HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy

CHARTER Study

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ABSTRACT

Objectives: This is a cross-sectional, observational study to determine the frequency and associated features of HIV-associated neurocognitive disorders (HAND) in a large, diverse sample of infected individuals in the era of combination antiretroviral therapy (CART).

Methods: A total of 1,555 HIV-infected adults were recruited from 6 university clinics across the United States, with minimal exclusions. We used standardized neuromedical, psychiatric, and neuropsychological (NP) examinations, and recently published criteria for diagnosing HAND and classifying 3 levels of comorbidity (minimal to severe non-HIV risks for NP impairment).

Results: Fifty-two percent of the total sample had NP impairment, with higher rates in groups with greater comorbidity burden (40%, 59%, and 83%). Prevalence estimates for specific HAND diagnoses (excluding severely confounded cases) were 33% for asymptomatic neurocognitive impairment, 12% for mild neurocognitive disorder, and only 2% for HIV-associated dementia (HAD). Among participants with minimal comorbidities (n = 843), history of low nadir CD4 was a strong predictor of impairment, and the lowest impairment rate on CART occurred in the subset with suppressed plasma viral loads and nadir CD4 ≥200 cells/mm^3 (30% vs 47% in remaining subgroups).

Conclusions: The most severe HAND diagnosis (HAD) was rare, but milder forms of impairment remained common, even among those receiving CART who had minimal comorbidities. Future studies should clarify whether early disease events (e.g., profound CD4 decline) may trigger chronic CNS changes, and whether early CART prevents or reverses these changes. ***Neurology***® **2010;75:2087–2096**

GLOSSARY

ANI = asymptomatic neurocognitive impairment; **CART** = combination antiretroviral therapy; **CHARTER** = CNS HIV Antiretroviral Therapy Effects Research; **CIDI** = Composite International Diagnostic Interview; **CLIA** = Clinical Laboratory Improvement Amendments; **CPE** = CNS penetration effectiveness; **HAD** = HIV-associated dementia; **HAND** = HIV-associated neurocognitive disorder; **IADL** = instrumental activities of daily living; **LP** = lumbar puncture; **MND** = mild neurocognitive disorder; **NP** = neuropsychological; **PAOFI** = Patient's Assessment of Own Functioning Inventory.

A growing armamentarium of potent antiviral drugs that target multiple steps in the HIV life cycle has led to vast improvements in HIV disease management. Combining these drugs (combination antiretroviral therapy [CART]) has greatly reduced medical morbidity and mortality, but neurologic complications remain common, manifested by HIV-associated neurocognitive disorders (HAND) and distal sensory polyneuropathy.[1-3] Although there appears to be a disconnection between the medical and neurologic benefits of CART, lack of large-scale comprehensive neurologic studies has made accurate estimates of the prevalence of HAND and its relationship to disease and treatment factors difficult.

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Stroke to examine a diverse group of HIV-infected persons broadly reflective of patients at university-affiliated HIV treatment centers in the United States. CHARTER was designed with broad inclusion criteria, and a large sample size so as to afford ascertainment of the frequency and severity of HAND, as well as the specific contributions of HIV vs other factors (comorbidities) to neurocognitive impairment.

Here we present the baseline CHARTER neurobehavioral and neuromedical findings, including the relationships between HAND and CART, disease history and current severity, and functional outcomes. We used recently published international expert consensus guidelines "Frascati Criteria"[4] to classify the participants with respect to 3 levels of HIV-related neurocognitive impairment.

METHODS

Subjects. The 1,555 participants in this study were HIV infected (HIV+) and were drawn from 6 participating university centers: Johns Hopkins University (Baltimore, MD, n = 230); Mt. Sinai School of Medicine (New York, NY, n = 271); University of California at San Diego (San Diego, CA, n = 262); University of Texas Medical Branch (Galveston, TX, n = 261); University of Washington (Seattle, WA, n = 262); and Washington University (St. Louis, MO, n = 269). Subject recruitment began in September 2003 and ended in August 2007. Demographic, HIV disease, and treatment characteristics of the total sample are summarized in table 1.

Procedures. For their baseline assessment, all subjects completed a venipuncture, neuromedical assessment, comprehensive neuropsychological (NP) testing, detailed substance use history, structured psychiatric interviews for detecting lifetime and current diagnoses of substance use disorders and affective disorders, a measure of current mood, and self-report assessments of cognitive symptoms, vocational functioning, and independence with instrumental activities of daily living. For those who consented (n = 1,205), CSF was withdrawn by lumbar puncture (LP).

Standard protocol approvals, registrations, and patient consents. These procedures were approved by the Human Subjects Protection Committees of each participating institution. Written informed consent was obtained from all study participants.

Neuromedical examination. This included medical history, structured neurologic and medical examination, as well as collection of blood and urine samples. These procedures were performed by physicians, nurse practitioners, or trained nurses and research associates. The staff performing CHARTER neuromedical and NP assessments were certified by the coordinating center (San Diego).

Laboratory assessment. HIV infection was diagnosed by ELISA with Western blot confirmation. Routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, and CD4+ T cells (flow cytometry) were performed at each site's Clinical Laboratory Improvement Amendments (CLIA)–certified, or CLIA equivalent, medical center laboratory. HIV RNA levels were measured centrally in plasma and CSF by reverse transcriptase PCR (Roche Amplicor, v. 1.5, lower limit of quantitation 50 copies/mL).

Table 1 Demographic, infection risk, HIV disease, and treatment characteristics of CHARTER cohort (n = 1,555)

	Mean (SD), median (IQR), or %
Age, y	43.2 (8.5)
Education, y	12.5 (2.5)
Women	23
Non-Hispanic white	39
African American	49
Hispanic	9
Other ethnicity	3
Infection risk group	
IDU; MSM	28; 58
Heterosexual contact only	31
CDC stage: A; B; C	36.4; 26.4; 37.2
AIDS	63
Nadir CD4	174 (IQR = 49–300)
Current CD4	420 (IQR = 262–603)
Currently on CART[a]	71
Duration current regimen, mo	11 (IQR = 4–27)
Prior CART only[b]	14
ART naïve	15
Detectable HIV in plasma (n = 1,537)	59 (44% if on CART)
Detectible HIV in CSF (n = 1,205)	34 (16% if on CART)

Abbreviations: CART = combination antiretroviral therapy; CHARTER = CNS HIV Antiretroviral Therapy Effects Research; IDU = injection drug user; IQR = interquartile range; MSM = men who have sex with men.
[a] Protease inhibitor (PI)-based = 55%; non-nucleoside reverse transcriptase inhibitor (NNRTI)-based = 33%; PI-NNRTI-based = 6%; other = 6%.
[b] Previously on combination antiretroviral therapy, but none at study baseline.

Neurobehavioral examination. All participants completed a comprehensive neurocognitive test battery, covering 7 cognitive domains known to be commonly affected by HIV-associated CNS dysfunction (administration time = 2–2.5 hours; see table e-1 on the *Neurology*® Web site at www.neurology.org for listing of specific tests). The best available normative standards were used, which correct for effects of age, education, sex, and ethnicity, as appropriate. Test scores were automatically converted to demographically corrected standard scores (*t* scores) using available computer programs. To classify presence and severity of neurocognitive impairment, we applied a published objective algorithm that has been shown to yield excellent interrater reliability in previous multisite studies.[5] This algorithm conforms to the Frascati criteria for diagnosing HAND,[4] which requires presence of a least mild impairment in at least 2 of the 7 ability domains.

Psychiatric examination. Psychiatric diagnoses were assessed using the computer-assisted Composite International Diagnostic

Table 2 Frequency of general classes of comorbid conditions within CHARTER cohort comorbidity subgroups

	A. Incidental (n = 843), %	B. Contributing (n = 473), %	C. Confounding (n = 239), %	Group differences*
Low reading level[a]	15.3	27.8	49.2	A < B < C
Special education	2.8	15.4	31.8	A < B < C
Other school problems[b]	5.2	40.0	51.9	A < B < C
Brain trauma[c]	3.4	30.4	40.6	A < B < C
Cerebrovascular events[d]	0.1	7.6	18.0	A < B < C
Epilepsy	0	1.1	4.6	A < B < C
Other seizure history	1.8	11.6	23.4	A < B < C
Systemic medical[e]	27.2	55.6	63.6	A < B, C
CNS opportunistic disease	1.2	2.3	5.4	A < B, C
Major depression				
Lifetime	47.1	55.9	57.8	A < B, C
Current	13.5	16.1	15.5	
Psychotic disorder[f]	2.5	16.9	16.7	A < B, C
Any substance use disorder				
Lifetime	71.6	76.5	71.5	
Current	5.8	6.2	7.8	
Alcohol use disorder				
Lifetime	54.4	55.6	55.2	
Current	1.7	1.7	1.3	
Cannabis use disorder				
Lifetime	29.8	29.6	31.0	
Current	1.5	1.1	2.2	
Cocaine use disorder				
Lifetime	41.9	48.8	43.1	
Current	2.1	2.4	3.4	
Opioid use disorder				
Lifetime	13.4	23.0	20.1	A < B, C
Current	0.2	0.0	0.0	
Methamphetamine use disorder				
Lifetime	17.4	16.9	14.6	
Current	0.7	1.5	0.9	
Hallucinogen use disorder				
Lifetime	10.0	8.9	9.6	
Current	0.2	0.2	0.0	
Sedative use disorder				
Lifetime	7.5	8.0	9.2	
Current	0.0	0.4	0.4	
Inhalant use disorder				
Lifetime	3.7	3.2	3.8	
Current	0.0	0.2	0.0	
Other drug use disorder				
Lifetime	2.6	2.1	1.7	
Current	0.0	0.0	0.0	

—Continued

Interview (CIDI),[6] a structured instrument widely used in psychiatric research. The CIDI classifies current and lifetime diagnoses of mood disorders and substance use disorders, as well as other mental disorders. Current mood was assessed with the Beck Depression Inventory II.[7]

Functional impairment in everyday life. Reports of cognitive difficulties in everyday life were assessed using the Patient's Assessment of Own Functioning Inventory (PAOFI[8]). Increased dependence in performing instrumental activities of daily living (IADLs) was assessed with a modified version of the Lawton and Brody Scale.[9] We also administered an employment questionnaire that asks about any decreases in work productivity, accuracy/quality of work, increased effort required to do one's usual job, and increased fatigue in association with the usual workload.

HAND classifications. See Antinori et al.[4] for details of the Frascati criteria for HAND and algorithms for establishing those criteria. In brief, asymptomatic neurocognitive impairment (ANI) and mild neurocognitive disorder (MND) both require the presence of at least mild neuropsychological impairment that involves 2 or more ability domains, and is not readily attributable to comorbid conditions. ANI is asymptomatic in the sense that specified criteria for establishing at least mild negative effects on everyday functioning have not been met. In the case of MND, functional decline is established by at least 2 types of evidence regarding decreased everyday functioning. The third HAND diagnosis, HIV-associated dementia (HAD), requires overall neuropsychological impairment of at least moderate severity that is not readily attributable to comorbid conditions. In addition, "major" functional decline must be established by evidence of at least 2 types of everyday functioning problems that are of greater severity than with MND.

Classification of comorbid conditions. All subtypes of HAND require a determination that the neurocognitive impairment and functional disability are believed to be due to effects of HIV on the brain, and are not readily attributable to comorbid conditions. This determination requires not only detailed information about the comorbid conditions themselves, but also clinical judgment about their severity, their likely impact on neurocognition and everyday functioning, and their timing in relation to the course of HIV disease and any functional limitations in everyday life.

To facilitate interrater reliability of these determinations, we utilized the online supplement to the Antinori et al.[4] report, which provided detailed guidelines for classifying the most commonly encountered comorbid conditions with respect to whether they should be considered incidental, contributing, or confounding. In the current study, a senior neuropsychologist (R.K.H.) used the Antinori et al.[4] guidelines, with all available historical and testing data, to rate the comorbidity status of participants in all 6 centers. As a check on the reliability of this process, a senior neurologist and principal investigator of the Washington University site (D.B.C.) independently rated his patients (n = 269). Seventy-four percent of the independent ratings were identical. After discussion, only 7% (19 of 269) of the original ratings changed, and less than 5% required a change in HAND classification (change to or from the confounded group).

A majority of the CHARTER participants (54.2%; n = 843) was classified as having only incidental comorbidities, and 30.4% (n = 473) had contributing conditions; 15.4% (n = 239) had confounding comorbidities that precluded a HAND diagnosis (see table 2 for details concerning rates of major comorbidities found in these three groups).

Table 2 Continued

	A. Incidental (n = 843), %	B. Contributing (n = 473), %	C. Confounding (n = 239), %	Group differences*
Substance overdose with complications[g]	1.8	13.1	15.1	A < B, C
Recent substance use[h]	16.3	26.7	29.0	A < B, C
Sum of above, mean ± SD	1.5 ± 1.0	3.2 ± 1.4	4.2 ± 1.8	A < B < C

Abbreviation: CHARTER = CNS HIV Antiretroviral Therapy Effects Research.
[a] Wide Range Achievement Test, 3rd edition, Reading <80.
[b] Special tutoring or grade retention.
[c] Traumatic brain injury with loss of consciousness or other neurologic sequelae.
[d] Range from TIAs to completed strokes.
[e] Potentially significant medical comorbidity (e.g., diabetes mellitus, myocardial infarction, hepatitis C infection).
[f] Schizophrenia or bipolar disorder.
[g] Overdose requiring cardiopulmonary resuscitation or hospitalization.
[h] Positive breathalyzer or urine toxicology for psychoactive substances on day of testing.
*$p < 0.01$.

RESULTS Comorbidity groups and NP impairment. Table 3 describes the 3 comorbidity groups with respect to demographics, HIV disease and treatment characteristics, depressed mood, and everyday functioning. See table e-2 for a summary of raw scores on the neuropsychological test battery.

Fifty-two percent of the total CHARTER cohort (814/1555) were neuropsychologically impaired. NP impairment rates in the comorbidity groups were as follows: 40% of incidental; 59% of contributing; 83% of confounded.

Associations of NP impairment with HIV disease severity and treatment. CHARTER hypothesized a priori that NP impairment would show the strongest relationships with HIV disease and treatment characteristics in participants with only minimal comorbidities (i.e., the incidental group). Table 4 summarizes these relationships for the 3 comorbidity groups. NP impairment was associated with AIDS diagnosis, and lower nadir CD4, but only in the incidental group.

Also only in the incidental group, participants on CART had a higher rate of NP impairment than those not currently being treated. The latter finding may seem counterintuitive, especially since participants on CART were more likely to have undetectable virus in plasma (55% vs 4%, $p < 0.001$), but is consistent with those on CART having more advanced HIV disease (e.g., a higher proportion with

Table 3 Comorbidity group comparisons on demographics, HIV disease characteristics, ART status, depressed mood, and everyday functioning

	A. Incidental (n = 843)	B. Contributing (n = 473)	C. Confounded (n = 239)	Group differences*
Age	42.7 (8.8)	44.0 (8.1)	43.4 (7.7)	A < B
Education	13.0 (2.5)	12.1 (2.3)	11.5 (2.6)	A > B > C
WRAT-3 Reading	95.3 (14.6)	89.0 (15.8)	80.6 (18.2)	A > B > C
% Male	79.1	73.4	74.5	A > B
% Caucasian	43.8	34.5	33.1	A > B, C
Known infection duration, mo	116.6 (77.1)	129.2 (89.3)	124.5 (102.2)	A < B
% AIDS	60.1	64.1	70.3	A < C
Nadir CD4	216.2 (200.4)	203.8 (199.3)	181.8 (169.2)	A > C
Current CD4	467.0 (278.4)	452.8 (300.6)	448.9 (279.6)	
% Detectable HIV RNA (plasma)	60.0	55.9	60.0	
Plasma viral load (log_{10})	2.87 (1.29)	2.82 (1.33)	2.81 (1.31)	
% Detectable HIV RNA (CSF; n = 1,205)	35.2	32.0	33.0	
CSF viral load (log_{10})	2.20 (.83)	2.12 (.79)	2.15 (.85)	
On CART now, %	69.9	71.7	74.1	
CPE rating	1.63	1.61	1.66	
Prior ART, none now, %	12.8	15.0	14.2	
ART naïve, %	17.2	13.3	11.7	
Beck Depression Inventory	12.3 (10.0)	15.7 (11.1)	16.5 (11.9)	A < B, C
Employed, %	33.0	19.7	13.0	A > B, C
Cognitive complaints	4.9 (6.3)	7.4 (8.0)	9.3 (9.0)	A < B < C
IADL impairments	1.3 (1.8)	1.9 (2.1)	2.1 (2.3)	A < B, C

Abbreviations: ART = antiretroviral therapy; CART = combination antiretroviral therapy; CPE = CNS Penetration Effectiveness Score[10]; IADL = independent activities of daily living; WRAT-3 = Wide Range Achievement Test, 3rd edition.
*$p < 0.01$.

Table 4 Neuropsychological impairment rates for comorbidity groups by HIV disease variables and current treatment status

	Incidental (n = 843), %	Contributing (n = 473), %	Confounding (n = 239), %
AIDS	43[a]	59	83
Non-AIDS	36	58	83
Nadir CD4 <200	44[b]	61	81
Nadir CD4 ≥200	35	56	87
Current CD4 <200	47	64	76
Current CD4 >200	39	58	85
Currently on CART	43[c]	61	84
Past ARVs (none currently)	28	54	82
ARV naïve	36	54	79
Plasma HIV RNA (n = 1,105 on CART)			
Detectable	45	63	80
Undetectable	42	59	87
CSF HIV RNA (n = 848 on CART)			
Detectable	42	49	83
Undetectable	43	61	85

Abbreviations: ARV = antiretroviral drugs; CART = combination antiretroviral therapy.
[a] Worse than incidental subgroups without history of AIDS ($p < 0.02$).
[b] Worse than incidental subgroups with less severe immunosuppression ($p < 0.01$).
[c] Worse than if had prior ARVs, but none currently.

AIDS diagnosis; 74% vs 27%, $p < 0.01$). It may be, therefore, that relationship of CART to NP outcomes depends upon multiple factors, including disease history and comorbidities, as well as the success of treatment in suppressing the virus.

A series of multivariate logistic regression analyses was performed to identify treatment and disease characteristics that, in combination, best predicted global NP impairment (impaired/normal). The candidate predictors included comorbidity group, nadir CD4 <200 (yes/no), current CD4 <200 (yes/no), cumulative duration of ART experience, CNS penetration effectiveness (CPE) rating[10] for current ART regimen, detectable HIV in plasma (yes/no), hepatitis C serostatus (yes/no), and their interactions with comorbidity group, plus interactions between nadir CD4 and detectable plasma viral load. The first analysis included all participants receiving CART having complete data on the predictor variables (n = 1,066), and revealed the following predictors: comorbidity group ($p < 0.001$), nadir CD4 <200 ($p = 0.007$), and detectable plasma viral load × nadir CD4 <200 ($p = 0.037$). The plot in the figure displays the size and directions of the effects, comparing the 4 nadir CD4 × detectable viral load subgroups at each comorbidity level. Follow-up logistic regressions for the 3 comorbidity groups separately revealed that, only for ARV-treated participants in the incidental group (n = 575), predictors of NP impairment included nadir CD4 <200 ($p = 0.007$), detectable plasma viral load ($p = 0.045$), and their interaction ($p = 0.017$). As the figure indicates, a substantially lower impairment rate was seen in treated participants with undetectable viral load and nadir CD4 >200 (30% vs 47% for the combined other Incidental subgroups, $p = 0.002$).

Functional disability and HAND diagnoses. According to the Frascati criteria, HAND diagnoses cannot be made in HIV-infected people with severe comorbidities (our confounded group). Therefore, HAND diagnoses were determined in the remaining CHARTER groups with lesser comorbidities (n = 1,316) by considering the results of the NP and self-report functional measures. NP impairment was noted in 617 participants (46.9%) and of these, 430 (70%) were considered "asymptomatic"; that is, their self-reports did not suggest their NP impairment was interfering significantly with their everyday functioning. Of the remaining 185, 154 had MND and only 31 had HAD.

It is emphasized that the above distributions of HAND classifications exclude the large subgroup of HIV-infected participants who were NP-normal (n = 699, or 53.2% of the combined incidental and contributing comorbidity groups). If we consider the entire CHARTER sample without severe comorbidities (n = 1,316), we obtain the following overall rates of HAND diagnoses: 32.7% ANI, 11.7% MND, and 2.4% HAD.

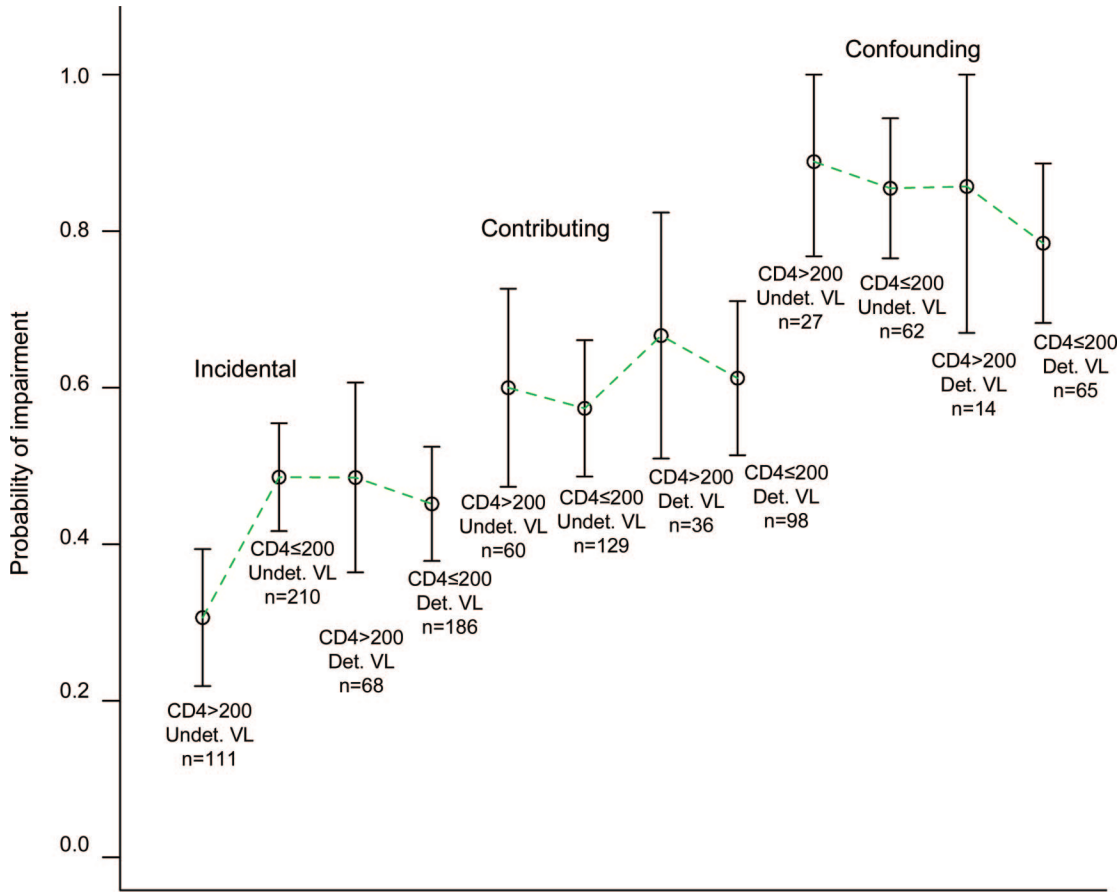
Other neuropsychiatric diagnoses. For the combined incidental and contributing comorbidity groups, NP impairment was not significantly related to either current or lifetime major depressive disorders, but people with a (mostly remote) history of any substance abuse or dependence were less likely to be NP impaired (44% vs 54%).

DISCUSSION

Although CART has had a major impact on the course and long-term prognosis of HIV infection, all but the most severe CNS manifestations of infection remain very common. One important finding of our study is that profound neurocognitive impairment—HAD—has become rare. Whereas estimates of HAD prevalence in the pre-CART era ranged from about 10% to 15%,[11,12] only 2% of the large CHARTER cohort met both NP and functional criteria for dementia. By contrast, 44% of CHARTER participants without severe comorbidities met criteria for milder forms of HAND, and this is consistent with pre-CART reports.[13,14]

Whereas Frascati criteria for HAND focus on neurocognitive impairment, higher rates of CNS abnormalities might be seen with additional consider-

Figure Probabilities of impairment, and 95% confidence intervals, for subjects on combination antiretroviral therapy, classified by comorbidity group (incidental, contributing, and confounding), plasma HIV-1 viral load (UD = undetectable, Det = detectable), and nadir CD4 (<200 vs >200 cells/μL)



Sample sizes (N) for each group are given.

ation of noncognitive neurologic findings (saccadic eye movement, tone, reflexes, facial minima).

As stated, the present subject sample was recruited with few exclusion criteria in an effort to be broadly representative of patients being followed in the university-based clinics. The results are not necessarily generalizable to other types of clinical settings, or to people who were unwilling to volunteer. Out of 1,900 potential participants who were screened and invited to participate, 1,555 (78.1%) agreed to do so. The 435 screened individuals who declined were comparable to the study participants with respect to age (mean = 43.9 vs 43.2 years), but had slightly lower education levels (mean = 12.1 vs 12.5 years), and somewhat higher rates of female gender (30.1% vs 23.3%) and nonwhite ethnicity (73.3% vs 60.7%). Again, NP test norms were corrected for demographics, which were unrelated to impairment status in CHARTER.

The CART era differences between lower frequencies of HAD and stable or increased prevalence of milder forms of HAND have not been fully explained. Studies have demonstrated some NP benefit of instituting CART regimens in patients having HAND,[15-18] but in many cases impairment persists. Relatively high percentages of CART-treated individuals continue to show some active viral replication as well; e.g., 482 of the 1,105 CHARTER participants on CART (44%) had detectable HIV RNA in plasma. Whereas rates of virologic suppression in recent clinical trials of ART typically reach 80%–90%, this is not the case in clinic-based samples, where rates of virologic suppression have been lower and similar to our findings.[19,20] Extended survival with incomplete viral suppression is likely to be associated with prolonged CNS inflammatory responses that are implicated in the pathogenesis of HAND.[21-24]

CHARTER findings also indicate that a history of more severe immunosuppression confers an increased risk for HAND, even after CART-related immune recovery; over 70% of our participants receiving CART had a nadir CD4 <200. This raises the question of whether better neurobehavioral outcomes could be achieved by initiating CART earlier

and preventing more advanced immunosuppression, rather than using declines in CD4 levels to trigger treatment. In fact, among CHARTER participants who did not have significant comorbid risks for CNS dysfunction, much lower rates of HAND were seen in those who achieved successful HIV suppression on CART and had nadir CD4 counts above 200. This was not explained by subgroup differences in other potentially influential factors, such as age or estimated duration of infection, or duration of CART, which was slightly longer in the nadir >200/undetectable group. It is possible that advanced immunosuppression reflected by low nadir CD4 is a "legacy" event whose neurologic consequences may persist. Recent reports of both neurocognitive impairment and brain imaging abnormalities in acute and early HIV infection are intriguing, and consistent with the possibility that such a "legacy" event might occur very early,[25,26] indicating the importance of conducting careful longitudinal studies that focus more on early stages of HIV infection. Such studies should investigate the timing of incident neurobehavioral impairment within the context of developing immunosuppression and clinical disease, and whether earlier CART intervention might prevent or reverse CNS injury.

The findings of this study may appear to conflict with those of other recent reports indicating that neurocognitive improvement was greatest in patients treated with better CNS-penetrating CART regimens[27] and that viral suppression in CSF corresponds to better neurocognitive outcomes.[17] However, the latter findings are derived from longitudinal studies where the clinical outcome measurements were synchronized with the initiation and follow-up of a new CART regimen. In contrast, the data reported here are from a single cross-sectional evaluation. Cross-sectional analyses complement but do not replace those of prospective longitudinal studies and randomized clinical trials, and one cannot expect the 2 designs to yield the same results. Additionally, CART probably benefits the brain via multiple mechanisms, including immune recovery, reduced immune activation, and viral suppression—both systemically and in the CNS. Optimizing all of these parameters and possibly others as well may be needed to obtain the best neurologic protection and recovery. Randomized clinical trials targeting each of these mechanisms are needed to determine what will be the most clinically useful approach to the prevention and treatment of HAND.

CHARTER has attempted to systematically implement the recently published Frascati guidelines[4] to classify comorbid conditions in a large, diverse sample of HIV-infected adults receiving care. Comorbidities in the HIV-infected population are numerous and complex, and in the past it has proven difficult to reliably determine whether they are severe enough to preclude diagnosing an HIV-related neurobehavioral disorder.[5] The Frascati guidelines clearly have improved this reliability: independent neurologist and neuropsychologist raters in CHARTER agreed on more than 95% of cases concerning whether there were confounds that preclude a HAND diagnosis.

The CHARTER experience suggests that, using the Frascati guidelines, 2 criteria for HAND diagnoses can be assessed reliably: NP impairment and confounding conditions. Impairment of everyday functioning also must be documented as a criterion for symptomatic HAND, and this remains a challenge. Self-reports of functional decline are easy to obtain, but may lead to false-positive classifications (e.g., exaggerated self criticism due to depression)[28] as well as false-negative ones due to lack of insight or avoidance of everyday situations that require abilities which have become impaired. Use of objective, performance-based functional assessments to supplement self-report may improve detection of symptomatic HAND,[4,9,29] but such assessments are impractical in most clinical settings. Therefore, an inability to document functional decline in a person who clearly meets the other HAND criteria will continue to be a common clinical experience. Such cases deserve careful attention and monitoring, though, because they may carry a negative medical prognosis[18,30,31] and the apparent lack of functional decline may change if life circumstances become more demanding.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by D.R. Franklin, Jr., Dr. Vaida, and Dr. Ake.

COINVESTIGATORS

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DISCLOSURE

Dr. Heaton serves on a scientific advisory board for the NINCDS; serves on the editorial boards of the *Journal of the International Neuropsychological Society*, the *Journal of Clinical and Experimental Neuropsychology*, and *The Clinical Neuropsychologist*; has received royalties from the publication of *Revised Comprehensive Norms for and Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults* (Psychological Assessment Resources, Inc., 1991-present), *Revised Comprehensive Norms for and Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults Scoring Program* (Psychological Assessment Resources, Inc., 1994-present), and Wisconsin Card Sorting Test Manual-Revised and Expanded (Psychological Assessment Resources, Inc., 1991-present); and receives research support from the NIH (P30 MH62512 [coinvestigator], P50 DA26306 [coinvestigator], P01 DA12065 [coinvestigator], R01 MH60720 [coinvestigator], R01 MH73433 [PI], N01 MH22005 [coinvestigator], R01 MH58076 [coinvestigator], R01 MH78748 [coinvestigator], R01 MH78737 [coinvestigator], U01 MH83506 [coinvestigator], R01 MH83552 [coinvestigator], and R01 MH81861 [coinvestigator]). 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