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Clinical Report

HIV-associated cognitive impairment before and after the advent of combination therapy

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The objective of this study was to describe the occurrence of HIV dementia and neuropsychological testing abnormalities in a new cohort of HIV-seropositive individuals at high risk for HIV dementia and to compare these results to a cohort before the advent of highly active antiretroviral therapy (HAART). HAART has been associated with improvements in cognitive performance in some HIV-infected patients. However, it is uncertain whether HAART has changed the frequency of specific neurocognitive abnormalities. Baseline data from 272 HIV-seropositive subjects in the Dana cohort recruited from January, 1994, to December, 1995, and 251 HIV-seropositive subjects in the Northeastern AIDS Dementia Consortium (NEAD) cohort recruited from April, 1998, to August, 1999, were compared. Participants in both cohorts received nearly identical assessments. After adjusting for differences in age, education, gender, race, and CD4 count between the two cohorts, there were no differences in the occurrence of HIV dementia or abnormalities either 1 SD or 2 SDs below established norms for any of the neuropsychological tests. Even though HAART has reduced the incidence of HIV dementia, HIV-associated cognitive impairment continues to be a major clinical problem among individuals with advanced infection. *Journal of NeuroVirology* (2002) **8,** 136–142.

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Introduction

In the early 1990s, human immunodeficiency virus type 1 (HIV-1)-associated dementia complex (HIV dementia) (Janssen *et al*, 1991) affected 16% of patients with acquired immune deficiency syndrome (AIDS) and had an annual incidence of 7% among patients with AIDS (McArthur *et al*, 1993). During this time period, HIV dementia was frequently a complication that progressed over several months to death (Bouwman *et al*, 1998). The introduction of highly active antiretroviral therapy (HAART) in 1996 has resulted in suppression of systemic HIV-1 viral load and improvements in survival for patients with HIV infection (Brodt *et al*, 1997). HAART has also been associated with an improvement in cognitive performance (Sacktor *et al*, 2000a) and a decreased incidence of HIV dementia (Brodt *et al*, 1997; Sacktor *et al*, 1999), as well as improvement in neuroimaging markers of HIV dementia (Chang *et al*, 1999; Sacktor *et al*, 2000b). However, despite these advances, therapeutic failures with HAART still occur in about 50% of patients (Fatkenheuer *et al*, 1997). It remains uncertain whether the frequency of specific neurocognitive abnormalities in HIV infection has changed.

In January 1994, the Charles A. Dana Foundation established a consortium of three centers (Columbia

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University, Johns Hopkins University, and the University of Rochester) to recruit a cohort of individuals (Dana cohort) at high risk for the development of HIV dementia to characterize their neurologic, cognitive, psychiatric, and functional deficits (The Dana Consortium, 1996). At this time, monotherapy or dual therapy were the predominant forms of treatment, and a significant number of individuals were still naive to antiretroviral medications. In April, 1998, a new National Institute of Neurological Disorders and Stroke (NINDS)-funded consortium of three centers (Columbia University, Johns Hopkins University, and the University of Rochester) known as the Northeastern AIDS Dementia Consortium initiated a cohort study (NEAD cohort) which was designed to investigate the relationships between viral load, immune activation, and progression of neurological dysfunction in HIV infection. In November, 1999, a fourth center at Northwestern University was added to the consortium. In contrast to antiretroviral treatment in the Dana cohort, HAART encompassing triple antiretroviral therapy was the predominant form of treatment when the NEAD cohort was established. The current study describes the characteristics of the NEAD cohort, notes the occurrence of HIV dementia and specific neuropsychological testing abnormalities at baseline in the NEAD cohort, and compares the occurrence of HIV dementia and specific neuropsychological testing abnormalities at baseline in the two longitudinal cohorts, one pre-HAART (Dana cohort) and the other post-HAART (NEAD cohort), both recruiting individuals with a high risk for HIV dementia, using nearly identical assessment tools.

Results

Recruitment and composition of the cohort

Recruitment sources for each site were described previously (The Dana Consortium, 1996). For the 272 subjects in the Dana cohort, 42.3% were from the Johns Hopkins University site, 34.9% were from the Columbia University site, and 22.8% were from the University of Rochester site. Similarly, for the 251 subjects in the NEAD cohort, 45.0% were from the Johns Hopkins University site, 31.9% were from the Columbia University site, and 23.1% were from the University of Rochester site.

Antiretroviral therapy

In the Dana cohort, 44% of subjects were on monotherapy, 11% of subjects were on dual therapy, and 43% of subjects were on no therapy. In contrast, in the NEAD cohort, 68% of subjects were on HAART, and 10% of subjects were on dual therapy (defined as two antiretroviral drugs [without a protease inhibitor]). In the Dana cohort, the most common antiretroviral drugs used were zidovudine (45.2%) and didanosine (15.1%). In contrast, in the NEAD cohort, the majority of subjects were on HAART regimes, including either stavudine (37.2%) or zidovudine (35.6%), lamivudine (56.8%), and a protease inhibitor.

Table 1 Demographic characteristics of Dana and NEAD cohorts

Recruitment years	*Dana n = 272 1994–1995*	*NEAD n = 251 1998–1999*	P *value*
Age: years, mean (SD)	39.7 (7.5)	41.4 (7.3)	0.01
Male gender (%)	77.9	66.5	0.004
Ethnicity (% White/Black/Hispanic)	50/40/7	21/66/12	<0.0001
Education: years, mean (SD)	13.5 (2.9)	12.3 (2.1)	<0.0001
AIDS defining illness (%)	37.9	61.8	<0.001
CD4 + count, mean (SD)	177.9 (182.2)	129.1 (85.1)	0.71*

*P value from t-test comparing log-transformed CD4 counts.

Demographic characteristics

The baseline demographic characteristics of the Dana and NEAD cohorts are shown in Table 1. Subjects in the NEAD cohort were slightly older (mean [SD] = 41.4 [7.3], $P = 0.01$) than subjects in the Dana cohort (mean [SD] = 39.7 [7.5]). Compared to other cohorts of HIV seropositive individuals, the Dana and NEAD cohorts both include a high proportion of women and subjects with minority ethnicity. As shown in Table 1, a greater proportion of subjects in the NEAD cohort were women (33% *versus* 22%, $P = 0.004$), and African-American (66% *versus* 40%, $P < 0.001$), and had fewer years of education (mean [SD] = 12.3 (2.1) *versus* 13.5 (2.9), $P < 0.0001$) compared to subjects in the Dana cohort. Due to the inclusion criteria there was no major difference in the CD4 lymphocyte count between the two cohorts, although subjects in the NEAD cohort were more likely to have had a previous AIDS-defining opportunistic infection (62% *versus* 38%, $P < 0.001$) than subjects in the Dana cohort. It should be noted that the history of an AIDS-defining illness variable was defined differently for the NEAD and Dana cohorts, with more AIDS defining illnesses in this variable in the NEAD cohort than for the equivalent variable in the Dana cohort.

Neurologic examination

The macroneurological exam score was lower in the NEAD cohort (mean [SD] = 6.9 [5.2]) compared to the Dana cohort (mean [SD] = 8.4 [5.6]) ($P = 0.002$), suggesting less impairment in the neurological examination in the NEAD cohort. However, there was no difference in the motor Unified Parkinson's Disease Rating Scale (UPDRS) score (NEAD—mean [SD] = 3.4 [4.9] *versus* Dana—mean [SD] = 4.8 [7.1]) ($P = 0.21$) between the two cohorts. There was also no difference in the frequency of symptomatic distal sensory polyneuropathy (NEAD—34.5% *versus* Dana—34.7%) between the two cohorts. However, the frequency of asymptomatic distal sensory polyneuropathy was slightly greater in the NEAD cohort (29.3%) compared to the Dana cohort (20.1%) ($P = 0.03$).

Table 2 Dementia classification for subjects in the Dana and NEAD cohorts

	Dana *n = 272*	*NEAD* *n = 251*	P *value*
AAN Classification (%)*			0.10
Normal	25.0	30.5	
HIV-Minor cognitive/motor disorder	47.7	37.4	
HIV dementia	27.3	32.1	
Overall Neuropsychologist Impression (%)			0.17
Unimpaired	25.7	24.0	
Mild impairment	51.1	56.2	
Moderate impairment	18.7	16.1	
Severe impairment	4.5	3.7	

*Using a computerized algorithm as described previously (The Dana Consortium, 1996).

Dementia and neuropsychological test assessments

As shown in Table 2, HIV-associated minor cognitive/motor disorder, (HIV-MC/MD) was the most common AAN classification for subjects in both the Dana and NEAD cohorts (Janssen *et al*, 1991). There were similar proportions of subjects rated as nonimpaired and having HIV dementia in both cohorts. The overall neuropsychologist's impression was also similar between the two cohorts.

The unadjusted mean (SD) score for each of the neuropsychological tests is shown in Table 3. The mean (SD) scores of subjects in the NEAD cohort were worse in tests of verbal memory (Total score [$P = 0.0001$], Trial 5 score [$P = 0.0002$], Delayed recall [$P = 0.003$], Recognition score [$P = 0.002$]), visual memory (Rey Complex Figure Recall [$P = 0.004$]), constructional skills (Rey Complex Figure Copy [$P = 0.03$]), and frontal systems (verbal fluency [$P = 0.03$], Odd Man Out tests [$P = 0.05$]). However, after adjusting for the differences in age, education, gender, race, and CD4 count between the two cohorts, there were no statistically significant differences in the mean score or in the frequency of abnormalities either 1 SD or 2 SDs below the mean for any of the neuropsychological tests (see Table 3).

When analyses were restricted to subjects having a CD4 count $\leq$200 at baseline, the results were similar to those for the full cohorts. Additional analyses were performed that compared the frequencies of HIV dementia and neuropsychological testing abnormalities among subjects in the Dana cohort, subjects in the NEAD cohort taking HAART, and subjects in the NEAD cohort not taking HAART. Again, after adjusting for differences in age, education, gender, race, and CD4 count among the three groups of subjects, there were no statistically significant differences among the groups in the proportions of subjects who were rated as not impaired or as having HIV dementia. The neuropsychologist's overall impression was also similar among the three groups of subjects. There were no significant differences among the groups in mean scores or in the frequencies of abnormalities either 1 SD or 2 SDs below the mean for any of the neuropsychological tests.

Table 3 Neuropsychological testing for subjects in the Dana and NEAD cohorts

	Dana *n = 272*	*NEAD* *n = 251*	P *value**
Verbal and visual memory			
RAVLT—Total, mean (SD)	44.6 (11.8)	41.0 (8.9)	0.33
2 SD below norm (%)	13.4	10.4	0.16
RAVLT—Trial 5, mean (SD)	11.0 (2.8)	10.1 (2.3)	0.15
2 SD below norm (%)	13.0	14.0	0.37
RAVLT—Delayed recall, mean (SD)	8.7 (3.6)	7.9 (3.0)	0.59
2 SD below norm (%)	8.4	5.6	0.21
RAVLT—Recognition score, mean (SD)	13.0 (2.4)	12.3 (2.4)	0.30
2 SD below norm (%)	14.1	14.0	0.99
RCF—Immediate recall, mean (SD)	16.6 (7.9)	14.7 (7.5)	0.40
2 SD below norm (%)	7.6	10.5	0.06
Psychomotor and motor speed			
GP-nondominant hand, mean (SD)	84.5 (22.6)	87.3 (22.7)	0.42
2 SD below mean (%)	20.3	16.2	0.48
GP-dominant hand, mean (SD)	78.3 (23.5)	77.7 (18.2)	0.08
2 SD below mean (%)	20.0	12.6	20.13
Symbol Digit, mean (SD)	47.1 (14.4)	45.6 (11.7)	0.19
2 SD below mean (%)	11.0	6.8	0.34
Constructional			
RCF—copy, mean (SD)	30.1 (6.8)	28.8 (6.9)	0.70
2 SD below norm (%)	22.8	25.7	0.61
Frontal/Executive			
Verbal fluency (FAS), mean (SD)	38.8 (14.7)	36.2 (11.7)	0.32
2 SD below norm (%)	3.4	3.6	0.20
Odd man out	36.3 (4.9)	35.4 (5.5)	0.94
2 SD below norm (%)	13.3	12.9	0.86

RAVLT—Rey Auditory Verbal Learning Test.
RCF—Rey Complex Figure.
GP—Grooved pegboard.
*Adjusted for age, education, gender, race, and CD4 count.

Discussion

Despite the introduction of HAART in 1996, HIV-associated cognitive impairment persists among HIV-seropositive individuals with advanced infection. HIV-associated cognitive impairment continues to be characterized by prominent deficits in psychomotor/motor speed, verbal and visual memory, as well as other cognitive domains.

One should not conclude that the incidence of HIV dementia in the era of HAART is unchanged from these results. The Dana and NEAD cohorts do not represent all subjects with HIV infection. These cohorts have purposefully recruited HIV-seropositive individuals at high risk for HIV dementia and cognitive impairment, by virtue of having a CD4 count $<$200 or by demonstrating cognitive impairment with a CD4 count $<$300. Thus, epidemiological results are only relevant to this select group of patients, and

not all individuals with HIV infection. However, as of 1996, HIV-seropositive subjects with a CD4 count <200 represented 53% of the US population with HIV infection receiving medical care (Bozette *et al*, 1998).

There were several important demographic differences between subjects in the Dana cohort and subjects in the NEAD cohort. The NEAD cohort had a greater proportion of women, African-Americans, and subjects with fewer years of education. These demographic changes between HIV-seropositive individuals in the early 1990s and HIV-seropositive individuals in the late 1990s are representative of epidemiological changes in HIV infection in the United States [Centers for Disease Control and Prevention (CDC), 1996]. In 1996, according to the CDC, African-Americans represented 41% of adults/adolescents reported with AIDS, exceeding the proportion who are Caucasian for the first time (Centers for Disease Control and Prevention, 1996). Rates in women, those who are injecting drug users, and those who contract infection through heterosexual contact have continued to rise in the United States. Thus, the NEAD cohort, given its high representation of minorities and women, will provide an excellent resource to evaluate neurocognitive dysfunction among those individuals most vulnerable for HIV-induced neurological dysfunction in the coming decade.

In addition to differences in demographics, compared to Dana cohort participants, subjects in the NEAD cohort may represent individuals with more advanced infection, as suggested by a greater proportion of subjects with a previous AIDS-defining illness (excluding CD4 count <200). Because HIV-associated cognitive impairment is associated with more advanced immunodeficiency, the lack of a difference in the occurrence of cognitive impairment between the Dana and NEAD cohorts could represent a beneficial effect of HAART on a group of subjects (the NEAD cohort) more likely to have cognitive impairment because of more advanced infection. However, another explanation is that the history of an AIDS-defining illness variable was defined differently for the NEAD and Dana cohorts, with more AIDS defining illnesses in this variable in the NEAD cohort than for the equivalent variable in the Dana cohort. This may account for the increased frequency of an AIDS defining illness among NEAD cohort subjects compared to Dana cohort participants. Of note, there was no major difference in the distribution of CD4 counts between the two cohorts at the baseline visit for each cohort. Data on the lifetime CD4 count nadir is not available for subjects in the Dana and NEAD cohorts to determine whether NEAD cohort subjects had a history of greater immune dysfunction.

Another potential difference between the two cohorts which could not be directly compared is the effect of psychiatric comorbidity. Different assessments of mood were used for the two cohorts. The extent to which subthreshold major depression at baseline may be contributing to cognitive impairment, and whether the frequency and extent of psychiatric comorbidity is different between the two cohorts is unclear. Further studies examining the role of psychiatric disease in subjects in the NEAD cohort are underway.

A factor that could account for a lack of difference in neuropsychological test results between the two cohorts is poor medication adherence among subjects in the NEAD cohort. If subjects in the NEAD cohort were not adherent to their antiretroviral medications, then they would be unlikely to have durable suppression of plasma and cerebrospinal fluid HIV RNA levels, and thus may resemble subjects in the Dana cohort on monotherapy and no therapy. Measures of adherence are not available for either cohort. Another potentially confounding factor is that some of the cognitive abnormalities may relate to complications of heavy drug/alcohol use rather than HIV itself. Equivalent measures of drug use are not available for the two cohorts.

An unsuppressed plasma or cerebrospinal fluid HIV RNA level was not part of the inclusion criteria. High plasma HIV RNA levels prior to neuropsychological testing have been associated with a greater risk for developing HIV dementia (Childs *et al*, 1999), and several reports demonstrate that elevated cerebrospinal fluid viral load correlates with neurocognitive dysfunction (Ellis *et al*, 1997; McArthur *et al*, 1997). Patients with unsuppressed viral load with a CD4 count >300 may also represent individuals at high risk for cognitive impairment.

The NEAD consortium is a diverse cohort of subjects with advanced infection that will provide a unique opportunity to investigate the relationships between plasma and cerebrospinal fluid viral load, markers of immune activation in the plasma, cerebrospinal fluid, and brain, and the progression of neurologic dysfunction and functional impairment. Both cross-sectional and longitudinal data from the NEAD consortium, a 5-year study, will be useful in investigating these associations.

Materials and methods

Subjects

Participants in both the Dana and NEAD cohorts were recruited with identical inclusion and exclusion criteria as described previously for the Dana consortium (The Dana Consortium, 1996). Inclusion criteria for the NEAD (and Dana) cohorts were HIV seropositive based on self-report and confirmed by ELISA and Western blot; capable of providing informed consent; ambulatory at initial visit; and either meeting Centers for Disease Control and Prevention criteria for AIDS (CD4 count of <200) or with a CD4 count of <300 and demonstrating cognitive impairment (defined as performance on neuropsychological testing that was 2 SDs below the appropriate mean on one test or 1 SD

below the mean on two tests). Exclusion criteria were current or past opportunistic CNS infection at study entry, with the exception of treated neurosyphilis; history or current clinical evidence of schizophrenia or current severe affective disorder believed to explain the subject's cognitive impairment; and history of chronic neurologic disorders such as multiple sclerosis or uncontrolled epilepsy. Current alcohol or drug use was discouraged but was not grounds for exclusion; however, subjects were not examined while intoxicated.

Historical information and neurologic examination
Clinical data assessments for both the Dana and NEAD cohorts were nearly identical. These procedures have been described previously for the Dana cohort (The Dana Consortium, 1996). For the NEAD (and Dana) cohort, a structured questionnaire was administered to each subject to obtain demographic information and medical history, including HIV-1-associated illnesses and medications. The neurological examination included the macroneurologic examination created for the AIDS Clinical Trials Group (ACTG) and the motor portion of the Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn *et al*, 1987).

Neuropsychological examination
The neuropsychological examinations for both the Dana and NEAD cohorts were identical. The neuropsychological testing battery covered seven domains. Verbal memory was assessed with the Rey Auditory Verbal Learning Test (Rey, 1941). Impaired performance on any of the components of the test was evaluated (Total score, Trial 5 score, Delayed Recall, Recognition score, and Immediate Recall). Visual memory was assessed with the Rey Complex Figure Recall test (Rey, 1941). Constructional skills were assessed with the Rey Complex Figure Copy (Rey, 1941). Psychomotor performance was measured with the Digit Symbol test (Wechsler, 1981). The Trail Making test (Reitan, 1958; Reitan, 1979) was also administered in the NEAD cohort, but these results were not used in the clinical characterizatio n of subjects so that identical criteria could be used for both cohorts. Motor speed was assessed with the Grooved Pegboard test (GP) with either the dominant or nondominant hand (Klove, 1963). Frontal systems were assessed with the Verbal Fluency (Benton, 1955) and the Odd Man Out tests (Flowers and Robertson, 1985). Reaction time was measured with the California Computerized Assessment Package (CALCAP) (Miller *et al*, 1991). General intellectual performance was assessed with the National Adult Reading Test (Nelson and O'Connell, 1978; Nelson, 1982).

An age and education adjusted Z score was used to quantify performance for each of the neuropsychological tests. Scores for subjects with $\leq$12 years of education were compared with norms established by the AIDS Link to Intravenous Experience (ALIVE) study (Concha *et al*, 1995). In the ALIVE study the mean (standard deviation [SD]) age was 24 (6.9) years, 73.7% were men, 95% were African-Americans, and the mean (SD) years of education for the entire study was 11.6 (2.0) years. Scores for subjects with >12 years of education were compared with norms established by the Multicenter AIDS Cohort Study (MACS) (Selnes *et al*, 1991). In the MACS study, the mean (SD) age was 37 (7.6) years, 100% were men, 92% were Caucasian, and the mean (SD) years of education for the entire study were 16 (2.3) years.

Functional assessment
Functional assessments for both cohorts were identical. These measures included the Instrumental Activities of Daily Living (IADL) scales of Lawton and Brody (Lawton and Brody, 1969), the Katz Activities of Daily Living (ADL)/Lawton Personal Self-Maintenance scale (Katz *et al*, 1963), the Role and Physical Functioning items of the Medical Outcomes Study (MOS) (Stewart and Ware, 1993), and the Karnofsky Performance Scale (Karnofsky *et al*, 1948).

Psychiatric assessment
In the Dana cohort, the Center for Epidemiologic Studies-Depression Scale (CES-D) was used to assess mood (Radloff, 1977). In the NEAD cohort, the Beck Depression Inventory was used (Beck *et al*, 1961).

Laboratory assessment
CD4 lymphocyte counts, hemoglobin, and hematocrit levels were obtained in both cohorts. In the NEAD cohort, plasma and cerebrospinal fluid viral load specimens and immune activation markers were also collected. The results from these assays will be described in detail in future analyses. Viral load specimens were not collected in the Dana cohort.

Dementia classification
The extensive neurologic, neuropsychological, functional, and psychiatric assessments were used to characterize subjects having HIV-associated minor cognitive/motor disorder (MC/MD) or HIV dementia (Janssen *et al*, 1991), according to the American Academy of Neurology (AAN) criteria, as described previously (The Dana Consortium, 1996). Other measures of cognitive performance included a Memorial Sloan Kettering (MSK) dementia stage (Price and Brew, 1988) assigned by a local consensus conference including a neurologist and neuropsychologist at each site, and an overall neuropsychologist's impression, using only the neuropsychological test results.

Data analysis
Baseline data from 272 HIV-seropositive subjects in the Dana cohort from January, 1994, to December, 1995, and 251 HIV-seropositive subjects in the NEAD cohort from April, 1998, to August, 1999, were compared. Subject recruitment at Northwestern University began after August, 1999, so these subjects were not included as part of this analysis.

Mean values for demographic, laboratory, neurologic, and cognitive variables were compared between the Dana and NEAD cohorts using *t* tests. For a small number of variables that did not appear to be normally distributed (e.g., total macroneurological exam score and motor UPDRS score), Wilcoxon rank sum tests were used to compare the distributions among the groups. Chi-square tests were used to compare proportions among the groups. The distributions of AAN dementia classifications and overall neuropsychologist impressions were compared among the groups after adjusting for group differences in age, education, gender, race, and CD4 count using polytomous logistic regression. Proportions of subjects with scores 1 SD or 2 SDs worse than normal performance on individual neuropsychological tests were compared among the groups after adjusting for group differences in age, education, gender, race, and CD4 count using logistic regression. Multiple regression was used to compare the groups regarding mean performance on individual neuropsychological tests after adjustment for the prior covariates. Analyses were repeated for the subset of subjects with baseline CD4 count $\leq$200. Additional analyses were performed that subdivided the NEAD subjects into those who were and were not taking HAART at baseline and compared them to subjects from the Dana cohort. All *P* values reported are two-tailed.

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