ORIGINAL CONTRIBUTION

# An Evaluation of Neurocognitive Status and Markers of Immune Activation as Predictors of Time to Death in Advanced HIV Infection

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**Background:** Several markers of immune activation have been identified as potential prognostic markers for human immunodeficiency virus (HIV)–associated morbidity and mortality, but the results from studies are conflicting.

**Objective:** To evaluate whether neurocognitive status and baseline levels of plasma and cerebrospinal fluid tumor necrosis factor α (TNF-α), macrophage chemoattractant protein 1 (MCP-1), matrix metalloproteinase 2 (MMP-2), or macrophage colony-stimulating factor (M-CSF) are associated with time to death in a cohort with advanced HIV infection.

**Design:** Cohort study.

**Setting:** Enrollees in the Northeast AIDS Dementia Study.

**Participants:** Three hundred twenty-nine subjects who were positive for HIV-1 and had a CD4 cell count of less than 200/μL (or <300/μL but with cognitive impairment at baseline) were assessed for CD4 cell count, neurocognitive status, pertinent demographic and clinical variables, and plasma and cerebrospinal fluid HIV RNA, TNF-α, MCP-1, MMP-2, and M-CSF levels.

**Main Outcome Measures:** Cox proportional hazards regression models were used to examine the associations between the variables of interest (using time-dependent covariates, where applicable) and time to death, adjusting for possible confounders.

**Results:** There were 50 deaths in the cohort after a median of 25.2 months of follow-up. The cumulative incidences of death were 7% at 1 year and 16% at 2 years. In Cox proportional hazards regression analyses adjusting for demographic, clinical, and immunological variables, HIV-associated dementia (hazard rate, 6.10; $P=.001$) was significantly associated with time to death; (log) plasma MCP-1 level (hazard rate, 3.38; $P=.08$) trended toward significance.

**Conclusion:** In patients with advanced HIV infection, HIV-associated dementia is an independent predictor of time to death.

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BEFORE THE WIDESPREAD USE of highly active antiretroviral therapy (HAART), plasma human immunodeficiency virus (HIV) RNA level and CD4 cell count were considered the best biological prognostic markers of morbidity and survival for patients with HIV infection.[1] The use of HAART has resulted in a significant and sustained decrease in HIV-associated morbidity and mortality,[2] presumably mediated through superior virological control enabling a more robust and durable immune reconstitution. Consequently, the predictive value of plasma HIV RNA level seems to have been attenuated by the potency of the new antiretroviral (ARV) therapies.[3]

Several other markers of immune activation, including neopterin,[4] $\beta_2$-microglobulin,[5] and plasma tumor necrosis factor α (TNF-α),[6] have been identified as potential prognostic markers for HIV-associated morbidity and mortality, but the results from these studies are conflicting. Possible associations were recently reported between plasma TNF-α and cerebrospinal fluid macrophage chemoattractant protein 1 (MCP-1) levels and the development of HIV-associated dementia (HIVD) in a HAART-experienced cohort with advanced HIV infection.[7]

Clinical and demographic criteria have been correlated with HIV-associated morbidity and mortality. Pre–HAART era studies[8-11] identified cognitive impairment and psychomotor slowing as predictors of mortality. These publications did not describe the relationship between the syndromic diagnosis of HIVD and mortality, but another pre–HAART era study[12] failed to find a significant association between onset of dementia and mortality. The objective of this study was to determine whether neurocog-

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nitive status and baseline levels of plasma and cerebrospinal fluid TNF-α, MCP-1, matrix metalloproteinase 2 (MMP-2), or macrophage colony-stimulating factor (M-CSF) are associated with time to death in a well-characterized cohort of HAART-experienced subjects with advanced HIV.

## METHODS

Participants in this study were enrolled in the Northeast AIDS Dementia Study cohort.[7] From April 14, 1998, through July 22, 2002, we recruited ambulatory subjects who were seropositive for HIV and had a $CD4^+$ cell count of less than 200/μL (or <300/μL but with cognitive impairment) at Columbia University, New York, NY; University of Rochester, Rochester, NY; The Johns Hopkins University, Baltimore, Md; and (beginning in 1999) Northwestern University, Chicago, Ill. Subjects with concurrent or past schizophrenia, severe affective disorder, central nervous system infection, or other chronic neurological disorders were excluded; subjects were not evaluated if they were under the influence of alcohol or illicit drugs, as judged by the examining physician. Subjects underwent semiannual evaluations. Institutional review board and ethics committee approval was obtained at each institution, and informed consent was obtained from each participant.

### CLINICAL AND DEMOGRAPHIC ASSESSMENTS

The clinical and demographic data collected included the following: age, sex, race/ethnicity, years of education, use of illicit drugs, date of HIV diagnosis, history of AIDS-defining illness (clinical category C), and type of ARV use. The type of ARV use was classified as none, 1 to 2 ARVs, or 3 ARVs or more (HAART). Age, years of education, and duration of HIV were treated as continuous variables and sex, race/ethnicity, use of illicit drugs, history of AIDS-defining illness, and type of ARV use were treated as categorical variables in the analyses.

### NEUROCOGNITIVE ASSESSMENTS

The clinical evaluations focused on the signs and symptoms associated with HIVD and included a neurological examination, neuropsychological battery, functional assessment, and psychiatric assessment, as previously described.[7] The neuropsychological battery included 8 tests covering the following 6 cognitive domains: verbal memory (Rey Auditory Verbal Learning Test), visual memory (Rey-Osterrieth Complex Figure Delayed Recall Test), construction (Rey-Osterrieth Complex Figure Copy), psychomotor (Digit Symbol Test), motor speed (Grooved Pegboard and Timed Gait), and frontal systems (Verbal Fluency and Odd-Man-Out Test).[7] Performance on each test was referenced to age- and education-appropriate norms where available.[13,14] Based on the results from these clinical assessments, subjects were categorized as nonimpaired, as having minor cognitive and motor disorder (MCMD), or as demented (having HIVD) using the American Academy of Neurology criteria.[15] Neurocognitive status was treated as a categorical variable in the analyses.

For purposes of enrollment, cognitive impairment was defined as performing at least 1 SD below the mean on 2 separate neuropsychological tests (or 2 SDs below the mean on 1 test). However, if Timed Gait was the only test for which a score was 2 SDs below the mean, then criteria for cognitive impairment were not met.

### LABORATORY ASSESSMENTS

Baseline assessments of CD4 cell count, hemoglobin level, and levels of HIV RNA, MCP-1, TNF-α, M-CSF, and MMP-2 in plasma and cerebrospinal fluid were performed. In addition, CD4 cell count, hemoglobin level, and plasma and cerebrospinal fluid HIV RNA levels were measured at follow-up visits (cerebrospinal fluid was measured only annually). The HIV RNA levels were determined using the NucliSens QT assay (logarithm of odds, 80 copies/mL; bioMerieux, Inc, Durham, NC); the TNF-α, MCP-1, M-CSF, and MMP-2 levels were determined using Quantikine ELISA kits (R&D Systems, Minneapolis, Minn). Values were log-transformed in base 10, except for CD4 cell count, for which the natural logarithm (ln) was used. All biological markers were treated as continuous variables in the analyses.

### DATA ANALYSES

The primary outcome for this study was time from study enrollment to death. Only subjects with at least 1 follow-up were included in the analyses. A subject was classified as deceased based on information from a friend, family member, medical record, or death certificate. Subjects not completing the study were classified as withdrawals. For subjects who withdrew or survived until the end of scheduled follow-up, follow-up time was censored at the last available visit. Baseline variables were compared among the deceased, those who completed follow-up, and those who withdrew from the study using $t$ and $\chi^2$ tests. A Kaplan-Meier curve was constructed to estimate the cumulative incidence of death for subjects with at least 1 follow-up assessment.

Associations between the independent variables and time to death were examined using Cox proportional hazards regression models. Independent variables with values that could change over time were treated as time-dependent covariates, except for plasma and cerebrospinal fluid immune markers, for which only baseline values were examined. Univariate analyses were performed on the independent variables. Next, Cox proportional hazards regression models were created to examine whether (in separate analyses) CD4 cell count, neurocognitive status (MCMD or HIVD), and plasma and cerebrospinal fluid levels of HIV RNA, MCP-1, TNF-α, MMP-2, and M-CSF were independent predictors of time to death, adjusting for the following core group of variables considered to be potential confounders: age, sex, hemoglobin level, HAART use (yes or no), race/ethnicity (nonwhite vs white), history of HIV-related illness, and National Adult Reading Test score (a measure of IQ). Finally, Cox proportional hazards regression models containing the core variables and various combinations of the immune markers, CD4 cell count, and neurocognitive status (nonimpaired, MCMD, or HIVD) were examined. All of the Cox regression models included site of enrollment as a stratification factor.

## RESULTS

Of 396 subjects enrolled into the study, 329 (83%) had at least 1 follow-up visit. The median total duration of follow-up for the cohort was 25.2 months (interquartile range, 14.3-41.7 months). One hundred seventy-four subjects (53%) completed all scheduled follow-up visits, 50 subjects (15%) died, and 105 subjects (32%) withdrew prematurely. The chief reason (90%) for withdrawal was loss to follow-up (eg, unavailability or chose not to continue among other reasons). Those who withdrew had a shorter median total duration of follow-up (19.5 months [interquartile range, 12.0-29.5 months]). The baseline characteristics of the cohort, overall and stratified by follow-up status (completed, died, or withdrew), are summarized in **Table 1**. The estimated cumulative incidences of death were 7% at 1 year and 16% at 2 years (**Figure**). Com-

**Table 1. Baseline Demographic, Clinical, and Biological Variables Among Subjects Who Completed the Study, Died, or Withdrew***

| Variable | Cohort (N = 329) | Completed (n = 174) | *P* Value (Completed vs Died) | Died (n = 50) | *P* Value (Died vs Withdrew) | Withdrew (n = 105) | *P* Value (Completed vs Withdrew) |
|---|---|---|---|---|---|---|---|
| Age, y | 41.9 (7.2) | 42.0 (7.5) | .26 | 43.3 (6.6) | .05 | 41.0 (6.9) | .24 |
| Male sex, % | 68.6 | 71.7 | .75 | 74.0 | .11 | 61.0 | .06 |
| Race/ethnicity, % | | | | | | | |
| Black | 65.4 | 63.2 | .49 | 52.0 | .02 | 75.2 | .08 |
| Hispanic | 10.0 | 11.5 | | 12.0 | | 6.7 | |
| White | 22.8 | 24.1 | | 34.0 | | 15.2 | |
| Other | 1.8 | 1.1 | | 2.0 | | 2.9 | |
| Education, y | 12.6 (2.4) | 12.8 (2.6) | .84 | 12.8 (2.0) | .03 | 12.0 (2.2) | .01 |
| AIDS-defining illness, % | 60.5 | 58.6 | .01 | 78.0 | .006 | 55.2 | .58 |
| Pattern of ARV therapy, % | | | | | | | |
| 0 | 23.2 | 22.5 | .44 | 22.4 | .16 | 24.8 | .71 |
| 1 | 0.3 | 0.6 | | 0 | | 0 | |
| 2 | 4.6 | 4.6 | | 0 | | 6.7 | |
| HAART | 71.9 | 72.3 | | 77.6 | | 68.6 | |
| Time since HIV diagnosis, y | 7.5 (4.2) | 7.3 (4.2) | .42 | 7.8 (3.7) | .68 | 7.5 (4.4) | .69 |
| Illicit drug use, % | 33.1 | 29.9 | .99 | 30.0 | .23 | 40.0 | .08 |
| NART score | 97.3 (11.3) | 98.3 (11.6) | .82 | 97.9 (11.8) | .19 | 95.3 (10.3) | .03 |
| Neurocognitive status, % | | | | | | | |
| Nonimpaired | 29.9 | 35.1 | .001 | 10.0 | .02 | 30.8 | .67 |
| MCMD | 32.6 | 32.2 | | 36.0 | | 31.7 | |
| HIVD | 37.5 | 32.8 | | 54.0 | | 37.5 | |
| Hemoglobin level, g/dL | 13.0 (1.8) | 13.2 (1.6) | .03 | 12.5 (2.1) | .22 | 12.9 (2.0) | .21 |
| CD4 count | | | | | | | |
| Cells/μL | 138.6 (88.6) | 144.7 (86.7) | | 98.8 (87.0) | | 147.6 (88.3) | |
| Log-transformed, base e | 4.60 (0.99) | 4.70 (0.88) | .001 | 4.04 (1.28) | .001 | 4.72 (0.91) | .91 |
| Plasma levels | | | | | | | |
| HIV RNA, % | | | | | | | |
| Undetectable | 21.0 | 23.0 | .004 | 13.3 | .20 | 21.7 | .14 |
| 80-10 000 | 28.5 | 34.5 | | 22.2 | | 22.7 | |
| >10 000-100 000 | 30.3 | 28.8 | | 26.7 | | 34.0 | |
| >100 000 | 20.3 | 13.7 | | 37.8 | | 21.7 | |
| HIV RNA† | 3.79 (1.31) | 3.60 (1.28) | .007 | 4.23 (1.35) | .12 | 3.85 (1.28) | .13 |
| MCP-1, median (interquartile range), pg/mL | 255 (163-378) | 245 (168-355) | | 378 (220-529) | | 231 (147-365) | |
| MCP-1† | −0.63 (0.36) | −0.66 (0.41) | .002 | −0.48 (0.29) | .002 | −0.66 (0.31) | .93 |
| M-CSF† | 0.35 (0.37) | 0.34 (0.37) | .18 | 0.43 (0.39) | .16 | 0.33 (0.37) | .90 |
| MMP-2† | 2.33 (0.16) | 2.32 (0.16) | .26 | 2.35 (0.17) | .46 | 2.33 (0.16) | .60 |
| TNF-α† | 0.74 (0.32) | 0.76 (0.29) | .72 | 0.78 (0.35) | .17 | 0.69 (0.33) | .13 |
| Cerebrospinal fluid levels | | | | | | | |
| HIV RNA, % | | | | | | | |
| Undetectable | 46.4 | 49.0 | .90 | 53.1 | .12 | 37.9 | .06 |
| 80-1000 | 26.8 | 22.1 | | 18.8 | | 39.7 | |
| >1000 | 26.8 | 28.9 | | 28.1 | | 22.4 | |
| HIV RNA (n = 194)† | 2.58 (0.86) | 2.55 (0.85) | .77 | 2.61 (0.96) | .98 | 2.62 (0.81) | .66 |
| MCP-1, median (interquartile range), pg/mL | 491 (289-722) | 393 (270-630) | | 644 (371-944) | | 514 (352-735) | |
| MCP-1 (n = 171)† | −0.36 (0.33) | −0.40 (0.29) | .02 | −0.24 (0.35) | .14 | −0.36 (0.36) | .41 |
| M-CSF (n = 169)† | −0.16 (0.36) | −0.21 (0.38) | .50 | −0.15 (0.41) | .39 | −0.09 (0.29) | .03 |
| MMP-2 (n = 171)† | 1.81 (0.35) | 1.77 (0.32) | .62 | 1.80 (0.33) | .39 | 1.87 (0.39) | .13 |
| TNF-α (n = 147)† | 0.19 (0.65) | 0.23 (0.71) | .64 | 0.30 (0.70) | .13 | 0.07 (0.50) | .16 |

Abbreviations: ARV, antiretroviral; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HIVD, HIV dementia; MCMD, minor cognitive and motor disorder; MCP-1, macrophage chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MMP-2, matrix metalloproteinase 2; NART, National Adult Reading Test; TNF-α, tumor necrosis factor α.

*Data are given as mean (SD) unless otherwise indicated.

†Log-transformed (base 10). Units for (log) MCP-1, (log) M-CSF, and (log) MMP-2 levels are nanograms per milliliter. Units for (log) TNF-α levels are picograms per milliliter.

pared with subjects who completed follow-up, those who died were more likely at baseline to have had an AIDS-defining illness, a lower hemoglobin level, a lower (ln) CD4 cell count, an abnormal neurocognitive status (MCMD or HIVD), a higher (log) plasma HIV RNA level, and higher (log) plasma and cerebrospinal fluid MCP-1 levels.

In univariate analyses, significant associations were found between time to death and HAART use, HIVD, hemoglobin level, (ln) CD4 cell count, history of AIDS-defining illness, (log) plasma MCP-1 level, (log) plasma HIV RNA level, and (log) cerebrospinal fluid MCP-1 level. These results are summarized in **Table 2**.

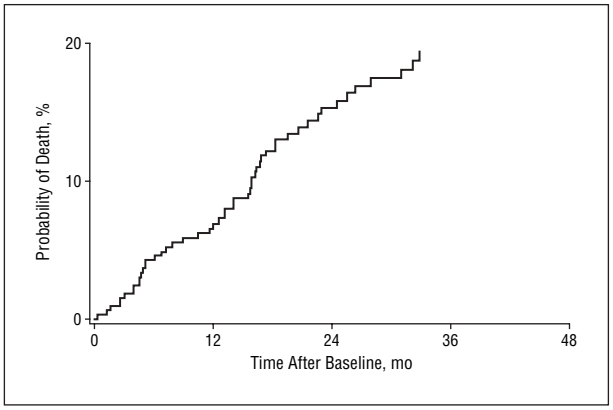


**Figure.** Kaplan-Meier curve of the cumulative incidence of death in the Northeast AIDS Dementia Study cohort.

**Table 2. Cox Proportional Hazards Regression Model Univariate Analyses of the Associations Between Selected Demographic, Clinical, and Biological Variables and Time to Death**

| Variable | Hazard Rate (95% Confidence Interval) | *P* Value |
|---|---|---|
| Age, y | 1.03 (0.99-1.07) | .13 |
| Male sex | 0.71 (0.38-1.33) | .28 |
| Education, y | 1.07 (0.94-1.21) | .31 |
| Nonwhite race/ethnicity | 2.08 (1.07-4.05) | .03 |
| Illicit drug use | 0.88 (0.48-1.61) | .67 |
| Duration of HIV, y | 1.04 (0.97-1.11) | .30 |
| AIDS-defining illness | 2.67 (1.46-4.91) | .002 |
| HAART use* | 0.55 (0.31-0.99) | .05 |
| NART | 1.00 (0.98-1.03) | .84 |
| Neurocognitive status* | | |
| Nonimpaired | 1.00 | |
| MCMD | 3.22 (1.13-9.22) | .03 |
| HIVD | 10.09 (3.87-26.30) | <.001 |
| Neurocognitive status* | | |
| Nonimpaired and MCMD | 1.00 | |
| HIVD | 5.20 (2.82-9.60) | <.001 |
| Hemoglobin level* | 0.77 (0.68-0.86) | <.001 |
| (ln) CD4 cell count* | 0.60 (0.50-0.71) | <.001 |
| (log) HIV RNA level | | |
| Plasma* | 1.41 (1.13-1.76) | .002 |
| Cerebrospinal fluid* | 0.92 (0.63-1.34) | .66 |
| (log) MCP-1 level | | |
| Plasma | 15.76 (4.43-56.11) | <.001 |
| Cerebrospinal fluid | 10.05 (2.45-41.20) | .001 |
| (log) M-CSF level | | |
| Plasma | 2.34 (0.93-5.83) | .07 |
| Cerebrospinal fluid | 1.78 (0.57-5.55) | .32 |
| (log) MMP-2 level | | |
| Plasma | 2.39 (0.30-18.96) | .41 |
| Cerebrospinal fluid | 0.75 (0.27-2.08) | .57 |
| (log) TNF-α level | | |
| Plasma | 2.04 (0.73-5.74) | .18 |
| Cerebrospinal fluid | 1.02 (0.54-1.93) | .95 |

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; HIVD, HIV dementia; ln, natural logarithm; MCMD, minor cognitive and motor disorder; MCP-1, macrophage chemoattractant protein 1; M-CSF, macrophage colony-stimulating factor; MMP-2, matrix metalloproteinase 2; NART, National Adult Reading Test; TNF-α, tumor necrosis factor α.
*Time-dependent covariate.

In the Cox proportional hazards regression analyses adjusting for the 7 core variables, the following were significantly associated with time to death: HIVD (**Table 3**, model A), (log) plasma MCP-1 level (**Table 4**, model A), and (ln) CD4 cell count (hazard rate [HR], 0.64; 95% confidence interval [CI], 0.51-0.81; $P<.001$). Not significant were MCMD (Table 3, model A), (log) cerebrospinal fluid MCP-1 level (Table 4, model A), (log) plasma HIV RNA level (HR, 1.17; 95% CI, 0.92-1.48; $P=.19$), and (log) cerebrospinal fluid HIV RNA level (HR, 0.89; 95% CI, 0.60-1.33; $P=.58$).

In models adjusting for the 7 core variables and (ln) CD4 cell count, HIVD (Table 3, model B) was significantly associated with time to death. Not significant were MCMD (Table 3, model B), (log) plasma MCP-1 level (Table 4, model B), and (log) cerebrospinal fluid MCP-1 level (Table 4, model B).

In a model containing the 7 core variables, neurocognitive status (MCMD or HIVD), (1n) CD4 cell count, and (log) MCP-1 (plasma or CSF), the following were significantly associated with time to death: HIVD (Table 3A, model C) and (1n) CD4 (HR, 0.73; 95% CI, 0.56-0.96; $P=.02$). Not significant were MCMD (Table 3, model C), (log) plasma MCP-1 (Table 4, model D), and (log) CSF MCP-1 (Table 4, model D).

Of the 1517 subject-visits that occurred, there were 427 subject-visits (28%) by 196 subjects (60%) at which the subject met criteria for HIVD. The most common neuropsychological test abnormalities found in subjects with HIVD at these visits were in the domains of verbal memory (Rey Auditory Verbal Learning Test: 72% ≥1 SD below age- and education-appropriate norms and 38% ≥2 SDs below norms), construction (Rey-Osterrieth Complex Figure Copy: 66% ≥1 SD below norms and 48% ≥2 SDs below norms), and motor speed (Grooved Pegboard: 63% ≥1 SD below norms and 38% ≥2 SDs below norms; Timed Gait: 59% ≥1.5 SDs below norms and 41% ≥2.5 SDs below norms).

## COMMENT

Human immunodeficiency virus–associated dementia but not MCMD was significantly associated with time to death after adjusting for immune markers (including CD4 cell count and plasma MCP-1 level) and other demographic and clinical covariates. In the pre–HAART era, dementia often preceded death by a few months in subjects with AIDS,[12] but (to our knowledge) a significant and independent association between dementia and time to death has not been observed.[12] In contrast, MCMD,[8] cognitive impairment,[9,10] and psychomotor slowing[11] have been reported as independent risks for death in studies of patients with less advanced HIV. Given the observed magnitudes of the HRs for MCMD (>2.5) and the widths of their associated CIs, the lack of statistical significance for the association between MCMD and time to death in this cohort may be because of too few deaths (50 deaths).

The Northeast AIDS Dementia Study cohort, in contrast to the cohorts described in the previous studies,[8-12] is HAART experienced, with 72% reporting its use at the baseline visit. The use of HAART is associated with a significant decline in HIV-associated morbidity and mortality[2,16,17] and is credited with a 50% reduced incidence of HIVD,[18] increased survival following the onset of HIVD,[19]

**Table 3. Contribution of Neurocognitive Status in Selected Cox Proportional Hazards Regression Models for Time to Death***

| Model and Adjustments | MCMD | | HIVD | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| A Core variables | 2.55 (0.89-7.36) | .08 | 7.00 (2.64-18.57) | <.001 |
| B Core variables and CD4 cell count | 2.58 (0.89-7.46) | .08 | 6.42 (2.42-17.03) | <.001 |
| C Core variables and CD4 cell count and plasma MCP-1 level | 2.62 (0.82-8.39) | .10 | 6.10 (2.05-18.17) | .001 |

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIVD, human immunodeficiency virus dementia; HR, hazard rate; MCMD, minor cognitive and motor disorder; MCP-1, macrophage chemoattractant protein 1; NART, National Adult Reading Test.

*Core variables include age, sex, NART score, HAART use, race/ethnicity, hemoglobin level, and history of AIDS-defining illness. Hazard rates are relative to nonimpaired. CD4 cell count is log-transformed (base e) and CD4 cell count, HIVD, and MCMD are time-dependent covariates. Plasma and cerebrospinal MCP-1 levels are log-transformed (base 10).

**Table 4. Contribution of Plasma and Cerebrospinal Fluid Macrophage Chemoattractant Protein 1 (MCP-1) Levels in Selected Cox Proportional Hazards Regression Models for Time to Death***

| Model and Adjustments | Plasma MCP-1 Level | | Cerebrospinal Fluid MCP-1 Level | |
|---|---|---|---|---|
| | HR (95% CI) | *P* Value | HR (95% CI) | *P* Value |
| A Core variables | 5.22 (1.44-19.00) | .01 | 4.01 (0.97-16.64) | .06 |
| B Core variables and CD4 cell count | 3.74 (0.98-14.37) | .05 | 2.66 (0.66-10.83) | .17 |
| C Core variables and HIVD/MCMD | 4.83 (1.37-17.09) | .01 | 3.63 (0.87-15.19) | .08 |
| D Core variables and HIVD/MCMD and CD cell count | 3.38 (0.88-12.97) | .08 | 2.40 (0.57-10.14) | .23 |

Abbreviations: CI, confidence interval; HAART, highly active antiretroviral therapy; HIVD, human immunodeficiency virus dementia; HR, hazard rate, MCMD, minor cognitive and motor disorder; NART, National Adult Reading Test.

*Core variables include age, sex, NART score, HAART use, race/ethnicity, hemoglobin level, and history of AIDS-defining illness. Hazard rates are relative to nonimpaired. CD4 cell count is log-transformed (base e) and CD4 cell count, HIVD, and MCMD are time-dependent covariates. Plasma and cerebrospinal MCP-1 levels are log-transformed (base 10).

and improvements in neuropsychological test performance[20] after its initiation. Subjects using HAART in this cohort were at decreased risk for death; however, HIVD remained a significant risk factor for death independent of HAART use.

Why should subjects with dementia be at an increased risk for death? Poorer medication adherence may be a contributing factor. Factors associated with poor adherence—regimen complexity, pill burden, adverse effects, and no immediate relief of symptoms—are inherent in HIV medication regimens.[21] Furthermore, patients having HIV with cognitive impairment demonstrate poor medication management and adherence.[22] This study was not designed to directly measure adherence, but subjects who died had higher plasma HIV RNA levels ($P=.007$) and were more cognitively impaired ($P=.001$) at baseline, despite no significant difference in the purported type of ARV use ($P=.44$) compared with those who completed the study, which suggests that the association between dementia and survival may be in part related to poor adherence. If our hypothesis is confirmed, cognitive assessments should become the standard of care, and rigorous adherence-enhancing programs[23] should be implemented in patients identified as having cognitive impairment.

Plasma and cerebrospinal fluid MCP-1 levels were associated with time to death in this cohort, although the magnitude and significance of these associations were attenuated after covariate adjustment. Adjustment for variables that were associated with plasma and cerebrospinal fluid MCP-1 levels, namely, CD4 cell count, hemoglobin level, and history of AIDS-defining illness, contributed most to this attenuation. Macrophage chemoattractant protein 1 is a chemokine (chemotactic cytokine) associated with acute and chronic inflammatory processes and is responsible for regulating leukocyte trafficking in these affected areas. Increased cerebrospinal fluid levels of MCP-1 have been reported in subjects with probable Alzheimer disease,[24] in patients with acute stroke,[25] and in those with HIV encephalitis[26] and dementia.[27] It was recently reported that baseline cerebrospinal fluid MCP-1 levels seemed to be associated with time to HIVD.[7]

The biological mechanism by which MCP-1 level may be associated with time to death is unknown. Plasma or cerebrospinal fluid values may be important clinically to risk-stratify patients with HIV. Standard plasma and cerebrospinal fluid values have not been determined for patients with HIV, but in a series of 279 healthy volunteers, the plasma median value was 157 pg/μL.[28] The median values from our cohort are substantially higher, with cerebrospinal fluid values higher than plasma values (Table 1). Future research is needed to determine normative values for patients with HIV.

The large number of subjects who withdrew may impart a bias in our analyses, particularly if subjects were likely to die soon after withdrawing. However, a comparison of baseline variables among the 3 groups (completed, died, and withdrew) suggests that those who withdrew much more closely resembled those who completed the study than those who died (Table 1). Therefore, although subject withdrawal limits the power of the study,

it is unlikely that it introduced substantial bias in our results. Also, we did not assess for proximate cause of death, adherence to ARV use, or hepatitis C coinfection, which may have an untoward effect on neurocognitive status in patients with HIV.[29] Finally, we did not control for multiple comparisons in the analyses, but the main finding of a significant association between HIVD and time to death would still hold even after applying a conservative Bonferroni correction.

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## REFERENCES

1. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4$^+$ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126:946-954.
2. Palella FJ Jr, Delaney KM, Moorman AC, et al; HIV Outpatient Study Investigators. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. *N Engl J Med.* 1998;338:853-860.
3. Tarwater PM, Gallant JE, Mellors JW, et al. Prognostic value of plasma HIV RNA among highly active antiretroviral therapy users. *AIDS.* 2004;18:2419-2423.
4. Mildvan D, Spritzler J, Grossberg SE, et al. Serum neopterin, an immune activation marker, independently predicts disease progression in advanced HIV-1 infection. *Clin Infect Dis.* 2005;40:853-858.
5. Brew BJ, Dunbar N, Pemberton L, Kaldor J. Predictive markers of AIDS dementia complex: CD4 cell count and cerebrospinal fluid concentrations of $\beta_2$-microglobulin and neopterin. *J Infect Dis.* 1996;174:294-298.
6. Macias J, Leal M, Delgado J, et al. Usefulness of route of transmission, absolute CD8$^+$ T-cell counts, and levels of serum tumor necrosis factor $\alpha$ as predictors of survival of HIV-1–infected patients with very low CD4$^+$ T-cell counts. *Eur J Clin Microbiol Infect Dis.* 2001;20:253-259.
7. Sevigny JJ, Albert SM, McDermott MP, et al. Evaluation of HIV RNA and markers of immune activation as predictors of HIV-associated dementia. *Neurology.* 2004;63:2084-2090.
8. Ellis RJ, Deutsch R, Heaton RK, et al; San Diego HIV Neurobehavioral Research Center Group. Neurocognitive impairment is an independent risk factor for death in HIV infection. *Arch Neurol.* 1997;54:416-424.
9. Mayeux R, Stern Y, Tang MX, et al. Mortality risks in gay men with human immunodeficiency virus infection and cognitive impairment. *Neurology.* 1993;43:176-182.
10. Wilkie FL, Goodkin K, Eisdorfer C, et al. Mild cognitive impairment and risk of mortality in HIV-1 infection. *J Neuropsychiatry Clin Neurosci.* 1998;10:125-132.
11. 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.
12. McArthur JC, Hoover DR, Bacellar H, et al; Multicenter AIDS Cohort Study. Dementia in AIDS patients: incidence and risk factors. *Neurology.* 1993;43:2245-2252.
13. Concha M, Selnes OA, McArthur JC, et al. Normative data for a brief neuropsychologic test battery in a cohort of injecting drug users. *Int J Addict.* 1995;30:823-841.
14. Selnes OA, Jacobson L, Machado AM, et al; Multicenter AIDS Cohort Study. Normative data for a brief neuropsychological screening battery. *Percept Mot Skills.* 1991;73:539-550.
15. 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.
16. Detels R, Munoz A, McFarlane G, et al; Multicenter AIDS Cohort Study Investigators. Effectiveness of potent antiretroviral therapy on time to AIDS and death in men with known HIV infection duration. *JAMA.* 1998;280:1497-1503.
17. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS.* 1999;13:1933-1942.
18. Sacktor N, Lyles RH, Skolasky R, et al. HIV-associated neurologic disease incidence changes: Multicenter AIDS Cohort Study, 1990-1998. *Neurology.* 2001;56:257-260.
19. Dore GJ, Correll PK, Li Y, Kaldor JM, Cooper DA, Brew BJ. Changes to AIDS dementia complex in the era of highly active antiretroviral therapy. *AIDS.* 1999;13:1249-1253.
20. Tozzi V, Balestra P, Galgani S, et al. Positive and sustained effects of highly active antiretroviral therapy on HIV-1–associated neurocognitive impairment. *AIDS.* 1999;13:1889-1897.
21. Chesney MA, Morin M, Sherr L. Adherence to HIV combination therapy. *Soc Sci Med.* 2000;50:1599-1605.
22. Hinkin CH, Castellon SA, Durvasula RS, et al. Medication adherence among HIV$^+$ adults: effects of cognitive dysfunction and regimen complexity. *Neurology.* 2002;59:1944-1950.
23. Andrade AS, McGruder HF, Wu AW, et al. A programmable prompting device improves adherence to highly active antiretroviral therapy in HIV-infected subjects with memory impairment. *Clin Infect Dis.* 2005;41:875-882.
24. Galimberti D, Schoonenboom N, Scarpini E, Scheltens P. Chemokines in serum and cerebrospinal fluid of Alzheimer's disease patients. *Ann Neurol.* 2003;53:547-548.
25. Losy J, Zaremba J. Monocyte chemoattractant protein-1 is increased in the cerebrospinal fluid of patients with ischemic stroke. *Stroke.* 2001;32:2695-2696.
26. Cinque P, Vago L, Mengozzi M, et al. Elevated cerebrospinal fluid levels of monocyte chemotactic protein-1 correlate with HIV-1 encephalitis and local viral replication. *AIDS.* 1998;12:1327-1332.
27. Kelder W, McArthur JC, Nance-Sproson T, McClernon D, Griffin DE. $\beta$-Chemokines MCP-1 and RANTES are selectively increased in cerebrospinal fluid of patients with human immunodeficiency virus–associated dementia. *Ann Neurol.* 1998;44:831-835.
28. de Lemos JA, Morrow DA, Sabatine MS, et al. Association between plasma levels of monocyte chemoattractant protein-1 and long-term clinical outcomes in patients with acute coronary syndromes. *Circulation.* 2003;107:690-695.
29. Ryan EL, Morgello S, Isaacs K, Naseer M, Gerits P. Neuropsychiatric impact of hepatitis C on advanced HIV. *Neurology.* 2004;62:957-962.