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Frailty, Neurocognitive Impairment, or Both in Predicting Poor Health Outcomes Among Adults Living With Human Immunodeficiency Virus

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Background. Neurocognitive impairment (NCI) is strongly associated with frailty in people living with human immunodeficiency virus (PLWH); the overlap of frailty and NCI and the impact on health outcomes in PLWH are unknown.

Methods. PLWH in a longitudinal, observational study of aging completed entry evaluations for frailty and NCI. Outcomes of falls (recurrent) increased limitations in independent activities of daily living (IADL), or mortality were combined. Poisson regression models estimated prevalence ratios (PR) for ≥1 outcome over 2 years.

Results. Among 987 participants, the median age at entry was 51 years; 19% were female; the median CD4 count was 616 cells/μL; and HIV-1 RNA was <200 copies/mL in 94%. Most (79%) participants had neither frailty nor NCI; 2% had both; 4% frailty only; and 15% NCI only. Over 2 years of observation, 100 (10%) participants experienced recurrent falls; 175 (18%) had worsening IADL limitations; 17 (2%) died; and 254 (26%) experienced ≥1 poor health outcome. In adjusted models, frailty with NCI was associated with more than double the risk of a poor health outcome (PR 2.65; 95% CI 1.98, 3.54); a significant association was also seen with frailty alone (PR 2.26; 95%CI 1.71, 2.99) and NCI alone (PR 1.73; 95% CI 1.36, 2.20).

Conclusions. The presence of frailty with NCI was associated with a greater risk of falls, disability, or death in PLWH than NCI alone. Interventions that target prevention or reversal of both frailty and NCI (such as increased physical activity) may significantly limit poor health outcomes among PLWH.

Keywords. frailty; neurocognitive impairment; disability; falls; HIV.

As effective antiretroviral therapy (ART) has markedly improved the life expectancy among people living with human immunodeficiency virus (HIV) infection, clinical care has shifted to the recognition and management of an increasing burden of age- and HIV-related, chronic, non-infectious comorbidities. As this population faces more complex comorbidities in combination with physiologic aging, social vulnerability, and medication burdens, optimization of comorbidity management becomes more challenging [1–3]. Aggressive blood pressure or blood glucose treatment may not be appropriate in a patient with recurrent falls, dementia, or a limited life expectancy [4, 5]. Thus, some HIV providers have advocated for incorporation of models of geriatric care [1, 3], with a focus on recognition and management of geriatric syndromes and maximizing individual care goals.

Frailty and neurocognitive impairment (NCI) are 2 geriatric syndromes that may co-occur [6–8] and can be associated with an increased risk of poor health outcomes, including falls, disability, hospitalizations, and mortality [9–13]. NCI and frailty represent vulnerability, with the latter marked by fatigue, limitations in activity, slowness, weakness, and weight loss; these are similar symptoms to those seen among many adults with advanced dementia. Furthermore, both cognition and motor skills (gait, grip) are highly-integrated processes that rely upon coordination and execution by the central nervous system [14]; thus, central nervous system impairment would be expected to impact both cognitive and physical functions. The overlapping vulnerability of frailty and NCI, and the potential impact on health outcomes in older adults, is increasingly recognized as a unique syndrome termed "cognitive frailty" [15] or "motoric cognitive risk" [16]. Multiple studies have shown a strong cross-sectional association between frailty, slow gait speed, or weak grip strength and NCI, both in the general population and among people living with HIV (PLWH) [17–20]. The link

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between frailty and NCI is likely evidence of a common pathogenesis, driven by inflammation, immune activation, and nutritional and metabolic influences [21], and both frailty and NCI may be manifestations of vascular disease [22].

In the AIDS (acquired immunodeficiency syndrome) Clinical Trials Group longitudinal aging study A5322 and in HAILO (The HIV Infection, Aging, and Immune Function Long-Term Observational Study), we have previously reported increased odds of frailty among PLWH with NCI [17] and an overlap between frailty and disability at baseline [23]. Furthermore, we have found increased falls over 2 years among pre-frail and frail participants and participants with baseline NCI [24]. We hypothesized that, in this cohort of older PLWH, the clinical syndromes of frailty and NCI would be highly overlapping, and that the presence of both frailty and NCI would be associated with a greater risk for poor health outcomes than either syndrome alone. To improve the potential utility of such an assessment in the clinical setting, we also sought to test the robustness of our findings by using a single, easily-obtainable measurement of gait speed or grip strength.

METHODS

HAILO is an observational study of PLWH aged ≥40 years who received randomized assignment of initial ART through an AIDS Clinical Trials Group trial and were followed in the AIDS Clinical Trials Group A5001 observational study after their trial participation ended [17, 23, 25]. HAILO enrollment occurred in 2013–2014; ongoing visits occur every 6 months. The current analysis reports on visits through the first 2 years.

Outcome Measures

Falls were reported every 6 months (beginning at month 6), using self-reported responses obtained through interview-administered questionnaires [24]. For this analysis, the outcome was recurrent falls, defined as ≥2 falls occurring within a 12-month period. Disability was assessed every 12 months with the Lawton-Brody Instrumental Activities of Daily Living Questionnaire, using self-reported limitations in performing 8 tasks: housekeeping, money management, cooking, transportation, telephone use, shopping, laundry, and medication management [23, 26]. Disability included an increase during follow-up in 1 or more limitations on the IADL Questionnaire. Mortality included death from any cause.

Exposure Variables

NCI at baseline was assessed with the A5001 Neuroscreen [27], using normalized, demographic-adjusted scores of the Trail Making A, Trail Making B, and Digit Symbol tests. A participant was considered impaired if they had at least 1 z-score ≥2 standard deviations (SD) below the mean, or at least 2 separate test z-scores ≥1 SD below the mean. Frailty was evaluated at baseline using the Fried frailty assessment, which includes 4-meter walk speed, grip strength, and self-reported unintentional weight loss, exhaustion, and low activity level [17, 28]. Individuals meeting 3–5 components were categorized as frail, 1–2 components as pre-frail, and 0 as non-frail. For this analysis, we used a 2-category frailty variable (frail vs. non-frail/pre-frail).

Potential Confounding Variables

Education was categorized as ≤ or > high school; smoking as current, prior, or never smoker; research site as Northeast, Midwest, South (including Puerto Rico), or West. Self-reported alcohol use in the past 30 days was defined as abstainer (0 drinks), light (men <7 drinks/week, women <3; no binge drinking), moderate (men 7–14 drinks/week, women 3–7; no binging), or heavy drinker (men >14 drinks/week, women >7/week or any binge drinking). Binge drinking (men ≥5 drinks, women ≥4 within a 2-hour period) was evaluated separately by frequency. Substance use was self-reported as use within the prior 30 days. Body mass index was included as a continuous and categorical variable. Waist circumference was dichotomized at >102 cm for men or >88 cm for women. Physical activity by the International Physical Activity Questionnaire [29] was dichotomized as low (< 3) or moderate/high (≥ 3) number of days/week of moderate or vigorous intensity physical activity.

Comorbidities were abstracted from medical records, except where indicated, and combined in this analysis as the presence of any comorbidity, including hepatitis C virus infection (positive HCV serology or diagnosis), malignancy (within 5 years, except non-melanoma skin cancer), renal disease (acute or chronic renal insufficiency, the latter defined by >1 estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m^2 ≥3 months apart with no intervening eGFR ≥60 using the CKD-EPI equation), diabetes (diagnosed or hemoglobin A1C level ≥6.5%), cardiovascular disease (myocardial infarction, stroke, coronary artery disease), liver disease, and hypertension (diagnosis or use of anti-hypertensive medications). Use of anti-anxiety or antidepressant medications were considered separately. History of an AIDS-defining condition, CD4 count (continuous), and HIV-1 ribonucleic acid (dichotomized as ≤200 or >200 copies/mL) at baseline were also included.

Statistical Methods

Participants were categorized into 4 groups based on frailty and NCI status at baseline: both frailty and NCI; frailty with no NCI; NCI with no frailty; and neither frailty nor NCI. We compared individuals in each of the 4 frailty/NCI groups by demographic, clinical, and behavioral characteristics, using chi-square tests for categorical variables and the Kruskal-Wallis test for continuous variables. Poisson regression models with robust variance were used to estimate the prevalence ratios (PR) for frailty and/or neurocognitive status and having 1 or more health outcome of recurrent falls, increase in disability, or mortality over the

2-year follow-up period. The *a priori* decision was made to include age in all models. Age-adjusted models were first built, then potential confounders were added 1 at a time. Variables that changed the age-adjusted PR for ≥1 exposure categories by ≥10% were considered for inclusion in the final model. Variables evaluated for confounding included sex, race/ethnicity, education, CD4 count, CD4 nadir, alcohol use, illicit substance use, physical activity, AIDS-defining condition, comorbidities, and anxiety/depression medication.

Normative data for neurocognitive testing was available only for White, Black, and Hispanic participants; analyses were restricted to these groups. If a participant was missing a fall assessment for 1 visit but indicated experiencing "no falls" at each of the other 3 visits, we assumed that the participant did not have recurrent falls during follow-up. If IADL assessments at baseline and year 2 indicated no increase in IADL limitations, we assumed no increase in IADL limitations during the intervening follow-up. Other participants without information available regarding both falls and IADLs and who did not experience a poor health outcome were considered missing outcome data. Restricting an analysis to complete cases (ie, individuals with no missing outcome data) can induce bias if the excluded individuals are systematically different from those included. Therefore, inverse probability weighting was used to reduce this bias [30]. Logistic regression was used to model the conditional probability of an individual being a complete case (vs. missing case), given a set of predictor variables, and to establish weighting. Variables included in the model were age, sex, race, smoking status, CD4, HIV ribonucleic acid level, anxiety/depression medication use, any comorbidities, and research site location. Several of these variables were previously found to be significantly associated with loss to follow-up in AIDS Clinical Trials Group A5001 [31]. To assess the robustness of the results, sensitivity analyses were performed based on different assumptions about missing falls and IADL assessments.

RESULTS

Of the 1035 participants enrolled in HAILO, 987 (95%) had both frailty and neurocognitive status assessed at baseline: 40 (4%) were frail but had no NCI, 144 (15%) had NCI but no frailty, 19 (2%) had both frailty and NCI, and 784 (79%) had neither frailty nor NCI. NCI was present in 11% of non-frail, 22% of pre-frail, and 32% of frail participants at baseline ($P < .001$), with corresponding median z-scores of 0.53 (interquartile range [IQR] -0.10, 1.23) among non-frail; 0.10 (IQR -0.60, 0.80) among pre-frail; and -0.33 (IQR -1.07, 0.70) among frail participants ($P < .001$).

Characteristics of participants by frailty and NCI group are shown in Table 1. Briefly, age, education, alcohol and illicit drug use, CD4 count, time since ART initiation, physical activity, waist circumference, and presence of kidney disease or diabetes differed across frailty/NCI groups.

Over 2 years of observation, 100 (10%) participants experienced recurrent falls, 175 (18%) experienced worsening IADL limitations, and 17 (2%) died; 254 (26%) participants experienced at least 1 of these poor health outcomes. Poor health outcomes were most common among persons with both frailty and NCI (74%) or frailty without NCI (60%; Table 2). Anxiety/depression medication changed the age-adjusted PR for the frailty without NCI exposure category by 10.5%, and was therefore included in the multivariable model as a confounder. No other variables changed the age-adjusted PR for ≥1 frailty/NCI exposure categories by ≥10%. In the models adjusted for age and use of anxiety/depression medications, the prevalence of a poor health outcome was 2.65 times greater among participants with both frailty and NCI compared to neither, 2.26 times greater among participants with frailty but no NCI, and 1.73 times greater among participants with NCI but no frailty (Table 3; all $P < .001$). Participants with both frailty and NCI had a significantly greater risk of poor health outcomes compared to NCI alone (PR 1.53, 95% CI 1.10, 2.13; $P = .011$), but not significantly greater than frailty alone (PR 1.17, 95% CI 0.8, 1.64; $P = .36$).

We also assessed the association between grip strength or gait speed with or without NCI on poor health outcomes. Similar to the frailty models, participants with weak grip or slow gait alone or in combination with NCI had a higher risk of poor health outcomes than those without the respective frailty component or NCI (Tables 4 and 5).

Several sensitivity analyses were conducted to test assumptions regarding missing data. When we assumed missing outcomes as not indicative of a poor health outcome, the results were similar to those from the primary analysis. When we assumed all missing outcomes as poor health outcomes, the PR were attenuated but still statistically significant. The results changed under more extreme assumptions about missing data; when we assumed missing outcomes were poor for participants with no frailty or NCI but not poor for participants with frailty and/or NCI, there was no significant difference ($P = .36$) in the prevalence of poor health outcomes between participants with frailty and no NCI or no frailty/no NCI. When we assumed missing outcomes as not being poor for participants without frailty or NCI and poor for participants with frailty and/or NCI, the PR for all groups compared to persons without frailty or NCI were relatively large (>3).

DISCUSSION

Among virally-suppressed middle-aged and older PLWH, the majority of participants had neither frailty nor NCI. NCI was more prevalent than frailty, and more than 50% of frail/pre-frail participants had NCI. Importantly, participants with both frailty

Table 1. Baseline Demographics and Clinical Characteristics by Frailty and Neurocognitive Impairment Categories

Characteristic	Frailty Without NCI (n = 40)	NCI Without Frailty (n = 144)	Frailty and NCI (n = 19)	No NCI or Frailty (n = 784)	*P*-value
Age	54 (50–57)	50 (46–55)	55 (51–62)	50 (45–56)	<.001
Female sex	10 (25%)	39 (27%)	7 (37%)	137 (17%)	.008
Race/Ethnicity					<.001
White (non-Hispanic)	17 (43%)	49 (34%)	5 (26%)	413 (53%)	
Black (non-Hispanic)	17 (43%)	30 (21%)	6 (32%)	247 (32%)	
Hispanic	6 (15%)	65 (45%)	8 (42%)	124 (16%)	
Less than high school education	6 (15%)	40 (28%)	8 (42%)	96 (12%)	<.001
Insurance					
Public only	26 (65%)	53 (37%)	9 (47%)	218 (28%)	<.001
Any private	12 (30%)	41 (28%)	6 (32%)	417 (53%)	
None or unknown	2 (5%)	50 (35%)	4 (21%)	149 (19%)	
Site region					
Northeast	9 (23%)	32 (22%)	1 (5%)	167 (21%)	.002
Midwest	11 (28%)	23 (16%)	9 (47%)	257 (33%)	
South	12 (30%)	35 (24%)	2 (11%)	155 (20%)	
West	8 (20%)	54 (38%)	7 (37%)	205 (26%)	
Smoking status					.63
Never smoker	13 (33%)	59 (41%)	11 (58%)	325 (41%)	
Prior smoker	17 (43%)	50 (35%)	4 (21%)	256 (33%)	
Current smoker	10 (25%)	35 (24%)	4 (21%)	203 (26%)	
Alcohol					<.001
Abstainer	26 (65%)	68 (47%)	14 (74%)	284 (36%)	
Light drinker	9 (23%)	49 (34%)	4 (21%)	303 (39%)	
Moderate/heavy	5 (13%)	27 (19%)	2 (5%)	197 (25%)	
Illicit substance use	6 (15%)	17 (12%)	0 (0%)	179 (23%)	.006
Physical activity					<.001
<3 days of vigorous/moderate activity	27 (68%)	61 (43%)	14 (74%)	338 (43%)	
≥ 3 days of vigorous/moderate activity	13 (33%)	67 (47%)	3 (16%)	411 (52%)	
Unknown	0 (0%)	16 (11%)	2 (11%)	35 (5%)	
Comorbidities					
Cardiovascular disease	3 (8%)	8 (6%)	1 (5%)	49 (6%)	.97
Liver disease	0 (0%)	3 (2%)	1 (5%)	5 (<1%)	.066
Kidney disease	9 (23%)	10 (7%)	4 (21%)	76 (10%)	.011
History of cancer within 5 years	0 (0%)	8 (6%)	1 (5%)	24 (3%)	.26
Diabetes	12 (30%)	18 (13%)	8 (42%)	101 (13%)	<.001
Hypertension	22 (55%)	52 (36%)	7 (37%)	291 (37%)	.15
Stroke	0 (0.00%)	3 (2%)	1 (5%)	17 (2%)	.62
Hepatitis C	9 (22.50%)	24 (17%)	3 (16%)	86 (11%)	.049
Body mass index category					.10
Underweight (<18.5 kg/m^2)	1 (3%)	0 (00%)	0 (0%)	5 (<%)	
Normal (18.5–<25 kg/m^2)	6 (15%)	45 (31%)	3 (16%)	252 (32%)	
Overweight (25–30 kg/m^2)	14 (35%)	56 (39%)	10 (53%)	309 (39%)	
Obese (>30 kg/m^2)	19 (48%)	43 (30%)	6 (32%)	218 (28%)	
Use of anti-anxiety or depression medications	27 (68%)	43 (30%)	11 (58%)	240 (31%)	<.001
Use of a statin	12 (30%)	36 (25%)	6 (32%)	212 (27%)	.88
HIV-specific					
Any AIDS-defining condition	7 (18%)	42 (29%)	5 (26%)	152 (19%)	.054
CD4 at baseline (cells/μL)	749 (583–958)	650 (469–850)	584 (292–966)	611 (447–821)	.051
CD4 at baseline > 500 cells/μL	34 (85%)	103 (72%)	12 (63%)	518 (66%)	.009
CD4 nadir (cells/μL)	256 (90–361)	210 (45–317)	87 (65–308)	191 (61–296)	.133
HIV-1 RNA at baseline <200 copies/ml	36 (90%)	140 (97%)	17 (89%)	741 (95%)	.20
Years since ART initiation	7.9 (4.6–11.9)	6.8 (4.0–10.5)	10.5 (6.7–14.5)	7.9 (4.4–12.1)	.002
ART regimen at baseline					.10
NRTI-backbone + PI	14 (35%)	67 (47%)	10 (53%)	298 (38%)	
NRTI-backbone + NNRTI	15 (38%)	42 (29%)	5 (26%)	317 (40%)	
NRTI-backbone + INSTI	8 (20%)	34 (24%)	4 (21%)	140 (18%)	

Chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables were used to assess differences in baseline demographics or clinical characteristics across frailty/NCI categories.

Abbreviations: AIDS, acquired immunodeficiency syndrome; ART, antiretroviral therapy; CD4, CD4+ T-lymphocyte cell count; HIV, human immunodeficiency virus; INSTI, integrase strand transferase inhibitor; NCI, neurocognitive impairment; NNRTI, non-nucleotide reverse transcriptase inhibitor; NRTI, nucleoside/tide reverse transcriptase inhibitor; PI, protease inhibitor; RNA, ribonucleic acid.

Table 2. Frequency of Poor Outcomes Over 2 Years by Frailty/Neurocognitive Impairment Status at The Human Immunodeficiency Virus Infection, Aging, and Immune Function Long-Term Observational Study Entry

Characteristic		Neurocognitive Impairment and Frailty Categories				*P*-value
		Frailty Without Neurocognitive Impairment (n = 40)	Neurocognitive Impairment Without Frailty (n = 144)	Frailty and Neurocognitive Impairment (n = 19)	No Neurocognitive Impairment or Frailty (n = 784)	
Poor outcome (recurrent falls, increased IADL limitations, death)	No	11 (28%)	63 (44%)	3 (16%)	470 (60%)	<.001
	Yes	24 (60%)	50 (35%)	14 (74%)	166 (21%)	
	Missing	5 (12.50%)	31 (22%)	2 (11%)	148 (19%)	
Recurrent falls within a year	No	21 (53%)	92 (64%)	8 (42%)	592 (76%)	<.001
	Yes	13 (33%)	22 (15%)	9 (47%)	56 (7%)	
	Missing	6 (15%)	30 (21%)	2 (11%)	136 (17%)	
Increase in number of IADLs	No	19 (48%)	79 (55%)	7 (37%)	557 (71%)	<.001
	Yes	16 (40%)	35 (24%)	10 (53%)	114 (15%)	
	Missing	5 (13%)	30 (21%)	2 (11%)	113 (14%)	
Death	No	39 (98%)	139 (97%)	19 (100%)	773 (99%)	.314
	Yes	1 (23%)	5 (3%)	0 (0%)	11 (1%)	

Abbreviation: IADL, Instrumental activities of daily living.

and NCI had more than 2.5 times the risk of a poor health outcome over 2 years than persons with neither frailty nor NCI. Both frailty, or components of frailty, and NCI were strong predictors of poor health outcomes, independent of age. Accounting for chronologic age fails to completely reflect biologic aging that can differ between individuals, particularly among PLWH with differing durations of HIV infection, severity, and ART exposure. Clinical manifestations of biologic aging are more accurately captured in measures of vulnerability, health, or functioning, such as physical frailty and cognitive capability.

The cross-sectional overlap between frailty and NCI is well-described in the general population, but few studies have described the overlap among PLWH in the current ART era. In addition to our finding of greater odds of frailty in the presence of NCI among HAILO participants [17], other studies have reported worse International HIV Dementia Scores among frail (59% impaired) compared to non-frail (34%) individuals [18], slower gait speeds with increasing neurocognitive impairment [19], and greater NCI by either the mini-mental state examination or the HIV International Dementia Score among frail PLWH but not HIV-uninfected controls [20]. "Frail" PLWH also appear to have less "successful cognitive aging" (lack of IADL impairments, depressive symptoms, or NCI) [32]. A longitudinal analysis involving the Veterans Aging Cohort Study (VACS) identified a greater decline in select NCI domains with increasing VACS index scores [33]; however, there was no association between the VACS Index and NCI as assessed by the Montreal Cognitive Assessment in a cross-sectional analysis [34].

As has been seen among aging HIV-uninfected persons, we found that both frailty and NCI were strong predictors of poor health outcomes. We had hypothesized that the combination of both frailty and NCI would be stronger than either alone. Our results partially support this hypothesis: the association observed for both frailty and NCI was stronger than that for NCI alone, but not stronger than for frailty alone. In one study, frailty and NCI were independently associated with greater mortality among older Mexican-American adults, although frailty was a stronger predictor [9], and in another, NCI and pre-injury frailty were both associated with poorer functional recovery following a trauma among older patients, with frailty the stronger predictor of mortality [11]. In the Singapore Longitudinal Ageing Study of 2300 adults

Table 3. Multivariable Model of the Association Between Frailty and Neurocognitive Impairment With Poor Outcomes

Variable	Prevalence Ratio	95% CI	*P*-value
Frailty and NCI vs. no NCI or frailty	2.65	(1.98, 3.54)	<.0001
Frailty without NCI vs. no NCI or frailty	2.26	(1.71, 2.99)	<.0001
NCI without frailty vs. no NCI or frailty	1.73	(1.36, 2.20)	<.0001
Age (years)	1.02	(1.00, 1.03)	.0069
Use of anxiety/depression medications	1.32	(1.07, 1.62)	.0084

Abbreviations: CI, confidence interval; NCI, neurocognitive impairment.

Table 4. Multivariable Model of the Association Between Gait Speed and Neurocognitive Impairment With Poor Outcomes

Variable	Prevalence Ratio	95% CI	*P*-value
Slow gait and NCI vs. no NCI or slow gait	2.48	(1.78, 3.45)	<.0001
Slow gait without NCI vs. no NCI or slow gait	1.96	(1.42, 2.70)	<.0001
NCI without slow gait vs. no NCI or slow gait	1.71	(1.35, 2.17)	<.0001
Age (years)	1.02	(1.01, 1.03)	.0019

Abbreviations: CI, confidence interval; NCI, neurocognitive impairment.

aged ≥55, only 1.8% of adults had both frailty and NCI: the presence of both frailty and NCI was associated with the greatest risk of disability and mortality [12]. Similarly, among nearly 2500 adults aged ≥60 in Sweden, physical function impairments were predictive of falls over 3 years, while deficits in processing speed, executive function, and gait speed were associated with injurious falls over 10 years [13]. Data on the impact of frailty and NCI on the risk of poor health outcomes among PLWH are limited, and very few other studies have described the impact of "cognitive frailty" on the risk of poor health outcomes among PLWH. In a Colorado cohort, we previously found that both frailty and dementia (clinical diagnosis) were independently associated with an increased risk of recurrent falls [35]. Factors impacting cognition, but not cognitive complaints, were associated with an increased risk for falls, but co-occurrence of frailty was not described in this cohort [36].

Frailty can also be conceptualized as an "accumulation of deficits," as described in the Rockwood model [37] and the VACS [38, 39]. Inclusion of HIV-specific variables, in addition to non-HIV comorbidities or laboratory abnormalities in these frailty indices, has demonstrated validity in predicting mortality or hospitalizations in cohorts of middle- and older-aged PLWH [38, 40, 41]. As such, we expected that a greater comorbid burden would explain most of the association between our measures of physical and cognitive frailty with poor health outcomes. In contrast, we found that education level and anxiety/depression medications, but not comorbidity burden or HIV-specific factors, partially explained the association between physical or cognitive function and poor health outcomes. Taken as a whole, our findings emphasize that other measures of economic and psychological vulnerability influence the likelihood of a frail or neurocognitively-impaired PLWH experiencing a poor health outcome to a greater extent than age, comorbidities, or HIV burden.

Our study is not without limitations. The cohort is comprised of participants with long-term engagement in clinical trials and observational studies and includes relatively few women, thus may not be representative of the general population of PLWH. Missing data may have influenced our findings, as persons who drop out or miss visits may either be healthier, with other obligations, or less healthy, with missed visits due to illness or conflicting appointments. Inverse probability weighting was used to reduce this potential bias and rebalance the set of complete cases. Also, the study results remained substantially similar under a variety of different assumptions regarding these missing data. We chose IADL impairments, recurrent falls, and mortality as outcomes of interest based on the geriatric literature and the available data; different outcomes (such as hospitalizations) may differ in relation to frailty and NCI. Lastly, the mean age of our cohort was 52 years, and frailty and/or NCI occurred in approximately 20%; the impact of frailty and NCI in older cohorts or cohorts with a greater prevalence of these geriatric syndromes may differ.

In summary, frailty (or gait speed or grip strength), alone or in combination with NCI, is a strong predictor of a poor health outcome within 2 years. As the ideal models of care for older PLWH are established, PLWH at highest risk for adverse outcomes may benefit most from frequent clinic visits, polypharmacy reductions, geriatric consultations, rehabilitative services, or home health assistance. As the impact of "social frailty" was a strong confounder in the association between frailty, NCI, and poor health outcomes, interventions directed at improving or reducing social frailty may reduce poor health outcomes among frail or neurocognitively-impaired PLWH. Similarly, interventions that target prevention or reversal of frailty or both frailty

Table 5. Multivariable Model of the Association Between Grip Strength and Neurocognitive Impairment With Poor Outcomes

Variable	Prevalence Ratio	95% CI	*P*-value
Weak grip and NCI vs. no NCI or weak grip	2.15	(1.64, 2.84)	<.0001
Weak grip without NCI vs. no NCI or weak grip	1.46	(1.13, 1.89)	.0037
NCI without weak grip vs. no NCI or weak grip	1.50	(1.10, 2.05)	.0098
Age (years)	1.02	(1.00, 1.03)	.0111
Higher education (12 years or more vs < 12 years)	0.68	(0.54, 0.85)	.0009

Abbreviations: CI, confidence interval; NCI, neurocognitive impairment.

and NCI (such as physical activity) may have the greatest potential to limit poor health outcomes among PLWH.

Notes

Disclaimer. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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K. M. E., J. P., M. A., and K. T. developed the analysis and interpretation. J. P. and M. A., under the supervision of K. T., performed the data analysis. K. M. E. prepared the first draft of the manuscript. All authors contributed to the study design, implementation, and interpretation of data; reviewed and revised the manuscript; and approved of the final draft.

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References

1. Siegler EL, Brennan-Ing M. Adapting systems of care for people aging with HIV. J Assoc Nurses AIDS Care **2017**; 28:698–707.
2. Slomka J, Prince-Paul M, Webel A, Daly BJ. Multimorbidity with HIV: views of community-based people living with HIV and other chronic conditions. J Assoc Nurses AIDS Care **2017**; 28:603–11.
3. Singh HK, Del Carmen T, Freeman R, Glesby MJ, Siegler EL. From one syndrome to many: Incorporating geriatric consultation into HIV care. Clin Infect Dis **2017**; 65:501–6.
4. Hyman DJ, Taffet GE. Blood pressure control in the elderly: can you have too much of a good thing? Curr Hypertens Rep **2009**; 11:337–42.
5. Moreno G, Mangione CM, Kimbro L, Vaisberg E. Guidelines abstracted from the American Geriatrics Society Guidelines for Improving the Care of Older Adults with Diabetes Mellitus: 2013 update. J Am Geriatr Soc **2013**; 61:2020–6.
6. Hooghiemstra AM, Ramakers IHGB, Sistermans N, et al.; 4C Study Group. Gait speed and grip strength reflect cognitive impairment and are modestly related to incident cognitive decline in memory clinic patients with subjective cognitive decline and mild cognitive impairment: findings from the 4C study. J Gerontol A Biol Sci Med Sci **2017**; 72:846–54.
7. Gray SL, Anderson ML, Hubbard RA, et al. Frailty and incident dementia. J Gerontol A Biol Sci Med Sci **2013**; 68:1083–90.
8. Montero-Odasso MM, Barnes B, Speechley M, et al. Disentangling cognitive-frailty: results from the gait and brain study. J Gerontol A Biol Sci Med Sci **2016**; 71:1476–82.
9. Cano C, Samper-Ternent R, Al Snih S, Markides K, Ottenbacher KJ. Frailty and cognitive impairment as predictors of mortality in older Mexican Americans. J Nutr Health Aging **2012**; 16:142–7.
10. Llibre Jde J, Lopez AM, Valhuerdi A, et al. Frailty, dependency and mortality predictors in a cohort of Cuban older adults, 2003–2011. MEDICC Review **2014**; 16:24–30.
11. Maxwell CA, Mion LC, Mukherjee K, et al. Preinjury physical frailty and cognitive impairment among geriatric trauma patients determine post-injury functional recovery and survival. J Trauma Acute Care Surg **2016**; 80:195–203.
12. Feng L, Zin Nyunt MS, Gao Q, Feng L, Yap KB, Ng TP. Cognitive frailty and adverse health outcomes: findings from the Singapore longitudinal ageing studies (SLAS). J Am Med Dir Assoc **2017**; 18:252–8.
13. Welmer AK, Rizzuto D, Laukka EJ, Johnell K, Fratiglioni L. Cognitive and physical function in relation to the risk of injurious falls in older adults: a population-based study. J Gerontol A Biol Sci Med Sci **2017**; 72:669–75.
14. Fritz NE, McCarthy CJ, Adamo DE. Handgrip strength as a means of monitoring progression of cognitive decline - A scoping review. Ageing Res Rev **2017**; 35:112–23.
15. Kelaiditi E, Cesari M, Canevelli M, et al.; IANA/IAGG. Cognitive frailty: rational and definition from an (I.A.N.A./I.A.G.G.) international consensus group. J Nutr Health Aging **2013**; 17:726–34.
16. Lauretani F, Meschi T, Ticinesi A, Maggio M. "Brain-muscle loop" in the fragility of older persons: from pathophysiology to new organizing models. Aging Clin Exp Res **2017**; 29:1305–11.
17. Erlandson KM, Wu K, Koletar SL, et al. Association between frailty and components of the frailty phenotype with modifiable risk factors and antiretroviral therapy. J Infect Dis **2017**; 215:933–7.
18. Önen NF, Patel P, Baker J, et al. Frailty and pre-frailty in a contemporary cohort of HIV-infected adults. J Frailty Aging **2014**; 3:158–65.
19. Robertson KR, Parsons TD, Sidtis JJ, et al. Timed gait test: normative data for the assessment of the AIDS dementia complex. J Clin Exp Neuropsychol **2006**; 28:1053–64.
20. Ding Y, Lin H, Liu X, et al. Higher prevalence of frailty among a sample of HIV-infected middle-aged and older Chinese adults is associated with neurocognitive impairment and depressive symptoms. J Infect Dis **2017**; 215:687–92.
21. Panza F, Solfrizzi V, Barulli MR, et al. Cognitive frailty: a systematic review of epidemiological and neurobiological evidence of an age-related clinical condition. Rejuvenation Res **2015**; 18:389–412.
22. Strandberg TE, Pitkälä KH, Tilvis RS, O'Neill D, Erkinjuntti TJ. Geriatric syndromes–vascular disorders? Ann Med **2013**; 45:265–73.
23. Johs NA, Wu K, Tassiopoulos K, et al. Disability among middle-aged and older persons with human immunodeficiency virus infection. Clin Infect Dis **2017**; 65:83–91.
24. Tassiopoulos K, Abdo M, Wu K, et al. Frailty is strongly associated with increased risk of recurrent falls among older HIV-infected adults. AIDS **2017**; 31:2287–94.
25. Smurzynski M, Collier AC, Koletar SL, et al. AIDS clinical trials group longitudinal linked randomized trials (ALLRT): rationale, design, and baseline characteristics. HIV Clin Trials **2008**; 9:269–82.
26. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist **1969**; 9:179–86.
27. Robertson KR, Smurzynski M, Parsons TD, et al. The prevalence and incidence of neurocognitive impairment in the HAART era. AIDS **2007**; 21:1915–21.
28. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci **2001**; 56:M146–56.
29. Booth M. Assessment of physical activity: an international perspective. Res Q Exerc Sport **2000**; 71:S114–20.
30. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. Stat Methods Med Res **2013**; 22:278–95.
31. Krishnan S, Wu K, Smurzynski M, et al.; ALLRT/A5001 Team. Incidence rate of and factors associated with loss to follow-up in a longitudinal cohort of antiretroviral-treated HIV-infected persons: an AIDS Clinical Trials Group (ACTG) Longitudinal Linked Randomized Trials (ALLRT) analysis. HIV Clin Trials **2011**; 12:190–200.
32. Wallace LM, Ferrara M, Brothers TD, et al. Lower frailty is associated with successful cognitive aging among older adults with HIV. AIDS Res Hum Retroviruses **2017**; 33:157–63.
33. Marquine MJ, Montoya JL, Umlauf A, et al.; HIV Neurobehavioral Research Program Group. The Veterans Aging Cohort Study (VACS) index and neurocognitive change: a longitudinal study. Clin Infect Dis **2016**; 63:694–702.
34. John MD, Greene M, Hessol NA, et al. Geriatric assessments and association with VACS index among HIV-infected older adults in San Francisco. J Acquir Immune Defic Syndr **2016**; 72:534–41.
35. Erlandson KM, Allshouse AA, Jankowski CM, et al. Risk factors for falls in HIV-infected persons. J Acquir Immune Defic Syndr **2012**; 61:484–9.

36. Sharma A, Hoover DR, Shi Q, et al. Longitudinal study of falls among HIV-infected and uninfected women: the role of cognition. Antivir Ther **2018**; 23:179–90.
37. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci **2007**; 62:738–43.
38. Justice AC, Modur SP, Tate JP, et al.; NA-ACCORD and VACS Project Teams. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. J Acquir Immune Defic Syndr **2013**; 62:149–63.
39. Justice AC, McGinnis KA, Skanderson M, et al.; VACS Project Team. Towards a combined prognostic index for survival in HIV infection: the role of 'non-HIV' biomarkers. HIV Med **2010**; 11:143–51.
40. Guaraldi G, Brothers TD, Zona S, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. AIDS **2015**; 29:1633–41.
41. Akgün KM, Tate JP, Crothers K, et al. An adapted frailty-related phenotype and the VACS index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals. J Acquir Immune Defic Syndr **2014**; 67:397–404.