

Attenuated Central Nervous System Infection in Advanced HIV/AIDS With Combination Antiretroviral Therapy

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Background: Before the introduction of combination antiretroviral therapy (CART), neurological disease correlated with cerebrospinal fluid (CSF) levels of human immunodeficiency virus (HIV) RNA.

Objective: To investigate the relationships among HIV RNA levels, immune activation markers, and neurological status in patients receiving CART.

Design: Multicenter cohort study.

Setting: Academic neurology departments.

Patients: A total of 371 patients unselected for neurological complaints and with CD4 cell counts less than 200/ μ L or with cognitive symptoms and CD4 cell counts less than 300/ μ L were enrolled into the Northeastern AIDS Dementia cohort in 1998-2002. Diagnoses of HIV-associated dementia (HIV-D) and minor cognitive-motor disorder (MCMD) were obtained with a computerized algorithm. Plasma and CSF levels of HIV RNA, monocyte chemotactic protein 1, macrophage colony-stimulating factor, and tumor necrosis factor α were quantified.

Results: The mean \pm SD age was 41.5 \pm 7.2 years, and the mean \pm SD educational level was 12.3 \pm 2.2 years. Seventy

percent of the cohort was black, and 30% were women. The mean \pm SD CD4 cell count was 136.8 \pm 87.9/ μ L, and CART was used in 71%. Twenty-nine percent of the patients were unimpaired (n = 106), 36% had MCMD (n = 133), and 35% had HIV-D (n = 128). Mean log₁₀ CSF HIV RNA copies per milliliter was 2.6 \pm 0.8, with no differences among the neurological groups, even after adjustments for baseline CD4 cell counts and antiretroviral therapy. Cerebrospinal fluid HIV RNA was undetectable in 47% of unimpaired, 46% of MCMD, and 43% of HIV-D patients (P = .91). Plasma levels of monocyte chemotactic protein type 1 and tumor necrosis factor α correlated weakly with HIV RNA levels but did not distinguish those with neurological deficits.

Conclusions: In contrast to observations in individuals not treated with CART, we found no relationship between CSF markers and neurological status in this CART-using cohort with advanced HIV/AIDS. This was not explicable by demographic differences or plasma virological control. CART may substantially attenuate the degree of central nervous system HIV infection and immune activation, and in CART users, CSF HIV RNA and immune activation markers may fail to discriminate milder degrees of HIV-D and MCMD.

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ONCE ESTABLISHED IN THE central nervous system (CNS),^{1,2} human immunodeficiency virus (HIV) produces a chronic infection that predominantly involves perivascular macrophages, with restricted infection of astrocytes.³ The quantification of HIV RNA in plasma is a powerful predictor of disease progression.^{4,5} The combined measurement of plasma HIV RNA and CD4 lymphocytes provides an even more accurate prognostication⁶ and can predict the development of HIV-associated dementia (HIV-D).⁷

Several research groups⁸⁻¹⁰ have demonstrated a significant relationship between ce-

rebrospinal fluid (CSF) HIV RNA levels and the severity of HIV-D, primarily before the introduction of combination antiretroviral therapy (CART) in 1996. In the pre-CART era, Cinque et al¹¹ showed a significant relationship between CSF HIV RNA levels and HIV-associated neuropathologic changes. McClernon et al¹² also determined that brain HIV RNA levels were generally significantly elevated with severe, but not mild, HIV-D. Persistent elevations in CSF simian immunodeficiency virus RNA levels also correlated with the development of simian immunodeficiency virus encephalitis.¹³ Thus, increasing levels of lentivirus replication in the CNS contribute to the development of neurological disease.¹⁴

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The introduction of CART has resulted in virological suppression and improved survival.¹⁵ Also, CART has been associated with improvements in cognitive performance¹⁶ and a decreased incidence of HIV-D,^{15,17} as well as changes in imaging markers.^{18,19} Reductions in CSF HIV RNA levels with CART correlate with improved neuropsychological performance.²⁰⁻²² Specific CART regimens may be more effective for CNS virological control. Thus, more prominent viral load reductions were observed in individuals receiving CNS-penetrating CART regimens than regimens considered to be less penetrant.²³ A recent trial²⁴ of established HIV-D confirmed additional virological suppression in plasma and CSF with adjunctive abacavir added to CART. Baseline levels of CSF HIV RNA were significantly lower than those observed in pre-CART studies. These observations suggest that the phenotype and the biological markers of HIV-D have undergone an evolution and may have been attenuated by CART. Paradoxically, our group¹⁷ recently demonstrated that the prevalence of HIV-associated cognitive impairment remains high among individuals with advanced infection. Herein we examine the effect of CART in a large neurological cohort on HIV RNA and immune activation markers, and their relation to cognitive impairment.

METHODS

SAMPLE

Beginning in 1998, the Northeastern AIDS Dementia cohort recruited individuals with advanced HIV infection to determine the predictors of HIV-D. Patients were recruited from infectious disease clinics or through targeted advertising initially at 3 sites—Columbia University, Johns Hopkins University, and the University of Rochester—and, beginning in 1999, at Northwestern University (data from Northwestern University are not included owing to the small numbers). All patients were reimbursed for their participation and provided informed consent, and the study was approved by the respective institutional review boards. Patients were eligible for inclusion in the cohort if they were HIV seropositive and had CD4 cell counts less than 200/ μ L or CD4 cell counts less than 300/ μ L with cognitive impairment on neuropsychological testing (defined as performance 2 SD below the appropriate mean on 1 test or 1 SD below the mean on 2 tests). Patients with CD4 cell counts less than 200/ μ L were not selected for any neurological complaints. Patients were excluded if they were nonambulatory or if they had other neuropsychiatric conditions (eg, current or past CNS infection, head injury, or major psychiatric disease) that might cause cognitive impairment. Patients were not excluded if they had a history of injection drug use or alcohol abuse.

PROCEDURES

Clinical assessments were performed semiannually. At each visit, patients underwent a standardized neurological examination; completed a battery of neuropsychological, functional, and psychiatric assessments; and had blood samples taken for laboratory studies. Samples of CSF were collected every 12 months. In this article, we focus on data collected from the baseline evaluation. Plasma and CSF HIV RNA levels were determined by one of us (D.M.) using the NucliSens assay (Organon-Teknika, Durham, NC) at GlaxoSmithKline. The limit of detection on this assay was 80 copies/mL. Selected immune activation markers were assayed by 1 of us (K.C.) using commercial enzyme-

linked immunosorbent assay kits at Johns Hopkins University: tumor necrosis factor α (TNF- α), monocyte chemotactic protein type 1 (MCP-1), and macrophage colony-stimulating factor (M-CSF) (Quantikine; R&D Systems, Minneapolis, Minn) (limit of detection, 31.2 pg/mL).

DEMOGRAPHIC AND ANTIRETROVIRAL THERAPY DATA

Independent variables included age at initial visit, years of HIV infection, years of education, sex, race, medical center of enrollment, patterns of antiretroviral therapy at baseline (categorized as none currently, monotherapy, dual therapy, or CART, defined as ≥ 3 Food and Drug Administration–approved antiretroviral agents). The patterns of antiretroviral use were determined only by self-report, with no check of pharmacy records or medication adherence.

NEUROLOGICAL AND MEDICAL EXAMINATIONS

A standardized history of AIDS diagnoses was collected, and the presence of any single illness was used as an independent variable. The neurological examination was designed to capture signs associated with HIV-D and included the macroneurological examination created by the AIDS Clinical Trials Group and the motor subscale (part III) of the Unified Parkinson's Disease Rating Scale²⁵ to rate extrapyramidal signs.

NEUROPSYCHOLOGICAL TESTING

The neuropsychological battery was designed to delineate HIV-D and HIV-associated minor cognitive-motor disorder (MCMD). The 8 tests covered 6 domains. Verbal memory was assessed using the Rey Auditory Verbal Learning Test.²⁶ Visual memory was assessed using the Rey-Osterrieth Complex Figure Delayed Recall Test.²⁶ Constructional skills were assessed using the Rey-Osterrieth Complex Immediate Recall Test. Psychomotor skills were measured using the Digit Symbol Test,²⁷ and motor skills were assessed using the Grooved Pegboard (both hands)²⁸ and Timed Gait tests. Reaction time was measured using the California Computerized Assessment package.²⁹ Frontal systems were assessed using the Verbal Fluency³⁰ and Odd-Man-Out³¹ tests. General intellectual performance was assessed using the New Adult Reading Test.^{32,33} Performance was judged relative to normative data as previously described.^{34,35}

FUNCTIONAL MEASURES AND PSYCHIATRIC ASSESSMENT

Selected functional measures measured how cognitive deficits compromised everyday function and were derived from the Instrumental Activities of Daily Living scales,³⁶ the Katz Instrumental Activities of Daily Living/Lawton Personal Self-Maintenance Scale,³⁷ and the role functioning items of the Medical Outcomes Study.³⁸ Two functional outcomes that reflect stress and stamina were also included: the Karnofsky performance scale³⁹ and the Medical Outcomes Study physical function subscale.³⁸

The presence of depression was determined using the Beck Depression Inventory, a widely used self-rating instrument for depressive symptoms.^{40,41} Patients with a level of 16 or greater were classified as clinically depressed.

CLINICAL CATEGORIZATION

We categorized patients according to neurological status in 2 separate ways. First, the extensive neurological, neuropsychological, functional, and psychiatric assessments were used to

Table 1. Baseline Demographic and Clinical Characteristics Across AAN Dementia Classification Categories

Characteristic	Unimpaired (n = 106)	MCMD (n = 133)	HIV-D (n = 128)	Total (N = 371)*	P Value
Age, mean ± SD, y	41.2 ± 6.7	41.7 ± 7.2	41.7 ± 7.5	41.5 ± 7.2	.86
Male sex, %	74.5	73.7	63.3	70.3	.10
Ethnicity, %					.02 (MCMD vs HIV-D)
White	17.9	26.3	12.5	19.1	
Black	76.4	60.9	73.4	69.8	
Hispanic	5.7	12.0	10.9	9.8	
Other	0.0	0.8	3.1	1.4	
Education, mean ± SD, y	12.3 ± 1.9	12.3 ± 2.5	12.5 ± 2.2	12.3 ± 2.2	.72
NART score, mean ± SD	97.0 ± 11.7	98.1 ± 10.5	95.3 ± 10.1	96.9 ± 10.8	.11
ART, %					.58
None	20.8	23.5	27.3	24.0	
Monotherapy or dual therapy	7.5	4.6	3.9	5.2	
CART	71.7	72.0	68.8	70.8	
Years since HIV diagnosis, mean ± SD	7.0 ± 4.2	7.4 ± 4.3	7.9 ± 4.1	7.5 ± 4.2	.64
HIV-related diagnosis, %	56.6	69.9	56.3	61.3	.03 (Unimpaired vs MCMD); .02 (MCMD vs HIV-D)
Beck Depression Inventory score, mean ± SD	8.5 ± 6.7	14.8 ± 9.2	17.3 ± 9.5	13.9 ± 9.3	<.001 (Unimpaired vs MCMD and unimpaired vs HIV-D); .02 (MCMD vs HIV-D)
Beck Depression Inventory score >16, %	11.4	40.6	51.6	36.1	<.001 (Unimpaired vs MCMD and unimpaired vs HIV-D)
Self-maintenance ADL deficit, %	0.9	3.8	10.2	5.2	.003 (Unimpaired vs HIV-D); .04 (MCMD vs HIV-D)
Instrumental ADL deficit, %	15.1	28.6	100.0	49.6	.01 (Unimpaired vs MCMD and unimpaired vs HIV-D); <.001 (MCMD vs HIV-D)
Physical function score, mean ± SD	23.4 ± 4.1	20.4 ± 4.7	18.3 ± 4.8	20.5 ± 5.0	<.001 (Unimpaired vs MCMD, unimpaired vs HIV-D, and MCMD vs HIV-D)
Karnofsky performance score, mean ± SD	86.1 ± 8.5	80.6 ± 8.6	74.8 ± 11.0	80.1 ± 10.5	<.001 (Unimpaired vs MCMD, unimpaired vs HIV-D, and MCMD vs HIV-D)
Macroneurological examination score >8, %	5.7	43.1	57.5	37.3	<.001 (Unimpaired vs MCMD and unimpaired vs HIV-D); .02 (MCMD vs HIV-D)
UPDRS motor score >4, %	10.6	30.8	41.9	28.8	<.001 (Unimpaired vs MCMD and unimpaired vs HIV-D)
Distal sensory polyneuropathy, %					.009 (Unimpaired vs MCMD); .03 (unimpaired vs HIV-D)
None	36.8	29.6	33.6	33.1	
Asymptomatic	39.6	28.0	27.3	31.2	
Symptomatic	23.6	42.4	39.1	35.8	

Abbreviations: AAN, American Academy of Neurology; ADL, Activities of Daily Living scale; ART, antiretroviral therapy; CART, combination antiretroviral therapy; HIV, human immunodeficiency virus; HIV-D, HIV-associated dementia; MCMD, minor cognitive-motor disorder; NART, National Adult Reading Test; UPDRS, Unified Parkinson's Disease Rating Scale.

*Four patients had missing data for AAN dementia classification.

classify patients as not impaired, HIV-associated MCMD, or HIV-D according to the American Academy of Neurology (AAN) criteria.^{34,42} Second, we used a modified version of the Memorial Sloan-Kettering scale to rate dementia severity.^{43,44} We assessed the reliability of this scale in consensus conferences, with κ statistics ranging from 0.7 to 0.91.⁴⁵

STATISTICAL ANALYSIS

The independent variables of interest were levels of HIV RNA, MCP-1, TNF- α , and M-CSF in plasma and CSF. These were treated as continuous log-transformed (base 10) variables. Logistic regression was used to examine the associations between the independent variables and outcome. For the AAN classification, separate models were fitted for the outcome of no impairment vs MCMD/HIV-D and the outcome of no impairment/MCMD vs HIV-D. Similar analyses were performed for the outcome of modified Memorial Sloan-Kettering stage (<1 vs \geq 1).

All analyses included adjustment for study site and CD4 count (log transformed). Separate analyses were performed that adjusted for CART use and that compared results in CART-naive patients with those in CART recipients. In a separate analysis, plasma HIV RNA levels were used as a surrogate for virological suppression, independent of reported antiretroviral use.

Pairwise comparisons of demographic and clinical variables among AAN classifications were performed using *t* tests and χ^2 tests, as appropriate. Spearman rank correlations were used to describe associations. Values are given as mean \pm SD.

RESULTS

PATIENT CHARACTERISTICS

The demographic, clinical, virological, and immune characteristics of the cohort are detailed in **Table 1**, **Table 2**,

Table 2. Baseline Laboratory Results Across AAN Dementia Classification Categories and Treatment Exposure

Laboratory Variable	Unimpaired		MCMD		Probable Dementia		P Value
	No ART (n = 22)*	CART (n = 76)	No ART (n = 31)	CART (n = 95)	No ART (n = 35)	CART (n = 88)	
Hemoglobin, mean ± SD, g/dL	13.09 ± 1.79	13.16 ± 1.80	12.67 ± 1.80	13.04 ± 1.68	12.32 ± 1.68	12.85 ± 2.17	.30
Hematocrit, mean ± SD, %	38.65 ± 4.86	39.46 ± 4.46	38.11 ± 4.85	37.99 ± 5.29	37.16 ± 4.88	37.65 ± 6.73	.02 (Unimpaired vs HIV-D, CART, and no ART)
Log ₁₀ CD4 count, mean ± SD, cells/μL	4.53 ± 0.90	4.53 ± 0.89	4.29 ± 1.01	4.65 ± 1.00	4.62 ± 1.19	4.64 ± 1.08	.60
Log ₁₀ plasma HIV RNA, mean ± SD, copies/mL (n = 319)	4.07 ± 1.32	3.49 ± 1.44	4.89 ± 0.94	3.69 ± 1.24	4.80 ± 1.03	3.36 ± 1.25	All <.001
Plasma HIV RNA, %							
Undetectable	21.1	36.4	3.9	19.5	6.7	28.8	<.001†
80-9999 copies/mL	21.1	16.7	7.7	33.3	6.7	38.4	
10000-100000 copies/mL	31.6	27.3	38.5	33.3	43.3	19.2	
>100000 copies/mL	26.3	19.7	50.0	13.8	43.3	13.7	
Log ₁₀ CSF HIV RNA, mean ± SD, copies/mL (n = 218)	2.82 ± 0.71	2.41 ± 0.76	2.93 ± 1.08	2.48 ± 0.84	3.51 ± 0.80	2.40 ± 0.71	<.001‡
CSF HIV RNA, %							
Undetectable	25.0	55.3	35.3	51.7	5.9	56.0	.002§
80-1000 copies/mL	33.3	23.4	17.7	30.0	29.4	26.0	
>1000 copies/mL	41.7	21.3	47.1	18.3	64.7	18.0	
Log ₁₀ plasma MCP-1, mean ± SD, pg/mL	-0.70 ± 0.32	-0.60 ± 0.32	-0.54 ± 0.27	-0.67 ± 0.46	-0.56 ± 0.37	-0.71 ± 0.31	.23
Log ₁₀ CSF MCP-1, mean ± SD, pg/mL	-0.53 ± 0.39	-0.31 ± 0.24	-0.29 ± 0.31	-0.40 ± 0.42	-0.45 ± 0.45	-0.35 ± 0.36	.47
Log ₁₀ plasma M-CSF, mean ± SD, pg/mL	0.46 ± 0.31	0.31 ± 0.36	0.41 ± 0.36	0.36 ± 0.38	0.51 ± 0.32	0.34 ± 0.43	.26
Log ₁₀ CSF M-CSF, mean ± SD, pg/mL	-0.17 ± 0.32	-0.15 ± 0.41	-0.15 ± 0.25	-0.11 ± 0.33	-0.13 ± 0.26	-0.22 ± 0.38	.76
Log ₁₀ plasma TNF-α, mean ± SD, pg/mL	0.83 ± 0.26	0.67 ± 0.33	0.79 ± 0.28	0.73 ± 0.30	0.89 ± 0.28	0.74 ± 0.32	.07
Log ₁₀ CSF TNF-α, mean ± SD, pg/mL	0.16 ± 0.60	0.35 ± 0.76	0.26 ± 0.40	0.21 ± 0.58	0.12 ± 0.47	0 ± 0.72	.33

Abbreviations: AAN, American Academy of Neurology; ART, antiretroviral therapy; CART, combination antiretroviral therapy; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; HIV-D, HIV-associated dementia; MCMD, minor cognitive-motor disorder; MCP-1, monocyte chemoattractant protein type 1; M-CSF, macrophage colony-stimulating factor; NS, not significant; TNF-α, tumor necrosis factor α.

*Four patients had missing data for AAN dementia classification.

†CART unimpaired vs no ART MCMD, *P* = .002; CART unimpaired vs no ART HIV-D, *P* = .003; and CART MCMD vs no ART MCMD, CART MCMD vs no ART HIV-D, CART HIV-D vs no ART MCMD, and CART HIV-D vs no ART HIV-D, *P* < .001.

‡CART unimpaired vs no ART HIV-D, CART MCMD vs no ART HIV-D, and CART HIV-D vs no ART HIV-D.

§CART unimpaired vs no ART HIV-D, CART MCMD vs no ART HIV-D, and CART HIV-D vs no ART HIV-D, *P* < .001.

and **Figure 1**. Three hundred seventy-one patients were enrolled: 196 at Johns Hopkins University, 104 at Columbia University, and 71 at the University of Rochester. Seventy percent of the cohort was male, and 70% were black. The mean patient age was 41.5 ± 7.2 years, and the mean educational level was 12.3 ± 2.2 years. The mean IQ measured using the New Adult Reading Test was 96.9 ± 10.8. The cohort had had documented HIV infection for a mean of 7.5 ± 4.2 years, and the mean CD4 count was 136.8 ± 87.9/mm³; 61% of patients reported an AIDS-defining illness, and 36% had symptomatic sensory neuropathy.

CATEGORIZATION OF PATIENTS USING THE AAN ALGORITHM

One hundred six patients were not impaired, 133 had MCMD, and 128 had HIV-D. There were site-specific differences in the proportions of patients with HIV-D: 14% at Rochester, 44% at Columbia, and 37% at Johns Hop-

kins. Using the modified Memorial Sloan-Kettering criteria for categorization, 4% of patients were rated as 0, 46% as 0.5, 24% as 1 (mild HIV-D), 17% as 2 (moderate HIV-D), and 9% as 3 (severe HIV-D). More patients classified as either MCMD or HIV-D had neurological abnormalities and symptomatic sensory neuropathy, were clinically depressed, and reported self-maintenance and instrumental ADL deficits than unimpaired patients (Table 1). Patients with MCMD and HIV-D also had lower scores on the Karnofsky and physical function scales than unimpaired patients (Table 1).

PATTERNS OF ANTIRETROVIRAL THERAPY AND VIROLOGICAL CONTROL

Twenty-four percent of patients were not using any antiretroviral medications at the baseline visit, 5% were using 2 antiretrovirals, and 71% reported the use of CART. Only 19 patients (5%) were antiretroviral naive

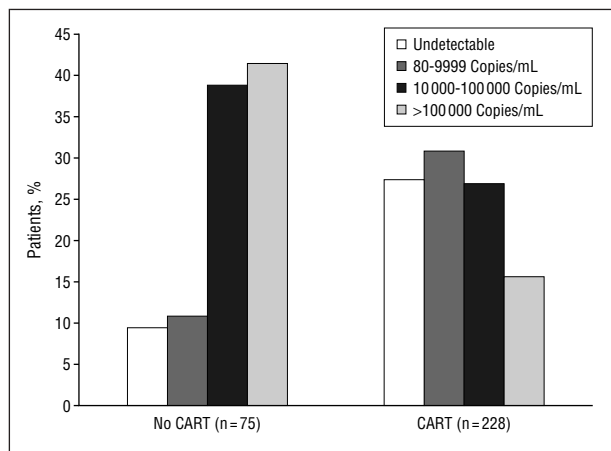


Figure 1. Distribution of plasma human immunodeficiency virus RNA levels based on combination antiretroviral therapy (CART) exposure at the baseline visit. The proportion of patients with high levels of plasma viremia (10000-100000 and >100000 copies/mL) was statistically significantly higher among nonusers of CART. Users of only 1 or 2 antiretrovirals (n=15) are not displayed.

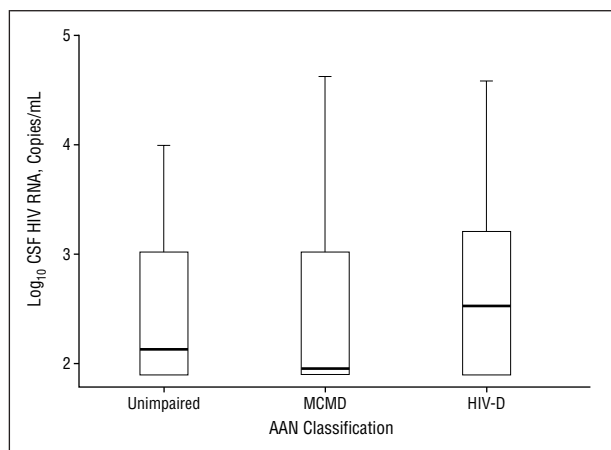


Figure 2. Cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) RNA levels stratified by American Academy of Neurology (AAN) classification (unimpaired, minor cognitive-motor disorder [MCMD], and HIV-associated dementia [HIV-D]). There were no statistically significant differences in CSF HIV RNA levels using the computerized algorithm to categorize patients. The thick horizontal lines represent mean values; boxes, 25th and 75th percentiles; and error bars, outlier values.

at baseline. The proportion of individuals with undetectable plasma HIV RNA levels (<80 copies/mL), independent of antiretroviral use, was 22% overall, and 22% had plasma HIV RNA levels greater than 100000 copies/mL. The patterns of antiretroviral use did not differ significantly across the neurological groups (Tables 1 and 2). Mean log₁₀ plasma HIV RNA copies per microliter were, in general, lower among CART users than nonusers, but did not differentiate the neurological groups (Table 2).

ASSOCIATIONS BETWEEN VIRAL LOAD AND IMMUNE MARKERS AND NEUROLOGICAL STATUS

Forty-six percent of patients had undetectable CSF HIV RNA levels (<80 copies/mL), with no significant differences among the neurological groups. Overall, the mean

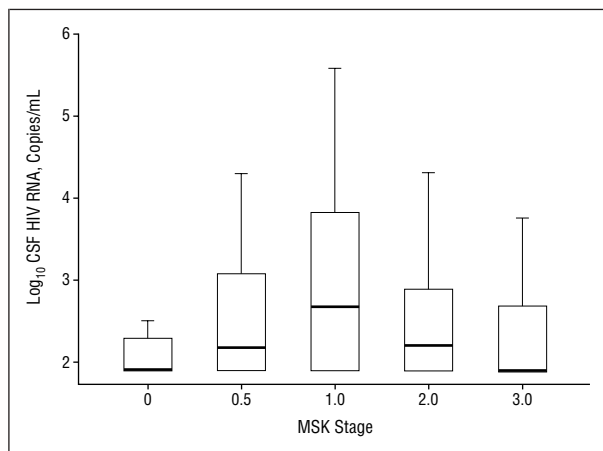


Figure 3. Cerebrospinal fluid (CSF) human immunodeficiency virus (HIV) RNA levels stratified by Memorial Sloan-Kettering (MSK) stage. There were no statistically significant differences in CSF HIV RNA levels using clinical consensus to categorize patients. The thick horizontal lines represent mean values; boxes, 25th and 75th percentiles; and error bars, outlier values.

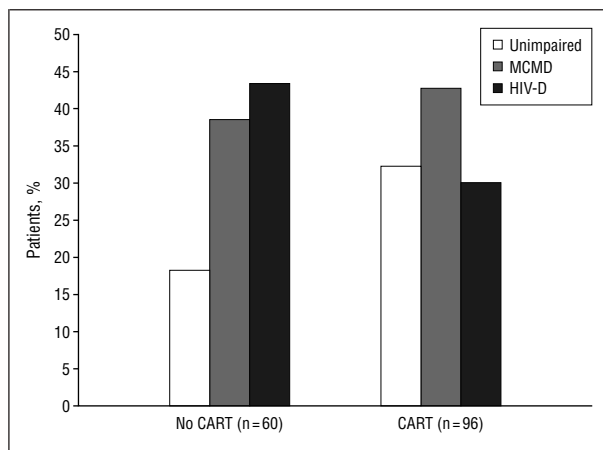


Figure 4. Distribution of the cohort by neurological status (unimpaired, minor cognitive-motor disorder [MCMD], and human immunodeficiency virus-associated dementia [HIV-D]), stratified by the use of combination antiretroviral therapy (CART) and the presence of high levels of plasma viremia (defined as ≥ 10000 copies/mL) at baseline. A greater proportion of nonusers with HIV-D have high-level plasma viremia while a greater proportion of unimpaired CART users have high levels of plasma viremia. Among CART users, there are no significant differences by neurological status.

log₁₀ CSF HIV RNA level was 2.6 ± 0.8 copies/mL, with group differences (**Figure 2** and Table 2). For patients not using antiretrovirals, mean log₁₀ CSF HIV RNA levels were higher and tended to increase according to dementia status (unimpaired, 2.8 ± 0.7 copies/mL; MCMD, 2.9 ± 1.1 copies/mL; and HIV-D, 3.5 ± 0.8 copies/mL). By contrast, for patients taking CART, mean levels were lower and unrelated to dementia status (unimpaired, 2.4 ± 0.8 copies/mL; MCMD, 2.5 ± 0.8 copies/mL; and HIV-D, 2.4 ± 0.7 copies/mL) (Table 2 and **Figure 3**). No differences were noted for mild, moderate, or severe HIV-D. Similar patterns were seen for mean log₁₀ plasma HIV RNA levels stratified by treatment. For patients not taking antiretrovirals, mean log₁₀ plasma HIV RNA levels tended to increase according to dementia status (unimpaired, 4.1 ± 1.3 copies/mL; MCMD, 4.9 ± 0.9 copies/mL; and HIV-D, 4.8 ± 1.0 copies/mL). For patients taking CART, mean log₁₀ plasma HIV RNA levels were relatively low

Table 3. Associations Between HIV RNA and Immune Markers and HIV-Associated Dementia

Variable	Odds Ratio (95% CI)*	P Value
Plasma viral load (log)		
Overall (n = 313)	0.98 (0.81-1.18)	.82
No ART (n = 75)	1.35 (0.81-2.26)	.26
CART (n = 223)	0.88 (0.70-1.11)	.29
CSF viral load (log)		
Overall (n = 213)	1.17 (0.83-1.66)	.37
No ART (n = 46)	2.34 (1.05-5.23)	.04
CART (n = 155)	0.97 (0.61-1.54)	.90
Plasma MCP-1 level (log)		
Overall (n = 272)	0.87 (0.39-1.93)	.73
No ART (n = 63)	1.28 (0.18-9.31)	.81
CART (n = 196)	0.75 (0.30-1.86)	.54
CSF MCP-1 level (log)		
Overall (n = 184)	1.01 (0.38-2.64)	.99
No ART (n = 37)	0.59 (0.09-4.05)	.59
CART (n = 136)	1.30 (0.41-4.13)	.65
Plasma M-CSF level (log)		
Overall (n = 272)	0.91 (0.44-1.89)	.80
No ART (n = 63)	2.31 (0.37-14.54)	.37
CART (n = 196)	0.66 (0.29-1.51)	.32
CSF M-CSF level (log)		
Overall (n = 182)	0.28 (0.10-0.80)	.02
No ART (n = 37)	0.83 (0.04-15.50)	.90
CART (n = 135)	0.22 (0.07-0.73)	.01
Plasma TNF- α level (log)		
Overall (n = 272)	1.59 (0.65-3.89)	.31
No ART (n = 63)	3.16 (0.33-30.64)	.32
CART (n = 196)	1.52 (0.53-4.38)	.43
CSF TNF- α level (log)		
Overall (n = 159)	0.70 (0.37-1.30)	.26
No ART (n = 32)	1.22 (0.19-8.05)	.84
CART (n = 119)	0.68 (0.34-1.38)	.29

Abbreviations: ART, antiretroviral therapy; CART, combination antiretroviral therapy; CI, confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; MCP-1, monocyte chemoattractant protein type 1; M-CSF, macrophage colony-stimulating factor; TNF- α , tumor necrosis factor α .

*All odds ratios are adjusted for study site and log CD4 count using logistic regression.

and unrelated to dementia status (unimpaired, 3.5 ± 1.4 copies/mL; MCMD, 3.7 ± 1.2 copies/mL; and HIV-D, 3.4 ± 1.2 copies/mL) (Figure 4). Mean \log_{10} values of immune activation markers did not differ with respect to dementia status except that CSF TNF- α levels were lower in patients with HIV-D than in unimpaired patients (Table 2).

The logistic regression analyses did not demonstrate any significant associations between the measures of viral load and immune activation and neurological grouping using either the AAN criteria (Table 3 and Table 4) or the modified Memorial Sloan-Kettering scale (Table 5). The results did not differ substantially after adjustment for antiretroviral regimen or plasma HIV RNA levels (a surrogate of virological suppression independent of reported CART use). The results for AAN dementia classification (Tables 3 and 4) suggested a weak association between HIV RNA levels and dementia status in those not taking antiretrovirals, although the interactions between HIV RNA levels and CART were not statistically significant.

Table 4. Associations Between HIV RNA and Immune Markers and MCMD/HIV-Associated Dementia Combined

Variable	Odds Ratio (95% CI)*	P Value
Plasma viral load (log)		
Overall (n = 313)	1.14 (0.94-1.38)	.18
No ART (n = 75)	1.90 (1.13-3.19)	.02
CART (n = 223)	1.09 (0.86-1.38)	.47
CSF viral load (log)		
Overall (n = 213)	1.19 (0.82-1.72)	.36
No ART (n = 46)	1.83 (0.78-4.31)	.16
CART (n = 155)	1.10 (0.69-1.74)	.69
Plasma MCP-1 level (log)		
Overall (n = 272)	0.88 (0.36-2.13)	.77
No ART (n = 63)	9.77 (0.70-136.32)	.09
CART (n = 196)	0.64 (0.22-1.92)	.43
CSF MCP-1 level (log)		
Overall (n = 184)	0.94 (0.32-2.77)	.91
No ART (n = 37)	5.64 (0.45-70.00)	.18
CART (n = 136)	0.59 (0.15-2.29)	.45
Plasma M-CSF level (log)		
Overall (n = 272)	0.97 (0.45-2.08)	.93
No ART (n = 63)	0.39 (0.04-3.58)	.40
CART (n = 196)	0.91 (0.39-2.13)	.82
CSF M-CSF level (log)		
Overall (n = 182)	0.59 (0.20-1.73)	.34
No ART (n = 37)	0.28 (0.01-11.94)	.51
CART (n = 135)	0.58 (0.17-1.95)	.38
Plasma TNF- α level (log)		
Overall (n = 272)	2.01 (0.82-4.93)	.13
No ART (n = 63)	0.77 (0.06-10.32)	.84
CART (n = 196)	2.21 (0.77-6.34)	.14
CSF TNF- α level (log)		
Overall (n = 159)	0.64 (0.33-1.23)	.18
No ART (n = 32)	2.61 (0.27-25.26)	.41
CART (n = 119)	0.70 (0.34-1.44)	.33

Abbreviations: ART, antiretroviral therapy; CART, combination antiretroviral therapy; CI, confidence interval; CSF, cerebrospinal fluid; HIV, human immunodeficiency virus; MCMD, minor cognitive-motor disorder; MCP-1, monocyte chemoattractant protein type 1; M-CSF, macrophage colony-stimulating factor; TNF- α , tumor necrosis factor α .

*All odds ratios are adjusted for study site and log CD4 count using logistic regression.

RELATIONSHIPS AMONG THE VIROLOGICAL AND IMMUNE ACTIVATION MARKERS

Correlation coefficients were calculated for all pairs of virological and immune activation markers. Most of these correlations were relatively weak ($r < 0.30$), except for plasma vs CSF HIV RNA level ($r = 0.37$), plasma HIV RNA level vs plasma MCP-1 level ($r = 0.32$), plasma HIV RNA level vs CSF MCP-1 level ($r = 0.31$), plasma vs CSF MCP-1 level ($r = 0.49$), and plasma MCP-1 level vs plasma TNF- α level ($r = 0.44$) ($P < .001$ for all).

COMMENT

Neither plasma nor CSF HIV RNA levels were statistically significantly associated with HIV-D or HIV-associated MCMD. In addition, the immune activation markers MCP-1, M-CSF, and TNF- α were not associated with neurological status in either plasma or CSF. Exposure to CART by itself did not account for the lack of association between neurological status and CSF viral load measures.

Previously, a strong correlation was noted between CSF HIV RNA levels and the severity of HIV-D. However, these studies either focused on severely demented individuals²³ or predated the introduction of CART.⁸⁻¹⁰ In contrast, we show relatively low CSF HIV RNA levels in patients treated with CART, and, furthermore, we found no definitive relationship among neurological status, CSF HIV RNA levels, and markers of immune activation. This suggests that the natural history of HIV-D has been altered by the widespread use of CART.

In our 1997 study,¹⁰ there was a graded relationship between the severity of neurological disease and CSF HIV RNA levels. We observed a similar relationship for plasma and CSF HIV RNA levels in the present study for patients not using CART but not for CART users. A recent placebo-controlled trial⁴⁶ of a TNF- α antagonist in HIV-D found that 79% of patients with HIV-D were using CART and had a mean log₁₀ CSF HIV RNA level of 2.3 (2117 copies/mL). This is comparable to the mean log₁₀ CSF level of 2.58 in our cohort. The frequency of undetectable CSF HIV RNA levels was approximately 70% in the TNF- α antagonist trial and was 58% in the trial of abacavir add-on therapy for HIV-D.²⁴ These rates are comparable to the 46% observed in our cohort and suggest that CSF HIV RNA levels are suppressed by CART. Ultrasensitive assays were not used in these studies, so it is plausible that very low levels of CSF HIV RNA might not have been detected.

Our results suggest that the measurement of levels of CSF HIV RNA and selected immune activation markers does not distinguish neurological status in patients with advanced HIV receiving CART. There are several possible explanations for the relatively low levels of CSF HIV RNA and immune activation markers in our cohort. There are inherent limitations of a selected cohort such as this. First, we considered the possibility of a selection bias with recruitment of "long-term" survivors, who perhaps have different patterns of HIV replication. This seems unlikely given that 1 of the entry criteria was a CD4 count less than 200/ μ L; thus, most patients had profound immunosuppression. Again, most of the cohort was unselected for any neurological symptoms, and the racial characteristics were representative of the state of the HIV epidemic in New York and Maryland.⁴⁷

Second, the cohort had a high rate of neurocognitive impairment, comparable to that in the pre-CART era. The prevalence of neurological impairment in the Dana cohort¹⁷ (with identical entry criteria) in the pre-CART era in 1994 was 23.2%, comparable to the current rate of 19.8%. In the statistical analyses, we examined the effect of CART by adjusting for the reported use of CART. There were no differences in our findings, but this may reflect the relatively high use of CART overall. We also adjusted for plasma HIV RNA as a surrogate for virological control and again could not demonstrate associations between marker levels and clinical grouping. Third, another factor that must be considered is the potential for nonspecific neurocognitive impairments unrelated to CNS HIV infection to "dilute" the results. Our cohort has a relatively high rate of drug and alcohol use and of depression, but there were no associations among these factors and the virological measures or immune activation

Table 5. Associations Between HIV RNA and Immune Markers and MSK Stage 1 or Higher

Variable	Odds Ratio (95% CI)*	P Value
Plasma viral load (log)		
Overall (n = 316)	0.93 (0.79-1.11)	.44
No ART (n = 75)	1.23 (0.78-1.94)	.38
CART (n = 225)	0.85 (0.69-1.06)	.15
CSF viral load (log)		
Overall (n = 216)	1.21 (0.87-1.68)	.25
No ART (n = 46)	1.02 (0.51-2.06)	.95
CART (n = 157)	1.28 (0.84-1.95)	.25
Plasma MCP-1 level (log)		
Overall (n = 275)	0.75 (0.35-1.61)	.46
No ART (n = 63)	1.40 (0.19-10.11)	.74
CART (n = 198)	0.62 (0.25-1.52)	.29
CSF MCP-1 level (log)		
Overall (n = 186)	0.96 (0.39-2.38)	.92
No ART (n = 37)	1.44 (0.21-9.69)	.71
CART (n = 138)	0.81 (0.28-2.37)	.70
Plasma M-CSF level (log)		
Overall (n = 275)	1.06 (0.54-2.11)	.86
No ART (n = 63)	2.03 (0.33-12.50)	.44
CART (n = 198)	0.84 (0.39-1.80)	.65
CSF M-CSF level (log)		
Overall (n = 184)	0.65 (0.25-1.68)	.37
No ART (n = 37)	6.04 (0.27-133.71)	.25
CART (n = 137)	0.34 (0.10-1.10)	.07
Plasma TNF- α level (log)		
Overall (n = 275)	1.28 (0.57-2.88)	.55
No ART (n = 63)	1.15 (0.12-10.69)	.90
CART (n = 198)	1.54 (0.59-3.98)	.38
CSF TNF- α level (log)		
Overall (n = 161)	0.81 (0.46-1.45)	.48
No ART (n = 32)	0.09 (0.01-1.37)	.08
CART (n = 121)	0.92 (0.48-1.73)	.78

Abbreviations: ART, antiretroviral therapy; CART, combination antiretroviral therapy; CI, confidence interval; CSF, cerebrospinal fluid; MSK, Memorial Sloan-Kettering; MCP-1, monocyte chemoattractant protein type 1; M-CSF, macrophage colony-stimulating factor; TNF- α , tumor necrosis factor α .
*All odds ratios are adjusted for study site and log CD4 count using logistic regression.

markers. This cohort showed a high rate of self-reported depression, but this has been reported from multiple studies among individuals with advanced HIV/AIDS.⁴⁸ In HIV/AIDS and other neurological diseases, including Parkinson disease, most studies have not determined any specific impact of depressive symptoms on neurocognitive functioning.^{49,50} We, therefore, believe that these potential confounds did not contribute to our findings. Misclassification of neurological status was minimized by using a validated computerized algorithm, and we observed similar results using a clinical categorization. Furthermore, we have shown a high degree of agreement for these classifications.⁴⁵

Another explanation for the lack of any observable relationship between neurological state and CSF HIV RNA levels is that brain levels of HIV RNA may in fact be low in this group, reflecting a lesser degree of productive CNS HIV replication. The concept that CART is inducing an attenuated form of HIV encephalitis manifest by less severe HIV-associated cognitive impairment has been recently proposed by Brew⁵¹ and Kudra et al⁵² and is supported by a reduced frequency of severe HIV encephalitis

in an autopsy series in the CART era.⁵³ Two pathological studies in the CART era have observed either no temporal changes in the frequency of mild HIV-associated neuropathologic changes⁵⁴ or an actual increased frequency of mild encephalitis.⁵⁵ It remains plausible that the neurological disorders that we observed had developed before exposure to CART and that the baseline examination of CART users reflected these earlier CNS insults.

Most Northeastern AIDS Dementia cohort patients (71%) were receiving CART at baseline. This mirrors the national patterns of CART use and use in HIV-seropositive cohorts.⁵⁶ Several studies^{57,58} have shown that either dual therapy or CART can suppress CSF HIV RNA levels rapidly, particularly in antiretroviral-naïve individuals. Cerebrospinal fluid virological suppression is correlated with predicted CNS antiretroviral drug penetration²³; however, neurocognitive improvement with CART seems to be independent of this variable.⁵⁹ The principal effect of CART may occur outside the CNS, perhaps by reducing the proportion of circulating activated monocytes, which are the cells presumed to carry HIV into the brain.⁶⁰

We chose to examine selected soluble immune markers in this study, focusing particularly on those that reflected activation of astrocytes and CNS macrophages. There was a degree of interdependence for many of these measures, as has been previously reported.⁶¹ The β chemokine MCP-1 has been shown to be significantly elevated in CSF in HIV-D.^{62,63} Produced by astrocytes and macrophages, this chemokine may play a role in attracting monocytes into the CNS.⁶² Levels of CSF MCP-1 are elevated in association with HIV-D and its pathological correlate, HIV encephalitis. In milder degrees of impairment, MCP-1 levels are elevated, although to a lesser degree.⁶⁴ Levels of CSF MCP-1 correlated with high CSF-plasma HIV RNA ratios and did not decline with CART.²³ In simian immunodeficiency virus infection, an elevated ratio of CSF-plasma MCP-1 predicts the subsequent development of encephalitis.⁶⁵ We noted no elevations in either plasma or CSF levels of MCP-1 or in the CSF-plasma MCP-1 ratio.

Tumor necrosis factor α is produced by activated microglia and macrophages, and levels are elevated in HIV/AIDS.⁶⁶ Tumor necrosis factor α has been associated with neurotoxicity in vitro, and it may also stimulate the release of matrix metalloproteinases (MMPs) and other inflammatory mediators from cells, including astrocytes. Like MCP-1, TNF- α messenger RNA levels are elevated in association with HIV-D.⁶⁷ In contrast to earlier studies that showed elevated serum levels,⁶⁸ we actually noted lower levels of CSF TNF- α in patients with HIV-D.

Macrophage colony-stimulating factor is produced by cell types, including astrocytes, and induces CD16 expression on monocytes and their activation.^{69,70} Elevated M-CSF levels in CSF⁷¹ and serum² have been observed in HIV-D; however, levels were not elevated in the present study. In a recent HIV-D trial⁷² in which most participants were using CART, CSF levels of interleukin 6, MIP-1 β , and MCP-1 were comparable to levels in neurologically healthy HIV-seropositive patients.^{46,72} Combined with our observations, these results suggest that

levels of immune activation markers are less frequently elevated in contemporary CART cohorts, at least compared with studies from 5 to 10 years ago.

Our observations may have a parallel with syphilis, in which reductions in the frequency of late-stage neurological manifestations have been attributed to the widespread incidental use of antibiotics. Further evidence that antiretroviral therapy may have led to changes in the patterns of progression of HIV-D comes from clinical studies. Before CART, only a third of HIV-D cases survived longer than 12 months.⁷³ In contrast, almost two thirds of patients with HIV-D improved neurologically after CART.⁷⁴

In summary, in this cohort with advanced HIV/AIDS, we found no significant associations between plasma or CSF HIV RNA levels, immune activation markers, and neurological status for patients using CART. This finding was not explicable by demographics or levels of plasma virological control. We suggest that CSF HIV RNA and immune activation markers are suppressed and that the severity of neurological disease may be attenuated by CART. Although the incidence of HIV-D has dropped by at least 50% since the introduction of CART,^{17,75} the prevalence of HIV-D has actually risen from 6.6 per 100 person-years in 1994 to 10.1 in 2000,⁷⁶ reflecting improving survival. This rising prevalence reinforces the necessity to develop sensitive and valid predictive markers for HIV-D. Recently, CSF HIV RNA levels were found to predict development of neuropsychological impairment,⁷⁷ and longitudinal study of the Northeastern AIDS Dementia cohort will allow us to relate clinical changes to temporal changes in viral load and immune activation markers.

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