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Cognitive Performance and Frailty in Older HIV-Positive Adults

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Abstract

Objective: This study examined the relative contribution of cognitive status to frailty among older individuals infected with HIV+.

Design: Participants included 122 HIV+ individuals [mean age = 57.5 (6.6)] with a median CD4 cell count of 546. Undetectable viral load (<50 copies per mL) was observed in 94% of the sample. The sample was defined as frail (n = 21) and nonfrail (n = 101) according to the Fried phenotype criteria. Cognitive tests included measures of executive function, motor/psychomotor, language, learning, and memory. Performances were converted to standardized scores and averaged to calculate individual domain scores and a global index of cognitive function.

Methods: Logistic and hierarchical regressions were completed to separately determine the associations between clinical, demographic, and cognitive variables with regards to frailty status.

Results: Results of the logistic regressions revealed that lower executive function, female sex, and higher symptoms of depression were associated with frailty. The hierarchical analysis revealed no significant contribution of executive function to frailty status after accounting for female sex and symptoms of depression (Nagelkerke $R^2 = 0.15$).

Conclusions: These results emphasize the importance of sex distribution and mental health in explanatory models of frailty in HIV. Further, interventions targeting symptoms of depression may increase resilience in older HIV+ individuals.

Keywords

frailty; human immunodeficiency virus; neuropsychology; executive function

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INTRODUCTION

The success of combination antiretroviral treatment (cART) has shifted the population dynamics of HIV from a fatal condition in young adult men to a chronic disease in older men and women. The average age of HIV+ individuals in the United States is now more than 50 years.[1,2] Furthermore, virally suppressed individuals are now capable of achieving full life expectancies compared with demographically similar peers without HIV.[3–5] These evolving demographic landscapes of HIV create a pressing need to examine patient care outcomes in the context of age-associated health conditions.

Frailty is an age-associated condition that has received significant attention in the HIV research and clinical literatures.[6,7] Frailty is often described as reduced resilience to health and wellness and a corresponding increase in morbidity and mortality.[8] Fried et al proposed standardized criteria that defined frailty as a distinct entity from comorbidities (risk factors for frailty) and disability (outcome of frailty). The Fried frailty phenotype was defined by a constellation of physical symptoms including unintentional weight loss >10 pounds, self-reported exhaustion, low physical activity, slow walking speed, and/or grip strength weakness.[9] In a large sample of adults aged 65 and older followed for 3 years, Fried et al demonstrated that individuals with 3 or more of these symptoms (ie, frail individuals) experienced a greater number of falls and hospitalizations, more severe loss of functional independence and mobility, and higher rates of death compared with nonfrail adults.

The aging population of HIV and potential overlap in HIV symptoms and the frailty phenotype have increased interest in defining the clinical correlates of frailty in this population.[10] Studies of untreated HIV+ individuals reveal strong correlations between more HIV disease severity and increased risk of frailty. For example, detectable viral load, low immune function (CD4 and CD8 cell counts), increased levels of immune activation markers, and more severe lipodystrophy correlate with frailty in HIV+ individuals.[11,12] Frailty is also prevalent in chronically infected individuals on suppressive treatment, but the disease and patient predictors of frailty classification are not as well understood in the context of sustained treatment.

Previous studies indicate that HIV+ individuals diagnosed with global cognitive impairment have higher rates of frailty than cognitively unimpaired individuals.[13–18] However, the degree to which specific cognitive abilities (eg, executive function and memory) relate to frailty risk remains unknown. This is an important consideration in the era of cART, in which cognitive difficulties are most commonly observed in select domains.[19–21] Evidence from the geriatric literature reveals that uninfected individuals with poor executive function and psychomotor speed[13,22,23] have an increased risk of frailty. By contrast, memory and language, the prototypical domains linked to Alzheimer disease, do not predict frailty status.[24–26] These results are congruent with models of aging that emphasize the role of executive abilities in maintaining functional independence and wellness.[27,28]

Successful identification of a cognitive signature corresponding to frailty risk in older HIV+ individuals could potentially guide intervention strategies aimed at enhancing resilience and health-adjusted quality of life. This study was completed to address this important

area of clinical care. Specifically, 122 HIV+ individuals were assessed to determine whether frailty was associated with performance in select cognitive domains above and beyond other clinical variables. We hypothesized that frailty older people living with HIV would correspond to worse cognitive performance on tests of executive function and motor/psychomotor speed compared with nonfrail, HIV+ individuals.

METHODS

Participants

Participants were recruited from the Washington University School of Medicine Infectious Disease Clinic and the Washington University School of Medicine AIDS Clinical Trial Unit. Inclusion criteria were as follows: at least 50 years of age, a minimum of 8 years of education, ability to provide informed written consent, and ability to read and write in English, on cART, and virologically well controlled (<200 copies per mL; allowing for viremic blips). Individuals were excluded if they reported a history of head injury with loss of consciousness >30 minutes, self-reported major psychiatric disorders {eg, severe depression [Beck Depression Inventory-II (BDI-II) ≥ 29], untreated anxiety, schizophrenia, and bipolar disorder}, central nervous system opportunistic infections, current use of illicit drugs other than marijuana, or alcohol/substance use disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) 5.[29] Five participants (2 frail and 3 nonfrail) were excluded from the analyses based on BDI scores ≥29. Individuals were financially compensated for participation. The study was approved by the institutional review boards of participating sites.

Determination of Frailty

Frailty was defined according to the Fried phenotype criteria.[9] Individuals who met 3 or more of the following symptoms were classified as frail: self-reported unintentional weight loss (>10 pounds), self-reported exhaustion, self-reported low activity, gross motor slowness (corrected for sex and height), or weakness (corrected for sex and body mass index) (n = 21). Primary analyses classified all other participants as nonfrail (n = 101). This classification is consistent with previous investigations of frailty in HIV.[30–32] For secondary analyses, we analyzed the data using a 3-group model of nonfrail (n = 47), prefrail (individuals who endorsed 1 or 2 of the symptoms) (n = 54), and frail (n = 21) participants. Demographic and clinical characteristics of the groups included in the primary analysis are provided in Table 1.

Neuropsychological Assessment

Participants completed neuropsychological tests representing 5 cognitive domains:

- Executive function: (1) Color Word Interference Test trial 3[33], (2) verb fluency,[34] (3) Trail Making Test B (trails B[35]), and (4) letter number sequencing[36]. Verb fluency was included in this domain rather than language based on results from previous studies revealing differential sensitivity of this task to frontal subcortical dysfunction[36];

- Motor/psychomotor speed: (1) Trail Making Test A (trails A[35]), (2) digit symbol,[37] (3) grooved pegboard dominant and nondominant hands,[38] and (4) symbol search.[37] The grooved pegboard task was included in this domain given the timed motor demands of the task and the lack of other motor tests available to create a separate motor domain;
- Learning: (1) Hopkins verbal learning test–revised[39] total recall across the 3 learning trials and (2) brief visuospatial memory test–revised[40] total recall across the 3 learning trials;
- Memory: (1) Hopkins verbal learning test–revised total recall on the delayed recall trial and (2) brief visuospatial memory test–revised total recall on the delayed recall trial;
- Language: (1) Letter fluency (FAS[41]) and (2) category fluency (animals[42]).

Raw scores were converted to standardized Z-scores per domain using published norms.[37,43–46] Domain scores were averaged to create an overall measure of cognition. Mean domain and global Z-scores are presented for each group in Table 2.

Mood Assessment

Symptoms of depression were quantified using the BDI-II.[47] To minimize overlap between symptoms of depression, frailty, and HIV (eg, slowed motor function), the affective subscale of the BDI-II was calculated following established methods.[48,49]

Statistical Analyses

Statistical analyses were completed using SPSS (Version 24; New York, NY). A series of logistic regression analyses examined each neuropsychological domain, followed by models that separately examined demographic (age, sex, years of education, race, and BDI-II score), and clinical variable (current CD4, nadir CD4, viral load, duration of infection, and hepatitis C coinfection). Finally, significant predictors were entered into a hierarchical regression model with demographic and clinical indices entered in the first block and cognitive domain scores entered in the second block. A forward stepwise procedure was used with entry level set at $\alpha = 0.10$ and retention at $\alpha = 0.05$. For the secondary analyses, the above methods were repeated using a 3-group classification of frailty (nonfrail, prefrail, and frail).

RESULTS

Global and Domain-Specific

Neuropsychological Performance and Frailty—Worse performance in the executive function domain corresponded to frailty status [odds ratio (OR) = 0.46; confidence interval (CI): 0.23 to 0.92; $P = 0.03$]. Performance in the motor/psychomotor speed domain trended toward significance (OR = 0.51, CI: 0.25 to 1.03, $P = 0.06$), but did not reach threshold. Performances in learning (OR = 0.76, CI: 0.43 to 1.34, $P = 0.29$), memory (OR = 0.77, CI: 0.46 to 1.32, $P = 0.35$), and language (OR = 0.94, CI: 0.57 to 1.56, $P = 0.82$) were unrelated to frailty status (Table 2). The global cognitive index (average Z-score across domains) did not predict frailty status (OR = 0.51, CI: 0.23 to 1.14; $P = 0.10$). Post hoc analyses revealed

that performance on the Color Word Interference Test Trial 3 ($P = 0.004$), a measure of inhibition, drove the association between executive function and frailty. Within the motor/psychomotor domain, which trended toward significance, low performance on digit symbol was the major correlate of frailty status ($P = 0.02$); no other tests emerged as significant predictors.

Demographic and Clinical Indices and Frailty—Logistic regression models revealed that female sex (OR = 3.98; CI: 1.44 to 11.01; $P = 0.008$) and higher affective BDI-II subscale scores (OR = 1.26, CI: 1.05 to 1.51, $P = 0.01$) were significant predictors of frailty status (Table 3). By contrast, models including current CD4 cell count, nadir CD4 count, and viral load were not significant. Individuals with hepatitis C coinfection were 2 times more likely to be classified as frail compared with HIV+ monoinfected individuals, but the difference was not statistically significant in this relatively small sample.

Integrated Analysis of Frailty—Stepwise hierarchical analysis revealed that female sex (OR = 3.50, CI: 1.22 to 10.02; $P = 0.02$) and BDI-II affective subscale scores (OR = 1.22, CI: 1.01 to 1.48; $P = 0.04$) but not executive function (OR = 0.67, CI: 0.32 to 1.41; $P = 0.29$) related to frailty classification (Nagelkerke $R^2 = 0.15$). Results did not differ according to detectable vs. undetectable (<50 copies per mL) viral load. Similarly, the results did not differ when examined using a 3-group model of nonfrail (n = 47), prefrail (n = 54), and frail (n = 21) HIV+ individuals. Comparisons of cognitive performances by domain revealed the same pattern as observed from the 2-group model. That is, frail individuals performed significantly worse than nonfrail individuals in the executive function domain ($P = 0.005$), but the association did not remain significant ($P = 0.08$) after including sex and symptoms of depression into the model.

DISCUSSION

Our primary aim focused on whether frailty in HIV+ individuals corresponded to a unique neuropsychological signature, particularly poor performance in executive function and motor/psychomotor speed. Results revealed that poor performance on tests of executive function, but not motor/psychomotor speed, corresponded to frailty status in this HIV+ population. Although modest in strength, the unique relevance of executive function to frailty aligns with outcomes reported previously in older HIV-uninfected individuals.[13,16,23,50,51] When compared with female sex and symptoms of depression, cognitive performance did not contribute to the explanatory model of frailty. Similarly, neither remote (eg, nadir CD4) nor recent (current CD4 and viral load) indices of disease severity correlated with frailty status.

The observation that executive function is associated with frailty status in older HIV+ individuals is consistent with the predilection for HIV disease mechanisms to disrupt frontal subcortical circuits that mediate higher-order thinking.[52–54] While concerns have been raised that the neuropsychological phenotype in older HIV+ individuals is likely to resemble cortical (eg, Alzheimer disease) or mixed cortical–subcortical patterns, results from empirical studies have not indicated a change in the cognitive[51,55] or molecular profile of older HIV + individuals.[56] Results from this study provide additional support for the

persistence of the frontal subcortical pattern in older HIV+ individuals, including those with viremia below 200 copies per mL. Furthermore, these findings underscore the importance of continued clinical focus on cognitive health independent of immunological markers of disease severity.

Symptoms of depression were tightly linked to frailty status. This finding is generally consistent with results from previous studies; yet, an important difference is that we observed this relationship among individuals with mild depression. This outcome suggests that reliance on formal psychiatric diagnoses (eg, medical chart clinical diagnoses[57]) is likely to miss individuals with subclinical mood symptoms who, nonetheless, are at heightened risk for frailty. We cannot rule out the possibility that other psychiatric symptoms (eg, anxiety) are equally relevant to frailty in HIV, but the high base rate of depression in this population argues for a continued emphasis on mental health assessment and intervention in routine clinical care.

It is important that disease comorbidities (depression) and HIV disabilities remain phenomenologically distinct from the classification of frailty as originally proposed by Fried et al. Self-reported “exhaustion” defined as “a feeling that everything I do is an effort” and/or “sometimes I just can’t get going”[57,58] might be conflated with apathy.[59–61] Relatedly, the frequency of frailty in HIV participants increased more than 2-fold when performance on grip strength was included into the frailty assessment.[11] The potential overlap between disease symptoms, age-related constructs such as sarcopenia, and the frailty clinical phenotype is likely reduced when frailty is defined within the framework of the cumulative deficit model,[62] but additional studies are needed.

Traditional clinical indices of HIV disease severity (eg, nadir CD4 and detectable viral load) were poor predictors of frailty in our sample. These findings differ from previous studies that examined HIV disease markers and frailty[11,17,32,63,64]. The discrepancy may be related to the general immunological health and the overall level of viral suppression achieved by individuals enrolled in this study. Future research on frailty in this population will need to consider alternative markers of disease activity. For example, despite no direct link between current or nadir CD4 on frailty status, Erlandson et al[58] observed elevated levels of immune activation markers (eg, CD38/HLA-DR expression on CD8 T cells) and interleukin-6 in aviremic, frail HIV+ individuals. Results from this study indicate that cART is insufficient to protect HIV+ individuals from ongoing disease mechanisms linked to frailty.

Finally, our data identified female sex as a strong correlate of frailty status. Among women, physical inactivity, exhaustion, and slow walking speed were the most common classifiers, whereas physical inactivity, exhaustion, and low grip strength were the most common classifiers of frailty in men. The association between female sex and frailty has been described previously.[9,65–67] In these studies, women had a 2-fold increased risk of frailty compared with men. The different point estimates of frailty by sex were often adjusted in analyses rather than incorporating sex as a primary predictor variable.[65–67] Identifying sex as a unique risk variable of frailty will be needed in future studies. A more complete understanding of the underlying biopsychosocial intermediaries is needed. Preliminary evidence suggests an interaction between sex and HIV-related comorbidities that increase

frailty risk, eg, diabetes, cigarette smoking, and cardiovascular disease.[63,64,68] These health comorbidities are becoming more prevalent in the cART era and may differentially affect men and women. For example, health-adjusted life expectancy is 2 times lower in HIV+ women compared with HIV+ men.[69] Other groups have raised concern that HIV+ women exhibit worse cognitive impairment compared with HIV+ men,[70] although sex-specific differences are not universal.[54] Additional studies focused on sex-specific risk of frailty in HIV are warranted.[71]

Limitations of our study include the absence of longitudinal data and the restricted sample size. Longitudinal studies will help to improve the specificity of frailty as a differentiated entity from overlapping psychiatric and/or disease symptoms. Although our sample was limited, the study was sufficiently powered to identify medium or larger effect sizes. A larger sample would be needed to identify small effects, but the clinical relevance of such outcomes would be questionable. Interestingly, nearly 18% of the older HIV+ individuals enrolled in this study met criteria for frailty. This frequency is high compared with previous studies of demographically similar HIV + and HIV2 cohorts and may reflect the challenges to the diagnosis of frailty that is inherent in the population.[9,11,72,73] Finally, advanced immunological indices of aging and HIV disease activity were not available for inclusion in this study. Future investigations that incorporate biomarkers of HIV-related disease activity (eg, systemic immune activation) in the context of otherwise successful cART are needed to further establish the biological substrates of frailty in HIV.

In summary, executive function is the primary cognitive domain associated with increased risk of frailty in older HIV+ individuals. Routine HIV disease markers are insensitive to frailty classification using the Fried model, whereas female sex and current symptoms of depression are of particular relevance. Additional research is needed to define the latent structure of frailty as a clinical entity. Finally, studies are needed that examine interactions and potentiating effects of sex, depression, and health comorbidities. Data science methods that include single- and multi-level interactions between patient-centered variables (female sex, cardiovascular disease, diabetes, and hepatitis coinfection) and HIV disease variables (eg, immune activation) may help to advance the current understanding and clinical application of frailty in this population.

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TABLE 1.

Demographic and Clinical Variables of HIV+ Individuals

	Frail (n = 21)		Nonfrail (n = 101)		
Variable	**Male (n = 12)**	**Female (n = 9)**	**Male (n = 85)**	**Female (n = 16)**	**Frail vs. Nonfrail *P***
Age (yrs)	58.3 (6.3)	54.0 (5.2)	57.3 (5.8)	60.4 (10.2)	0.41
Race (% African American)	67%	67%	54%	81%	0.48
Education (yrs)	12.7 (2.8)	12.9 (2.8)	13.8 (2.7)	12.9 (2.8)	0.16
Affective BDI-II subscale	3.5 (2.5)	2.7 (3.1)	1.5 (1.9)	2.6 (3.1)	**0.01**
Duration of infection (mo)	204 (91)	150 (70)	222 (108)	177 (95)	0.17
Hepatitis C coinfection, %	33%	11%	13%	6%	0.15
Undetectable viral load (<50 copies/mL), %	100%	89%	94%	100%	0.41
Current CD4 count, median (IQR)	672 (457–816)	688 (371–980)	514 (383–699)	476 (234–913)	0.12
Nadir CD4 count, median (IQR)	128 (68–280)	139 (20–396)	78 (20–270)	31 (21–99)	0.69

BDI-II, Beck Depression Inventory-II; IQR, interquartile range.

Bolded text represents significance at $P < 0.05$.

TABLE 2.

Neuropsychological Z-Scores: Mean (SD)

	Frail	Nonfrail	*P*	Cohen's d
Global	−0.43 (0.8)	−0.18 (0.6)	0.10	0.4
Executive function	−0.69 (0.8)	−0.30 (0.7)	**0.02**	0.5
Motor/psychomotor speed	−0.36 (0.8)	−0.03 (0.7)	0.06	0.4
Learning	−0.57 (1.1)	−0.37 (0.8)	0.34	0.2
Memory	−0.53 (1.1)	−0.31 (0.9)	0.35	0.2
Language	0.02 (0.9)	0.07 (0.9)	0.82	0.1

Bolded text represents significance at $P < 0.05$.

TABLE 3.

Odds Ratios of Frailty

	OR (95% CI)	*P*
Neuropsychological variables		
Global NPZ	0.51 (0.23 to 1.14)	0.10
Motor/psychomotor speed	0.51 (0.25 to 1.03)	0.06
Executive function	0.46 (0.23 to 0.92)	**0.03**
Learning	0.76 (0.43 to 1.34)	0.34
Memory	0.77 (0.46 to 1.32)	0.35
Language	0.94 (0.57 to 1.56)	0.82
Demographic variables		
Age	0.97 (0.89 to 1.05)	0.40
Sex	**3.98 (1.44 to 11.01)**	**0.01**
Education	0.87 (0.72 to 1.01)	0.16
Race	0.70 (0.26 to 1.89)	0.48
Affective BDI-II subscale	**1.26 (1.05 to 1.51)**	**0.01**
Clinical variables		
Plasma current CD4	1.01 (1.00 to 1.03)	0.12
Plasma nadir CD4	1.01 (0.99 to 1.03)	0.69
Plasma viral load	1.00 (0.99 to 1.01)	0.30
Duration of infection	1.00 (0.99 to 1.01)	0.17
Hepatitis C coinfection	2.32 (0.72 to 7.48)	0.16

Variables in bold font remained significant in adjusted models.

NPZ, neuropsychological Z-score.