Journal of NeuroVirology, 14: 480–485, 2008

ISSN 1355-0284 print / 1538-2443 online
DOI: 10.1080/13550280802304746

informa
healthcare

Cognitive changes in asymptomatic drug-naïve human immunodeficiency virus type 1 clade C infection

K Gopukumar,[1] Shobini L Rao,[1] P Satishchandra,[2] Jayashree Dasgupta,[1] Ronald J Ellis,[6] DK Subbakrishna,[4] P Mariamma,[4] Anupa Kamat,[5] Anita Desai,[5] V Ravi,[5] BS Rao,[7] KS Satish,[7] and Mahendra Kumar[8]

Departments of [1]Mental Health and Social Psychology, [2]Neurology, [4]Biostatistics and [5]Neurovirology, National Institute of Mental Health and Neurosciences, Bangalore, India; [3]University of California, San Diego, La Jolla, California, USA; [6]Dept. of Neurosciences and HIV Neurobehavioral Research Center, University of California, San Diego; [7]Seva Free Clinic, Bangalore, India; [8]University of Miami School of Medicine, Miami, Florida, USA

Asymptomatic human immunodeficiency virus (HIV) infection is associated with impaired cognitive functioning in both clade B and C infections. The nature of cognitive change longitudinally has not been studied in asymptomatic clade C infection. The present study evaluated changes in neuropsychological functioning over a 2½-year period in a cohort of HIV-1 clade C–infected asymptomatic individuals from South India. Participants with CD4 counts below 250 were started on highly active antiretroviral therapy (HAART) as per National AIDS Control Organisation (NACO) guidelines and hence excluded. The sample consisted of 68 patients (30 men and 38 women), with a mean age of 29.4 years (SD = 5.6 years) and a mean education of 10.0 years (SD = 2.7 years). A comprehensive neuropsychological assessment with 12 tests yielding 21 variables was used to examine cognitive functioning at baseline and subsequently at 6-monthly intervals for five follow-ups. Shift in CD4 and viral load categories measured by the McNemar's test indicated disease progression. Latent growth curve (LGC) modeling assessed the nature of change in cognition over the 2½-year study period. Ten variables representing attention, executive functions, and long-term memory fit the LGC model. Excepting visual working memory, the slope was nonsignificant for nine variables, indicating absence of deterioration in cognition over a 2½-year period. However, CD4 and viral load levels worsened, indicating disease progression. Asymptomatic individuals with HIV-1 clade C infection do not show any significant decline on individual neuropsychological functions over 2½ years despite disease progression, as evidenced by immune suppression and viral loads. *Journal of NeuroVirology* (2008) **14,** 480–485.

Keywords: cognition; HIV I clade C; natural history

Introduction

Asymptomatic human immunodeficiency virus (HIV) infection is associated with impaired cognitive functioning in both clade B and C virus types. In studies from the United States and Europe, where clade B predominates, deficits of verbal memory, abstraction, speed of information processing, attention, fluency, and psychomotor skills are present (Grant *et al,* 1987). Studies in India on individuals with HIV-1 infection with clade C virus have shown similar deficits in the domains of attention, motor speed, fluency, working memory, and long-term memory (Yepthomi *et al*, 2006; Das Gupta *et al*, 2007). The prevalence of cognitive deficits in asymptomatic HIV-1 infection is 30% to 66% in

Address correspondence to Prof. Dr. Shobini L. Rao, PhD, Mental Health and Social Psychology, National Institute of Mental Health and Neurosciences, P.B. 2900, Bangalore, 560029 India. E-mail: shobini.rao@gmail.com

The authors are grateful to all the research staff of NIMHANS, Bangalore, and Miami University, Florida, for their cooperation. This study was supported by NIH grant R01 NS 41205.

Received 14 February 2008; revised 2 April 2008; accepted 27 May 2008.

clade B virus (White, 1995). In clade C virus type, cross-sectional studies with detailed neuropsychological evaluation found the prevalence of cognitive deficits to be 56% (Yepthomi *et al*, 2006) and 60% (Das Gupta *et al*, 2007).

The progress of cognitive deficits in HIV infection is examined with repeated neuropsychological assessments. Three approaches have examined cognitive changes in asymptomatic individuals with clade B virus. The first approach is longitudinal and examines clinical progression from the asymptomatic to the symptomatic stage and further to the acquired immunodeficiency syndrome (AIDS) stage in the same set of individuals. The study duration is long extending over 8 to 9 years. Concurrent to the examination of clinical progression, changes in cognitive functioning are also studied (MACS; Baldewicz *et al*, 2004). The second approach is cross-sectional and examines cognitive changes in three different groups of individuals, i.e., asymptomatic individuals, symptomatic individuals, and individuals with AIDS (Heaton *et al*, 1995). The third approach examines cognitive changes only in the asymptomatic group. The study duration is short and has been 3 years (Villa *et al*, 1996; Karlsen *et al*, 1993). None of the above three approaches have found cognitive decline in the asymptomatic stage.

Nature of cognitive changes in the asymptomatic stage has not been studied in HIV 1 clade C infection. The present study is the first attempt to evaluate changes in neuropsychological functioning in HIV-1 clade C–infected asymptomatic cohort longitudinally. A baseline neuropsychological assessment was done and then subsequently followed by 6-monthly neuropsychological assessments. Thus each participant was evaluated systematically over a 2½-year period. The present study is the first of its kind to investigate the rate of progression of cognitive changes among clade C HIV-1–seropositive individuals.

Results

Changes in performance across follow-up assessments

Latent growth curve (LGC) analysis was performed on the 21 neuropsychological variables belonging to the 12 tests across the six time points, i.e., baseline and five follow-up assessments. For each score, the fit of the observed data with the LGC model was calculated using chi-square test. The fit index of each variable is also shown. A fit index greater than 0.90 indicates a good fit with LGC model (Bollen, 1989). Even though the literature on latent structure modeling methods suggest that a fit index of 0.9 and above will be good, we strongly feel that in substantive research, flexibility is needed given the nature of measurement, the sample in which it is measured, the repeated measurement design, etc. As the study was carried out with repeat assessments in an infected sample, variation in performance could be present. Hence a fit index greater than 0.80 was taken as an indication of good fit with the LGC model. The 10 variables for which the chi-square was significant and the fit index exceeded 0.80 are shown in Table 1. Intercept and slope values are also given. Slopes that are not significant indicate that there was no change across the six time points. Significant slopes have a positive or negative sign. Accuracy scores with a positive sign and reaction time scores or error scores with a negative sign indicate improvement over time. Table 1 shows that the slope was not significant in 9 of the 10 variables, indicating that there was no change in these variables across the 2½-year followup. The slope of visual working memory 1 back hits was significant but negative. As the score of hits is an accuracy score, the negative slope indicates deterioration.

Changes in immune suppression

The mean (SD) CD4 values at baseline, 6 months, 1 year, 1.5 years, 2 year, and 2.5 years, respectively, were 417.6 (210.9), 415.9 (239.9), 370.1(187.0), 383.8 (202.2), 361.4 (197.7), and 389.3 (184.3). The CD4 values at each of the time points were calculated on the chi-square = 597.5 based on 17 degrees of freedom (*df*) with $P < .001$. Comparative fit index (CFI) = 0.483, with a root mean square error of application (rmsea) = 0.576 and 90% confidence interval of rmsea (0.534, 0.613). The intercept (INT) is given by $F1 = 400.620 \times V999 + 1.000\ D1$. The slope (SLP) is given by $F2 = -2.274 \times V999 + 1.000\ D2$. The LGC shows a slow decline in CD4 count. The shift from a higher to a lower CD4 count indicates greater immune suppression and hence disease progression.

Changes in viral load

The mean (SD) log viral load values at baseline, end of 1st year, and end of 2nd year, respectively, were 4.95 (0.89), 5.19 (0.66), and 5.29 (0.73). Analysis of variance (ANOVA) showed a significant time effect ($F = 5.32$, $df = 2$, $P < .006$). Post hoc comparisons with Bonferroni tests showed significant increase at the end of the 1st year and 2nd year as compared with the baseline. The viral load values between the end of the 1st and 2nd years did not differ. The shift from a lower to a higher viral load indicates progression of the disease. The disease has progressed from baseline to the end of the 1st year but stabilized subsequently.

Association between CD4 and viral load

CD4 and viral load were not correlated at baseline and the 1-year follow-up. On the other hand, at the 2-year follow-up, CD4 and viral load were negatively correlated ($r = -.257$; $P > .05$).

Table 1 Latent growth curve (LGC) analysis of neuropsychological performance across six assessments

NP variables	Baseline assessment (mean ± SD)	1st follow-up	2nd follow-up	3rd follow-up	4th follow-up	5th follow-up	Fit statistics		Growth parameter estimates	
		mean ± SD	mean ± SD	mean ± SD	mean ± SD	mean ± SD	χ2-value	Comparative fit index (CFI)	Intercept	Slope
CT2_1	159.67 ± 56.49	142.34 ± 48.67	128.56 ± 43.55	125.33 ± 51.01	121.94 ± 42.59	128.55 ± 43.95	46.88*	0.88	149.35	−7.33
FT_LH	39.17 ± 5.78	38.79 ± 5.89	39.33 ± 5.48	39.08 ± 5.77	37.93 ± 5.25	36.95 ± 6.90	39.34*	0.91	39.34	−0.25
PF	6.78 ± 3.06	6.52 ± 3.08	7.67 ± 3.17	6.56 ± 2.90	6.58 ± 2.44	6.09 ± 2.93	58.28*	0.87	6.95	−0.09
CAT_FLY	11.93 ± 3.34	12.03 ± 2.75	12.74 ± 3.06	11.75 ± 2.79	11.46 ± 2.61	12.15 ± 2.54	31.45*	0.85	12.10	−0.05
DF_FIX	9.2 ± 4.41	11.57 ± 5.17	11.55 ± 4.69	11.82 ± 5.18	9.83 ± 5.12	6.40 ± 3.87	122.33*	0.93	11.56	−0.49
VIM_1	7.29 ± 1.56	7.29 ± 0.46	7.29 ± 0.31	7.01 ± 0.85	7.11 ± 0.57	7.16 ± 1.44	25.84**	0.80	7.30	−0.04**
AVLT_IR	10.64 ± 2.57	10.39 ± 2.45	11.18 ± 2.32	10.37 ± 2.96	10.69 ± 2.15	11.07 ± 2.38	35.73*	0.88	10.60	0.63
AVLT_DR	10.83 ± 2.68	10.03 ± 2.77	11.1 ± 2.56	10.26 ± 3.00	10.57 ± 2.38	10.52 ± 2.65	37.00*	0.85	1.62	−0.02
CFT_IR	16.86 ± 7.26	19.75 ± 7.64	19.78 ± 7.35	22.65 ± 7.73	20.69 ± 6.53	23.38 ± 7.01	44.00*	0.87	17.82	1.07
CFT_DR	16.2 ± 7.19	19.96 ± 7.82	19.5 ± 7.49	22.34 ± 7.64	19.77 ± 6.13	23.26 ± 6.98	57.35*	0.82	17.45	1.06

Note. *Significant at $P < .01$ level. **Significant at $P < .05$ level.
CT1 = Color Trails1; CT2 = Color Trails 2; PF = Phonemic Fluency; CAT_FY = Category Fluency; DF_Fix = Design Fluency Fixed Condition; VM1 = Verbal Working Memory 1—back hits; AVLT_IR = Auditory Verbal Learning Test Immediate Recall; AVLT_DR = Auditory Verbal Learning Test Delayed Recall; CFT_IR = Complex Figure Test Immediate Recall; CFT_DR = Complex Figure Test Delayed Recall.

Discussion

This is the first study examining neuropsychological changes longitudinally over time associated with clade C virus in asymptomatic HIV-1+ individuals from South India. The transmission of the virus was through heterosexual contact. The study was prospective in nature. Findings show that over the 2-year period, there was a shift in CD4 categories, with a significant number of participants having lower CD4 counts. There was also a significant category shift to higher levels of viral load over the 2 years, indicating clinical progression of the illness over the 2½-year period in ART-naïve HIV-1+ participants.

Change in neuropsychological functioning was assessed using latent growth curve modeling. Of the 10 variables that fit the model and could be interpreted, there was only a significant deterioration in visual working memory. There was no significant change in any of the other neuropsychological functions. As there was no change in majority of neuropsychological functions, results suggest absence of cognitive decline over a 2½-year period in this cohort of asymptomatic, drug-naïve individuals with HIV-1 clade C infection.

The repeated assessments could have led to a practice effect, which could have masked a deterioration in cognition. However, use of the LGC for analyzing changes in cognition over time appears to have removed the effects of practice for the following reasons: (a) LGC assumes a model of linear growth. Table 1 shows that the slope values are small for most variables, i.e., around 1 or below 1, which indicates that the assumption of linear growth is valid. As there are no sudden jumps in the mean values across the assessments, practice effects are unlikely. (b) Further on, the tests of Color Trails, Phonemic and Category fluency, Auditory Verbal Learning Test (AVLT), and Complex Figure Test (CFT) alternate forms were used on successive assessments to mitigate practice effects.

One of the reasons for there not being a decline in the cognitive functioning could be that individuals who had significantly worsened (CD4 less than 250/mm^3) to require administration of HAART were excluded. Subjects whose CD4 counts declined below 250/mm^3 required ART according to ethical guidelines prescribed by NACO. As ART can improve cognition, subjects who were on ART were excluded from this study. Only the drug-naïve participants who had CD4 more than 250/mm^3 were longitudinally followed in this study over the 2½ years. The results showed a clinical progression of the illness, as evidenced by the decline of CD4 counts and increasing viral load. However, the cognitive functioning did not decline significantly.

Longitudinal studies have examined cognitive functioning in relationship to disease progression in clade B virus. These studies have found that

deterioration in cognitive functioning is related to disease progression. As individuals progress onto acquired immunodeficiency syndrome (AIDS), a greater number of cognitive deficits are seen. (Selnes *et al*, 1990). Karlsen *et al* (1993) carried out a 2-year follow-up study examining cognitive functioning in HIV-seropositive adults from the Norway where clade B virus predominates. Over the 2-year period, they found no correlation between CD4 count and neuropsychological performance. Only a few participants progressed from asymptomatic HIV to AIDS, indicating slow progression of the illness. In addition, there was no significant cognitive decline over this time period. Supporting the absence of cognitive decline found in the above study, the present study also did not find worsening of cognitive functions in the drug-naïve HIV clade C–infected individuals over 2½ years.

Our study found that stability of cognitive functioning in the asymptomatic stage is present even in clade C virus, which is similar to findings in clade B virus (Heaton *et al*, 1995). A limitation of the study is the short follow-up period of 2½ years. As studies in clade B virus have shown, cognitive decline when the duration of follow-up has been long, i.e., 8 to 9 years (Baldewicz *et al*, 2004). Further studies with longer duration of follow-up would throw light on the nature of cognitive decline with clade C infection.

Conclusion

Asymptomatic drug-naïve individuals with HIV-1 clade C infection do not show cognitive decline over 2½ years despite disease progression, as evidenced by immune suppression and viral loads.

Methodology

Sample

HIV-seropositive adult participants were recruited from a peripheral outpatient HIV clinic and a weekly HIV outpatient clinic of the National Institute of Mental Health and Neuro Sciences (NIMHANS), Bangalore. The selection criteria for the sample have been described in detail previously (Das Gupta *et al*, 2007). The participants were recruited between October 2003 and December 2004. Consecutive HIV-1–seropositive, educated, adult individuals not on antiretroviral therapy (ART), who gave informed consent, were inducted into the study. The study had clearance from both the Institutional Review boards of NIMHANS and the University of Miami. A total of 103 participants were inducted. From study entry to the fifth follow-up after 2½ years, there was an exclusion of 35 participants. The causes for exclusion were administration of highly active antiretroviral therapy (HAART) ($N = 28$), death ($N = 6$), and drop out ($N = 1$). Participants whose CD4 cell count dropped below 250/mm^3 were administered HAART as per the NACO guideline and were excluded, as the study was on asymptomatic individuals. The nature of cognitive changes in individuals on HAART is being analyzed and will be reported in another paper. The number of participants at each of the followups and the attrition rates are as follows: First follow-up, 98 participants (2 on HAART, 2 deaths, 1 dropout); second follow-up, 89 participants (7 on HAART, 2 deaths); third follow-up, 80 participants (9 on HAART); fourth follow-up, 71 participants (7 on HAART, 2 deaths); fifth follow-up, 68 participants (3 on HAART). The final sample consisting of subjects who completed all the five follow-ups, comprised of 68 patients (30 men and 38 women), with a mean age of 29.4 years (SD = 5.6 years) and a mean education of 10.0 years (SD = 2.7 years).

All participants in this cohort underwent a detailed clinical and serological examination. Methods to confirm the HIV serostatus and measurement of viral load and CD4 counts have been described (Kamat *et al*, 2007). CD4 were assessed at study entry and after 6, 12, 18, and 24 months, i.e., at the first, second, third, and fourth follow-ups. Viral load were assessed at the study entry and after the second follow-up (1 year) and fourth follow-up (2 years) using a real-time polymerase chain reaction (PCR) assay as described previously (Kamat *et al*, 2007). During the follow-up of 2½ years, clinically none of the participants in this cohort had persistent weight loss, fever, diarrhea, or other recurrent systemic illnesses associated with acquirede immunodeficiency syndrome (AIDS). None of the participants had clinically obvious cognitive impairment due to HIV infection or neurological focal signs. The cohort thus consisted of ''neurologically asymptomatic'' HIV 1 clade C individuals.

Neuropsychological tests

An initial baseline neuropsychological assessment was followed by five follow-up neuropsychological assessments. The first follow-up assessment was conducted 6 months after the baseline assessment. Subsequent follow-ups occurred at 6-monthly intervals. The total duration of the follow-up was 2½ years. Each of the six neuropsychological assessments was comprehensive and was carried out by the trained neuropsychologists. The subjects were administered 12 neuropsychological tests, which yielded 21 variables. These were tests of attention (Digit Vigilance, Color Trails 1 and 2), motor speed (finger tapping), fluency (category, phonemic, and design), working memory (verbal and visual), planning (Tower of London), response inhibition (Stroop), verbal learning and memory (auditory verbal learning and memory), and visual learning and memory (Rey's Complex Figure Test). The tests have been standardized for use in the Indian population (Rao *et al*, 2004). The tests and

standardization procedures are described in our earlier publication (Das Gupta *et al*, 2007). Alternate forms were used in the second, fourth, and sixth assessments for the tests of attention, phonemic fluency, category fluency, verbal learning and memory, and visual learning and memory. Reliability of the alternate forms was established using the test-retest method with an interval of 6 to 8 weeks between the two assessments. The sample size for the reliability was 26 normal volunteers. The Cronbach's alpha and overall correlation are given under each test. The alternative forms are described below.

Attention—alternate form

The alternate form of the Color Trails Test (D'Elia *et al*, 1996), version B, had the same type of stimuli as version A. The change in this version was that the order of number placed in the sheet was changed for both part 1 and part 2. The administration, instructions and scoring was similar to that of version A. Part 1 had a Cronbach's alpha of .78 and overall correlation of .65. Part 2 had a Cronbach's alpha of .82 and overall correlation of .70.

Phonemic fluency—alternate form

In the alternate form the subject was asked to generate words beginning with the letters 'B,' 'R,' and 'T' if responding in English and beginning with the consonants 'Tha,' 'Na,' and 'Sa' if responding in their mother tongue. Administration, instructions, and scoring was similar to that described in Das Gupta *et al* (2007). The Cronbach's alpha was .90 and overall correlation was .83.

Category fluency—alternate form

In alternate form the subject was asked to generate vegetable names. The administration, instructions, and scoring were similar to that of the animal names test described in Das Gupta *et al* (2007). The Cronbach's alpha was .65 and overall correlation was .48.

Verbal learning and memory—alternate form

An alternate form of Rey Auditory Verbal Learning Test (AVLT) was constructed by choosing words that were appropriate to our cultural context. Fifteen common nouns were chosen and randomly arranged. The words in the recognition part of the test were chosen such that among the distracters, there were equal number of words that were semantically and phonetically similar to the words in the list A of the alternate form. The administration, instructions, and scoring were similar to that of the original Rey Auditory Verbal Learning Test. Reliability was established for the three variables of total learning, immediate recall, and delayed recall. The Cronbach's alpha for the total learning was .84 and overall correlation was .73. The Cronbach's alpha for immediate recall was .71 and overall correlation was .85. The Cronbach's alpha for delayed recall was .73 and overall correlation was .58.

Visual learning and memory—alternate form

Taylor's version of the Complex Figure Test (Spreen and Strauss, 1998) was used as an alternate form for visual learning and memory. It is similar to the Rey Osterith Test, in that it has an overall structure and multiple subcomponents within it. Initially, the subject copied the figure. Subsequently, the subject was asked to recall the figure twice: the first time in an immediate recall 3 min after the copying, and the second time in a delayed recall 30 min after immediate recall. In all the three trials, the subject drew the figure freehand. The scores were the correctly placed facts in the copy, immediate recall, and delayed recall trials. Reliability was established for the three variables of copy, immediate recall, and delayed recall. The Cronbach's alpha for copy was .62 and overall correlation was .45. The Cronbach's alpha for immediate recall was .74 and overall correlation was .59. The Cronbach's alpha for delayed recall was .79 and overall correlation was .65.

Data analysis

Nature of change in neuropsychological performance

Latent growth curve (LGC) modeling (Duncan *et al*, 1999) was used to assess the nature of change over a 2½-year period. LGC models use variances and covariances to examine linear and nonlinear aspects of change (McArdle and Epstein 1987; Willett and Sayer, 1994; Muthen, 1997). LGC models represent repeated measures of dependent variables as a function of time and other covariate measures. The relative standing of an individual at a specific time point is modeled as a function of an underlying process, the parameter values of which vary randomly across individuals. LGC can be used to investigate systematic change or growth and inter-individual variability in this change, more specifically the correlation of the growth parameters, namely initial status and the growth rate with varying time. The method assumes that the variation between individuals (within-group variance) is produced by both means and variances. The effect of practice is taken care of by the assumption of linear growth, which implies the rate of growth is uniform over the entire measurement period. This uniform rate of growth is reflected by the numerical values of the slope (Byrne, 2006). Thus even though practice effects may level off after several assessments, the use of LGC ensures a stringent approach to the removal of practice effects as LGC assumes a uniform rate growth.

LGC was used to calculate the line of slope across the six data points for each test variable. The line of

slope is a weighted average of repeated observations and indicates the improvement or deterioration in standard deviations over the six data points. Deterioration over time was indicated by a negative-slope line for accuracy scores and by a positive-slope line for reaction time and error scores. EQS (3.2) statistical software was used to compute the latent growth curve modeling (Bentler, 1992).

Changes in immune suppression

The CD4 values were available at baseline, and every 6-month follow-up. Plasma viral load values were available at baseline and 1-year and 2-year follow-ups. The CD4 and viral load values were obtained on the 68 subjects who had completed all the five follow-up assessments. Log transformation was done and when the viral load was undetected, a log scale value of 0 was assigned. Changes in the CD4 and in the viral load indicated change in disease status. LGC was used to examine the changes in CD4 over time. Analysis of variance was used to examine the changes in viral load over time. LGC could not be used for viral load because only three measurements were available and LGC requires a minimum of four measurements. Pearson's correlations were used to analyze the relationship between CD4 and viral load groups at baseline and 1-year and 2-year follow-ups.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

References

Baldewicz TT, Leserman, J, Silva, SG, Petitto, JM, Golden RN, Perkins, DO, Barroso, J, Evans, DL (2004). Changes in neuropsychological functioning with progression of HIV-1 infection: results of an 8-year longitudinal investigation. *AIDS Behav* **8:** 345–355.

Byrne, BM (2006). *Structural equation modeling with EQS,* 2nd ed. London: Lawrence Erlbaum Associates.

Das Gupta, J, Rao, SL, Satishchandra, P, Gopukumar, K, Wilkie, FL, Waldrop-Valverde, D, Ellis, R, Ownby, T, Subbakrishna, DK, Desai, A, Kamat, A, Ravi, V, Rao, BS, Satish, KS, Kumar, M (2007). Neuropsychological deficits in HIV-1 clade C–seropositive adults from South India. *J NeuroVirol* **13:** 195–202.

D'Elia, LF, Satz, P, Uchiyama, CL, White, T (1996). *Color Trails Test.* New York: Psychological Assessment Resources Inc.

Duncan, TE, Duncan, SC, Strycker, LA, Li, A, Alpert, A. (1999). *An introduction to Latent variable growth curve modeling: concepts, issues, and applications.* Mahwah, NJ: Lawrence Erlbaum.

Bentler, PM (1992). *EQS: Structural Equations Program manual.* Los Angeles: BMDP Statistical Software.

Grant, I, Atkinson, JH, Hesselink, JR, Kennedy, CJ, Richman, DD, Spector, SA, McCutchan, JA (1987). Evidence for early central nervous system involvement in the acquired immunodeficiency syndrome (AIDS) and other human immunodeficiency virus (HIV) infections. *Ann Intern Med* **107:** 828–836.

Heaton, RK, Grant, I, Nelson, B, White, DA, Kirson, D, Atkinson, HJ (1995). The HNRC 500—neuropsychology of HIV infection at different disease stages. *J Int Neuropsychol Soc* **1:** 231–251.

Karlsen NR, *et al* (1993). A follow-up study of neuropsychological function in asymptomatic HIV-infected patients. *Acta Neurol Scand* **87:** 83–87.

Kamat, A, Ravi, V, Desai, A, Satishchchandra, P, Satish, KS, Borodowski, I, Kumar, M (2007). Quantitation of HIV-1 RNA levels in plasma and CSF of asymptomatic HIV-1 infected patients from South India using a TaqMan Real Time PCR assay. *J Clin Virol* **39:** 9–15.

Multicenter AIDS Cohort Study (MACS). Web site located at http://www.statepi.jhsph.edu/macs/macs.html.

McArdle JJ, Epstein DB (1987) Latent growth curves within developmental structural equation models. *Child Dev* **29:** 110–133.

Muthen B (1997) Latent variable modeling with longitudinal and multilevel data. In: *Sociological methodology.* Raferty A (ed). Boston: Blackwell, pp 453–580.

Rao, SL, Subbakrishna, DK, Gopukumar, K (2004). *NIMHANS Neuropsychology Battery—2004 manual.* India: NIMHANS Publication.

Selnes, OA, Miller, E, McArthur, J, Gordon, B, Muñoz, A, Sheridan, K, Fox, R, Saah, AJ (1990). No evidence of cognitive decline during the asymptomatic stages. *Neurology* **40:** 204.

Spreen, O, Strauss, J (1998). A compendium of neuropsychological tests. Administration, norms and commentary, 2nd ed. New YorK: Oxford University Press.

Villa, G, Solida, A, Moro, E, Tavolozza, M, Antinori, A, De Luca, A, Murri, R, Tamburrini, E (1996). Cognitive impairment in asymptomatic stages of HIV infection. A longitudinal study. *Eur Neurol* **36:** 125–133.

White, DA, Heaton, RK, Monsch, AU, The HNRC Group (1995). Neuropsychological studies of asymptomatic human immunodeficiency virus-type 1 infected individuals. *J Int Neuropsychol Soc* **1:** 304–315.

Willett JB, Sayer AG (1994) Using covariance structure analysis to detect correlates and predictors of individual change over time. *Psychol Bull* **116:** 363–381.

Yepthomi T, Paul R, Vallabhaneni S, Kumarasamy N, Tate DF, Solomon S, Flanigan T (2006).Neurocognitive consequences of HIV in southern India: a preliminary study of clade C virus. *J Int Neuropsychol Soc* **12:** 424–430.

This paper was first published online on iFirst on 19 November 2008.