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Frailty and All-Cause Mortality among People with HIV Engaged in Clinical Care in the United States

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ABSTRACT

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Background

Frailty occurs at younger ages among people with HIV (PWH) than those without HIV, but its impact on mortality is unknown.

Methods

We examined the association between frailty (defined by a validated phenotype including inactivity, fatigue, weight loss, and immobility) and mortality (ascertained from state and national death data) among PWH in the CFAR Network of Integrated Clinical Systems (CNICS) cohort between 1/2015-3/2024 using adjusted Cox proportional hazards models.

Results

Among 6,750 PWH in this study, average age was 50 years, 15% were female, 44% were prefrail, 11% were frail at baseline, and the incidence of frailty was 9.7 per 1000 person-years (95% Confidence Interval [CI]:8.8-10.8) over an average of 5.5 years of follow-up. In adjusted models, frailty was associated with 2.7-times (95%CI:2.0-3.6), and prefrailty with 1.5-times (95%CI:1.2-2.0), higher risk of mortality. Prefrailty and frailty were consistently associated with an increased risk of death in models stratified by age (<50 vs. ≥50) and sex (male vs. female). Frailty was associated with 3.6-times (95%CI:2.2-6.1) and 2.5-times (95%CI:1.7-3.5) higher risk of mortality among PWH <50 and ≥50, respectively, and with 2.6-times (95%CI:1.9-3.6) and 3.9-times (95%CI:1.7-8.9) higher risk among male and female PWH, respectively.

Conclusions

In a large cohort of PWH, frailty and prefrailty were associated with a greater risk of death among PWH of all ages. Preventing frailty in this high-risk population is an important public health priority.

Key Words: Frailty, Mortality, HIV, Aging with HIV

Introduction

A decade ago, predictions indicated that by 2030, the majority of people with HIV (PWH) in high income countries would be 50 years or older and have correspondingly high rates of chronic disease and polypharmacy, increasing demand for healthcare systems to manage complex patients with multimorbidity.[1] Current predictions suggest that the median age of PWH on antiretroviral therapy (ART) will increase from 50 in 2020 to 56 by 2030, and nearly one quarter of this population is expected to be over 65 years old by 2030.[2] Causes of death in PWH have shifted from AIDS and AIDS-related illnesses to comorbidities similar to people aging without HIV.[3] As PWH age longer, they face both accelerated aging, wherein HIV itself contributes to and speeds the aging process, and accentuated aging, where HIV is an additional factor present at all ages and stages and may increase the prevalence of other comorbidities.[4] A notable increase in research has improved our understanding of aging in PWH, but major gaps in knowledge persist and should be filled in order to understand how to successfully promote healthy aging in this population.[5]

Accelerated aging among PWH leads to earlier presentation of conditions typically associated with older age, such as frailty, a state characterized by increased vulnerability to health stressors, while accentuated aging contributes to the high prevalence of comorbidities and aging-related conditions among PWH.[4-7] Physical frailty is most often measured by phenotypes originally defined by Fried and colleagues that combine weakness, slowness, weight loss, low physical activity, and fatigue into a single measure.[8] The impact of frailty is pervasive with greater risk of adverse events including falls, fractures, hospitalizations, and mortality.[9-11] Studies of frailty and related outcomes have been primarily conducted in the general population. One study of nearly half a million people in the UK Biobank found over 2-times (up to 2.7-times) higher risk of death associated with frailty across most subgroups.[12] Importantly, this study highlighted the prevalence and impact of frailty among adults under 65 who have largely been excluded from studies on frailty and other aging-related conditions. These findings underscore the need for research on frailty in younger adults with attention to high rates of multimorbidity and potential interventions to mitigate the impact of frailty.

While studies of frailty in PWH have included a wider age range to address the known acceleration of aging and population demographics, a common limitation in the existing literature is small numbers and lack of diversity by location or demographic factors.[10,13] Some studies using meta-analysis to address small sample sizes in individual studies have found elevated risk of mortality associated with frailty ranging from 1.7- to 2.7-times.[10,13] However, these results combined multiple definitions of frailty (e.g., frailty phenotype and frailty index) and were unable to differentiate the intermediate stage of prefrail from frail.[10,13] To fill these gaps, we examined the association between frailty status and all-cause mortality in a large cohort of PWH leveraging robust clinical and demographic data to control for a wide range of factors and evaluated important subgroups by age and sex.

Methods

Study Setting and Participants

This study was conducted in the Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort of adult PWH in care at ten academic clinical sites across the US.[14] CNICS operates a centralized data repository to harmonize inpatient and outpatient data across multiple domains. Demographic, laboratory, medication, and diagnosis information, as well as results from the CNICS clinical assessment of patient-reported outcomes (PROs) are integrated across all sites.[15,16] All PWH in CNICS who had a visit between 01/2015-03/2024 at a site that collects frailty data (University of Washington, Case Western Reserve University, Fenway Health Institute, University of North Carolina at Chapel Hill, University of Alabama Birmingham, and University of California San Diego) were eligible for this study. Participants were censored at the earliest date of: (1) death, (2) last activity in CNICS, or (3) date of administrative censoring (03/31/2024). All CNICS sites obtained local Institutional Review Board approval, which includes secondary analysis of deidentified data.

Data

Frailty was measured using a modified, validated frailty phenotype consisting of four self-reported components (inactivity, fatigue, unintentional weight loss, and immobility) described in detail elsewhere.[17] Frailty status was categorized as robust (0 components present), prefrail (1-2 components present), and frail (≥3 components present).

All-cause mortality was ascertained using multiple approaches at the local, state, and national level including state death certificate data and national death indices.

We examined demographic data (age, sex, race/ethnicity), site, HIV clinical data including time-updated HIV viral load and CD4 cell count, and CNICS operational definitions for diabetes mellitus, treated dyslipidemia, treated hypertension, co-infection with hepatitis C virus (HCV) and hepatitis B virus (HBV), liver fibrosis (FIB-4 score), renal function measured by estimated glomerular filtration rate (eGFR), and body mass index (BMI).[18-20] We calculated the VACS Index 1.0 for multimorbidity as published using age, CD4 cell count, HIV viral load, hemoglobin, FIB-4, eGFR, and HCV status.[21] Substance use data collected from the PROs included alcohol use (measured by AUDIT-C), smoking status, and illicit drug use including methamphetamine, cocaine/crack, and illicit opioids. We categorized alcohol use based on AUDIT-C scores and history of alcohol use disorder (AUD), defined using AUD diagnosis or self-report of attendance at alcohol use treatment, into 4 groups: 1) no alcohol use (AUDIT-C=0), 2) no alcohol use with AUD (AUDIT-C=0), 3) current non-hazardous alcohol use (AUDIT-C: 1-3 if female/1-4 if male), and 4) current hazardous alcohol use (AUDIT-C ≥4 if female/≥5 if male). We categorized smoking and illicit drug use as Never, Former, or Current use, or Missing.

PWH were included in analyses if they met complete case criteria for all demographic and clinical covariates; among 7,539 PWH with data on frailty 6,750 (90%) had complete case data (Supplemental Table 1).

Statistical Analysis

We examined demographic and clinical characteristics by baseline frailty status using frequencies and percents for categorical variables and mean and standard deviation (SD) or median and interquartile range (IQR) for continuous variables. We compared characteristics by

baseline frailty status using Chi-squared tests for categorical variables and t-tests for continuous variables. We calculated unadjusted mortality rates overall by frail vs. not frail (combination of robust and prefrail to dichotomize these estimates), and by age (<50 vs. ≥50) and sex subgroups, and compared the incidence rate difference between these groups.

We used Cox proportional hazards models to examine the association between time-updated frailty status and all-cause mortality. Frailty status was modeled as a three-level variable including robust (reference group), prefrail, and frail. The proportional hazards assumption was evaluated using Schoenfeld residuals, and no models were found to be in violation.[22] Models were adjusted for baseline measures including age, sex, race/ethnicity, site, diabetes, treated dyslipidemia, treated hypertension, HCV, HBV, FIB-4, eGFR, and BMI category, as well as time-updated HIV viral load and current CD4 cell count to control for potential confounders, which were selected *a priori*.[7]

We stratified models by age (<50 vs. ≥50) and sex (male vs. female) to evaluate potential differences in the association between frailty and mortality by key subgroups. We also conducted sensitivity analyses including a) the VACS Index 1.0 as an adjustment variable; for this model we removed redundant factors that were in our main adjustment that are part of the VACS Index (e.g., age, HCV, eGFR), b) additionally adjusting for substance use status (smoking, illicit drugs, and alcohol) and c) additionally adjusting for entry year into CNICS. Finally, we conducted an analysis evaluating our censoring approach by incorporating an alternative censoring mechanism extending time at-risk through the end of the study period (i.e., administratively censoring at 3/31/2024) for all participants who did not have a death date.[23] All analyses were conducted using Stata version 18.0 (StataCorp, College Station, TX).

Results

Cohort Characteristics

Among 6,750 PWH meeting study eligibility, the average age at baseline was 50, and frail PWH were older (average age: 53 years, SD: 10.7) than those who were robust (49, SD: 12.3) and prefrail (50, SD: 12.1). Nearly half (45%) of PWH were non-Hispanic White, one-third were non-Hispanic Black, and 17% were Hispanic (Table 1). Overall, 15% of PWH were female and were more likely to be frail at baseline compared to male PWH. PWH who were frail at baseline were also more likely to have unsuppressed HIV viral load (≥200 copies/mL), low current CD4 cell count (<350 cells/mm^3), and several comorbidities including diabetes, dyslipidemia, hypertension, and HCV, compared to robust and prefrail PWH (Table 1). Additionally, frail PWH reported greater tobacco smoking and illicit drug use than robust and prefrail PWH, but less alcohol use (Table 1). Baseline demographic and clinical characteristic breakdown by sex and age is available in Supplemental Table 2.

There were 360 deaths (5.3%) over an average of 5.5 years of follow-up (median: 5.8 years, IQR: 3.6-7.7). An average of 3.2 (SD: 2.5) frailty assessments were collected per person during follow-up. The overall crude mortality rate was 9.7 per 1,000 person-years (95% Confidence Interval [CI]: 8.8-10.8); among frail PWH the mortality rate was 22 per 1,000 person-years (18.2-

27.4) and among PWH who were not frail (combination of robust and prefrail) the mortality rate was 8.1 per 1,000 (7.2-9.1) person-years. Mortality among men and women was similar: 9.7 per 1,000 person-years (8.7-10.9) for men and 9.6 per 1,000 person-years for women (7.4-12.4) (p=0.9). The mortality rate in PWH 50 years and over (11.5 per 1,000 person-years [10.1-13.0]) was significantly higher than in PWH under 50 (7.4 per 1,000 person-years [6.2-8.9]) (p<0.001).

Main Findings

Frailty and prefrailty were associated with greater risk of mortality compared to robust status in all models. Among the entire cohort, frailty was associated with a 2.7-times (95% CI: 2.0-3.6) greater hazard of death, and prefrailty was associated with a 1.5-times (95% CI: 1.2-2.0) higher hazard of death in the primary adjusted models (Table 2, Figure 1). Associations remained in models stratified by age: among PWH under 50 years old, frailty was associated with a 3.6-times (95% CI: 2.2-6.1) greater hazard of death, whereas prefrailty was associated with a 1.6-times (95% CI: 1.1-2.5) greater hazard (Table 2). Among PWH 50 years and older, both frailty (HR: 2.5, 95% CI: 1.7-3.5) and prefrailty (HR: 1.5, 95% CI: 1.1-2.0) remained associated with greater hazard of death. Similarly in models stratified by sex, among both men (prefrailty: HR: 1.5, 95% CI: 1.1-1.9; frailty: HR: 2.6, 95% CI: 1.9-3.6) and women (prefrailty: HR: 2.4, 95% CI: 1.1-5.0; frailty: HR: 3.9, 95% CI: 1.7-8.9), frailty status was associated with greater risk of mortality (Table 2).

Sensitivity Analyses

In models adjusting for the VACS Index 1.0 after dropping redundant covariates such as HCV, we found stable hazard ratio estimates (Table 3). In a sensitivity analysis additionally adjusting for substance use (smoking, alcohol use, and illicit drug use, which includes methamphetamine, cocaine/crack, and illicit opioids), the hazard of mortality remained elevated for PWH with frailty (HR: 2.5, 95% CI: 1.9-3.3) and prefrailty (HR: 1.4, 95% CI: 1.1-1.8), with mildly attenuated effect estimates (Table 3). Our findings were also consistent when we additionally adjusted for entry year into CNICS as well as the alternative censoring approach (Table 3).

Discussion

We observed a significant increase in risk of all-cause mortality associated with frailty and prefrailty among PWH engaged in care in the US. Frail PWH had 2.7-times, and prefrail PWH had 1.5-times, greater risk of death over 5.5 years of follow-up in models adjusted for demographic and clinical characteristics. Elevated mortality risk was associated with frailty in older and younger groups as well as in men and women. Among PWH under 50 years old, frailty was associated with a 3.6-times greater risk of death and prefrailty 1.6-times, underscoring the necessity of identifying and addressing frailty among PWH of all ages. Further, over half (55%) of the cohort were either prefrail or frail at baseline (Table 1). Our findings demonstrate both a high prevalence and significant impact of frailty on the risk of death in this aging population that necessitates prioritizing frailty among PWH in care.

Our findings are comparable to published data from two meta-analyses on frailty and mortality among PWH and expand on this work by evaluating prefrailty, key subgroups of PWH by age and sex, and by accounting for numerous demographic and clinical factors.[10,13] In addition, our study cohort is much larger (N=6,750) than prior individual studies included in meta-analyses (largest N ~3,500, majority <1,000), and includes updated data that is more relevant in the current era of HIV care compared with prior studies that predate 2020. Our findings are nearly identical to the large UK Biobank study in the general population that found approximately 2.5-times elevated risk of mortality associated with frailty among age- and sex-subgroups (except women aged 37-45) in models adjusted for multimorbidity and demographic factors.[12] Here, we contribute to the growing evidence that frailty is a risk factor for mortality, independent of clinical markers, and warrants increased attention across PWH of all ages.[10,12,13,24]

Our finding that frailty is associated with mortality in older and younger PWH as well as among men and women is notable. Importantly, our results indicate that younger PWH and women may have elevated mortality risk associated with frailty, although we were underpowered to evaluate whether the association between frailty and mortality varied significantly by age or sex (i.e., effect measure modification). Among PWH under 50, we observed an increased risk of death of 3.6, and among PWH over 50, 2.5 times the risk. This trend may suggest that younger PWH with frailty experience worse outcomes than older PWH with frailty. In terms of sex, we found an increased risk of mortality associated with frailty of 3.9 for women and 2.6 for men. Our study population is generalizable to PWH in the US, and as such, women comprise only about 15% of the cohort, limiting our power to detect statistically significant differences though this remains an intriguing differential in risk by sex. In the general population, women possess a life expectancy advantage that appears to be lost in the setting of HIV, and our findings support this trend.[25,26] Additionally, recent work in the CNICS cohort has reported greater immune activation among women compared to men and even more pronounced differences in women compared to men over age 47.[27,28] Immune activation is associated with greater frailty thus, it will be essential to understand risk differences in particular subgroups when managing mortality risk in PWH.[29] If borne out in other analyses, these trends warrant particular attention and more specified approaches to preventing and mitigating frailty in different subgroups. Additionally, future work may incorporate activities of daily living and other markers of day-to-day functional status to aid in elucidating the impacts of frailty on the time of healthy living, or health-span, of PWH.[30,31]

We examined all-cause mortality as an initial endpoint to understand the overall burden of death related to frailty in this population. A study on frailty and cause-specific mortality in the general population found 2.8 to 3.5-times greater risk of death due to heart disease, cancer, respiratory illness, and dementia after adjusting for history of comorbid diagnoses, suggesting an independent role of frailty in specific causes of mortality.[32] Frailty is, by definition, a state of heightened vulnerability to health-related stressors and as such is not a direct cause death but rather reduces the ability to recover from a new condition or other health event.[8,33] While this vulnerability and diminished capacity to recover may vary in degree by specific causes of death, frailty likely has an impact across all individual causes/illnesses as suggested by the range of outcomes affected by frailty. Potential underlying factors identified as contributing to both frailty and mortality that may explain this trend include chronic inflammation, immunosenescence,

behavioral factors (e.g., sedentary lifestyle) and social factors, which are particularly important in PWH as these factors are likely exacerbated in this population.[29,32,34]

Our results were consistent in sensitivity analyses adjusting for additional measures. Findings were identical to our main model after adjusting for the VACS Index (Table 3). While the VACS Index was initially developed as a mortality risk score, it has sometimes been considered a frailty-related measure.[21,24,35] After controlling for substance use, findings were mildly attenuated. Together these results suggest a highly robust association between frailty and mortality among PWH independent of physiological markers and comorbidities and thus, frailty should be considered when managing health and mortality risk of PWH.

Our findings have some limitations. We lack sufficient subgroup sample size to examine multiple factors concurrently (age and sex), although this analysis is one of the largest studies on frailty and mortality in PWH. We examined all-cause mortality and as deaths accrue in CNICS, future analysis of cause-specific mortality may offer additional insight regarding potential mechanisms seen in the general population.[32] Our frailty phenotype includes only 4 of the 5 components in the full Fried frailty phenotype, however, it has been validated against it and found to perform very well.[17] Our study has several important strengths. The timeframe of this study (2015-2024) encompasses contemporary HIV care and treatment; thus, our results are timely and applicable to PWH currently engaged in care. Our cohort is geographically and demographically diverse (e.g., six sites across the US) ensuring generalizability to PWH in care across the US. We controlled for a wide range of factors including comorbidities, lab results, and other markers that could potentially confound this association.

A remaining, and crucially important, question is the degree of reversibility of frailty. The dynamic nature of frailty has often been touted as a promising aspect and central focus for intervention especially among PWH, and there have been a few publications on predictors of frailty transitions.[5,34,36,37] A recent study in the ACTG HAILO cohort found 8% of PWH with worsening frailty and 9% with frailty improvement over time.[37] In studies of frailty trajectories, there appears to be significant overlap in factors that predict both worsening and improvements in frailty; older age, female sex, physical activity, and depression all predicted both.[37] The authors interpret these overlaps as factors associated with fluctuations, such that people with particular characteristics could be more likely to transition, but not specifically in one direction. Whether people can recover to robust (ideally) or prefrail states from being frail would dictate next steps and priorities in managing care for aging PWH. Most evidence points to exercise and physical activity as potent priorities for frailty intervention.[34,37] In particular, activity regimens that integrate multiple components of exercise (e.g., cardiovascular, resistance training and balance/flexibility exercise) and significant repetition for several months had positive impact on several frailty components.[34,38] This work has primarily been conducted among older adults without HIV who often reside in long-term care or other facilities; therefore, it remains unclear how well this would translate to typical daily life of PWH with regular (i.e., biannual) clinic visits.[38,39]

Accelerated aging and senescence among PWH has often been attributed to chronic immune activation, even in the presence of controlled HIV, and approaches to managing inflammation continue to be at the forefront of ongoing research.[5,29] Early and sustained ART, as is

recommended by current guidelines, remains a top preventive measure against frailty.[36] Management of comorbidities including cardiovascular risk is another important factor in supporting healthy aging with HIV by managing disease consequences.[37] For example, recent work in CNICS showed that treatment with diabetes medications may reduce the risk of frailty associated with elevated glycemia.[40] As the REPRIEVE study continues to report findings, additional results regarding the potential impact of statins on frailty incidence and progression will be of great interest. Early reports have not found a modifying impact of frailty on typical statin mechanisms of action, while data from the Modena HIV Clinic in Italy reported decreases in frailty index scores associated with statin use.[41,42] Integration of lifestyle changes such as physical activity and nutrition should continue to be prioritized as initial steps in care and investigating potential interventions.

Conclusion

We found that PWH have significantly higher risk of death associated with frailty. We identified an independent association between frailty and mortality after adjusting for demographic characteristics, clinical/lab factors, and comorbid diagnoses. Early identification of frailty symptoms and interventions, such as exercise training, to minimize and mitigate frailty progression, are crucially important in prioritizing healthy aging among PWH and reducing mortality. Advancements in HIV care have been monumental in saving lives; to continue this trend, clinicians and researchers need to continue to expand the focus of care with emphasis on management of aging.

Supplemental Tables - http://links.lww.com/QAI/C637

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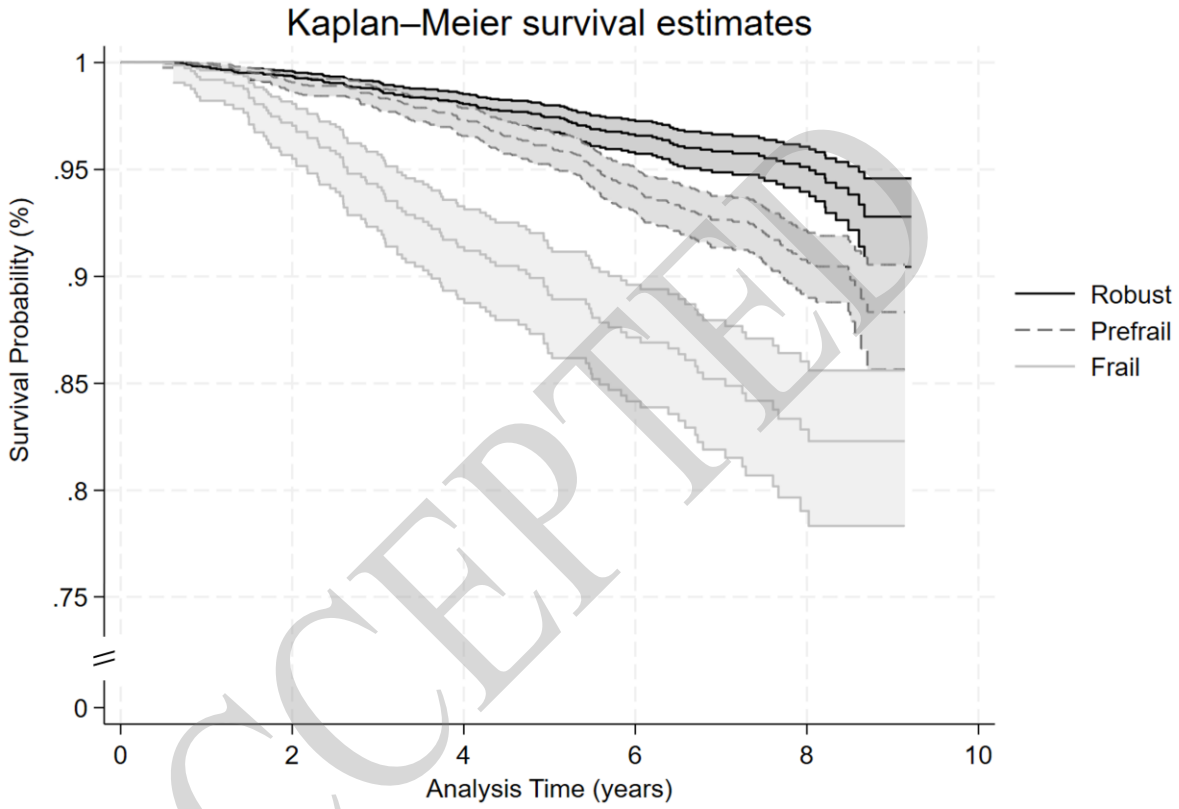
Figure 1. Kaplan-Meier survival curves stratified by frailty status among people with HIV (PWH). Frail PWH (green) had the lowest survival probability over time, followed by prefrail PWH (red), while robust PWH (blue) had the highest survival probability. All strata had survival probabilities greater than 75%.



Tables.

Table 1. Baseline Demographic and Clinical Characteristics of PWH by Frailty Status

N (%) unless noted	Baseline Frailty Status				P-value
	Robust (N=3,028)	**Prefrail** (N=2,949)	**Frail** (N=773)	**Total** (N=6,750)	
Age (years), mean (SD)	48.6 (12.3)	49.9 (12.3)	53.1 (10.8)	49.7 (12.2)	<0.001
Age (years), median (IQR)	49 (38, 58)	51 (40, 59)	55 (46, 61)	51 (40, 59)	
<50 years old	1,526 (50.4%)	1,344 (45.6%)	247 (32.0%)	3,117 (46.2%)	
≥50 years old	1,502 (49.6%)	1,605 (54.4%)	526 (68.0%)	3,633 (53.8%)	
Race/Ethnicity					
Non-Hispanic White	1,324 (43.7%)	1,330 (45.1%)	374 (48.4%)	3,028 (44.9%)	0.328
Non-Hispanic Black	1,016 (33.6%)	983 (33.3%)	241 (31.2%)	2,240 (33.2%)	
Hispanic	522 (17.2%)	475 (16.1%)	124 (16.0%)	1,121 (16.6%)	
Unknown/Other	166 (5.5%)	161 (5.5%)	34 (4.4%)	361 (5.3%)	
Sex					
Female	359 (11.9%)	503 (17.1%)	168 (21.7%)	1,030 (15.3%)	<0.001
Male	2,669 (88.1%)	2,446 (82.9%)	605 (78.3%)	5,720 (84.7%)	
HIV Viral Load					
<200 copies/mL (suppressed)	2,774 (91.6%)	2,634 (89.3%)	654 (84.6%)	6,062 (89.8%)	<0.001
≥200 copies/mL (unsuppressed)	242 (8.0%)	304 (10.3%)	111 (14.4%)	657 (9.7%)	
Current CD4 Count					
≥350 cells/mm^3	2,549 (84.2%)	2,416 (81.9%)	574 (74.3%)	5,539 (82.1%)	<0.001
<350 cells/mm^3	479 (15.8%)	533 (18.1%)	199 (25.7%)	1,211 (17.9%)	
Diabetes Status					
No Diabetes	2,787 (92.0%)	2,605 (88.3%)	641 (82.9%)	6,033 (89.4%)	<0.001
Diabetes	241 (8.0%)	344 (11.7%)	132 (17.1%)	717 (10.6%)	
Treated Dyslipidemia					
No	2,379 (78.6%)	2,156 (73.1%)	529 (68.4%)	5,064 (75.0%)	<0.001
Yes	649 (21.4%)	793 (26.9%)	244 (31.6%)	1,686 (25.0%)	
Treated Hypertension					
No	2,188 (72.3%)	1,933 (65.5%)	439 (56.8%)	4,560 (67.6%)	<0.001
Yes	840 (27.7%)	1,016 (34.5%)	334 (43.2%)	2,190 (32.4%)	
Hepatitis C Virus					
No	2,823 (93.2%)	2,683 (91.0%)	649 (84.0%)	6,155 (91.2%)	<0.001
Yes	205 (6.8%)	266 (9.0%)	124 (16.0%)	595 (8.8%)	
Hepatitis B Virus					
No	2,927 (96.7%)	2,855 (96.8%)	747 (96.6%)	6,529 (96.7%)	0.939
Yes	101 (3.3%)	94 (3.2%)	26 (3.4%)	221 (3.3%)	
FIB-4					
Stage 0-1	2,247 (74.2%)	2,187 (74.2%)	518 (67.0%)	4,952 (73.4%)	<0.001
Stage 2-3	697 (23.0%)	657 (22.3%)	207 (26.8%)	1,561 (23.1%)	
Stage 4-6	84 (2.8%)	105 (3.6%)	48 (6.2%)	237 (3.5%)	
BMI Category					
<18.5 (m/kg^2)	62 (2.0%)	53 (1.8%)	16 (2.1%)	131 (1.9%)	<0.001
18.5-24.9 (m/kg^2)	1,373 (45.3%)	1,214 (41.2%)	314 (40.6%)	2,901 (43.0%)	
25.0-29.9 (m/kg^2)	1,076 (35.5%)	992 (33.6%)	232 (30.0%)	2,300 (34.1%)	
≥30 (m/kg^2)	517 (17.1%)	690 (23.4%)	211 (27.3%)	1,418 (21.0%)	
eGFR					
≥30 mL/min/1.73m^2	3,206 (94.7%)	3,150 (95.8%)	828 (95.7%)	7,184 (95.3%)	0.038
<30 mL/min/1.73m^2	18 (0.5%)	24 (0.7%)	3 (0.3%)	45 (0.6%)	
VACS Index 1.0 Score					
Mean (SD)	18.2 (16.3)	20.8 (17.7)	26.4 (17.7)	20.3 (17.3)	<0.001

Median (IQR)	16 (6, 28)	18 (10, 29)	23 (12, 37)	18 (7, 28)	
Tobacco Smoking Status					
Never	1,201 (39.7%)	984 (33.4%)	187 (24.2%)	2,372 (35.1%)	<0.001
Former	964 (31.8%)	898 (30.5%)	228 (29.5%)	2,090 (31.0%)	
Current	858 (28.3%)	1,063 (36.0%)	358 (46.3%)	2,279 (33.8%)	
Missing	5 (0.2%)	4 (0.1%)	0 (0.0%)	9 (0.1%)	
Illicit Drug Use Status					
Never	1,295 (42.8%)	1,025 (34.8%)	180 (23.3%)	2,500 (37.0%)	<0.001
Former	1,181 (39.0%)	1,253 (42.5%)	395 (51.1%)	2,829 (41.9%)	
Current	549 (18.1%)	669 (22.7%)	197 (25.5%)	1,415 (21.0%)	
Missing	3 (0.1%)	2 (0.1%)	1 (0.1%)	6 (0.1%)	
Alcohol Use Status					
No Current Use	405 (13.4%)	520 (17.6%)	143 (18.5%)	1,068 (15.8%)	<0.001
No Current Use with history of AUD	118 (3.9%)	179 (6.1%)	67 (8.7%)	364 (5.4%)	
Current Non-Hazardous Use	1,583 (52.3%)	1,424 (48.3%)	365 (47.2%)	3,372 (50.0%)	
Current Hazardous Use	922 (30.4%)	824 (27.9%)	198 (25.6%)	1,944 (28.8%)	
Missing	0 (0.0%)	2 (0.1%)	0 (0.0%)	2 (0.0%)	

Abbreviations: PWH (people with HIV), SD (standard deviation), IQR (interquartile range), FIB-4 (Fibrosis-4 Stage), BMI (body mass index), eGFR (estimated glomerular filtration rate), AUD (alcohol use disorder)
Note: Illicit Drug Use includes methamphetamine, cocaine, and illicit opioids

Table 2. Hazard Ratio (HR) for the association between time-updated frailty status and mortality among people with HIV in adjusted[a] Cox proportional hazards models overall and stratified by age (<50 vs. ≥50) and sex

Strata	Frailty Status	HR (95% CI)	p-value	
Everyone	Robust	Ref		PH=0.07 [b]
N=6750	Prefrail	1.54 (1.20-1.97)	<0.01	
Deaths=360	Frail	2.69 (2.01-3.61)	<0.001	
Age <50	Robust	Ref		PH=0.27 [b]
N=3120	Prefrail	1.62 (1.06-2.48)	0.03	
Deaths=119	Frail	3.62 (2.15-6.10)	<0.001	
Age ≥50	Robust	Ref		PH=0.39 [b]
N=3630	Prefrail	1.46 (1.07-2.00)	0.02	
Deaths=241	Frail	2.45 (1.72-3.49)	<0.001	
Male	Robust	Ref		PH=0.10 [b]
N=5720	Prefrail	1.46 (1.12-1.91)	0.01	
Deaths=302	Frail	2.61 (1.90-3.59)	<0.001	
Female	Robust	Ref		PH=0.36 [b]
N=1030	Prefrail	2.35 (1.10-5.03)	0.03	
Deaths=58	Frail	3.89 (1.70-8.93)	<0.01	

[a] Adjusted for age, sex, race/ethnicity, site, HIV viral load (time-updated), current CD4 count (time-updated), diabetes status, treated dyslipidemia, treated hypertension, hepatitis C virus, hepatitis B virus, liver fibrosis (FIB-4), kidney function (eGFR), and BMI category

[b] PH=proportional hazards: p>0.05 means the model does not violate proportional hazards assumption

Table 3. Sensitivity analyses for the association between time-updated frailty status and mortality among people with HIV in adjusted Cox proportional hazards models

Sensitivity Analysis	Frailty Status	HR (95% CI)	p-value
Adjusting for VACS Index 1.0 [a]	Robust	Ref	
N=6528	Prefrail	1.59 (1.24-2.05)	<0.001
Deaths=353	Frail	2.70 (2.01-3.63)	<0.001
Adjusting for substance use [b]	Robust	Ref	
N=6735	Prefrail	1.42 (1.10-1.83)	0.01
Deaths=360	Frail	2.48 (1.85-3.33)	<0.001
Adjusting for CNICS entry year [c]	Robust	Ref	
N=6750	Prefrail	1.53 (1.20-1.97)	<0.01
Deaths=360	Frail	2.69 (2.01-3.61)	<0.001
Alternative censoring approach [d]	Robust	Ref	
N=6750	Prefrail	1.55 (1.21-1.99)	<0.01
Deaths=360	Frail	2.72 (2.03-3.64)	<0.001

[a] Adjusted for: sex, race/ethnicity, site, HIV viral load (time-updated), current CD4 count (time-updated), diabetes status, treated dyslipidemia, treated hypertension, HBV, BMI category, VACS Index

[b] Adjusted for age, sex, race/ethnicity, site, HIV viral load (time-updated), current CD4 count (time-updated), diabetes status, treated dyslipidemia, treated hypertension, HCV, HBV, FIB-4, eGFR, BMI category, illicit drug use, smoking status, alcohol use

[c] Adjusted for age, sex, race/ethnicity, site, HIV viral load (time-updated), current CD4 count (time-updated), diabetes status, treated dyslipidemia, treated hypertension, HCV, HBV, FIB-4, eGFR, BMI category, CNICS entry year

[d] Adjusted for age, sex, race/ethnicity, site, HIV viral load (time-updated), current CD4 count (time-updated), diabetes status, treated dyslipidemia, treated hypertension, HCV, HBV, FIB-4, eGFR, BMI category