Frailty in medically complex individuals with chronic HIV

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Objectives: Multimorbidity and frailty are consequences of aging with HIV, yet not everyone with medical disease is frail. Our objective was to identify factors associated with frailty in a multimorbid HIV-infected cohort.

Design: Analysis of a prospective, observational, longitudinal cohort.

Methods: Three hundred and thirty-two participants in the medically advanced National NeuroAIDS Tissue Consortium (NNTC) study were categorized as frail, prefrail, or robust with the Fried Frailty Index. A series of logistic regression analyses (first univariate, then multivariable) were conducted to determine whether medical comorbidities, immunologic and virologic parameters, and/or neuropsychiatric variables predicted increased odds of frailty.

Results: The mean number of medical comorbidities per participant was 2.7, mean $CD4^+$ T-cell count was 530 cells/μl, and 77% had undetectable HIV RNA in blood. Twenty-two percent were frail, 55% prefrail, and 23% robust. Significant predictors of frailty in multivariable analysis were cognitive diagnosis rendered by Frascati criteria, depressive symptoms, diabetes mellitus, chronic obstructive pulmonary disease (COPD), and sex. Men were less likely to be frail than women. Higher odds of frailty were seen with: symptomatic, but not asymptomatic, cognitive impairment (compared with cognitive normals); more depressive symptoms; diabetes mellitus; and COPD.

Conclusion: Neuropsychiatric illness increased odds of being frail on a predominantly physical/motoric measure, but only when symptomatic. Lack of association with asymptomatic impairment may reflect the importance of functional limitation to frailty, or possibly a unique resilience phenotype. Understanding why sex and symptomatic neuropsychiatric illness are associated with frailty will be important in managing HIV-associated morbidity in aging populations.

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Introduction

Medical illness accrues with age, yet for each level of comorbidity burden, individual medical outcomes are variable. Frailty is a phenotype that accounts for some of this variability; within each stratum of disability, frailty predicts survival [1,2]. Adults living with HIV exhibit frailty more frequently than HIV-negative individuals of similar age, but whether this increase is a consequence of HIV itself or of its comorbidities is debated [3,4]. Some also question the validity of frailty measurement tools in populations with mean ages under 50 [3,4]. As combination antiretroviral therapy (cART)-era HIV populations enter decades for which common frailty measures were designed, determinants of frailty will be important to identify in order to optimize clinical management.

The most widely deployed and validated instrument to measure frailty in HIV-positive and HIV-negative populations has been the Fried Frailty Index (FFI), which is heavily weighted to physical characteristics, but lacks measures of cognition, disability, and comorbidity [5,6]. Accordingly, studies have investigated the relationship between FFI and these other components. In the context of HIV, the Study to Understand the Natural History of HIV and AIDS in the Era of Effective Therapy (SUN study) assessed comorbidity burden by the Veterans Aging Cohort Study (VACS) index [7]. Comorbidity was related to frailty and prefrailty, but transitions in frailty status were not reflected by changes in VACS index values [7]. Multimorbidity, defined as three or more medical illnesses, was correlated with frailty in a sample of people living with HIV (PLWH) visiting a metabolic clinic in Italy [8]. In a functionally intact [i.e. without impairments in activities of daily living (ADL)] subsample from this clinic, cognitive status assessed by three neuropsychologic tests, and depressive symptom index was also correlated with frailty status [9]. In a sample from a tertiary care center in Mexico that excluded severe illnesses, such as COPD and advanced cardiac disease, frailty was related to functional cognitive impairments assessed with the NEUROPSI battery [10]. In an AIDS Clinical Trials Group (ACTG) longitudinal observational study (ACTG A5001), cognitive impairment was associated with frailty, and when present in combination, resulted in a greater risk of falls, disability, or death than either factor alone [11].

To date, no studies have examined the simultaneous relationships between frailty status and neuropsychiatric dysfunction, medical illness, and immune and virologic biomarkers in an aging HIV cohort. As increased medical illness burden is usually an inevitable consequence of aging, we sought to determine the factors associated with frailty in a highly multimorbid sample of aging PLWH. Analysis of a multimorbid patient population allowed identification of specific illnesses or factors that increased the likelihood of frailty when individuals had already attained a state of medical compromise. Furthermore, as cognitive abnormalities without functional impairment (asymptomatic neurocognitive impairment, ANI) are common in PLWH, we wanted to ascertain whether ANI was associated with frailty on a medically morbid background, as this could have implications for clinical screening [12].

Methods

Patient population

The National NeuroAIDS Tissue Consortium (NNTC) is a longitudinal cohort and organ donation study, whose mission is to serve as a research resource providing tissue and fluid biospecimens from well characterized HIV-infected individuals. Participants for this analysis were enrolled at the four clinical sites of NNTC, located at Galveston, Texas; Los Angeles, California; New York City, New York; and San Diego, California. Participants were part of the ongoing, longitudinal study conducted under oversight of each medical center's local Institutional Review Board. All participants consented to the use of their data for the purposes of HIV and neuroHIV research. All informed consent procedures included tests of comprehension to ensure cognitively impaired participants were able to consent. Criteria for entry into the NNTC study include willingness to be an organ donor upon demise, and neuromedical conditions for which adequate or curative therapy is unavailable, thus enriching the cohort for significant medical morbidity. Qualifying medical conditions include illnesses, such as solid organ or hematologic cancers, advanced liver disease, and significant cardiac disease, but are not limited to these categories and are at the discretion of NNTC site PIs. In the most recent 5-year cycle, advanced age (60 years or older) was added to the list of qualifying conditions, enabling NNTC to support a research focus on aging. Exclusion criteria for NNTC include unwillingness to be a brain donor upon demise, and age under 18 years (the age of consent for organ donation).

Participants were included in this analysis if the central NNTC database, located at Emmes Corporation in Rockville, Maryland, contained a complete FFI assessment collected between 2014 and 2018, along with a full elaboration of neuromedical disorders active at the time of assessment. Assessments with missing values were not included. Of 603 participants active in the study, 332 met this criteria, and additional information from standardized NNTC evaluations was collected and analyzed, as described below. Analyses were conducted on all individuals with available data, and not on the basis of representativeness of the active cohort, as we did not have any a priori hypotheses to test regarding which factors

would be associated with frailty. At the time of analysis, the demographic composition of the larger cohort from which the sample was selected was: 77% male, 23% female; 29% African American, 30% Hispanic, 36% Caucasian, 5% other race; and 20% intravenous drug use (IVDU) risk for HIV.

Neuromedical assessment

Participants in the NNTC receive a multimodal evaluation that includes: laboratory analysis to determine current $CD4^+$ T-cell count and plasma HIV RNA (lower limit of quantitation was set at 40 copies/ml); review of all current medications including cART and adherence; review of medical illnesses, inclusive of hypertension (HTN), diabetes mellitus, hyperlipidemia, viral hepatitis, chronic renal disease, cardiac disease, chronic obstructive pulmonary disease (COPD), non-AIDS defining cancers, cerebrovascular disease, and lipodystrophy; review of other medical and behavioral symptoms (as for example, weight loss, apathy, fever); review of recent tobacco smoking; and neurologic examination to evaluate signs and symptoms of distal symmetric polyneuropathy (DSPN), and other significant neurologic disorders. Specific medical illnesses for review were selected on the basis of their general prevalence in HIV, and because they collectively accounted for the majority of illness burden in NNTC. Information was collected both from participant examination, participant interview, and whenever available, caregiver interview and review of the medical record.

Neurobehavioral assessment

The NNTC neuropsychological test battery has been previously published; in brief, a battery of tests is administered to examine global cognitive function and the following seven putative cognitive domains: learning; memory; abstraction/executive functioning; speed of information processing; verbal fluency; working memory; and motor [13]. Global and domain *T* scores are calculated and used to derive clinical ratings. Functional impacts are assessed through a modified Lawton and Brody ADL questionnaire and the Patient's Assessment of Own Functioning Inventory (PAOFI), and cognitive diagnoses are assigned at clinical sites by experienced neuropsychologists according to the research nosology for diagnosis of HIV-associated neurocognitive disorders (HAND) established in Frascati [14]. This nosology results in the following sub-categories: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), HIV-associated dementia (HAD), and cognitive impairment because of other causes (NPI-O). Cognitive assessments were utilized only if they occurred in the same study visit as the FFI and neuromedical assessment; for 16 individuals, a Frascati diagnosis was not available in this interval. A structured psychiatric interview (the Composite International Diagnostic Interview version 2.1) is conducted, and depressive symptoms quantified by administration of the Beck Depression Inventory (BDI) version 2. Depressive symptom scores were utilized only if they occurred in the same study visit as the FFI and neuromedical assessment; for 17 individuals, a BDI score was not available in this interval.

Frailty assessment

Administration of the FFI at each site was standardized, and presence or absence of criteria in its five dimensions (weight loss, exhaustion, grip strength, physical activity, timed walk) were recorded. Participants were classified as frail when they had three or more positive criteria; prefrail with one or two criteria; and robust when no criteria were present.

Statistical modeling and analysis

Frailty status was modeled as an ordinal outcome. Cumulative logistic regression analysis (SAS 9.4 procedure LOGISTIC) was used to determine statistical significance, odds ratios (ORs), and 95% confidence intervals (CIs) for associations between potential risk factors and all frailty outcomes. Each factor was initially modeled in a univariate setting against frailty status; factors significant at $P = 0.10$ or less were retained for a multivariable model. In the multivariable model, factors were removed via backward elimination until all remaining factors were statistically significant at $P = 0.05$ or less. ORs and 95% CIs were computed for these factors for each frailty outcome model. Analyses were not adjusted for multiple comparisons. Potential risk factors assessed in the initial univariate analyses included: age, race/ethnicity, sex, IVDU/sexual risk factor for HIV acquisition, current and nadir $CD4^+$ T-cell count, plasma HIV RNA, medical illnesses (described above), smoking, presence of DSPN, cognitive diagnosis rendered via Frascati criteria, depressive symptom score from the BDI, use of antidepressant medication, BMI, literacy level assessed by the Wide Range Achievement Test – version 3 (WRAT-3), and study site.

Secondary analyses included: tests of association with individual components of the FFI; tests of association between each nonnormal Frascati diagnosis vs. unimpaired; a univariate analysis of global *T*-score on frailty outcomes; and a multivariable analysis of individual domain *T*-scores without adjustments for other factors. As with other multivariable models, factors were removed via backward elimination until all remaining factors were significant at P less than 0.05.

Results

Cohort characteristics

The study population was demographically diverse: there was relatively equal distribution of African American, Hispanic, and Caucasian race/ethnicity, and 28% were

Table 1. Participant characteristics.

	Total	Robust	Prefrail	Frail	*P*
Sample size, *N* (%)	332	78 (23%)	181 (55%)	73 (22%)	n/a
Mean age (SD)	59.7 (8.9)	58.9 (9.4)	59.5 (8.2)	60.8 (9.9)	0.36
Male sex	72%	85%	71%	63%	**<0.01**
Race/ethnicity					0.5
African American	29%	27%	33%	21%	
Hispanic	32%	35%	28%	38%	
Caucasian	34%	33%	33%	37%	
Other	5%	5%	6%	4%	
IVDU risk	23%	21%	21%	29%	0.17
Mean current $CD4^+$ cell count (SD)	530 (299)	489 (299)	552 (314)	520 (257)	0.29
Median nadir $CD4^+$ cell count [IQR]	50 [8–180]	45 [6–145]	65 [7–190]	50 [12–149]	0.55
Median log plasma HIV load [IQR]	1.6 [1.6–1.6]	1.6 [1.6–1.6]	1.6 [1.6–1.6]	1.6 [1.6–1.6]	0.93
Tobacco smoking	46%	35%	52%	44%	**0.03**
Hypertension	46%	45%	44%	53%	0.36
Diabetes mellitus	20%	6%	23%	27%	**<0.01**
Hyperlipidemia	48%	50%	49%	47%	0.91
Viral hepatitis	21%	22%	19%	23%	0.76
Chronic renal disease	10%	9%	8%	15%	0.25
Cardiac disease	20%	19%	18%	25%	0.45
Chronic obstructive pulmonary disease	15%	6%	16%	22%	**0.03**
Cerebrovascular disease	17%	10%	19%	18%	0.23
Non-AIDS defining cancer	14%	13%	12%	21%	0.17
Lipodystrophy	11%	10%	13%	8%	0.57
Peripheral neuropathy	58%	51%	58%	69%	0.15
BMI (mean)	27.1 (6.4)	25.7 (4.6)	27.6 (7.2)	27.5 (5.7)	0.07
WRAT-3 raw score (mean)	44.8 (9.0)	44.3 (8.5)	44.9 (9.2)	45.0 (9.1)	0.88
Beck Depression Inventory (median)	8 [2–16]	3 [0–9]	8 [2–16]	16 [7–22]	**<0.01**
Antidepressant medication use	38%	30%	37%	46%	0.12
Cognitive diagnosis					**<0.01**
Normal	35%	47%	35%	21%	
Asymptomatic impairment (ANI)	14%	24%	15%	3%	
Mild neurocognitive disorder (MND)	21%	16%	20%	29%	
HIV-associated dementia (HAD)	11%	3%	11%	21%	
Impairment because of other causes (NPI-O)	19%	10%	19%	26%	

Percentages represent within frailty category totals. IQR, interquartile range. Bold indicates *P* values less than 0.05.

women. Although most of the population had a low nadir $CD4^+$ T-cell count, the mean current $CD4^+$ T-cell count was 530 cells/μl. Median plasma HIV RNA was undetectable (77% of the sample). There was a significant burden of medical comorbidities, with an average of 2.7 medical conditions per person (median 3, IQR [1–4]). Almost one-half of the sample smoked, had hypertension, and hyperlipidemia, and over one-half displayed DSPN. Depressive symptoms were generally within the minimal to mild range; 38% of the sample was actively prescribed antidepressant medication. Thirty-five percent of the sample was cognitively normal, with ANI in 14% and symptomatic cognitive impairments in 51% (21% MND, 11% HAD, 19% NPI-O) (Table 1).

Associations with overall frailty

Twenty-two percent of the population was frail, 55% prefrail, and 23% robust. The frequency of abnormal FFI components included: 15% weight loss, 40% exhaustion, 35% decreased grip strength, 29% reduced physical activity, and 30% abnormal timed walk. In univariate analyses, overall frailty status was associated with sex, diabetes mellitus, COPD, depressive symptoms, and cognitive diagnosis at the P 0.01 or less level; with DSPN and use of antidepressant medication at the $P = 0.05$ or less level; and with BMI and cancer diagnosis at P value 0.10 or less. In the multivariable model, female sex [OR for men 0.58 (95% CI: 0.35–0.97), $P = 0.04$], more depressive symptoms [OR 1.07 per unit BDI (95% CI: 1.05–1.10), $P < 0.01$], cognitive abnormality [symptomatic impairment vs. normal cognition OR 2.35 (95% CI: 1.39–3.99), $P < 0.01$], and the presence of diabetes mellitus [OR 1.81 (95% CI: 1.02–3.22), $P = 0.04$] or COPD [OR 1.94 (95% CI: 1.03–3.66), $P = 0.04$) were associated with frailty (model r^2 0.27, $P < 0.01$). Viral suppression had no effect in the model. The proportional odds assumption was met ($P = 0.51$). Twenty-nine percent of women were frail in contrast to 19% of men; 30% of those with diabetes mellitus were frail in contrast to 20% of those without; 32% of those with COPD were frail in contrast to 20% of those without; the mean BDI in the frail was 15.9 in contrast to 5.4 in the robust (38% of those with a BDI score ≥ 14 – the threshold for mild depression – were frail compared with 14% of those with BDI < 14); and 32% of those with symptomatic cognitive impairment were frail in contrast to 13% of cognitive normals (Tables 1 and 2).

Associations with frailty components

In multivariable analysis (Table 2), depressive symptoms had the most consistent associations with FFI components, significant in all except grip strength. Other factors

Table 2. Factors correlated with frailty and its individual components.

Factor	Overall	Frailty component OR (95% CI)				
	Frailty[a] OR (95% CI)	Weight loss	Exhaustion	Physical activity	Timed walk	Grip strength
Gender (male)	0.58 (0.35–0.97)[b]					
BDI total score	1.07 (1.05–1.10)[d]	1.06 (1.02–1.09)[d]	1.13 (1.09–1.17)[d]	1.04 (1.01–1.06)[c]	1.04 (1.00–1.07)[b]	
Frascati diagnosis (MND/HAD/NPI-O vs. NL)	2.35 (1.39–3.99)[c]					2.30 (1.35–3.92)[c]
Peripheral neuropathy					1.96 (1.03–3.76)[b]	
DM	1.81 (1.02–3.22)[b]				2.50 (1.23–5.07)[b]	
COPD	1.94 (1.03–3.66)[b]			2.34 (1.23–4.42)[c]		
Non-AIDS defining cancer		2.91 (1.32–6.38)[c]			2.47 (1.07–5.73)[b]	
Lipodystrophy			0.28 (0.11–0.71)[c]			
Tobacco smoking		1.96 (1.02–3.78)[b]				
BMI			1.05 (1.01–1.09)[c]	1.04 (1.00–1.08)[b]		

BDI, Beck Depression Inventory; CI, confidence interval; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HAD, HIV-associated dementia; MND, mild neurocognitive disorder; NPI-O, cognitive impairment because of other causes; OR, odds ratio.
[a]Participants characterized as robust, prefrail, or frail.
[b]Factor significant at $0.01 < P < 0.05$.
[c]Factor significant at $0.001 < P < 0.01$.
[d]Factor significant at P less than 0.001.

significantly associated with FFI components after multivariable analysis were for the most part conceptually congruent: for example, weight loss was associated with smoking and cancer, worse physical activity and exhaustion with increased BMI, and worse physical activity with COPD.

Neurobehavioral associations with frailty

As neurobehavioral abnormalities had the greatest and most consistent associations with frailty and individual FFI components, the next set of analyses examined these associations. First, for the 104 individuals who had a BDI value in the range of depression (BDI ≥ 14), the use of antidepressant medication (55% of this sub-sample of 104) was not associated with a greater or lesser percentage of frailty.

We then examined which cognitive diagnoses displayed associations with frailty, and within the entire range of diagnoses, whether any particular neuropsychological domains (particularly motor domain, given the physical emphasis of FFI) accounted for significant associations. With regard to diagnoses, only symptomatic cognitive abnormalities, and not asymptomatic, were associated with frailty [ORs: 2.6 (MND), 5.2 (HAD), and 3.0 (NPI-O), all P values < 0.01] (Table 3 and Fig. 1). Individuals with ANI could not be distinguished from those with normal cognition with regard to the odds of being frail, or with regard to the odds of abnormality on any individual frailty component (Table 3). Those with ANI, while accounting for 14% of the overall sample, accounted for only 3% of those who were frail, whereas all other cognitive categories (including normal) accounted for over 20% of those with frailty (Table 1). The group with ANI could not be distinguished from other cognitive categories on the basis of their number of medical comorbidities. With regard to depressive symptoms, they were similar to both the cognitively normal group and those with NPI-O (mean BDI score 8.6, 9.4, and 7.0 for normal, NPI-O, and ANI, respectively), with more depressive symptoms in MND (mean score 14.3) and HAD (mean score 15.1) (overall ANOVA $P < 0.01$). The group with ANI had a similar proportion of women compared with other cognitive categories (27.9%), but displayed low prevalence of diabetes mellitus (11.6%) and COPD (4.7%).

Global T scores were associated with frailty and all its components except weight loss (higher T scores indicate better function; significant odds ratios ranged from 0.94 to 0.97, with P values ≤ 0.02). In the model predicting overall frailty using neuropsychological domain scores (but not the global score), only motor domain remained significant (OR 0.95 [95% CI 0.94–0.97], $P < 0.01$); that is, other domains did not make independent contributions to frailty when the motor score was accounted for. Domain associations with individual frailty components are reported in Table 3.

Table 3. Cognitive associations with frailty and its components.

Cognitive diagnosis (reference: normal)	Frailty OR (95% CI)	Frailty component OR (95% CI)				
		Weight loss	Exhaustion	Physical activity	Timed walk	Grip strength
ANI	NS	NS	NS	NS	NS	NS
MND	2.6 (1.4–3.8)[b]	NS	2.6 (1.4–4.8)[b]	NS	NS	2.0 (1.0–3.9)[a]
HAD	5.2 (2.4–11.2)[c]	NS	2.6 (1.2–5.7)[a]	4.4 (1.9–9.9)[c]	2.3 (1.0–5.2)[a]	2.5 (1.1–5.6)[a]
NPI-O	3.0 (1.6–5.8)[c]	NS	NS	NS	2.4 (1.2–4.8)[a]	2.5 (1.3–5.0)[b]
Cognitive Domain T score						
Global T Score[d]	0.94 (0.92–0.97)[c]	NS	0.96 (0.93–0.99)[b]	0.96 (0.93–0.99)[b]	0.94 (0.91–0.97)[c]	0.97 (0.94–0.99)[a]
Abstraction executive function domain	NS	0.97 (0.94–1.00)[a]	NS	NS	NS	NS
Memory domain	NS	NS	0.96 (0.94–0.99)[b]	NS	NS	NS
Verbal fluency domain	NS	NS	NS	0.97 (0.95–0.99)[b]	NS	NS
Motor domain	0.95 (0.94–0.97)[c]	NS	NS	NS	0.94 (0.92–0.97)[c]	0.96 (0.94–0.98)[c]

ANI, asymptomatic neurocognitive impairment; HAD, HIV-associated dementia; MND, mild neurocognitive disorder; NPI-O, cognitive impairment because of other causes; NS, not significant at P less than 0.05; OR, odds ratio.
[a]Factor significant at $0.01 < P < 0.05$.
[b]Factor significant at $0.001 < P < 0.01$.
[c]Factor significant at P less than 0.001.
[d]Global T score was modeled individually, and not in conjunction with domain scores.

Sex and frailty

As women had greater odds of being frail when all factors were considered, we examined sex differences in the sample to gain insight into this association. Although most of the women (74%) were located in the New York NNTC site, there was no site-specific association with frailty status. Women were more often African American (43 vs. 23%) and less often Caucasian (18 vs. 40%) than men ($P < 0.01$),

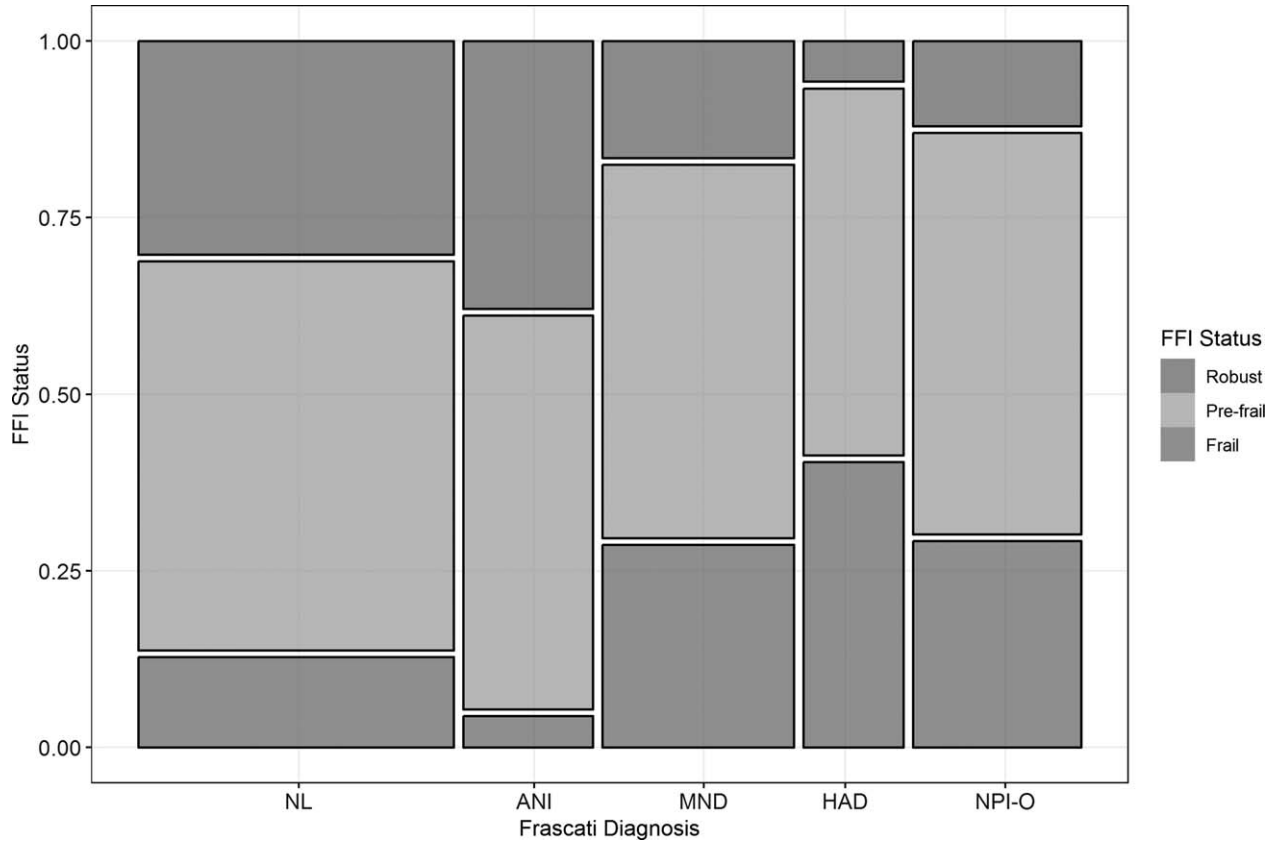

Fig. 1. Distribution of frailty phenotypes by cognitive diagnosis. Percentage of individuals with frail, pre-frail, or robust status within each diagnostic cognitive category. NL: Cognitively normal; ANI: asymptomatic neurocognitive disorder; MND: mild neurocognitive disorder; HAD: HIV-associated dementia; NPI-O: cognitive impairment due to other (non HIV) causes.

but race/ethnicity was not associated with frailty. Women in this sample had higher $CD4^+$ T-cell counts and nadirs than men [$CD4^+$ T-cell count 617 (31 SEM) vs. 496 (19 SEM) cells/μl, $P < 0.01$; nadir 151 (17 SEM) cells/μl vs. 102 (10 SEM) cells/μl, $P < 0.01$)]; again, factors not associated with frailty. Women also had a greater frequency of diabetes mellitus (33 vs. 15%, $P = 0.03$), and higher BMI [29.9 (0.6 SEM) vs. 26.1 (0.4 SEM), $P < 0.01$].

Discussion

Frailty is a useful construct across diverse medical conditions and populations, as it is an indicator of decreased physiologic reserve predicting morbidity and mortality in the face of stressors, and can be used to guide therapy for medical disease [1,2,15]. It is thought that HIV is an independent risk factor for frailty, supported by observations of increased prevalence in HIV cohorts equivalent to older HIV-negative populations [3,16]. However, PLWH also experience rates of medical illnesses comparable with older HIV negative adults, and medical multimorbidity is associated with frailty in many populations regardless of serostatus [4,8,17]. Accordingly, the purpose of this study was to evaluate conditions associated with frailty within the context of multimorbidity using data from the NNTC cohort, which is a population selected for serious medical disorders.

In our study, neuropsychiatric illness, manifested by depressive symptoms and functional cognitive impairment, was significantly associated with frailty and its components. No consensus currently exists for an operational definition of frailty, and many have suggested that measures of mental health should be included [18]. Our findings support this suggestion, and are consistent with prior studies in HIV demonstrating an association between neuropsychiatric abnormality and frailty status [9,10]. Although the underlying mechanism of this association cannot be determined in our study, prior studies have demonstrated an association between motor abnormality (and with particular relevance to frailty, abnormal gait) and cognitive impairment, both in PLWH and HIV-negative populations [19–21]. In turn, motor and cognitive abnormalities may be correlated with cerebral white matter disease on neuroimaging [22–24]. Thus, it could be hypothesized that cerebral disorders impacting connectivity between brain regions via white matter abnormality form a common basis for both motor aspects of frailty and abnormal cognition.

Our study also demonstrates that asymptomatic cognitive impairments are not associated with frailty; lack of association between ANI and frailty has been previously noted in a population from Mexico City [10]. Although the group with ANI in our study had a low prevalence of frailty, they also had low frequencies of other frailty-associated factors, such as diabetes mellitus, COPD, and depressive symptoms. There is controversy surrounding ANI; some suggest that mild disorders based solely on cognitive testing may represent a form of false positive HAND diagnosis; others, that individuals with ANI have a unique neurobiology manifesting an increased risk of progression to symptomatic HAND [25–29]. It is also possible that individuals with ANI have an abnormal neurobiology dissimilar to other forms of HAND. Pertinent to a hypothesis implicating white matter abnormality in the generation of motor deficits and frailty, a recent study demonstrated that neuroradiographic white matter abnormalities in ANI could be distinguished from patterns in cognitive normals and in MND [29]. Pertinent to frailty measures, individuals with ANI may not display HIV-associated motor abnormalities. In a study of motor correlates of HAND, ANI was similar to cognitive normal in its lack of motor manifestations, whereas all forms of syndromic HAND displayed greater motor impairments [19]. However, it is also possible that ANI represents a resilience phenotype in the face of a deleterious neurobiological process in the continuum of HAND. These may be individuals who maintain functionality and resist frailty, despite a significant burden of HIV-associated brain disease. Continued monitoring of our cohort over time should determine whether individuals with ANI show adverse medical and cognitive outcomes, or progression in their frailty phenotypes.

With regard to other cognitive diagnoses, individuals with the most severe form of impairment (HAD) displayed the greatest odds of frailty, and with the exception of weight loss, pervasive association with all FFI components. The milder MND and NPI-O had smaller odds ratios for frailty phenotype, shared an association with grip strength, and differed with regard to associations with exhaustion and timed walk.

Frailty in our cohort was also characterized by a pervasive relationship with depressive symptoms. Antidepressant medication did not appear to influence this relationship. The association with depressive symptoms was seen not only with overall frailty phenotype but also with all frailty components except grip strength. The significance of this association is unclear; depressive phenomena are common correlates of a wide spectrum of neurodegenerative disorders, but are also encountered with medical illness and loss of physical function. Whether this association reflects a causative or reactive phenomenon, or is simply a correlation in the absence of a primary pathogenetic mechanism, is unclear. Regardless of pathogenesis, the association of neurobehavioral phenomena (cognition, depression) with frailty in HIV suggests that these should be accounted for in future studies of frailty conducted with regard to single medical disease outcomes.

With regard to the diverse medical disorders encountered in our population, diabetes mellitus and COPD were

independently associated with frailty. In the National Health and Nutrition Examination Survey (NHANES), 56.6% of individuals with COPD were frail, and this association has received significant attention [30]. It was observed that individuals with COPD had more than double the number of medical comorbidities than those without [30]. In our cohort individuals with COPD had significantly more medical illnesses than those without (4.4 vs. 2.4, $P < 0.01$). However, COPD was not unique: the same was true for every medical condition examined. For example, individuals with renal disease in the NNTC had an average of 4.5 medical illnesses in comparison to 2.5 in those without; yet, renal disease did not increase the odds of frailty. The association of diabetes mellitus and frailty has been previously observed, and is hypothesized to reflect an 'accelerated aging' process in this disorder, or alternatively, complications, such as renal dysfunction [31]. In our cohort, renal disease was not a plausible mechanistic pathway for frailty, and in the absence of biomarkers, we cannot comment on 'accelerated aging'.

Finally, women in our cohort had greater odds of being frail than men, which is similar to general populations, where female sex is associated with frailty [32]. In the Women's Interagency HIV Study (WIHS), it has been suggested that social and behavioral risk factors are important in the occurrence of frailty [32]. The WIHS is not selected for medical morbidity, with an overall frailty prevalence of 10%, less than half of what is seen in the women of NNTC. The NNTC study was not designed to examine social or cultural/behavioral factors, and this is an important area for future investigation, as issues such as socioeconomic status, healthcare access and utilization, and other behaviors and belief systems, could play a role in the development of frailty. Alternatively, it is possible that biological factors not routinely ascertained in NNTC could play a role, such as hormonal status, bone mineral density, and a more general burden of central nervous system (CNS) active medications, such as antipsychotics, sedatives, and anxiolytics. Further study is warranted to explain this sex disparity.

In summary, the NNTC cohort provides a unique opportunity to study frailty in the context of medical multimorbidity, and demonstrates the importance of symptomatic neuropsychiatric dysfunction to the frailty phenotype. It also raises questions with regard to why women and particular medical illnesses have increased odds of frailty, and suggests that further study will be necessary to determine if there are modifiable aspects of these associations that can improve outcomes for adults aging with HIV.

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Conflicts of interest

There are no conflicts of interest.

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