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Neuropsychological Changes in a Prospectively Followed Cohort of Intravenous Drug Users with and without HIV

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Summary: We followed a cohort of 223 intravenous drug users (99 HIV^- and 124 HIV^+) for up to 3.5 years, examining change in performance over time as a function of HIV status, disease severity, and neurological signs and symptoms. Analyses were performed by applying generalized estimating equations (GEE) to regression analyses with repeated measures, and controlled for age, education, and length of substance use. None of the subjects had AIDS at baseline. There were 147 men (85 HIV^+ and 62 HIV^-) and 76 women (39 HIV^+ and 37 HIV^-). Memory performance was worse in the HIV^+ than HIV^- women. In the men, performance on the memory, executive, language, and attention factors improved significantly over time, but this improvement was attenuated in the HIV^+ men for the attention and orientation factors. In the HIV^+ women, AIDS was associated with worsening performance on attention tests. The presence or onset of clinically significant neurological findings was associated with poorer language and motor speed performance. In the HIV^+ men, memory performance was worse when the CD4 count fell below 200; it declined over time in men with AIDS but not in those without. A learning effect for language was attenuated in men who developed AIDS. The presence or development of a clinically significant neurological sign was associated with poorer memory, executive, language, attention, and motor speed performance. Our findings parallel those that we previously reported in a prospectively followed cohort of gay men. In combination, our studies of gay men and IDU cohorts suggest that (a) HIV can affect cognition early, even when the patient is medically asymptomatic; (b) cognitive difficulties worsen as the severity of HIV infection increases; and (c) the advent of clinically significant neurologic signs is associated with progression to more severe cognitive deficits. Our data suggest that the neurological and neuropsychological changes are both manifestations of the central effect of HIV on the CNS. **Key Words:** HIV—Cognition—Intravenous drug use—Prospective cohort studies. **NNBN 9:83–90, 1996**

Intravenous drug users (IDU's) are the fastest growing portion of the HIV epidemic. Still, relatively little attention has been afforded to potential neuropsychological changes in this group, and prospective studies are rare. Studies of IDU's are more complex, in that they must carefully control for potential covariates, including socioeconomic factors such as lower education, medical features such as head injury, and drug use. However, studies of IDU's may be more likely to detect subtle neuropsychological changes, because these individuals' lower education and socioeconomic status might provide a lower threshold for observing the effects of the virus on the central nervous system. In addition, they allow the opportunity to evaluate the effects of alternate modes of HIV trans-

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mission as well as the potential effects of HIV on women, another understudied group.

Two studies found that HIV^+ IDU's had more rapid decline of neuropsychological test performance than HIV^- controls (1,2), but a third study (3) did not. We previously reported a cross-sectional analysis that demonstrated subtle differences between seronegative and seropositive IDU's performance on a neuropsychological test battery (4). We also noted an interaction between history of head injury and serostatus such that neuropsychological performance was significantly worse in the HIV^+ subjects reporting a history of head injury. We have now followed this cohort of IDU's for up to 3.5 years and describe change in performance over time as a function of HIV status, disease severity, and neurological signs and symptoms. Because of their particular salience in this group, we paid close attention to the potential effects of previous and current drug use, education, and head injury. In addition, systematic differences between the men and women in our cohort prompted us to analyze their data separately.

We hypothesized that HIV's effect on cognitive function in IDU's would be similar to that already noted in gay men. In a prospective study of our gay men cohort, we found that neuropsychological test performance tended to improve over time, but that this improvement was attenuated or eliminated in the HIV^+ group for some tests (5). In addition, lower CD4 counts, more advanced disease stage, and the presence of neurological signs were each associated with poorer test performance and more marked decline over time. Observing a similar pattern of cognitive changes in the IDU's would provide additional evidence for the direct effect of HIV on the CNS, in the form of interrelated cognitive and neurological changes.

METHODS

Subjects

Two hundred and twenty-three IDU's (99 HIV^- and 124 HIV^+) were recruited in late 1988 through 1989. These included 147 men (85 HIV^+ and 62 HIV^-) and 76 women (39 HIV^+ and 37 HIV^-). The majority (170) were recruited from the Harlem Hospital Infectious Disease Clinic, New York; 53 were recruited from the St. Luke's Roosevelt Methadone Maintenance Clinic, New York. Inclusion and exclusion criteria and screening procedures have been described elsewhere (4,6). All subjects were volunteers and gave informed consent. All participants had used intravenous drugs at least 10 times since 1982. In the HIV^+ subjects, 41% used heroin in the 6 months before their initial visit, 71% used cocaine or crack, and 50% used alcohol. For the same period, 43% of the HIV^- subjects used heroin, 61% cocaine or crack, and 55% alcohol.

Assessments

All subjects who entered the longitudinal phase were examined every 6 months for up to eight visits (3.5 years). At each visit, subjects received a standardized medical examination for staging, and neurological, neuropsychological, psychiatric, and psychosexual assessments. These assessments have been described previously (7,8); relevant assessments are summarized below.

Medical Assessment

Physicians performed physical examinations targeted at HIV-related symptoms and signs. Subjects who met 1987 CDC criteria for AIDS (9) at baseline were not included in the study, with two exceptions. Because of the difficulty in distinguishing clinically between oral and esophageal candidiasis on routine physical exam, we did not exclude men with esophageal candidiasis, which is, on its own, a criterion for AIDS. We also did not use the presence of cognitive impairment as an exclusion criterion because the purpose of the study was to assess nervous system abnormalities in relatively medically asymptomatic individuals. Blood for CD4 counts was obtained at each visit.

Following each study visit, HIV^+ patients were classified into disease stages, based on previously described criteria (10). For the present analyses we consider three severity stages: asymptomatic or mildly symptomatic, signs and symptoms consistent with AIDS-related complex (ARC), and AIDS.

Neurological Assessment

All neurological examinations were performed by neurologists who were blind to the HIV status of the subjects. An overall measure of neurological disability was calculated for each subject, based on the Kurtzke Disability Status Scale for Multiple Sclerosis (11). The Kurtzke scale reflects both the number of areas of neurological dysfunction (i.e., pyramidal tract, cerebellar, brainstem, etc.) and the severity of impairment. Derivation of the Kurtzke for use in HIV has been previously described (12). We subdivided subjects into those with and without clinically significant neurological findings, using a score of three or above on the Kurtzke scale as the cut-off point.

Neuropsychological Assessment

The neuropsychological battery was also administered blind to HIV status and included the following tests.

The 10 orientation items from the Mini-Mental State Examination (13) were used to assess orientation to time and place. Attention was assessed with two types of cancellation tasks, one utilizing a shape and another a letter triad as targets (14), and the WAIS-R Digit Symbol subtest (15). Verbal fluency was assessed with the controlled oral word association test (60 s for each of the letters C, F, and L) (16) and animal naming (17). The Odd Man Out Test (18,19) was used to assess executive or "frontal lobe" function. The Trail Making Test was also administered as a test of speeded performance and, in part B, of rapid sequencing and set shifting (20). Motor speed and praxis was assessed with the Grooved Pegboard (21). A 12-item, six-trial selective reminding test assessed verbal memory (22).

In our prospective study of gay men (12), we performed a factor analysis of the neuropsychological test scores at the baseline visit and assessed stability of the factors at the follow-up visits. Then, using these factor analyses as a guide, we constructed six neuropsychological factor scores. To provide comparability to the studies of gay men, these factor scores were used in the current analyses. The factors were (a) memory: selective reminding test total score; (b) motor speed: grooved pegboard, time to insert pegs with dominant hand; (c) executive: Odd Man Out total score and Trails B time; (d) language: number of words reported on animal naming and CFL; (e) attention: Digit Symbol Age Scaled score, shape and letter cancellation time; and (f) orientation: orientation score. Although the name of each factor reflects our view of the primary cognitive function tapped, certainly these factors reflect multiple processes. For example, the tests included in the attention factor also require psychomotor speed and scanning.

To calculate summary scores for each patient, each component score was first transformed into a z score based on the mean and SD of test scores of all subjects assessed at the baseline visit. The z scores were adjusted for direction (i.e., whether higher scores indicate better or worse performance). Factor scores then were calculated as sums of the z scores for measures within each factor. The range of scores on the orientation test was severely restricted (i.e., few errors were made). For statistical purposes, performance on this factor was expressed as the number of errors. Thus, for orientation and motor speed (which is expressed as time to completion), higher scores represent poorer performance.

Drug Use

All subjects were systematically interviewed at each visit about their drug and alcohol usage. Use of all forms of heroin, all forms of cocaine, benzodiazepines, hallucinogens, and phencyclidine was assessed. We created a composite variable to reflect the length of time subjects had used either heroin, cocaine, or alcohol. The number of years since first substance use was highly correlated with the age of the subjects, so the variable included both age and years of drug use. Based on median values, years of illicit drug use were dichotomized into "long" ($\geq$15 years) and "short" ($>$15 years), and alcohol use was dichotomized into "long" ($\geq$20 years) and "short" ($<$20 years). If either drug use or alcohol use was considered "long," the subject was considered to have a "long" history of substance abuse. Women's age was dichotomized at 40 years and men's at 45 years. Because no subjects in the higher age groups had a short history of use, men and women were divided into three age/substance abuse groups reflecting younger individuals with short- and long-term use and older individuals with long-term use. In this way, the proportion of subjects' lives during which they used drugs or alcohol was captured.

As another index of substance use, frequency of drug and alcohol use in the 6 months before each visit was dichotimized into "high" (weekly use or more) and "low" (monthly use or less). These data were available only for visits 2–7 and were therefore used only for supplemental analyses.

Statistical Analysis

Analyses of the longitudinal data were done by applying generalized estimating equations (GEE) to regression analyses with repeated measures (23). This statistical method takes into account the multiple visits per subject and the fact that the characteristics of a single individual over time are likely to be correlated with one another. The repeated measures for each subject (up to eight per variable) are treated as a cluster. A second advantage of GEE is that it takes into account the status or changing value of each covariate at each visit. Tabled values for regression analyses involving the factor scores are regression coefficients and their SE. All analyses controlled for age and education by including them as covariates.

The distributions of all factors except orientation were approximated by a normal distribution. As

noted above, scores for the orientation factor had an attenuated range and were converted to error scores; their distribution was approximated by a Poisson distribution.

Data on recent (past 6 months) substance use was available only for visits 2–7. We assessed the potential influence of the frequency of recent substance use on neuropsychological factor scores by calculating models that included substance use and follow-up time, controlling for age and education. To best assess the influence of substance use, analyses were limited to the HIV^- subjects. There were no significant substance use effects for any of the neuropsychological factors. Because including recent substance use in all analyses would require truncating the data set and based on the lack of current drug use effects in the HIV^- subjects, we chose not to control for recent substance use in the analyses.

Data analysis was divided into two series: the first included both HIV^- and HIV^+ subjects, whereas the second included only the HIV^+ subjects.

The initial series of analyses included both HIV^- and HIV^+ subjects, and examined test factor performance over time as a function of serostatus. Because men and women differed significantly on several demographic and clinical variables, their data were analyzed separately. The regression models provided estimates of the association of neuropsychological factor scores with serostatus, follow-up time, and the interaction of serostatus and time. A significant interaction of HIV status and time would indicate differential rates of change in a factor score as a function of HIV status. All analyses controlled for age, education, and the composite drug use history variable. Because a history of head injury interacted with serostatus in our previously reported analysis of the data from the baseline visit, this interaction was investigated as well. If a specific component of the model was not significant at the $p \leq 0.05$ level, it was eliminated from the model. Thus, drug use or head injury effects are reported only when they were significant.

The second series of analyses were restricted to the HIV^+ subjects, with the data for men and women again evaluated separately. Two groups of regression analyses explored the contribution of disease severity, first as a function of CD4 count (stratified into three ranges: <200, 200–500, >500), and then as a function of disease stage. A third group of analyses evaluated the relationship between neuropsychological performance and clinically significant neurological findings (Kurtzke score: <3 versus ≥3). The same analytic approach was taken as described above for the first series of analyses, with two exceptions. First, because the substance abuse history variable correlated strongly with age, it was not included. Second, if interactions with follow-up time were not significant, they were also trimmed from the model. Thus, the reported results reflect only the components of the model that were significant and were retained.

RESULTS

Demographics

CD4 count was significantly lower ($p < 0.0001$) and the Kurtzke score significantly higher ($p < 0.01$) in HIV-positive subjects compared with HIV-negative subjects (Table 1). Reported substance use did not significantly differ by HIV status at baseline.

Men were significantly older ($p < 0.05$) but had significantly lower Kurtzke scores ($p < 0.01$) than women, indicating that men had less neurological impairment at baseline. Men were more likely to be long-term abusers of drugs and alcohol ($p < 0.05$) and to report head injury with loss of consciousness ($p < 0.05$).

None of the subjects met our criteria for AIDS at baseline. A similar proportion of men and women were asymptomatic/mildly symptomatic, or met criteria for AIDS related complex (ARC). The proportion of HIV^+ men and women with CD4 of ≤200 was also similar.

Two men and four women seroconverted during the study. In the HIV^+ subjects, there were 32 deaths (22 men, 10 women), and 33 subjects (24 men, nine women) were lost to follow-up (did not complete all eight visits, but did not die). Among HIV-negative subjects, there were four deaths (all men) and 35 subjects lost to follow-up (19 men, 16 women). One HIV-negative woman seroconverted during follow-up and subsequently died; she was counted among the HIV-positive deaths. Two of the HIV-positive subjects died soon after completing their eighth visit and were considered among the deaths. Not all deaths in the HIV^+ subjects were directly HIV-related. At visit 8, there were 66 HIV^+ subjects (41 men, 25 women) and 55 HIV^- subjects (38 men, 17 women).

HIV^+ Versus HIV^- Women

Older women with long-term drug use performed more poorly than younger women with short-term use on the memory, executive, attention, and motor speed factors (Table 2). Controlling for education and the composite age/drug use variable, performance on the memory, executive, and attention factors improved over time and HIV^+ women performed more

TABLE 1. *Baseline characteristics for HIV⁻ and HIV⁺ subjects followed longitudinally*[a]

	HIV⁻		HIV⁺	
	Men	Women	Men	Women
n	62	37	85	39
Age (years)	39.6 (7.6)	37.4 (7.9)	39.8 (6.6)	37.5 (6.2)
Education (years)	12.0 (2.2)	11.4 (1.9)	11.4 (2.1)	12.1 (1.8)
CD4 count	1036.2 (353.7)	1135.4 (321.2)	419.6 (300.6)	395.5 (260.1)
CD4 ≤ 200 (%)	0	0	25.9	23.1
Kurtzke score	1.52 (0.92)	1.92 (0.80)	1.91 (0.83)	2.18 (0.76)
Kurtzke ≥ 3 (%)	16.3 (10)	18.92 (7)	23.53 (20)	33.33 (13)
Stage at baseline (%)				
Asym/mild sym	—	—	55.3 (47)	38.5 (15)
ARC	—	—	44.7 (38)	61.5 (24)
ETOH ≥ 20 years (%)	62.9 (39)	51.4 (19)	69.4 (59)	41.0% (16)
Drug use ≥ 15 years (%)	71.0 (44)	56.8 (21)	82.4 (70)	53.9% (21)
Any long-term drug use (%)	77.4 (48)	59.5 (22)	87.1 (74)	61.5% (24)
Head injury with LOC (%)	41.9 (26)	27.0 (10)	47.1 (40)	30.8% (12)

[a] Values in parentheses are SD for means and actual numbers for percentages.

poorly on the memory factor. There was no difference detected in the rate of change over time in any score.

There was a significant serostatus × head injury interaction for the orientation factor, such that performance was significantly worse in the HIV⁺ (but not HIV⁻) subjects reporting a history of head injury with loss of consciousness.

HIV⁺ Versus HIV⁻ Men

Older men with long-term drug use performed more poorly than younger short-term users on the memory attention and motor speed factors (Table 3). Adjusting for education and age/drug use, performance on the memory, executive, language, and attention factors improved significantly over time. The time × serostatus interaction term for these four factors was negative, suggesting that improvement was attenuated in the HIV⁺ men. This attenuation was significant for the attention factor and is illustrated in the figure (Fig. 1). Time trends can be estimated separately for HIV⁻ and HIV⁺ men by summing the regression coefficients for the time and interaction terms. Using this approach, HIV⁻ men had learning effects for the memory, executive, language, and attention factors, but HIV⁺ men had a learning effect only for the executive and language factors.

The error score for orientation was unchanged over time in the HIV⁻ men, but increased in the HIV⁺ men, yielding a significant time × serostatus interaction.

TABLE 2. *For women, regression coefficients (SE) assessing the association of each factor score with serostatus, follow-up time, and their interaction*[a]

Factor	Serostatus	Time	Serostatus × Time
Memory	−0.44 (0.20)[b]	0.11 (0.05)[b]	0.06 (0.07)
Executive	−0.49 (0.36)	0.20 (0.07)[b]	−0.06 (0.13)
Language	−0.19 (0.35)	0.11 (0.09)	0.15 (0.13)
Attention	−0.87 (0.53)	0.25 (0.12)[b]	0.18 (0.18)
Motor speed	0.15 (0.29)	−0.07 (0.06)	0.05 (0.09)
Orientation	0.28 (0.35)	0.18 (0.10)	−0.26 (0.17)

[a] Analyses control for age and education. Note that for motor speed and orientation, higher scores denote poorer performance, so the directionality of the regression coefficients is reversed.
[b] $p < 0.05$.

HIV⁺ Women

In the HIV⁺ women, no association between a low CD4 count and neuropsychological test performance was detected. AIDS was associated with worsening performance on the attention factor (Table 4). The presence or onset of clinically significant neurological findings was associated with poorer performance on the language and motor speed factors ($p < 0.05$ for both), and weakly associated with the memory ($p = 0.07$) and attention ($p = 0.06$) factors (Table 4).

HIV⁺ Men

In the HIV⁺ men, memory performance was worse in subjects when the CD4 count fell below 200 (Table 5). There was also a significant AIDS × time interaction for memory and language: memory performance declined over time in the men with AIDS but not in those without, and the learning effect for language was attenuated in men who developed AIDS (Table 5). The presence or development of a clinically significant neurological sign was associated with poorer per-

TABLE 3. *For men, regression coefficients (SE) assessing the association of each factor score with serostatus, follow-up time, and their interaction*[a]

Factor	Serostatus	Time	Serostatus × Time
Memory	−0.16 (0.15)	0.11 (0.04)[b]	−0.07 (0.06)
Executive	−0.06 (0.25)[b]	0.28 (0.07)[b]	−0.06 (0.09)
Language	−0.36 (0.26)	0.19 (0.07)[b]	−0.04 (0.09)
Attention	0.25 (0.43)	0.55 (0.12)[b]	−0.51 (0.17)[b]
Motor speed	0.13 (0.14)	−0.03 (0.04)	−0.02 (0.05)
Orientation	−0.19 (0.28)	−0.10 (0.10)	0.30 (0.12)[b]

[a] Analyses control for age and education. Note that for motor speed and orientation higher scores denote poorer performance, so the directionality of the regression coefficients is reversed.
[b] $p < 0.05$.

TABLE 4. *In HIV$^+$ women only, regression coefficients (SE) for the disease stage (no AIDS vs. AIDS), and the presence or absence of clinically significant neurological findings (Kurtzke score stratified at 3)*[a]

Factor	Stage	Kurtzke score
Memory	—	−0.31 (0.17)[c]
Language	—	−0.65 (0.31)[b]
Attention	−1.34 (0.50)[b]	−0.81 (0.42)[c]
Motor speed	—	0.72 (0.35)[b]

[a] All analyses control for age, education and follow-up time (when they are significant). Note that for motor speed, higher scores denote poorer performance, so the directionality of the regression coefficients is reversed.
[b] $p < 0.05$.
[c] $p < 0.07$.

formance on the memory, executive, language, attention, and motor speed factors (Table 5).

DISCUSSION

The present findings confirm and extend previous prospective observations of cognitive change in HIV among well-educated, high-socioeconomic gay and bisexual men, and our initial cross-sectional evaluations of our IDU cohort. Because none of our cohort had AIDS at their initial visit, any effects of HIV on test performance would be expected to be quite subtle. In addition, the ability to observe HIV-related cognitive changes in the IDU cohort is complicated by variability in socioeconomic background, more pronounced medical problems, and drug usage. Still, we reported small but statistically significant differences between the performance of HIV$^-$ and HIV$^+$ subjects on some tests at baseline (4). Because tests were administered every 6 months, subjects would be expected to become quite familiar with the test materials. In fact, a striking feature of the present prospective analyses is the general trend for improved performance over time on all the neuropsychological test factors considered. The potential effects of HIV on performance therefore must be judged against a background of improving scores. We found that HIV was associated with poorer performance on some tests and a blunting or reversal of a learning effect on others. In addition, poorer neuropsychological performance was noted as a function of the presence or development of more advanced disease or of clinically significant neurologic findings. Test findings parallel those that we previously reported in a prospectively followed cohort of gay men (12), and suggest that the effect of HIV on the central nervous system is similar in gay men and IDU's.

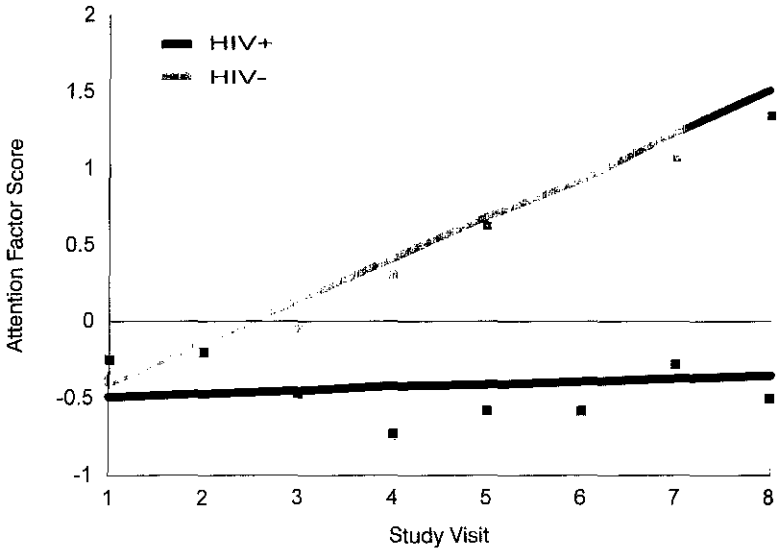

FIG. 1. Change in attention factor scores for HIV$^-$ and HIV$^+$ subjects over each study visit. The regression lines are derived from the GEE model. The squares indicate the mean observed value at that study visit.

TABLE 5. *In HIV$^+$ men only, regression coefficients (SE) for selected clinical variables*[a]

Factor	CD4	Stage × time	Kurtzke score
Memory	−0.35 (0.16)[b]	−0.59 (0.25)[b]	−0.32 (0.12)[b]
Executive	—	—	−0.47 (0.17)[b]
Language	—	−0.61 (0.21)[b]	−0.55 (0.20)[b]
Attention	—	—	−0.90 (0.34)[b]
Motor speed	—	—	0.27 (0.12)[b]

[a] Variables include CD4 count (<200 vs. >500), disease stage (no AIDS vs. AIDS), and the presence or absence of clinically significant neurological findings (Kurtzke score stratified at 3). All analyses control for age and education and follow-up time (when they are significant). The interaction coefficients are included when they were significant. Note that for motor speed higher scores denote poorer performance, so the directionality of the regression coefficients is reversed.

[b] $p < 0.05$.

We analyzed women's and men's data separately because they differed at baseline on several demographic and disease severity variables and because our data suggested that their drug use patterns differed during follow-up. The power of the analyses of the women's data was comparatively reduced because of this group's smaller size. Thus, for example, the relation between CD4 count and memory performance noted in the men could not be detected in the women. Still, the pattern of results was quite similar in the men and women.

Few studies have prospectively investigated neuropsychological changes in HIV$^+$ IDU's. In a follow-up study of 128 methadone-maintained IDU's, neuropsychological performance declined more rapidly in the HIV$^+$ than the HIV$^-$ subjects (1). In another study of 220 IDU's (2) (27 HIV$^-$, 193 HIV$^+$), symptomatic patients (in CDC stage IV) were impaired on Trails B, two-choice decision time, delayed recall of the Wechsler Logical Memory Test, and most components of the Auditory Verbal Learning Test. A total of 101 patients was retested at a mean of 16 months after their initial assessment. Performance on Trails A and B, Block Design, and delayed recall of the Wechsler Logical Memory Test deteriorated more for patients at or progressing within CDC stage IV, than performance of patients at stage III. Performance on all tests of memory function declined independent of clinical staging. The MACS study also evaluated a group of 102 AIDS-free, HIV$^+$ IDU's along with 49 HIV$^-$ controls (3). At baseline, there were no significant differences in test performance attributable to HIV. There were also no differences in performance by serostatus group at either 6- or 12-month follow-up visits. Improvement in performance secondary to practice effects was comparable in both serostatus groups. Thus, two other studies, but not the MACS group, have noted cognitive changes that progress over time associated with HIV in IDU's. Bornstein (24) reviews some potential explanations for the discrepancies between the MACS group's and others' findings.

Analysis of data from an IDU population is more complex than that from gay men cohorts for many reasons (25). This population has more variable SES, educational background, and medical history. Overall, baseline performance on all tests was significantly lower than that observed in a gay men cohort. A notable concern is the possible effect of drug use on neuropsychological test performance. Evaluation of this issue is complicated by difficulties in documenting current and past drug use. In addition, the potential effect of drug use on test performance has not been extensively investigated. The literature on neuropsychological performance in intravenous drug users is sparse. However, it does suggest that some drugs, particularly opiates, can affect performance on neuropsychological testing (26). The issue is complicated by the variations in the pattern of drug use. Logically, factors such as duration of drug abuse, the actual drug/s used, or whether the patient is currently intoxicated or not might have direct effects on neuropsychological test performance. We addressed these issues in several ways. First, patients were not tested when they were acutely intoxicated. Second, we evaluated the relation of measures of recent substance use to neuropsychological test performance. Similar to the MACS group (3,27), we found no relationship. Still, this might reflect a limitation in our ability to reliably characterize drug use in ways that are most relevant to test performance. Finally, we attempted to control for past substance abuse, and although we found that older patients with histories of long-term substance use were more likely to perform poorly on some tests, independent effects of HIV status were still apparent. Our ability to prospectively relate changes in test performance to changes in disease severity suggests that we are truly assessing HIV-related changes and not simply changes due to drug use.

We also noted a relationship between clinically significant neurological changes and neuropsychological test performance. We have described a similar relationship in gay men (5). In combination, our studies of gay men and IDU cohorts suggest that (a) HIV can affect cognition early, even when the patient is medically asymptomatic; (b) cognitive difficulties worsen as the severity of HIV infection increases; and (c) the advent of clinically significant neurologic signs is associated with progression to more severe cognitive deficits. Our data suggest that the neurological and neuropsychological changes are manifestations of the central effect of HIV on the CNS.

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