ORIGINAL CONTRIBUTION

Factors Associated With Incident Human Immunodeficiency Virus–Dementia

Yaakov Stern, PhD; Michael P. McDermott, PhD; Steven Albert, PhD; Donna Palumbo, PhD; Ola A. Selnes, PhD; Justin McArthur, MD; Ned Sacktor, MD; Giovanni Schifitto, MD; Karl Kieburtz, MD, MPH; Leon Epstein, MD; Karen S. Marder, MD, MPH; for the Dana Consortium on the Therapy of HIV–Dementia and Related Cognitive Disorders

Background: Antecedents to human immunodeficiency virus–dementia (HIV-D) are poorly understood.

Objective: To identify risk factors for HIV-D.

Methods: Subjects who are positive for HIV who have CD4+ counts either below 200/µL or below 300/µL with evidence of cognitive impairment were enrolled in this study. Neurologic, cognitive, functional, and laboratory assessments were done semiannually for up to 30 months. Human immunodeficiency virus–dementia was diagnosed using American Academy of Neurology criteria for probable HIV-1–associated dementia complex.

Results: One hundred forty-six nondemented patients were enrolled, 45 of whom subsequently met criteria for incident HIV-D. In univariate analyses using the Cox proportional hazards regression model, the following variables were significantly associated with time to develop dementia: cognitive: abnormal scores on Timed Gait, Verbal Fluency, Grooved Pegboard, and Digit Symbol tests; attention-memory, psychomotor, and executive function domain scores; and the diagnosis of minor cognitive/motor disorder; neurologic and medical: increased abnormalities on the neurologic examination, extrapyramidal signs, history of HIV-related medical symptoms; functional: higher reported role or physical function difficulties. Depression was also a strong risk factor, along with sex, hematocrit, hemoglobin, and β_2-microglobulin levels. In a multivariate model that used cognitive domain scores, covariates with significant hazard ratios included depression, executive dysfunction, and the presence of minor cognitive/motor disorder.

Conclusion: Cognitive deficits, minor cognitive/motor disorder, and depression may be early manifestations of HIV-D.

Arch Neurol. 2001;58:473-479

FEW STUDIES have examined the risk factors for dementia in patients with human immunodeficiency virus (HIV) infection and these have focused primarily on demographic and medical factors. Previous studies have suggested that older age, history of HIV-related medical symptoms, lower hemoglobin levels, higher plasma viral load,[1] lower CD4+ cell counts,[2] and intravenous drug use[3] are associated with a greater risk of developing dementia. There has been some suggestion that zidovudine treatment is protective.[4] While many studies have demonstrated subtle cognitive changes in patients with HIV, and psychomotor slowing has been associated with an increased risk of dementia,[5] it is unclear whether these are unrelated to later dementia or represent the early stages of a dementing process. Similarly, diagnostic criteria have been proposed for HIV-associated minor cognitive/motor disorder (MCMD), which applies to HIV-positive patients with subtle cognitive, neurologic, and psychiatric symptoms but minimal functional complaints.[6] To our knowledge, the relationship between this diagnosis and a later diagnosis of dementia has been unexplored. This study prospectively followed up HIV-positive patients to evaluate which clinical features noted at the initial visit were associated with an increased risk of developing dementia. Potential correlates of incident dementia included demographic, medical, neurologic, functional, and psychiatric features as well as laboratory study results. In addition, all participants completed a battery of neuropsychological tests, allowing us to assess the predictive use of poor test performance and the presence of MCMD.

The affiliations of the authors appear in the acknowledgment section at the end of this article.

RESULTS

FOLLOW-UP

The follow-up experience of the 146 subjects was as follows: 146 at 6 months, 126 at 12 months, 99 at 18 months, 58 at 24

SUBJECTS AND METHODS

SAMPLE

The Dana Consortium on the Therapy of HIV–Dementia and Related Cognitive Disorders was formed in 1994 to recruit a cohort of HIV-infected individuals and examine risk factors for human immunodeficiency virus–dementia (HIV-D). Subjects were recruited from infectious disease clinics or through targeted advertising at 3 sites: Columbia University, New York, NY; Johns Hopkins University, Baltimore, Md; and the University of Rochester, Rochester, NY. Subjects were eligible for inclusion in the cohort if they were positive for HIV, had subjective reports of memory or concentration problems, and had $CD4^+$ cell counts either below 200/μL or below 300/μL, and cognitive impairment on neuropsychological testing (see "Neuropsychological Testing" subsection). They were excluded from the cohort if they were not ambulatory or if they had other neuropsychiatric conditions (eg, current or past central nervous system infection, head injury, or schizophrenia) that might cause cognitive impairment.

PROCEDURES

Assessments were performed semiannually for up to 30 months. At each visit, subjects underwent a neurologic examination; completed a battery of neuropsychological, functional, and psychiatric assessments; and had blood drawn for laboratory studies. Data collected from all of these evaluations were used to examine potential risk factors for incident HIV-D.

POTENTIAL CORRELATES OF INCIDENT HIV-D

Demographic Data

Age at initial visit, number of years of education, sex, race (white vs other), use of antiretroviral therapy at the initial visit, consumption of alcohol (at least weekly, less than weekly), and intravenous drug use during the year prior to enrollment (all intravenous drug users in our study had used drugs during that year) were used as independent variables.

Neurologic and Medical Examinations

A standardized history of HIV-related diagnoses was collected. The presence of any one diagnosis (yes, no) was used as an independent variable in our analyses. The neurologic examination was designed to capture signs associated with HIV-D. The macroneurologic examination created for the AIDS (Acquired Immunodeficiency Syndrome) Clinical Trials Group was used. The motor subscale (Part III) of the Unified Parkinson Disease Rating Scale[7] was administered to rate the presence or absence of extrapyramidal signs. Total scores for the macroneurologic examination and the Unified Parkinson Disease Rating Scale were dichotomized at or near their median values for analysis.

Neuropsychological Testing

The neuropsychological battery was designed to delineate HIV-D and MCMD. Where possible, tests recommended by the National Institute of Mental Health[8] and the AIDS Clinical Trials Group were included.

The 8 tests included in the core neuropsychological battery covered 6 domains. Verbal memory was assessed with the Rey Auditory Verbal Learning Test.[9] Visual memory was assessed with the Rey-Osterrieth Complex Figure Delayed Recall Test.[9] Constructional skills were assessed with the Rey-Osterrieth Complex Figure Immediate Recall Test. Psychomotor skills were measured with the Digit Symbol Test.[10] Motor skills were assessed with the Grooved Pegboard (dominant and nondominant hand)[11] and Timed Gait tests. Frontal systems were assessed with Verbal Fluency[12] and the Odd-Man-Out tests.[13,14]

Performance for each test was referenced to age- and education-appropriate norms. Norms for subjects with an educational level above high school were those reported for the Multicenter AIDS Cohort Study, a cohort of homosexual men[15]; norms for subjects with an education at the high school level or below were those reported for the ALIVE (AIDS Link to Intravenous Experience) cohort, a cohort of intravenous drug users.[16] For the Odd-Man-Out Test, unpublished norms from the homosexual men and intravenous drug user cohorts followed up at Columbia University[17,18] were used.

At the initial visit, the presence of cognitive impairment sufficient to meet study enrollment criteria was defined as performance 2 SDs below the appropriate mean on 1 test, or 1 SD below the mean on 2 tests. If Timed Gait performance was the only measure in which subjects scored 2 SDs below the mean, subjects were not considered to have met criteria for cognitive impairment.

For statistical analysis, neuropsychological test scores were dichotomized at 1 SD below the mean. For the Grooved Pegboard Test, a score greater than 1 SD below the appropriate norm for either the dominant or nondominant hand was considered to be a deficit. For Timed Gait performance, 1.5 SDs below the mean was used as the cutoff because of the nature of the available normative data.

Composite scores were created from the neuropsychological test battery with the aid of a principal component factor analysis using Varimax rotation. Three factors were identified that accounted for 68.4% of the total variance: attention-memory (Rey Auditory Verbal Learning Test—total score, trial 5 score, recall after interference, delayed recall, and correct recognition), psychomotor speed

months, and 29 at 30 months. There were 33 subjects who prematurely dropped out of the study, 23 because of death.

DEMOGRAPHICS

During the course of follow-up, 45 of the 146 subjects met criteria for incident HIV-D. Baseline characteristics of the subjects who did and did not become demented are listed in **Table 1** and **Table 2**. Compared with the subjects who did not become demented, those who became demented were more likely to be female, nonwhite, have higher macroneurologic and motor Unified Parkinson Disease Rating Scale scores, have lower hematocrit and hemoglobin levels, and have higher β_2-microglobulin levels. They were also more likely to have poorer role function, Karnofsky performance scale[23] and physical function scores, and higher Center for Epidemiologic Studies–Depression Scale scores. A Kaplan-Meier curve summarizing time to reach the dementia end

(Grooved Pegboard, dominant and nondominant hands and Digit Symbol Test), and executive function (Rey-Osterreith Complex Figure Immediate Recall Test, Odd-Man-Out Test, and Verbal Fluency Test). Composite scores for each of these factors were formed by first creating a z score for each neuropsychological test variable (using the Multicenter AIDS Cohort Study and ALIVE age- and education-based norms) and then averaging the z scores across the appropriate variables. These composite scores (average z scores) were dichotomized at 0 for statistical analysis.

We also used the presence of HIV-associated MCMD at the initial study visit as an independent variable. Subjects received this diagnosis if they had at least 2 deficits in cognitive tests (Digit Symbol Test, Rey Auditory Verbal Learning Test) or neurologic examination (finger agility, alternating movement, gait and coordination, limb coordination, emotional lability) and a deficit in at least 1 role function. These are the same criteria used in the diagnostic algorithm previously published based on American Academy of Neurology guidelines,[19] except in this study we did not require the role function deficit to be attributed to a cognitive source.

Functional Measures

Functional measures were chosen that would reflect the degree to which cognitive deficits compromised everyday function. Measures were derived from the Instrumental Activities of Daily Living (IADL) scales of Lawton and Brody,[20] the Katz Instrumental Activities of Daily Living/Lawton Personal Self-Maintenance Scale,[21] and the role functioning items of the Medical Outcomes Study.[22] Two functional outcomes that reflect stress and stamina were also included: the Karnofsky performance scale[23] and the Medical Outcomes Study physical function subscale.[22] All scores were dichotomized at or near their median values for analysis except for the Karnofsky performance scale, which was categorized as less than 80, 80 to 89, and 90 to 100. A score of less than 80 on this scale would suggest the need for assistance with some Instrumental Activities of Daily Living and an inability to work outside the home.

Psychiatric Assessment

The 20-item Center for Epidemiologic Studies–Depression Scale[24] was used to assess mood. The Center for Epidemiologic Studies–Depression Scale score was considered a continuous variable in the statistical analyses.

Laboratory Assessment

The $CD4^+$ cell counts, hemoglobin and β_2-microglobulin levels, and hematocrit were obtained. For analysis, these were treated as continuous variables. The $CD4^+$ cell count and β_2-microglobulin level were transformed using the natural logarithm.

DIAGNOSIS OF HIV-D

The primary end point for all analyses was the diagnosis of HIV-D. A standardized algorithm was used to diagnose HIV-D, based on data from the neurologic, neuropsychological, psychiatric, and functional assessments.[19] To receive the HIV-D diagnosis, subjects had to fulfill cognitive criteria based on a set of test cutoff scores, as well to report a deficit in at least 1 of 8 Instrumental Activities of Daily Living items. In addition subjects were required to meet fixed criteria for either neurologic or neuropsychiatric problems characteristic of HIV-D.

DATA ANALYSIS

The primary outcome variable for this investigation was the time from enrollment to the development of HIV-D, as determined at a subsequent follow-up visit. The original cohort consisted of 272 subjects; however, 71 of these were diagnosed as having HIV-D at the baseline visit. An additional 55 subjects did not have follow-up (postbaseline) assessments for HIV-D. All analyses were performed on the resulting cohort of 146 subjects. For subjects who did not develop HIV-D, the follow-up time was censored at the last available visit at which an assessment for HIV-D was performed.

The analytic strategy focused on examination of the associations between independent variables measured at the initial study visit (baseline) and the time to development of HIV-D. The Cox proportional hazards regression model was used.[25] An initial set of analyses was performed to examine these associations separately for each of the independent variables described earlier. A best subsets model selection procedure based on the score statistic[26] was used in conjunction with clinical judgment to help identify reasonable Cox proportional hazards regression models for time to development of HIV-D. Two sets of multiple regression analyses were performed: one that included all of the individual neuropsychological test scores as independent variables, and another that instead used the composite neuropsychological test scores. All Cox proportional hazards regression analyses included study site as a stratification factor.

Baseline variables were compared among subjects who did and did not reach the end point of HIV-D using t tests or χ^2 tests, as appropriate. A Kaplan-Meier curve was constructed for the time to dementia outcome.[25] All analyses were performed at the 5% level of significance (2-tailed).

point across the entire group of patients is shown in the **Figure**. In our cohort of 146 subjects, the estimated probability of incident HIV-D was approximately 25% at 12 months and 40% at 24 months.

UNIVARIATE ANALYSES

We first examined the associations between the presence of individual features noted on the initial evaluation and incident dementia; results are summarized in **Table 3** and **Table 4**. For individual tests in the neuropsychological battery, defective scores on Timed Gait performance, Verbal Fluency, Grooved Pegboard, and Digit Symbol tests were associated with an increased risk of incident dementia (Table 3). Also, the composite z scores for attention-memory, psychomotor speed, and executive function, as well as the diagnosis of MCMD at baseline, were associated with an increased risk of incident dementia (Table 3). Survival curves for patients with and without a diagnosis of MCMD at baseline are shown in the Figure.

Table 1. Summary Statistics for Demographic and Medical Variables Measured at the Initial Visit*

Variable†	All Subjects (N = 146)	Nondemented Subjects (n = 101)	Subjects Who Became Demented (n = 45)	*P*
Age, y	40.5 (7.1)	40.7 (6.8)	40.2 (7.8)	.69
Female sex	21.2	14.9	35.6	.005
Educational level, y	13.7 (2.9)	13.9 (2.8)	13.4 (3.0)	.39
White	52.1	57.4	40.0	.05
Antiretroviral therapy use (any type)	61.0	61.4	60.0	.87
Alcohol use (at least weekly, less than weekly)	35.2	34.0	37.8	.66
Intravenous drug use	12.0	9.5	17.7	.23
History of HIV-related diagnoses	32.2	27.7	42.2	.08
Macroneurological score >8	35.7	25.3	59.1	<.001
Motor UPDRS score >4	29.2	22.3	44.2	.009
Hematocrit	0.39 (0.44)	0.39 (0.40)	0.38 (0.50)	.05
Hemoglobin level, g/L	133 (16)	135 (14)	129 (18)	.05
β_2-Microglobulin level, nmol/L	297 (127)	280 (110)	323 (136)	.06
$CD4^+$ cell count, cells/μL	1.81 (1.47)	1.77 (1.46)	1.90 (1.50)	.49
Self-maintenance ADL score <18	4.1	3.0	6.7	.31
Instrumental ADL score <24	18.1	14.0	27.3	.06
Role function score <11	42.3	34.7	59.1	.006
Karnofsky performance score‡				
90-100	64.1	70.0	51.1	
80-89	20.7	16.0	31.1	.07
<80	15.2	14.0	17.8	
Physical function score <23	45.5	37.8	62.2	.006
CES-D score	18.4 (10.4)	15.8 (9.1)	24.4 (10.7)	<.001

*Values are expressed as either means (SDs) for continuous variables or percentages for categorical variables.
†HIV indicates human immunodeficiency virus; UPDRS, Unified Parkinson Disease Rating Scale; ADL, Activities of Daily Living, and CES-D, Center for Epidemiologic Studies–Depression Scale.
‡Scoring was determined using the scale created by Karnofsky et al.[23]

Table 2. Summary Statistics for Neuropsychological Tests Administered at the Initial Visit*

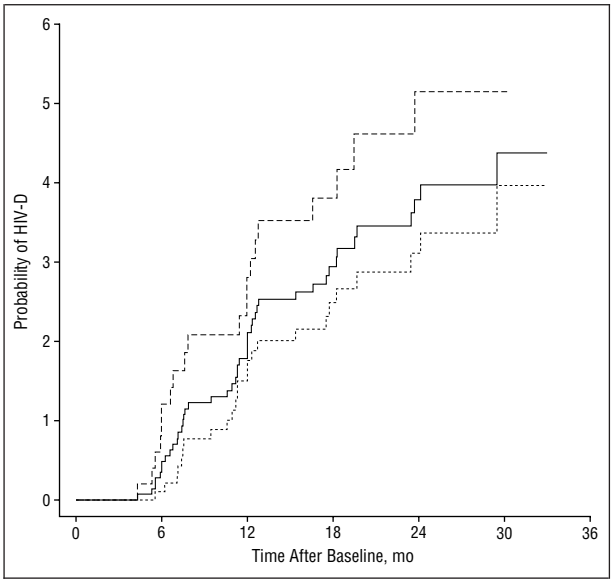
Test Name†	All Subjects (N = 146)	Nondemented Subjects (n = 101)	Subjects Who Became Demented (n = 45)	*P*
Rey AVLT, total score	33.6	33.7	33.3	.97
Rey-Osterrieth Complex Figure, Copy	28.2	24.5	36.4	.15
Rey-Osterrieth Complex Figure, Recall	23.2	19.4	31.8	.11
Timed Gait	33.3	26.9	46.7	.02
Grooved Pegboard	33.3	27.8	46.7	.03
Verbal Fluency	14.2	11.3	20.5	.15
Odd-Man-Out	15.9	15.1	18.0	.68
Digit Symbol	22.5	16.3	36.4	.008
Attention-memory	59.4	53.8	71.1	.05
Psychomotor speed	57.9	51.0	72.7	.02
Executive function	54.6	46.7	73.7	.005
MCMD	65.7	56.8	85.7	<.001

*All values are expressed as percentages of patients meeting criteria for performance deficit. Performance deficit was defined as 1 SD below the norm for all individual tests except for timed gait (1.5 SDs below norm). See "Potential Correlates of Incident HIV-D" subsection of the "Subjects and Methods" section for the sources of normative data. z score less than 0 for domain scores.
†AVLT indicates Auditory Verbal Learning Test; MCMD, minor cognitive/motor disorder.

For demographic and medical variables, female sex, race (nonwhite), increased abnormalities on the neurologic examination, the presence of extrapyramidal signs, and a history of HIV-related medical symptoms were all associated with an increased risk of incident HIV-D. Increased risk was also noted in subjects with higher reported role or physical function difficulties and with higher depression scores. Finally, lower hematocrits and hemoglobin levels and higher β_2-microglobulin levels were associated with an increased risk of HIV-D (Table 4).

MULTIVARIATE ANALYSES

Best-subsets model selection was used to generate a series of multivariate models for the HIV-D end point. A series of models containing 1 to 8 independent variables were generated. The first model considered demographic and medical variables and individual neuropsychological test results as potential covariates. The selected model included depression as assessed with the Center for Epidemiologic Studies–Depression Scale, sex, Digit



Cumulative of incidence of human immunodeficiency virus–dementia (HIV-D) in the study cohort (solid line). In addition to incidence in the entire cohort, incidence in patients with (long dashed line) and without (short dashed line) a diagnosis of minor cognitive/motor disorder at the initial visit is shown.

Table 3. Hazard Ratios for Univariate Analyses of Neuropsychological Test Results Administered at the Initial Visit*

Test Name†	Hazard Ratio	95% Confidence Interval	*P*
Rey AVLT, total score	1.16	0.62-2.17	.65
Rey-Osterrieth Complex Figure, Copy	1.30	0.70-2.42	.40
Rey-Osterrieth Complex Figure, Recall	1.44	0.75-2.75	.27
Timed Gait	2.99	1.46-6.10	.003
Grooved Pegboard	2.24	1.23-4.07	.008
Verbal Fluency	2.20	1.03-4.73	.04
Odd-Man-Out	1.29	0.55-3.02	.57
Digit Symbol	2.80	1.49-5.28	.002
Attention-memory	1.97	1.02-3.80	.04
Psychomotor speed	2.45	1.25-4.80	.009
Executive function	2.44	1.16-5.13	.02
MCMD	3.95	1.66-9.42	.002

**Performance deficit was defined as 1 SD below the norm for all individual tests except for Timed Gait (1.5 SDs below the norm). See "Potential Correlates of Incident HIV-D" subsection of the "Subjects and Methods" section for the sources of normative data. z score less than 0 for domain scores. The hazard ratio for a continuous variable may be interpreted as follows: for every 1-unit increase in that variable, the ratio of the risk of reaching the end point per unit of time is multiplied by the given hazard ratio.*

†AVLT indicates Auditory Verbal Learning Test; MCMD, minor cognitive/motor disorder.

Symbol Test, Verbal Fluency Test, history of HIV-related diagnoses, and Timed Gait performance (**Table 5**). A second, similar model was created using the cognitive domain scores. The selected model included depression, sex, executive function, history of HIV-related diagnoses, Timed Gait performance, and the presence of MCMD (**Table 6**).

Table 4. Hazard Ratios for Univariate Analyses of Demographic and Medical Variables Measured at the Initial Visit*

Variable†	Hazard Ratio	95% Confidence Interval	*P*
Age, y	1.00	0.95-1.04	.93
Female sex, %	1.99	1.04-3.78	.04
Educational level, y	0.96	0.86-1.06	.40
Antiretroviral therapy use (any type)	0.88	0.47-1.64	.69
Alcohol use (at least weekly, less than weekly)	1.08	0.59-1.98	.81
Intravenous drug use	1.52	0.62-3.73	.36
White	0.53	0.28-1.00	.05
History of HIV-related diagnoses	1.95	1.06-3.56	.03
Macroneurological score >8	3.48	1.89-6.40	<.001
Motor UPDRS score >4	2.47	1.29-4.73	.006
Hematocrit	0.90	0.84-0.97	.004
Hemoglobin level, g/L	0.76	0.62-0.92	.006
β_2-Microglobulin level, log	3.18	1.16-8.73	.02
$CD4^+$ cell count, log	0.98	0.76-1.25	.85
Self-maintenance ADL score <18	1.67	0.50-5.57	.41
Instrumental ADL score <24	1.70	0.87-3.33	.12
Role function score <11	2.23	1.22-4.08	.01
Karnofsky performance score‡			
90-100	1.00		
80-89	2.39	1.21-4.72	.04
<80	1.35	0.57-3.17	
Physical function score <23	2.49	1.34-4.60	.004
CES-D score	1.06	1.03-1.10	<.001

**The hazard ratio for a continuous variable may be interpreted as follows: for every 1-unit increase in that variable, the ratio of the risk of reaching the end point per unit of time is multiplied by the given hazard ratio.*

†HIV indicates human immunodeficiency virus; UPDRS, Unified Parkinson Disease Rating Scale; ADL, Activities of Daily Living; and CES-D, Center for Epidemiologic Studies–Depression Scale.

‡Scoring was determined using the scale created by Karnofsky et al.[23]

Table 5. Selected Multivariate Model, Including Individual Neuropsychological Test Results*

Variable†	Hazard Ratio	95% Confidence Interval
CES-D Score	1.05	(1.02-1.08)
Female sex	1.60	(0.70-3.62)
History of HIV-related diagnoses	1.55	(0.76-3.15)
Digit Symbol Test‡	2.23	(1.02-4.89)
Verbal Fluency Test‡	2.74	(1.10-6.82)
Timed Gait Test§	2.70	(1.22-5.96)

**The hazard ratio for a continuous variable may be interpreted as follows: for every 1-unit increase in that variable, the ratio of the risk of reaching the end point per unit of time is multiplied by the given hazard ratio.*

†CES-D indicates Center for Epidemiologic Studies–Depression Scale; HIV, human immunodeficiency virus.

‡Performance deficit was defined as 1 SD below the norm for all individual tests.

§Performance deficit was defined as 1.5 SDs below the norm for timed gait.

COMMENT

This prospective study identified a set of variables that were associated with increased risk of dementia in a co-

Members of the Dana Consortium on the Therapy of HIV–Dementia and Related Cognitive Disorders

Columbia University, New York, NY: Karen S. Marder, MD, MPH; Yaakov Stern, PhD; Steven Albert, PhD; George Todak, MSW; Ronda Clouse, RN; Carmen Polanco, MS; Richard Mayeux, MD, MS. *Johns Hopkins University, Baltimore, Md:* Ned Sacktor, MD; Ola A. Selnes, PhD; Deborah Hasenaue, MA; Deneen Esposito, BA; Justin McArthur, MB,BS, MPH. *University of Rochester, Rochester, NY:* Giovanni Schifitto, MD; Michael P. McDermott, PhD; Donna Palumbo, PhD; Connie Orme, BA; Charlyne Hickey, RN; Cindy Casaceli, MBA; Lisa Rumfola, RN; Carol Zimmerman, RN; Karl Kieburtz, MD, MPH. *Northwestern University Medical School, Chicago, Ill:* Leon Epstein, MD.

Table 6. Selected Multivariate Model, Including Neuropsychological Summary Scores*

Variable†	Hazard Ratio	95% Confidence Interval
CES-D score	1.06	1.02-1.10
Female sex	1.46	0.65-3.27
Executive function test‡	3.71	1.59-8.68
History of HIV-related diagnoses	1.90	0.87-4.12
Timed Gait Test§	2.17	0.95-4.97
MCMD	3.47	1.19-10.13

**The hazard ratio for a continuous variable may be interpreted as follows: for every 1 unit increase in that variable, the ratio of the risk of reaching the endpoint per unit of time is multiplied by the given hazard ratio.*

†CES-D indicates Center for Epidemiologic Studies–Depression Scale; HIV, human immunodeficiency virus; and MCMD, minor cognitive/motor disorder.

‡Based on z scores that were dichotomized at 0.

§Performance deficit was defined as 1.5 SDs below the norm for Timed Gait.

hort of HIV-positive subjects identified as having cognitive deficits and/or severe immunosuppression. In the univariate analyses, variables were identified in all of the categories evaluated. For medical variables, similar to observations in a separate cohort studied by McArthur et al,[1] an increased risk of dementia was associated with history of HIV-related medical symptoms and lower hemoglobin levels. In addition, lower hematocrit and increased β_2-microglobulin levels were associated with greater risk, consistent with previous observations linking these variables with cognitive deficits and dementia in HIV-D. The observation that abnormalities on the neurologic examination and the presence of extrapyramidal signs were associated with an increased risk is also consistent with the observation that these features are typically noted as parts of the AIDS dementia complex. It is, therefore, logical to expect that in some cases their presence would precede the actual onset of dementia. Similarly, depression is one of the defining features of the dementia complex and, thus, logically might precede the onset of the entire syndrome. Lower role and physical function scores were associated with an increased risk of dementia; this may represent the earliest manifestation of the dementing process.

Poor performance on a series of neuropsychological tests, including Timed Gait, Verbal Fluency, Grooved Pegboard, and Digit Symbol, was also associated with an increased risk of incident dementia. Similarly, poorer performance in the following cognitive domains was associated with greater risk: attention-memory, psychomotor, and executive function. In an analysis of data from the Multicenter AIDS Cohort Study, Sacktor et al[5] reported that sustained psychomotor slowing was associated with an increased hazard of dementia, AIDS, and death. Cognitive decline in other domains was not predictive, however. Their analysis differs from ours because we considered only performance at the initial visit, as opposed to change in performance over time. In addition, the current study specifically recruited individuals with cognitive deficits or advanced immunosuppression, perhaps increasing the probability that they would become demented.

The association between cognitive performance at baseline and later dementia suggests that poorer performance could represent the earliest sign of a dementing process. However, the significance of mild cognitive changes in individuals who are HIV positive has been unclear. To our knowledge, it has not been previously established whether the presence of subtle cognitive deficits has any implications for the later development of dementia. Further, it has not been clear whether the presence of MCMD has any relation to dementia. This study suggests that at least in some cases, cognitive deficits and MCMD are related to the later advent of dementia.

Female sex may also be a risk factor for dementia. This observation is consistent with previous reports that HIV-positive women have more rapid progression of neurologic signs and symptoms.[27]

The multivariate models presented herein were selected from several candidate models and require validation in other samples. Still, they provide some insight into the independent contribution of the variables identified in the univariate analyses. It is notable that sex, depression, Timed Gait performance, and a history of HIV-related diagnoses are included in both models. In addition, both models implicate poorer executive function as an independent risk factor for dementia. Since executive dysfunction is often one of the earliest cognitive changes noted in HIV, this suggests that there may be a common underlying mechanism between dementia and early cognitive change. Finally, in the second model presented, MCMD remained a significant risk factor for dementia, independent from depression and executive dysfunction. Thus, the presence of this syndrome seems to have unique predictive value, over and above the presence of some features that contribute to its diagnosis.

Accepted for publication July 28, 2000.

From the Departments of Neurology (Drs Stern, Albert, and Marder) and Psychiatry (Dr Stern), Sergievsky Center and the Taub Institute, Columbia University College of Physicians and Surgeons, New York, NY; New York

Presbyterian Hospital, New York (Drs Stern and Marder); Departments of Neurology and Biostatistics, University of Rochester Medical Center, Rochester, NY (Dr McDermott); Department of Neurology (Drs Palumbo, Schifitto, and Kieburtz) and Biostatistics (Drs Palumbo and Schifitto), University of Rochester School of Medicine and Dentistry, Rochester; Department of Neurology (Drs Selnes and McArthur) and Epidemiology (Dr McArthur), The Johns Hopkins University School of Medicine, Baltimore, Md; Department of Neurology, Johns Hopkins Bayview Medical Center, Baltimore (Dr Sacktor); and the Department of Pediatrics, Children's Memorial Hospital, Northwestern University Medical School, Chicago, Ill (Dr Epstein). A complete list of the members of the Dana Consortium on the Therapy of HIV–Dementia and Related Cognitive Disorders appears on page 478.

This study was supported by the Charles A. Dana Foundation, New York, NY, and grants RR00645 and 5MO1 00044 from the National Institutes of Health, Bethesda, Md.

Corresponding author and reprints: Yaakov Stern, PhD, Sergievsky Center, 630 W 168th St, New York, NY 10032 (e-mail: ys11@columbia.edu).

REFERENCES

1. McArthur JC, Hoover DR, Bacellar H, et al, for the Multicenter AIDS Cohort Study. Dementia in AIDS patients: incidence and risk factors. *Neurology.* 1993;43:2245-2252.
2. Childs EA, Lyles RH, Selnes OA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology.* 1999;52:607-613.
3. Chiesi A, Vella S, Dally LG, et al, for AIDS in Europe Study Group. Epidemiology of AIDS dementia complex in Europe. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;11:39-44.
4. Baldeweg T, Catalan J, Gazzard BG. Risk of HIV dementia and opportunistic brain disease in AIDS and zidovudine therapy. *J Neurol Neurosurg Psychiatry.* 1998;65:34-41.
5. Sacktor NC, Bacellar H, Hoover DR, et al. Psychomotor slowing in HIV infection: a predictor of dementia, AIDS and death. *J Neurovirol.* 1996;2:404-410.
6. Report of a Working Group of the American Academy of Neurology AIDS Task Force. Nomenclature and research case definitions for neurological manifestations of human immunodeficiency virus type-1 (HIV-1) infection. *Neurology.* 1991;41:778-785.
7. Fahn S, Marsden C, Calne D. *Recent Developments in Parkinson's Disease.* Florham Park, NJ: Macmillan Healthcare Information; 1987.
8. Butters N, Grant I, Haxby J, et al. Assessment of AIDS-related cognitive changes: recommendations of the NIMH Workshop on Neuropsychological Assessment Approaches. *J Clin Exp Neuropsychol.* 1990;12:963-978.
9. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique. *Arch Psychol.* 1941;28:286-340.
10. Wechsler D. *Wechsler Adult Intelligence Scale-Revised.* New York, NY: Psychological Corp; 1981.
11. Klove H. Clinical neuropsychology. *Med Clin North Am.* 1963;46:1647-1658.
12. Benton AL, Hamsher KD. *Multilingual Aphasia Examination.* Iowa City: University of Iowa; 1976.
13. Flowers KA, Robertson C. The effects of Parkinson's disease on the ability to maintain a mental set. *J Neurol Neurosurg Psychiatry.* 1985;48:517-529.
14. Richards M, Cote LJ, Stern Y. Executive function in Parkinson's disease: set-shifting or set-maintenance? *J Clin Exp Neuropsychol.* 1993;15:266-279.
15. Selnes OA, Jacobson L, Machado AM, et al, for the Multicenter AIDS Cohort Study. Normative data for a brief neuropsychological screening battery. *Percept Mot Skills.* 1991;73:539-550.
16. Concha M, Selnes OA, McArthur J, et al. Normative data for a brief neuropsychologic test battery in a cohort of injecting drug users. *Int J Addict.* 1995;30:823-841.
17. Stern Y, Marder K, Bell K, et al. Multidisciplinary baseline assessment of homosexual men with and without human immunodeficiency virus infection, III: neurologic and neuropsychological findings. *Arch Gen Psychiatry.* 1991;48:131-138.
18. Marder K, Stern Y, Malouf R, et al. Neurologic and neuropsychological manifestations of human immunodeficiency virus infection in intravenous drug users without acquired immunodeficiency syndrome: relationship to head injury. *Arch Neurol.* 1992;49:1169-1175.
19. The Dana Consortium on Therapy for HIV–Dementia and Related Cognitive Disorders. Clinical confirmation of the American Academy of Neurology algorithm for HIV-1-associated cognitive/motor disorder. *Neurology.* 1996;47:1247-1253.
20. Lawton MP, Brody EM. Assessment of older people: self-maintaining and Instrumental Activities of Daily Living. *Gerontologist.* 1969;9:179-186.
21. Katz S, Ford A, Moskowitz R, et al. Studies of illness in the aged: the index of ADL. *JAMA.* 1963;183:914-919.
22. Stewart AL, Ware JE. *Measuring Function and Well-being: The Medical Outcomes Study Approach.* Durham, NC: Duke University Press; 1993.
23. Karnofsky DA, Abelman WH, Carver LF, et al. The use of nitrogen mustards in the palliative treatment of carcinoma. *Cancer.* 1948;1:634-656.
24. Radloff LL. The CES-D: a self-report depression scale for research in the general population. *Appl Psychol Meas.* 1977;1:385-401.
25. Cox DR, Oakes D. *Analysis of Survival Data.* London, England: Chapman & Hall; 1984.
26. SAS Institute Inc. *SAS/STAT Software: Changes and Enhancements Through Release 6.11.* Cary, NC: SAS Institute Inc; 1996.
27. Liu X, Marder K, Stern Y, et al. Gender differences in HIV-related neurological progression in a cohort of injecting drug users followed for 3.5 years. *J Neuro-AIDS.* 1996;1:17-29.