Asymptomatic HIV-associated neurocognitive impairment increases risk for symptomatic decline

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Editorial, page 2046

Supplemental data at Neurology.org

ABSTRACT

Objective: While HIV-associated neurocognitive disorders (HAND) remain prevalent despite combination antiretroviral therapy (CART), the clinical relevance of asymptomatic neurocognitive impairment (ANI), the most common HAND diagnosis, remains unclear. We investigated whether HIV-infected persons with ANI were more likely than those who were neurocognitively normal (NCN) to experience a decline in everyday functioning (symptomatic decline).

Methods: A total of 347 human participants from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort were NCN (n = 226) or had ANI (n = 121) at baseline. Neurocognitive assessments occurred approximately every 6 months, with median (interquartile range) follow-up of 45.2 (28.7–63.7) months. Symptomatic decline was based on self-report (SR) or objective, performance-based (PB) problems in everyday functioning. Proportional hazards modeling was used to generate risk ratios for progression to symptomatic HAND after adjusting for baseline and time-dependent covariates, including CD4+ T-lymphocyte count (CD4), virologic suppression, CART, and mood.

Results: The ANI group had a shorter time to symptomatic HAND than the NCN after adjusting for baseline predictors: adjusted risk ratios for symptomatic HAND were 2.0 (confidence interval [CI] 1.1–3.6; $p = 0.02$) for SR, 5.8 (CI 3.2–10.7; $p < 0.0001$) for PB, and 3.2 (CI 2.0–5.0; $p < 0.0001$) for either SR or PB. Current CD4 and depression were significant time-dependent covariates, but antiretroviral regimen, virologic suppression, and substance abuse or dependence were not.

Conclusions: This longitudinal study demonstrates that ANI conveys a 2-fold to 6-fold increase in risk for earlier development of symptomatic HAND, supporting the prognostic value of the ANI diagnosis in clinical settings. Identifying those at highest risk for symptomatic decline may offer an opportunity to modify treatment to delay progression. ***Neurology*® 2014;82:2055–2062**

GLOSSARY

ANI = asymptomatic neurocognitive impairment; **ART** = antiretroviral therapy; **BDI** = Beck Depression Inventory-II; **CART** = combination antiretroviral therapy; **CHARTER** = CNS HIV Anti-Retroviral Therapy Effects Research; **CI** = confidence interval; **HAD** = HIV-associated dementia; **HAND** = HIV-associated neurocognitive disorders; **HCV** = hepatitis C virus; **IADL** = instrumental activities of daily living; **MMT-R** = revised version of the Medication Management Test; **MND** = mild neurocognitive disorder; **NCN** = neurocognitively normal; **NNRTI** = non-nucleoside reverse transcriptase inhibitor; **PAOFI** = Patient's Assessment of Own Functioning Inventory; **PB** = performance-based; **PI** = protease inhibitor; **SR** = self-report.

Combination antiretroviral therapy (CART) has reduced morbidity and mortality among those living with HIV (HIV+), but HIV-associated neurocognitive disorders (HAND) remain prevalent.[1–3] While the prevalence of the most severe form of HAND, HIV-associated dementia (HAD), is now uncommon (2%[2]), milder forms of HAND (termed asymptomatic neurocognitive impairment [ANI] and mild neurocognitive disorder [MND] according to the Frascati criteria[1]) have been reported in 40%–56% of HIV+ cases and may be more prevalent at earlier (less severe) disease stages in the CART era.[2,4,5]

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The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Government.

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ANI is the most common form of HAND,[2] accounting for approximately 70% of cases, and is characterized by impairment on neurocognitive testing with no obvious accompanying interference in daily functioning.[1] Recent commentaries have called into question the clinical relevance of ANI,[6,7] suggesting that the diagnostic criteria for ANI generate an unacceptably high false-positive rate[6] and a lack of evidence that patients with ANI are at greater risk for progression to more severe impairment.[7] Although previous studies have shown that an antemortem ANI diagnosis is related to both increased dendritic injury and HIV encephalitis in individuals without significant comorbidities,[8,9] these studies involved terminally ill patients, limiting generalizability to medically stable HIV+ patients on CART. The clinical relevance of ANI would be bolstered if ANI predicted future symptomatic disease, i.e., problems with everyday functioning. To evaluate this, we performed a longitudinal study comparing risk of developing symptomatic decline in HIV+ persons who at baseline were neurocognitively normal (NCN) vs those with ANI.

METHODS

Participants. Study participants were from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study, details of which were reported previously.[2] Individuals from the longitudinal CHARTER cohort were selected for this study on the basis of being classified as ANI (n = 121) or NCN (n = 226) at baseline according to the Frascati criteria based on comprehensive neuromedical, neurocognitive, psychiatric, and functional evaluations.[1] No individuals had non-HIV, severely confounding comorbidities[2] that would preclude a HAND diagnosis (table 1). A total of 2,749 visits were analyzed.

Procedures. ***Neuromedical examination.*** The standardized neuromedical examination included a medical history, structured neurologic and medical examination, as well as collection of blood, CSF, and urine samples.[2]

Laboratory assessment. Laboratory measurements included routine clinical chemistry panels, complete blood counts, rapid plasma reagin, hepatitis C virus antibody, CD4+ T lymphocytes, and HIV RNA levels measured in plasma and CSF.[2]

Neurocognitive examination. The CHARTER comprehensive neurocognitive test battery covered 7 cognitive domains: motor function (perceptual-motor speed), verbal fluency, executive function, attention/working memory, speed of information processing, learning, and memory.[2,10] ANI and NCN diagnoses were rendered according to Frascati criteria.[1] Premorbid verbal IQ estimates were obtained using the oral reading subtest from the Wide Range Achievement Test.[11]

Psychiatric examination. The computer-assisted Composite International Diagnostic Interview[12] was administered to establish current and lifetime diagnoses of mood disorders and substance use disorders. Current depressive symptoms were assessed with the Beck Depression Inventory–II (BDI).[13]

Self-report measures of daily functioning. Reports of cognitive difficulties in everyday life were assessed using the Patient's Assessment of Own Functioning Inventory (PAOFI).[14] Increased dependence in performing instrumental activities of daily living (IADL) was assessed with a modified version of the Lawton and Brody Scale.[15] 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.

Performance-based measures of daily functioning. Medication management was assessed via a revised version of the Medication Management Test (MMT-R[15]). Briefly, the MMT-R consists of both pill dispensing and medication inference questions. Vocational function was assessed using standardized work samples (MESA SF2)[16] and the next-generation Valpar COMPASS programs.[17] The Valpar assessment consists of multimodal, criterion-referenced instruments designed to establish participant skill level in areas of vocational functioning.[15]

Classification of symptomatic status. Data-driven formulas were used to determine symptomatic status 3 ways: (1) using only self-report (SR) measures of daily functioning; (2) using only performance-based (PB) measures of daily functioning; and (3) a dual method that classifies a person as symptomatic if he or she meets any 2 of the SR or PB criteria for symptomatic impairment of daily functioning. Employment status that was associated with cognitive decline (reported decline in work ability or inability to work due at least in part to cognitive issues on the IADL) counted as one area of functional decline in all formulas, in accordance with the Frascati criteria.[1]

To determine functional decline in the SR formula, scores on the PAOFI and IADL were examined. A PAOFI score of 3 or higher (reflecting at least 3 cognitive symptoms) was used to indicate functional impairment on that measure. To control for depression in SR, participants with elevated BDI scores (BDI $\geq$ 17) needed to exhibit a higher level of complaint on the PAOFI (PAOFI $\geq$10 complaints) to qualify for functional impairment on this measure. Scores on the IADL that showed decline from "best"' to "'now" in 2 or more areas that were identified as being at least partially due to cognitive problems (vs physical impairment) also qualified as functionally impaired.[1,18,19] In order to be called symptomatic by SR, participants had to be (1) PAOFI and IADL impaired or (2) PAOFI or IADL impaired and either unemployed or employed, but with self-reported difficulty in job performance, which was at least partially due to cognitive problems.

Since published, demographically adjusted normative standards are not available for the performance-based tests, we derived cutpoints for the MMT-R and Valpar from the neurocognitively normal subset of CHARTER participants (n = 375; mean age = 43.4 years; 80% male; 42% Caucasian; mean education = 12.5 years). Based on prior studies,[15] cutpoints were determined based on a normal distribution, so that 16% of the NCN cohort would be impaired at 1 SD (cutoff scores: MMT-R $<$5 and Valpar $<$24) and 2% of the cohort would be impaired at 2 SDs (cutoff scores: MMT-R $<$2 and Valpar $<$17). The MMT-R and Valpar were administered at the first longitudinal visit (6 months after the CHARTER baseline) and every 6 months thereafter, but were not performed at the baseline (entry) visit.

In the PB formula, functional impairment was defined as scores 1 or 2 SDs below the mean on the MMT-R and Valpar, also consistent with the Frascati criteria.[1] Participants were coded as symptomatic if (1) both MMT-R and Valpar scores were at least 1 SD below the mean or (2) one task was 2 or more SDs

Table 1 Comparison of participants who were neurocognitively normal and asymptomatically neurocognitively impaired at baseline

	NCN (n = 226), mean (SD), %, or median (IQR)	ANI (n = 121), mean (SD), %, or median (IQR)	p Value[a]
Age, y[b]	43.0 (8.6)	44.8 (8.0)	
Education, y[b]	12.9 (2.4)	13.5 (2.2)	0.04
Estimated verbal IQ[b]	97.4 (13.2)	92.6 (14.5)	0.002
% Male[c]	81.9	81.8	
% Caucasian[c]	45.6	46.3	
% Lifetime substance use diagnosis[c]	71.2	69.4	
% Lifetime major depression[c]	52.6	45.4	
% With contributing comorbidity[c,d]	22.6	44.6	<0.0001
% AIDS[c]	56.2	62.8	
Current CD4, cells/mm^3[e]	459 (290–669)	425 (286–578)	
Nadir CD4, cells/mm^3[e]	201 (61–370)	162 (38–273)	0.03
% On ART[c]	66.2	72.7	
% Undetectable in plasma[c]	38.6	45.8	
% Undetectable in CSF[c]	59.6	75.9	0.006
Estimated duration HIV+, mo[b]	117.7 (75.0)	120.7 (81.6)	
% HCV+[c]	20.4	27.3	

Abbreviations: ANI = asymptomatic neurocognitive impairment; ART = antiretroviral therapy; CHARTER = CNS HIV Anti-Retroviral Therapy Effects Research; HCV = hepatitis C virus; IQR = interquartile range; NCN = neurocognitively normal.
[a] Only p values <0.05 are reported.
[b] t test.
[c] χ^2 test.
[d] Comorbidity status was based on CHARTER classification.[2] Contributing comorbidities are non-HIV factors that can influence neurocognitive impairment but are not considered the primary cause of the impairment.
[e] Wilcoxon rank test.

below the mean and the subject was unemployed due to cognitive issues.

All the diagnostic criteria described above for functional decline were also used to define functional impairment in the SR/PB method. Measures included in each formula criterion are summarized in table e-1 on the *Neurology*® Web site at Neurology.org (at least 2 criteria were necessary for functional impairment).

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.

Statistical methods. Kaplan-Meier estimates were generated comparing NCN and ANI participants on time to symptomatic threshold defined by the 3 criteria: using only SR symptoms, only PB symptoms, and having SR, PB, or both (SR/PB). Proportional hazards modeling was used to generate risk ratios and their 95% confidence interval (CI) estimates for symptomatic HAND, after adjusting for baseline or time-dependent variables (table 1). Separate models were developed based on each of the 3 criteria: SR, PB, and SR/PB. Multivariable models initially included all univariably significant ($p < 0.10$) predictors. Time-varying predictors of earlier decline to symptomatic status in univariable survival analyses that were screened for inclusion in multivariate models included current CD4 count, current major depressive disorder, antiretroviral therapy (ART) use status, ART regimen type (protease inhibitor [PI]-based vs non-nucleoside reverse transcriptase inhibitor [NNRTI]-based/PI-NNRTI-based/other), CNS penetration effectiveness score of ART regimen,[20] viral load in plasma and CSF, and current substance use disorder. Nonsignificant ($p \geq 0.05$) predictors were subsequently removed from the final multivariable models. Interactions of the remaining variables were tested and retained if significant at a $p < 0.05$ level. Baseline demographic characteristics, HIV disease–related laboratory measures, AIDS status, treatment-related variables, substance use variables, and psychiatric variables were compared using t tests, Wilcoxon rank tests, or χ^2 tests, as appropriate, between ANI vs NCN cases (table 1) and between participants who became symptomatic vs those who remained asymptomatic (table 2).

RESULTS **Survival analysis of ANI as a predictor of symptomatic HAND.** Kaplan-Meier estimates comparing ANI and NCN on time to symptomatic HAND showed that ANI was a predictor of earlier time to symptomatic status using any of the 3 measures: SR ($p = 0.003$), PB ($p < 0.0001$), or SR/PB ($p < 0.0001$) (figure). The survival analyses were repeated considering only those cases that were virally suppressed in plasma at baseline (NCN = 85, ANI = 55). ANI remained a strong predictor of earlier time to symptomatic status using PB and SR/PB ($p < 0.0001$). For SR only, the relationship did not attain significance, but was suggestive of an association ($p = 0.08$). At baseline, the ANI group had higher education than the NCN

Table 2 Adjusted relative risk for symptomatic progression: Asymptomatic neurocognitive impairment vs neurocognitively normal

Criteria for symptomatic status	Relative risk[a]	95% CI	*p* Value
Self-report	2.00	1.09–3.62	0.02
Performance-based	5.81	3.24–10.75	<0.0001
Self-report or performance-based	3.18	2.04–4.99	<0.0001

Abbreviations: ANI = asymptomatic neurocognitive impairment; CI = confidence interval; NCN = neurocognitively normal.
[a] Relative risk for ANI vs NCN; all risk ratios adjusted for baseline education, estimated verbal IQ, nadir CD4, $\log_{10}$ CSF viral load, and comorbidity classification[2] in proportional hazards models.

group (13.5 [2.2] vs 12.9 [2.4], $p = 0.04$), but had lower verbal IQ estimates (92.5 [14.5] vs 97.4 [13.2], $p = 0.002$), lower nadir CD4 counts (162 [38–273] vs 201 [61–370], $p = 0.03$), were more likely to have an undetectable viral load in CSF (75.9% vs 59.6%; $p = 0.004$), and a greater percent of people with moderate "contributing" vs "incidental" (minimal) comorbidities (table 1). Using proportional hazards modeling, we generated risk ratios for earlier decline to symptomatic HAND that adjusted for these variables. After adjustment, ANI remained a predictor of earlier decline to symptomatic HAND using all 3 methods of measurement (SR, PB, and SR/PB, all p values <0.05, table 3).

Baseline predictors of decline to symptomatic HAND (other than ANI status). Overall, 110 (31.7%) of the entire group (50.4% for ANI and 21.7% for NCN, $p < 0.0001$) experienced a decline to symptomatic HAND measured by either SR or PB. When comparing baseline characteristics between those who declined to symptomatic HAND and those who did not, those who declined were older, had less education, were more often female, were more likely to have a lifetime substance use disorder, had greater than incidental (minimal) comorbidity, were more likely to have an AIDS diagnosis, had a lower nadir CD4, and were more likely to be hepatitis C virus (HCV)+. Race/ethnicity, CART status, current CD4 count, plasma and CSF viral load, and estimated duration of HIV infection did not predict decline (table 3). Of the 49 patients with NCN who ultimately became symptomatic, 13 developed neurocognitive impairment at a visit before the SR or PB decline, and 36 experienced the NC decline simultaneously with the SR/PB decline. The patients with NCN who declined had worse initial global deficit scores than nondecliners and scored worse in the ability areas of learning, recall, working memory, and motor coordination (all $p < 0.05$; table e-2).

Time-dependent predictors of earlier symptomatic status. Together, baseline ANI vs NCN status and a time-dependent current diagnosis of major depressive disorder were significant predictors of time to decline using SR-based measures to define symptomatic status. Baseline ANI vs NCN status and current CD4 count, in combination, were significant predictors of time to decline using PB only and SR/PB measures to define symptomatic status (table 4).

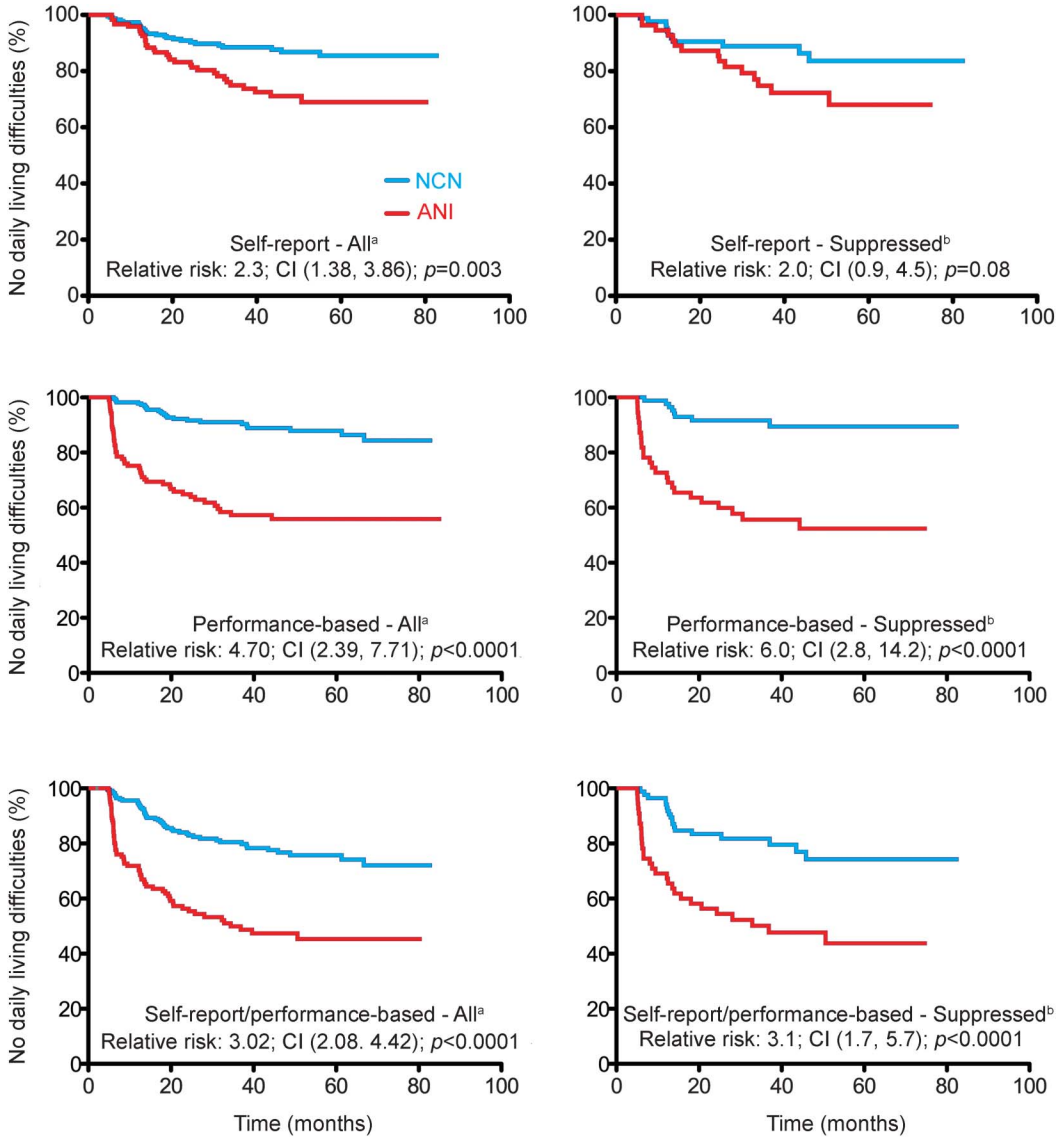
DISCUSSION While the introduction of CART has markedly reduced the rate of the most severe form of HAND—HAD—from an estimated 15% in the 1980s[5] to perhaps 2% currently,[2] this has not been accompanied by a similar reduction in the milder forms of HAND (ANI and MND),[1] with at least 40% of HIV+ patients manifesting some level of neurocognitive impairment.[4] In the cross-sectional CHARTER study of 1,316 patients without major neurologic comorbidities, 617 (47%) had some level of NCI; of these, 70% were classified as ANI, 25% as MND, and 5% as HAD.

Given that ANI is the most prevalent form of HAND, the clinical relevance of this diagnosis is clearly important. It has been argued that since ANI is "asymptomatic," it may have little clinical significance. Indeed, some have contended that establishing the diagnosis may be wasteful of resources and needlessly worrying to patients. For instance, ANI could represent brain injury that occurred in the early stages of HIV infection, is not progressive, and has no future consequences. However, our findings of increased progression in ANI argue against that interpretation. ANI patients progress to symptomatic status faster than those without ANI regardless of whether functional worsening was measured by self-report, performance, or either of these indices. Therefore, a major criticism of ANI—that it does not predict anything clinically important—is inaccurate according to this study's findings.

The magnitude of ANI as a predictor of decline to symptomatic status was substantial, ranging from relative risk of 2.3 CI (1.4–3.9) for decline based on self-report, arguably the weakest measure, to 4.7 CI (2.4–7.7) on performance-based criteria, which likely has greater reliability. Considering both criteria (the most likely scenario in many settings), the relative risk is 3.0 CI (2.1–4.4) (figure, all participants analyses). The size of this effect, therefore, is clinically meaningful.

Second, it has been suggested that ANI may simply be a statistical artifact of the particular testing procedures and algorithms proposed in the Frascati criteria.[6] While a detailed treatment of the statistical argument is beyond the scope of this article, the following 2 comments may be warranted: (1) statistical arguments rooted primarily in assumptions of Gaussian distributions of test scores may not be the most appropriate[7]; and (2) it seems unlikely that the growing number of studies that report differences in rates of impairment between HIV+ and HIV− participants can be dismissed as artifactual. In

Figure **Asymptomatic neurocognitive impairment increases risk for earlier decline to symptomatic HIV-associated neurocognitive disorders, even with viral suppression on combination antiretroviral therapy**



Relative risk for asymptomatic neurocognitive impairment (ANI) vs neurocognitively normal (NCN) as a predictor of earlier decline to symptomatic HIV-associated neurocognitive disorders (HAND) using self-report only, performance-based only, and self-report or performance-based criteria for symptomatic HAND. Viral suppression = plasma viral load ≤50 copies per mL at baseline. CI = confidence interval. [a] Total sample: ANI = 121; NCN = 22. [b] Sample with viral suppression at baseline: ANI = 55; NCN = 85.

addition, neuroimaging studies find detectable structural, functional, and spectroscopic evidence of brain abnormalities even in the acute and early phases of HIV infection.[21–25]

Of interest, those with ANI at baseline had evidence of more advanced prior HIV disease, e.g., lower nadir CD4 and greater likelihood of an AIDS diagnosis. This finding supports the concept that ANI is an HIV-driven process that, like more severe forms of HAND, is more likely with greater levels of prior immunosuppression.

We noted that women were overrepresented among those who experience symptomatic decline (table 3). Possible explanations may include that they had less education (13.4 years men vs 11.9 women; $p < 0.0001$) and had higher lifetime rates of major depression (47.5% men vs 61.9% women), both of which track with worse everyday functioning. They were also less likely to be on ART at baseline (ART = 71% men vs 51% women; $p = 0.0.03$) and had more visits during which HIV was detectable in plasma (23.0% men vs 31.8% women).

Several other cofactors such as substance use disorders and HCV coinfection were independently associated with symptomatic progression of ANI. This

Table 3 Baseline characteristics of nondecliners and decliners to symptomatic HAND (SR/PB)

	No decline (n = 237), mean (SD), %, or median (IQR)	Decline (n = 110), mean (SD), %, or median (IQR)	*p* Value	Cohen *d*/OR (95% CI)[a]
Background factors				
Age, y[b]	42.6 (8.7)	45.7 (7.4)	0.002	0.37
Education, y[b]	13.2 (2.3)	12.6 (2.2)	0.007	−0.26
% Male[c]	86.9	70.9	0.0003	2.7 (1.6–4.8)
% Lifetime substance use diagnosis[c]	65.8	80.9	0.004	2.2 (1.3–3.8)
% With comorbidity[c]	24.9	41.8	0.001	2.2 (1.3–3.5)
Disease factors				
% AIDS[c]	54.4	67.3	0.02	1.7 (1.1–2.8)
Nadir CD4, cells/mm^3[d]	204 (56–378)	163 (55–277)	0.03	−0.26
% HCV+[c]	18.1	32.7	0.003	2.2 (1.3–3.7)

Abbreviations: CI = confidence interval; HAND = HIV-associated neurocognitive disorders; IQR = interquartile range; OR = odds ratio; PB = performance-based; SR = self-report.
Ethnicity, on/off antiretroviral therapy, CD4, plasma viral load, CSF viral load, and estimated duration of HIV infection were nonsignificant ($p \geq 0.05$).
[a] *t* test.
[b] χ^2 test.
[c] Wilcoxon rank test.
[d] Cohen *d* = effect size.

is consistent with cross-sectional data showing that, for example, methamphetamine confers greater risk of poorer functional outcomes in HIV.[26] Together with the 3-year greater age of the decliners, these cofactors may produce greater CNS vulnerability to HIV-associated decline. Only 2 time-dependent factors, current CD4 and current major depression, predicted decline to symptomatic status using 1 or more criteria for symptomatic status. It is interesting that current CART, CART regimen, and virologic control did not contribute to the relative risk of decline.

Self-report of cognitive symptoms, at any point in time, requires not only the presence of everyday-functioning difficulties themselves but also awareness or insight on the part of the individual being assessed. We are unable to tell whether our participants' "declines" to symptomatic status by SR reflect actual increases in functional impairment or simply increased awareness of such impairment that may have existed even at baseline. Such increased awareness might occur if a person is faced with more cognitively demanding situations in everyday life or if there is reduced support

Table 4 Time-dependent correlates of decline to symptomatic HAND

	Univariable *p* Value	Multivariable		
		RR	95% CI for RR	*p* Value
Self-report				
ANI vs NCN	0.0007	2.81	1.65–4.76	0.0001
Current MDD	0.011	3.00	1.56–5.77	0.001
Performance-based				
ANI vs NCN	<0.0001	5.17	3.19–8.39	<0.0001
Current CD4	0.0014	1.21	1.08–1.35	0.0006
SR or PB				
ANI vs NCN	<0.0001	3.41	2.33–5.00	<0.0001
Current CD4	0.033	1.10	1.01–1.20	0.021

Abbreviations: ANI = asymptomatic neurocognitive impairment; CI = confidence interval; HAND = HIV-associated neurocognitive disorders; MDD = major depressive disorder; NCN = neurocognitively normal; PB = performance-based; RR = relative risk; SR = self-report.
Antiretroviral therapy treatment, regimen type, CNS penetration effectiveness score, plasma viral load, CSF viral load, and current substance use diagnoses were nonsignificant in univariable analyses.

from others in such situations. Whatever the mechanisms, SR of functional decline should be of clinical concern, requiring further evaluation.

Some limitations of this study include the selection of the sample and the lack of demographically adjusted norms for the performance-based measures. It is possible that requirements of participation in the longitudinal component of CHARTER (i.e., visits every 6 months, willingness to complete extra assessments) resulted in sample bias where the highest functioning (employed) participants would be less represented since they might not have the time to spare, whereas lower functioning or disabled participants might not be able to participate due to physical or cognitive limitations. In regard to norms, we used the best data available to set cutpoints for the performance-based measures that have shown evidence of construct validity in prior studies[27]; however, norms based on HIV− controls with similar demographics would improve the accuracy of any such cutpoints.

This study found that patients with ANI were about 3 times more likely to develop everyday life problems as those who were initially cognitively normal. This finding suggests that those in whom ANI has been detected deserve regular monitoring in terms of progression to symptomatic status. Future intervention studies may need to focus on such individuals to thwart further neurocognitive and functional decline.

AUTHOR CONTRIBUTIONS

Dr. Grant is the primary author on this manuscript and as such he was responsible for study conceptualization and design. All study data were available to him and he planned the statistical analyses and performed the interpretation of the results. Dr. Grant thereby assumes responsibility for the accuracy of the data, analysis, and interpretation. Donald R. Franklin is the CHARTER center manager and he provides integral coordination and dissemination of CHARTER data. Additionally, he contributed to this manuscript by assisting with study design, data analysis, drafting and revision of the manuscript. Dr. Deutsch contributed to all aspects of the manuscript, including study design, statistical analysis, and interpretation of results. Dr. Woods significantly contributed to all aspects of the manuscript, including study design, statistical analysis, and interpretation of results. He also strongly contributed in revising the manuscript. Dr. Vaida assisted with the interpretation of results along with drafting and revising the manuscript. Dr. Ellis made considerable contributions through management and coordination of the neuromedical data, and assisted with study design, analysis, and interpretation, as well as revisions to the manuscript. Dr. Letendre made considerable contributions through management and coordination of the laboratory data, and assisted with study design, analysis, and interpretation, as well as revisions to the manuscript. Dr. Marcotte assisted with the interpretation of results along with drafting and revising the manuscript. Dr. Collier assisted with primary data collection, drafting, and revising the manuscript. Dr. Marra assisted with primary data collection, drafting, and revising the manuscript. Dr. Clifford assisted with primary data collection, drafting, and revising the manuscript. Dr. Gelman assisted with primary data collection, drafting, and revising the manuscript. Dr. McArthur assisted with primary data collection, drafting, and revising the manuscript. Dr. Morgello assisted with primary data collection, drafting, and revising the manuscript. Dr. Simpson assisted with primary data collection, drafting, and revising the manuscript. Dr. McCutchan assisted with primary data collection, drafting, and revising the manuscript. Dr. Abramson assisted with drafting and revising the manuscript. Dr. Gamst assisted with drafting and revising the manuscript. Dr. Fennema-Notestine assisted with drafting and revising the manuscript. Dr. Smith assisted with drafting and revising the manuscript. Dr. Heaton significantly contributed to all aspects of the manuscript, including study design, statistical analysis, and interpretation of results. He also strongly contributed in revising the manuscript.

STUDY FUNDING

The CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) study is supported by awards N01 MH22005, HHSN271201000036C, and HHSN271201000030C from the NIH.

DISCLOSURE

I. Grant receives ongoing research support from NIH P30 MH62512, NIH P50 DA26306, NIH P01 DA12065, NIH U01 MH83506, NIH R01 MH78748, NIH R01 MH83552, NIH/University of Nebraska P01 DA026146, HHSN271201000030C, and HHSN271201000036C. He has also received honoraria from Abbott Pharmaceuticals as part of their Educational Speaker Program. D. Franklin receives support from HHSN271201000030C and HHSN271201000036C. R. Deutsch receives support from HHSN271201000036C, NIH P30 MH62512, and NIH P50 DA26306. S. Woods receives ongoing research support from NIH P30 MH62512, NIH P50 DA26306, NIH R01 MH73419, NIH T32 DA031098, and NIH R01 MH084794. F. Vaida receives ongoing research support from NIH P30 MH62512, NIH P50 DA26306, NIH R01 MH083552, NIH R01 AI47033, NIH U01 AI74521, NIH R01 MH085608, HHSN271201000030C, HHSN271201000036C, and Precision Photonics Corporation AI068543. Dr. Vaida has also served on a data safety and management board for Ardea Biosciences, Inc. R. Ellis received consultant fees from NeurogesX and is funded by NIH grants R01MH058076, U01MH83506, P30MH62512, R01MH83552, P50DA26306, R01MH095621, 2U01NS32228, and HHSN271201000036C. S. Letendre's salary is funded by NIH research awards, including HHSN271201000036C, R01 MH58076, R01 MH92225, P50 DA26306, and P30 MH62512. He has received support for research projects from Abbott, Merck, Tibotec, and GlaxoSmithKline. He has consulted for Gilead Sciences, GlaxoSmithKline, Merck, and Tibotec and has received lecture honoraria from Abbott and Boehringer-Ingelheim. T. Marcotte receives ongoing research support from NIH P30 MH62512, NIH P50 DA26306, NIH HHSN271201000030C, NIH R01 MH83552, NIH R01 MH78748, and NIH R01 MH73433. J. Atkinson has received research support from NIH: P50 DA26306, U01 MH83506, HHSN271201000036C, HHSN271201000036C; coinvestigator; 2010-2015; Department of Veterans Affairs: NURA 01909-S, B4767-R; Principal Investigator, 2009-2015. A. Collier has ongoing research support from HHSN271201000036C, NIH UM1 AI069434, AI27757, AI057005, and R01 AI090783, current research support from Merck & Company, and past research support from Schering-Plough, Boehringer-Ingelheim, Gilead Sciences, Koronis, and Tibotec-Virco. She and an immediate family member previously owned stock in Abbott Laboratories, Bristol Myers Squibb, Johnson & Johnson, and Pfizer. C. Marra receives research support from the NIH (National Institute of Neurological Disorders and Stroke and NIMH). She receives royalties from Lippincott Williams & Wilkins and from UptoDate. D. Clifford is supported by NIH grants NS077384, AI69495, DA022137, HHSN271201000036C, NR012907, and the Alzheimer Association. He has also received research support from Lilly, Roche, Pfizer, Bavarian Nordic, and Biogen. In addition, Dr. Clifford has provided scientific advisory or consulting to Amgen, Biogen Idec, Drinker, Biddle and Reath (PML Consortium Scientific Advisory Board), Quintiles, Roche, Genentech, Novartis, GlaxoSmithKline, Millennium, Bristol Meyers Squibb, Genzyme, and Pfizer. B. Gelman receives support for NIH grants U24MH100930-01, R01NS079166, R01NS072005, 1R01MH101017, and HHSN271201000036C. J. McArthur receives support from HHSN271201000036C. S. Morgello reports no disclosures. D. Simpson receives research support from the NIH (National Institute of Neurological Disorders and Stroke and NIMH). He provided consultancy to GlaxoSmithKline and Gilead. J. McCutchan authors chapters on HIV for the Merck Manual and receives research funding related to NIH P30 MH62512, NIH U01 MH83506, NIH/Centers for Disease Control

and Prevention (CDC) U2G PS00623, NIH U01 AI69432, HHSN271201000036C, NIH K30 RR22681, NIH R01 MH58076, and NIH U13 MH81676. I. Abramson receives ongoing research support from NIH P30 MH62512, NIH P50 DA26306, NIH R01 MH61146, NIH HHSN271201000036C, NIH R01 DA21115, and NIH R21 MH78728. A. Gamst receives ongoing research support from NIH P30 MH62512, NIH P50 DA26306, NIH R01 HL95089, NIH U01 MH83506, NIH R01 HL84229, NIH R01 MH79752, NSF DBI-0446389, NIH HHSN271201000030C, and NIH U01 AG10483. C. Fennema-Notestine has received research support from the NIH (R21 NS069355, N01 MH22005, HHSN271201000036C, P30 MH062512, P50 DA026306, R01 MH079752, R01 AG031224, R01 AG022381, R01 MH084796, R01 MH042984-18S1, R01 MH092225-02S1) and from the Alzheimer's Association (IIRG-09-132430), and she serves as an Associate Editor for the *Journal of Alzheimer's Disease* (2012). D. Smith receives ongoing research support grants from the NIH: DA034978, MH62512, MH83552, MH097520, AI100665, and AI36214. R. Heaton receives ongoing research support from R01 MH92225, P50 DA26306, P30 MH62512, R01 MH60720, R01 MH58076, R01 MH78737, U01 MH83506, R01 MH83552, R01 MH80150, and HHSN271201000036C. Go to Neurology.org for full disclosures.

Received October 29, 2013. Accepted in final form February 13, 2014.

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