Neurologic and Neuropsychological Manifestations of Human Immunodeficiency Virus Infection in Intravenous Drug Users Without Acquired Immunodeficiency Syndrome

Relationship to Head Injury

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• We examined 99 human immunodeficiency virus (HIV)–negative and 122 HIV-positive intravenous drug users (IVDUs) without acquired immunodeficiency syndrome (AIDS) to determine whether HIV-positive IVDUs had more neurologic and neuropsychological impairment than their HIV-negative counterparts. Controlling for age, education, drug use, history of head injury, and interactions between head injury and HIV status and drug use, HIV-positive subjects had more extrapyramidal signs and frontal release signs. These findings persisted when asymptomatic HIV-positive subjects without systemic signs of infection and HIV-negative subjects were compared. Neurologic findings were more severe in those with more systemic illness. Among those reporting a history of head injury with loss of consciousness, neuropsychological performance was significantly worse in the HIV-positive subjects, and this increased with severity of illness. This was not true in the group without head injury, suggesting an interaction between history of head injury and the seropositive state. No relationship was noted between head injury and either drug use or HIV state. Therefore, subtle neurologic and neuropsychological abnormalities may precede clinical evidence of AIDS in IVDUs and may be more evident in those with head injury.

(*Arch Neurol.* 1992;49:1169-1175)

The association between human immunodeficiency virus type 1 (HIV-1) and intravenous drug use (IVDU) has been known since 1981.[1] Estimates of HIV seroprevalence range from 0% to 65% among IVDUs in drug treatment programs.[2] While the rate of HIV seroconversion in the gay population has stabilized, the rate of seroconversion among IVDUs has continued to increase, up to 14% annually.[2]

Little attention has been directed to the neurologic and neuropsychological consequences of HIV-1 in IVDUs because it is difficult to follow them up[3-5] and to determine what neurologic and neuropsychological effects are attributable to HIV-1 alone. Drug use may affect performance, and other factors, such as education, head injury, alcohol use, infection, and vascular complications of drug use, may interfere with performance.

SUBJECTS AND METHODS

Subjects

A total of 221 IVDUs (145 men and 76 women) volunteered and gave informed consent to participate in the study; 168 subjects were recruited from the Harlem Hospital Infectious Disease Clinic, New York, NY, and 53 were recruited from the St Luke's/Roosevelt Methadone Maintenance Clinic, New York, NY.

By definition, all subjects had used intravenous drugs at least 10 times since 1982. The Harlem subjects were not enrolled in a methadone maintenance program and were also required to have used intravenous drugs at least once in the year prior to enrollment. Detailed alcohol and other drug usage history was obtained for the 6 months and the 24 hours before evaluation.

Subjects who met criteria for acquired immunodeficiency syndrome (AIDS) according to the Centers for Disease Control National Surveillance Criteria (1985)[6] on entry were excluded. All were required to know their HIV status before entry, but enzyme-linked immunosorbent assay and Western blot analyses were repeated in all subjects. All subjects were required to speak English, although it was not necessarily their first language.

Procedure

Overview.—The neurologic examination, performed by a neurologist, took about 30 minutes. The neuropsychological examination was administered by a trained examiner and took about 75 minutes. These two examinations were not always performed on the same day but were always administered within 1 month. If a subject was obviously intoxicated or had any alteration in level of consciousness, he or she was asked to return. This occurred twice for the neurologic examination and 12 times for the neuropsychological examination.

Medical Examination.—All subjects underwent a medical examination and staging by medical symptoms and signs with use of a previously described rating scale.[7] Subjects were grouped as follows: (1) HIV negative; (2) HIV positive, completely physically asymptomatic (these subjects had no physical symptoms or signs believed to be related to HIV infection that in themselves were severe enough to warrant clinical attention); (3) HIV positive,

Accepted for publication April 27, 1992.

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Table 1.—Description of Neurologic Factors

Factor	Name	Individual Variables
1	Symptoms	Combination of all elicited symptoms: cognitive, motor, and mood
2	Extrapyramidal	Reflects number of extrapyramidal signs
3	Alternating movements	Reflects number of alternating movement abnormalities
4	Sensory	Reflects number of sensory abnormalities
5	Frontal release	Reflects number of frontal release signs
6	Cranial nerve	Reflects number of abnormalities on cranial nerve examination

mildly symptomatic (signs, such as lymphadenopathy, diarrhea for 2 weeks, or fever for 2 weeks, that would not meet criteria for stage 3 disease); and (4) HIV positive, symptomatic (significant medical signs but would not meet criteria for AIDS, eg, oral thrush, fever or diarrhea for >30 days, or oral hairy leukoplakia).

Neurologic Examination.—Standardized neurologic examinations were performed before the elicitation of pertinent medical symptoms and history to be certain that the examiner did not know the HIV status of the subject. Details of the neurologic examination were previously described.[8] It included items to rate extrapyramidal signs from the Unified Parkinson's Disease Rating Scale.[9] Cognitive function was screened briefly with use of a 19-item mental status test.

Neurologic symptoms were evaluated with a questionnaire created by Richard Price, MD (unpublished) to assess cognitive function, motor function, and mood.[8] History of seizures, stroke, multiple sclerosis, psychiatric illness requiring hospitalization, and head injury with loss of consciousness was elicited.

Analysis of Neurologic Data.—To simplify data analysis, we grouped individual items into larger categories and used factor scores derived from factor analysis of signs and symptoms at different stages of illness.

Individual Signs on Examination—Individual signs were recorded separately, but for purposes of data analysis, some neurologic signs were grouped as follows: (1) alternating movements, (2) sensory abnormalities, (3) frontal release signs, (4) cranial nerve signs, and (5) extrapyramidal signs. The presence of any of the individual signs rendered the whole category positive, while the absence of all the signs in a category rendered the category negative.

Factor Creation.—We used neurologic data for the entire cohort of HIV-positive and HIV-negative subjects for a factor analysis. A total of 77 individual variables were reduced to eight summary variables. These eight summary variables were included in a principal components factor analysis with subsequent VARIMAX rotation. Six factors were produced (Table 1). Factor analysis provided a description of severity of illness because the number of abnormalities, rather than just presence or absence, was reflected in each factor.

Neuropsychological Examination.—The neuropsychological examination, performed by an investigator "blinded" to HIV status, assessed a range of cognitive functions (Table 2). The battery was a truncated version of one described elsewhere.[8]

Analysis of Neuropsychology Data.—Neuropsychological test performance was evaluated in two ways, as described below.

Comparisons With Normal Data.—One set of summary measures was based on the number of SDs from the group mean performance for each subject for each test expressed in terms of z scores. Tests were subdivided into cognitive functions: general intelligence, memory, language, executive, visuospatial, attention, and motor speed. Performance in each area was considered defective if one test score was 2 or more SDs or greater below the mean. Overall performance was considered defective if two or more areas were impaired. The mean of z scores for all tests in each area was calculated as a summary score.

Table 2.—Individual Neuropsychological Tests and the Cognitive Areas They Represent

General intelligence
- Modified Mini-Mental State examination[10,11]
- WAIS-R* Similarities[12]

Memory
- Selective Reminding Test[13]
- Visual Reproduction subtest of Wechsler Memory Scale[14]

Language
- Boston Naming Test[15]
- Controlled Oral Word Association Test[16]
- Animal Naming[17]

Executive
- Odd Man Out Test[18]
- Trail Making Test Part B[19]

Visuospatial
- WAIS-R Block Design[12]

Attention
- Cancellations[20]
- WAIS-R Digit Symbol[12]

Motor Speed
- Grooved Pegboard[21]
- Trail Making Test Part A[19]

*WAIS-R indicates Wechsler Adult Intelligence Scale–Revised.

Clinical Impression.—Neuropsychological performance graded normal, borderline, or abnormal was assessed by two experienced neuropsychologists (Y.S. and M.S.) who were blinded to HIV status.

Risk Behavior Assessment.—All subjects were systematically questioned about alcohol and other drug use. A variable was created to represent any drug use in the 6 months preceding the initial evaluation. Any use of cocaine, heroin, benzodiazepines, hallucinogens, or phencyclidine was considered a positive history. For a subset of subjects (n=146), information on frequency of drug use was available. Drug use of less than two to six times per week was considered low-frequency use, and any amount greater than this was considered high-frequency drug use. Alcohol use was considered separately. Alcohol and other drug use for the 24 hours before evaluation was rated as yes or no. All the same drugs were included, with the addition of marijuana.

Statistical Analysis

Age, education, and CD4 cell counts were contrasted in HIV-positive and HIV-negative subjects with independent sample t tests. Individual neuropsychological test scores in subjects with and without head injury within HIV-positive and HIV-negative groups were compared with the use of independent sample t tests. Categories describing the presence or absence of individual signs were examined with the use of Pearson's ϕ^2 tests.

Neurologic and neuropsychological indexes were contrasted in HIV-positive and HIV-negative subjects with the use of multivariate analysis of variance (MANOVA). Individual main effects and interactions were included in each model based on preliminary analysis of their significance. The MANOVA for the neurologic indexes (the six factors listed in Table 1) included the following main effects: serostatus, history of head injury with loss of consciousness, current IVDU, and head injury × IVDU and head injury × serostatus interactions. Age and educational level were covariates. In the neuropsychological model, the following main effects were examined: serostatus, sex, first language, and history of head injury with loss of consciousness. A serostatus × head injury interaction was also included in the model, but a head injury × IVDU interaction was not, based on preliminary obser-

Table 3.—Demographic, Neurologic, and Immunologic Data*

	HIV Negative (n=99)	HIV Positive (n=122)
Sex		
M	62	83
F	37	39
Ethnicity		
W	16	12
B	65	91
Hispanic/W	11	15
Hispanic/B	7	4
Age, y	38.8 (7.8)	39.0 (6.6)
Handedness		
R	86	112
L	9	9
Ambidexterous	4	1
Neurologic history		
Head injury	36	51
Seizures	16	14
Stroke	1	0
Education, y	11.7 (2.1)	11.6 (2.4)
English (primary language)	90	114
CD4 count, $\times 10^9$/L	1.07 (0.74)	0.42 (0.29)
History of drug use		
In past 6 mo	87	108
In past 24 h	46	67
History of alcohol use		
In past 6 mo	67	84
In past 24 h	35	33

*Values in parentheses are SDs. HIV indicates human immunodeficiency virus.
†$P<.01$.

vations of no relationship between these variables. Years of education and age were included as covariates.

For the neurologic and neuropsychological models, after contrasting seropositive and seronegative patients, two additional approaches were taken to grouping subjects. In the first approach, HIV-positive subjects were subdivided into two stages—asymptomatic plus mildly symptomatic and symptomatic but not having AIDS. Analyses of variance (ANOVAs) and Bartholomew's test for nonlinearity[22] were performed on neurologic factor scores and on individual neuropsychological test scores in the HIV-positive and HIV-negative groups to determine between-group differences and whether there was a linear relationship between stage of illness and test scores. In the second approach, a direct contrast was made between HIV-positive and HIV-negative asymptomatic subjects.

For a subset of 146 subjects in whom frequency of drug use was available, two-way ANOVA was performed with HIV status and high- and low-frequency drug use as main effects.

RESULTS

Demographics

A total of 145 men and 76 women underwent neurologic and neuropsychological examinations. The cohort comprised 122 HIV-positive subjects (83 men and 39 women) and 99 HIV-negative subjects (62 men and 37 women). Of the HIV-positive subjects, 33 (27%) (24 men and nine women) were completely physically asymptomatic; 28 (23%) (22 men and six women) had mild medical signs, such as lymphadenopathy, and 61 (50%) (37 men and 24 women) had medical signs of HIV infection but did not meet criteria for AIDS.

The HIV-positive and HIV-negative subjects were comparable in age, gender, education, ethnic group, primary language, and handedness. There was no significant difference in medical history of seizures or cerebrovascular accidents reported by HIV-positive and HIV-negative subjects. Head injury with loss of consciousness was no different for HIV-positive and HIV-negative subjects. The mean CD4 cell count for HIV-negative subjects was 1.07×10^9/L compared with 0.42×10^9/L for HIV-positive subjects (Table 3).

Table 4.—Demographic, Neurologic, and Immunologic Data for Subjects With and Without Head Injury*

	HIV Negative (n=99)		HIV Positive (n=122)	
	No Head Injury (n=63)	Head Injury (n=36)	No Head Injury (n=71)	Head Injury (n=51)
Sex				
M	38	24	43	39
F	25	11	27	12
Age, y	38.3 (7.9)	39.6 (7.4)	38.7 (6.9)	39.6 (6.2)
Education, y	11.7 (2.1)	11.8 (1.9)	11.9 (2.2)	11.0 (2.4)
CD4 count, $\times 10^9$/L	1.07	1.07	0.43	0.39
Seizure history	7	9	6	8
Stroke history	1	0	0	0
History of drug use				
In past 6 mo	54	33	61	47
In past 24 h	30	16	38	29
History of alcohol use				
In past 6 mo	40	27	47	37
In past 24 h	20	15	18	15

*Values in parentheses are SDs. HIV indicates human immunodeficiency virus.

When HIV-positive and HIV-negative subjects were separated into those with and without head injury, no significant differences were seen in any of the demographic variables (Table 4).

Relationship of Drug Use to HIV Infection and Head Injury

Frequency of drug use was examined in relation to HIV status and head injury. When drug use was categorized as high or low frequency, a relationship between high-frequency drug use in the 6 months before evaluation and HIV-positive state was seen (χ^2 [1 *df*], 3.81; $P<.05$). To further examine the relationship between frequency of drug use and HIV status, subjects were categorized as high- or low-frequency users according to stage of infection. The percentage of high-frequency drug users was as follows: HIV negative, 75%; asymptomatic, 95%; mildly symptomatic, 65%; and moderately symptomatic but not AIDS, 87%. Although HIV-positive subjects used drugs more frequently than did HIV-negative subjects, no relationship between frequency of drug use and stage of infection was seen.

No relationship between history of head injury and high- or low-frequency drug use was seen in the entire co-

Table 5.—Mean Scores for Each of Six Neurologic Factors in HIV-Negative and Two Groups of HIV-Positive Subjects Are Contrasted With One-Way ANOVAs*

	HIV Negative (n=99)	Asymptomatic or Mild Symptoms† (n=61)	Symptomatic (n=61)
Symptoms‡	3.36 (82)	2.54 (50)	4.75 (58)
Extrapyramidal	0.25 (25)	0.33 (20)	0.49 (30)§
Alternating movements	0.12 (12)	0.10 (6)	0.10 (6)
Sensory	0.68 (67)	0.72 (44)	0.69 (42)
Frontal release	0.31 (31)	0.52 (30)	0.56 (34)§
Cranial nerve	0.58 (57)	0.62 (38)	0.52 (32)

*HIV indicates human immunodeficiency virus; ANOVAs, analyses of variance. Values are mean scores. Values in parentheses are the number of subjects demonstrating each factor on examination.
†Mild medical signs, eg, lymphadenopathy.
‡Combination of elicited symptoms (cognitive, motor, and mood).
§$P<.01$.

Table 6.—Number of Cognitive Areas With a Test Score at Least 2 SDs Below the Mean in HIV-Negative and HIV-Positive Patients*

Areas With z Scores ≤ -2	HIV Negative	HIV Positive
0	67 (68)	78 (64)
1	20 (20)	29 (23)
2	6 (6)	11 (9)
3	5 (5)	2 (2)
4	0 (0)	2 (2)
5	1 (1)	0 (0)

*HIV indicates human immunodeficiency virus. Values in parentheses are percent of total.

hort or when HIV-positive and HIV-negative subjects were considered separately.

Neurologic Signs

No differences were seen in the percentages of HIV-positive and HIV-negative subjects who had any impairment in cranial nerves, fine alternating movements, or sensory perception. Significantly more HIV-positive than HIV-negative subjects had extrapyramidal signs ($P<.02$) and frontal release signs ($P<.002$).

Rigidity was the only extrapyramidal sign present more often in the HIV-positive subjects (7.4%) than in the HIV-negative subjects (0%). Tremor, bradykinesia, postural instability, or hypomimia occurred rarely but at similar frequencies in HIV-positive and HIV-negative subjects.

Neurologic Symptoms

Frequency of impaired concentration, memory, or word-finding difficulty did not differ in HIV-positive and HIV-negative subjects, and no differences were seen in the reported frequency of motor dysfunctions, such as impaired dexterity or gait or reported disorders of mood (depression, apathy, or emotional lability).

Neurologic Factors

Mean scores for each of the six factors in HIV-negative patients and two stages of HIV-positive patients—asymptomatic or mildly symptomatic and HIV-positive symptomatic but not AIDS—were contrasted with the use of one-way ANOVAs (Table 5). Between-group differences were seen only for the extrapyramidal factor and the frontal factor. These two factor scores showed a linear increase with stage of illness, suggesting that subjects with more systemic illness also had more extrapyramidal and frontal release signs.

The six neurologic factors were included in a MANOVA, with the main effects of serostatus (HIV positive vs HIV negative), current IVDU (present or absent), head injury (present or absent), a serostatus × IVDU interaction, and a serostatus × head injury interaction, covaried by age and education. The overall MANOVA was significant ($P<.001$), as were serostatus (Hotelling $T^2=.11$, $P<.002$), head injury with loss of consciousness (Hotelling $T^2=.08$, $P<.02$), and IVDU (Hotelling $T^2=.14$, $P<.001$) main effects.

In follow-up univariate F tests, a significant serostatus effect was seen for extrapyramidal signs ($F=7.3$, $P<.008$), sensory abnormalities ($F=6.9$, $P<.009$), and frontal release signs ($F=6.7$, $P<.01$). When all other main effects and covariates were controlled, HIV-positive subjects had significantly more extrapyramidal signs, frontal release signs, and sensory signs.

In a second MANOVA, stage of illness was substituted for serostatus as follows: (1) HIV negative; (2) HIV positive, asymptomatic; (3) HIV-positive, mildly symptomatic; and (4) HIV positive, moderately symptomatic. The MANOVA remained highly signficant ($P<.001$). Stage of illness (Hotelling $T^2=.21$, $P<.003$), head injury (Hotelling $T^2=.08$, $P<.02$), and IVDU (Hotelling $T^2=.10$, $P<.006$) main effects were all significant.

In follow-up univariate F tests, a significant stage-of-illness main effect was seen for symptoms ($F=4.2$, $P<.007$), extrapyramidal signs ($F=4.2$, $P<.007$), and frontal release signs ($F=2.7$, $P<.04$). Therefore, with all other main effects and covariates controlled, subjects with the most systemic illness also had the highest frequencies of neurologic signs and symptoms.

A third MANOVA contrasted HIV-negative and HIV-positive asymptomatic patients. The MANOVA was significant ($P<.05$), and the HIV negative/HIV positive contrast was the only significant main effect (Hotelling $T^2=.13$, $P<.03$).

In follow-up univariate F tests, a significant serostatus effect was seen for extrapyramidal ($F=5.4$, $P<.02$), sensory ($F=4.2$, $P<.04$), and frontal release ($F=4.8$, $P<.03$) signs, indicating that even when the comparison was limited to asymptomatic HIV-positive subjects and HIV-negative subjects, significant increases in neurologic signs were seen.

Neuropsychological Summary Scores

No difference was seen between HIV-positive and HIV-negative subjects in the distribution of ratings of overall performance by the neuropsychologist's impression or in the frequency of defective summary scores (Table 6).

We calculated a set of omnibus MANOVAs. The overall MANOVA was significant ($P<.001$). Neither the overall serostatus (HIV positive vs HIV negative) or serostatus × head injury interaction effect reached significance. However, in follow-up univariate F tests, a significant serostatus × head injury main effect was seen for tests of mem-

Table 7.—A Comparison of Human Immunodeficiency Virus (HIV)–Negative and HIV-Positive Subjects With and Without a History of Head Injury*

	No Head Injury		Head Injury	
	HIV Negative	HIV Positive	HIV Negative	HIV Positive
Modified Mini-Mental State examination	50.0 (4.5)	50.2 (4.3)	50.4 (3.4)	47.7 (5.6)†
Selective Reminding Test				
Total recall	50.4 (10.5)	51.7 (8.1)	50.4 (9.7)	46.8 (11.9)
Long-term retrieval	42.2 (15.4)	44.2 (12.3)	42.1 (12.7)	35.7 (14.1)†
Long-term storage	45.3 (14.9)	47.3 (12.5)	45.4 (13.0)	38.7 (14.5)†
Consistent long-term retrieval	34.5 (17.5)	36.2 (14.1)	34.6 (13.7)	27.7 (13.9)†
Delayed recall	7.7 (3.1)	8.4 (2.6)	7.7 (2.8)	7.0 (2.9)
Boston Naming Test	23.3 (4.7)	23.9 (4.0)	24.5 (4.0)	21.8 (5.3)†
WAIS-R Block Design	18.7 (8.4)	22.1 (9.5)	22.7 (8.9)	18.1 (7.9)†
Wechsler Memory Scale				
Visual reproduction subtest	29.1 (7.4)	30.2 (5.6)	29.4 (7.4)	26.6 (14.1)
Delayed visual reproduction subtest	22.4 (9.3)	23.6 (9.1)	23.8 (9.2)	18.1 (9.2)†
Cancellations (omissions)	0.5 (0.96)	1.9 (11.2)	0.7 (1.3)	1.3 (1.4)
Grooved pegboard, nondominant	88.6 (24.3)	89.9 (20.2)	82.5 (25)	100.3 (29.4)†
Digit Symbol (raw score)	43.4 (13.0)	45.7 (12.4)	43.4 (11.4)	39.4 (12.0)
Trail Making Test Part B (sec)	111.6 (60.9)	106.9 (52)	115.3 (75)	130.2 (59.7)
Neuropsychologist's clinical impression	1.1 (0.89)	1.0 (0.88)	1.0 (0.92)	1.4 (0.79)†

*Two-way analysis of variance was performed. WAIS-R, indicates Wechsler Adult Intelligence Scale–Revised. Values are mean (SD) scores.
†$P<.05$ significant HIV status × head injury interactions.

ory (F=5.5, $P<.02$), language (F=3.7, $P<.05$), and visuospatial ability (F=5.3, $P<.02$).

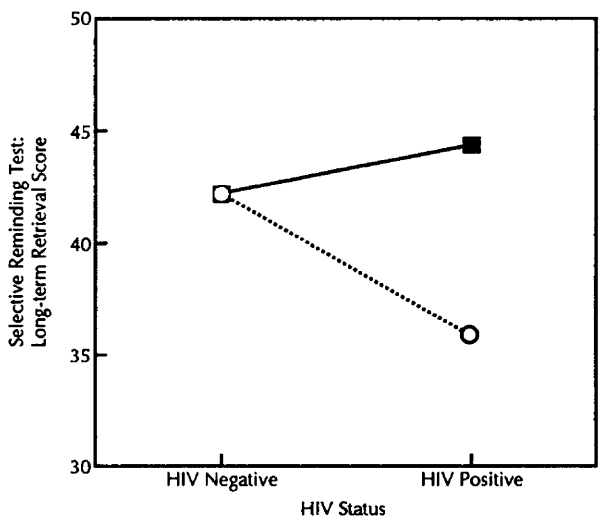
In a second MANOVA, when serostatus was replaced in the MANOVA by stage-of-illness (HIV negative vs three stages of HIV positive), stage-of-illness and serostatus × head injury main effects were not significant, nor were any of the univariate F tests.

Finally, in a third MANOVA, HIV-positive and HIV-negative asymptomatic subjects were contrasted. The overall MANOVA was significant ($P<.004$), but the HIV negative/HIV positive contrast and the serostatus × head injury interaction were not. In the follow-up univariate F test, a significant serostatus effect was seen for executive function (F=5.3, $P<.02$).

Individual Neuropsychology Test Scores

Mean individual test scores were calculated for subjects with or without head injury within HIV-positive and HIV-negative groups (Table 7). With the use of two-way ANOVAs with HIV status and history of head injury as main effects, significant differences were present in the subjects with head injury on a number of individual tests. No differences were seen between HIV-positive and HIV-negative subjects within the subject group without head injury. There was an interaction between HIV status and history of head injury for most variables (Figure).

Subjects with and without head injury were then divided by stage of illness: (1) HIV negative; (2) HIV, asymptomatic and mildly symptomatic; and (3) HIV positive, symptomatic but not AIDS. No between-group differences were seen in subjects without head injury. In contrast, in the subjects with head injury, there was a linear relationship between stage of illness and neuropsychological test performance on the Mini-Mental State examination, Selective Reminding Test, Delayed Visual Reproduction subtest of the Wechsler Memory Scale, and the grooved pegboard. More severe stage of illness was associated with worse neuropsychological test performance in the subjects with head injury only, again suggesting an interaction between HIV status and head injury (Table 8).



Performance on the Selective Reminding Test (long-term retrieval) in subjects with (circle) and without (square) head injury. An interaction between head injury and human immunodeficiency virus–positive (HIV) state is seen.

Individual neuropsychological tests were included in a MANOVA with serostatus, head injury, first language, sex, and a serostatus × head injury interaction main effects, covaried by age and education. Neither serostatus nor the serostatus × head injury interaction was a significant main effect. When univariate F tests were inspected, there were significant serostatus × head injury interactions for the Mini-Mental State examination (F=4.5, $P<.04$), the Boston Naming Test (F=5.5, $P<.02$), the Wechsler Adult Intelligence Scale–Revised (WAIS-R) Block Design (F=5.9, $P<.02$), WAIS-R Similarities (F=4.1, $P<.05$), Wechsler

Table 8.—Relationship Between Stage of Illness and Neuropsychological Test Performance in Subjects Reporting a History of Head Injury*

	HIV Negative	HIV Positive, Asymptomatic or Mild Symptoms	HIV Positive, Symptomatic
Mini-Mental State examination	50.4 (3.4)	47.9 (5.8)	47.6 (5.5)†
Selective Reminding Test			
Long-term retrieval	42.1 (12.7)	38.2 (13.5)	33.0 (14.9)†
Long-term storage	45.3 (13.0)	41.0 (13.9)	36.2 (15.3)†
Consistent long-term retrieval	34.6 (13.7)	30.2 (13.10)	25.0 (14.9)†
Wechsler Memory Scale			
Delayed Visual Reproduction	23.8 (9.2)	20.3 (10.6)	15.8 (6.2)†
Grooved pegboard, nondominant	82.5 (25.6)	92.7 (26.3)	107.8 (30.8)†

*HIV indicates human immunodeficiency virus. Values are mean (SD) scores on neuropsychological tests compared by analyses of variance.
†$P<.05$.

Memory Scale Visual Reproduction subtest ($F=4.7$, $P<.03$), and Delayed Visual Reproduction ($F=4.6$, $P<.03$). The interactions suggested that the performance was more impaired in HIV-positive patients who sustained head injury.

When the serostatus was replaced with HIV stage in the MANOVA model (HIV negative and three medical stages of HIV positive), the stage-of-illness main effect was not significant. In the univariate F tests, there was a significant HIV stage effect for the modified Mini-Mental State examination ($F=2.9$, $P<.04$) and the Boston Naming Test ($F=3.7$, $P<.01$). No significant stage × head injury interaction was seen.

When HIV-positive and HIV-negative asymptomatic subjects were contrasted, a significant HIV positive/HIV negative main effect was seen (Hotelling $T^2=.43$, $P<.02$), but the serostatus × head injury interaction was not significant. Univariate F tests did not reveal an HIV status or an interaction effect for any individual tests.

COMMENT

The influence of HIV on neurologic and neuropsychological function is difficult to determine in IVDUs for many reasons. First, the group is demographically diverse and includes men and women with a wide range of cultural and educational backgrounds. Second, many subjects have complex medical histories that include head trauma with loss of consciousness. Third, long-term drug use may affect neuropsychological test performance or the presence of neurologic signs. Also, acute intoxication (alcohol or other drugs) can affect performance. We therefore took a conservative approach to these preliminary analyses, controlling statistically for these possible effects. In addition, we used omnibus MANOVAs to adjust for multiple comparisons. Nevertheless, two major findings emerged from this cross-sectional approach.

First, the only neurologic findings that differed between the HIV-positive and the HIV-negative subjects were the presence of extrapyramidal signs, most notably rigidity, and frontal release signs. These increased in linear fashion with stage of illness, appearing most prominent in those with the most systemic illness. When current IVDU, head injury, age, and education were included in an omnibus MANOVA, these findings persisted and were present even when totally asymptomatic HIV-positive subjects were contrasted with HIV-negative subjects.

Second, there was no difference in the frequency of defective neuropsychological scores between HIV-positive and HIV-negative subjects. Examination of neuropsychological summary scores included within a MANOVA revealed no significant serostatus main effects but did reveal a number of univariate head injury × HIV status interactions. When individual neuropsychological tests were included in a MANOVA, again no significant main effects were seen, although many univariate head injury × HIV status interactions were noted. A total of 157 cases were included in this analysis. Because the MANOVAs were suggestive of specific relationships and were limited by smaller sample size, a simpler analysis, a two-way ANOVA with status and head injury main effects, was utilized, including all 221 subjects. A head injury × serostatus interaction was evident on numerous tests. Many of these tests showed a worsening with stage of infection within the group with head injury only. The significant interaction between serostatus and head injury suggests that the effect of HIV on performance may be additive if there has been a brain injury.

We found that the moderately symptomatic subjects who did not meet criteria for AIDS had more extrapyramidal signs and frontal release signs. This finding is consistent with the idea that neurologic signs and symptoms increase with systemic disease and decline with immune function.[23] Early motor symptoms of HIV-1–associated cognitive impairment include gait impairment, leg weakness, and tremor.[24] In patients with HIV-1–associated dementia complex, neurologic findings include frontal release signs, slowed rapid alternating movements, gait impairment, hyperreflexia, hypertonia, and peripheral neuropathy.[25]. Our finding of extrapyramidal signs and frontal release signs even in those without systemic illness compared with HIV-negative subjects may reflect early subcortical hypermetabolism, which has been described in the early stages of HIV dementia with the use of positron emission tomography.[26]

Whether specific behavior patterns predispose to nervous system dysfunction, including exposure to HIV infection and head trauma, deserves further exploration. No attempt was made at the time of the initial assessment to determine duration of unconsciousness, age at the time of head injury, or number of head injuries. We have included a more detailed head injury questionnaire in subsequent evaluations, including age at time of head injury, number of incidents, duration of loss of consciousness, and need for hospitalization. Magnetic resonance imaging evaluations in 115 of the IVDUs at subsequent evaluations will also provide further documentation of the degree of brain injury.

Few studies have documented neurologic impairment in IVDUs. In a retrospective study of HIV infection conducted before the advent of HIV antibody testing, 64% of subjects were IVDUs and 23% had abnormal neurologic signs.[3]

In another survey of asymptomatic HIV-positive and

HIV-negative IVDUs, neurologic abnormalities were equally prevalent: 81% of the seropositive group and 76% of the seronegative group.[5,27] In a subsequent study of this cohort of 109 HIV-positive, predominantly mildly symptomatic and 51 HIV-negative subjects, Royal et al[28] found neurologic signs with similar frequency in seropositive and seronegative groups. Neuropsychological performance was similar in HIV-positive and HIV-negative groups, except for the Digit Span tests. When these tests were examined with an ANOVA, only education was significantly associated with the outcome. Royal et al did not report an interaction effect between serostatus and head injury with loss of consciousness, although head injury was common: HIV positive, 18%; HIV negative, 35%. The higher frequency of head injury and alcohol use in the seronegative subjects may have made any differences associated with serostatus more difficult to detect.

In a prospective survey at Harlem Hospital Center, New York, NY, of 190 inpatients with AIDS or AIDS-related complex, 80% were IVDUs and 91% had neurologic symptoms or signs, the most common of which was altered mental status, followed by focal cerebral signs.[4]

No difference was noted between IVDUs and non-IVDUs in the prevalence of neurologic findings, nor was there a difference in neurologic findings between patients with AIDS and lymphadenopathy/AIDS-related complex. Clearly, the heightened awareness of the neurologic complications of HIV-1 infection, a detailed neurologic examintion, and detection of seropositivity in a high-risk patient population accounted for the higher frequency in the prospective study.

Neuropsychological impairment was found by McKegney et al[29] in finger tapping, Digit Span (forward), and WAIS-R Similarities measures when 83 HIV-positive IVDUs were compared with 137 HIV-negative IVDUs. Follow-up examinations of 91 patients 7 months after the baseline visit showed similar findings without deterioration of function.

In contrast, in Edinburgh, no significant differences were noted in cognitive function between the HIV-positive and HIV-negative IVDUs. The authors of the Edinburgh study concluded that AIDS dementia is a late complication of HIV infection and that intellectual impairment is more likely due to drug use.[30]

Our data indicate that IVDUs who do not have AIDS show similar but less severe neurologic and neuropsychological impairment than those seen in patients with AIDS. These signs are more apparent in those with more advanced disease. Neuropsychological impairment was present only among HIV-positive subjects with a history of head injury and loss of consciousness. When HIV-positive subjects were compared with HIV-negative subjects in the population without head injury, no differences were seen, suggesting an interaction between head injury and HIV status. Further attention must be given to head injury as a contributor to neuropsychological impairment in HIV-infected individuals.

This research was supported by center grant 5-P50MH43520 from the National Institute of Mental Health/National Institute on Drug Abuse and by grant 3-MO1-RR00645-19S1 from the National Institutes of Health, Bethesda, Md, to the Clinical Research Center, Presbyterian Hospital, New York, NY.

We thank W. Allen Hauser, MD, and Lewis P. Rowland, MD, for their contributions to the preparation of the manuscript.

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