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## Lower CSF A $\beta$ is Associated with HAND in HIV-Infected Adults with a Family History of Dementia

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## Abstract

**Background**—Both family history of dementia (FHD) and lower levels of A $\beta$ -42 are independently associated with worse neurocognitive functioning in HIV-infected patients.

**Objective**—To examine the relationships between cerebrospinal fluid (CSF) A $\beta$ -42 and FHD with HIV-associated neurocognitive disorders (HAND).

**Methods**—One hundred eighty-three HIV+ adults underwent neuropsychological and neuromedical assessments, and determination of CSF A $\beta$ -42 concentration and FHD (defined as a self-reported first or second-degree relative with a dementia diagnosis). Univariate analyses and multivariable logistic regressions were used.

**Results**—FHD was not associated with HAND ( $p = 0.24$ ); however, CSF A $\beta$ -42 levels were lower ( $p = 0.03$ ) in the HAND group, but were not associated with FHD ( $p = 0.89$ ). Multivariable models showed a main effect of CSF A $\beta$ -42 ( $p = 0.03$ ) and a trend-level ( $p = 0.06$ ) interaction between FHD and CSF A $\beta$ -42, such that lower CSF A $\beta$ -42 was associated with HAND in those with FHD ( $p < 0.01$ ) compared to those without FHD ( $p = 0.83$ ). An analysis in those with follow-up data showed that higher baseline CSF A $\beta$ -42 was associated with lower risk of neurocognitive decline ( $p = 0.02$ ). While we did not find an FHD X CSF A $\beta$ -42 interaction ( $p = 0.83$ ), when analyses were stratified by FHD, lower CSF A $\beta$ -42 was associated at the trend-level with neurocognitive decline in the FHD group ( $p = 0.08$ ) compared to the no FHD group ( $p = 0.15$ ).

**Conclusions**—FHD moderates the relationship between of CSF A $\beta$ -42 and HAND. The findings highlight the complexities in interpreting the relationships between biomarkers of age-related neurodegeneration and HAND.

## Keywords

HIV; dementia; biomarkers; cerebrospinal fluid; family history; neurocognitive impairment

## 1. INTRODUCTION

Combination antiretroviral therapy (ART) has decreased the incidence of HIV-associated dementia (HAD) [1 – 6], however, the prevalence of milder forms of HIV-associated neurocognitive disorders (HAND) remains high [1·4·6 – 8]. Thus, isolating factors that predict neurocognitive (NC) impairment in HIV is an important research area.

HIV-induced damage to neurons can be mediated through indirect neurotoxic mechanisms and is associated with NC impairment [9 – 11]. Commonly described morphologic correlates of HAND are synaptodendritic damage, astrocytosis, and microgliosis [12 – 15]. Other neuropathologies have also been described [16 – 19], including  $\beta$ -amyloid deposition in HIV-infected persons [16·18]. As such, cerebrospinal fluid (CSF) measurements of amyloid may be helpful in identifying risk for HAND. In this way, low CSF A $\beta$ -42 levels (amyloid beta-protein ending at amino acid position 42) are considered pathologic, as low

levels indicate  $\beta$ -amyloid is being deposited elsewhere (i.e., the brain). Studies have noted CSF A $\beta$ -42 concentrations in HAND patients similar to those of Alzheimer's disease (AD) patients, supporting this biomarker as a proxy for neuropathology [20 – 21]. There is also some evidence for neuroprotective therapies in reversing A $\beta$ -42 neuronal toxicity in HAND [22 – 23].

Given that neurodegenerative diseases, such as AD, can be partially inherited, examining family history of dementia (FHD) may be a useful and feasible approach for identifying and predicting those HIV+ individuals who may have a predisposition for NC impairment. Furthermore, gathering FHD may capture familial neurodegenerative conditions for which genetic correlates or screenings are not available. A study in adults with HIV found that those who reported a FHD had poorer cognitive performance [24], however no biomarkers were examined in that study.

Thus, we sought to examine the associations between CSF levels of A $\beta$ -42, FHD, and HAND. The specific objectives were: 1) to assess whether FHD was associated with CSF A $\beta$ -42 levels, and 2) to examine if these two variables were associated with a greater likelihood of HAND, and if there was a synergistic effect of FHD and CSF A $\beta$ -42.

## 2. MATERIALS AND METHOD

### Participants

This study included a convenience sample of 183 individuals with confirmed HIV disease who were enrolled in the larger multisite CNS HIV Antiretroviral Therapy Effects Research (CHARTER) study at one of six US academic medical centers. This study received approval from each institution's ethical standards committee and all subjects received informed consent prior to participation. We identified 90 HIV+ individuals with a FHD and then selected a sample of 93 HIV+ individuals without FHD who were comparable to the FHD group on demographic factors (i.e., age, education, sex and ethnicity) and all HIV disease factors (e.g., nadir CD4+ T-cell count, plasma viral load, ART use, AIDS diagnosis). All participant selection was done blinded to NC functioning, HAND diagnosis, and research biomarker concentrations.

Participants completed a comprehensive neuropsychological, neuromedical, and psychiatric examination. This study excluded those with severe comorbid psychiatric, medical, and neurological conditions that would negatively affect neurocognitive functioning and thus prevent a HAND diagnosis (i.e., subjects rated as “confounding” [6]), thus including only those subjects rated as having either “contributing” or “incidental” conditions. For this study participants were also excluded if they were not currently taking antiretrovirals (ARVs), as treatment status may affect/obscure the associations among biomarkers and HAND.

### Procedure

**Family History of Dementia Determination**—We coded persons as FHD positive if they reported that a first-degree (biologic parent, sibling, or offspring) or second-degree (i.e., biologic grandparent, grandchild, uncle, aunt, nephew, niece, half-sibling) relative was diagnosed with “dementia” or AD. When participants were unable to provide all of this

information, they were coded as not having FHD to avoid overestimation. Participants who were adopted and could not provide information about their family history were excluded [24].

**NC Assessment**—All participants completed a comprehensive NC battery that assessed seven domains commonly affected by HIV [25]: verbal fluency, executive functions, speed of information processing, visual and verbal learning, visual and verbal recall (i.e., memory), working memory, and motor skills. This battery is the consensus NC battery for the CHARTER study and is widely used across the HIV Neurobehavioral Research Program [6].

Raw NC test scores were converted into *T*-scores (standard scores with a mean of 50 and SD of 10) using demographically adjusted norms to control for the effects of age, education, gender, and where available ethnicity [26–28]. Trained clinical neuropsychologists then used these demographically corrected *T*-scores to assign clinical ratings based on a highly specified algorithm described elsewhere [29], which were also discussed in a case conference format to determine HAND diagnoses using the accepted published guidelines for diagnosing HAND for research purposes (i.e., Frascati criteria [25]). Similar methods were also used to determine impairment in each neurocognitive domain. Thus, outcomes included impairment in each of the seven domains (impaired vs. NC normal) and HAND (any form of HAND vs. NC normal). These binary categorical variables were used in analyses.

**Neuromedical and Psychiatric Evaluation**—The following information was gathered during the neuromedical assessment: medical history, current medications and medication history, neurological examination, physical examination, and laboratory evaluations (e.g., blood and cerebrospinal fluid collected for banking and testing). Lifetime substance dependence diagnoses were assessed via the computer-assisted Composite International Diagnostic Interview, version 2.1 [30], which included any past diagnosis of dependence for the following substances: amphetamine (including methamphetamine), cocaine, hallucinogen, inhalant, sedative, opioid, PCP, alcohol, and marijuana.

**Biomarker Assessment**—CSF A $\beta$ -42 was measured using a commercial suspension array immunoassay (EMD Millipore, Billerica, MA). HIV RNA levels were measured in blood and CSF by reverse transcriptase-polymerase chain reaction (RT-PCR, lower limit of quantitation 50 copies/mL) (Roche, Nutley, NJ). CD4+ T-cells were counted by flow cytometry. Other analytes were measured by routine methods in CLIA-certified clinical laboratories.

## Statistical Analyses

All statistical testing was two-sided and done at the 5% significance level. CSF A $\beta$ -42 and plasma HIV RNA concentration were log<sub>10</sub> transformed, as they were not normally distributed. Preliminary analyses (chi-square analyses or independent samples *t*-tests when appropriate) were conducted to determine whether any demographic or physical health variables differed at  $p < 0.05$  between those with and without HAND and should thus be

considered as covariates, and also to determine whether FHD and A $\beta$ -42 were associated with HAND at the bivariate level. We also examined whether CSF A $\beta$ -42 concentrations differed between those with and without FHD using independent samples t-tests. Final preliminary bivariate analyses were conducted between both CSF A $\beta$ -42 levels and FHD with the Table 1 variables to further determine any potential covariates (criteria  $p < 0.05$ ). Primary analyses included multivariable logistic regressions including relevant covariates, FHD, and CSF A $\beta$ -42, and their interactions with HAND and domain specific impairment as the dependent variables. The minimum Akaike Information Criterion (AIC) was used to determine the optimal set of predictors to be entered in the final logistic regressions. To investigate effects of CSF A $\beta$ -42 levels and FHD on neurocognitive performance over time, survival analysis using Cox proportional hazard (PH) regression was applied. Specifically, we measured time (months) from baseline and the visit where neurocognitive decline was determined and regressed it on baseline levels of CSF A $\beta$ -42. Decline was determined based on those who had any neurocognitive decline over the study period using published [31], regression-based norms. Briefly, z-scores were created for each for the 15 neuropsychological measures based on normative data, and then these were averaged to create a summary regression change score. Additionally, the interaction between CSF A $\beta$ -42 and FHD on HAND over time was investigated. Effect size of CSF A $\beta$ -42 (Hazard Ratio [HR]) in Cox PH models was estimated as hazard ratio for 1 unit increase in log-transformed values of CSF A $\beta$ -42. A statistically significant HR below 1 means that higher values of CSF A $\beta$ -42 are associated with lower risk of decline over time, or equivalently, that lower values of CSF A $\beta$ -42 are associated with higher risk of decline over time.

### 3. RESULTS

The HAND group and the NC normal group were similar on all potential covariate variables except comorbidity rating, with the NC normal group having a significantly higher proportion of incidental comorbidities ( $p = 0.02$ ) (Table 1). Individuals with HAND had significantly lower levels of CSF A $\beta$ -42 ( $p = 0.03$ ) (Table 1), as did non-white subjects ( $p = 0.007$ ). No other Table 1 variables were associated with CSF A $\beta$ -42. As the FHD groups were matched, there were no significant differences on any variables in Table 1 between those with and without a FHD (all  $p$ -values  $> 0.10$ ). Those with HAND had a higher prevalence of FHD (52%) than those who were NC normal (45%), but this difference was not significant ( $p = 0.24$ ). There was also no significant association between FHD status and CSF A $\beta$ -42 concentrations ( $p = 0.89$ ).

Forward stepwise multivariable logistic regression was conducted with HAND entered as the dependent variable and comorbidity rating (i.e., incidental vs. contributing), CSF A $\beta$ -42, FHD, race, and the FHD X CSF A $\beta$ -42 interaction as independent variables. Using the minimum AIC value to determine the optimal set of predictors to be entered in the final logistic regression, all predictors were retained except race. The overall model was significant (df = 4,  $\chi^2 = 14.14$ ,  $p = 0.01$ ) and there was a significant main effect of CSF A $\beta$ -42 ( $p = 0.03$ ) as well as a trend-level interaction between FHD and CSF A $\beta$ -42 ( $p = 0.06$ ). Specifically, higher CSF A $\beta$ -42 was only associated with lower odds of HAND in the FHD group (OR = 0.04, CI = 0.003 – 0.37,  $p < 0.01$ ) compared to the no FHD group (OR = 0.79, CI = 0.09 – 7.33,  $p = 0.83$ ). Post-hoc power estimates for this primary model

predicting HAND from comorbidity rating, CSF A $\beta$ -42, FHD, and FHD  $\times$  CSF A $\beta$ -42 interaction were conducted using bootstrap method with 5000 replications. Based on the observed effects reported above, and assuming significance level of 0.05, the model had 45% power to detect a significant interaction, 80% power to detect a significant effect of CSF A $\beta$ -42 within each group (FHD and no FHD), and 17% power to detect a significant difference in log-odds of HAND between FHD and no FHD groups.

The associations between FHD and HAND were not strengthened when examining inheritance type (maternal vs. paternal), type of dementia (AD vs. non-AD), or number of relatives with a dementia diagnosis. Furthermore, while age was not associated with any of our variables of interest (i.e., FHD, CSF A $\beta$ -42, HAND), we forced this variable in as a covariate in the prior model, and the results remained unchanged. For visual representation of this interaction, a median split was conducted on raw CSF A $\beta$ -42 values to create high and low CSF A $\beta$ -42 groups (median = 573.7) and a CSF A $\beta$ -42 by FHD four-group graph was created, which shows that individuals with low CSF A $\beta$ -42 and FHD had the highest prevalence of HAND (74%), while the prevalence in the other three groups was similar (high CSF A $\beta$ -42 FHD: 49%; high CSF A $\beta$ -42 no FHD: 52%; low CSF A $\beta$ -42 no FHD: 57%) (Figure 1).

Post-hoc analyses examined domain impairment using identical independent variables as in the previous models and revealed the following associations: working memory (trend for CSF A $\beta$ -42,  $p = 0.07$ ); verbal (FHD significant main effect,  $p = 0.03$ ); executive functioning (CSF A $\beta$ -42 significant main effect,  $p = 0.03$ ); speed of information processing (CSF A $\beta$ -42 by FHD interaction,  $p = 0.01$ ); memory (trend for FHD,  $p = 0.06$ ); learning and motor (no associations with FHD or CSF A $\beta$ -42). Most associations were in the expected direction, such that those with HAND had lower levels of CSF A $\beta$ -42 or higher prevalence of FHD than those who were NC normal for each domain, except for an anomalous memory domain finding, where those with FHD had a lower prevalence of impairment.

In order to examine the predictive value of CSF A $\beta$ -42 and FHD on cognitive trajectory (decline versus stable), a post-hoc survival analysis was conducted with 64 subjects who had available longitudinal neurocognitive data and met the criteria of having between 4–7 study visits. The range of time between baseline and the visit in which trajectory was determined was between 5 – 52 months ( $M = 31.2$ ,  $SD = 12.8$ ) and 11 of the 64 experienced a decline in neurocognitive performance while the remaining 53 remained stable. Note that the 64 subjects with longitudinal data did not significantly differ from those without longitudinal data on any Table 1 variables (all  $p$ -values  $> 0.05$ ). The survival analysis supported our cross-sectional main findings such that those who had higher baseline CSF A $\beta$ -42 concentrations were at lower risk of neurocognitive decline over time ( $HR = 0.03$ , 95% CI = 0.001 – 0.58,  $p = 0.02$ ). While we did not find an FHD  $\times$  CSF A $\beta$ -42 interaction ( $p = 0.83$ ), when conducted separately in those with and without FHD survival analysis showed that lower CSF A $\beta$ -42 was associated at the trend level with cognitive decline in the FHD group ( $HR = 0.02$ , 95% CI = 0.0001 – 1.51,  $p = 0.08$ ) compared to the no FHD group ( $HR = 0.04$ , 95% CI = 0.0004 – 3.37,  $p = 0.15$ ).

## 4. DISCUSSION

The goal of this study was to examine the relationships between FHD, levels of A $\beta$ -42 in CSF, and HAND in a sample of adults with HIV on ART. Consistent with the aging literature (and some HIV studies [20 – 21], cf. [32]), we found that those with worse NC function (i.e., HAND) had lower CSF A $\beta$ -42 levels. When examined together, our multivariable models confirmed that lower CSF A $\beta$ -42 levels were significantly associated with higher odds of HAND, and also revealed that FHD moderated the effect of CSF A $\beta$ -42 on odds of HAND at the trend level. Specifically, CSF A $\beta$ -42 was only associated with HAND in those who had FHD, with those with both FHD and low CSF A $\beta$ -42 having the highest prevalence of HAND at 74% compared to those without FHD and those with FHD and high CSF A $\beta$ -42 levels (HAND proportions ranging from 49% - 57%). Further exploration of the interaction trend in HAND on domain impairment showed a significant interaction on speed of information processing impairment suggesting that this domain may have been driving the initial interaction that approached significance with HAND and that perhaps this cognitive domain is more sensitive to amyloid-associated alterations than other domains. Contrary to our hypotheses, we found that those with and without FHD did not differ in CSF A $\beta$ -42 concentrations and a statistically higher prevalence of HAND was not found in those with FHD. Furthermore, consistent with the literature on higher incidence of AD [33] and pathological A $\beta$ -42 levels in African Americans [34], we found that non-white subjects (who were majority African American) had lower CSF A $\beta$ -42 levels than white subjects.

These findings support the idea of using a combined approach of family history and biomarkers to identify those HIV+ individuals who may be at risk for cognitive decline and impairment. Our post-hoc longitudinal analysis supported our primary cross-sectional findings, such that higher baseline CSF A $\beta$ -42 concentrations were associated with lower odds of neurocognitive decline. In the classic amyloidogenic pathology of AD, CSF biomarkers are important clinical tools that have been used as prognostic indicators [35]. Studies have shown that AD patients with low CSF A $\beta$ -42 have worse clinical outcomes, quicker dementia progression, worse response to cholinesterase inhibitor treatment and greater mortality [36], and that CSF A $\beta$ -42 alterations may be a precursor to future cognitive decline in those without initial impairment [37, 38]. It was interesting that CSF A $\beta$ -42 was only associated with impairment in those with FHD despite there being no significant association between FHD and CSF A $\beta$ -42 levels. This highlights the complex relationships of biomarkers in the prediction of NC impairment in HIV. It may be that those with FHD have some other underlying neuropathology that is explained by biomarkers we did not examine in the current study that makes them more susceptible to the effects of pathological (low) CSF A $\beta$ -42 levels. In other words, those without FHD may have a higher “cognitive reserve” to tolerate amyloid deposition before presentation of neurocognitive impairment.

Most of our findings followed the directions of our hypotheses based on the literature. The lack of association between FHD and CSF A $\beta$ -42 may be an artifact of the self-report nature of our FHD variable. Perhaps underreporting of FHD incidence due to a participants’ lack of knowledge about familial diagnoses resulted in less utility of this variable. Nonetheless, we still had an adequate sample size of those with and without FHD, and further analysis

revealed that even focusing on inheritance type (maternal vs. paternal), type of dementia (AD vs. non-AD), or number of family members with a diagnosis did not improve the utility of FHD. This is in contrast to studies that have shown that abnormal biomarker concentrations (particularly A $\beta$ -42) are more likely in patients who have a family history of AD particularly via maternal inheritance [39]. While future research should determine FHD in a more objective format, perhaps via confirmation with clinicians of family members, this study and others [24] provide support for the use of self-report FHD as an easy to gather and inexpensive proxy for familial risk/genotype for dementia.

Limitations of this study include the cross-sectional nature of the primary analyses, preventing causal ascertainment to be made regarding the predictive value of A $\beta$ -42 and FHD on cognitive decline over time. Furthermore, while the subjects in our post hoc longitudinal analysis were similar to those without longitudinal data, supporting the generalizability of these findings, our longitudinal analysis only included a small subset of subjects with available data. Nonetheless, these findings support longitudinal studies in the non-HIV literature demonstrating that abnormal biomarker changes precede NCI [37]. The relatively young age of our sample may have also influenced our findings. Older adults would not only be more susceptible to age-related neuropathology but would also have older parents and other relatives who would be more likely to have developed dementia. Nonetheless, the findings from this study provide several insights into identifying a CSF profile of NCI in HIV. Specifically, the A $\beta$ -42 abnormalities seen in NCI in HIV seem to mirror those seen in other neurodegenerative diseases such as AD and we also provide evidence for the utility of FHD as a moderator of biomarkers on NCI in HIV. While it may perhaps be that HIV disease characteristics and biomarkers are more influential to NCI than traditional aging biomarkers, the interplay between these factors warrants further investigation, with the ultimate goal of isolating factors that may signal those patients at risk for incident neurocognitive impairment or future neurocognitive decline.

## 5. CONCLUSION

In conclusion, this study provides support for the relevance of FHD in influencing biomarker associations with neurocognitive outcomes in HIV, particularly A $\beta$ -42 and speed of information processing impairment. The inconsistency of the association of CSF A $\beta$ -42 and NCI in the HIV literature may be partially explained by considering this biomarker in the context of other risk factors, such as FHD. Future research is warranted to further examine A $\beta$ -42 and other biomarkers (e.g., neurofilament light chain) on incident neurocognitive impairment and longitudinal cognitive trajectories as individuals age with HIV.

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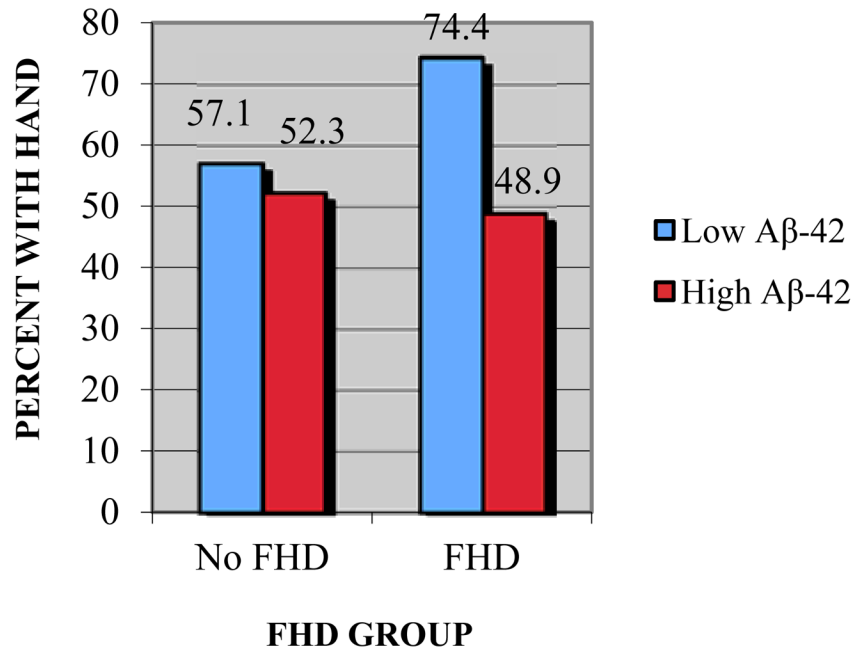
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**Figure 1.**

FHD, Aβ-42, and HAND

**Notes.** Aβ-42=amyloid beta 42; FHD=family history of dementia; HAND=HIV-associated neurocognitive disorder. Low and high Aβ-42 determined by median split (median = 573.7).

\*Omnibus  $p = 0.07$ ; Low Aβ-42 FHD vs. High Aβ-42 no FHD:  $p = 0.03$ ; Low Aβ-42 FHD vs. Low Aβ-42 no FHD:  $p = 0.08$ ; Low Aβ-42 FHD vs. High Aβ-42 FHD:  $p = 0.01$ ; High Aβ-42 FHD vs. High Aβ-42 no FHD:  $p = 0.75$ ; High Aβ-42 FHD vs. Low Aβ-42 no FHD:  $p = 0.42$ ; High Aβ-42 no FHD vs. Low Aβ-42 no FHD:  $p = 0.64$ .

**Table 1**

Demographics, Clinical Characteristics, FHD, and Biomarkers by HAND (N=183)

	<b>HAND (n = 106)</b>	<b>NC Normal (n = 77)</b>	
<b>Variable</b>	<b>M (SD) or No. (%)</b>	<b>M (SD) or No. (%)</b>	<b>p-value</b>
Age	43.4 (8.2)	44.4 (7.4)	0.43
Gender, No. (%) Men	86 (81%)	59 (77%)	0.46
Education	13.0 (2.1)	13.1 (2.5)	0.84
Race, No. (%) White *	55 (52%)	41 (53%)	0.86
AIDS, No. (%)	80 (75%)	56 (73%)	0.67
Current CD4+ T-Cell Count (cells/ $\mu$ L)	460.0 (319.4)	461.5 (283.6)	0.73
Nadir CD4+ T-Cell Count (cells/ $\mu$ L)	163.4 (167.6)	159.5 (138.2)	0.67
Plasma Viral Load <sup>†</sup> (copies/mL)	2.3 (0.90)	2.4 (1.1)	0.92
Plasma Viral Load, No. (%) UD	56 (53%)	43 (56%)	0.69
No. (%) w/HCV co-infection	25 (24%)	23 (30%)	0.36
No. (%) w/Lifetime Substance Dependence Dx	51 (48%)	46 (60%)	0.12
CSF A $\beta$ -42 (pg/mL)	624.1 (314.3)	691.4 (291.0)	0.03
No. (%) w/FHD	55 (52%)	35 (45%)	0.24
HAND Diagnoses			
No. (%) ANI	79 (75%)	--	
No. (%) MND	19 (18%)	--	--
No. (%) HAD	8 (8%)	--	
CHARTER Comorbidity Rating			
No. (%) Contributing	48 (45%)	22 (29%)	0.02
No. (%) Incidental	58 (55%)	55 (71 %)	

Notes. CSF = cerebrospinal fluid; FHD = family history of dementia; HCV = Hepatitis C virus; NC = neurocognitively; UD = undetectable.

\* For HAND, 35 black, 13 Hispanic, and 3 reported “other”; for NC Normal, 30 black and 6 Hispanic.

<sup>†</sup> For plasma viral load log values are reported.