Variable benefit in neuropsychological function in HIV-infected HAART-treated patients

Abstract—The authors examined cognitive performance change in 101 individuals with advanced HIV infection on highly active antiretroviral therapy (HAART), using standard neuropsychological testing in three visits, over a 27-month-period. Cognitive performance stabilized in a majority of HIV+ participants over time. A neuroactive HAART regimen was associated with neuropsychological improvement. Decline occurred in a minority with lower nadir CD4. The current CD4 count and plasma viral load were not associated with cognitive change.

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In the highly active antiretroviral therapy (HAART) era, AIDS dementia complex (ADC)[1] still occurs, but prospective studies addressing illness activity and stability have had shortcomings[2-3]: entry has been restricted to those already with impairment, and the observation period has been relatively short.

Therefore, we sought to prospectively examine the neuropsychological performance in individuals at risk of HIV-related cognitive change and treated with HAART for 5 years.[4]

Methods. *Subjects.* One hundred HIV+ individuals with stage C3 HIV disease were randomly invited to participate from the outpatient clinics at St. Vincent's Hospital. Eighty-one individuals came for a second visit at 6 months, 51 for a third visit at 15 months, and 38 for a fourth visit at 27 months. Demographic, clinical, and laboratory data are presented in table 1. Thirty seronegative controls matched for age and education were recruited to develop norms for change and assessed at one follow-up session.[4]

Procedure. The neuropsychological battery included the assessment of attention, learning, memory, motor coordination, complex attention/psychomotor speed, language, visuoconstruction (see Cysique et al.[4] for additional details).

Data analysis. Decline was classified using the within SD (WSD)–based reliable change index (RCI).[5] The control group WSD was used as the statistical reference of stability over time to compute the RCI in all individuals in the short term (6 months) and long term (27 months). To identify HIV+ individuals with significant cognitive decline over the first 6 months, we defined it as an RCI of less than −1.96 on two or more of the 10 tests.[6] To identify which of the neuropsychological tests was most sensitive to HIV-related cognitive change, we compared performance on each of the 10 measures between the HIV+ with cognitive decline and HIV+ without (nondecliners) using *t* tests. Six tests sensitive to HIV-related cognitive decline over the short term were used to compute a composite change score (composite RCI) to identify decline over the long term. Standardized composite RCIs of −1.96 and −1.5 were classified as abnormal (i.e., significant decline).[6] Relationships between demographic, treatment-related, and clinical variables were explored with the composite RCI and multiple regression as well as Pearson correlations when appropriate.[7] To explore a potential attrition effect, HIV+ individuals who dropped out were compared at baseline with the patients who remained in the study on all variables, and no differences were found. The rate of decline between dropout cases and remaining participants was also explored and no differences were found.

Results. Over the short term, the prevalence of neuropsychological decline was higher in the HIV+ group than in controls (30% vs 13%, $p < 0.05$). HIV+ decliners and nondecliners differed on six neuropsychological measures (effect sizes >0.4): domains of verbal learning, memory, motor coordination, psychomotor speed, and complex attention (these were retained to compute the composite RCI). When decline was defined as an RCI of less than −1.5 SD and based on the six measures to develop the composite RCI, we found that 13 individuals were classified as decliners. When the 10 initial measures were used to develop a composite RCI, we also found that 13 individuals were classified as decliners. Therefore, fewer tests did not alter significantly the frequency of classification of decline. Moreover, of the 13 decliners, nine individuals were identical in both composite RCI representing a 70% agreement in the classification of decline.

Based on the composite RCI, the prevalence of decline varied between 5.88% and 13.72% at session III and remained static at 5.26% at session IV The profile of change for individual cases is illustrated in the figure.

Cognitive decline over the long term was related to lower nadir CD4 cell counts, past depressive episode, past HIV-related brain diseases, and initial number of AIDS-defining illnesses. Individuals with a longer disease duration, older individuals, and individuals with lower level of education showed improvements in cognitive performance over time. Self-reported anxiety and depressive symptoms were also associated with decline in cognitive functioning. Complex attention was positively associated with the presence of at least three neuroactive antiretrovirals composing HAART (neuroactive was defined as a HAART regimen including at least three neuroactive antiretrovirals[8]). Current CD4 cell count and plasma viral load were not associated with cognitive performance overtime (table 2).

Discussion. In this study, we examined the extent to which cognitive function changed overtime in HAART-treated individuals with advanced HIV infection. First, we found that 30% of HIV+ participants showed reliable cognitive decline over the short term, but the majority improved over the long term, albeit with considerable variability. Second, change in cognitive performance was not related to

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Table 1 *Demographic, clinical, treatment, and laboratory characteristics of advanced HIV-infected individuals at baseline and over the study period*

	HIV+ baseline	HIV+ session II	HIV+ session III	HIV+ session IV	*P*1	*P*2
No.	101	81	51	38	—	—
Age	48.51 ± 9.32	49.20 ± 8.92	51.00 ± 7.88	52.34 ± 8.15	0.02	0.001
Educational level (y)	14.05 ± 2.85	—	—	—	—	—
Estimated FSIQ	115.71 ± 8.64	—	—	—	—	—
Estimated HIV duration	11.97 ± 4.84	12.81 ± 4.80	13.38 ± 4.50	14.77 ± 4.44	0.001	0.001
Past HIV-related brain diseases	19.8% (20)	—	—	—	—	—
Initial % of ADI						
0/1/2/3/4/5/6	36.6/31.7/19.8/7.9/2/1/1	—	—	—	—	—
New ADI	—	3.7% (3)	7.8% (4)	0	—	—
Date of initial HAART	1996 ± 1.5	—	—	—	—	—
Neuro-HAART	41.6% (42)	39.5% (32)	37.3% (19)	28.9% (11)	—	—
STI	—	1..2% (1)	5.9% (3)	5.3% (2)	—	
ART change	—	28.4% (23)	31.4% (16)	31.6% (12)	—	—
Nadir CD4 (count/μL)	73.17 ± 62.07	—	—	—		—
Current CD4 (count/μL)	352.50 ± 229.89	385.88 ± 196.08	379.78 ± 199.33	357.97 ± 196.11	ns	ns
Plasma HIV RNA (log_{10} cpy/mL) [min-max]	2.83 ± 1.43 [49–750,000]	2.63 ± 1.14 [49–750,000]	2.72 ± 1.23 [49–820,000]	2.41 ± 1.18 [49–347,000]	ns	ns
% of patients with undetectable viral load (<50 cpy/mL)	53.5% (54)	42% (34)	43.13% (22)	63.2 (24)	—	—
% >30.000 cpy/mL	21.8% (22)	11.3% (9)	17.6 (9)	23.7 (9)		
Antidepressant medication	16.83% (17)	17.28% (14)	23.52% (12)	23.68% (9)	—	—
Depression	7.30 ± 7.56	9.34 ± 8.84	7.92 ± 7.96	8.10 ± 7.63	ns	ns
Anxiety	5.07 ± 5.52	5.45 ± 5.86	5.92 ± 6.27	5.15 ± 4.89	ns	ns
Stress	9.09 ± 7.06	11.17 ± 9.00	9.74 ± 7.38	9.31 ± 7.63	ns	ns
Depressive episode documented in the past 10 y	25.74% (26)	—	—	—	—	—

*P*1 = $p < 0.05$ two tailed for paired *t* test between session 2 and baseline; *P*2 = $p < 0.05$ two tailed for repeated analysis of variance over the study period. The statistical results take into account the number of patients who remained at each session on continuous variables only. Seronegative controls (n = 30) were 47.40 ± 9.39 years old at baseline and 47.86 ± 9.17 years old at 6 months' follow-up ($p < 0.01$). Their educational level in years was 15.00 ± 3.08 at baseline. Depression, anxiety, and stress symptoms were assessed with the Depression, Anxiety, and Stress Scale (DASS).

FSIQ = full-scale IQ; HAART = highly active antiretroviral therapy; ART = antiretroviral therapy; Neuro-HAART = neuroactive highly active antiretroviral therapy regimen composed of at least three neuroactive antiretrovirals; ns = not significant.

HAART optimization, at least when plasma viral load was considered. Third, cognitive deterioration over the study period was as frequent in participants with an undetectable or detectable plasma viral load. Fourth, a three-neuroactive drug regimen was associated with better complex attentional function. Finally, lower nadir CD4 cell counts were associated with cognitive impairment in the long term.

When the stability of cognitive function was considered over the longer term, it became evident that the initial cognitive decline was generally not sustained. The illustration of individual profiles shows six cases of sustained cognitive decline over the study period. Another pattern observed in the data was an abrupt decline from one session to another with a mild improvement afterward, but incomplete recovery (three cases). The attrition rate may have only partially altered the ability to detect more decliners because the proportion of decliners and nondecliners was not different in the patients who remained and those who dropped out.

Some factors may render long-term analyses complex in HAART-treated advanced HIV+ patients. We found that the course of HIV-associated cognitive impairment may vary in individuals according to age and education in a counterintuitive way. Performance on neuropsychological tests was more likely to improve over the study period in older and less educated individuals. This has been observed in other studies and interpreted to reflect the combined effects of regression toward the mean and task familiarization.[9]

The reason that performance stabilized in the majority of participants over time may reflect the efficacy of HAART.[3] This may be a consequence of the nature of the drugs used in the HAART regimen, but importantly it is not related to control of the plasma viral load. It also means that an undetectable viral load is no guarantee against cognitive deterioration. Across the study period, between 8% and 34% of individuals with undetectable viral load declined. It is therefore important to search for new HIV illness markers that are associated with cognitive change (such as host susceptibility to cognitive impairment[10]). We also found that factors such as past depressive episode and the presence of past HIV-related brain diseases play a role in the occurrence of decline.

Our finding that the majority of patients showed improved neuropsychological performance argues

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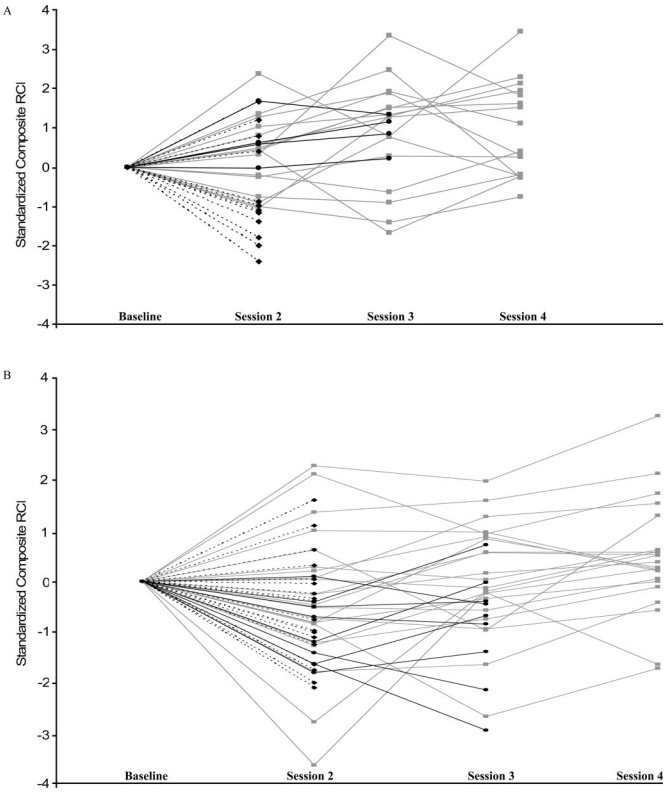

Figure. Illustration of performance change over the study period in HIV+ individuals. Dashed black line and diamonds indicate patients who did not return after session II. Plain black line and round dots indicate patients who did return after session III. Plain gray line and squares indicate patients who came to all sessions. A negative reliable change index indicates cognitive decline. (A) Illustration of 32 HIV+ cases impaired at baseline among the 81 who came back for at least one follow-up. (B) Illustration of 49 HIV+ cases unimpaired at baseline among the 81 who came back for at least one follow-up. Distinction between neuropsychologically impaired and unimpaired HIV+ individuals at baseline was made for the clarification of the illustration (see also Cysique et al.[4] for additional details in the definition of impairment).

Table 2 *Regression and correlation results for the relationship between demographic, clinical, and HIV illness markers and composite reliable change index*

Time-variant variables	*R*	*p*
Age	0.37	0.001
Estimated HIV duration	0.40	0.001
Current CD4 cell count	0.02	0.95
Log 10 plasma HIV RNA	−0.09	0.35
Plasma HIV RNA undetectable versus detectable	−0.01	0.89
New AIDS-defining illnesses	−0.10	0.18
Depression	−0.30	0.003
Anxiety	−0.36	0.001
Stress	−0.14	0.13
Antidepressant	−0.10	0.34
ART change	0.17	0.09
No. of neuroactive drugs	−0.02	0.43
Structured treatment interruption	0.14	0.16
Neuro-HAART learning	0.04	0.62
Neuro-HAART delayed recall	0.02	0.84
Neuro-HAART motor	0.04	0.68
Neuro-HAART TMTA	0.10	0.32
Neuro-HAART TMTB	0.03	0.74
Neuro-HAART SDMT oral	0.22	0.04

Time-invariant variables	Session II	Session III	Session IV
Education	−0.08	−0.31*	−0.37*
Estimated FSIQ	0.03	−0.15	−0.26
Nadir CD4	0.12	0.14	0.41†
Year of HAART initiation	−0.06	0.13	−0.11
Past depressive episode	−0.17	−0.23	−0.37*
Past HIV-related brain diseases	−0.16	−0.04	−0.44†
Initial number of AIDS-defining illnesses	−0.19	−0.19	−0.35*
Baseline cognitive status‡	0.22*	0.41†	0.21

For time-invariant variables: *$p < 0.05$, †$p < 0.01$. Depression, anxiety, and stress symptoms were assessed with the Depression, Anxiety, and Stress Scale (DASS).

‡Baseline cognitive status, see Cysique et al.[4]

ART = antiviral therapy; Neuro-HAART = highly active antiretroviral therapy regimen composed of at least three neuroactive antiretrovirals (see Cysique et al.[8] for additional information); TMTA/B = Trail Making Test A/B; SDMT: Symbol Digit Modalities Test; FSIQ = full-scale IQ.

strongly against the possibility that burnt-out or inactive HIV-related brain disease is common. Indeed, it argues against the possibility of stable disease. Previously, we found no change in the prevalence of neuropsychological impairment in neurologically asymptomatic patients between the pre-HAART and HAART eras.[4] This was despite the known efficacy of HAART in improving HIV-related brain disease. There are at least two possible explanations. First, HAART was ineffective because the deficits were "old," representing inactive or burnt-out disease, or HAART was variably effective with some improving and others deteriorating, leading to no net change. Given the current results, it appears that HIV-related brain disease in most patients is still dynamic. The net lack of change seen in our previous study may be explained by a bidirectional flow: net improvement in neuropsychological performance in asymptomatic patients counterbalanced by net improvement in dementia patients to an asymptomatic but still impaired state.

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Correction

Fascicular hypoglossus nerve lesion

In the Neuro*Image*, "Fascicular hypoglossus nerve lesion" (*Neurology* 2006;66:441) by Ingo Nolte, Carsten Wessig, and Martin Bendszus, the author Martin Bendszus was incorrectly listed as Bendszus Martin. The publisher regrets this error.

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