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Frailty Predicts Fractures among Women with and At-risk for HIV: Results from the Women's Interagency HIV Study

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Abstract

Objective: To determine associations between frailty and fracture in women with and without HIV infection.

Design: Prospective longitudinal cohort study evaluating associations between baseline frailty status and frailty components, with first and second incident fractures.

Methods: We evaluated associations of frailty with fracture among 1332 women with HIV and 532 uninfected women without HIV. Frailty was defined as ≥3 of 5 Fried Frailty Index (FFI) components: slow gait, reduced grip strength, exhaustion, unintentional weight loss, and low physical activity. Cox proportional hazards models determined predictors of time to first and second fracture; similar models evaluated FFI components.

Results: Women with HIV were older (median 42 vs. 39 yr, p<0.0001) and more often frail (14% vs. 8%, p=0.04) than women without HIV; median follow-up was 10.6 years. Frailty was independently associated with time to first fracture in women with and without HIV combined [adjusted hazard ratio, (aHR) 1.71, 95%CI: 1.30–2.26; p=0.0001], and among women with HIV only (adjusted hazard ratio, aHR 1.91, 95%CI: 1.41–2.58; p<0.0001), as well as with time from1st to 2nd fracture among women with HIV (aHR 1.86, 95% CI: 1.15 – 3.01; p=0.01).

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Conclusions: In this cohort of middle-aged racial and ethnic minority women with or at-risk for HIV, frailty was a strong and independent predictor of fracture risk. As women with HIV continue to age, early frailty screening may be a useful clinical tool to help identify those at greatest risk of fracture.

Keywords

Frailty; fracture; HIV; aging; women

INTRODUCTION

As life-expectancy increases for people living with HIV (PLWH) receiving effective antiretroviral therapy (ART), the number of older PLWH has expanded greatly.[1–3] The Centers for Disease Control estimates that currently 45% of PLWH in the US are >50 years old. As PLWH age, they experience an excess burden of non-AIDS comorbidities at younger than expected ages,[4,5] including cognitive impairment,[6–8] osteoporosis,[9] and geriatric syndromes such as frailty, falls, and fractures.[10,11] It is estimated that PLWH have over 3 times the risk of osteoporosis and almost 7 times the risk of osteopenia compared with their uninfected counterparts,[9] and several large cohort studies have found a higher fracture incidence in PLWH compared with uninfected persons.[12–14] We previously reported that middle-aged women with HIV had higher fracture incidence than women without HIV over a 10 year follow up period in the Women's Interagency HIV Study (WIHS).[13] As women with HIV age and transition through menopause, their risk of sustaining a fracture is expected to further increase.

Frailty, a geriatric phenotype characterized by diminished strength, endurance, and reduced physiologic function, is associated with numerous adverse outcomes among the elderly HIV-uninfected persons, including falls, fracture, disability, and death.[15–17] Frailty occurs with greater frequency among women than in men[15,18–21] and with increasing age;[15,19,22] moreover, associations between mortality and frailty are stronger among older women than men.[18,23,24] Among WIHS women with HIV, frailty is common and is associated with low CD4+ count and AIDS diagnoses.[25,26] Although frailty predicts recurrent falls and death in middle-aged PLWH,[27–30] the relationship between frailty and fracture risk among PLWH remains unknown.

We undertook this study to determine the association between frailty status and incidence of first and second fractures among middle-aged women with or at-risk for HIV enrolled in the WIHS, including the specific contribution of individual components of the Fried Frailty Index (FFI) on fracture risk.

METHODS

Study Population

The WIHS is an ongoing, multicenter cohort study of the natural and treated history of HIV infection in women, which initially enrolled women with and at risk for HIV infection at six consortia (Bronx/Manhattan NY, Brooklyn NY, Chicago IL, Washington DC, San Francisco

CA, and Los Angeles, CA) in 1994–95, and subsequently in 2001–02 and 2011–12, and four Southern U.S. sites were added in 2013. WIHS methods have been described previously.[31, 32] Women without HIV were recruited from groups at high risk for HIV infection, and are comparable to participants with HIV for a wide array of characteristics, including drug use, history of chronic illness, perceived health status, reproductive history and income.[33] At semiannual visits, participants complete face-to-face interviews and physical examinations, and provide biological specimens. Written informed consent was obtained from each participant using procedures approved by committees on human research at all of the collaborating institutions.

Study Sample

Starting in 2003 (visit 18), all WIHS participants were asked about personal history of fracture of the hip, wrist and spine, both ever and within the prior 6 months. Of 3766 participants enrolled, 2393 had at least one additional study visit after the introduction of the fracture questionnaire, and 18 participants who seroconverted during follow up were excluded; 1713 women with HIV and 662 women without HIV remained. In 2005, measures to determine the frailty phenotype were added to WIHS.[15] Participants from the original 6 study sites who completed at least 3 of 5 measures of FFI components were included in this analysis. Because we were interested in prediction of incident fractures, 125 women (88 with HIV and 37 without HIV) with history of fracture prior to index visit were excluded from analyses. Compared with the study population included, women excluded due to history of prior fracture were more likely to be frail (18% of women excluded vs. 12% included, p=0.03), and to have frailty components of weight loss, low physical activity, and exhaustion. They were also more likely to be white, to smoke, and to use illicit substances including ever cocaine and opiates.

The current study sample includes 1332 women with HIV and 534 women without HIV who completed frailty measures in 2005 as well as fracture questionnaires. For the purposes of analyses, the visit in which frailty was measured is considered the index visit.

Fracture Ascertainment and Definitions

Among women reporting fracture, fracture type was classified as fragility (resulting from fall from standing height or less) or non-fragility. At each subsequent semi-annual study visit, participants reported fractures of the hip, wrist, spine and/or other site since their last visit. Two investigators reviewed and adjudicated all self-reported fractures, and excluded non-fractures. We considered all fractures (fragility and non-fragility combined) as study outcomes given recent data that high-trauma fractures are associated with lower bone mineral density and are similar to fragility fractures in predicting future fractures.[34] This analysis includes fracture data from semiannual observations from April 2005 (visit 22) through September 2016 (visit 44).

Frailty Definition

Frailty was defined according to a modified FFI, which has been utilized in numerous population based studies and cohorts including the WIHS,[15,25,26] and is based on the presence of three or more of five characteristics: slow gait, reduced grip strength,

exhaustion, unintentional weight loss of 10 pounds within 6 months, and low physical activity. Exhaustion was defined by responding “Yes” to the following question: “During the past four weeks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra efforts?)” Low physical activity was defined by responding “Yes” to the following question: “Does your health now limit you in vigorous activities, such as running, lifting heavy objects, or participating in strenuous sports?” Unintentional weight loss was defined by responding “Yes” to the following question: “Since your last visit, have you had unintentional weight loss of at least 10 pounds?” Gait speed was measured using a 3–4 meter timed gait. Grip strength was measured using a hand-held dynamometer with maximum force using the participant’s dominant hand. Slow gait and reduced grip strength were defined as the lowest quintile of performance by site among HIV-seronegative women; exhaustion, weight loss, and physical activity were based on self-report.[25,26]

Statistical analyses

Means, medians, standard deviations, interquartile ranges, and proportions summarized continuous or categorical study variables. The primary outcome was time from index visit to first self-reported fracture event, defined as any fracture (fragility or non-fragility) at any body site. Incidence rates were calculated as the number of participants with a new fracture divided by the total time in person-years (py) at risk for new fracture during the study period. The initial visit in which frailty was assessed was considered the start time; the end of follow-up was either the visit at which the first fracture event was observed or, if no fracture was observed, the last visit prior to October 2016 censored time to first fracture for each participant. For women reporting multiple fractures, additional analyses of time from first to second fracture were performed, with the start point from time from first to second fracture being the date of first fracture, and the end time being the earliest of date of second fracture and last visit prior to October 2016 with second fracture being censored in the later case.

Demographics were measured at WIHS enrollment. Other covariates were time invariant and measured at the index visit. Previously identified prognostic factors for fracture[35] were candidate covariates: age, menopause (no menses for greater than one year), personal history of fracture, parental history of hip fracture, body mass index (BMI, in kg/m^2), race/ethnicity, current cigarette smoking, 14 or more alcoholic drinks per week, ever glucocorticoid use, and history of other causes of secondary osteoporosis. In addition, we obtained: history of diabetes; current calcium or multivitamin use; any use of injection drugs (IDU), opiates or cocaine, statins, hormonal contraception, or hormone replacement therapy; and estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD).[36] Chronic hepatitis C virus (HCV) status was determined at study entry by the presence of HCV seropositivity and detectable HCV RNA level. HIV-specific variables included: current and nadir CD4+ lymphocyte counts, history of AIDS-defining illness (ADI), protease inhibitor (PI)-based ART before or at index visit, tenofovir (TDF) use before or at index visit, other ART use before or at index visit (excluding PIs and TDF), and cumulative ART exposure, as well as cumulative exposure to PIs or TDF from initiation, whether before or after enrollment into WIHS, to either last visit or fracture event.

Proportional hazards models were constructed to determine predictors of first fracture incidence, and separate models determined predictors of subsequent second fracture incidence, among women with one fracture. Bivariate analyses evaluating each predictor in association with the outcome were considered for all participants together, and for women with HIV separately. All variables were entered into multivariate models and a stepwise selection strategy with a two sided p-value of ≤0.05 used to determine which variables remained in the final model. A two sided p-value ≤0.05 was considered statistically significant in other analyses. HIV status and frailty were forced into models that evaluated the association between FFI and time to fracture. In analyses of frailty components and time to fracture, only HIV status was forced into models, and frailty components were allowed to enter models and retained if they met the stepwise selection criteria. Separate multivariate models restricted to women with HIV were constructed using similar methodology to allow assessment of HIV disease severity measures and effects of ART on the relationships between frailty and fracture.

RESULTS

Participant characteristics at index visit

Table 1 presents participant characteristics at the index visit. Women with HIV were older, more likely to use statins, had lower BMI, and were more often HCV-infected or postmenopausal. Women with HIV were also less likely than women without HIV to report history of cocaine use, heavy alcohol consumption, or current smoking. At index visit, among 1332 women with HIV, 42% reported a prior ADI; 67% reported current PI-based ART, 43% reported current use of TDF, and 47% reported current ART containing neither PI nor TDF. Women with HIV were more likely to be frail (14%) compared to women without HIV (8%), (p=0.0006), and were more likely to have slow gait, reduced grip strength, and report exhaustion, weight loss, and low physical activity (all p<0.01, Table 1).

Incident Fractures

We previously published on the 10-year fracture incidence in WIHS, in which unadjusted incidence rates of fracture at any site were higher in women with HIV than women without HIV (2.19/100py vs. 1.54/100py, p=0.002).[13] In the current study period, 20% (n=1072) of women with HIV reported a fracture, including 14% (n=181) with one fracture and 6% (79%) with 2 or more fractures; among uninfected women, 15% (n=452) reported fracture, including 10% (n=56) with one fracture and 5% (n=26) with 2 or more fractures during the study period.

Association between Frailty and Time to Fracture among Women with and without HIV

HIV was significantly associated with quicker time to first fracture in multivariate models (adjusted Hazards Ratio, aHR1.32, 95% Confidence Interval, CI: 1.02 – 1.70, p=0.035), but not with time from first to second fracture (Table 2). Frailty was significantly associated with both quicker time to first fracture (aHR 1.71, 95%CI: 1.30–2.256, p=0.0001) and quicker time from first to second fracture (aHR 1.69, 95%CI: 1.09–2.62, p=0.019). Other factors associated with faster time to first fracture included older age, white race, current

smoking, ever use of cocaine, and ever use of opiates. Postmenopausal status was associated with faster time from first to second fracture in multivariate models (Table 2).

Association between Frailty Components and Incident Fractures in Women with and without HIV

In models assessing relationships between frailty components and fracture incidence, HIV status was not significantly associated with time to fracture. Exhaustion (aHR 1.60, 95%CI: 1.26–2.04, p=0.0001), unintentional weight loss (aHR 1.44, 95%CI: 1.06–1.94, p=0.019), and reduced grip strength (aHR 1.35, 95%CI: 1.06–1.72, p=0.017), were significantly associated with faster time to first fracture (Table 3). Self-reported exhaustion was the only frailty component associated with time from first to second fracture (aHR 1.98, 95% CI: 1.34–2.93, p=0.0007).

Relationship between Frailty, Frailty Components, and Fracture among Women with HIV

In multivariate analyses limited to women with HIV, frailty was significantly associated with faster time to first fracture (aHR 1.91, 95%CI: 1.41–2.48, p<0.0001) and time from first to second fracture (aHR 1.86, 95%CI: 1.15–3.01, p=0.01) (Table 4). Current smoking, ever use of opioids, and white race were associated with faster time to first fracture among women with HIV. Postmenopausal status was associated with faster time to second fracture among women with HIV, whereas undetectable HIV viral load (aHR 0.49, 95%CI: 0.31–0.77, p=0.002) was associated with longer time from first to second fracture.

In analyses of frailty components, exhaustion (aHR 1.57, 95%CI: 1.20–2.07, p=0.0012), unintentional weight loss (aHR 1.44, 95%CI: 1.03–2.01, p=0.032), and reduced grip strength (aHR 1.36, 95%CI: 1.03 – 1.79, p=0.028) were associated with faster time to first fracture; exhaustion (aHR 2.22, 95%CI =1.40–3.53, p=0.0007) and postmenopausal status were associated with faster time from first to second fracture, and undetectable HIV viral load (aHR 0.47, 95%CI: 0.29–0.74, p=0.001) was associated with longer time to second fracture (Table 5).

DISCUSSION

In this cohort of middle-aged, racial and ethnic minority women with or at-risk for HIV, frailty was a strong and independent predictor of fracture risk. Frailty status was associated with 70% greater hazard of first fracture and second fracture among women after first fracture. While HIV status was also independently associated with first fracture, frailty carried twice the fracture risk as did HIV serostatus. Among women with HIV, frailty remained a strong and independent predictor of fracture, and was associated with almost double the hazard of first fracture and second fracture. Of frailty components, self-reported exhaustion and unintentional weight loss, as well as reduced grip strength, independently predicted first fracture incidence among the full WIHS cohort as well as among women with HIV, whereas only exhaustion was independently predictive of subsequent fracture. Ours is the first study to characterize the long-term relationship of frailty and its components with fracture among PLWH, and particularly among women with or at risk for HIV.

While many frailty indices have been utilized in research settings, the WIHS defines frailty using a modified version of the widely used FFI, based on data from the Cardiovascular Health Study (CHS).[15] The FFI has been associated with adverse outcomes in PLWH ≥65 years of age, including falls, hospitalization, disability, and mortality,[15] and has also been shown to predict mortality in middle-aged PLWH including men initiating ART,[29]and women on ART in WIHS,[28] as well as to predict falls in PLWH.[30] Among male veterans with HIV, the Veterans Aging Cohort Study (VACS) index was associated with fracture risk, as were some VACS index components- specifically age, log HIV RNA, and hemoglobin level.[37] The VACS index utilizes demographic information and laboratory measures routinely assessed in the clinical care of PLWH, and has been previously associated with all-cause mortality, hospitalization, medical intensive care unit admission, and functional performance in PLWH.[38–40] Because of its documented association with outcomes associated with frailty, the VACS Index might be conceptualized as a marker of physiologic frailty, as well as a proxy for severity of illness; however the VACS Index was not designed to specifically measure frailty.

Frailty has been associated with fracture risk in several studies among community-dwelling elderly uninfected persons. In the Study of Osteoporotic Fractures (SOF) conducted in women with mean age of 77 years and which excluded Black women, frailty defined by the FFI was associated with an increased age-adjusted risk of hip fracture and any non-spine fracture, as well as with recurrent falls and all-cause mortality.[17] Similarly, when comparing the FFI to the SOF index (a simpler frailty index consisting of weight loss, inability to rise from a chair 5 times without using arms, and reduced energy level), frail women had a higher age-adjusted risk of recurrent falls, disability, non-spine fracture, hip fracture, and death regardless of the frailty index used.[16]

The SOF findings were confirmed among older men in the Osteoporotic Fractures in Men (MrOS) Study, in which frail men had a higher age-adjusted risk of recurrent falls, non-spine fracture, and death, with no difference in the SOF vs. Fried frailty indices in predicting adverse events.[41] In the Women's Health Initiative Observational Study (WHI-OS), which included over 40,000 women aged 65 to 79, baseline frailty independently predicted risk of hip fracture, disability, hospitalization, and death; however because gait speed and grip strength were not measured in the WHI-OS, self-reported muscle weakness and impaired walking based on responses to the Rand-36 physical function scale were utilized to create a modified FFI.[22] Although frailty definitions vary across studies, a systematic review and meta-analysis by Kojima et al found that that frailty was a significant predictor of fractures among community-dwelling older people (pooled OR=1.70, 95% CI: 1.34–2.15, p <0.0001).[42]

Although the WIHS study population is several decades younger than geriatric cohorts in which frailty is studied, and includes predominantly Black and Latina women who are often excluded or underrepresented in research, our finding that frailty is a strong and independent risk factor for fracture among women with or at risk for HIV is consistent with the relationships observed in white, community dwelling elderly uninfected persons. Among the frailty components, only self-report of exhaustion was associated with fracture in all models, including time to first fracture and time to second fracture, both in the full WIHS cohort and

in the subset of women with HIV. Reduced grip strength and self-reported weight loss were also predictive of first fracture in WIHS. Thus, these measures may be useful and simple tools to identify middle aged women at-risk for fracture in clinical practice. We previously reported that the FRAX fracture risk assessment tool underestimates 10-year fracture risk among women with HIV in WIHS.[43] Further research is needed to determine whether the incorporation of FFI or other factors not currently included in FRAX, or additional modifications of existing fracture risk prediction algorithms may better identify women with HIV at significant 10-year risk of fracture. Future research should also determine the extent to which identifying and treating frailty among middle-aged women with or without HIV lowers their future fracture risk.

Substance use was also an important risk factor for incident fracture in the WIHS. Current smoking, ever use of cocaine, and ever use of opioids were significantly associated with greater risk of first fracture in the overall WIHS; among the subset of women with HIV, current smoking and ever use of opioids remained associated with first fracture. Earlier WIHS analyses which did not include frailty measures found associations between ever use of cocaine and fracture, as well as with current smoking and fracture among women with HIV; however opioid use was not associated with fracture in multivariate models.[13] Several studies have found associations between opioid use and fractures in older HIV-uninfected populations,[44–47] and some[48,49] but not all[47,50] have reported greater risk of falls in association with opioid use. While understudied, frailty was associated with a higher prevalence of both pain, and analgesic use, including opioid use, among community-dwelling Finnish elderly.[51] Our data suggest that frailty and substance use are important and potentially modifiable risk factors that predispose women with HIV, or at risk for HIV, to fracture over time.

Interestingly, women with HIV and undetectable HIV viral loads were half as likely to sustain a second fracture as those with detectable viral load. We did not find significant associations with other HIV disease or treatment related factors and fracture risk. While the specific mechanism by which HIV viremia could predispose to fracture is unclear, it may be a marker for lack of effective HIV treatment, advanced HIV disease, or may exert effects via inflammation associated with untreated HIV, and manifest in the context of more severe adverse consequence (i.e. recurrent fracture).

Our study has several strengths. The WIHS is a predominantly racially and ethnically minority cohort that includes women with HIV with similar demographic and behavioral characteristics to women without HIV, allowing comparison by HIV serostatus. Our analysis includes a large sample size with data covering approximately 10 years of follow-up. Participants are well characterized with regard to not only frailty, but also comorbid medical conditions that may affect fracture risk. Our study also has several limitations. Frailty was measured at only a single time point in mid-life, although frailty status may change over time. Our study also includes only women, and findings may not be generalizable to men.

Given greater vulnerability to geriatric syndromes such as frailty, fracture, and falls experienced by women, future studies of aging PLWH should examine whether the predictive ability of overall measures of frailty or its components differ by sex in persons

with and at risk for HIV, and elucidate mechanisms by which frailty and fracture are related. As women with HIV continue to age, early frailty screening is an important clinical tool to identify those at greatest risk of fracture, in order to develop targeted fracture prevention strategies.

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Table 1.

Characteristics of 1332 HIV+ and 534 HIV- WIHS Participants at the Index Visit

	HIV-infected (N=1332)	HIV-uninfected (N=534)	P value
Demographics			
Age, median (IQR)	42.1 (36.4–48.2)	38.6 (30.8–45.7)	<0.0001
Race/Ethnicity White Black Hispanic/Other	292 (22%) 797 (60%) 243 (18%)	99 (19%) 343 (64%) 92 (17%)	0.17
Weight (kg) (IQR)	69.9 (60.3–84.2)	77.6 (64.9–93.0)	<0.0001
BMI (kg/m^2) (IQR)	27.3 (23.5–32.2)	29.4 (24.6–35.0)	<0.0001
Current smoking at index visit	572 (43%)	271 (51%)	0.0022
Ever injection drug use	342 (26%)	108 (20 %)	0.013
Ever opiate use	522 (39%)	227 (43%)	0.19
Ever cocaine use	227 (17%)	140 (26%)	<0.0001
Heavy alcohol use (≥14 drinks/wk)	26 (2%)	28 (5%)	<0.0001
Menstrual history			
Self-reported menopause at index visit	320 (24%)	76 (14%)	<0.0001
Medical history			
Diabetes at index visit	197 (15%)	89 (17%)	0.31
HCV positive at study entry (HCV Ab+ RNA+)	302 (23%)	82 (15%)	0.0004
Estimated GFR ≤60 (MDRD) at index visit	97 (7%)	8 (1.5%)	<0.0001
Calcium supplementation	93 (7%)	20 (4%)	0.0081
Vitamin D supplementation	14 (1%)	1 (0.2%)	0.059
Statin use	102 (8%)	17 (3%)	0.0004
Fracture status during study			0.11
No fracture	1072 (80%)	452 (85%)	
One fracture	181 (14%)	56 (10%)	
More than one fracture	79 (6%)	26 (5%)	
Frailty score			0.0006
0–2	1151 (86%)	492 (92%)	
3–5	181 (14%)	42 (8%)	
Components of Frailty Index			
Slow gait	334 (28%)	102 (21%)	0.0015
Reduced grip strength	360 (30%)	109 (22%)	0.0007
Exhaustion	431 (32%)	128 (24%)	0.0003
Unintentional weight loss	184 (14%)	48 (9%)	0.0043
Low physical activity	314 (24%)	93 (17%)	0.0033
HIV disease related characteristics			
AIDS defining illness ever, prior to index visit	558 (42%)	NA	
CD4+ cell count, at index visit (cells/μl)	442 (277–651)	NA	

	HIV-infected (N=1332)	HIV-uninfected (N=534)	P value
CD4+ cell count, nadir (cells/μl), at index visit	239 (128–360)	NA	
Undetectable HIV RNA viral load, at index visit	663 (50%)	NA	
PI-based ART before or at index visit	898 (67%)	NA	
Tenofovir (TDF) use before or at index visit	573 (43%)	NA	
ART use before or at index visit (regimens which do not include TDF or PI)	628 (47%)	NA	

Abbreviations: HIV: human immunodeficiency virus; IQR: interquartile range; SD: standard deviation; BMI: Body Mass Index (calculated as weight in kilograms divided by height in meters squared); HCV: Hepatitis C Virus; GFR: glomerular filtration rate; MDRD: Modification of Diet in Renal Disease; ART: antiretroviral therapy; PI: protease inhibitor; NNRTI: non-nucleoside analog reverse transcriptase inhibitor

Table 2.

Multivariate models for the Association of Frailty with Incident Fractures in HIV-infected and uninfected women

	Time to 1st Fracture aHR (95% CI)	P value	Time from 1st to 2nd Fracture aHR (95% CI)	P value
Frailty	**1.71 (1.30 – 2.26)**	**0.0001**	**1.69 (1.09 – 2.62)**	**0.019**
HIV infection	**1.32 (1.02 – 1.70)**	**0.035**	**0.80 (0.51 – 1.26)**	**0.34**
Age (per 10 year increase)	**1.20 (1.06 – 1.36)**	**0.0037**		
Race/Ethnicity (ref=White) **Black** **Hispanic/Other**	 **0.67 (0.52 – 0.86)** **0.53 (0.37 – 0.76)**	 **0.002** **0.0005**		
Current smoking	**1.57 (1.17 – 2.10)**	**0.0026**		
Cocaine use ever	**1.31 (1.02 – 1.69)**	**0.034**		
Opiate Use ever	**1.59 (1.26 – 2.01)**	**0.0001**		
Post-menopausal			**1.52 (1.02 – 2.27)**	**0.040**

Abbreviations: aHR: adjusted Hazard Ratio; CI: Confidence Interval. Only variables that were independently significant at P< 0.05 in the multivariate model are shown. HIV status and frailty were forced into models. Variables listed in table were measured at index visit and considered in the multivariate model and eliminated if they did not meet stepwise selection criteria of p-value ≥0.05.

Table 3.

Multivariate Models for Frailty Components Associated with Incident Fractures in HIV-infected and Uninfected Women

	Time to 1st Fracture aHR (95% CI)	P value	Time from 1st to 2nd Fracture aHR (95% CI)	P value
Components of Frailty Index				
Exhaustion	**1.60 (1.26 – 2.04)**	**0.0001**	**1.98 (1.34 – 2.93)**	**0.0007**
Unintentional weight loss	**1.44 (1.06 – 1.94)**	**0.019**		
Reduced grip strength	**1.35 (1.06 – 1.72)**	**0.017**		
HIV infection	**1.18 (0.91 – 1.54)**	**0.22**	**0.81 (0.52 – 1.26)**	**0.35**
Age (per 10 year increase)	**1.22 (1.07 – 1.39)**	**0.0025**		
Race/Ethnicity (ref= White) **Black** **Hispanic/Other**	 **0.67 (0.51 – 0.87)** **0.57 (0.39 – 0.82)**	 **0.003** **0.003**		
Current smoking	**1.48 (1.10 – 2.00)**	**0.0099**		
Opiate use ever	**1.61(1.26 – 2.06)**	**0.0001**		
Postmenopausal			**1.53 (1.03 – 2.28)**	**0.036**

Abbreviations: aHR: adjusted Hazard Ratio; CI: Confidence Interval. Only variables that were independently significant at P< 0.05 in the multivariate model are shown. HIV status was forced into models. All other variables listed in table were measured at index visit and considered in the multivariate model and eliminated if they did not meet stepwise selection criteria of p-value ≥0.05.

Table 4.

Multivariate models for the Association of Frailty with Incident Fractures in HIV-infected Women Only

Variable	Time to 1st Fracture aHR (95% CI)	P value	Time from 1st to 2nd Fracture aHR (95% CI)	P value
Frailty	**1.91 (1.41 – 2.58)**	**<0.0001**	**1.86 (1.15 – 3.01)**	**0.01**
Race/Ethnicity (ref= White) **Black** **Hispanic/Other**	 **0.65 (0.49 – 0.86)** **0.52 (0.34 – 0.78)**	 **0.0027** **0.0015**		
Current smoking	**1.84 (1.32 – 2.56)**	**0.0003**		
Opioid use ever	**1.94 (1.50 – 2.51)**	**<.0001**		
Undetectable HIV RNA viral load			**0.49 (0.31 – 0.77)**	**0.002**
Postmenopausal			**1.84 (1.17 – 2.89)**	**0.008**

Abbreviations: aHR: adjusted Hazard Ratio; CI: Confidence Interval. Only variables that were independently significant at $P < 0.05$ in the multivariate model are shown. Frailty was forced into models. All other variables listed in table were measured at index visit and considered in the multivariate model and eliminated if they did not meet stepwise selection criteria of p-value ≥0.05.

Table 5.

Multivariate Models for Frailty Components Associated with Incident Fractures in HIV-infected Women Only

Variable	Time to 1st Fracture aHR (95% CI)	P value	Time from 1st to 2nd Fracture aHR (95% CI)	P value
Components of Frailty Index				
Exhaustion	**1.57 (1.20 – 2.07)**	**0.0012**	**2.22 (1.40 – 3.53)**	**0.0007**
Unintentional weight loss	**1.44 (1.03 – 2.01)**	**0.032**		
Reduced grip strength	**1.36 (1.03 – 1.79)**	**0.028**		
Race/Ethnicity (ref= White) **Black** **Hispanic/Other**	 **0.65 (0.48 – 0.88)** **0.56 (0.36 – 0.86)**	 **0.0057** **0.0076**		
Undetectable HIV RNA viral load			**0.47 (0.29 – 0.74)**	**0.001**
Current smoking	**1.64 (1.16 – 2.31)**	**0.0055**		
Opioid use ever	**1.86 (1.41 – 2.46)**	**<0.0001**		
Postmenopausal			**1.78 (1.13 – 2.80)**	**0.012**

Abbreviations: aHR: adjusted Hazard Ratio; CI: Confidence Interval. Only variables that were independently significant at $P < 0.05$ in the multivariate model are shown. All variables listed in table were measured at index visit and considered in the multivariate model and eliminated if they did not meet stepwise selection criteria of p-value ≥0.05.