Frailty is an independent risk factor for mortality, cardiovascular disease, bone disease and diabetes among aging adults with HIV

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Summary:
Among persons with HIV, frailty is associated with risk for cardiovascular disease, diabetes mellitus, and bone disease. An increase in frailty is associated with mortality. Frailty assessments as part of standard HIV care may help in chronic disease risk stratification.

Abstract

Background: We characterized associations between frailty and incidence of cardiovascular disease (CVD), diabetes mellitus (DM), bone disease and mortality within a cohort of aging persons with HIV (PWH).

Methods: Participants underwent frailty evaluations using the Fried's frailty assessment at baseline and then annually. Frailty was defined as having ≥3 frailty criteria. Clinical outcomes of mortality, incident CVD events, DM, and bone disease events were recorded throughout the study period (baseline to most recent study or clinic visit, or date of clinical outcome occurrence, whichever came first). Poisson regression models evaluated associations between baseline frailty, change in frailty score over 48 weeks, and each clinical outcome.

Results: Among 821 men and 195 women (median age 51 years), 62 (6%) were frail at baseline. Frailty scores increased in one or more components among 194 participants (19%) from baseline to 48 weeks. Baseline frailty was associated with an increased risk of incident CVD and DM with a trend towards a significant association with incident bone events. Among the components of frailty, slow gait speed was associated with incident DM and borderline-associated with incident CVD. An increase in frailty from baseline to week 48 was associated with mortality, but not with the other clinical outcomes.

Conclusions: Baseline frailty was associated with multiple adverse health outcomes (incident CVD, DM and bone disease), while increase in frailty score was associated with mortality among PWH engaged in care. Incorporation of frailty assessments into the routine care of PWH may assist in improvement of functional status and risk stratification for age-related chronic diseases.

Key Words: HIV; Frailty; Chronic Diseases; Mortality

Introduction:

As potent antiretroviral therapy (ART) has markedly improved survival of persons with HIV (PWH) [1], chronic age-related diseases have emerged as predominant causes of death among ART-treated persons [2]. These conditions disproportionally affect aging PWH and include cardiovascular disease (CVD), metabolic diseases, and bone demineralization [3-5]. Further compromising health among aging PWH is frailty, a syndrome of dysregulation of multiple biologic systems that leads to physical weakness and functional decline. Frailty prevalence increases with age after age 65 in the general population [6], however it has been observed to occur up to a decade earlier among PWH [7] and is associated with excess burden of mortality and morbidity [8]. The frailty phenotype is a constellation of age-related symptoms that is associated with multiple adverse health consequences; previous studies have demonstrated an association between frailty and risk of poor health outcomes among PWH (such as neurocognitive impairment, falls, and disability) [9-11], however the role of frailty as a predictor for subsequent development of specific age-related chronic diseases in this population is poorly understood. In this report, we sought to ascertain associations between baseline frailty and changes in frailty over 48 weeks with clinical outcomes including mortality, incident CVD, diabetes mellitus (DM) and bone disease. We postulated that frailty is positively associated with the occurrence of non-fatal disease-specific clinical events and mortality, and may therefore serve as a clinical predictor for these events.

Methods:

Study population:

AIDS Clinical Trials Group (ACTG) A5322 (HAILO: The HIV Infection, Aging, Immune Function Long-Term Observational Study) is an ongoing, observational study of 1035

older PWH (age ≥40 years at enrollment) that longitudinally evaluates associations between antiretroviral therapy, aging and inflammation with incidence of non-AIDS clinical events, mortality and functional status. Participants were recruited from a previous United States longitudinal cohort, ACTG Longitudinal Linked Randomized Trials (ALLRT), which enrolled participants between 2000 and 2007 who were followed through 2013 [12]. HAILO participants were enrolled in 2013-2014; the 1016 participants who had a baseline frailty assessment are included in this analysis. Study visits for HAILO participants occur semiannually with medication review, chart abstractions, plasma/serum collection, fasting laboratory tests, and falls interview. Frailty assessments, body measurements, neurocognitive evaluations, additional specimen collection, and questionnaires regarding substance use, sexual behavior, insurance status and Instrumental Activities of Daily Living (IADLs) are performed annually.

Frailty assessment:

Frailty was assessed among all participants using the Fried's frailty assessment [6]. As previously described, the assessment includes the 5 components of weak grip, slow gait speed on a 4-meter walk, and self-reported weight loss, exhaustion, and limitations in ability to undertake vigorous physical activity [13]. Frailty at baseline (time of HAILO entry visit) was evaluated, and participants were categorized as frail if they met 3-5 criteria, pre-frail if they met 1-2 criteria, or non-frail if they did not meet any criteria. Change in frailty was defined as ≥1 component increase in frailty (versus no change or a decrease in frailty; separate assessment of decrease in frailty was not possible due to small numbers) from baseline to week 48.

Clinical outcomes:

We included clinical events that occurred after the baseline frailty assessment. Individuals with prevalent disease (any history of a diagnosis prior to baseline) with the

exception of bone disease (for this outcome, history of bone disease was evaluated as a potential confounder) were excluded. CVD included coronary artery disease (with or without revascularization surgery), myocardial infarction, stroke/transient ischemic attack, angina, peripheral arterial disease, cardiomyopathy/heart failure, arrhythmia, deep vein thrombosis, and pulmonary embolism. Diabetes was defined as use of diabetic medication, hemoglobin A1c ≥6.5%, or a medical diagnosis of diabetes, and bone disease included fracture, avascular necrosis, osteopenia, or osteoporosis. Mortality was defined as death due to any cause.

Demographic, behavioral and clinical factors considered as confounders:

All covariates were assessed at baseline unless otherwise indicated. Race/ethnicity was categorized as black (non-Hispanic), white (non-Hispanic), Hispanic/other, age as 40-49, 50-59, and ≥60 years, sex as male or female. Education level was categorized as "did not complete high school", "completed high school", or "completed education beyond high school". Self-reported smoking was categorized as "never smoker", "former smoker", or "current smoker". Alcohol use assessment included a categorical variable for binge drinking (≥5 drinks for men, ≥4 for women within a 2-hour period), categorized as "no drinking", "no binging drinking", "binge drinking once/month", and "binge drinking more than once/month". A separate variable for self-reported frequency of alcohol use was categorized as "no drinking", "light/moderate drinking" (1-14 drinks/week for men, 1-7 drinks/week for women, and no binge drinking), or "heavy drinking" (>14 drinks/week for men, >7 drinks/week for women, or binge drinking). Physical activity was defined as ≥ 3 days of moderate or vigorous activity per week. Body mass index (BMI) was categorized as underweight (BMI: <18.5 kg/m^2), normal (BMI: 18.5 - <25 kg/m^2), overweight (BMI: 25-30 kg/m^2), and obese (BMI: >30 kg/m^2). Waist circumference was categorized as low (≤94cm for men, ≤80cm for women), high (>94cm for men, >80cm for women), or unknown.

Hypertension was defined as use of anti-hypertensive medications or diagnosed hypertension. Hyperlipidemia was defined as any of the following: use of lipid-lowering medications, diagnosis of hyperlipidemia, or laboratory values consistent with hyperlipidemia (low-density lipoprotein [LDL] ≥ 160 mg/dL, total cholesterol ≥ 200 mg/dL, or triglycerides ≥ 200 mg/dL). HIV-related characteristics considered included CD4 T-lymphocyte cell count/mm^3 (CD4) at time of ART initiation and at baseline, plasma HIV-RNA level at time of ART initiation, and proportion of time under observation prior to baseline with HIV RNA level <200 copies/mL. ART exposure-related factors included duration of ART, whether or not the participant remained on their initial, randomized ART regimen, history and duration of protease inhibitor (PI) use, and history and duration of tenofovir disoproxil fumarate (TDF) use. Likely HIV transmission route was categorized as injection drug use, men who have sex with men (MSM), heterosexual sex, or other/unknown (assessed at enrollment into initial clinical trial). Hepatitis C virus (HCV) infection was defined by a positive HCV serology. History of CVD, non-AIDS defining cancers, AIDS-defining events, liver disease, renal disease, bone disease, diabetes, family history of CVD, family history of diabetes, and depression were also considered as potential confounders for specific outcomes.

Statistical Analysis:

For each clinical outcome, we calculated overall rates per 100 person-years and their 95% confidence intervals using exact Poisson confidence limits. Follow-up time was time from baseline to date of the most recent visit, last clinic date for off-study participants, or date of clinical outcome, whichever occurred first.

Separate Poisson regression models were used to estimate the associations between frailty and each clinical outcome. For each frailty-outcome model, we made the *a priori* decision

to force variables into the model that are known strong risk factors for the outcome (Figure 1). We then proceeded to assess other covariates as potential confounders. Each covariate was added individually into the model including frailty and the variables that were included *a priori*. Covariates that changed the effect estimate by ≥10% were kept in the final multivariable model. After fitting the final multivariable model for baseline frailty and the clinical outcome, we replaced frailty with (a) grip and (b) walk speed.

The same model-building procedures were used to evaluate the association between frailty change from baseline to week 48 and each clinical outcome. For this evaluation, we included clinical events that occurred after the second frailty assessment at week 48. All participants lost to follow up or who experienced the clinical outcome before week 48 were excluded (with the exception of bone disease, where history of bone disease prior to week 48 was evaluated as a potential confounder). While physical activity at baseline was not included as a potential confounder in any of the evaluations of baseline frailty and clinical outcomes (since frailty at baseline may be affected by physical activity), baseline physical activity was evaluated as a potential confounder when evaluating change in frailty from baseline to week 48.

We also summarized the time to event in months for each outcome to examine whether any outcomes occurred close to the time of the frailty assessment.

Results:

Among 821 men and 195 women, 48% were white, non-Hispanic and 46% were between 40-49 years of age at study entry. The majority (926, 91%) were virally suppressed (HIV RNA <50 copies/mL) at baseline with a median baseline CD4 of 621 cell/μL. With the exception of seven participants, all were taking antiretroviral therapy upon study entry (five of those seven started antiretroviral therapy after study entry). Participant demographic and clinical

characteristics are shown in Table 1. At baseline, 390 (38%) were pre-frail and 62 (6%) frail. Frailty scores increased in one or more components among 194 (19%) participants from baseline to 48 weeks; among these participants, increases in the following frailty components were observed: weight loss (N=22), low physical activity (N=53), exhaustion (N=72), grip weakness (N=80), slow gait speed (N=26).

Median length of follow-up was 4.0 years (interquartile range = 0.3 years). Twenty-seven participants died during follow up; the median time from their first frailty assessment to death was 22.8 months. The highest event rate was observed for diabetes with 84 events (incidence rate per 100 person-years: 2.58 [95% CI 2.06 – 3.19]), followed by bone disease with 61 events (incidence rate per 100 person-years: 1.65 [95% CI 1.26 – 2.12]), CVD with 43 events (incidence rate per 100 person-years: 1.23 [95% CI 0.89 – 1.66]) and death with 27 events (incidence rate per 100 person years: 0.7 [95% CI 0.46 – 1.02]). Median time from first frailty assessment to incident diabetes was 23.0 months, median time to bone disease event was 23.3 months, and median time to incident CVD event was 21.1 months.

As shown in Figure 1, in the multivariable analyses, baseline frailty was associated with an increased risk of incident CVD (Incidence Rate Ratio [IRR] 3.83 [1.59-9.23], p=0.003) and incident diabetes (IRR 2.29 [1.03-5.10], p=0.04), with a trend towards a significant association with incident bone events (IRR 2.31 [0.96 – 5.52], p=0.06). Among the components of frailty, slow gait speed was associated with incident diabetes (IRR 1.61 [1.05-2.46], p=0.03) and borderline-associated with incident CVD (IRR 1.85 [0.97-3.49], p=0.06), but was not associated with bone events. Grip strength was not significantly associated with any of the clinical outcomes.

An increase in frailty from baseline to week 48 was significantly associated with mortality (IRR 3.78 [1.52-9.39], p=0.004), but was not associated with incident CVD, diabetes, or bone events (Table 2). Baseline pre-frailty was not significantly associated with any of the clinical outcomes.

Discussion

In this large, well-characterized cohort of PWH, the vast majority of whom were virally suppressed with CD4 count >600 cells/μL, the presence of frailty at study entry was associated with greater risk for subsequent incident CVD, diabetes, and bone disease independent of traditional risk factors for such diseases, while increase in frailty over 48 weeks was associated with increased risk for death. Furthermore, the objective frailty component of slow gait, a strong predictor of mortality among older adults without HIV [14], was associated with incident diabetes and CVD (borderline), but not with mortality or bone disease event. These observations illustrate an intimate relationship between frailty, a marker of vulnerability and physiologic dysregulation, with the development of age-related chronic diseases and death among middle-aged and older PWH.

The occurrence of the frailty phenotype prior to clinical disease onset suggests that frailty is associated with the development of these chronic diseases in our cohort. The detrimental impact of frailty on many subsequent poor health outcomes (including falls, hospitalization, disability, and mortality) has been well-described among both PWH and in the general population [9-11, 15-22]. Increases in frailty score have also been shown to be associated with increased mortality risk in the general population [23], so our observed mortality association is not unexpected. Nonetheless, since PWH have a higher prevalence of frailty and progress to

frailty faster than persons in the general population [7, 24], our observation underscores a potentially greater risk of mortality consequent to frailty among PWH.

Prior studies evaluating associations between frailty and risk of chronic diseases, however, have reported variable results. Among the general population, frailty (as well as pre-frailty) has been found to be independently associated with an increased risk of CVD [25, 26], with slow gait speed, or variations of it, also associated with this increased risk [26, 27]. In the Multicenter AIDS Cohort Study (MACS), frailty was associated with subclinical atherosclerosis in men without HIV but not PWH. An association between higher frailty score and CVD was suggested in a prior cross-sectional analysis of our cohort [13], however this association was not statistically significant in the final multivariable model. In this current, prospective analysis, the association between baseline frailty and risk of incident CVD, as well as the borderline association between slow gait speed and risk of incident CVD, among PWH appears to increasingly corroborate findings observed in the general population.

The association between frailty and DM is less clear. Insulin resistance and/or DM have been identified as an antecedent to frailty among elderly persons without HIV as well as PWH, but not *vice versa* [28-30]. Our current finding of frailty (and specifically slow gait speed) as an independent risk for incident DM presents an opposing sequence of events, further underscoring the multifarious relationship of frailty to age-related changes in physiologic processes. Frailty as a predictor of fracture, conversely, has also been widely demonstrated in the general population and PWH [20, 31, 32], and our findings are consonant with these associations. Despite the low number of clinical events and relatively low prevalence of frailty (6%) in our cohort, the significant impact of frailty on risk of several chronic diseases and mortality within a single cohort is noteworthy. Further, our cohort has a high rate of durable viral suppression, which

renders our observed associations between frailty and age-related, chronic diseases clinically relevant and generalizable to virally-suppressed PWH in clinical care. Another strength of this analysis is that our population was recruited from a well-characterized cohort with at least several years of prior clinical data available, optimizing accuracy in our clinical and HIV-specific variables.

While our findings suggest that baseline frailty can precede certain chronic diseases among PWH, they do not establish a causal pathway between frailty and chronic disease development. Pathophysiologic mechanisms may exist, however, that are common to both. Similar to the widely-studied associations between chronic immune activation and inflammation as contributors to specific chronic diseases among PWH, elevations in levels of multiple systemic markers of inflammation have been associated with the development of frailty among PWH [33-37]. Indeed, levels of specific markers of inflammation associated with CVD among PWH, such as interleukin-6 (IL-6), high sensitivity C-reactive protein (hsCRP), sCD14 and sCD163 have been independently associated with frailty [33, 35, 37-40]. Inflammation associated with frailty and age-related chronic disease may be particularly relevant to PWH, since increased inflammation is fundamental to HIV pathophysiology. Additionally, accelerated sarcopenia and adiposity can occur in the setting of HIV [41], which may consequently contribute to sedentary lifestyle, thereby hastening metabolic derangements (such as insulin resistance) and contributing to chronic disease development. Functional impairments characteristic of frailty can further compound this process. These are especially important considerations in risk stratification for certain diseases, as traditional screening tools, such as the American College of Cardiology/American Heart Association (ACC/AHA) pooled cohort equation and the FRAX score, under-predict disease-specific clinical events for PWH [42, 43].

Our findings support the utility of frailty assessments in the standard health maintenance of aging PWH. This may serve as a simple yet high-impact predictor of chronic, age-related diseases and better inform current predictive risk models, however further investigation is needed to determine optimal strategies to incorporate use of frailty scores in chronic disease risk stratification. Once identified, frailty development may be halted or reduced by physical activity training; such progams have been shown to increase strength, balance and physical activity among elderly HIV-negative participants, ultimately leading to reduction in frailty [44-46]. For aging PWH, structured exercise programs have been shown to improve weight, strength, and cardiorespiratory fitness, and even reduce the number of frailty criteria [47, 48]. Such interventions are low-risk and, at minimum, may improve health outcomes directly consequent to frailty.

Limitations to our work exist. While our median age of 51 is consistent with the median age of PWH in the United States, our outcomes may not be generalizable to younger PWH. The majority of HAILO participants are durably virally suppressed and compliant with healthcare and research participation. Our study results may therefore not be generalizable to individuals with intermittent virologic non-suppression or gaps in care. We observed a small number of deaths relative to the other outcomes in our study, therefore our analysis may have been underpowered for the mortality outcome. In our final regression models, we adjusted for covariates known to be traditionally strong risk factors for each outcome of interest. It is possible, however, that there exist other risk factors we did not consider, which may have resulted in unmeasured confounding. Further, the self-reported nature of smoking and other substance use, as well as family history of specific diseases, may have led to underrerporting of these entities. Three components of the frailty evaluation (weight loss, exhaustion and low

physical activity) require subjective reporting and may, in part, be consequent to clinical HIV infection itself rather than age-related frailty. Ascertaining HIV-induced functional declines, which may imply reversibility with optimization of HIV care (versus frailty associated with factors other than HIV), should be attempted when assessing frailty among PWH.

In summary, we found that the presence of frailty and increases in frailty scores over time among treated, virally-suppressed PWH preceded multiple chronic disease-specific events and mortality. Routine incorporation of annual frailty assessments in the care of PWH (perhaps beginning as early as the sixth decade of life) can enhance the characterization of age-related functional declines, and may thereby aid in risk stratification for the development of age-associated chronic diseases. Further, frailty may comprise a modifiable target for interventions aimed at improvement of functional status and, potentially, co-morbidity avoidance.

Author contributions:

All authors contributed to study design, data interpretation, manuscript revision, and approved of the final draft. KW and KT performed the data analysis. SGK and FLP prepared the initial manuscript.

Acknowledgements:

We wish to thank all study volunteers of A5001 (ALRRT) and A5322 (HAILO), the ACTG clinical units, and the ACTG.

Disclaimer:

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

Funding:

Research reported in this publication was supported by the National Institute of Allergy and Infectious Diseases of the National Institutes of Health under Award Number UM1 AI068634, UM1 AI068636 and UM1 AI106701.

Potential conflicts of interest:

K. M. E. has received grant support from Gilead Sciences and serves on an advisory panel for ViiV. S. L. K. has received grant support from Gilead Sciences. F. J. P. is a consultant and/or on the speakers bureau for Gilead Sciences, Janssen Pharmaceuticals, Merck and Co. and ViiV. All other authors report no potential conflicts of interest.

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Table 1: Demographic and clinical characteristics of study participants

Characteristic		Total (N=1016)
Age at baseline, years	Median (Q1, Q3)	51 (46, 56)
	<50	446 (44%)
	50-59	412 (40%)
	≥ 60	158 (16%)
Sex	Male	821 (81%)
	Female	195 (19%)
Race/Ethnicity	White, non-Hispanic	486 (48%)
	Black, non-Hispanic	300 (29%)
	Hispanic+other	230 (23%)
Education level	<High school	152 (15%)
	High school	223 (22%)
	>High school	641 (63%)
Frailty status	Non-frail	564 (56%)
	Pre-frail	390 (38%)
	Frail	62 (6%)
4-meter walk time (seconds) at baseline	≤4 seconds	602 (59%)
	>4 seconds	414 (41%)
Weak grip at baseline		224 (22%)
BMI category at baseline	Underweight	6 (1%)
	Normal	324 (32%)
	Overweight	394 (39%)
	Obese	292 (28%)
Likely route of HIV transmission	IDU	33 (3%)
	MSM	607 (60%)
	Heterosexual	301 (30%)
	Other/Unknown	75 (7%)
HIV RNA at baseline (copies/mL)*	<50	926 (91%)
	≥50	87 (9%)
Proportion of time with HIV RNA <200 copies/mL before baseline	≤75%	185 (24%)
	>75%	602 (76%)
CD4 count at baseline (cells/μL)	Medan (Q1, Q3)	621 (452, 827)
Smoking status at baseline	Never	415 (41%)
	Prior smoker	344 (34%)
	Current smoker	257 (25%)
Diabetes history at baseline		113 (11%)
Family history of diabetes at baseline		381 (38%)
History of CVD at baseline		68 (7%)
Family history of CVD at baseline		312 (31%)
History of hypertension at baseline		599 (59%)

Characteristic		Total (N=1016)
History of hyperlipidemia at baseline		880 (87%)
Days of vigorous/moderate activities per week at baseline**	<3 days	454 (45%)
	≥3 days	506 (50%)
History of bone disease at baseline		181 (18%)

IDU = Intravenous drug use; MSM = Men who have sex with men; CVD = Cardiovascular disease

*3 individuals (0%) missing baseline HIV RNA information

**56 individuals (6%) missing physical activity information

Table 2: Multivariable associations between frailty change from baseline to week 48 and incident events

		Change in frailty score from baseline to week 48 (≥1 vs ≤ 0)*	
Event type	**Number of events**	**IRR [95% CI]**	**P-value**
Cardiovascular disease	26	1.16 [0.47, 2.84]	0.8
Diabetes	51	1.00 [0.48, 2.06]	>0.9
Bone Disease	45	1.27 [0.64, 2.50]	0.5
Death	19	3.78 [1.52, 9.39]	0.004

*Model for CVD adjusted for age, family history of CVD, history of diabetes, smoking, hypertension and hyperlipidemia.

*Model for diabetes adjusted for family history of diabetes, age, race/ethnicity and BMI.

*Model for bone disease adjusted for age and physical activity.

*Model for mortality adjusted for sex, age and physical activity.

Figure 1: Multivariable associations between baseline frailty, grip strength, gait speed and rates of incident events

CVD = Cardiovascular disease

*Slow gait speed is defined as >4 seconds for 4-meter walk.

Each panel summarizes 3 separate multivariable models: (1) Frail/pre-frail and incident event, (2) Grip strength and incident event, (3) Walk speed and incident event

Model for CVD adjusted for route of HIV transmission, with age, history of diabetes, smoking, hyperlipidemia, and hypertension and family history of CVD forced in as covariates.

Model for diabetes with age, race/ethnicity, family history of diabetes, BMI and hyperlipidemia forced in as covariates

Model for bone disease with age forced in as a covariate.

Model for mortality adjusted for sex, history of diabetes and route of HIV transmission, with age forced in as a covariate.