1-year follow-up evaluation.

*Neuropsychological evaluation* The neurocognitive test battery was based on that used at HIV Neurobehavioral Research Center (HNRC), San Diego, as well as in other international studies (Heaton et al. 2008). The tests were modified for administration in the local language (Marathi), and efforts were made to ensure and retain specific cultural relevance to the local Marathi-speaking population (e.g., modification of the words on the Verbal Learning Test). The neuropsychological evaluation

assessed seven ability domains: Executive Functioning (Category Test, Color Trails Test 2, Stroop Color-Word Test); Fluency (letter fluency); Speed of Information Processing (WAIS-III Digit Symbol Test, Symbol Search Test, Trail Making Test A, Color Trails Test 1, Stroop Color-Word Test): Attention/Working Memory (Paced Auditory Serial Addition Test, WMS-III Spatial Span Test); Learning (Brief Visuospatial Memory Test-Revised, Hopkins Verbal Learning Test-Revised); Memory (Brief Visuospatial Memory Test-Delayed, Hopkins Verbal Learning Test-Delayed); and Motor Performance (Grooved Pegboard Test—Dominant and Nondominant).

*Laboratory evaluation* Blood samples were collected at baseline to test for complete blood count, liver function test, renal function test, blood sugar, thyroid function tests (TSH, T3, and T4) and vitamin B12 levels for both groups. Additionally, CD4 count and viral load assays were performed in HIV-1-infected individuals at both visits. Participants were assessed for illicit drug use via urine toxicology screen at the time of NP testing. All the investigations mentioned above were done to rule out any confounding factors for neurocognitive impairment.

## Statistical analysis

To determine neurocognitive change from baseline to the follow-up visit, the multivariable regression change score approach was applied (Cysique et al. 2010; Heaton et al. 2014). In brief, longitudinal data from 140 HIV-seronegative control participants were used to generate regression-based change scores, which account for practice effect, regression toward the mean and other factors that may influence normal test-retest variability in neurologically stable people; these included test-retest interval, demographics, and overall baseline NP competence. These formulas were then applied to the current HIV-seropositive cohort and a subset of demographically matched HIV-seronegative controls in order to determine how much the actual follow-up scores (global and domain specific) varied from the predicted value. To determine the percent of the HIV-infected group who evidenced cognitive improvement or decline, the change scores that represented the upper 5th percentile (improved) and lower 5th percentile (declined) of the change score distribution in the normative group were applied.

Within-domain, global multivariable regression change scores were tested for equality between HIV+ (infected) and HIV− (normative) groups using *t* tests (Wilcoxon rank sum test for Working Memory). *P* values and 95 % confidence intervals of the group differences of the means were calculated. Since the extent of distribution of ART drugs into the central nervous system (CNS) may influence cognition (Cysique et al. 2011), the CNS Penetration Effectiveness (CPE) score was calculated for each regimen that each participant was on at the follow-up visit (Letendre et al. 2008). A higher number indicates greater penetration. Mean regression change score comparisons among ART regimens at the follow-up visit were made using ANOVA or Kruskal-Wallis tests (3 comparisons) and *t* tests or Wilcoxon rank-sum tests (2 comparisons); a Tukey HSD test was applied for post hoc paired comparisons for 3-regimen comparisons. The statistical analysis was done using JMP® (SAS Institute Inc. 2013. JMP® 11. Cary, NC: SAS Institute Inc.) and *R* statistical software (*R* core team 2013 http://www.R-project.org/).

## Results

Table 1 provides a summary of baseline demographic, clinical and laboratory characteristics for the HIV+ group. By design and the selection criteria, the group was immunocompromised [mean CD4 count=117.9 cells/mm$^3$ (SD 53.6)], with a nadir CD4 at a similar level to the current CD4 levels. All participants had detectable HIV RNA levels in plasma. Twenty-four percent of the participants had a history of an AIDS-defining illness (CDC stage C). Applying the demographically corrected NP scores computed using a large normative sample, global cognitive impairment was seen in 44.6 % of the patients, with 51 % of the impaired having mild, 27 % having

**Table 1** Baseline demographic, clinical and laboratory characteristics of the HIV-infected participants in Pune, India

| Characteristics | HIV infected ($n$=92) |
|---|---|
| Age (year) | 35.59 (6.86) |
| Gender (% male) | 59 % |
| Education (year) | 9.14 (2.46) |
| Employed (%) | 73 % |
| Time since the first positive HIV test | 6.78 (5.25) |
| Current mean CD4 (cells/mm$^3$) | 117.9 (53.6) |
| Nadir CD4 count (cells/mm$^3$) | 113.1 (51.5) |
| Plasma HIV RNA ($\log_{10}$) | 4.93 (0.73) |
| Disease stage (%) | |
| CDC A | 60 % |
| CDC B | 15 % |
| CDC C | 25 % |
| Triiodothyronine (T3) levels (ng/ml)[a] | 1.07 (0.9 -1.20) |
| Thyroxin (T4) levels (μ/dl)[a] | 6.92 (5.85 - 8.58) |
| Vitamin B12 levels (pg/ml)[a] | 204 (143–278) |
| Thyroid stimulating hormone (TSH) levels (IU/ml)[a] | 1.85 (1.23 - 3.00) |
| HBsAg positive (%)[b] | 3.20 % |
| Neuropsychologically impaired (%) | 44.6 % |

[a] Median (Interquartile range [IQR])

[b] Hepatitis B surface antigen (HBsAg)

mild to moderate, and 22 % having moderate levels of impairment. Within the globally impaired group, impairment rates were relatively similar across all domains (Working Memory [39 %], Motor Functioning [41 %], Verbal Fluency [45 %], Executive [46 %], Speed of Information Processing [56 %], Learning [41 %], and Recall [41 %]).

At the 1-year follow-up, the ART regimens consisted of 3TC/NVP/ZDV (62 % of participants), 3TC/NVP/D4T (25 %), 3TC/D4T/EFV (9.8 %), 3TC/EFV/ZDV (2 %), and 3TC/EFV/TDF (1 %). The median time on the current regimen was 11.7 months (IQR 10.1, 11.9). The HIV+ group demonstrated a significant improvement in CD4+ T cells [mean increase of 152.5 (SD 94.7) cells/mm$^3$], achieving a mean CD4+ T cell count of 270.3/mm$^3$ (SD 111.3; $p<0.0001$). Plasma HIV RNA was undetectable (<400 copies/ml) in 86/92 (93.5 %) of the participants.

As shown in Fig. 1, using the summary regression-based change scores (RCS) that adjust for baseline performance and other factors, the degree of global cognitive change in the HIV-infected group was not significantly different from the values that would be expected in a normal, uninfected group at the global (overall) level. With respect to specific cognitive domains, the HIV+ group showed significantly greater improvement in the Learning domain, while changes in other cognitive domains were not significantly different from predicted values (all $p>0.18$). Improvement in Learning was seen in both HIV+ NP impaired (RCS=0.25 [0.73]) and HIV+ NP normal (RCS=0.36 [0.76]), compared to the expected improvement (HIV−; RCS=0.01 [0.79]; overall $p=0.031$; HIV+ NL>expected using Tukey HSD). There was a nonsignificant trend ($p=0.09$) for an interaction between baseline CD4 and HIV RNA to be associated with improvement in the Learning domain, with greater improvement seen in individuals with relatively low baseline CD4 cell counts and high HIV RNA levels, while those who started with a relatively high CD4 (and high RNA) showed lower levels of improved functioning. The participants who evidenced the greatest increase in CD4 and decrease in HIV RNA levels at follow-up tended to have the greatest degree of improvement in the Learning domain (Fig. 2; $p=0.11$).

In order to determine the possible impact of ART CPE on cognitive change at the follow-up visit, we examined the 3 regimens with >2 participants on the regimen: 3TC/NVP/ZDV ($n=57$), 3TC/NVP/D4T ($n=23$), and 3TC/D4T/EFV ($n=9$) and grouped them into either higher (CPE=10 [3TC/NVP/ZDV]) or lower (CPE=8 [3TC/NVP/D4T] or CPE=7 [3TC/D4T/EFV]) CPE groups. The higher CPE group was on their regimen for a significantly greater number of months (11.3 [1.7]) compared to the lower CPE group (9.3 [3.5]; $p<.001$). CPE status had a significant effect on Working Memory ($p=0.029$), with the lower CPE group exhibiting a decline at the follow-up visit (change score=−.36 [.92]), while the higher CPE group performed near expected levels (change score=.09 [.94]). Differences were not seen in the other domains. Controlling for months on the current regimen, the statistical significance weakened slightly, but the subjects on the lower CPE regimen still had greater decline than those in the higher CPE group ($p=0.06$).

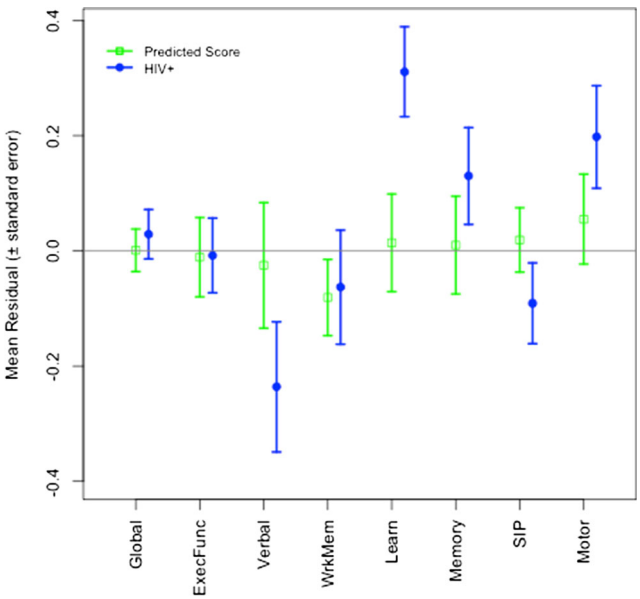


**Fig. 1** Global and domain-specific residuals from multiple regression change scores that adjust for baseline performance, practice effects, regression to the mean, and other factors described in the text. Predicted scores indicate the amount of change seen in demographically matched HIV-controls. A positive residual indicates better-than-expected performance at follow-up, while a negative score indicates lower-than-expected performance

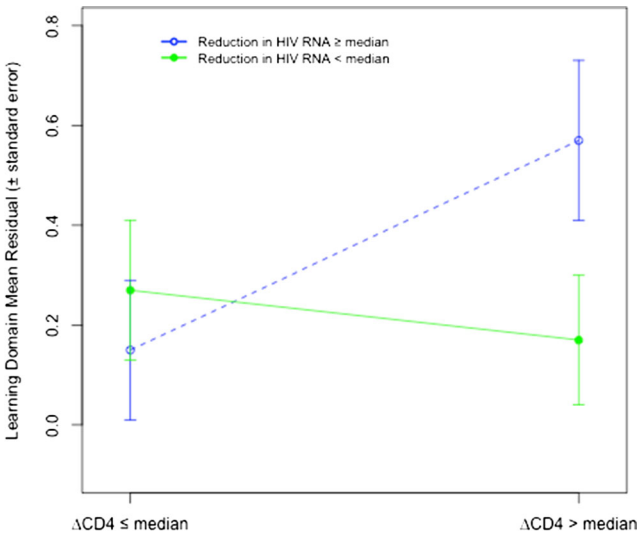


**Fig. 2** Graph demonstrating the interaction between CD4 and HIV RNA changes over 1 year on regression-based change scores for the 1-year, post-ART initiation visit. Higher values indicate better-than-predicted performance. While improvement was seen broadly within the entire HIV+ group, the greatest improvement was seen in participants with greater changes in CD4 (increase) and HIV RNA (decrease)

When comparing the four baseline impairment categories on global cognitive changes, differences fell short of significance ($p$=0.07), but the moderately globally impaired group had the greatest improvement (RCS=0.28 [0.31]) as compared to the mild (RCS=−0.11 [0.38]) and the group with mild to moderate (RCS=−0.09, [0.32]) being closer to the unimpaired levels (RCS=0.07 [0.44]).

In applying norms for change, which classify *individuals* as significantly improved or declined, 15.2 % of HIV-infected participants were classified as globally improved, 6.5 % deteriorated, and 78.3 % were cognitively stable. The HIV-infected individuals that showed improvement did not differ from the other HIV+ participants in demographics nor baseline HIV RNA levels (all $p$>0.30), but they did start at significantly lower baseline CD4 cell counts (71.6 [31.1] vs. 129.7 [57.1]; $p$=0.0004).

## Discussion

This study examined the effects of ART initiation on cognition in a cohort of ART-naïve individuals with advanced HIV disease using a comprehensive NP test battery assessing seven cognitive domains. A significant rise in the mean CD4 counts and suppression in viral load in the majority of the infected individuals indicated excellent medication adherence. Overall, the level of improvement in cognition was modest. Approximately 15 % were classified as improved globally; the group with the lowest level of functioning at baseline demonstrated the greatest degree of improvement. Within the cognitive domains, significant improvement was seen only in the Learning domain, with the most improvement seen in participants who had the largest recovery of CD4 cell counts and greatest decline in plasma HIV RNA. Of note, there were no indications of overall cognitive *decline* in the HIV-infected group, and ~80 % of the cohort was stable and did not deteriorate in spite of low CD4 counts at baseline.

There have been a number of reports on beneficial aspects of ARV therapy (Sacktor et al. 1999, 2003; Cohen et al. 2001; Marra et al. 2003; Letendre et al. 2004). Cysique et al. (2009) found that improvement with treatment was seen with longer periods of treatment (up to 48 weeks), and that the degree of improvement was greatest in those with the worst baseline performance, although improvement was seen in participants with less severe impairments as well. More recent studies have also reported benefits of ART, but have had some methodological limitations. For example, a large study conducted across numerous resource-limited settings with participants with a CD4<300 reported significant improvements on a brief NP battery after ART initiation, with the exception of semantic verbal fluency (Robertson et al. 2012a, b). These improvements, in relation to baseline performance, were sustained over 3 years of follow-up. Greater NP performance was associated with better NP scores, lower RNA, and higher CD4 cell counts at baseline. Given the complexities of capturing this data longitudinally across diverse sites, the study lacked longitudinal norms and thus was limited in its ability to address whether the improvement was due to improved CNS functioning, greater overall health, practice effects, or a combination of these factors. Similarly, a recent study from Nigeria reported that ART helped in significantly improving cognitive performances among treated HIV-positive patients in all tested domains with the exception of motor speed (Obiabo et al. 2012), although the authors did not adjust for possible practice effects.

Despite generally positive findings regarding the cognitive benefits of ART initiation, such findings are not universal and not all patients improve with treatment (Cysique et al. 2009; Al-Khindi et al. 2011; Joska et al. 2012). Indeed, some patients show neuropsychological decline while on apparently effective treatment (Robertson et al. 2007a, b; Cysique et al. 2006). A recent study in South Africa found significant improvement in individuals with late stage HIV disease after commencing HAART. However, while improvement across a number of NP domains was observed, high rates of impairment persisted (Joska et al. 2012). In this vein, concerns have been raised about the possible neurotoxicity of ARV treatments (Robertson et al. 2012a, b).

Overall, a meta-analytic review of cognitive function after ART initiation concluded that although ART was associated with modest improvements in attention, executive function, and motor function, there was not much improvement in language, visual memory, or visuospatial function (Al-Khindi et al. 2011). The authors noted that the degree of cognitive improvement was often correlated with the change in CD4 cell count, indicating a possible connection between cognitive status and immune system integrity.

There are a number of challenges in trying to compare NP results across treatment studies, including significant variability in sample sizes, participant characteristics (e.g., level of immunosuppression), comprehensiveness of the cognitive battery, and application/availability of country-specific or population-based normative corrections. Importantly, ART studies frequently lack the ability to address the complexities inherent in controlling for practice effects and regression to the mean, which may result in an overestimate of the level of improvement seen in individuals who start at lower performance levels.

The current study adds to the growing literature on the effects of ART initiation on cognition, and addresses some of the limitations of prior studies. We utilized a comprehensive battery assessing seven cognitive domains, thus likely providing good sensitivity to cognitive changes over time. Importantly, we were able to adjust our analyses for not only practice effects, but also for regression to the mean and other predictors of follow-up NP performance. In addition, we applied

regression change scores and norms for change to identify individuals who improved or declined on treatment.

As noted in a number of review articles, we found the cognitive benefits of ART to be modest, at least over the 1-year follow-up period for this study. In contrast to Robertson et al. (2007a, b), but consistent with Cysique et al. (2009), in our cohort, the greatest global improvement was seen in those who were the most impaired at baseline. Importantly, unlike most studies examining cognitive change, by using the regression-based approach, we were able to minimize the possibility that this improvement in low-scoring individuals simply represents a regression to the mean. The degree of improvement was associated with the magnitude of rise in CD4 and decline in HIV RNA, corroborating with a review (Al-Khindi et al. 2011) indicating a link between immune function, virologic control, and cognitive change. ART regimens with lower estimated effectiveness in the CNS tended to be associated with decline in Working Memory, although no other differences were observed in other domains or in global change. The power of this study to detect differences between regimens may have been suboptimal, with a constrained distribution of CPE values (7–10) that fall in the upper half of the CPE distribution. Given that the time on regimen also varied by CPE, examining the possible benefit or cost of CNS penetration over longer treatment periods will be important. Improvement was also seen in HIV+ individuals who were not classified as impaired at baseline, suggesting the possibility that early, mild subclinical declines may also benefit from treatment before reaching more severe stages.

There are a number of hypothetical reasons why cognitive impairment may persist despite ART and viral suppression in the periphery. Although the cut-off of <400 RNA copies/μl is commonly employed for a classification of viral suppression, newer assays enable detection of even a very small number of RNA copies. It is important to consider the possibility that even limited HIV replication results in neural damage, in part possibly due to on-going inflammatory processes (Cysique and Brew 2011). A failure to fully eradicate the virus, despite nondetectability using common assays, may also result in on-going processes that are injurious to the CNS. For example, the detection of proviral DNA has been associated with impairment (Valcour et al. 2013). In addition, it has been suggested that a subgroup of patients who have achieved virological suppression may have chronic, inactive impairments, perhaps occurring during periods of immunosuppression (McArthur et al. 2005). This could be the case in a subset of the individuals in the current study who initiated treatment when CD4 cell counts were less than 200.

There are limitations to the current study. While we were able to control for factors predicting follow-up scores, and use the improvement in performance that one might expect from similar uninfected controls, it would have been ideal to also have a more direct comparison group of individuals with advanced HIV disease who did not initiate ART. This would have enabled us to better differentiate not only cognitive improvements associated with ART, but also whether such treatment helps prevent cognitive decline. However, with given current guidelines, such a study would not have been ethical. For this project lumbar punctures were not feasible, and thus we cannot comment on whether participants achieved CNS viral suppression in addition to suppression in the periphery. In addition, the study only examined 1 year of follow-up, and it is possible that the cognitive benefits, or potential neurotoxicity-associated changes, may only emerge over longer time periods (Joska et al. 2012). Future studies should include cognitive evaluations among individuals who have achieved sustained viral suppression.

The present findings suggest that it is important for clinicians and health care providers to ask patients with advanced disease about any difficulties with cognition or performing daily activities. Given some of the limitations of self-report, it would also be important to institute routine, brief screening for cognitive impairments. It would be helpful to inform the patients regarding the possibility of neurocognitive impairment during counseling sessions. The family members or the care givers of these individuals should also be informed about the same so that they can detect these changes and seek timely advice from the health care providers. This would help HIV-infected individuals in coping with their condition and deficiencies. The same information could help the neuropsychiatrists in employing specific and targeted cognitive and behavioral therapies and will also help to manage their patients better thereby helping them to improve the quality of life. They could explore this area further through focused research.

It would also be important to follow AIDS patients for the changes in neurocognition even after ART initiation, to study the course of the changes in impairment. The central nervous system penetration scores of antiretroviral drugs in the first-line regimen in the Government ART Program in India are high (Letendre et al. 2008, 2009) and, hence, timely initiation of ART may be helpful in restricting neurocognitive impairment. The beneficial effect of ART observed in our study supports the initiative to ensure timely initiation of ART and the importance of drug adherence in HIV-infected individuals. It would also be important to explore neurocognitive impairment and the effect of ART in patients on second line treatment in the national ART program as they have lower central nervous system penetration scores.

This study may be valuable in planning further studies on the long-term effects of antiretroviral drugs, imaging and cerebrospinal fluid (CSF) studies in HIV-infected individuals with neurocognitive disorders. The need to undertake multicenter and larger studies in India has emerged out of this study if this and future findings are to be translated into policies and programs for HIV prevention and control. It would be helpful

to sensitize and train HIV clinicians and counselors in diagnosis and management of neurocognitive impairment.

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**Conflict of interest** The authors declare that they have no conflict of interest.

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