Taylor & Francis
Taylor & Francis Group

Clinical Report

Prevalence and pattern of neuropsychological impairment in human immunodeficiency virus–infected/acquired immunodeficiency syndrome (HIV/AIDS) patients across pre- and post-highly active antiretroviral therapy eras: A combined study of two cohorts

Lucette A Cysique,[1] Paul Maruff,[2] and Bruce J Brew[3]

[1]Faculty of Medicine, St. Vincent's Clinical School, University of New South Wales, Sydney, Australia; [2]School of Psychology, LaTrobe University, Melbourne, Australia; [3]Departments of Neurology and HIV Medicine, St Vincent's Hospital, and National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia

The objective of this study was to assess the prevalence and pattern of neuropsychological impairment in cohorts of human immunodeficiency virus (HIV)-infected individuals across pre- and post-HAART (highly active antiretroviral therapy) eras. Two cohorts of HIV-infected individuals attending tertiary referral hospital outpatient clinics were studied. The cohorts represented two eras of antiretroviral medication: monotherapy ($n = 51$) and HAART ($n = 90$). Each was compared in nine neuropsychological domains in regard to the prevalence as well as pattern of neuropsychological impairment. Because the authors intended to characterize the prevalence and pattern of neuropsychological deficits in nondemented advanced HIV-infected individuals, patients with a current diagnosis of acquired immunodeficiency syndrome (AIDS) dementia complex were not included. The prevalence of impairment was not significantly different across pre-HAART and HAART eras using a standard criterion to define impairment: -2 SD in two neuropsychological measures (41.1%/38.8%). Prevalence of deficits was not significantly reduced in patients with undetectable plasma viral load. The pattern of neuropsychological impairment was different across pre-HAART and HAART eras, with an improvement in attention, verbal fluency, visuoconstruction deficits, but a deterioration in learning efficiency and complex attention. This change remained even in patients with an undetectable plasma viral load, although the severity was partially diminished. Neuropsychological deficits remain common in the HAART era, essentially uninfluenced by HAART. The finding that some neuropsychological functions are improving while other are deteriorating indicates that these deficits do not reflect "burnt out" damage but rather that there is an active intracerebral process occurring, the nature of which is still to be determined. *Journal of NeuroVirology* (2004) **10,** 350–357.

Keywords: HAART; HIV/AIDS; neuropsychological function

Introduction

Before the introduction of highly active antiretroviral therapy (HAART), the median prevalence of HIV-associated neuropsychological (NP) impairment in individuals with acquired immunodeficiency syndrome (AIDS) was 55% (Heaton *et al*, 1995). AIDS dementia complex (ADC), the most severe form of NP impairment, had a pre-HAART prevalence of between 20% and 30% (Sacktor *et al*, 2002) and an annual incidence of 7% among patients with AIDS (McArthur *et al*, 1993). These and other studies have demonstrated that ADC tends to appear with advanced human immunodeficiency virus (HIV) infection and severe immunosuppression (Brew, 2001). However, since the introduction of HAART, this may be changing. ADC now occurs with higher CD4 cell counts (Dore *et al*, 1999), and the relation between HIV RNA markers and neurological status appears to be partly altered (McArthur *et al*, 2002). Moreover, emerging data show that ADC prevalence is increasing (Dore *et al*, 2003) and that the neuropathological features of ADC are more frequent in the HAART era (Neuenburg *et al*, 2002).

Although it is true that several studies have shown that HAART generally has a positive effect on HIV-associated NP impairment (Ferrando *et al*, 1998; Sacktor *et al*, 1999; Tozzi *et al*, 1999; Suarez *et al*, 2001), these have only assessed the effect in the short term, and have not taken into account the influence of increased patient age. The short-term efficacy of HAART may be compromised in the long term because of the increasing frequency of resistance to antiretroviral drugs (Cunningham *et al*, 2000; Venturi *et al*, 2000), with the resultant therapeutic failure (Hirschel and Opravil, 1999). Increased patient age, because of increased survival time (Moore and Chaisson, 1999), may also be important. Age-related NP dysfunction shares some common features with HIV-associated NP impairment. Therefore, an additive or interactive effect of age on HIV may amplify some minor neurocognitive disturbances (Goodkin *et al*, 2001).

Additionally, most studies have shown that not all aspects of NP functioning improve uniformly with HAART. For example, although psychomotor slowing improves with HAART, dysfunction in other cognitive domains such as verbal memory and executive function may not (Ferrando *et al*, 1998; Suarez *et al*, 2001). There are several explanations: the deficits may be fixed or "burnt out," or HAART may variably affect different parts of the brain. Indeed, the importance of the ability of the component drugs in the HAART regimen to effectively enter the brain remains controversial (Sacktor *et al*, 2001; Antinori *et al*, 2002). Consequently, these factors may influence the prevalence and pattern of neurocognitive changes usually found in HIV infection.

Our study aimed to monitor the prevalence and pattern of NP impairment among patients with advanced HIV infection in the HAART era and to compare these with similar indices from pre-HAART data. We chose two different cohorts recruited from Sydney, Australia, for this study as they are stable in regard to sociodemographics and mode and rate of HIV infection (McDonald, 2002). Because we intended to characterize the prevalence and pattern of NP impairment in nondemented, advanced HIV-infected individuals, patients with ADC were not included in this study.

Results

Demographic, clinical, and laboratory measures are presented in Table 1.

Prevalence of neuropsychological impairment
In the monotherapy cohort, prevalence of NP impairment reached 41.1% (21/51) in HIV+ individuals compared to 6.4% (2/31) in controls ($\chi^2 = 11.52$, $df = 1$, $P < .001$). For the HAART cohort, the prevalence of NP impairment reached 38.8% (35/90) in HIV+ individuals compared to 6.6% (2/30) in controls ($\chi^2 = 10.95$, $df = 1$, $P < .001$). The prevalence of impairment was 37.5% (27/72) when we excluded patients with previous HIV-related brain diseases (resolved on HAART at the time of the examination). When only patients with undetectable viral load in the plasma were included, the prevalence of impairment was 34.7% (16/46). For all subgroup analyses, there were no significance differences. Comparisons of pre-HAART and HAART prevalence in the HIV+ individuals showed no significant difference. There was no statistical difference with the HAART cohort subgroups. Results were not significantly different when calculating prevalence with a stricter criterion: -2 standard deviation (SD) in one NP measure.

Pattern of neuropsychological impairment
Frequency of impairment: Figure 1 shows the frequency of impairment for the monotherapy and the HAART cohorts on 14 NP measures. The monotherapy cohort showed a higher frequency of moderate impairment (-2 SD) on digit span forward (measure 1) ($P < .01$), verbal fluency (measure 12) ($\chi^2 = 15.08$, $df = 1$, $P < .000$), and copy of the Rey figure (measure 13) ($\chi^2 = 5.04$, $df = 1$, $P < .05$). The HAART cohort showed a higher frequency of impairment on verbal memory learning (measure 3) ($\chi^2 = 10.04$, $df = 1$, $P < .01$) and Symbol Digit Modalities Test (SDMT) oral version (measure 11) ($P < .05$). Other measures did not differ significantly. HAART-treated patients with undetectable viral load also showed a higher frequency of moderate impairment on verbal memory learning (measure 3) ($P < .05$), and SDMT oral version (measure 11) ($P < .01$).

Table 1 Demographical, clinical, and laboratory characteristics of HIV+ and HIV− individuals in monotherapy and HAART cohorts

	Monotherapy		HAART	
	HIV+	HIV− controls	HIV+	HIV− controls
N	51	31	90	30
Age[a]	36.37 ± 8.07	35.64 ± 8.63	47.37 ± 9.09	47.4 ± 9.39
Educational level (years)	13.68 ± 2.42	14.12 ± 2.81	13.88 ± 2.76	15 ± 3.08
Premorbid IQ*	114.35 ± 6.61	115.58 ± 5.27	115.9 ± 8.8	117.4 ± 6.61
Depression**[b]	.32 ± 1	−0.00006 ± 1	.44 ± 1.32	0.001 ± .99
Anxiety**	0.09 ± 1.05	0.0005 ± 1	.17 ± .97	0.0008 ± 1
Time since HIV diagnosis	—	—	11.9 ± 4.7	—
Treatment duration	2.5 ± 3.88 months	—	5.5 ± 1.54 years	—
Nadir CD4 cells count (count/μl)	—	—	66.94 ± 57.95	—
Current CD4 cells count (count/μl)[b]	120.69 ± 85.32	—	337.63 ± 225.4	—
Current HIVRNA (plasma)*** (copies/ml)	—	—	49 (49–750000.0)	—
% of patients with undetectable viral load****	—	—	51.1%	—

Note. Data are means ± SD unless otherwise notified.
*NART FSIQ (see Table 2).
**Standard scores derived from the matched controls in each cohort represent depression and anxiety measures. Raw scores were compared in each cohort between patients and controls and there were no significant differences.
***Median, minimum, and maximum.
****Undetectable viral load was defined as below 50 copies/ml.
[a]The HAART cohort was older compared to pre-HAART cohort ($P < .0001$).
[b]The HAART cohort showed higher current CD4 cells count compared to pre-HAART cohort ($P < .0001$).

Severity of impairment in the complete cohorts: Effects sizes (ESs) between the cohorts were greater than .4 in two measures: SDMT oral version (.42) and the copy of the Rey figure (.40). Patients in the monotherapy cohort were significantly more impaired than patients in the HAART cohort for the Rey copy figure ($t(139) = 2.3$, $P < .023$). Patients in the HAART cohort were significantly more impaired than patients in the monotherapy cohort for the SDMT oral version ($t(139) = -2.39$, $P < .018$).

HAART-treated patients with undetectable viral load showed a trend for a better performance on visuo-construction ($t(95) = 1.84$, $P < .069$; ESs = .45) and a trend for worse performance on the SDMT oral version ($t(95) = -1.87$, $P < .064$; ESs = .45) compared to patients in the monotherapy cohort.

Severity of impairment in impaired patients
Figure 2 shows the standard scores for impaired patients in the monotherapy, HAART and HAART-treated patients with undetectable plasma viral load
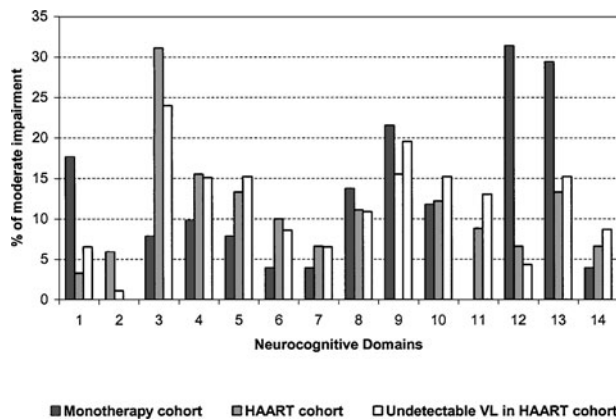

Figure 1 Frequency of moderate impairment for the monotherapy cohort, the HAART cohort, and the HAART-treated patients with undetectable viral load on 14 neuropsychological measures. Impairment defined as 2 SD for moderate degree in the impaired direction below controls' mean. Neuropsychological measures: 1 = digit span forward; 2 = digit span backward; 3 = verbal memory, learning; 4 = verbal memory, delayed recall; 5 = rey figure delayed recall; 6 = motor coordination, dominant hand, 7 = motor coordination, nondominant hand; 8 = TMT A; 9 = TMT B; 10 = SDMT, written version; 11 = SDMT, oral version; 12 = verbal fluency; 13 = rey figure, copy; 14 = similarities. For measure 11, monotherapy cohort = 0%. VL: viral load.
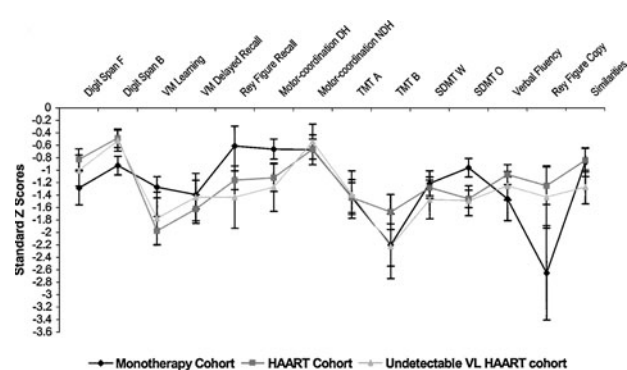

Figure 2 Neuropsychological profiles for the *impaired* patients in the monotherapy cohort ($N = 21$), HAART cohort ($N = 35$), and HAART-treated patients with undetectable viral load ($N = 16$) on 14 neuropsychological measures. Standard *Z* scores (mean and standard error [SE]). The neuropsychological measures are digit span forward (F); digit span backward (B); verbal memory (VM), learning; verbal memory (VM), delayed recall; Motor Coordination, dominant hand (DH) and nondominant Hand (NDH); SDMT written (W) version; and SDMT oral (O) version. Statistical comparisons only include measures when effect sizes were greater than .4, but all measures are represented for illustration (see Figure 3). A negative score represents worse performance. Mean and SE scores for control subjects are .00 ± .18 on all measures with no statistical differences between cohorts.

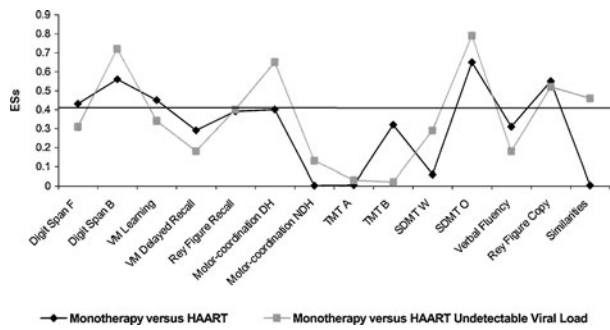Pre- and post-HAART neuropsychological impairment
LA Cysique *et al*
353

Figure 3 Effect sizes (ESs) in *impaired* patients between the monotherapy cohort ($N = 21$) and HAART cohort ($N = 35$), and between the monotherapy ($N = 21$) and the HAART-treated patients with undetectable viral load ($N = 16$). For the clarity of illustration, each ESs represents the absolute difference between the cohorts.

on 14 NP measures. ESs between the monotherapy and HAART cohort are presented in Figure 3. Impaired patients in the monotherapy cohort showed worse performance on the digit span backward ($t(54) = 2.02$, $P < .05$; ESs $= .56$) and the copy of the Rey figure ($t(54) = 1.98$, $P < .05$; ESs $= .55$) compared to the impaired patients in the HAART cohort. Impaired patients in the HAART cohort showed worse performance on verbal memory learning ($t(54) = -2.1$, $P < .04$; ESs $= -.45$) and SDMT oral version ($t(54) = -2.33$, $P < .02$; ESs $= -.65$) compared to the impaired patients in the monotherapy cohort. Impaired patients in the HAART cohort with undetectable viral load showed a trend for worse performance on the SDMT oral version ($t(35) = -1.92$, $P < .06$; ESs $= -.79$).

Contribution of the nadir and current CD4 cells count to NP performance on complete cohorts and selected impaired patients (on NP measures that differed in severity between the two cohorts)
The linear regression models showed that only the current CD4 cell count was a significant predictor of performance on the Rey copy figure ($R^2 = .070$, $F(1, 88) = 6.61$, $P < .012$) in the complete HAART cohort.

Discussion

Our study has demonstrated that the prevalence of neuropsychological impairment among comparable cohorts of HIV-infected individuals with advanced HIV disease was not different before or after the use of HAART treatment (pre-HAART 41.1%, post-HAART 38.8%). Furthermore, the prevalence of impairment remains essentially unaltered in patients with and without viral suppression in the plasma. Despite the lack of change in prevalence, there was evidence to suggest that there have been both quantitative and qualitative changes in the pattern of cognitive impairments post HAART.

First, when comparing complete monotherapy and HAART cohorts, the monotherapy cohort showed a greater frequency of deficits in immediate attention (digit span forward), verbal fluency, and visuoconstruction ability (copy of the Rey figure) compared to the HAART cohort. In contrast, the HAART cohort showed higher frequency of deficits in verbal memory learning and one measure of complex attention (SDMT oral version). This was also true for the HAART-treated patients with undetectable plasma viral load.

Second, HAART-treated patients were less impaired on a measure that involves visuoconstructional ability as well as organisation skills (copy of the Rey figure). On the other hand, they showed more impairment in a measure of complex attention (SDMT oral version) compared to patients in the monotherapy cohort. When considering HAART-treated patients with undetectable viral load, we found a trend for less impairment on visuoconstruction and a trend for worse performance on complex attention (SDMT oral version) compared to patients in the monotherapy cohort.

Third, impaired HAART-treated patients were less impaired on a measure reflecting working memory capacity (digit span backward) and on visuoconstruction (copy of the Rey figure). On the other hand, they showed more impairment on a measure that reflects verbal memory learning efficiency. They also demonstrated a marked deficit for a measure of complex attention (SDMT oral version) that is indicative of complex attention capacity without the influence of the motor component.

It should be noted that Crowe *et al* (1999) have shown that the elementary motor operations (graphic/writing skills) involved in the written version of SDMT are the main determinants of the performance. This may indicate that the difference between the cohorts on the SDMT oral, but not SDMT written, version is that the oral test is partly based on processing speed as well as other functions such as verbal availability (Lezak, 1995) and learning abilities (Smith, 1982).

In essence, our results show a trend toward a profile change in the nature of cognitive impairment associated with advanced HIV infection. However, some limitations (small sample sizes in subgroups and comparisons of cross-sectional designs) may have influenced the results. Potential preexisting differences between the cohorts may have impacted on the results. However, this is unlikely because patients' mode of selection was identical and we found that a measure of premorbid abilities (National Adult Reading Test Full IQ Scale [NART-FIQS]) was identical for both cohorts. Moreover, some differences in selected tests could have impacted on the degree of impairment observed. Thus, when tests are not exactly similar, but are compared on the assumptions that they refer to similar cognitive domains, the results should be interpreted more cautiously. This is particularly

the case in verbal memory where the task difficulty is known to be higher for the California Verbal Learning Test than the Selective Reminder Word Learning Test (Lezak, 1995). This may have accentuated the impaired performances in the HAART cohort and more specifically in impaired patients. Nevertheless, we have opted for two methodological approaches to lessen this limitation. First, we have only selected measures with notable effect sizes (>.4), in order to compare clinically meaningful levels of impairment. Second, we have used standard scores that are based on controls' performances, which remain identical in all cohorts.

Our results tend to confirm and extend previous data (Sacktor *et al*, 2002) showing that despite HAART, neurocognitive impairment remains common. However, our study is the first to include HIV+ individuals on long-term HAART over a period of five years on average. One recent study has reported a prevalence of 43% of neurocognitive deficit after 3 years of HAART, mainly in mildly impaired patients (Tozzi *et al*, 2001). However, the sample size was small and the authors used normative data rather than matched controls.

ADC incidence has decreased and prevalence increased in the HAART era and this appears to be due to the longer survival of ADC patients (Dore *et al*, 2003). Therefore, it might be expected that neuropsychological deficits would be less severe but more common. This was not the case, possibly because of differences in data acquisition. Indeed, the ADC epidemiological data do not reflect incidence over the lifetimes of patients but rather relate to ADC as the initial AIDS defining illness and do not capture ADC occurring after such an illness.

The simultaneous presence of improving and declining neuropsychological functions in the HAART cohort compared to the monotherapy cohort argues against the possibility that the deteriorating deficits simply reflect past fixed damage or "burnt out" disease. Rather, this may be indicative of an active intracerebral process, which would be characterized by the functions that are deteriorating. Nevertheless, longitudinal validation will be necessary to confirm these trends.

Age could account for some of these differences, especially worsening of complex attention and memory learning (Goodkin *et al*, 2001). However, a simple age effect should also alter attention and most, if not all, psychomotor speed measures—a finding we did not observe in the HAART cohort. Additionally, comparisons were made on adjusted standard scores for age and education. Thus age may only partially contribute to the change but other yet-to-be-determined factor(s) must be important.

In these cohorts, the CSF viral load was not available. The explanation for an active intra-cerebral process that would be related to viral activity in the brain should be considered. Indeed it could be anticipated that patients with CSF viral suppression may be less neuropsychologically impaired (Brew *et al*, 1997; Ellis *et al*, 1997). However with the introduction of HAART, the role of the CSF viral load is becoming unclear. There is emerging evidence of a dissociation between neurocognitive deficits and CSF viral load levels (Brew *et al*, 1998; McArthur *et al*, in press) and this may indicate that other neuropathological processes may be responsible.

The nature of this process, however, is speculative. Age may be playing a role although as discussed above it cannot explain the data fully. Other possibilities are the differential effects of neurologically active antiretrovirals (Cysique *et al*, in press); the possible brain mitochondrial toxicity from some of the antiretrovirals drugs and new neuropathological mechanisms as discussed by Brew (2004).

Traditional psychomotor measures (Trail Making Test and SDMT written version) did not differ between cohorts. This suggests that the initial improvement in psychomotor slowing with HAART that was observed in previous studies (Ferrando *et al*, 1998; Sacktor *et al*, 1999; Tozzi *et al*, 1999; Suarez *et al*, 2001) is not sustained in the longer term. Thus, psychomotor slowing remains an important feature of HIV-associated NP deficits (Sacktor *et al*, 1996). However, in the HAART era, it may be associated with an increased frequency and severity of memory learning difficulty as well as some aspects of complex attention that may be partially independent of psychomotor speed. This last point requires to be further explored.

Finally, in consideration of these findings in neuropsychologically impaired advanced HIV-infected patients, it is important to determine whether similar nonclassical changes may be occurring in ADC patients treated with HAART.

Further studies will be necessary to confirm the pattern observed and to determine the nature of the ongoing intracerebral process.

Materials and methods

The methodology used in the pre-HAART cohort has been described in detail previously (Dunbar *et al*, 1992).

Subjects
In the monotherapy cohort, 51 homosexual or bisexual men were invited to participate in the study from a larger cohort recruited from St. Vincent's Hospital clinics, Albion Street Centre, and Sydney Hospital between January 1987 and December 1989. Patients were randomly selected and had been treated with zidovudine (ZDV) monotherapy for 2.5 ± 3.88 months. They have all been reclassified as stage C3 according to the Centers for Disease Control and Prevention (CDC) classification, 1993.

In the HAART cohort, 90 patients (1 female) with stage C3 HIV disease (CDC Classification, 1993) were

Pre- and post-HAART neuropsychological impairment
LA Cysique *et al*
355

Table 2 Detailed procedures in the two cohorts*

	Monotherapy cohort	*HAART cohort*
Premorbid abilities	National Adult Reading Test (NART) Full IQ Scale (FIQS)	National Adult Reading Test (NART) Full IQ Scale (FIQS)
Depression and anxiety instruments	Centre of Epidemiology Scale for Depression (Radloff, 1977); State-Trait Anxiety Inventory (Spielberger *et al*, 1970)	Depression, Anxiety and Stress Scale (Lovibond and Lovibond, 1995)
Attention, immediate attention and working memory	Digit span forward and backward (WAIS-R)	Digit span forward and backward (WAIS III-R)
Speed processing	Trail Making Test A	Trail Making Test A
Complex attention	Trail Making Test B	Trail Making Test B
Psychomotor speed/mental flexibility	Symbol Digit Modalities Test, written/oral	Symbol Digit Modalities Test, written/oral
Fine motor coordination	Purdue Pegboard dominant and nondominant hand	Lafayette Grooved Pegboard, dominant and nondominant hand
Verbal memory, learning and long-term recall	Selective Reminder Word Learning Test, total words recall, and long-term recall	California Verbal Learning Test, total word learning and long-term free recall
Visual memory	Rey-Osterrieth complex figure, delayed recall	Rey-Osterrieth complex figure, delayed recall
Visuoconstruction	Rey complex figure, copy	Rey complex figure, copy
Language	Controlled Oral Word Association Test, verbal fluency (total letter FAS)	Controlled Oral Word Association Test, verbal fluency (total letter CFL)
Reasoning	Similarities (WAIS-R)	Similarities (WAIS III-R)

*All tests have been extensively described elsewhere (Lezak, 1995).
WAIS: Wechsler Adult Intelligence Scale.

randomly invited to participate in the study from the outpatient's clinics at St. Vincent's Hospital, Sydney, between August 2001 and December 2002. They had been taking HAART for a mean of 5.5 ± 1.5 years.

For both cohorts, exclusion criteria were neurological disorders (predating or unrelated to HIV) that had not fully resolved, current or history of major depression or psychosis, head injury with loss of consciousness greater than 30 min, alcohol abuse or drug dependence, current active opportunistic infection, and a history of HIV-related CNS opportunistic infection in pre-HAART cohorts. Patients with a current clinical diagnosis of ADC were excluded. In the HAART cohort, patients with a previous brain HIV-related disease were included as long as there had been clinical resolution on HAART at least 6 months prior to study entry. Further analyses showed that they did not differ in their NP performance compared to other patients.

Seronegative controls for the monotherapy cohort (31 subjects) and the HAART cohort (30 subjects) were recruited from advertisements in the gay press and through a study on gay men's sexual behaviour. They had to be seronegative at least 3 months prior to the examination on a screening test (enzyme-linked immunosorbent assay; ELISA) for HIV-1–specific antibody and screened for significant neurological or psychiatric diseases. Seronegative controls were recruited at the same time as the seropositive individuals in each cohort and were matched for age and education.

Procedure
An interview was conducted to record demographics, medical information, treatment information, immunological markers, depression, and anxiety

(Table 1). Standard neuropsychological tests were selected in order to evaluate cognitive functions sensitive to impairment found in HIV-infected individuals (Butters *et al*, 1990) (Table 2). Administration time varied between 1 and 2 hours. For each cohort, a qualified neuropsychologist (MP, LC) conducted the examination. All patients signed an informed consent and ethics committees approved the research protocol.

Data analysis
Groups within each cohort were compared on demographic, clinical, and laboratory measures using *t* test or Mann-Whitney tests when appropriate. Between-cohort comparisons were made with *t* tests on raw scores or standard scores when appropriate.

NP standard Z scores were derived from the matched controls' mean and standard deviation (SD) in each cohort, and prevalence of impairment was calculated on 14 NP measures using a standard criterion (Grunseit *et al*, 1994): two standard deviations below the controls' mean in two NP measures. Comparisons of prevalence were calculated with chi-square.

The frequency of impairment was examined by calculating the proportion of moderate impairment based on standard scores for the 14 NP measures (defined as two standard deviations in the impaired direction). Comparisons between cohort were calculated with chi-square. When one comparison cell had an expected count less than 5, we reported Fisher's exact test.

We examined the pattern of impairment, in the *complete* cohorts and in *impaired* patients as defined by the standard criterion, on the 14 NP measures. Effects sizes (ESs) (Howell, 2002) were calculated

between the pre-HAART and the HAART cohorts in order to evaluate the magnitude of any difference in NP performance.

Statistical comparisons between cohorts only included NP measures where ESs were found to be greater than .4 (see Figure 3). Between-cohort comparisons were made on standard scores with t-test. All tests of significance were set at the conventional $P < .05$ two-tailed. We chose not to control for experiment-wise error rate (Perneger, 1998) but

rather use ESs to guide our interpretation of clinically meaningful results (Zakzanis, 2001). There were nine missing values in the HAART cohort, which were excluded list-wise. Finally, linear regression analyses were conducted to determine how the CD4 cell counts might impact on the NP scores that differed between the cohorts. The predictor variable (current CD4 cells count) was entered at $P < .05$ and removed at $P < .10$. Statistical analyses were conducted with SPSS 10.05 (SPSS Inc, Chicago, Illinois 1999).

References

Antinori A, Giancola ML, *et al* (2003). Factors influencing virological response to antiretroviral drugs in cerebrospinal fluid of advanced HIV-1-infected patients. *AIDS* **16:** 1867–1876.

Brew BJ (2001). *AIDS dementia complex in HIV neurology.* Oxford: Oxford University Press, pp. 53–90.

Brew BJ (2004). Evidence for a change in AIDS dementia complex in the era of highly active antiretroviral therapy and the possibility of new forms of AIDS dementia complex. *AIDS* **18:** S75–S78.

Brew BJ, Brown SJ, *et al* (1998). Safety and efficacy of Abacavir (ABC, 1952) in AIDS dementia complex (Study CNAB 3001). In: *12th World AIDS Conference*, Geneva, 28 June–3 July.

Brew BJ, Pemberton L, *et al* (1997). Levels of human Immunodeficiency virus type 1 RNA in cerebrospinal fluid correlate with AIDS dementia stage. *J Infect Dis* **175:** 963–966.

Butters N, Grant I, *et al* (1990). Assessment of AIDS-related cognitive changes: recommendations of the NIMH workgroup on neuropsychological assessment approaches. *J Clin Exp Neuropsychol* **12:** 963–978.

Crowe S, Benedict T, *et al* (1999). Cognitive determinants of performance on the Digit Symbol-coding test, the Symbol Search Test of the WAIS-III, and the Symbol Digit Modalities Test: an analysis in a healthy sample. *Aust Psychol* **34:** 204–210.

Cunningham P, Smith D, *et al* (2000). Evidence for independent development of reverse transcriptase inhibitor resistance patterns in the cerebrospinal fluid. *AIDS* **14:** 1949–1954.

Cysique L, Maruff P, *et al* (in press). Antiretroviral therapy in HIV-infection: are neurologically active drugs important? *Arch Neurol*

Dore GJ, Correll PK, *et al* (1999). Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS* **13:** 1249–1253.

Dore GJ, McDonald A, *et al* (2003). Marked improvement in survival following AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS* **17:** 1539–1545.

Dunbar N, Perdices M, *et al* (1992). Changes in neuropsychological performance of AIDS-related complex patients who progress to AIDS. *AIDS* **6:** 691–700.

Ellis RJ, Hsia K, *et al* (1997). Cerebrospinal fluid human immunodeficiency virus type 1 RNA levels are elevated in neuro cognitively impaired individuals with Acquired Immuno Deficiency Syndrome. *Ann Neurol* **42**(**5**): 679–688.

Ferrando S, Van Gorp W, *et al* (1998). Highly active antiretroviral treatment in HIV infection: benefits for neuropsychological function. *AIDS* **12:** F65–F70.

Goodkin, K, Wilkie FL, *et al* (2001). Aging and neuro-AIDS conditions and the changing spectrum of HIV-1 associated morbidity and mortality. *J Clin Epidemiol* **54:** S35–S43.

Grunseit AC, Perdices M, *et al* (1994). Neuropsychological function in asymptomatic HIV-1 infection: methodological issues. *J Clin Exp Neuropsychol* **16:** 898–910.

Heaton R, Grant I, *et al* (1995). The HNRC 500-Neuropsychology of HIV infection at different disease stages. *J Int Neuropsychol Soc* **1:** 231–251.

Hirschel B, Opravil M (1999). The year in review: antiretroviral treatment. *AIDS* **13:** S177–S187.

Howell DC (2002) *Statistical methods for psychology*, 5th ed. Duxbury: Thomson Learning.

Lezak MD (1995) *Neuropsychological assessment*, 4th ed. New York: Oxford University Press.

Lovibond SH, Lovibond PF (1995) *Manual for the Depression Anxiety Stress Scales (2nd. Ed.)*. Sydney: Psychology Foundation.

McArthur JC, Hoover DR, *et al* (1993). Dementia in AIDS patients: incidence and risk factors. *Neurology* **43:** 2245–2252.

McArthur JC, McClernon DR, *et al* (2002). Viral load markers and neurological status: a report from the North-East Dementia Cohort. *J NeuroVirol* **8(Suppl 1):** Abstract 19.

McArthur JC, McDermott MP, *et al* (In press). Attenuated CNS infection in advanced HIV/AIDS with combination antiretroviral therapy. *Arch Neurol*

Mc Donald A (2002). *HIV/AIDS, viral hepatitis and sexually transmissible infections*. In: *Australia Annual Surveillance Report 2002*. National Centre in HIV Epidemiology and Clinical Research University of New South Wales Sydney.

Moore RD, Chaisson RE (1999). Natural History of HIV infection in the era of combination antiretroviral therapy. *AIDS* **13:** 1993–1942.

Neuenburg JK, Brodt HR, *et al* (2002). HIV-related neuropathology, 1985 to 1999: rising prevalence of HIV encephalopathy in the era of highly active antiretroviral therapy. *J Acquir Immune Defic Syndr* **31:** 171–177.

Perneger TV (1998). What's wrong with Bonferroni adjustments. *BMJ* **316:** 1236–1238.

Radloff LS (1977). The CES-D scale: a self-report depression scale for research in the general population. *Appl Psychol Measure* **1:** 385–401.

Sacktor N, McDermott M, *et al* (2002). HIV-associated cognitive impairment before and after the advent of combination therapy. *J NeuroVirol* **8:** 136–142.

Sacktor N, Tarwater PM, *et al* (2001). CSF antiretroviral drug penetrance and the treatment of HIV-associated psychomotor slowing. *Neurology* **57:** 542–544.

Sacktor NC, Bacellar H, *et al* (1996). Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death. *J NeuroVirol* **2:** 404–410.

Sacktor NC, Lyles RH, *et al* (1999). Combination antiretroviral therapy improves psychomotor speed performance in HIV-seropositive homosexual men. *Neurology* **52:** 1640–1647.

Smith, A. (1982) *Symbol Digit Modalities Test manual.* Los Angeles: Western Psychological Services.

Spielberger CD, Gorsuch RL, Lushene RE (1970). *Manual for the State-Trail Anxiety Inventory*. Palo Alto: Consulting Clinical Psychologists Press.

Suarez S, Baril L, *et al* (2001). Outcome of patients with HIV-1 related cognitive impairment on highly active antiretroviral therapy. *AIDS* **15:** 192–200.

Tozzi V, Balestra P, *et al* (1999). Positive and sustained effects of highly active antiretroviral therapy on HIV-1 associated neurocognitive impairment. *AIDS* **13:** 1889–1897.

Tozzi V, Balestra P, *et al* (2001). Changes in neurocognitive performance in a cohort of patients treated with HAART for 3 years. *J Acquir Immune Defic Syndr* **28:** 19–27.

Venturi G, Catucci M, *et al* (2000). Antiretroviral resistance mutations in human immunodeficiency virus type 1 reverse transcriptase and protease from paired cerebrospinal fluid and plasma samples. *J Infect Dis* **181:** 740–745.

Zakzanis KK (2001). Statistics to tell the truth, the whole truth, and nothing but the truth: formulae, illustrative numerical examples, and heuristic interpretation of effect sizes analyses for neuropsychological researchers. *Arch Clin Neuropsychol* **16:** 653–667.