

ORIGINAL RESEARCH

Depression and neurocognitive performance in individuals with HIV/AIDS: 2-year follow-up

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Objectives

The aims of this study were to follow a cohort of HIV-infected individuals for 2 years to assess changes in depression and neuropsychological performance over time, to explore the relationship between depression, HIV illness and neuropsychological performance, and to examine the natural history of the effect of highly active antiretroviral therapy (HAART) on depression and neurocognitive performance.

Methods

HIV-seropositive out-patients were assessed at baseline and at 2-year follow-up. At each assessment, patients were assessed for depression [using the Beck Depression Inventory (BDI) and Structured Clinical Interview (SCID-CV)] and completed a battery of neuropsychological tests including the Cambridge Neuropsychological Test Automated Battery (CANTAB) and the Hopkins HIV Dementia Scale (HDS).

Results

At baseline, 34.8% scored $\geq$ 14 on the BDI [$\geq$ 14 suggests depressive symptoms (DS)]. The SCID-CV revealed that 27% of participants met the criteria for current mood disorder. Seven per cent of the participants' scores on the HDS indicated HIV-associated cognitive changes. Eighty participants were re-tested at 2-year follow-up and were split into two groups based on BDI scores at baseline. CANTAB results revealed that the cohort were significantly impaired on nine of 10 measures compared with age-matched normative data. Neurocognitive performance significantly improved for participants with no DS at baseline, whereas participants with DS at baseline did not show as much improvement. Multivariate analysis revealed that 40% of the change in cognitive performance was attributable to the variables age, AIDS and HAART regimen.

Conclusion

These results suggest a significant decline in depression scores and an improvement in several neurocognitive domains over time, with a relationship between HIV illness, HAART, symptoms of depression and neurocognitive performance.

Keywords: depression, HAART, HIV/AIDS, neuropsychological impairment

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Introduction

HIV/AIDS has been shown to have detrimental effects on neurocognitive function. Impairment can range from mild cognitive and motor difficulties to AIDS dementia complex (ADC) and is consistent with frontal-subcortical pathology with evidence of decreased attention and concentration, memory problems and psychomotor slowing [1,2]. Neuropsychological impairment is associated with increased mortality risk, increased risk of developing ADC and higher rates of unemployment, and persists in the era of highly active antiretroviral therapy (HAART) [2]. Further, individuals with neuropsychological impairment are at risk of medication nonadherence and poor self-care [3].

Numerous investigations have revealed that up to 50% of people with HIV/AIDS experience depression [4–6].

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Several hypotheses have been developed to explain the aetiology of depression in HIV-infected populations. These include a reactive depression related to a negative psychological impact at HIV infection diagnosis and during the progression of the illness [7], and an 'organic' depression caused by HIV penetration of the blood–brain barrier and infection of the central nervous system (CNS). HIV-related opportunistic illness such as infections and tumours of the brain may also cause an organic mood disorder [8]. Medications used in the treatment of HIV/AIDS may have a variety of side effects, including depression, affecting mental health [9]. Finally, mental health disorders may be premorbid conditions which are exacerbated by the presence of HIV [10].

Since the introduction of HAART in 1996, a decline in HIV-associated depression has been suggested. Judd *et al.* [11] assessed HIV-infected participants for symptoms of depression, HIV illness progression and antiretroviral treatment at 6-monthly intervals over 2 years. Antiretroviral medications changed significantly over the study period, with most participants commencing treatment with HAART. Participants enrolled in this study reported fewer psychological stressors, improved symptoms of depression, improved psychosocial adjustment to illness and improved HIV/AIDS symptoms and illness markers over the study period, with a temporal relationship to changes in antiretroviral treatment. These findings indicate that HAART was associated with a decrease in HIV-related depression in this group. Although depression rates may have fallen since the introduction of HAART, depression remains predictive of poorer treatment outcomes, reduced adherence and increased mortality [12–15].

The possible association of HIV infection and 'organic' depression has led to interest in the relationship between depression and neuropsychological performance. Two possible mechanisms underlie depression as a risk factor for neuropsychological impairment in HIV-infected individuals. Depression may cause poor concentration, lack of interest and apathy towards neuropsychological testing, or it may be an early manifestation of HIV-related brain disease [16]. In some studies, HIV-positive individuals with depression have been shown to continue to perform within normal limits on neuropsychological measures, despite the presence of significant cognitive complaints [9,17]. The accuracy of these complaints has been found to be mixed, with some groups reporting good agreement between perceived cognitive functioning and performance on neuropsychological tests [9], whereas other studies have demonstrated poor agreement between complaints and test performance but found complaints to be related to depression scores [18].

Vazquez-Justo *et al.* [19], investigating the influence of depressed mood on neuropsychological performance in HIV-positive and HIV-negative injecting drug users, demonstrated that neuropsychological performance in HIV-positive participants with depression was significantly more impaired than in the HIV-negative groups and in the HIV-positive individuals without depression. These investigators concluded that symptoms of depression constitute a risk factor for neuropsychological impairment in HIV-infected individuals.

With the changing nature of HIV treatment, it is important to further our understanding of HIV-related depression and neuropsychological impairment in the era of HAART and longer patient survival. The natural history of both depression and neuropsychological impairment for patients receiving HAART needs further exploration if the full health benefits of treatment advances are to be realized. Investigation of the possible underlying mechanisms by which depression acts as a risk factor for neuropsychological impairment in HIV-infected individuals requires a longitudinal follow-up study tracking changes in HIV illness indicators, neuropsychological performance and depression levels.

The aims of this study were to follow a cohort of HIV infected individuals for 2 years to (1) assess changes in depression and neuropsychological performance over time; (2) explore the relationship between depression, HIV infection and neuropsychological performance; and (3) examine the influence of HAART on the natural history of depression and neuropsychological performance over 2 years. We hypothesized (1) that HIV-seropositive individuals with depression would show more impairment on neuropsychological tests over time than those without depression, (2) that individuals who were not depressed at baseline but who developed depression during the follow-up period would have poorer responses to HAART (increased viral load and decreased CD4 count between baseline and follow-up) and reduced neurocognitive performance, and finally (3) that HAART would improve depression and neuropsychological impairment in the group over time.

Method

Participants

During 2002, 129 HIV-seropositive participants (95% male) were recruited from hospital out-patient clinics, a sexual health centre clinic and general practice clinics with high HIV/AIDS patient caseloads located in metropolitan Melbourne (which together provide care for 91% of HIV-diagnosed individuals in this Australian state). Participants were aged 18 years and older, were HIV seropositive, were able to read and write in English and gave informed consent. In 2004, 80 participants consented to participate in the follow-up phase of the study. At both baseline and

follow-up assessments, each participant completed a structured clinical interview and a series of neuropsychological tests, as well as completing a set of self-rated questionnaires at home. HIV illness-related information was obtained from the participant's medical record. The Alfred Hospital and Melbourne Health's Human Research Ethics Committee approved the recruitment and testing of participants for this study.

Measures

HIV illness progression was determined using laboratory assays of current CD4-lymphocyte cell count and HIV RNA viral load. Information on HIV symptoms and AIDS-defining illnesses was obtained, with patient consent, from medical records. The following sociodemographic variables were recorded by the researcher: age, education, current living situation, current relationship status, current and past alcohol and illicit drug use, and personal psychiatric history.

Neuropsychological measures

The battery of neuropsychological tests was chosen to include tasks shown to be sensitive to the effects of HIV infection and to represent a broad range of functions. The instruments used included measures of executive function, reaction time, working memory, attention and general intelligence. A series of tests taken from the Cambridge Neuropsychological Test Automated Battery (CANTAB) [20] were used to measure spatial working memory, attentional set shifting, planning and problem solving, and reaction time. The CANTAB is a computerized touch-screen method of cognitive assessment that has been shown to be sensitive to cognitive changes in a wide range of brain disorders [21–23]. Scores are calculated by the test and are converted to *z*-scores, and are compared to age-matched norms. The four CANTAB tests used included:

1 Intra/extra Dimensional Shift (IED), which measures attention and mental flexibility;
2 Reaction Time (RTI), which measures psychomotor speed;
3 Stocking of Cambridge (SOC), which measures spatial planning and problem solving;
4 Spatial Working Memory (SWM), which measures spatial working memory.

The Hopkins HIV Dementia Scale (HDS) [24], which takes approximately 10 min to complete, tested memory recall, inhibitory control assessed by antisaccadic eye movements, psychomotor speed and construction assessed by cube copying time and accuracy. Participants were scored out of 16, with a score of 10 or less suggestive of ADC.

Psychomotor function was measured by the Grooved Pegboard (GPB) [25], a manipulative dexterity test where participants are timed placing 25 grooved pegs in randomly positioned slots on a pegboard. Premorbid IQ was assessed using the National Adult Reading Test (NART) [26], a literacy test used to assist in delineating cognitive impairment from pre-existing intellectual disability.

Depression

The Beck Depression Inventory (BDI) [27] was administered to assess the prevalence and severity of depressive symptoms. The BDI has been shown to have high validity and reliability in measuring depressive symptoms, and takes approximately 10 min to complete. Respondents are required to rate 21 items from 0 to 3 according to how they have felt during the past week. The BDI focuses on both the cognitive-affective symptoms of depression, such as pessimism and diminished self-esteem, and the somatic symptoms of depression, such as weight loss. A score of 14 or more is widely used as a cut-off score indicating depression when using the 21-item BDI. To avoid confounding HIV illness symptoms and the somatic symptoms of depression, scores on the first 13 cognitive-affective items on the BDI were summed, where a score of 10 or more indicates depression [28].

The Structured Clinical Interview for the DSM-IV Axis I Disorders (SCID) [29] was administered to identify the presence of current major depressive disorder and lifetime (past episode) major depressive disorder. The SCID also assesses other Axis I disorders including substance use/abuse disorder, anxiety disorders, post-traumatic stress disorder and psychotic disorder. The interview takes between 15 and 45 min to complete.

Statistical analysis

The associations between the different groups and variables of interest were studied in univariate analyses using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous variables. Correlation coefficients are reported for changes in depression category over time. CANTAB and GPB scores were compared to published age and gender-matched norms using *z*-scores.

The relationships between the dependent variables (differences in the neurocognitive battery and changes in CANTAB performance) and baseline depression group membership were studied using multiple linear regression models. Associations were considered statistically significant if the *P*-value was less than 0.05. All statistical analyses were performed using SPSS, Version 10 (SPSS Inc., Chicago, IL, USA).

The relationships between the dependent variables (change in global neuropsychological score) and baseline depression

group were adjusted for demographic factors (age), HIV treatment (CNS-penetrating HAART regimens that included zidovudine, abacavir, stavudine, nevirapine, efavirenz or indinavir; and individual antiretrovirals) and surrogate markers (CD4 nadir and current plasma HIV RNA).

Results

A total of 129 HIV-seropositive individuals completed baseline testing. Eighty of these individuals completed the follow-up phase approximately 2 years after initial testing. Reasons for non-completion were death in four individuals, loss to follow-up in 30 individuals and failure to attend the appointment/declining to participate in 15 individuals. Table 1 presents a comparison of completers versus non-completers on psychosocial and illness-related variables. There was no difference in the baseline characteristics of participants who completed follow-up and those who did not, indicating that the final study sample is representative of the original cohort (Table 1).

Sociodemographic and medical data

The study sample reflected the epidemiology of HIV infection in Melbourne and was comprised predominantly of men who have sex with men, with an average age of 44.7 years (at baseline). Approximately 59% were in paid employment, either on a part-time or on a full-time basis, and 44% received a sickness or disability support pension. Forty-four per cent of participants were in an intimate relationship. The majority of participants were medically well, had been HIV seropositive for more than 10.3 years and had been on antiretroviral treatment for 6 years [standard deviation (SD) 4 years]. At baseline, the median viral load was 200 HIV-1 RNA copies/mL (range 25–723 600 copies/mL) and the median CD4 cell count was 458 cells/μL (range 3–1512 cells/μL). At follow-up, the median viral load was <50 copies/mL (range <50–100 000 copies/mL) and the median CD4 count was 526 cells/μL (range 9–1325 cells/μL). At baseline, 93% of participants were taking HAART and 22% of participants had a history of an AIDS-defining illness. At follow-up, a further 8% of the participants had progressed to AIDS and 91% were taking HAART. Fifteen of the 129 participants were taking antidepressant medication at baseline, 66.6% (10 of 15) of whom continued to be prescribed antidepressant medication during follow-up. Four individuals commenced antidepressant medication during follow-up.

Neuropsychological performance

Hopkins HIV Dementia Scale (HDS)

Nine of 129 participants (7%) obtained a score of 10 or less on the HDS at baseline. At follow-up, only three of 79 (4%) scored less than 10, suggesting a reduction in the prevalence of HIV-related neurocognitive impairment. Two individuals were unable to perform testing because of poor vision. Of individuals who scored 10 or less at baseline on the HDS, six participants' scores (66.7%) improved above 10 at follow-up, one score (11.1%) remained less than 10, one participant (11.1%) declined to participate in follow-up and one participant (11.1%) was

Table 1 Comparisons between completers and noncompleters on HIV illness and sociodemographic variables

Variables	Completers ($n = 50$)	Noncompleters ($n = 49$)	t-test or χ^2 (P-value)
Gender (%)			
Male	95	96	$P > 0.05$
Female	5	4	
Employed (%)			
Full-time	35	37	$P > 0.05$
Part-time	22	25	$P > 0.05$
Receiving sickness or disability support pension (%)	48	41	$P > 0.05$
Involved in an intimate relationship (%)	44.1	48.9	$P > 0.05$
CD4 count (cells/μL) [mean (SD)]	480.67 (291.25)	515.75 (279.88)	$P > 0.05$
HIV RNA load (copies/mL) [median (range)]	200 (25–182 475)	127.5 (25–723 600)	$P > 0.05$
AIDS diagnosis (%)	22.1	22.4	$P > 0.05$
On antiretroviral therapy (%)	94	92	$P > 0.05$
Currently using illicit drugs (%)	39	56	$P > 0.05$
BDI score			
Full-scale score	12.3	12.1	$P > 0.05$
Cognitive-affective items	7.3	7.4	$P > 0.05$
Hopkins HIV Dementia Scale	14.5	14.4	$P > 0.05$
On antidepressant medication (%)	18.1	14.2	$P > 0.05$

BDI, Beck Depression Inventory; SD, standard deviation.

Table 2 Participant neuropsychological performance compared with age-matched norms on the Grooved Pegboard and Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline and follow-up (z-scores), and depression scores on the Beck Depression Inventory (BDI) and Structured Clinical Interview (SCID) at baseline and follow-up

	Baseline ($n = 129$)			Follow up ($n = 78$)		
Variable (domain)	**Mean difference from 0**	**SE**	**95% CI**	**Mean difference from 0**	**SE**	**95% CI**
Grooved Pegboard						
Psychomotor speed						
Dominant hand	−1.743*	0.09	−1.50, −0.76	−0.47*	0.19	−0.85, 0.01
Nondominant hand	−1.333*	0.18	−1.48, −0.41	−0.35*	0.13	−0.62, 0.01
CANTAB						
Mental flexibility and attention (IED3)	−1.195*	0.16	−1.50, −0.86	−0.54*	0.17	−0.89, −0.18
Reaction time						
(RTI1)	−0.709*	0.10	−0.89, −0.49	0.35*	0.00	0.17, 0.52
(RTI2)	−0.654*	0.17	−1.00, −0.33	−0.41*	0.14	−0.68, −0.13
Spatial planning and problem solving						
(SOC1)	0.449*	0.08	0.25, 0.59	0.008	0.17	−0.26, 0.46
(SOC2)	−0.233	0.13	−0.54, −0.04	0.007	0.11	−0.13, 0.29
(SOC3)	−0.478*	0.09	−0.71, −0.34	0.006	0.10	−0.13, 0.27
Spatial working memory						
(SWM1)	−0.601*	0.09	−0.80, −0.42	−0.31*	0.11	−0.530, 0.007
(SWM2)	−0.507*	0.08	−0.70, −0.37	−0.40*	0.12	−0.65, −0.15

	Baseline ($n = 129$)	Follow up ($n = 78$)
BDI		
Mean (SD)	12.3 (8.2)	10.1 (7.9)
$\geq$ 14 (%)	34.8%	31%
SCID		
% current mood	27% (35/129)	14% (11/78)
% lifetime mood	26% (33/129)	39% (30/78)

CI, confidence interval; IED, measure of mental flexibility; RTI, measure of psychomotor speed; SOC, measure of problem solving and planning; SWM, measure of spatial working memory; SCID current mood diagnosis, depressive symptoms within the past 2 weeks; SCID lifetime mood diagnosis, past depressive episode, no symptoms within the past month; SE, standard error; SD, standard deviation;
*Significantly (two-tailed) different from 0 ($P < 0.05$).

lost to follow-up. Two participants who initially scored above 10 at baseline had a decline to below 10 at follow-up.

CANTAB and Grooved Pegboard

z-scores were calculated for participant performance on the CANTAB measures and Grooved Pegboard, based on test supplied normative data. A *z*-score has a mean of 0 and a standard deviation of 1, where scores above 0 indicate performance above the mean and scores less than 0 indicate performance below the mean. A single sample *t*-test showed that performance on the Grooved Pegboard at baseline and follow-up was significantly below 0, indicating a performance deficit in our sample (Table 2). All CANTAB measures at baseline, apart from Stocking of Cambridge 2 (mean subsequent thinking time), were significantly below 0. At follow-up, all measures apart from Stocking of Cambridge (mean initial thinking time, mean subsequent thinking time and problems solved in minimum moves) were significantly below 0.

Mental health

Beck Depression Inventory

Results from the BDI revealed that approximately one-third of participants at both baseline and follow-up scored 14 or above (Table 2). Removing the somatic items of the BDI to avoid confounding of HIV illness-related variables with symptoms of depression, it was revealed that 20% of participants scored above 10 on the first 13 cognitive-affective items of the BDI at follow-up.

SCID-CV

On the SCID-CV, 35 participants (27%) at baseline met the criteria for a current mood disorder and another 33 participants (26%) had experienced mood disorder in the past but were not currently depressed. At follow-up (approximately 2 years later), 14.1% ($n = 11$) met the criteria for a current mood disorder and 30 participants (38.5%) had experienced mood disorder in the past. Mean BDI full item scores and cognitive-affective score decreased significantly between baseline and follow-up ($P < 0.05$).

Table 3 Comparisons between changes in depression groups [Beck Depression Inventory (BDI) $\geq$ 14] over time on demographic and HIV-illness related variables at follow-up

	Follow-up group			
	Depressed		Not depressed	
	Newly depressed at follow up ($n = 10$)	Ongoing depression ($n = 15$)	Not depressed at baseline or follow up ($n = 43$)	Recovered from depression at baseline ($n = 10$)
Age (years)	48.4	47.6	48	47
BDI $\geq$ 14 at baseline [% (n)]	0 (0/10)	100 (15/15)	0 (0/43)	100 (10/10)
SCID FU Dx† (%)	30	46.7	7	10
HIV RNA* change from BL to FU (copies/mL)	8439.7	− 13100	2917	10064
HIV RNA below detection at FU (%)	70	66.7	58	30
CD4 change (cells/μL)	89.5	18.7	36.5	− 7.9
AIDS-defining illness (%)	10	46.7	29	30
Time since HIV infection diagnosed (mean months)	136	124	119	125
Time since AIDS diagnosed (mean months)	94	73	42	38
Nadir CD4 count (cells/μL) [median (range)]	100 (4–687)	139 (11–546)	180 (2–726)	136 (2–390)
On HAART at FU (%)	100	93.3	88	90
BL CNS-penetrating ART (%)	100	93.3	93	100
FU CNS-penetrating ART (%)	80	93.3	83.7	80
Receiving psychiatric treatment	20	33.3	4.7	10

Newly depressed, not depressed at baseline but depressed at follow-up; Ongoing depression, depressed at both baseline and follow-up; Not depressed, not depressed at both baseline and follow-up; Recovered from depression, depressed at baseline but not depressed at follow-up.
ART, antiretroviral therapy; BL, baseline; CNS, central nervous system; FU, follow-up; HAART, highly active antiretroviral therapy.
†Structured Clinical Interview (SCID) follow-up diagnosis of current mood disorder.
*Undetectable viral loads were scored using the mid-point of the detection limits of the assay.

Although we planned to compare those with ongoing depression with individuals who were newly identified as depressed at follow-up, only 10 participants who were not depressed at baseline (scored below BDI cut-off) were newly identified as depressed at follow-up (scored above BDI cut-off), and 10 participants who scored above the BDI cut-off at baseline were no longer identified as depressed at follow-up (scored below BDI cut-off), a sample too small for meaningful statistical analysis. A description of these participants has been included as a subgroup in Table 3.

To explore the variables contributing to changes in depression scores, intercorrelations between changes in depression category (scoring above or below 14 on the BDI) and HIV illness, neuropsychological performance and socio-demographic characteristics were examined. The following variables were significantly correlated with change in depression category: spatial working memory at baseline ($r = -0.265$, $P = 0.021$) and follow-up ($r = -0.330$, $P = 0.003$); Grooved Pegboard (nondominant hand, $r = -0.226$, $P = 0.047$); receiving treatment for psychiatric problems ($r = -0.234$, $P = 0.039$); and current living situation ($r = 0.275$, $P = 0.015$). BDI scores at baseline correlated significantly with spatial working memory ($r = -31$, $P = 0.006$), that is, as depression scores increased, spatial working memory scores decreased. No other neuropsychological test scores correlated significantly with depression scores.

Participants who scored above the BDI cut-off at follow-up were significantly less likely to be in a current relationship and more likely to be living alone than those who scored below the BDI cut-off ($P = 0.007$). Further, these participants were significantly more likely to have a past history of psychiatric illness ($P = 0.045$) and were more likely to be receiving a disability support pension ($P = 0.029$).

Comparisons of participants with and without symptoms of depression on neuropsychological performance

In order to examine the effect of depression and HIV illness-related variables on neurocognitive performance, we compared performance on baseline and follow-up neuropsychological measures using nonparametric testing (Table 4). The results revealed significant improvement on five out of eight CANTAB measures for those who scored less than 14 on the BDI at baseline (no symptoms of depression). Participants who scored 14 or more on the BDI (symptoms of depression) at baseline improved significantly on three out of eight CANTAB measures. However, these differences between baseline groups did not reach statistical difference.

In order to examine the predictors of observed changes in neuropsychological performance between baseline and follow-up, we calculated a global neuropsychological

Table 4 Comparisons between baseline depressed and not depressed groups on neurocognitive performance at 2-year follow-up

	Depressed ($n = 25$)			Not depressed ($n = 53$)		
	Mean change from BL	SEM	95% CI	Mean change from BL	SEM	95% CI
IED3a	0.84	0.43	−1.7, 0.05	0.63*	1.74	−0.98, −0.28
RTI1a	0.67*	0.26	−1.2, −0.12	0.96*	0.09	−1.13, −0.77
RTI2a	0.26	0.33	−0.94, 0.43	0.36	0.30	−0.96, −0.24
SOC1a	0.11	0.13	−0.16, 0.38	0.37	0.23	−0.09, 0.84
SOC2a	0.28*	0.11	−0.52, −0.04	0.75*	0.21	−1.18, −0.30
SOC3a	0.42*	0.16	−0.76, −0.07	0.55*	0.13	−0.82, −0.27
SWM1a	0.004	0.17	−0.41, 0.32	0.26*	0.11	−0.49, −0.03
SWM2a	0.004	0.16	−0.39, 0.31	−0.001	0.11	−0.25, 0.22

IED, measure of mental flexibility; RTI, measure of psychomotor speed; SOC, measure of problem solving and planning; SWM, measure of spatial working memory.
BL, baseline; CI, confidence interval; SEM, standard error of the mean.
*Significant (two-tailed) change between baseline and follow-up ($P < 0.05$).

performance summary score (average of CANTAB and Grooved Pegboard *z*-scores) [23]. Utilizing this global neuropsychological performance summary score, we calculated a global difference score, a change score from baseline to follow-up. We used a backward elimination regression model to further examine both positive and negative changes in neurocognitive performance between baseline and follow-up (Table 5). This procedure revealed age, a history of an AIDS-defining illness and receipt of a CNS-penetrating HAART regimen (at follow-up) as well as tenofovir and nevirapine at baseline as being significant at the 0.05 level. An inverse relationship with AIDS-defining illness and as age was revealed; that is, being AIDS-defined and as age increased, change in neuropsychological performance decreased (less improvement). Forty per cent of the variation in global difference scores between baseline and follow-up could be explained by the variation in age, AIDS-defining illness, tenofovir and nevirapine at baseline, and CNS-penetrating HAART at follow up ($R^2 = 0.405$).

Discussion

The prediction that participants with depression would show more neuropsychological impairment than those without depression over time was partially supported as, although the two groups did not differ significantly from each other, those without depression improved significantly between baseline and follow-up whereas those with depression did not show this improvement. The prediction that depression would be related to HIV illness indicators (viral load and CD4) indicating an 'organic' depression was not supported, as depression was not related to HIV illness-related variables but was associated with sociodemographic variables. The hypothesis that HAART would improve depression and neuropsychological performance in this group was supported by the results of this study, as depression levels and neuropsychological scores improved between baseline and follow-up.

The findings of this study indicate that HIV-infected individuals on HAART continue to experience high levels of depressive symptoms (31% at baseline and follow-up scored above the BDI cut-off) and current mood disorder (26% at baseline and 14% at follow-up identified with current mood disorder by the SCID). However, levels of depressive symptoms were shown to decrease significantly between baseline and follow-up. The prediction that HIV illness indicators (CD4 count and viral load) would be associated with depressive symptoms or illness was not supported by the results of this study. Because of the low number of participants who developed depression during the study period ($n = 10$), it was difficult to determine the relative contribution of HIV disease to depression levels. Also, as this cohort displayed relatively good physical health (58% had viral loads below detectability) relative to those in previous studies, the lower rates of depression in the current study may be attributable to enhanced physical well-being. Whilst it is possible that increased rates of depression and HIV-associated neuropsychiatric disorders occurred in those lost to follow-up, comparisons of baseline psychological and sociodemographic variables revealed no differences between those who did not complete follow-up and those that did, suggesting that those who completed the study were a representative sample.

The prevalence of current depression in this study was lower than that found in past research. For example, 14% met the criteria for current major depression as measured by the SCID at follow-up. These findings represent a lower prevalence of depression in HIV-infected populations than that previously reported, as past research has identified approximately 50% of study samples as depressed [4–6]. As

Table 5 Backward elimination regression analysis examining factors associated with changes in global neuropsychological performance scores over 2 years

	Multivariate*		95% confidence interval		
Factor	**Coefficient**	**SE**	**Lower**	**Upper**	***P*-value**
R^2	0.405				
Adjusted R^2	0.292				
Age (years)	−0.014	0.005	−0.024	−0.003	0.013
Previous ADI	0.311	0.108	0.094	0.528	0.006
On lamivudine at BL	0.154	0.101	−0.049	0.357	0.135
CNS-penetrating ART at FU	0.306	0.148	0.0100	0.603	0.043
On stavudine at FU	0.262	0.136	−0.010	0.536	0.059
On didanosine at FU	0.240	0.133	−0.023	0.507	0.077
On tenofovir at BL	−0.286	0.133	−0.553	−0.020	0.035
On nevirapine at BL	0.263	0.110	0.042	0.484	0.020
On nevirapine at FU	−0.232	0.123	−0.480	0.015	0.065
On indinavir at BL	0.206	0.136	−0.066	0.479	0.135
On abacavir at BL	0.157	0.106	−0.056	0.370	0.147
On lopinavir at FU	−0.149	0.116	−0.382	0.082	0.202

ADI, AIDS-defining illness; ART, antiretroviral therapy; BL, baseline; CNS, central nervous system; FU, follow-up; SE, standard error.
*Included in the model were treatment, illness and lifestyle variables.

the majority of HIV-infected participants in the current study were on HAART, it may be that this relatively new therapy is contributing, at least in part, to the lower prevalence of depression observed. Because HAART represents a relatively recent advancement in HIV treatment, the higher prevalence of past depressive episodes (38.5%) may indicate pre-HAART depression rates in HIV-seropositive participants. The findings of Judd *et al.* [12] support this speculation, as these authors found a decreased prevalence of depression in those treated with HAART. The health-enhancing effects of HAART may also explain the lack of association found in this study between depression and HIV illness indicators. Further studies comparing the prevalence of depression in individuals with HIV infection who are either on or not on HAART are necessary to determine accurately the impact of this type of treatment on depression rates in this population. Such studies are, however, problematic, given that they necessarily involve restricting the availability of HAART in a proportion of HIV-infected individuals.

The role of relationship status and living situation suggests that social support may act as a protection against depression. Whether limited social support played a role in the development of depression (i.e. having no social support leads to depression) or was caused by depression (i.e. being depressed causes social withdrawal which erodes social support) is unknown and very difficult to determine accurately. Nevertheless, the findings of this study support the theoretical proposition that the high prevalence of depression in HIV-infected populations is attributable to the infection having a considerable psychological impact at the time of diagnosis and during the progression of the illness [8].

It is alarming that, despite improved physical health with access to HAART, the cohort demonstrated continuing neurocognitive impairment. This remained despite some improvement in performance over follow-up (66.7% of individuals with HDS <10 at baseline improved to be above that threshold 2 years later), yet domains of psychomotor speed (GPB dominant and nondominant), spatial working memory (CANTAB SWM) and mental flexibility (CANTAB IED) remained impaired. For the majority of participants, mean neuropsychological *z*-scores were less then 1.5 SD below norms, suggesting relatively mild to moderate impairment. Those without depression at baseline significantly improved on cognitive tests; however, those with depression at baseline showed less improvement. In a multivariate analysis, factors predicating ongoing neurocognitive deficit included older age, prior AIDS-defining illness and current HAART regimens (which include agents that penetrate the CNS), which explained 40% of the variance in neuropsychological change scores. Psychiatric treatment did not predict neurocognitive improvement despite changes in depression scores. That is, improving symptoms of depression did not improve neuropsychological impairment. It is not yet known whether early treatment of depression may help to negate the associated neuropsychological impairment over time.

It is concerning that, despite HAART, HIV-infected individuals remain at significant risk for depression and neurocognitive impairment, factors that impact significantly on quality of life. These findings emphasize the need for early diagnosis and monitoring of depressive symptomatology and neuropsychological impairment, and suggest that improved access to psychiatric and psychological

therapy and optimization of the CNS activity of antiretroviral regimens may minimize the risk of developing depression and neurocognitive impairment. Finally, further elucidation of the pathogenesis of HIV in the brain is required, particularly in the era of longer survival of individuals with access to HAART.

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