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Baseline Neurocognitive Impairment (NCI) Is Associated With Incident Frailty but Baseline Frailty Does Not Predict Incident NCI in Older Persons With Human Immunodeficiency Virus (HIV)

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Background. Neurocognitive impairment (NCI) and frailty are more prevalent among persons with human immunodeficiency virus (HIV, PWH) compared to those without HIV. Frailty and NCI often overlap with one another. Whether frailty precedes declines in neurocognitive function among PWH or vice versa has not been well established.

Methods. AIDS Clinical Trials Group (ACTG) A5322 is an observational cohort study of older PWH. Participants undergo annual assessments for NCI and frailty. ACTG A5322 participants who developed NCI as indexed by tests of impaired executive functioning and processing speed during the first 3 years were compared to persons who maintained normal cognitive function; those who demonstrated resolution of NCI were compared to those who had persistent NCI. Participants were similarly compared by frailty trajectory. We fit multinomial logistic regression models to assess associations between baseline covariates (including NCI) and frailty, and associations between baseline covariates (including frailty) and NCI.

Results. In total, 929 participants were included with a median age of 51 years (interquartile range [IQR] 46–56). At study entry, 16% had NCI, and 6% were frail. Over 3 years, 6% of participants developed NCI; 5% developed frailty. NCI was associated with development of frailty (odds ratio [OR] = 2.06; 95% confidence interval [CI] = .94, 4.48; $P = .07$). Further adjustment for confounding strengthened this association (OR = 2.79; 95% CI = 1.21, 6.43; $P = .02$). Baseline frailty however was not associated with NCI development.

Conclusions. NCI was associated with increased risk of frailty, but frailty was not associated with development of NCI. These findings suggest that the presence of NCI in PWH should prompt monitoring for the development of frailty and interventions to prevent frailty in this population.

Keywords. frailty; neurocognitive impairment; HIV; aging

Despite use of virally suppressive combination antiretroviral therapy (ART), persons with human immunodeficiency virus (HIV, PWH) experience both earlier onset and increased rates of chronic aging-related comorbidities compared to the general population [1]. In addition to chronic inflammation, coinfections, and immune dysfunction, excess comorbidity burden contributes to higher rates of neurocognitive and physical impairment and frailty, a composite measure reflecting vulnerability, among older PWH. Previous studies among PWH in the United States have found that 15% of those over the age of 65 are frail, and 40%–60% of those who are middle-aged are prefrail [1, 2]. Frailty and neurocognitive impairment (NCI) have been associated with increased risk for mortality and poor health outcomes such as hospitalization, disability, falls, and reduced quality of life among older PWH [3].

NCI and frailty are geriatric syndromes that co-occur in the general aging population [4]. Frailty is characterized by weight loss, fatigue, limitations in activity, slowness, and weakness—symptoms that are also common among adults with advanced dementia. Both cognition and the motor components of frailty are highly integrated processes that rely on central nervous system coordination. Numerous studies have identified cross-sectional and longitudinal associations between frailty, its motor components (gait speed and grip strength), and NCI [5–7]. Whether frailty precedes future declines in neurocognitive function or vice versa has not been well established [8]. On one hand, cognitive dysfunction could inhibit ability to perform motor tasks and planning, leading

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to or exacerbating declines in physical function and frailty. Alternatively, the impaired physical function and decreased physical activity of frailty may reduce cerebral blood flow and, consequently, cognitive function [9].

Because HIV and aging are both associated with NCI and frailty, the overlap between NCI and frailty may be exacerbated among PWH compared to the general population. Multiple cross-sectional analyses have identified associations between NCI and frailty and its motor components among PWH, including in the AIDS Clinical Trials Group (ACTG) study A5322, which is also known as HAILO (HIV Infection, Aging, and Immune Function Long-term Observational Study) [10–12]. Similar to the general aging population, whether NCI is a risk factor for frailty or vice versa has not been evaluated longitudinally in PWH. Clarifying relationships between frailty and NCI can inform understanding of the pathogenesis of these processes, help to identify PWH at greatest risk of decline with advancing age and inform potential interventions.

The current study aimed to identify factors associated with longitudinal development of or improvement in NCI and frailty among participants enrolled in ACTG A5322/HAILO, including the association of each syndrome with the other.

METHODS

Study Population

This longitudinal analysis included participants with ≥2 visits during the first 3 years of follow-up in HAILO, an ongoing observational multisite cohort study of older PWH. All HAILO participants initiated ART through an ACTG randomized clinical trial and were subsequently followed up in the observational study ACTG A5001[13]. Between November 2013 and July 2014, a subset of A5001 participants (n = 1035) ≥ 40 years old were enrolled in HAILO for continued long-term follow-up.

Outcome

NCI was assessed annually using the A5001 Neuroscreen, which includes Trailmaking tests A and B and the Wechsler Adult Intelligence Scale-Revised Digit Symbol tests [14]. Neurocognitive performance is summarized in a demographically adjusted mean z-score, the NPZ3 [15]. NCI was defined by ≥1 z-score ≥2 standard deviations (SDs) below the mean or ≥2 z-scores ≥1 SD below the mean on separate tests within the A5001 Neuroscreen. Frailty was evaluated annually using the Fried Frailty phenotype with grip strength, 4-meter walk speed, and self-reported low activity, exhaustion, and unintentional weight loss. Individuals meeting 3–5 criteria were considered frail; 1–2, prefrail; and 0, nonfrail. For this study, participants were categorized either as frail or nonfrail (prefrail/nonfrail) [11].

Covariates

Baseline (HAILO entry visit) covariates included age, sex, race/ethnicity, education, nadir CD4 + T-lymphocyte count/mm^3 (CD4), history of AIDS defining illness, most recent CD4 count, plasma, human immunodeficiency virus type 1 (HIV-1) RNA (viral load), body mass index (BMI, obesity defined as BMI >30 kg/m^2, overweight 25–30 kg/m^2, normal weight 18.5–24.9 kg/m^2, underweight <18.5 kg/m^2), waist circumference (elevated if >102 cm in men, >88 cm in women) [16], hemoglobin A1C % (HbA1C), physical activity (≥3 vs <3 days of moderate or vigorous activity), smoking, use of antidepressant/anxiolytic medication, and efavirenz (EFV) use at baseline. Substance use status was self-reported as use of a nonprescribed psychoactive substance (marijuana, cocaine, heroin, amphetamines, or other nonprescribed drugs) at least once within the past month. Self-reported alcohol use was categorized as abstinence (no drinking); light (men: <7 drinks/week and no binging; women: <3 drinks/wk and no binging [binging defined as ≥5 drinks/2-hour period for men, ≥4 drinks for women]); moderate (men: 7–14 drinks/week and no binging; women: 3–7 drinks/week and no binging); and heavy (men: >14 drinks/week or binging; women: >7 drinks/week or binging). Moderate and heaving drinking categories were combined. Comorbidities considered were cardiovascular disease (myocardial infarction, stroke, coronary artery disease), liver disease, kidney disease, malignancy, diabetes (self-reported diagnosis or HbA1C ≥6.5%), hypertension (diagnosis or use of anti-hypertensive medications) and hepatitis C virus (HCV) infection (positive HCV antibody).

Statistical Analysis

Participants were categorized into 4 groups based on their neurocognitive function after 3 years of follow-up: persistently unimpaired, persistent NCI, development of NCI, or resolution of NCI. Participants who developed NCI were compared to those who remained unimpaired, and those who had resolution of NCI were compared to those who had persistent NCI, by demographic, clinical, and behavioral characteristics. Participants were similarly grouped and compared by frailty status over time. χ^2 tests were used for categorical variables and the Kruskal-Wallis test for continuous variables.

A multinomial logistic regression model with 4 levels of outcome was fit to assess associations between baseline covariates and development of NCI (vs stable unimpaired) or a return to normal neurocognition (vs persistent NCI). Similarly, a model was fit to assess associations between baseline covariates and development of frailty (vs stable nonfrail) or a return to nonfrail (vs persistent frailty). Analyses of NCI included presence of frailty or frailty score (0–5) at baseline as covariates. Frailty analyses included NCI or NPZ3 score at baseline as covariates. Age was forced into all models. Each of the covariates defined above were included separately in the age-adjusted models; those associated with the outcome at $P < .1$ were included in

the final models. A 2-sided 5% significance level was used for all analyses.

Because our models indicated that NCI was associated with development of frailty but not vice versa, a post hoc analysis was also conducted to more fully evaluate this association. We considered additional variables (CD4, alcohol use, substance use, physical activity, cardiovascular disease, kidney disease, history of cancer, diabetes, and hypertension) by adding each individually to the multivariable model. Those that changed the effect estimate by ≥10% were added to the model.

We also fit age-adjusted models stratified by race/ethnicity and sex. Analyses were conducted in SAS v.9.4.

RESULTS

Characteristics of Neurocognitive and Frailty Trajectory Groups

Of 929 participants included in the analysis, the baseline median age was 51 years (interquartile range [IQR], 46–56). Eighty-one percent were male, 31% Black, and 20% Hispanic. Most individuals had well-controlled HIV infection at study entry: 92% had undetectable plasma HIV-1 RNA (viral load <50 copies/mL) with median CD4 = 631 cells/mm^3 (IQR 458–840). At study entry, 16% of participants had NCI, and 6% were frail.

Over 3 years of observation, 727 (78%) maintained normal neurocognition, 57 (6%) developed NCI, 56 (6%) had resolution of NCI, and 89 (10%) had persistent NCI. Characteristics of participants by NCI trajectory group are shown in Table 1.

During the study period, 829 (89%) remained non-frail, 43 (5%) developed frailty, 28 (3%) had resolution of frailty, and 29 (3%) remained frail. Characteristics of participants by frailty trajectory group are shown in Table 2.

Characteristics Associated With Development of NCI

Neither frailty nor frailty score at baseline were associated with development of NCI as indexed by tests of executive functioning and processing speed in age-adjusted bivariate models and therefore not included in the multivariable model. In the multivariable model (Table 3), development of NCI was associated with increasing age (adjusted odds ratio [aOR] = 1.05 per year; 95% confidence interval [CI] = 1.01, 1.09; P = .023). Nadir CD4 higher than 350 cells/uL (vs less than 200) was also associated with development of NCI (aOR = 2.54; 95% CI = 1.27, 5.04; P < .01).

Characteristics Associated With Resolution of NCI

In the multivariable model (Table 3), among participants with baseline NCI, those who used EFV at the study's baseline had greater odds of NCI resolution (aOR 3.18; 95% CI = 1.41, 7.15; P < .01).

Multivariable models stratified by both race/ethnicity and sex are shown in Supplementary Tables 1–5. Greater odds of NCI development were associated with increased age among men and Hispanic participants, higher nadir CD4 among women and Black participants, and overweight BMI among White participants. Lower odds of NCI development were associated with suppressed viral load among White participants, former (vs never) cigarette use among men. Odds of NCI resolution was greater among men with EFV use at baseline, women, and White participants, and less among women with a comorbidity.

Characteristics Associated With Development of Frailty

Both NCI (dichotomized) and NPZ3 score (continuous) were associated with development of frailty in age-adjusted models. NCI was associated with development of frailty (aOR = 2.06; 95% CI = .94, 4.84; P = .07), Table 4. We further evaluated this association between NCI and development of frailty by including additional variables (current CD4, substance use) in the model that confounded this association; the observed association with NCI and frailty became stronger (aOR = 2.79; 95% CI = 1.21, 6.43; P = .02). Similarly, higher NPZ3 score, indicative of better neurocognitive function, was associated with a lower odds of developing frailty (aOR = 0.64; 95% CI = .46, .89; P < .01), Table 5. Black, non-Hispanic (vs White, non-Hispanic) race and current or former smoking were also associated with development of frailty.

Characteristics Associated With Resolution of Frailty

In the multivariable analysis (Table 4), only alcohol use was significantly associated with resolution of frailty. Both moderate to heavy (aOR = 13.3; 95% CI = 1.33, 132; P = .03) and light alcohol use (OR = 6.30; 95% CI = 1.33, 30.0; P = .02) were associated with greater odds of frailty resolution compared to abstinence.

Multivariable models stratified by both race/ethnicity and sex are shown in Supplementary Tables 6–10. Briefly, odds of developing frailty were associated with increasing age and Black race among men, anti-anxiety or antidepressant medications among women and White participants, female sex among White participants, and current or former cigarette use among Hispanic participants. Higher education was associated with lower odds of frailty among Black participants. Alcohol use (both light and moderate to heavy vs abstinence) among men and former smoking among Hispanics were associated with greater odds of frailty resolution.

DISCUSSION

This is the first longitudinal analysis to examine the relationship between NCI and frailty among PWH. In this large cohort of men and women living with HIV, baseline NCI as indexed by tests of executive functioning and processing speed was associated with a greater than 2-fold increased risk of developing frailty over 3 years, whereas frailty was not associated with development of NCI. These findings suggest that NCI may increase vulnerability to frailty and its associated poor health outcomes. Prior literature has suggested that cognitive function

Table 1. Demographic and Clinical Characteristics by Neurocognitive Trajectory Groups

Characteristic		Persistently Normal Cognition (N = 727)	Development of NCI (N = 57)	Resolution of NCI (N = 56)	Persistent NCI (N = 89)	*P*-Value
Age	Median (Q1,Q3)	51 (45, 56)	54 (47, 58)	51 (47, 55)	51 (46, 56)	.311
Female sex		125 (17%)	13 (23%)	13 (23%)	27 (30%)	.018
Race/Ethnicity	White non-Hispanic	381 (52%)	26 (46%)	22 (39%)	27 (30%)	<.001
	Black non-Hispanic	235 (32%)	18 (32%)	16 (29%)	16 (18%)	
	Hispanic (regardless of race)	111 (15%)	13 (23%)	18 (32%)	46 (52%)	
Less than high school education		85 (12%)	9 (18%)	15 (27%)	26 (29%)	<.001
Nadir CD4 count (cells/uL)	Median (Q1,Q3)	191 (64,294)	240 (78 374)	222 (68, 315)	205 (55, 329)	.380
	<200	377 (52%)	23 (40%)	26 (46%)	43 (48%)	.196
	200–350	235 (32%)	17 (30%)	21 (37%)	29 (33%)	
	>350	115 (16%)	17 (30%)	9 (16%)	17 (19%)	
CD4 count (cells/uL)	Median (Q1,Q3)	621 (453, 833)	689 (493, 860)	663 (483, 840)	641 (442, 884)	.740
	≤500	204 (28%)	12 (21%)	14 (25%)	22 (25%)	.946
	501–700	164 (23%)	11 (19%)	15 (27%)	17 (19%)	
	>700	254 (35%)	21 (37%)	21 (38%)	31 (35%)	
	Missing	105 (14%)	13 (23%)	6 (11%)	19 (21%)	
Undetectable VL (<50 copies/mL)		669 (92%)	49 (86%)	54 (96%)	82 (92%)	.233
Hemoglobin A1C (%)	Median (Q1, Q3)	5.50 (5.20, 5.80)	5.70 (5.45, 6.00)	5.60 (5.30, 6.00)	5.60 (5.30, 5.90)	.035
BMI	Median (Q1, Q3)	27.19 (23.95, 30.77)	28.75 (26.63, 31.00)	27.64 (25.28, 32.11)	26.80 (24.50, 29.77)	.095
	Underweight	5 (1%)	0 (0%)	0 (0%)	0 (0%)	.582
	Normal	234 (32%)	12 (21%)	13 (23%)	30 (34%)	
	Overweight	281 (39%)	26 (46%)	23 (41%)	37 (42%)	
	Obese	206 (28%)	19 (33%)	20 (36%)	22 (25%)	
High waist circumference		245 (34%)	25 (44%)	25 (45%)	33 (37%)	.179
Efavirenz use		254 (35%)	18 (32%)	20 (36%)	13 (15%)	.002
Days of vigorous/moderate activities per week by the International Physical Activity Questionnaires	<3 days on both vigorous and moderate activities	319 (44%)	26 (46%)	28 (50%)	38 (43%)	.562
	≥3 days on either vigorous or moderate activities	384 (53%)	25 (44%)	24 (43%)	40 (45%)	
Alcohol	Abstainer	272 (37%)	25 (44%)	26 (46%)	46 (52%)	.022
	Light drinker	280 (39%)	13 (23%)	18 (32%)	30 (34%)	
	Moderate/heavy drinker	175 (24%)	19 (33%)	12 (21%)	13 (15%)	
Cigarette use	Never	282 (39%)	29 (51%)	25 (45%)	38 (43%)	.469
	Former	241 (33%)	14 (25%)	21 (38%)	26 (29%)	
	Current	184 (25%)	13 (23%)	10 (18%)	24 (27%)	
Illicit substance use within the past month		171 (24%)	8 (14%)	8 (14%)	9 (10%)	.030
Anti-anxiety or depression medications		233 (32%)	22 (39%)	17 (30%)	33 (37%)	.584
NPZ3 score	Median (Q1, Q3)	0.63 (0.07,1.23)	-0.20 (-0.57, 0.23)	-1.00 (-1.23, 0.66)	-1.47 (-1.73, 1.13)	<.001
Frail		37 (5%)	2 (4%)	6 (12%)	11 (12%)	.015
Frailty score	Median (Q1, Q3)	0 (0, 1)	0 (0, 1)	1 (0, 1)	1 (0, 2)	<.001
Comorbidities						
Cardiovascular disease		46 (6%)	4 (7%)	3 (5%)	3 (3%)	.713
Liver disease		4 (1%)	2 (4%)	1 (2%)	4 (4%)	.003
Kidney disease		74 (10%)	8 (14%)	7 (13%)	7 (8%)	.630
History of cancer within the past 5 years		22 (3%)	1 (2%)	4 (7%)	5 (6%)	.218
Diabetes		91 (13%)	6 (11%)	4 (7%)	13 (15%)	.568
Hypertension		284 (39%)	21 (37%)	21 (38%)	31 (35%)	.875
Stroke		13 (2%)	2 (4%)	3 (5%)	1 (1%)	.232
Hepatitis C		80 (11%)	8 (14%)	7 (13%)	17 (19%)	.161
AIDS-defining conditions		133 (18%)	14 (25%)	16 (29%)	24 (27%)	.063

χ^2 tests were used for categorical variables and the Kruskal-Wallis test for continuous variables to assess differences in demographic and clinical characteristics between neurocognitive trajectory groups. Characteristics were measured at baseline unless otherwise indicated.
Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CD4, CD4 + T-lymphocyte count; EFV, efavirenz; HAILO, HIV Infection, Aging, and Immune Function Long-term Observational Study; HIV, human immunodeficiency virus; NCI, neurocognitive impairment; VL, viral load.

should be included in the frailty phenotype and that studying such "cognitive frailty" may better assess vulnerability [17]. Among HAILO participants, we previously found that the presence of NCI with frailty conferred greater risk of falls, disability, or death than NCI or frailty alone [18]. Together with our current study, these findings suggest that consideration of "cognitive frailty" may better capture PWHs' vulnerability to poor health than frailty alone.

Table 2. Demographic and Clinical Characteristics by Frailty Trajectory Groups

Characteristic		Persistently Nonfrail (N = 829)	Development of Frailty (N = 43)	Resolution of Frailty (N = 28)	Persistently Frail (N = 29)	*P*-Value
Age	Median (Q1, Q3)	50 (45, 56)	54 (47, 59)	56 (51, 59)	53 (51, 56)	<.001
Female sex		146 (18%)	16 (37%)	9 (32%)	6 (21%)	.004
Race/Ethnicity	White Non-Hispanic	422 (51%)	13 (30%)	13 (46%)	9 (31%)	.008
	Black Non-Hispanic	242 (29%)	20 (47%)	7 (25%)	16 (55%)	
	Hispanic (regardless of race)	165 (20%)	10 (23%)	8 (29%)	4 (14%)	
Less than high school education		112 (14%)	12 (28%)	6 (21%)	5 (17%)	.043
Nadir CD4 count (cells/uL)	Median (Q1,Q3)	195 (61, 296)	209 (66, 325)	249 (71, 328)	154 (66, 321)	.604
	<200	423 (51%)	20 (47%)	11 (39%)	16 (55%)	.788
	200–350	264 (32%)	17 (40%)	12 (43%)	8 (28%)	
	>350	142 (17%)	6 (14%)	5 (18%)	5 (17%)	
CD4 count (cells/uL)	Median (Q1, Q3)	620 (458, 834)	684 (413, 840)	798 (592, 1155)	652 (433, 848)	.176
	≤500	229 (28%)	12 (28%)	4 (14%)	7 (24%)	.470
	501–700	179 (22%)	11 (26%)	7 (25%)	10 (34%)	
	>700	288 (35%)	17 (40%)	14 (50%)	9 (31%)	
	Missing	133 (16%)	3 (7%)	3 (11%)	3 (10%)	
Undetectable VL (<50 copies/mL)		763 (92%)	39 (91%)	25 (89%)	27 (93%)	.936
Hemoglobin A1C (%)	Median (Q1, Q3)	5.50 (5.20, 5.80)	5.60 (5.30, 6.00)	5.80 (5.40, 6.20)	5.80 (5.40, 6.50)	.001
BMI	Median (Q1, Q3)	27.14 (24.09, 30.57)	29.24 (24.12, 32.33)	28.65 (27.28, 31.48)	27.93 (25.17, 33.95)	.082
	Underweight	3 (1%)	1 (2%)	1 (4%)	0 (0%)	.011
	Normal	269 (32%)	12 (28%)	3 (11%)	6 (21%)	
	Overweight	332 (40%)	12 (28%)	13 (46%)	10 (34%)	
	Obese	225 (27%)	18 (42%)	11 (39%)	12 (41%)	
High waist circumference		278 (34%)	17 (40%)	18 (64%)	14 (48%)	.003
EFV use		275 (33%)	14 (33%)	9 (32%)	7 (24%)	.790
Days of vigorous/moderate activities per week	<3 days on both vigorous and moderate activities	349 (42%)	21 (49%)	21 (75%)	21 (72%)	<.001
	≥3 days on either vigorous or moderate activities	438 (53%)	20 (47%)	7 (25%)	7 (24%)	
Alcohol	Abstainer	320 (39%)	12 (28%)	13 (46%)	25 (86%)	<.001
	Light drinker	308 (37%)	20 (47%)	10 (36%)	3 (10%)	
	Moderate/heavy drinker	201 (24%)	11 (26%)	5 (18%)	1 (3%)	
Cigarette use	Never	346 (42%)	7 (16%)	9 (32%)	12 (41%)	.003
	Former	258 (31%)	23 (53%)	15 (54%)	7 (24%)	
	Current	203 (24%)	13 (30%)	4 (14%)	10 (34%)	
Illicit substance use within the past month		180 (22%)	10 (23%)	4 (14%)	2 (7%)	.159
Anti-anxiety or depression medications		248 (30%)	20 (47%)	18 (64%)	20 (69%)	<.001
NCI		116 (14%)	11 (26%)	9 (32%)	8 (28%)	.002
NPZ3 score	Median (Q1, Q3)	0.40 (-0.30, 1.10)	-0.20 (-0.97, 0.63)	0.17 (-0.90, 0.70)	-0.37 (-1.00, 0.70)	<.001
Frailty score	Median (Q1, Q3)	0 (0, 1)	2 (0, 2)	3 (3, 3)	3 (3, 4)	<.001
Cardiovascular disease		48 (6%)	4 (9%)	1 (4%)	3 (10%)	.542
Liver disease		7 (1%)	2 (5%)	0 (0%)	2 (7%)	.003
Kidney disease		77 (9%)	6 (14%)	5 (18%)	8 (28%)	.006
History of cancer within the past 5 years		27 (3%)	4 (9%)	1 (4%)	0 (0%)	.135
Diabetes		92 (11%)	5 (12%)	9 (32%)	9 (31%)	<.001
Hypertension		309 (37%)	20 (47%)	15 (54%)	13 (45%)	.182
Stroke		16 (2%)	2 (5%)	0 (0%)	1 (3%)	.497
Hepatitis C		92 (11%)	8 (19%)	5 (18%)	7 (24%)	.062
AIDS-defining conditions		167 (20%)	8 (19%)	6 (21%)	6 (21%)	.992

χ^2 tests were used for categorical variables and the Kruskal-Wallis test for continuous variables to assess differences in demographic and clinical characteristics between neurocognitive trajectory groups. Characteristics were measured at baseline unless otherwise indicated.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; CD4, CD4 + T-lymphocyte count; HAILO, HIV Infection, Aging, and Immune Function Long-term Observational Study; HIV, human immunodeficiency virus; NCI, neurocognitive impairment; VL, viral load.

Table 3. Factors Associated With Neurocognitive Change in Multivariable Models

Baseline Characteristics	Development of NCI aOR (95% CI)	Resolution of NCI aOR (95% CI)
Age (per 1 year increase)	1.05 (1.01, 1.09) $P = .01$	0.98 (.94, 1.03) $P = .40$
Light drinker vs abstainer	.54 (.27, 1.09) $P = .09$	
Moderate/heavy drinker vs abstainer	1.16 (.60, 2.27) $P = .66$	
BMI: obese vs normal	1.92 (.89, 4.16) $P = .10$	
BMI: overweight vs normal	1.72 (.83, 3.56) $P = .15$	
BMI: underweight vs normal	.00 (.00, 1.00) $P = .99$	
Race/Ethnicity: Black, non-Hispanic vs White, non-Hispanic		1.25 (.51, 3.07) $P = .63$
Race/Ethnicity: Hispanic vs White, non-Hispanic		.49 (.22, 1.08) $P = .08$
Cigarette use: current vs never	.72 (.35, 1.46) $P = .36$	
Cigarette use: former vs never	.54 (.28, 1.07) $P = .08$	
Suppressed VL (<50 copies/mL)	.47 (.21, 1.09) $P = .08$	
Nadir CD4 (cells/uL): 200–350 vs <200	1.25 (.64, 2.44) $P = .52$	
Nadir CD4: >350 vs <200	2.54 (1.27, 5.04) $P < .01$	
EFV use		3.18 (1.41, 7.15) $P < .01$

Characteristics were measured at baseline unless otherwise indicated.
Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; EFV, efavirenz; NCI, neurocognitive impairment; VL, viral load.

Table 4. Factors Associated With Change in Frailty Status in Multivariable Models. NCI as a Covariate

Baseline Characteristics	Development of Frailty aOR (95% CI)	Resolution of Frailty aOR (95% CI)
NCI	2.06 (.96, 4.48) $P = .07$	
Age (per one year increase)	1.03 (.99, 1.08) $P = .13$	1.06 (.99, 1.14) $P = .12$
Alcohol: light drinker vs abstainer		6.30 (1.33, 30.0) $P = .02$
Alcohol: moderate/heavy drinker vs abstainer		13.3 (1.33, 132) $P = .03$
Anti-anxiety or depression medications	1.88 (.97, 3.63) $P = .06$	
BMI: obese vs normal	1.76 (.79, 3.92) $P = .17$	
BMI: overweight vs normal	.99 (.42, 2.31) $P = .98$	
BMI: underweight vs normal	8.20 (.69, 97.1) $P = .09$	
Education: ≥12 yrs vs < 12 yrs	.58 (.26, 1.30) $P = .19$	
Race/Ethnicity: Black, non-Hispanic vs White, non-Hispanic	2.30 (1.04, 5.06) $P = .04$	.32 (.08, 1.35) $P = .12$
Race/Ethnicity: Hispanic vs White, non-Hispanic	1.42 (0.53, 3.80) $P = .49$	3.29 (.63, 17.2) $P = .16$
Female	1.90 (.93, 3.90) $P = .08$	
Cigarette use: current vs never	2.60 (.96, 7.05) $P = .06$	
Cigarette use: former vs never	4.52 (1.85, 11.0) $P < .01$	
CD4 count (per every 50 cells increase)		1.07 (.99, 1.16) $P = .11$

Characteristics were measured at baseline unless otherwise indicated.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval.

The finding that NCI predicted incident frailty suggests that persons with NCI may constitute a group that could benefit from interventions that can slow progression to frailty. Interventions should ideally target mechanisms linking frailty and NCI, including chronic inflammation, physical inactivity, obesity, and comorbidities [19]. Physical exercise and cognitive training interventions have been effective in reducing frailty and improving physical function in older adults with and without HIV [20–22]. Intranasal insulin reversed neuronal injury in an animal model of HIV-associated NCI and presently is undergoing clinical trials in PWH (ClinicalTrials.gov Identifier NCT03081117). Tesamorelin, a growth hormone releasing hormone analog, reduces visceral adiposity and inflammation and has shown positive effects on cognition in older adults without HIV [23]. A Phase II randomized controlled trial of tesamorelin's effect on neurocognition in older PWH currently is underway (ClinicalTrials.gov Identifier NCT02572323). Furthermore, the diabetes medication metformin has demonstrated senolytic properties, and its use has been associated with cognitive function preservation [24–27] and physical function benefit in the general aging population [28]. As a result, the randomized controlled Targeting Aging with Metformin trial is underway in older adults without HIV to examine metformin's impact on aging endpoints, including cognitive and mobility outcomes [29]. Because metformin improves insulin resistance and reduces inflammation, both of which are associated with cognitive and physical function impairments in PWH [30–32], it could prove to be a particularly beneficial agent for HIV-related NCI and frailty in the future.

Use of EFV at baseline was associated with resolution of NCI in this analysis. This finding was likely related to discontinuation of EFV rather than a neuroprotective effect of this medication: 54% of the participants on EFV at baseline discontinued it over 3 years of follow-up. Of those who on EFV at baseline and had resolution of NCI, 70% stopped EFV during follow-up. EFV-based ART regimens have been associated with greater neurotoxicity and worse neurocognitive performance [33]. Discontinuation of EFV has also been associated with improved neurocognitive performance [34].

Our finding that nadir CD4 greater than 350 compared to <200 was associated with development of NCI contrasts with previous studies where lower nadir CD4 counts and higher HIV

Table 5. Factors Associated With Change in Frailty Status in Multivariable Models. NPZ3 as a Covariate

	Development of Frailty	Resolution of Frailty
Baseline Characteristics	aOR (95% CI)	aOR (95% CI)
NPZ3 score (per 1 unit increase in z-score)	.64 (.46, .89) $P = .01$	
Age (per 1 year increase)	1.03 (.99, 1.08) $P = .12$	1.06 (.99, 1.14) $P = .12$
Alcohol: light drinker vs abstainer		6.30 (1.33, 29.95) $P = .02$
Alcohol: moderate/heavy drinker vs abstainer		13.27 (1.33, 132.16) $P = .03$
Anti-anxiety or depression medications	1.79 (.92, 3.48) $P = .09$	
BMI: obese vs normal	1.77 (.79, 3.96) $P = .17$	
BMI: overweight vs normal	.96 (.41, 2.24) $P = .92$	
BMI: underweight vs normal	8.51 (.70, 102) $P = .10$	
Education: ≥12 yrs vs <12 yrs	.60 (.27, 1.34) $P = .21$	
Race/Ethnicity: Black, non-Hispanic vs White, non-Hispanic	2.33 (1.05, 5.16) $P = .04$	.32 (.08, 1.35) $P = .12$
Race/Ethnicity: Hispanic vs White, non-Hispanic	1.22 (.45, 3.30) $P = .70$	3.29 (.63, 17.19) $P = .16$
Female	1.69 (.81, 3.53) $P = .16$	
Cigarette use: current vs never	2.43 (.89, 6.59) $P = .08$	
Cigarette use: former vs never	4.34 (1.78, 10.6) $P < .01$	
CD4 count (per every 50 cells increase)		1.07 (.99, 1.16) $P = .11$

Characteristics were measured at baseline unless otherwise indicated.
Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval.

viral load portend worse neurocognitive function in PWH [35, 36]. Other studies have indicated that once PWH are on suppressive ART, HIV viral load and CD4 counts are no longer associated with neurocognitive performance [37]. By the current study's baseline in 2013–2014, the mean duration of ART was 8.4 years, and over 90% of participants were virally suppressed on ART and achieved immune recovery (median CD4 631). Compared to other HAILO participants, those who developed NCI during the study period tended to be older, use more anxiolytic or antidepressant medications, and have higher BMIs and hemoglobin A1C levels. This suggests that among older adults with well-controlled HIV, age-associated rather than HIV-specific risk factors may be driving NCI.

Other associations should be noted, including a higher odds of frailty among Black participants, an association previously noted in the general aging population [38] as well as in observational studies of PWH [39]. These differences are incompletely understood but have been linked to socioeconomic inequalities [40]. In the current study, higher education (completion of high school or beyond) was protective against development of frailty among Black participants, suggesting that socioeconomic disparity may in part be driving this difference. Current and former smokers had an increased risk of developing frailty, underscoring the importance of smoking cessation or avoidance to prevent frailty in PWH. Former smokers may have had greater lifetime tobacco exposure than current smokers, accounting for their higher risk of frailty. The protective effect of alcohol use on frailty seen in this study has been previously shown [41]. This paradoxical effect may reflect a more unhealthy population that does not consume alcohol due to medications and multimorbidity rather than a protective effect of alcohol per se. Although our results show that alcohol use was associated with resolution of frailty, the CIs of these aORs were quite large and should be interpreted with caution.

Several limitations of this study must be acknowledged. First, categorization by frailty and neurocognitive trajectory, particularly in subgroups by race/ethnicity and sex, allowed us to study the progression to a clinically defined syndrome but resulted in small numbers in the impaired groups. This limited our power to detect modest effects as well as the precision of the observed associations. Despite these small numbers, our models still predicted development of frailty with baseline NCI. Due to the small number of events, we were limited in the number of risk factors of frailty and NCI that we were able to evaluate. As this cohort continues to age, the prevalence of both frailty and NCI is expected to continue to increase among its participants and further characterization of the complex relationships between these 2 clinical syndromes will be possible. In addition, the A5001 Neuroscreen is a limited assessment of neurocognitive function and may not capture all cognitive domains. Furthermore, formal screening tools for mood disorders, which can be significant contributors to both cognitive and physical dysfunction, are not yet available in the HAILO cohort. Although this analysis incorporated use of antidepressant or anxiolytic medications as a proxy for mood disorders, this measure is imperfect. Moreover, this analysis accounted only for baseline medication and substance use, which may fluctuate over time and differentially affect cognitive and frailty outcomes. HAILO participants have been continuously enrolled in ACTG trials and observational studies since at least 2009. As a result, HAILO participants may be more adherent to treatment and medical care and not be fully representative of the general population of older PWH. The average age of participants at baseline in this study was 51 years old, which also limits generalizability to much older PWH. Additionally, women only account for 19% of participants in this cohort; however, as a cohort of both men and women the HAILO cohort does allow for simultaneous comparison of risk factors by sex. Finally, without a control group of participants who do not have HIV, it remains unclear whether our findings are specific to or accentuated among PWH.

As the number of older PWH grows, the prevalence of age-related comorbidities, including frailty and NCI, will undoubtedly continue to rise. Identification of individuals at greatest risk for these conditions and development of interventions to avert their onset are imperative. Although we did not find that frailty predicted the development of NCI, the relationship between

NCI and subsequent development of frailty suggests that NCI may be on the pathway to the development of frailty. Targeting modifiable risk factors associated with NCI and frailty may ultimately benefit both conditions and enhance both the quality and quantity of life for older adults aging with HIV.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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