Multidisciplinary Baseline Assessment of Homosexual Men With and Without Human Immunodeficiency Virus Infection

III. Neurologic and Neuropsychological Findings

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• **We explored the possibility that neurologic and neuropsychological changes constitute the earliest detectable manifestations of human immunodeficiency virus (HIV) infection. Without knowledge of HIV status, we assessed neurologic signs and symptoms and administered a battery of neuropsychological tests to 208 homosexual men, of whom 84 were HIV negative, 49 were HIV positive and asymptomatic, 29 were mildly symptomatic, and 46 had significant medical symptoms but not the acquired immunodeficiency syndrome. There was no difference between the HIV-negative and HIV-positive men in the frequency of neurologic signs or of defective or borderline performance on any neuropsychological test. However, HIV-positive men performed slightly but significantly worse than HIV-negative men on tests of verbal memory, executive function, and language. Similar results were obtained when comparisons were limited to HIV-positive medically asymptomatic and HIV-negative men. There was no degradation of neurologic status or neuropsychological performance across stages of HIV severity, but neurologic and neuropsychological summary scores correlated with CD4/CD8 ratios in the HIV-positive group. Ratings of neurologic signs and symptoms correlated with neuropsychological summary scores in the HIV-positive group only. Cognitive complaints were more frequent in the HIV-positive men; they correlated with actual test performance in the HIV-positive but not HIV-negative men. The constellation of subjective and objective neuropsychological and neurologic findings suggests the possibility of a definable syndrome associated with HIV infection in asymptomatic individuals.**

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The present study explored the possibility that neurologic and neuropsychological changes constitute the earliest detectable manifestations of human immunodeficiency virus (HIV) infection.

Even before immunologic changes or constitutional symptoms emerge, HIV infection can be detected in the central nervous system. For example, infection of the leptomeninges occurs in seropositive subjects with and without neurologic signs and symptoms.[1-4] Also, in a study of 400 HIV-positive Air Force personnel, 60% of the neurologically and immunologically asymptomatic group had at least one abnormal cerebrospinal fluid measure, suggesting that infection of the nervous system is common.[5] These observations suggest that the central nervous system may be a very early site of involvement in HIV infection.

Similarly, while dementia related to the acquired immunodeficiency syndrome (AIDS) is recognized, the presence of intellectual changes in HIV-positive individuals without AIDS remains controversial. A number of studies have demonstrated significant differences between neuropsychological performance in HIV-positive medically asymptomatic subjects and HIV-negative controls,[6-8] and others have noted a continuum of neuropsychological change across medically asymptomatic patients and those with lymphadenopathy syndrome or AIDS-related complex (ARC).[9,10] Several large studies[4,11,12] found no differences between HIV-positive, medically asymptomatic and HIV-negative groups. In addition, the relationship between neurologic and neuropsychological changes has not been systematically evaluated; if such a relation exists, it would strongly implicate central nervous system involvement.

For the present study, homosexual men who were HIV seropositive, as well as seronegative controls, underwent in-depth neurologic and neuropsychological evaluations as part of a multidisciplinary study.[13,14] The evaluations were designed to investigate the presence of subtle neurologic and cognitive changes in these men, possible interrelationships between these changes, and the relationship of neurologic and neuropsychological changes to indexes of disease severity.

Self-reports of cognitive and neurologic complaints were also elicited to explore the relationship between perceived and objectively measured changes.

SUBJECTS AND METHODS

Subjects

Two hundred eight homosexual or bisexual men volunteered and gave informed consent. Inclusion and exclusion criteria, as well as subject enlistment and screening procedures, are described in an accompanying article.[13] All subjects had to be able to follow instructions and be tested in English.

Neurologic Evaluation

All neurologic evaluations were performed by neurologists. To make the examination as blind to HIV status as possible, the examination of neurologic signs was conducted before the elicitation of symptoms and medical history. The neurologic evaluation required 45 minutes to complete.

Signs.—Full standardized neurologic evaluations were administered to all subjects. Each specific aspect of the examination was coded separately so that the presence of individual signs could be investigated. For example, extrapyramidal signs, believed to be among the earliest signs of neurologic dysfunction in HIV,[15] were rated by means of selected parts of the Unified Parkinson's Disease Rating Scale.[16] Other aspects of the examination, such as motor strength and reflexes, were rated by means of standard neurologic terminology and measures. To evaluate cognitive function, a short 19-item mental status screen was included.

Summary scores indicating an abnormality in five different categories of neurologic signs were created: (1) alternating movements: any impairment in finger tapping, pronation/supination of the hands, opening/closing of the hands, or heel-toe tapping; (2) sensory abnormality: any increase, decrease, or distortion of pain, temperature, tactile sense, position, or vibratory sense; (3) frontal release signs: the presence of a glabellar, snout, suck, palmomental, or grasp reflex; (4) cranial nerve signs: any abnormality in the results of cranial nerve examination; and (5) extrapyramidal signs: the presence of tremor, rigidity, bradykinesia, sialorrhea, gait changes, hypomimia, hypophonia, or postural instability.

Functional Categories.—The neurologist used the presence or absence of specific neurologic signs to determine whether specific functional systems mediated by the central and peripheral nervous system were impaired. This involved interpreting the presence of diverse signs as reflecting dysfunction in a single system. For example, pyramidal dysfunction might be associated with different neurologic signs, such as weakness, impaired rapid alternating movements, or increased tone. Guided by a modified version of the Kurtzke Disability Status Scale for Multiple Sclerosis,[17] the severity of impairment in nine categories of neurologic function was rated. Standardized conventions were developed for associating specific constellations of signs with particular functional categories and for rating the severity of dysfunction. Ratings in each of the nine categories ranged from 0 (not present) to 5 or 6 (maximal severity). The categories and examples of associated signs are as follows: pyramidal (deficit in rapid alternating movements, paraparesis or hemiparesis); cerebellar (ataxia [truncal or limb]); brain stem (nystagmus, extraocular weakness, dysarthria); sensory (vibratory loss, stocking-glove neuropathy); bowel and bladder (urgency, incontinence); visual (scotoma, decreased visual acuity); cerebral (impairment on 19-item mental status test); peripheral nerve (mild weakness, pain or sensory loss in an asymmetric distribution, excluding stocking-glove neuropathy); and extrapyramidal (rigidity, bradykinesia, tremor).

Three summary scores were derived from these functional categories and their ratings: (1) functional score (the number of functional categories, listed above, that yielded abnormal findings); (2) functional severity (the sum of the scores in each functional category, used to assess the overall severity of neurologic dysfunction); and (3) modified Kurtzke score (ranging from 0 to 10, reflecting both the severity and the number of defective categories). In a preliminary reliability trial, two independent raters agreed on Kurtzke scores in 10 of 13 subjects; scores were one point apart in the remaining cases.

Symptoms.—Neurologic symptoms consisted of the patient's reported complaints as opposed to the objectively measured neurologic signs. After the rating of signs was complete, subjective complaints were elicited. Subjects were asked about their self-perceived functioning in a structured format (R. Price, unpublished). This interview rated the presence of 11 symptoms grouped into three broad symptom areas: cognitive, motor/coordination, and behavior/mood. Cognitive symptoms included the following: concentration/speed of thought (diminished concentration; mental slowing); reading/television (increased effort required); memory (more forgetful than usual; may miss appointments); and speech (word-finding difficulty). Motor/coordination symptoms included the following: gait (unsteadiness, imbalance, or slowness); dexterity (slowing or clumsiness of hands); involuntary movements (tremor or other adventitious movements); and bladder incontinence (hesitancy, urgency, or incontinence). Behavior/mood symptoms included the following: mood (depression, interference with function, requiring medication or therapy); apathy/withdrawal (diminished interest in social activities); and emotional lability (easily agitated, may affect interactions).

For each symptom, the examiner read to the subject a series of choices ranging from denial of the symptom through four descriptions of progressively more severe symptomatic complaints; the subject was asked to choose the response that was appropriate for him at the time of the visit. This provided a rating for each symptom ranging from 0, representing normal function, to 4, very severe dysfunction. Additional summary scores included indexes of the presence or absence of symptoms in the three general areas assessed and a final measure summarizing the presence or absence of any subjective complaint. (A copy of this interview is available on request.)

Neuropsychological Examination

The neuropsychological examination, performed without knowledge of HIV status, lasted approximately 2 hours. There were several considerations taken in selecting the test battery. First, preliminary reports of studies in seropositive asymptomatic subjects and patients with ARC indicated deficits in visuomotor abilities and attention.[5] Similarly, these areas are reportedly affected in AIDS-related dementia.[18] The present battery was designed to characterize these deficits more effectively. Our test selection was also guided by our experience in assessing cognitive deficit in other diseases where the initial manifestations are quite subtle. For example, since there are suggestions that HIV might affect the basal ganglia and other subcortical structures, we selected tests that in our experience were sensitive to the cognitive functions associated with these areas.[19] However, since relatively little is known about early AIDS-related changes, the battery was also designed to assess a wide range of abilities to search for patterns of strengths and weaknesses that might not have been apparent from the early studies. Finally, since the present cohort was to be followed up longitudinally, some tests were included that might be more useful for assessing changes in mentation associated with dementia than for any possible early changes in cognition.

Tests used are described below, loosely organized by the cognitive functions they were intended to assess.

A modified version of the Mini–Mental State Examination was administered as a brief mental status screening test.[20,21] Included in the modified Mini–Mental State Examination is the Wechsler Adult Intelligence Scale digit span subtest,[22] which was scored separately and included with the tests of attention described below. General intelligence and visuospatial reasoning were assessed with a 24-item version of Raven's Progressive Matrices.[23] To assess abstract reasoning, the first half of the Conceptual Levels Analogies Test, consisting of 21 verbal analogies, was administered.[24]

Two tests were used to assess memory. The first was a 12-item, six-trial selective reminding test that assessed verbal memory.[25] Fifteen minutes later, the subject's delayed recall for the word list was assessed and words not recalled were administered in multiple-choice arrays to assess delayed recognition. The second test, the Benton Visual Retention Test, assessed nonverbal memory.[26] Delayed recognition was assessed 15 minutes later with multiple-choice arrays.

A series of tests assessed different aspects of language ability. Naming was assessed with the Boston Naming Test,[27] abbreviated by administering every other item for a total of 30 pictures to be named. Verbal fluency was assessed with the Controlled Oral Word Association Test (60 seconds for each of the letters C, F, and L)[28] and the Animal Naming Test.[29] The sentence repetition subtest of the Boston

Diagnostic Aphasia Examination assessed repetition of high- and low-probability phrases.[29]

The Stroop Color-Word Test[30] and the Odd Man Out Test[31] were used to assess executive or "frontal lobe" function. The final section of the Stroop Color-Word Test requires the subject to attend selectively to one of two competing stimuli. The Odd Man Out Test is a test of the ability to switch set. The subject is asked to use a consistent selection rule to determine which of three symbols on a card does not belong with the other two. The subject must then systematically alternate between two selection rules over four trials, each consisting of 10 cards. The Trail Making Test was also administered as a screening test, test of speeded performance and, in part B, a test of rapid sequencing and set shifting.[32]

Visuospatial function was assessed with Wechsler Adult Intelligence Scale–Revised Block Design,[33] the Benton Line Orientation Test,[34] and the Benton Visual Retention Test (form C, copy).[26]

To assess attention, two types of cancellation tasks, one using a shape and another a letter triad as targets,[35] and the Wechsler Adult Intelligence Scale–Revised digit symbol subtest[33] were administered. A 20-trial choice reaction time task was also administered. In this task, two simple shapes appear on the computer screen simultaneously and without a preceding warning signal. The subject responds with a differential button-press indicating whether the designs are the same or different. Reported data are for performance after a 20-trial practice block.

Motor speed and praxis were assessed with the Perdue Pegboard.[36] Two trials for dominant and nondominant hands as well as both hands together were administered.

In addition to comparing raw scores across groups of interest, neuropsychological test performance was evaluated in two ways: summary scores were constructed on the basis of evaluation of subjects' performance in comparison with normative populations, and experienced clinicians evaluated overall performance on the examination and derived a clinical impression. These are described below.

Comparisons With Normative Populations.—Performance on each test was compared with that expected on the basis of extant norms derived from populations of the the same age and education and then rated as normal, borderline (at least 1 SD below the mean), or defective (at least 2 SDs below the mean). One set of summary scores was the number of areas, as described above, in which a subject produced borderline or defective performance.

A global performance rating (GPR) was derived to summarize overall neuropsychological performance with reference to normative data and to rank performance along a continuum of severity. Criteria are summarized in Table 1.

Clinical Impression.—Although it is informative to compare groups' performance on individual neuropsychological tests or to contrast norm-based summary measures, clinical neuropsychological evaluation typically is based on interpretation of a full battery of tests by a trained clinician. Often, there are patterns of performance or areas of interrelated performance that can be appreciated and interpreted by the clinician but are not amenable to statistical summary measures. The clinical impression variable was created to evaluate subjects' neuropsychological performance in this manner. Based on the independent judgment of two experienced neuropsychologists who were blind to HIV status, a clinical impression of neuropsychological performance—normal, borderline, or abnormal—was generated. While the clinician had access to the test scores and norms, the impression was not based purely on the presence or number of borderline or defective scores, but on the clinician's overall impression of the subject's performance. The raters had not administered the tests, but the testers were available to describe any factors particular to any individual's testing session that might influence performance. Disagreements between raters occurred in 12% of cases. These were discussed and a consensus was reached for every case.

Other Evaluations

As described in an accompanying article,[14] subjects underwent a structured psychiatric interview to determine if they met *DSM-III-R* criteria for past or present major depression, drug abuse, or other psychiatric diagnoses. Other psychiatric rating scales, including the Hamilton Depression Scale and Hamilton Anxiety Scale, were administered.

Table 1.—Definition and Distribution of Global Ratings in HIV-Negative and HIV-Positive Groups*

Global Performance Rating	HIV Negative	HIV Positive
0. No performance deficit	40 (47.6)	52 (41.9)
1. Borderline performance ($-2<z\leq-1$) in 2 or more areas†	3 (3.6)	20 (16.1)
2. Defective performance ($z\leq-2$) in 1 area†	32 (38.1)	34 (27.4)
3. Defective performance in 2 or more areas†	7 (8.3)	17 (13.7)
4. Defective performance in memory and in 2 or more other areas†	2 (2.4)	1 (0.8)

*HIV indicates human immunodeficiency virus. Numbers in parentheses are within-group percentages represented by each frequency.
†Based on age- and education-appropriate norms.

RESULTS

Demographics

As described in more detail in an accompanying article,[13] the cohort was composed of 124 HIV-positive men and 84 HIV-negative men. Of the HIV-positive subjects, 49 were completely asymptomatic, 29 had mild medical symptoms such as lymphadenopathy, and 46 had significant medical symptoms consistent with ARC but did not meet criteria for AIDS.

Age ranged from 18 to 60 years. The HIV-positive and HIV-negative men were comparable in age, education, and handedness (Table 2). As described in detail in an accompanying article,[13] the groups were also comparable with regard to the frequency of psychiatric diagnosis, rated depression and anxiety, and global functioning.

Although all men were tested in English, 18 men reported that English was not their first language. The distribution of these men across disease stage was not equal: two were HIV negative, 12 were HIV positive and asymptomatic, two had mild medical symptoms, and two had significant medical symptoms consistent with ARC. Hollingshead socioeconomic status was also not equally distributed; mean socioeconomic status in the HIV-positive men was 49.2 ± 12.4 as compared with 53.1 ± 9.3 in the HIV-negative men ($t = 2.61$; $P<.1$).

Comparisons of HIV+ and HIV− Men

Summary Measures.—There was no difference between HIV-positive and HIV-negative subjects on any of the summary measures for neurologic signs, including functional ratings and Kurtzke scores (Table 2).

In the entire study cohort, neurologic summary variables correlated with age and with Hamilton Anxiety Scale and Hamilton Depression Scale scores (Table 3). In each case, there was a tendency for increased severity of neurologic signs to be associated with higher age or increased depression or anxiety. These relationships were also seen when correlations were calculated separately for HIV-negative and HIV-positive men (Table 3).

On the neuropsychological evaluation, there was no difference between the HIV-positive and HIV-negative men in mean GPR scores. However, there was a significant difference in the distribution of GPR scores ($\chi^2 = 11.4$; $P<.05$). Based on inspection of standardized residuals in each cell, this difference was due primarily to a higher frequency of HIV-positive men with a GPR of 1, that is, borderline performance on tests of at least two cognitive areas (Table 1).

There was a small but significant correlation of the GPR and education, such that subjects with higher levels of education tended to have lower ratings (Table 3). Education did not correlate with the neuropsychologist's impression, however.

In the entire study cohort, both the GPR and the neuropsychologist's impression correlated with the assessments of anxiety and depression. In each case, increased anxiety or depression was related to poorer performance on the neuropsychological battery (Table 3). However, when these correlations were calculated separately for

Table 2.—Demographic, Neurologic, and Neuropsychological Data*

	Mean ± SD		
		HIV Positive	
	HIV Negative	Asymptomatic	Symptomatic
N	84	49	75
Handedness, % R/L/both	87/13/0	76/20/4	84/15/1
Age, y	37.7 ± 8.9	39.7 ± 8.1	37.5 ± 8.2
Education, y	16.5 ± 2.1	16.2 ± 2.6	15.7 ± 2.4
Socioeconomic status	53.1 ± 9.3	50.2 ± 12.1	48.5 ± 12.7
CD4/CD8 ratio	1.7 ± 0.6	0.7 ± 0.4	0.5 ± 0.3
CD4 cell count, $\times 10^9$/L	0.833 ± 0.267	0.388 ± 0.216	0.411 ± 0.232
CD8 cell count, $\times 10^9$/L	0.539 ± 0.203	0.656 ± 0.256	0.946 ± 0.544
Neurologic findings			
Kurtzke scale	1.2 ± 0.7	1.1 ± 0.7	1.1 ± 0.7
Functional scale	1.4 ± 1.1	1.4 ± 1.0	1.3 ± 1.1
Functional severity	1.8 ± 1.5	1.7 ± 1.3	1.6 ± 1.5
Neuropsychological findings			
Global Performance Rating	1.1 ± 1.2	1.3 ± 1.1	1.1 ± 1.2
Neuropsychologist's impression	0.4 ± 0.7	0.5 ± 0.7	0.5 ± 0.7

*HIV indicates human immunodeficiency virus.

Table 3.—Relationship of Neurologic and Neuropsychological Summary Scores to Age, Education, Depression, and Anxiety*

	Functional Score	Functional Severity	GPR	Neuropsychologist's Impression
All men				
Age	.216†	.173‡	−.107	−.012
Education	.031	.048	−.143‡	−.143‡
Hamilton Anxiety Scale	.285†	.308†	.160‡	.146‡
Hamilton Depression Scale	.229†	.223†	.145‡	.144‡
HIV-negative men				
Age	.092	.025	−.205‡	−.111
Education	.070	.035	−.274†	−.246†
Hamilton Anxiety Scale	.434†	.392†	.122	.065
Hamilton Depression Scale	.299†	.278†	−.035	−.053
HIV-positive men				
Age	.312†	.294†	−.033	.059
Education	.003	.050	−.071	−.083
Hamilton Anxiety Scale	.187‡	.257†	.168‡	.187‡
Hamilton Depression Scale	.206†	.207†	.232†	.241†

*HIV indicates human immunodeficiency virus; GPR, Global Performance Rating. Values given are Pearson's product-moment correlations.
†$P<.01$.
‡$P<.05$.

HIV-negative and HIV-positive men, a different pattern was seen: the neuropsychological summary variables correlated with the Hamilton Depression Scale and the Hamilton Anxiety Scale only in the HIV-positive men. This suggests that depression and anxiety may have played a greater role in the neuropsychological performance of the HIV-positive then the HIV-negative men. In contrast, education correlated with neuropsychological summary scores in the HIV-negative men only.

Although the present study used extant norms for the neuropsychological tests administered to determine the rate of defective performance, other studies have derived norms from the study population itself.[4,12] One summary measure that has been used in this regard is the mean deviation from average performance on each test, expressed in terms of SDs from the group mean performance. To address this issue, the mean and SD of all (both HIV-negative and HIV-positive) subjects' scores on each neuropsychological test were calculated. Each subject's score on every test was then expressed in terms of z scores, and the mean of all z scores for each subject was then calculated. There was a small but significant difference between the mean z score in the HIV-negative and HIV-positive groups (mean z score = 0.072 and −0.051, respectively; $P<.01$). This difference remained significant when only asymptomatic HIV-positive men were contrasted with the HIV-negative group.

Individual Scores.—The frequency of individual neurologic signs did not differ between HIV-positive and HIV-negative subjects. In the HIV-negative and HIV-positive subjects, respectively, the following were the percentages of men with specific neurologic signs: difficulties with alternating movements, 3.6% and 7.3%; sensory abnormalities, 53.6% and 43.5%; frontal release signs, 27.4% and 31.3%; cranial nerve signs, 25.0% and 25.0%; and extrapyramidal signs, 17.9% and 18.5%.

All test scores were included in an omnibus multivariate analysis of

Table 4.—Significant Univariate F Tests From Omnibus MANOVA*

	Stage		Language		Stage × Language	
	F	P	F	P	F	P
CLAT	2.89	.05	12.25	.001	1.56	NS
Selective Reminding Test						
Total recall	3.11	.05	0.31	NS	1.58	NS
Long-term storage	3.02	.05	0.15	NS	1.49	NS
Long-term retrieval	2.63	.052	0.08	NS	1.43	NS
Boston Naming Test	4.28	.01	66.65	.001	9.30	.001
Controlled Word Association	2.98	.03	0.76	NS	5.49	.001
Sentence Repetition						
High probability	1.52	NS	7.35	.01	3.34	.021
Low probability	2.53	NS	15.37	.001	6.72	.001
Odd Man Out						
Trial 1	2.87	.05	2.91	NS	2.63	NS
Trial 2	2.95	.05	8.47	.01	4.84	.01
Digit Symbol (age scaled)	2.94	.05	0.46	NS	2.73	.05
Cancellations						
Letter triad	0.64	NS	1.26	NS	3.30	.05
Shape	0.57	NS	0.97	NS	2.73	.05
Backwards Digit Span	3.34	.05	0.01	NS	2.98	.05

*MANOVA indicates multivariate analysis of variance; CLAT, Conceptual Levels Analogies Test; and NS, not significant. Only variables with significant stage (human immunodeficiency virus [HIV] negative, asymptomatic HIV positive, mildly symptomatic HIV positive, and acquired immunodeficiency syndrome–related complex), language (first language English vs other), or stage × language interactions are listed.

variance (MANOVA) comparing the performance of the men at four stages of HIV infection: seronegative, seropositive and asymptomatic, mildly symptomatic, and ARC. To control for possible confounding effects, the following variables were included as factors in the MANOVA as well: first language (English vs other), history of learning disability, history of psychiatric disorder or substance abuse, and current psychiatric disorder or substance abuse. Also included were appropriate interactions of these factors. Socioeconomic status ratings and Hamilton Depression Scale and Hamilton Anxiety Scale scores were included as covariates. Significant effects included HIV stage (Hotelling $T^2 = 2.05$, $P < .011$), language (Hotelling $T^2 = 1.8$, $P < .01$), and the stage × language interaction (Hotelling $T^2 = 2.32$, $P < .01$). None of the other potential contributing variables approached significance.

The univariate F tests from the omnibus MANOVA for which there was a significant stage or stage × language effect were examined. These are summarized in Table 4. For many of the tests in which there was a significant stage effect, there was also a significant stage × language interaction, implicating the role of fluency in English in the relationship between HIV stage and performance. However, this was not the case for the several measures from the selective reminding test, as well as for the initial trial of the Odd Man Out Test, where only the stage effect was significant. For the Conceptual Levels Analogies Test, there were significant stage and language effects, but no significant interaction.

Post hoc analyses were calculated from the omnibus MANOVA to determine which of the four HIV stages accounted for the significant stage effect. In simple contrast analyses, the HIV-negative and HIV-positive men differed significantly (Hotelling $T^2 = 0.86$, $P < .01$).

Although the MANOVA protected against type I error, its power to detect potential significant effects was reduced because of the large number of dependent variables included, as well as possible failure of the distribution of several neuropsychological test score results to meet assumptions underlying the MANOVA. In addition, the presence of a missing value on any variable is sufficient to eliminate a subject from the MANOVA. Since an issue of specific interest was the potential performance difference between HIV-negative and HIV-positive asymptomatic men, a series of exploratory univariate regression analyses were calculated to compare these two groups' performance on the neuropsychological test battery. Based on the results of the omnibus MANOVA, all the univariate regression analyses controlled for language. The following variables differed significantly in the two groups: digit span forward ($t = -2.28$, $P < .05$); selective reminding test total recall ($t = -2.35$, $P < .05$), long-term retrieval ($t = -2.61$, $P < .01$), long-term storage ($t = -2.69$, $P < .01$), consistent retrieval ($t = -2.40$, $P < .05$), and delayed recall ($t = -2.08$, $P < .05$); Controlled Oral Word Association Test ($t = -2.21$, $P < .05$); and Odd Man Out Test ($t = -2.05$, $P < .05$). Along with and independent of the significant serologic status effect, the effects of first language were apparent for many variables.

Table 5.—Pearson's Correlations of CD4/CD8 Cell Ratio and Summary Variables*

	Entire Cohort	HIV Negative	HIV Positive
Neurologic findings			
Functional score	−.024	.081	−.294†
Functional severity	.0	.079	−.242†
Kurtzke scale	.024	.096	−.105
Neuropsychological findings			
Global performance rating	.004	.194	−.206‡
Neuropsychologist's impression	−.005	.184	−.147

*HIV indicates human immunodeficiency virus.
†$P < .01$.
‡$P < .05$.

Relationship of Performance to Severity of HIV Infection

An inverse correlation between the neurologic summary variables and CD4/CD8 cell ratio was seen in the HIV-positive group but not in the HIV-negative group. As the CD4/CD8 cell ratio decreased, the neurologic summary indexes increased, implying an increased number of defective areas or increasing severity of neurologic disease (Table 5). Similarly, the CD4/CD8 ratio correlated with the GPR only in the HIV-positive group (Table 5).

Table 6.—Pearson's Correlations of Neuropsychological and Neurologic Summary Variables*

	Global Performance Rating	Neuropsychologist's Impression
All men		
Functional score	.194†	.215†
Functional severity	.142†	.148†
Kurtzke scale	.113	.076
HIV-negative men		
Functional score	.127	.066
Functional severity	.115	.014
Kurtzke scale	.076	−.083
HIV-positive men		
Functional score	.242‡	.325‡
Functional severity	.162†	.251‡
Kurtzke scale	.139	.185†

*HIV indicates human immunodeficiency virus.
†$P<.05$.
‡$P<.01$.

Table 7.—Percentages of HIV-Negative and HIV-Positive Men Reporting Neurologic Symptoms*

	HIV Negative	HIV Positive	P<†
Cognitive symptoms			
Concentration/speed of thought	15.5	25.8	NS
Reading/television	7.1	15.3	NS
Memory	11.9	25.0	.03
Speech	9.5	14.5	NS
Cognitive index	22.6	38.7	.02
Motor/coordination symptoms			
Gait	2.4	7.3	NS
Dexterity	1.2	8.8	NS
Involuntary movements	6.3	5.8	NS
Bladder incontinence	1.3	5.0	NS
Motor index	8.3	17.7	NS
Behavior/mood symptoms			
Mood	17.8	35.5	.009
Apathy/withdrawal	8.3	26.6	.002
Emotional lability	13.1	20.2	NS
Behavior index	26.2	46.8	.004
Overall index	38.6	59.7	.005

*HIV indicates human immunodeficiency virus; NS; not significant.
†By χ^2 analysis.

Relationship Between Neurologic and Neuropsychological Evaluations

To investigate the possible relationship between subtle neurologic and neuropsychological changes, correlations between summary variables in the two domains were calculated. Significant correlations were seen between summary variables of the neurologic and the neuropsychological examinations in the entire cohort. However, when the cohort was stratified into HIV-positive and HIV-negative groups, significant correlations were seen only in the HIV-positive group, suggesting that this relationship is particular to the HIV-positive men (Table 6). In addition, in all cases the coefficients of the correlation between neurologic and neuropsychological summary measures were significantly higher in the HIV-positive than the HIV-negative group ($P<.05$).

Since neurologic summary measures correlated with scores on the Hamilton Depression Scale and the Hamilton Anxiety Scale in both HIV-positive and HIV-negative groups, while neuropsychological measures correlated with these scales in the HIV-positive group only, the unique relationship between neurologic and neruopsychological measures in the HIV-positive group might be a function of the effects of anxiety or depression. To evaluate this possibility, partial correlations were calculated to investigate the relationship of neurologic and neuropsychological findings independent of the contribution of depression and anxiety. Results were comparable with those described above: controlling for depression, anxiety, or both, there were no significant correlations between neurologic and neuropsychological summary variables in the HIV-negative group. In contrast, the relationships between neurologic and neuropsychological summary measures remained significant in the HIV-positive group.

The neurologist's assessment of intellectual function is reflected in the neurologic summary variables, so we considered the possibility that the correlations between neurologic and neuropsychological variables might reflect some redundancy in the measures. To address this possibility, the cognitive component was eliminated from the neurologic summary variables, and correlation coefficients with neuropsychological variables were recalculated. A similar pattern and magnitude of correlations were found, indicating that the relationship is not a function of redundant assessment of intellectual capacity.

Relationship of Symptoms to Neurologic Signs and Neuropsychological Test Performance

In the symptom interview section of the neurologic evaluation, HIV-positive men reported memory difficulty, depressed mood, and loss of interest in socializing more often than did their HIV-negative counterparts. When summary indexes were calculated for cognitive and affective complaints, HIV-positive men had one or more subjective complaints more often than did HIV-negative men (Table 7).

We compared men with and without specific cognitive complaints to see if their symptoms were reflected in their neuropsychological performance as measured by GPR or the clinical impression. Two-way analyses of variance using HIV status (positive or negative) and symptom complaint (present or absent) were calculated, with GPR and clinical impression as the dependent variables. There were no significant main or interaction effects when clinical impression was the dependent variable. For GPR, the main effect of symptom complaint was significant, suggesting that, overall, complaints were associated with poorer performance. The main effect for HIV status was not present, confirming the observation of no significant difference in GPR between HIV-negative and HIV-positive men. There was no significant interaction between the two main effects, which suggests that the relationship between symptom complaint and actual performance was similar in the HIV-positive and HIV-negative groups.

In the HIV-positive group there was excellent agreement of subjects' self-reported problems, including speed of thought, reading/watching television, and memory, with neuropsychological performance as measured either by summary scores or by performance on tests that assess function in the area of the complaint. In contrast, there was no significant association between self-report of these cognitive complaints and the actual neuropsychological performance in the HIV-negative group.

COMMENT

Although comparison of the HIV-negative and HIV-positive men revealed no difference in the frequency of defective or borderline performance in any cognitive area and no difference in the frequency of neurologic signs or severity of neurologic dysfunction, other analyses suggest that there are significant differences between the HIV-negative and HIV-positive men in both neurologic and neuropsychological functions. First, HIV-positive men performed slightly but significantly worse on several neuropsychological tests. Second, neuropsychological and neurologic changes were interrelated in the HIV-positive but not the HIV-negative men, suggesting that they may have a common cause. Third, CD4/CD8 ratios correlated with neurologic and neuropsychological summary variables in the HIV-

positive men only. Finally, symptomatic complaints in the HIV-positive, but not the HIV-negative, men correlated with objective measures of performance. These findings are discussed in more detail below.

More HIV-positive men had borderline performance in at least two cognitive areas, and the HIV-positive men performed significantly worse on tests of memory, executive function, attention, and abstract reasoning. These differences, although statistically significant, actually represented only small raw score differences and have no apparent clinical meaning. However, they are striking because they remain detectable even when only HIV-positive men who are completely medically asymptomatic are considered. Also, they do not appear to be a function of other possible variables, such as learning disability, psychiatric status or history, alcohol or other drug abuse, or language. It would be reasonable to hypothesize that the subtle neuropsychological findings noted here represent one of the earliest HIV-related changes detectable.

Because the changes are subtle, their interpretation is problematic. Other groups, using similar tests and population groups of comparable or even larger sizes, have not reported differences. For example, the Air Force studies[11] found no difference between HIV-negative and HIV-positive medically asymptomatic men on a battery of neuropsychological tests. However, this study suffered from an inadequate control group: servicemen who had sustained some head injury. The potential contributions of head injury to neuropsychological performance and the possible lack of comparability of life-styles of subjects and controls are potential confounds. The Multicenter AIDS Cohort Study groups[4] also found no differences between asymptomatic seropositive and seronegative individuals on a brief battery of neuropsychological tests or on a larger battery administered to a selected subset of patients either at baseline or on follow-up at 1 year.[31] Janssen et al[12] also reported no difference in neuropsychological performance in HIV-negative and asymptomatic HIV-positive men. In their article, comparison of individual scores was restricted to a short screening battery. The results of the full battery were presented only in terms of the frequency of defective scores, which, as we report here, did not differ in the two groups.

The disparity between these previous negative reports and the subtle findings we now report could in some cases be a function of the specific tests used. For example, the present study as well as that of Wilkie et al[8] used a selective reminding procedure to assess verbal list learning, while the Multicenter AIDS Cohort Study and Centers for Disease Control groups used tests that did not, such as the Rey Auditory Verbal Learning Test. The difference between the two procedures is subtle: in the selective reminding procedure, the subject is reminded only of the words he did not recall on his most recent attempt, while in the Rey test the subject is supplied with the entire list after each recall attempt. However, the selective reminding procedure clearly places additional demands on the subject that may entail set switching (ie, switching between short- and long-term memory stores) or organizational or attentional capacities. Along with potential differences between neuropsychological tests ostensibly assessing the same cognitive function, many factors can contribute to different findings across studies. These particularly include variations in subject recruitment techniques or in time from serocon-version.

Despite these caveats, our data lend support to findings of others, such as Grant et al,[6] Wilkie et al,[8] and Claypoole et al,[38] which were similar to those described here. Whether these subtle neuropsychological changes are predictive of later medical or cognitive change remains to be determined.

Although a great deal of effort has been focused on describing the neuropsychological changes seen in asymptomatic HIV-positive individuals, little information is available on the prevalence or incidence of neurologic signs, and standardized neurologic examinations have rarely been used. The relationship between the presence of neurologic signs and neuropsychological or immunologic measures has also not been described.

The vast majority of neurologic symptoms and signs in HIV-positive patients occur at a time when other systemic complaints abound and the immunologic status of the patient has declined. In the early stages of HIV infection, the mechanism of disease may be an autoimmune process dependent on an intact immune system. Later, when the immune status is further depressed, the mechanism may be the direct effect of the virus.

Neurologic signs that may or may not be clinically significant are often present in asymptomatic HIV-positive individuals, but frequencies do not differ from those in seronegative controls. In a study of drug users, 76% of the seronegative and 81% of the seropositive subjects had one or more neurologic findings.[39] Larger studies, including the Multicenter AIDS Cohort Study[2,4] and the Air Force,[11] also found no significant differences in medically asymptomatic homosexual men on the basis of the neurologic examination.

The present study also did not find differences in the frequencies of neurologic findings in the HIV-negative and HIV-positive groups. Neurologic summary scores did relate to indexes of depression and anxiety in both seropositive and seronegative men. The subtle neurologic findings observed in the HIV-negative and HIV-positive men might then be interpreted as being related to the subjects' emotional state. It should be noted that the great majority of neurologic signs were of indeterminate clinical significance. In addition, it is possible that many of these signs are state dependent and will not be present at follow-up assessment. Despite these observations, our data may suggest that there is a constellation of subtle neurologic and neuropsychological signs associated with early HIV infection. There was an inverse correlation between the presence of neurologic signs and CD4/CD8 ratios in the HIV-positive men. In addition, there was a relationship between the neurologic findings and the neuropsychological variables that was unique to the HIV-positive men. Both of these findings might suggest a common underlying factor for these manifestations in the HIV-positive men: the viral effect on the central (and perhaps simultaneously the peripheral) nervous system could produce both neurologic and neuropsychologic manifestations, resulting in significant correlations between them. In contrast, neurologic signs in the HIV-negative men did not covary with neuropsychological performance and may be more related to the other factors, such as age, depression, and anxiety.

Self-reports of cognitive symptoms are subject to myriad influences, including mood, medical status, and concern related to disease state. The ability to detect a relationship between self-perceived and actual abilities may be highly dependent on the instruments used both to elicit symptoms and to assess cognitive function.

The present data suggest that HIV-positive men experience more cognitive symptoms than do their HIV-negative counterparts. Further, these symptoms have validity: subjective complaints are associated with poorer performance as assessed by neuropsychological summary scores and by specific assessments of the area of self-reported complaint. Some of our data using specific test scores as opposed to summary measures suggest that the complaints of the seropositive men were better related to the neuropsychological indexes. It is possible that the range and severity of self-complaints in the HIV-negative group were lower, making it more difficult to relate them to other variables.

There was little evidence of a relationship between HIV

severity and neurologic or neuropsychological symptoms. In the the HIV-positive men, neurologic and some neuropsychological summary variables correlated with CD4/CD8 ratios, suggesting poorer function as this ratio is diminished. However, medically asymptomatic men, the majority of whom had CD4 counts above 0.4×10^9/L, had the same pattern of performance relative to the HIV-negative men that was seen in the HIV-positive group as a whole. The HIV-positive men in this cohort were specifically selected to be relatively asymptomatic to allow us to describe the early natural course of HIV infection; accurate analysis of relationships between the range of HIV infection and neurologic or neuropsychological changes awaits follow-up data.

The interpretation of the present results is complicated by the subject recruitment techniques employed. These are described in more detail in an accompanying article[13]; in general, volunteers were recruited with newspaper advertisements or by word of mouth. It is possible that this could produce a bias toward individuals who were concerned about the possible presence of HIV-related symptoms. Alternately, men with more severe symptoms may not have wished to or been capable of volunteering. In addition, the men's knowledge of their serologic status might have influenced their performance and self-reports in some fashion. Although these concerns are applicable to many of the studies in this area, they do limit the generalizability of the present findings beyond this particular cohort of men.

The present data suggest that subtle neuropsychological changes, associated with subtle neurologic signs and subjective complaints, can be found in the medically asymptomatic HIV-positive patient. This constellation may reflect a syndrome that will be recognized as one of the early manifestations of the direct effect of HIV on the nervous system. Although these changes are not sufficient to impact on a person's day-to-day functioning, they may be predictive of later cognitive changes or of disease progression.

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