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Frailty Is Associated With Mortality and Incident Comorbidity Among Middle-Aged Human Immunodeficiency Virus (HIV)–Positive and HIV-Negative Participants

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(See the Editorial Commentary by McMahon and Hoy, on pages 883–4.)

Background. Frailty is associated with mortality and morbidity in the general geriatric population, but less is known about its impact among the aging but generally younger population with human immunodeficiency virus (HIV).

Methods. The impact of frailty on all-cause mortality during 6 years of follow-up and incident comorbidity during 4 years of follow-up was assessed among 598 HIV-positive and 550 comparable HIV-negative participants aged ≥ 45 years of the AGE$_h$IV Cohort Study. Frailty encompasses 5 domains; weight loss, low physical activity, exhaustion, decreased grip strength, and slow gait speed. Presence of ≥ 3 denotes frailty, 1–2 prefrailty, and 0 robust. Multivariable Cox and logistic regression models were used to assess the independent relationships of frailty with both outcomes, adjusting for HIV infection and traditional risk factors.

Results. At baseline, 7.5% (n = 86) of participants were frail. During follow-up, 38 participants died. Mortality rate was significantly higher among frail participants: 25.7/1000 person-years of follow-up (PYFU) (95% confidence interval [CI], 14.2–46.4) compared with prefrail (7.2/1000 PYFU [95% CI, 4.7–11.2]) and robust (2.3/1000 PYFU [95% CI, 1.1–4.9]). In fully adjusted analyses, frailty remained strongly associated with death (hazard ratio, 4.6 [95% CI, 1.7–12.5]) and incident comorbidity (odds ratio, 1.9 [95% CI, 1.1–3.1]). No interactions were observed between frailty and HIV status in all analyses.

Conclusions. Frailty is a strong predictor of both mortality and incident comorbidity independent from other risk factors.

Clinical Trials Registration. NCT01466582.

Keywords. frailty; mortality; comorbidities; HIV; inflammation.

With the use of combination antiretroviral therapy (cART), the life expectancy of people living with human immunodeficiency virus (PLWH) has notably improved [1], and non-AIDS-defining comorbidities have thereby gained increased importance as causes of morbidity and mortality [2]. Consequently, identifying PLWH at increased risk of poor outcomes as they age has become a research priority with important implications for clinical management.

The Frailty Phenotype (frailty) described by Fried was developed in the general population aged ≥ 65 years to predict morbidity and mortality [3]. Frailty is conceptualized as a state of decreased physical resilience due to deficits across multiple organ systems, leading to increased vulnerability and adverse outcomes such as falls, hospitalization, disability, and death in the general geriatric population [3, 4]. Human immunodeficiency virus (HIV) infection and related chronic systemic inflammation are hypothesized to increase vulnerability to stressors and potentially mediate the association between frailty and adverse health outcomes [5, 6]. Frailty is not synonymous with comorbidities, although there is a bidirectional relationship between frailty and comorbidity whereby frailty can be both a predictor and an outcome of comorbidities [3, 4, 7, 8].

Frailty has also been shown to be present among younger HIV-positive [5, 9] and -negative individuals [10]. Moreover, previous analyses from our cohort demonstrated that middle-aged (≥ 45 years) PLWH were more likely to be frail [11] and to have a higher comorbidity burden than lifestyle-comparable HIV-negative participants [12]. Few studies prospectively reported on the development of adverse health outcomes in relation to frailty in younger PLWH [10, 13, 14], often not including an appropriately selected HIV-negative comparison group [14].

Because PLWH are disproportionally affected by non-HIV-related comorbidities as they age, evaluating the extent to which frailty is predictive of adverse health outcomes could assist in identifying—at an early stage—those at increased risk. We report on the association between frailty status and the development of mortality and comorbidity among HIV-positive and highly comparable HIV-negative participants of the AGE$_h$IV Cohort Study.

METHODS

Study Population

The AGE$_h$IV Cohort Study included 598 HIV-positive participants from the Academic Medical Center HIV outpatient clinic of the Amsterdam University Medical Centers and 550 HIV-negative participants from either the sexual health clinic or the Amsterdam Cohort Studies on HIV/AIDS at the Public Health Service in Amsterdam, the Netherlands [15]. As described previously [12], all participants were ≥ 45 years of age at enrollment. HIV-negative participants were a highly comparable control group regarding geographic characteristics, sociodemographic characteristics, and sexual behavior. The majority of HIV-negative participants were men who have sex with men (MSM) at increased risk for HIV infection. Data prospectively collected between October 2010 and October 2018, encompassing 4 biennial study visits, were included in the current analysis. Written informed consent was obtained from all participants. The study protocol was approved by the Academic Medical Center ethics review board and was registered at ClinicalTrials.gov (NCT01466582).

Data Collection

During each study visit, standardized measurements of hip and waist circumference, waist-to-hip ratio, height, and weight were performed and blood samples were collected. A standardized questionnaire collected data on smoking behavior, alcohol use, medication use, recreational drug use, and depressive symptoms, defined as a score of ≥ 16 on the Center for Epidemiologic Studies Depression questionnaire (CES-D) [16], excluding 2 questions that were also used in the frailty score, as done previously [11]. Data only collected at baseline were hepatitis B/C virus serology, cytomegalovirus serology, and plasma levels of intestinal fatty acid–binding protein (I-FABP), interleukin 6 (IL-6), soluble CD14 (sCD14), and soluble CD163 (sCD163) as

biomarkers of intestinal permeability, inflammation, and innate immune activation, respectively.

Definitions of Comorbidities

Comorbidities objectively assessed during each study visit were (1) chronic obstructive pulmonary disease (forced expiratory volume in 1 second/forced vital capacity ratio z score < –1.64 using Global Lung Initiative guidelines) [17]; (2) hypertension grade 2 (measured systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg in 3 measurements with a 1-minute interval, following European guidelines [18] or use of antihypertensive medication); (3) decreased kidney function (estimated glomelular filtration rate < 60 mL/minute/1.73 m^2 using the Chronic Kidney Disease Epidemiology Collaboration equation) [19]); (4) osteoporosis (dual-energy X-ray absorptiometry t score < –2.5 standard deviations for men aged ≥ 50 years and postmenopausal women or a z score < –2.0 for men aged < 50 years and premenopausal women using World Health Organization definitions) [20]; (5) diabetes mellitus (hemoglobin A1c ≥ 48 mmol/mol or elevated blood glucose [nonfasting ≥ 11.1 mmol/L or fasting ≥ 7.0 mmol/L]) or using antidiabetic medication) [21]. Self-reported but subsequently validated comorbidities included heart failure (diagnosed by cardiologist); non-AIDS-defining cancers (confirmed by pathologist, excluding nonmelanoma skin cancers); and atherosclerotic diseases (diagnosed by specialist: myocardial infarction, angina pectoris, peripheral arterial disease, ischemic stroke, or transient ischemic attack). Self-reported diagnoses were validated using hospital records for HIV-positive participants, and general practitioner (GP) records for HIV-negative participants who provided consent to contact their GP. For participants who died during follow-up, information on comorbidities and cause of death was obtained using hospital and GP records. Unvalidated diagnoses were used when validation was not possible (ie, participants not providing consent, or absence of clinical documentation when care received in other hospitals). Of the 262 self-reported comorbidities, 146 (55.7%) were validated as correct, 93 (35.5%) were rejected, and 23 (8.8%) could not be validated. Rejected self-reported comorbidities were excluded from analyses. Incident comorbidities were defined as those which were not present during previous study visits.

Mortality data were confirmed through the Municipal Personal Records Database, even if participants were lost to follow-up or declined participation in follow-up study visits. Mortality data were missing only for 15 participants (1.3%) who relocated abroad during follow-up.

Frailty Definition

Frailty based on the Fried Frailty Phenotype was assessed at each study-visit [11], including 5 dichotomous items, each scored as absent (0) or present (1): (1) self-reported unintentional weight loss (≥ 4.5 kg in the last year or > 2.3 kg in the last 6 months),

(2) self-reported low physical activity, (3) self-reported exhaustion, (4) slow walking speed (4.57-m walk), and (5) low grip strength (Jamar Plus + Digital Hand Dynamometer). The summary score of this 5-item scale classifies an individual as robust (0 points), prefrail (1–2 points), or frail (3–5 points). In line with current practice [22], but in contrast to our previous analysis [11], we used the highest measured grip strength (of 3 measurements) and the highest walking speed (of 2 measurements). If frailty items were missing, we assumed these items to be normal (having a score of 0); 90 visits from HIV-positive and 12 visits from HIV-negative participants were missing 1 frailty item (< 0.7% of all visits), 7 visits from HIV-positive participants were missing 2 frailty items. We considered the overall frailty score as missing if ≥ 2 frailty items were missing (n = 14 [<0.5%] among 3022 study visits). Data from 2 participants were excluded because of missing frailty scores at all study visits.

Statistical Analysis

Baseline characteristics were compared between groups using Wilcoxon rank-sum test, analysis of variance, and χ^2 tests as appropriate.

All-cause mortality by baseline frailty status was analyzed using Kaplan–Meier curves and Cox proportional hazards models. For all models with mortality as outcome, follow-up time was censored at the date of death, the fourth study visit (6 years of follow-up), withdrawal of consent, or at the first missed study visit for those who were lost to follow-up or not attending 2 consecutive study visits. We used a stepwise forward selection procedure to identify variables potentially influencing the association of frailty with mortality: all variables with a main effect $P < .2$ in univariable analyses were retained in the multivariable model if they changed the frailty regression coefficients by at least 10%, or if they remained independently associated with the outcome. Variables explored for their confounding or mediating effects were: age; a composite of gender and sexual behavior (ie, MSM, heterosexual male, and female; hereafter called "sexual risk group"); body composition (body mass index, waist circumference, hip circumference, and waist-to-hip ratio); smoking (never, ever, or current); alcohol use (never, ever, or current); recreational drug use; number of preexisting comorbidities (0, 1, 2, or ≥ 3); depressive symptoms, defined as a CES-D score of ≥ 16 (yes/no); chronic hepatitis B or C virus infection; cytomegalovirus seropositivity; high-sensitivity C-reactive protein (hs-CRP); D-dimer; and the previously mentioned biomarkers of intestinal permeability, inflammation, and immune activation. To investigate whether the frailty phenotype has different predictive properties in HIV-positive compared to HIV-negative participants, HIV status and an interaction term between HIV status and frailty status were added to the models.

Incident comorbidities were defined as comorbidities newly diagnosed after the first but before or at the second of a pair of consecutive study visits. If a specific comorbidity known to be chronic (eg, hypertension) was present during a particular study visit, we considered it to be present during all subsequent study visits. Data collected from the initial 3 study visits (4 years of follow-up) were used, as validation of self-reported comorbidities had not yet been completed for the fourth study visit. All participants who contributed 1 or more consecutive visit-pairs (ie, visit 1 to visit 2 or visit 2 to visit 3) were included. As frailty tends to be more transitional in younger populations [23], we chose to only include consecutive visit-pairs, and not nonconsecutive visit-pairs (ie, visit 1 to visit 3). To assess potential selection bias, characteristics of participants at time of enrollment included in this analysis were compared with those who were excluded. Frailty status as predictor of incident comorbidity was analyzed using logistic regression models with generalized estimating equations using an exchangeable working correlation matrix to account for the clustered observations within an individual. Frailty status was assessed as a time-updated variable in this model. In the incident comorbidity model, number of preexisting comorbidities, sexual risk group, nonwhite ethnicity, and level of education were forced into the model based on a priori knowledge. Furthermore, all potential confounding or mediating factors listed under the mortality analyses were also analyzed in the incident comorbidity analysis.

Finally, mediating properties of several HIV-related factors between frailty and both outcomes were investigated among HIV-positive participants only. HIV-related factors explored were current CD4 cell count, CD4 cell nadir (per 100 cells), CD4/CD8 ratio at time of the study visit, level and duration of HIV viremia (time spent above 1000, 5000, 10 000, 75 000, or 200 000 copies/mL), level and duration of immunosuppression (time spent with a CD4 cell count below 50, 100, 200, or 350 cells/uL), having been diagnosed with a Centers for Disease Control and Prevention class C AIDS-defining event, type of first AIDS-defining illness, type and duration of prior ART use, and time since HIV diagnosis. Moreover, we assessed whether hip or waist circumference, and the waist-to-hip ratio as possible proxy for lipodystrophy, were associated with both outcomes or attenuated the effect of frailty on both outcomes. Missing categorical or dichotomized variables from all participants were not imputed but categorized as "missing" and thus included in the model. Missing continuous variables were imputed using mean values stratified by HIV status and risk group. The amount of missing data was very limited: .6% of continuous and 2.3% of categorical variables.

All reported P values are 2-tailed. Interaction effects between covariates were explored in all final models and retained when $P \leq .1$. Analyses were performed using Stata version 12 (StataCorp LP).

RESULTS

Characteristics of study participants at time of enrollment, by frailty status, are shown in Table 1. Stratified by frailty status,

Table 1. Baseline Characteristics of Participants Included in the AGEhIV Cohort, Stratified by Frailty Status

Characteristic	Robust (n = 547)	Prefrail (n = 513)	Frail (n = 86)	P Value
Demographics				
HIV positive	214 (39.1)	313 (61.0)	69 (80.2)	<.001*
HIV negative	333 (60.9)	200 (39.0)	19 (19.8)	
Age, y, median (IQR)	51.5 (47.6–56.9)	53.3 (48.6–60.1)	55.1 (49.7–60.0)	<.001**
Sexual risk group				
MSM	399 (72.9)	378 (73.7)	61 (70.9)	.29*
Heterosexual male	79 (14.4)	62 (12.1)	8 (9.3)	
Female	69 (12.6)	73 (14.2)	17 (19.8)	
Nonwhite ethnicity	39 (7.1)	46 (9.0)	12 (14.1)	.085*
White ethnicity	508 (92.9)	467 (91.0)	74 (86)	
Higher education[a]	276 (50.5)	211 (41.1)	22 (25.6)	<.001*
Behavioral characteristics				
Smoking status				
Never	198 (37.8)	152 (31.6)	21 (27.3)	.023*
Former	194 (37.0)	170 (35.3)	27 (35.1)	
Current	132 (25.2)	159 (33.1)	29 (37.7)	
Pack-years (if ever smoked), median (IQR)	15.0 (3.4–31.5)	18.7 (8.1–35.0)	22.8 (7.0–39.0)	<.001**
Alcohol use				
Never	31 (5.9)	27 (5.5)	12 (15.4)	<.001*
Former	43 (8.1)	63 (12.8)	12 (15.4)	
Current	454 (86.0)	401 (81.7)	54 (69.2)	
Heavy daily alcohol use past 6 mo[b]	28 (5.1)	24 (4.7)	2 (2.3)	.009*
Binge alcohol during past 6 mo[c]	147 (26.9)	112 (21.8)	12 (14.0)	.006*
Injection drug use (ever)	8 (1.5)	11 (2.1)	6 (7.0)	<.001*
THC use during last 6 mo	53 (10.3)	68 (14.6)	8 (11.0)	.120*
Body composition, mean ± SD				
Waist-circumference, cm	91.9 ± 9.9	93.2 ± 11.1	95.5 ± 11.7	.005***
Waist-to-hip ratio	0.9 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	<.001***
BMI, kg/m²	25.0 ± 3.3	24.9 ± 3.8	25.4 ± 4.6	.48***
Comorbidities[d]				
No. of age-associated comorbidities				
0	334 (61.1)	264 (51.5)	37 (43.0)	<.001*
1	152 (27.8)	162 (31.6)	23 (26.7)	
2	47 (8.6)	58 (11.3)	17 (19.8)	
≥3	14 (2.6)	29 (5.7)	9 (10.5)	
Hepatitis B virus DNA positive	12 (2.2)	25 (4.9)	4 (4.7)	.052*
Hepatitis C virus RNA positive	5 (0.9)	15 (2.9)	7 (8.2)	<.001*
Cytomegalovirus IgG positive	450 (82.3)	449 (87.9)	78 (90.7)	.013*
Depressive symptoms[e]				
CES-D score ≥ 16	41 (7.5)	101 (19.7)	36 (41.9)	<.001*
Markers of inflammation, median (IQR)				
hs-CRP, mg/L	1.0 (0.6–2.0)	1.5 (0.7–3.1)	1.8 (0.7–3.9)	<.001**
D-dimer, mg/L	0.2 (0.2–0.3)	0.3 (0.2–0.4)	0.3 (0.2–0.5)	.009**
IL-6, pg/mL	1.8 (1.1–3.1)	1.7 (1.1–2.8)	1.8 (1.1–3.8)	.54**
sCD14, ng/mL	1472 (1166–1872)	1496 (1229–1935)	1423 (1148–1873)	.15**
sCD163, ng/mL	260 (189–352)	279 (190–379)	320 (244–495)	<.001**
I-FABP, ng/mL	1.4 (0.9–2.2)	1.8 (1.1–3.0)	2.0 (1.4–3.3)	<.001**

Data are presented as No. (%) unless otherwise indicated.

Abbreviations: BMI, body mass index; CES-D, Center for Epidemiologic Studies Depression scale; HIV, human immunodeficiency virus; hs-CRP, high-sensitivity C-reactive protein; I-FABP, intestinal fatty acid–binding protein; IgG, immunoglobulin G; IL-6, interleukin 6; IQR, interquartile range; MSM, men who have sex with men; sCD14, soluble CD14; sCD163, soluble CD163; SD, standard deviation, THC, tetrahydrocannabinol.

[a]Higher vocational education: attained at least a bachelor's degree

[b]Heavy daily alcohol use defined as > 5 alcohol units almost daily for a man and > 4 units for a woman during the last 6 months.

[c]Binge alcohol defined as > 6 alcohol units a day, minimally once per month during the last 6 months.

[d]Comorbidities included are chronic obstructive pulmonary disease or asthma (defining obstruction as having < 1.64 z score for forced expiratory volume in 1 second/forced vital capacity ratio using Global Lung Initiative guidelines), diabetes (hemoglobin A1c ≥ 48 mmol/mol and/or elevated blood glucose (nonfasting ≥ 11.1 mmol/L or fasting ≥ 7.0 mmol/L) or on antidiabetic medication), hypertension (use of antihypertensive medication or measured grade 2 hypertension following European guidelines (systolic blood pressure 160 mm Hg and/or diastolic blood pressure 100 mm Hg in all 3 measurements), decreased kidney function (estimated glomerular filtration rate < 60 mL/minute/1.73 m²) based on Chronic Kidney Disease Epidemiology Collaboration equation, osteoporosis (having a t score of −2.5 SD or lower, in men aged < 50 years and premenopausal women; a z score of −2 SD or lower in men aged ≥ 50 years and postmenopausal women), self-reported and validated heart failure, non-AIDS-associated cancer (excluding nonmelanoma skin cancers), cardiovascular disease (myocardial infarction, angina pectoris, peripheral artery disease, ischemic stroke, and/or transient ischemic attack).

[e]CES-D ≥ 16, with 2 questions used in the frailty scale excluded from CES-D score calculation.

*Pearson χ^2 test.

**Kruskal–Wallis test.

***Analysis of variance.

the age distribution was not significantly different between the HIV-positive and HIV-negative participants. During follow-up, 35 (7.9% of 441 nonfrail) HIV-positive and 25 (5.4% of 466 nonfrail) HIV-negative participants became frail. Additionally, 103 (56.9% of 181 robust) HIV-positive and 144 (49.3% of 292 robust) HIV-negative participants became prefrail. The majority of the participants were MSM and of white ethnicity. Frail participants tended to more frequently be HIV positive, older, a current smoker, and to have more preexisting comorbidities. However, they reported less alcohol use. Levels of hs-CRP, D-dimer, sCD163, and I-FABP were higher among frail participants. The majority of the HIV-positive participants used cART (95.8%), of whom 95.1% were virologically suppressed (defined as HIV RNA < 200 copies/mL) in the year prior to enrollment. Median time since HIV-1 diagnosis was 12.0 years (Table 2). During follow-up, 7 HIV-negative participants seroconverted, after which they contributed as HIV-positive participants in the analyses.

Mortality

During a median of 4.0 (interquartile range, 2.1–5.9) years of observation, 38 (3.3%) of 1146 participants died, including 31 (5.2%) HIV-positive and 7 (1.3%) HIV-negative participants. Of the 38 deaths, 11 (29%) were frail at study enrollment, 20 (53%) prefrail, and 7 (18%) robust. None of the deaths were AIDS related. For causes of death, see Supplementary Table 1.

The mortality analysis included 428, 2771, and 3000 person-years of follow-up (PYFU) for participants who were frail, prefrail, and robust at enrollment, respectively. Mortality rates/1000 PYFU were notably higher among those who were

frail 25.7 (95% confidence interval [CI], 14.2–46.4) compared to those who were either prefrail (7.2 [95% CI, 4.7–11.2]) or robust (2.3 [95% CI, 1.1–4.9]) ($P < .001$ for both comparisons). See Figure 1 for the corresponding Kaplan–Meier cumulative mortality curve.

In stepwise proportional hazards models, the frail phenotype remained independently associated with an increased risk of mortality after stepwise adjustment for age, HIV status, smoking status, alcohol use, and sCD163 plasma concentration (Table 3). The effect of the independent variables included in the final model (model 6), is shown in Supplementary Table 2. All other variables were not associated with mortality nor influenced the effect of frailty on mortality, and were therefore excluded from the final models. There was no interaction effect of HIV and frailty on mortality. Within the HIV-positive group only, after additional adjustment for nadir CD4 count, frailty remained independently associated with mortality (Table 4 and Supplementary Table 3). Other HIV-related variables, including hip or waist circumference, and the waist-to-hip ratio as potential proxy for lipodystrophy, were not independently associated with mortality, nor did they attenuate the association between frailty and mortality.

Incident Comorbidity

Comorbidity data were available for 497 HIV-positive and 479 HIV-negative participants, including 1833 visit-pairs, in which 107 (5.8%), 788 (43.0%), and 938 (51.2%) participants were classified as frail, prefrail, or robust at the first of the paired study visits, respectively. There were 33 (30.8%), 160 (20.3%), and 127 (13.5%) incident comorbidities within the frail, prefrail, and robust visit-pairs, respectively. Hypertension grade 2 (n = 87), chronic obstructive pulmonary disease (n = 69), decreased kidney function (n = 41), and osteoporosis (n = 39) comprised 74% of all incident comorbidities (n = 320 in total).

In unadjusted analyses, being frail or prefrail were each associated with an increased risk of incident comorbidity compared to being robust (odds ratio [OR], 2.59, $P < .001$; OR, 1.60, $P = .003$; Table 5). For both frailty and prefrailty, the association was attenuated by age (model 2) and HIV status (model 3), but remained statistically significant. No further attenuation of these associations was observed after inclusion of the number of preexisting comorbidities, sexual risk group, nonwhite ethnicity, and level of education to the model. No significant interactions were found between variables included in the final model (Table 4 and Table 5, model 5), including for HIV and frailty status.

Within the HIV-positive group, frailty, but not prefrailty, was crudely associated with incident comorbidity (OR, 2.34, $P = .002$; Supplementary Table 4). Adding age and number of preexisting comorbidities to the model slightly attenuated the association between frailty and incident comorbidity. Further addition of sexual risk group, level of education, and nonwhite

Table 2. Characteristics of Human Immunodeficiency Virus–Positive Participants (n = 596)

Characteristic	No. (%) or Median (IQR)
Years since HIV diagnosis	12.0 (6.6–17.1)
CD4 cell count, cells/μL	
Nadir CD4 count	170 (70–260)
Mean CD4 in 12 mo prior to enrollment	565 (432–740)
Cumulative duration of CD4 count <200/μL, y	0.9 (0.0–10.5)
CD4/CD8 ratio at enrollment	0.7 (0.5–1.0)
History of CDC class C AIDS-defining diagnosis	192 (32.2)
Using cART at enrollment	571 (95.8)
Cumulative exposure to ART, y	10.3 (4.5–14.5)
ART experienced before starting cART	120 (21.0)
Having used zalcitabine	169 (28.4)
Duration of zalcitabine use[a], y	2.7 (0.9–6.9)
HIV RNA <200 copies/mL in year prior to enrollment[b]	542 (95.1)
Cumulative duration of HIV RNA <200 copies/mL[b], y	8.7 (3.9–12.6)

Abbreviations: ART, antiretroviral therapy; cART, combination antiretroviral therapy; CDC, Centers for Disease Control and Prevention; HIV, human immunodeficiency virus; IQR, interquartile range.

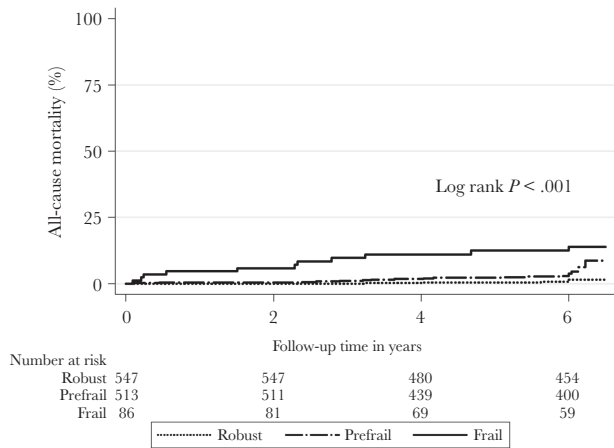[a]For those who had used zalcitabine.

[b]If currently on cART.

Figure 1. Kaplan–Meier cumulative mortality curve for the 1146 participants of the AGE$_h$IV Cohort for all-cause mortality by frailty status at enrollment from October 2010 until October 2018. Follow-up time was censored at date of death, the fourth study visit, withdrawal of consent, loss to follow-up, or 6 years after inclusion for participants who did not complete their fourth study visit. Participants who missed 2 consecutive study visits were considered lost to follow-up and were censored at time of the first missed study visit. Frailty was defined based on the presence of ≥ 3 criteria, "prefrail" if 1–2 criteria were present, and "robust" when none of the criteria were met. The numbers of participants at risk are noted in the table below the graph.

ethnicity to the model did attenuate the association; frailty remained significantly associated with a 2-fold higher risk for incident comorbidity (OR, 1.92; $P = .027$). While the cumulative duration of zalcitabine use and cumulative exposure to a detectable HIV viral load were each independently associated with incident comorbidity, the addition of these variables to the model did not substantively impact the association between

Table 3. Association Between Frailty Status at Enrollment and Subsequent Mortality: Results of Proportional Hazards Model Analysis

| Model[a] | HR (95% CI) of Frailty Phenotype Compared to Robust Phenotype | |
	Prefrail	Frail
Model 1	3.08 (1.30–7.28)	10.87 (4.21–28.07)
	$P = .10$	$P < .001$
Model 2	2.68 (1.12–6.40)	8.87 (3.38–23.28)
	$P = .026$	$P < .001$
Model 3	2.25 (.93–5.39)	6.21 (2.31–16.73)
	$P = .071$	$P < .001$
Model 4	1.96 (.81–4.69)	5.84 (2.21–15.46)
	0.133	$P < .001$
Model 5	1.85 (.77–4.47)	5.26 (1.97–14.05)
	0.172	$P = .001$
Model 6	1.86 (.77–4.49)	4.64 (1.72–12.50)
	0.165	$P = .002$

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Model 1: unadjusted; model 2: adjusted for age; model 3: further adjusted for human immunodeficiency virus; model 4: further adjusted for smoking status; model 5: further adjusted for alcohol status; model 6: further adjusted for log-transformed soluble CD163 plasma concentration.

frailty and incident comorbidity. Other HIV- and ART-related variables, including hip or waist circumference, and the waist-to-hip ratio were not associated with incident comorbidity nor did they influence the association between frailty and comorbidity development.

DISCUSSION

We found that in comparable populations of middle-aged HIV-positive and -negative participants, the frailty phenotype was strongly and consistently associated with increased risk for both all-cause mortality and incident comorbidity. Both effects were independent of other traditional risk factors such as age and smoking behavior. Those who were prefrail were at intermediate risk for both outcomes. These data further contribute to the growing evidence base for the utility of a frailty phenotype for predicting adverse clinical outcomes in aging but generally younger HIV-positive populations, even among those whom have maintained excellent control of their HIV disease for prolonged periods of time.

Although frailty prevalence was relatively low and we observed few deaths, frailty was strongly predictive of mortality. Similarly observations have been reported from a middle-aged cohort of HIV-positive and -negative injection drug users, albeit they had notably higher levels of frailty and mortality with poorer levels of virologic control [5]. Due to the limited number of deaths we observed, potential drivers of this effect could not be extensively investigated. While the association of frailty with mortality was notably attenuated by age, other traditional risk factors (eg, behavioral factors such as tobacco and alcohol use), HIV-related factors (eg, CD4 nadir, viral suppression, prior AIDS), or immune activation and inflammation markers had minimal impact on the observed risk and do not explain the association of frailty with mortality. While current smoking was strongly associated with mortality, we interestingly found that current alcohol use was notably less common among frail individuals and was inversely associated with mortality, suggesting that unhealthy participants had likely reduced or stopped their alcohol consumption. Among our virologically controlled HIV-positive participants, most markers of HIV disease stage or a panel of immune activation and chronic inflammation biomarkers were not significantly associated with mortality. CD4 nadir, a previously reported risk factor for mortality [24], was associated with a 50% reduced survival per 100-cell decrease. sCD163, similar to a report by Knudsen et al [25], was the only measured marker associated with mortality in our analysis. However, neither CD4 nadir nor sCD163 attenuated the association between frailty and mortality. The interaction between HIV and frailty status was deemed nonsignificant, which suggests equivalent predictive ability of frailty for mortality in virologically controlled HIV-positive patients and lifestyle-comparable HIV-negative persons. This conclusion should,

Table 4. Final Multivariable Models Showing the Association of Independent Variables on Mortality and on Incident Comorbidity, Among Human Immunodeficiency Virus–Positive Participants Only

Dependent Variable	Outcome Mortality HR (95% CI)	P Value	Outcome Incident Comorbidity OR (95% CI)	P Value
Frailty phenotype				
Robust	Ref		ref	
Prefrail	1.96 (.71–5.39)	.192	1.08 (.74–1.57)	.678
Frail	3.19 (1.02–9.98)	.047	1.90 (1.06–3.41)	.032
Age (per 10 y)	1.94 (1.23–3.07)	.005	1.53 (1.20–1.96)	.001
Sexual risk group				
MSM	…		ref	
Heterosexual male	…		.90 (.50–1.63)	.731
Female	…		1.84 (1.08–3.12)	.024
Nonwhite ethnicity	…		1.18 (.62–2.22)	.617
Higher vocational education	…		.91 (.63–1.31)	.608
Smoking status				
Never	Ref		ref	
Former	1.16 (.35–3.87)	.804	1.04 (.67–1.62)	.847
Current	3.41 (1.19 –9.77)	.022	1.46 (.93–2.27)	.099
Alcohol use				
Never	Ref		ref	
Former	.27 (.06–1.16)	.078	.74 (.34–1.61)	.451
Current	.20 (.05–.77)	.019	.69 (.35–1.35)	.274
No. of preexisting comorbidities				
0	…		ref	
1	…		.85 (.57–1.28)	.439
2	…		.87 (.51–1.47)	.596
≥3	…		.66 (.34–1.27)	.212
CD4 nadir (per 100 cells/µL higher)	1.51 (1.06–2.14)	.022	…	
Duration of zalcitabine use (y)	…		1.35 (1.09–1.67)	.005
Cumulative duration of viral load > 1000 copies/mL	…		1.06 (1.00–1.12)	.046

For further details, see Supplementary Table 3, model 5 and Supplementary Table 4, model 6.

Abbreviations: CI, confidence interval; HR, hazard ratio; MSM, men who have sex with men; OR, odds ratio.

Table 5. Association Between Frailty Status and Incident Comorbidity Risk: Results of a Logistic Regression Model Analysis With Generalized Estimating Equations

Model[a]	OR (95% CI) of Frailty Phenotype Compared to Robust Phenotype	
	Prefrail	Frail
Model 1	1.60 (1.24–2.08)	2.59 (1.62–4.13)
	P = .003	P < .001
Model 2	1.46 (1.12–1.92)	2.24 (1.40–3.61)
	P = .005	P = .001
Model 3	1.38 (1.06–1.82)	2.01 (1.24–3.26)
	P = .019	P = .005
Model 4	1.38 (1.05–1.82)	2.03 (1.23–3.34)
	P = .020	P = .005
Model 5	1.34 (1.02–1.77)	1.87 (1.13–3.10)
	P = .036	P = .015

Abbreviations: CI, confidence interval; OR, odds ratio.

[a]Model 1: unadjusted; model 2: adjusted for age; model 3: further adjusted for human immunodeficiency virus; model 4: further adjusted for nonwhite ethnicity, education, risk group, and number of preexisting comorbidities; model 5: further adjusted for smoking behavior and alcohol use.

however, be taken with caution as the number of deaths among the HIV-negative participants was only 7.

Frailty was also associated with a higher risk of developing 1 or more comorbidities. This association was independent of the number of prevalent comorbidities at enrollment and of other traditional risk factors such as age, tobacco use, and alcohol use. A recent study among PLWH has shown frailty to be predictive of bone disease, diabetes, and cardiovascular disease [26]. To our knowledge, we are the first to report the predictive value of frailty on a composite of age-associated comorbidities in PLWH. This is especially relevant for our aging PLWH population, which is at increased risk for a wide variety of comorbidities spanning multiple organ systems. Fried et al describe frailty as a "physiologic precursor and etiologic factor of disability," but not as being synonymous with comorbidity or disability [3]. We show that frailty indeed predicts comorbidity development independently from preexisting diagnosed comorbidities or other risk factors. Although several HIV-related variables (duration of zalcitabine use and the cumulative duration of a detectable

viral load) and HIV status itself were associated with incident comorbidity, frailty remained independently associated with incident comorbidities in PLWH. Although hypothesized to drive comorbidity risk in PLWH, markers of chronic inflammation [27, 28], immune activation [29], and microbial translocation [30] did not influence the association between frailty and incident comorbidity. These findings suggest a distinct independent pathophysiological pathway not captured by factors measured in our study.

Our study has several practical limitations. We observed few deaths, so we had limited statistical power to analyze factors associated with mortality. Markers of inflammation and immune activation (IL-6, sCD14, sCD163, and I-FABP) were only measured at enrollment. For the analysis of comorbidity development, follow-up time was limited to 4 years. As the majority of our participants had been diagnosed with HIV for a long time, and many had experienced severe immunosuppression or AIDS, these results may not be generalizable to individuals who were more recently diagnosed with HIV and immediately treated with contemporary ART regimens. Additionally, we were unable to analyze the impact of frailty on both outcomes in HIV-negative participants only, as the number of frail HIV-negative participants was low, and the number of outcomes even lower.

The strengths of our study are the longitudinal prospective design, the extensive and standardized data collection, and the highly comparable HIV-negative control group. This allowed us to investigate the association between frailty and mortality and incident comorbidity in both HIV-positive and negative participants, controlling for a wide set of possible mediators and confounders. Additionally, the majority of self-reported diagnoses could be validated by review of medical charts, and other comorbidities were based on objective clinical, physiologic, or laboratory data.

Conclusions

Frailty was a strong predictor of mortality and incident comorbidity in this predominantly middle-aged HIV-positive population which, although aging, would not yet be considered of geriatric age. Moreover, frailty impacted the risk of these adverse outcomes independently from other recognized risk factors. PLWH are known to develop frailty and age-associated comorbidities both more frequently and at a younger age. Implementing a frailty assessment in HIV care and clinical trials could therefore be useful for improving risk stratification and clinical management and preventing adverse health outcomes in this high-risk population. Furthermore, evidence suggests that once identified as being frail, sustained physical activity may improve the frailty score among elderly persons [31]. Future studies should investigate if such interventions may similarly modify the frailty phenotype in aging PLWH to reduce their risk of morbidity and mortality.

Supplementary Data

Supplementary materials are available at *The Journal of 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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