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Higher cystatin C levels are associated with neurocognitive impairment in older HIV+ adults

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Abstract

Objective: The study aims to determine whether cystatin C is associated with HIV disease and HIV-associated neurocognitive impairment (NCI).

Methods: Participants included 124 (HIV+ n = 77; HIV- n = 47) older adults (age ≥ 50 years) examined at the UCSD HIV Neurobehavioral Research Program. Cystatin C, a biomarker of kidney functioning that has been linked to poor health outcomes, was measured in blood. Participants completed a comprehensive neurocognitive assessment that was used to define both global and domain NCI.

Results: The HIV+ group had significantly higher cystatin C concentrations than the HIV- group (d=0.79 $p<0.001$). Among HIV+ participants, those with NCI had higher cystatin C concentrations than those without NCI (d=0.42, $p=0.055$), particularly among participants taking tenofovir (d=0.78, $p=0.004$). A receiver-operator characteristic curve identified that cystatin C levels ≥ 0.75 mg/L were associated with NCI in the HIV+ group. Using this binary variable and including relevant covariates, multivariate modeling confirmed that NCI was associated with higher cystatin C levels (OR = 3.0; $p = 0.03$).

Conclusions: Our results confirm that HIV+ older adults have higher cystatin C than HIV- older adults and further identify that cystatin C may be associated with NCI in this population, particularly if they use tenofovir. This blood biomarker may be a useful clinical tool to identify older HIV+ persons at greater risk for cognitive decline.

Key Words: HIV/AIDS, biomarkers, cognition, aging

Introduction

The number of Americans who are older than 50 years of age living with HIV is increasing both due to improvements in antiretroviral therapy (ART) and to new infections in this age group (24% of new infections/year).[1,2] By 2020, 70% of the U.S. HIV-infected (HIV+) population is estimated to be 50 years or older.[2] Aging increases the risk for neurocognitive impairment (NCI) in HIV+ adults.[3,4,5,6] Given the prevalence of HIV among older adults and the increased risk for NCI, a priority in the field should be to identify those persons who are at greatest risk. Since lumbar puncture and specialized neuroimaging are not feasible in all clinical settings, measuring diagnostic or prognostic biomarkers in blood should have wider clinical impact and acceptance.

One potential biomarker is cystatin C, a low molecular weight protein and member of the cystatin superfamily of cysteine protease inhibitors.[7] Cystatins are secreted by macrophages and microglia and may play a role in neuroregulatory responses.[8] Cystatin C levels have been examined as a biomarker for "preclinical" kidney dysfunction; have been associated with poorer physical function and cardiovascular disease in older adults; and have been found to be predictive of earlier mortality.[9-11] High cystatin C has also been linked to worse baseline and longitudinal decline of cognitive performance in healthy older adults.[12] Decline in cystatin C levels are also associated with improved cognition after bariatric surgery.[13] Cystatin C levels are elevated in HIV+ adults[14-16] and in the plasma of young HIV+ Hispanic women with NCI.[13] The correlation between cystatin C and neurocognitive function has not yet been investigated, however, in HIV+ older adults.

The objective of this analysis was to compare cystatin C levels in blood between HIV+ and HIV-uninfected (HIV-) older adults, and to determine whether cystatin C is associated with NCI in the HIV+ older adults. We hypothesized that HIV+ older adults would have higher cystatin C levels than HIV- older adults, and that cystatin C levels would be higher in HIV+ older adults with NCI.

Methods

Participants and Procedures

This study examined 124 (n=77 HIV+, n=47 HIV-) community-dwelling, older (i.e., at least 50 years old) adults from the UCSD HIV Neurobehavioral Research Program's Successfully Aging Seniors

with HIV (SASH) cohort. All participants provided Institutional Review Board-approved informed consent and were screened for enrollment via structured interview. Participants with a history of severe comorbid neuropsychiatric conditions that could confound attribution of cognitive impairment to HIV were excluded (e.g., traumatic brain injury). Exclusion criteria were generally minimal with the exception of acute intoxication (e.g., positive urine toxicology screen), significant neurologic/neurodegenerative disorders (e.g., Parkinson's Disease) and serious psychotic disorders (e.g., schizophrenia). Our goal was to enroll a representative cohort of both HIV+ and HIV- subjects, rather than exclude participants with certain conditions prior to enrollment. Further, in the current study, we limited HIV+ participants to those who were currently taking suppressive ART (plasma viral load ≤ 50 copies/mL). The most common ART regimens were tenofovir (TDF)-emtricitabine (FTC) with either efavirenz (EFV, n=13) or atazanavir (ATV)-ritonavir (RTV) (n=9). The most commonly used individual ART drugs were TDF (n=58), FTC (n=56), RTV (boosting doses, n=39), EFV (n=19), darunavir (n=19), lamivudine (n=18), abacavir (n=17), ATV (n=13), and raltegravir (n=11). See Table 1 for other sample characteristics.

Blood from all participants was collected; processed for routine clinical labs; and stored at (-80) C for future analysis. CD4+ T-cell counts were measured by clinical flow cytometry and HIV RNA was measured by RT-PCR (Abbott Diagnostics, lower limit of quantitation ≤ 50 copies/mL). Plasma cystatin C was measured in stored blood plasma using a quantitative enzyme-linked immunosorbent assay (ELISA). Soluble CD14 (sCD14) was measured in plasma by ELISA as a comparator biomarker (R&D Systems, Minneapolis, Minnesota for both biomarkers). Biomarker precision was ensured by assaying specimens in duplicate and repeating measurements with coefficients of variation greater than 20% or outliers that were more than 4 standard deviations from the mean; 10% of the assays were also repeated to assess operator and batch consistency. For consistency with published data, cystatin C levels were converted from ng/mL to mg/L.

Self-reported nadir CD4+ count was used unless lab values gathered on study were lower than the self-report. AIDS status was determined using Center for Disease Control and Prevention criteria. The Composite International Diagnostic Interview (v2.1)[22] was used to diagnose MDD and substance use disorders.

Neurocognitive Functioning

Participants were evaluated using a standardized, comprehensive, neurocognitive test battery assessing seven domains: verbal fluency, working memory, speed of information processing, verbal and visual learning and delayed recall, executive function, and motor function.[17] Test scores were normatively corrected to adjust for age, sex, education, and race, as indicated [18,19,20] and converted to standard T-scores. Scores were converted to global and domain deficit scores and standard cutoffs applied (≥ 0.5 global impairment, > 0.5 domain impairment).[21]

Statistical Analyses

Cystatin C values were $\log_{10}$-transformed to improve normality for parametric analyses. Univariate t-tests were used to test differences in cystatin C between the HIV+ and HIV- groups as well as in cystatin C between NCI and unimpaired groups. A one-sided p-value < 0.05 was regarded as statistically significant and trend-level association was regarded as p-value < 0.10. After examination of the association of continuous cystatin C values with NCI, a planned categorical analysis was conducted using a receiver-operator characteristic (ROC) curve to determine the optimal threshold in cystatin C levels relative to NCI in the HIV+ sample. Common covariates that may influence the relationship between cystatin C, HIV status, and NCI were examined using t-tests, chi-square, and correlation analyses (when appropriate) to determine if the measures listed in Table 1 were associated with global NCI, cystatin C, or HIV status, including demographic factors (age, sex, ethnicity/race), HIV disease characteristics (estimated duration of HIV infection, current and nadir CD4+ T-cell count, AIDS diagnosis), substance use disorder diagnosis (current and lifetime), and major depressive disorder (MDD) diagnosis (current and lifetime). Variables associated with either NCI, cystatin C, or HIV status at p < 0.10 were included as candidate covariates in multivariable modeling.

Results

Sample characteristics

Demographic and clinical characteristics are summarized in Table 1. Age was comparable between the HIV+ and HIV- groups; however, the two groups differed significantly in sex and ethnicity/race with a higher proportion of men and those who identified as white in the HIV+ group.

HIV+ participants were more likely to have lifetime or current MDD diagnoses than the HIV- group. The two groups did not significantly differ in lifetime or current substance disorder diagnoses. Approximately two-thirds of the HIV+ participants had a diagnosis of AIDS, but most had currently well-controlled disease (average CD4+ cell count of 646 cells/mL [range 6-1606]). The average estimated duration of HIV disease was 18 years (range 1-31).

Race was associated with cystatin C in the HIV+ sample (p = 0.02) but not in the HIV- sample (p = 0.5): white HIV+ subjects had higher levels of cystatin C than non-white subjects. Cystatin C levels also correlated with levels of the comparator biomarker, sCD14, in plasma (r=0.21, p=0.02). NCI was associated with sex (p = 0.04) and current MDD diagnosis (p = 0.04) in the HIV+ sample, but not in those without HIV: HIV+ men and those with current MDD were more likely to have NCI than women or those without current MDD, respectively. Thus, candidate covariates for multivariable models included sex, ethnicity/race, and current MDD.

Comparison of cystatin C concentration between HIV+ and HIV- groups

Plasma cystatin C concentrations were significantly higher in HIV+ than in HIV- participants (mean 0.74 vs. 0.61 mg/L, t[122] = 4.3, p < 0.001, Figure 1). The comparator biomarker, plasma sCD14, was also higher in HIV+ than in HIV- participants (mean 2,220 vs. 1,746 pg/mL, t[122]=3.9, p<0.001). Analysis of covariance (ANCOVA) showed that the main effect of HIV status remained significantly associated with cystatin C after adjusting for sex, race, current MDD, and sCD14 levels (p < 0.01).

Association of cystatin C with NCI

The proportion of participants with NCI did not significantly differ between the groups (HIV+: 47%, HIV-: 34%, p = 0.20). Among HIV- participants, NCI was not associated with cystatin C levels (t[45] = -0.4, p = 0.70). Within the HIV+ group, cystatin C concentrations tended to be higher in those with global NCI compared to those who were neurocognitively normal (t[75] = -1.9, d = 0.42, p = 0.055) (Figure 2a). In comparison, sCD14 levels in plasma did not differ by NCI status among either HIV+ (p = 0.99) or HIV- (p = 0.23) participants.

The planned ROC curve analysis identified 0.75 mg/L as the optimal threshold of cystatin C for NCI in the HIV+ group. The sensitivity (61%) and specificity (66%) of this threshold value were modest,

although values ≥ 0.75 were associated with a nearly 80% increased risk of NCI (relative risk 1.79, *p* = 0.023). Both continuous and binary cystatin C variables were included as candidate covariates in multivariate modeling, which also included the other candidate covariates noted above. The binary cystatin C variable was more strongly associated with NCI than the continuous variable and remained statistically significant after including in the model other covariates (sex, race/ethnicity, MDD) (odds ratio for binary cystatin C = 3.0; 95% CI = 1.1-8.5, *p* = 0.03) (Figure 2b). Including sCD14 in this model did not significantly reduce the variance in NCI explained by cystatin C.

Within the HIV+ group, cystatin C levels were not statistically significantly associated with impairment in any single neurocognitive domain. Recall and Learning had the largest effect sizes (Recall: d=0.39, p=0.09; Learning: d=0.37, p=0.12). In contrast, comparisons between sCD14 and domain impairment failed to yield any p values less than 0.40.

Secondary Analyses of Tenofovir Use

Considering our results and the risk of kidney dysfunction from tenofovir disoproxil fumarate (TDF)[23] we examined the influence of TDF on the relationship between cystatin C and NCI. While TDF use was not clearly associated with cystatin C levels (p=0.11), TDF did appear to modify the relationship between cystatin C and NCI: Higher cystatin C levels were associated with NCI among participants using TDF (d=0.74, p=0.003) but not among those using other ART drugs (p=0.68). Testing the significance of this apparent interaction using logistic regression identified a statistical trend (parameter estimate p value = 0.055). Among TDF users, the relative risk of NCI with cystatin C levels ≥ 0.75 rose to 2.4 (p=0.008), although the sensitivity (66%) and specificity (72%) only modestly improved.

Discussion

The results of our study confirm prior findings that cystatin C levels differ between HIV+ and HIV- individuals, including in the older, age-matched population assessed in our project. When examining whether cystatin C levels differed by neurocognitive status among our HIV+ participants, we found a medium-size, statistical trend-level elevation in cystatin C among HIV+ persons with NCI compared to those who were neurocognitively normal. Our follow-up analyses used an ROC curve to

explore the optimal threshold of cystatin C to predict NCI among older HIV+ persons, and showed that older HIV+ subjects with cystatin C levels ≥ 0.75 mg/L had a 79% increased relative risk of NCI. Cystatin C also was more strongly associated with NCI than a comparator biomarker, sCD14, that has been previously implicated in HAND. [24]

Our findings on cystatin C in older adults are consistent with the literature demonstrating pathological cystatin C levels in HIV+ persons. For example, results from the Fat Redistribution and Metabolic Change in HIV Infection (FRAM) study[14] found a significantly higher cystatin C level among HIV+ participants compared to HIV- controls even though other biomarkers of kidney function (e.g., creatinine) were similar. Similarly, a study by Neuhaus et al. also found that cystatin C levels in HIV+ individuals remained elevated during suppressive ART, along with other biomarkers of inflammation (hsCRP, IL-6, D-dimer).[15] In 2013, Cantres-Rosario et al. also found increased plasma cystatin C levels when comparing HIV+ and HIV- groups.[16] Unlike that group of patients, which was only female and all had a diagnosis of HIV-associated dementia, our cohort contained both HIV+ male and female patients at a time point before the development of HIV-associated dementia. Thus, this is a unique population based on age, gender, and cognitive status.

Cystatin C levels have been previously shown to increase with age,[25] and higher cystatin C levels, even within the range of relatively normal kidney function, has been associated with unsuccessful aging (defined as cardiovascular disease, cancer, chronic obstructive pulmonary disease, and decreased physical and cognitive functioning in elderly populations).[26] Individuals with high cystatin C are at increased risk to develop cardiovascular disease, physical disability, subclinical brain infarcts, and cerebrovascular events. [10,26-28] In the Health, Aging and Body Composition (HABC) study, high cystatin C level was a better predictor of mortality than chronological age over 13 years of follow-up.[26] Higher cystatin C levels within our HIV+ group may indicate increased risk for these adverse outcomes compared to our HIV- group. Within the FRAM study, HIV+ individuals had a 9-fold increased odds of having a cystatin C level greater than a threshold associated with increased risk for death, cardiovascular and kidney disease.[10]

The association we found between higher cystatin C concentration and NCI is consistent with previous studies performed with older adults, but has only been recently studied in the context of HIV. In a group of Hispanic HIV+ women, women with HIV-associated neurocognitive disorder (HAND) trended toward higher plasma cystatin C compared to women without HAND. Cystatin C measured in CSF and intracellularly in monocytes was not associated with HAND in this study.[16] The study did not evaluate informative threshold values of cystatin C and did not include men or people of other ethnicities. Among HIV- elderly adults from the HABC study, high cystatin C was associated with both worse baseline cognitive scores and incident cognitive decline.[26] Within the HABC study, the participants (average age 74 years) in the highest tertile of cystatin C level showed greater cognitive impairment and cognitive decline over 7 years than those in the lower two tertiles.[12] Interestingly, we found an association between higher cystatin C concentration and NCI within our HIV+ group but no association in the HIV- group. Our HIV- group was both younger (mean age 59.7 years) and had a lower mean cystatin C than the HABC study groups.

Preventing the progression of NCI in HIV+ patients is important since it is associated with earlier mortality[29] and lower quality of life. NCI during HIV disease can affect tasks of everyday functioning such as medication adherence, employment status and ability to drive.[30,31] Older HIV+ patients, even while on stable ART, may age prematurely[32] and are at increased risk for age-related conditions such as NCI.[33] Thus, the observation in our HIV+ individuals approximately in their sixth decade (mean age 58) may reflect those of HIV- adults in their seventh or eight decades.[12] Comparing our findings to the HABC study (mean age 74 years), our HIV sample is showing an association between NCI and cystatin C, on average, 16 years younger. The HIV- participants in our study, although over age 50, may be too young to show the association reported in the literature in older community-dwelling elders.

The findings between cystatin C and NCI in the HIV+ group were most robust with the binary variable defined by the ROC curve. Optimal thresholds of cystatin C for predicting adverse outcomes have been used in several studies.[10,34,35] Direct cross-project comparisons are possible but are complicated by the use of research assays, such as ours, that are not standardized between labs and by differences in outcomes. In published studies, threshold values that predicted death and adverse

health outcomes were 0.94 mg/L[34] and 0.95 mg/L[35] and low risk groups being those with cystatin C

below 0.89 mg/L.[10] In our analysis, only 10 HIV+ participants had cystatin C levels ≥ 0.95 but the effect

size was similar to the one identified by our sample- and outcome-specific ROC curve (relative risk 1.66,

p=0.10, data not shown). Regardless of the exact categorical transformation, multiple studies have now

supported that higher cystatin C levels confer greater risk of a spectrum of adverse, aging-related

health outcomes, including frailty, cardiovascular disease and impaired cognition.[12,26,36] Our data

suggest that plasma cystatin C may be a useful clinical tool in the recognition and management of NCI

in adults aging with HIV.

A possible mechanism underlying the association between higher cystatin C and NCI in HIV+

older individuals is the connection several studies have drawn between chronic kidney disease (CKD)

and cognitive function. Initially studied as a measurement of kidney function, elevated cystatin C levels

have been shown to detect a "preclinical kidney disease" state.[10] Several studies have reported cystatin

C to have a higher sensitivity for detecting kidney dysfunction than widely used clinical measurements

(e.g., estimated GFR (eGFR) or creatinine), especially in the setting of chronic disease and aging.

[9,10,37,38] Thus, elevated cystatin C could reflect the higher prevalence of kidney disease in HIV+

populations observed in other studies,[39-41] or other HIV infection related processes, such as persistent

inflammation, could be increasing cystatin C levels. Participants of the Cardiovascular Health Cognition

Study who had CKD also had an elevated risk of developing dementia.[42] Worse eGFR has also been

associated with poorer performance of postmenopausal women on cognitive function tests.[43] Cystatin C

levels measured from all participants in this study were much lower on average than cutoffs used to

classify CKD, but this could be a reflection of the research assay used. Of note, no participants in our

analysis had clinically significant renal insufficiency, although a substantial proportion used TDF. The

association between cystatin C and NCI solely among TDF users supports a possible renal mechanism

and raises questions about whether changing therapy will reverse NCI or whether the association will

persist as TDF is replaced by tenofovir alafenamide fumarate.

The association of cystatin C with cognition may also be independent of kidney function. In-vitro

HIV infection can increase cathepsin B activity. Cathepsin B, a cysteine protein secreted by lysosomes,

is neurotoxic and can lead to apoptosis, inflammation and neurodegeneration in macrophages. Cystatin C along with cystatin B are direct inhibitors of cathepsin B and also rise during HIV infection in response to increased cathepsin B activity.[8] Cystatin C can also colocalize with beta-amyloid in the brains of patients with Alzheimers disease[44] and elevated cystatin C has also been associated with structural brain changes, especially small vessel disease and gray matter atrophy in elders.[45] Our group has recently shown the that the presence of mild cerebral small vessel disease in the brains of persons dying with HIV disease is associated with impaired neurocognitive functioning prior to death.[46]

Limitations of this study include the cross-sectional design and the relatively small sample size. By design, our study lacked younger HIV- and HIV+ groups. While this precluded comparisons in these groups, we attempted to address this by comparing our findings with previously published data. The impact of cystatin C on longitudinal cognitive change in the setting of HIV remains unclear, and this longitudinal effect would have to be proven before it cystatin C be used clinically. Cystatin C was not associated with impairments in any specific neurocognitive domain, which may be attributed to a more systemic effect of cystatin C or our relatively small sample size. Since research biomarker assays can vary between manufacturers, batches, and labs, comparing the exact cystatin C values with other projects is difficult. Despite this, our findings are consistent with those previously reported in HIV- cohorts or with different outcomes.

Cystatin C could be a useful clinical tool to identify HIV+ persons with increased risk for cognitive decline. As the proportion of HIV+ persons in older age groups grows, clinically relevant biomarkers of pathologic and successful aging are important to identify. An essential component of successful aging is intact cognitive functioning. Blood biomarkers such as cystatin C, if confirmed to be associated with neurocognition in those living with HIV, may be highly clinically relevant especially since the assay is inexpensive and easily performed. Future research of cystatin C as a risk factor for neurocognitive decline in aging HIV+ adults would benefit from larger cohorts with a broader age range, longitudinal examinations, as well as mechanistic studies.

Acknowledgments

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Figure 1. Comparison of cystatin C concentrations and HIV serostatus. HIV+ adults had higher cystatin C concentrations than HIV- adults (mean 0.74 vs. 0.61 mg/L). The graph shows $\log_{10}$-transformed values to better reflect the analyzed data.

Table 1. Demographic, HIV disease, psychiatric, and substance use descriptive data

	HIV+ (n=77)		HIV- (n=47)		p-value
	M(SD) or No. (%)	Range	M(SD) or No. (%)	Range	
Age (years)	58.26 (6.06)	50-79	59.68 (7.33)	50-79	0.24
No. Male (%)	66 (86%)		27 (57%)		<0.01
Education (years)	14.57 (2.62)	8-20	14.06 (2.66)	6-19	0.30
Race [No. White] (%)	63 (82%)		30 (64%)		0.02
Current CD4+ (cells/µL)	646 (341)	6-1606	---	---	---
Nadir CD4+ (cells/µL)	185 (192)	2-850	---	---	---
% Undetectable Plasma HIV RNA	77 (100%)	---			
AIDS Status (Yes) (%)	52 (68%)	---	---	---	---
EDI (yrs)	18.34 (8.03)	1-31	---	---	---
Lifetime MDD Dx (Yes) (%)	48 (62%)	---	14 (30%)	---	<0.01
Current MDD Dx (Yes) (%)	12 (16%)	---	1 (2%)	---	0.02
Lifetime Substance Disorder Dx (Yes) (%)	52 (68%)	---	25 (54%)	---	0.12
Current Substance Disorder Dx (Yes) (%)	2 (3%)	---	0	---	0.26

Figure 1. Comparison of cystatin C concentrations and HIV serostatus. HIV+ adults had higher cystatin C concentrations than HIV- adults (mean 0.74 vs. 0.61 mg/L). The graph shows $\log_{10}$-transformed values to better reflect the analyzed data.
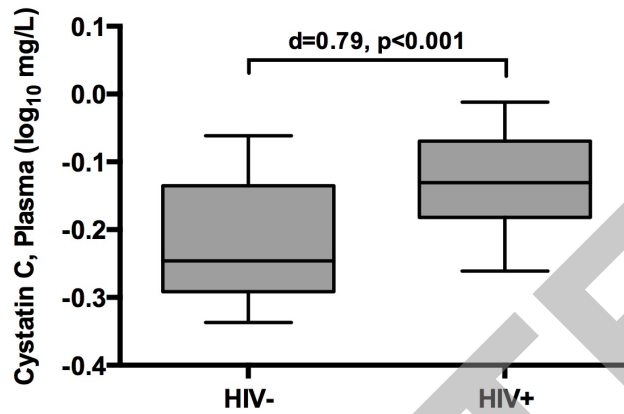
Figure 2. a) Comparison of cystatin C concentrations by neurocognitive status within the entire HIV+ group (n=77) and the subgroup using TDF (n=58). The dashed line indicates the ROC curve-defined threshold of -0.12 $\log_{10}$ mg/L (0.75 mg/L). Error bars indicate the 10th and 90th percentiles

b) Comparison of cystatin C ROC curve-defined threshold value to neurocognitive impairment among HIV+ participants. Error bars indicate the 95% confidence interval for the impairment estimates.