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Prevalence and Correlates of Frailty Among Older Adults Living With HIV in the CHANGE HIV Cohort

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Background: Advancements in treatment have resulted in improved survival among people living with HIV. However, additional years of life are not necessarily spent in good health, as frailty tends to develop at a younger age among people living with HIV. We set out to examine the prevalence of frailty and its correlates among older adults living with HIV in Canada, with a primary interest in nadir CD4 count.

Methods: We performed a cross-sectional analysis of the Correlates of Healthy Aging in Geriatric HIV (CHANGE HIV) study, a Canadian cohort of people living with HIV aged 65 years or older. Participants were assessed using the Fried Frailty Phenotype at cohort entry, and those meeting ≥3 criteria were characterized as frail. We used Poisson regression with robust standard errors to estimate the association between nadir CD4 count and frailty, as well as age, gender, time since HIV diagnosis, comorbidities, marital status, and loneliness.

Results: Among 439 participants included in this analysis (median age 69 years, interquartile ranges 67–73), prevalence of frailty was 16.6%. Frailty was not associated with nadir CD4 count. Not being in a relationship (aRR 2.09, 95% CI 1.01 to 4.30) and greater degree of loneliness (aRR 1.25 per 10 point increase on UCLA loneliness scale, 95% CI 1.09 to 1.44) were associated with frailty.

Conclusions: Frailty occurred in 16.6% of older adults living with HIV in this cohort. While nadir CD4 count did not correlate with frailty, being single and lonely did, highlighting the importance of recognizing and addressing these social vulnerabilities among people aging with HIV.

Key Words: HIV, aging, frailty, loneliness, CD4 nadir

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INTRODUCTION

Frailty is a common age-related syndrome resulting in increased vulnerability to a wide variety of stressors, such that the ability to maintain homeostasis is impaired.[1] Frailty is characterized by reduced reserve in multiple physiological systems (i.e. musculoskeletal, endocrine, cardiovascular), which results in increased risk of adverse clinical outcomes including falls, cognitive impairment, increased healthcare utilization, and mortality.[2]

Although multiple metrics have been developed to detect and measure frailty, the Fried Frailty Phenotype is the most commonly used.[3] Prevalence of frailty using the Fried Frailty Phenotype varies geographically across populations and tends to increase with chronological age.[4] In the Canadian context, the prevalence of frailty among 7353 Canadians (aged 18–79 years) enrolled in the Canadian Health Measures Survey was 5.3% in the 18–34 age group, compared with 7.8% among those who were 65 years and older.[5] Importantly, studies have demonstrated that frailty is a dynamic process with transitions occurring between frailty states in a significant proportion of individuals.[6] Transitions have been noted both in progression to and remediation of frailty, suggesting there is opportunity for interventions to prevent and reverse frailty.

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Frailty plays a significant role in the health and well-being of people living with HIV. With advances in antiretroviral therapy, HIV is no longer considered a life-limiting illness, as life expectancy among people living with HIV now approaches that of the general population.[7] However, people living with HIV enjoy fewer years in good health as they may develop age-related comorbidities and geriatric syndromes earlier in life.[8] People living with HIV are more likely to be frail than their HIV-negative counterparts and tend to develop frailty at a younger age, as previously shown among cohorts of people with a history of injecting drugs,[9] men who have sex with men,[10] and women.[11] Persistent immune dysregulation seems to play an important role in the development of frailty in people living with HIV in addition to the drivers of frailty observed in the general population, such as multimorbidity, lifestyle factors, and social determinants of health.[12,13] Specifically, frailty has been linked to low-grade inflammation and immune activation among people living with HIV, which persists even after the initiation of effective antiretroviral therapy.[14] Although there are limited data on the relationship between social determinants of health and frailty among people living with HIV, existing studies indicate that frailty may be linked to loneliness, low educational attainment, and low income.[15–17]

More than half of people living with HIV in North America are now over the age of 50 years, and the median age is expected to continue rising to greater than 65 years over the next decade.[18] Improved survival among people living with HIV is a reflection of superior efficacy and tolerability of modern antiretroviral regimens and ongoing efforts to diagnose and initiate treatment as soon as possible following the infection, thereby limiting depletion of the immune system. There are limited data regarding frailty prevalence among persons living with HIV over the age of 65 years, and whether degree of immune depletion before treatment initiation (as estimated using the nadir CD4 cell count) has an impact on development of frailty. Recognizing the poor clinical outcomes among frail individuals and the need to identify actionable factors associated with frailty in this growing population, we examined the prevalence of frailty in a Canadian cohort of persons living with HIV aged 65 years and older and evaluated correlates of frailty with the hypothesis that frailty is associated with lower nadir CD4 count.

METHODS

We performed a cross-sectional analysis using data from the Correlates of Healthy Aging in Geriatric HIV (CHANGE HIV) study.[19] This is an ongoing Canadian cohort of people living with HIV aged 65 years and older, established in 2019. Participants are recruited from 7 clinical sites across 3 Canadian provinces (British Columbia, Ontario, and Quebec) where they receive HIV care. The study has received research ethics approval at the coordinating study site (University Health Network in Toronto, Ontario REB # 18-6311), as well as at each of the additional 6 sites. All participants gave written informed consent.

At cohort entry, participants completed a comprehensive evaluation of their medical history (including assessment of comorbidities, smoking, and alcohol use history), sociodemographic factors (including age, gender, race, education, household income, marital status, living arrangements), HIV-specific parameters (including nadir and current CD4 count, time since HIV diagnosis), and the UCLA Loneliness Scale (scored from 20 to 80, where higher scores suggest higher degree of loneliness).[20] In addition, the primary outcome of frailty was assessed using the original Fried Frailty Phenotype criteria, comprising unintentional weight loss (≥10 lb in previous year), self-reported exhaustion, weakness (evaluated by grip strength using a dynamometer), slow walking speed (evaluated using a 4-meter gait speed test), and self-reported low physical activity.[3] Individuals meeting 3 or more criteria were considered to be frail and were compared with nonfrail individuals (those meeting 1–2 criteria, termed prefrail and those meeting no criterion, termed robust). All participants enrolled in the CHANGE HIV cohort and evaluated for the Fried Frailty Phenotype up until November 1, 2023, were included in the analysis.

Baseline demographic and clinical variables at cohort entry were compared according to frailty status. Medians and interquartile ranges (IQR) were used to describe continuous variables, and counts and frequencies to describe categorical variables. χ^2 tests were used to compare categorical variables, and Wilcoxon rank-sum tests were used to compare medians for continuous variables.

Owing to the relatively high prevalence of the outcome, relative risk regression was used to evaluate the relationship between the primary exposure (nadir CD4 count) and the primary outcome (frailty) of interest. The following variables were selected a priori as they may enhance (or mask) the association between nadir CD4 count and frailty: age, gender, time since HIV diagnosis, number of comorbidities, marital status, and loneliness. Comorbidity was included as a continuous variable, according to the number of identified comorbidities. The presence of the following 20 comorbidities were evaluated using standard criteria: coronary artery disease, heart failure, stroke, diabetes, chronic obstructive pulmonary disease, cancer, chronic kidney disease, hypertension, addiction, asthma, HIV-associated neurocognitive disorder, Parkinson disease, peripheral arterial disease, peripheral neuropathy, dyslipidemia, osteoporosis, thrombosis, chronic liver disease, arthritis, and depression. Marital status was dichotomized into those in a steady relationship (including those who are married or common law) and those who are unpartnered (including those who are single, divorced, separated, or widowed). There was no evidence of collinearity between the selected variables. Sensitivity analyses were performed to assess the impact of different comorbidity thresholds within the model, including presence of ≥2 comorbidities (referred to as multimorbidity) or ≥3 comorbidities (referred to severe multimorbidity) in the same individuals.[21,22] Poisson regression with robust standard errors was used the estimate the prevalence or risk ratios.

RESULTS

A total of 439 participants were included in the analysis, of whom 73 (16.6%) were characterized as frail

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TABLE 1. Characteristics of CHANGE HIV Cohort Participants

Characteristic	Overall (n = 439)	Frail (n = 73)	Not frail (n = 366)	*P*
Age, years—median (IQR)	69 (67–73)	69 (67–72.5)	69 (67–73)	0.54*
Gender, n (%)				0.22†
Men	396 (90.2)	63 (86.3)	333 (91.0)	
Women	43 (9.8)	10 (13.7)	33 (9.0)	
Race, n (%)				
White	332 (75.8)	55 (75.3)	277 (75.9)	0.92†
Non-White‡	106 (24.2)	18 (24.7)	88 (24.1)	
Smoking history, n (%)				0.15†
Nonsmoker or past smoker	380 (87.4)	60 (82.2)	320 (88.4)	
Current smoker	55 (12.6)	13 (17.8)	42 (11.6)	
Alcohol use, n (%)				0.50†
None	106 (24.3)	20 (27.4)	86 (23.7)	
Any	330 (75.7)	53 (72.6)	277 (76.3)	
Education, median level	University certificate or diploma	College, or nonuniversity certificate	University certificate or diploma	0.14*
Household income, n (%)				0.004†
Under $20,000	79 (18.3)	22 (30.1)	57 (15.9)	
Above $20,000	352 (81.7)	51 (69.9)	301 (84.1)	
Marital status, n (%)				0.003†
In a relationship	153 (34.9)	14 (19.4)	139 (38.0)	
Unpartnered	285 (65.1)	58 (80.6)	227 (62.0)	
Living arrangement, n (%)				0.024†
With another person	188 (43.4)	23 (31.5)	165 (45.8)	
Alone	245 (56.6)	50 (68.5)	195 (54.2)	
Loneliness score, median (IQR)	27 (22–40)	36 (25–46)	26 (21–37)	<0.001*
Time since HIV diagnosis, years, median (IQR)	26 (19–31)	26 (21–30)	25 (19–31)	0.68*
Nadir CD4 count, cells/mm^3, median (IQR)	200 (100–335)	222 (100–351)	198 (100–323)	0.46*
Current CD4 count, cells/mm^3—median (IQR)	558 (409–737)	510 (363–786)	560 (411–728)	0.34*
Number of comorbidities, median (IQR)	3 (2–4)	3 (2–5)	3 (2–4)	0.09*

*Wilcoxon rank-sum test;
†χ^2 test.
‡Self-identified as Indigenous, Asian, Black, Hispanic, or other.

(62.4% were prefrail and 21.0% robust). Baseline characteristics of the CHANGE HIV cohort are summarized in Table 1. The median age of participants at the time of study enrollment was 69 years (IQR 67–73), with majority identifying as men (90%) and White (76%). Majority did not have a partner (65%) and were living alone (57%). While most participants had postsecondary education (72%), nearly 1 in 5 were living on a gross household income of less than $20,000 (18%), which is at the deep poverty line in Canada for a 1-person household.[23] The median nadir CD4 count among study participants was 200 cells/mm^3 (IQR 100–335). Majority of individuals had evidence of a robust immunologic response to therapy with a current median CD4 cell count of 558 cells/mm^3 (IQR 409–737). All participants were on antiretroviral therapy, and the viral load was < 200 copies/mL in 99.5%. The median number of comorbidities among study participants was 3 (IQR 2–4), with 78% meeting the definition of multimorbidity (≥2 comorbidities) and 54% for severe multimorbidity (≥3 comorbidities). When comparing baseline characteristics by the primary outcome of interest, there was a statistically significant difference in the prevalence of frailty according to household income, marital status, living arrangement, and degree of loneliness (Table 1). Weakness was the most commonly encountered Fried Frailty Phenotype criterion, observed in 43% of study participants (Fig. 1).

Both in the univariable and multivariable analysis, there was no association identified between nadir CD4 count and frailty (Table 2). Looking at the other predictor variables, frailty was associated with marital status and loneliness. Specifically, not being in a relationship (aRR 2.09, 95% CI 1.01 to 4.30) and higher scores on the UCLA Loneliness Scale (aRR 1.25 per 10 point increase on the score, 95% CI 1.09 to 1.44) were associated with frailty, after adjusting for nadir CD4 count, age, gender, time since HIV diagnosis, and the number of comorbidities (Table 2). In sensitivity analyses, neither multimorbidity (aRR 1.23, 95% CI 0.57 to 2.63) nor severe multimorbidity (aRR 1.76, 95% CI 0.98 to 3.17) was associated with frailty.

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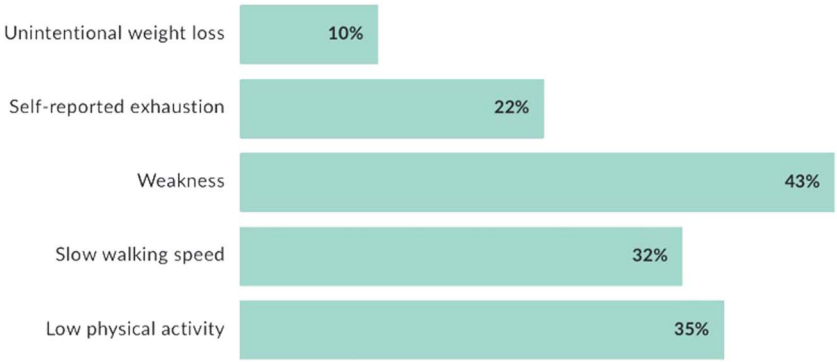

FIGURE 1. Prevalence of each of the 5 Fried Frailty Phenotype criteria among people living with HIV in the CHANGE HIV cohort.

DISCUSSION

We observed a higher prevalence of frailty (16.6%) in this cohort of older adults living with HIV in Canada, compared with the general geriatric Canadian population (ranging between 6.5% and 11.7% across studies) and other cohorts of community dwelling older adults aged 65 years and older in the United States and Europe.[3–5,24,25] For example, the prevalence of frailty was 6.9% among participants in the American Cardiovascular Health Study, the derivation cohort for the Fried Frailty Phenotype, and 8.7% in a large sample of community-dwelling older adults living in the Netherlands.[3,25] The prevalence of frailty among CHANGE HIV study participants was similar to several other cohorts of people living with HIV. In the Canadian Positive Brain Health Now (PBHN) cohort, frailty was present in 15.2% of 854 people living with HIV (age ≥35 years).[26] Among 143 people living with HIV (age range 50–79 years) in Alberta, Canada, 14% were deemed to be frail according to the Fried Frailty Phenotype.[27] In the United States, prevalence of frailty was 17.3% among women living with HIV enrolled in the Women's Interagency HIV Study (WIHS) (median age 41 years, IQR 36–47) and 14.6% among HIV-positive participants who inject drugs (median age 49 years, IQR 45–53) in the AIDS Linked to IntraVenous Experience (ALIVE) cohort.[9,11] However, there is substantial variability across studies in frailty prevalence among people living with HIV (5%–28.6%) based on the frailty criteria used and differences in cohort composition.[28]

Unlike younger HIV cohorts, we did not observe an association between nadir CD4 count and frailty among older people living with HIV.[10,11] Among 1946 men who have sex with men enrolled in the Multicenter AIDS Cohort Study (MACS) in the United States, men living with HIV were more likely to be categorized as frail at least once during a 4-year follow-up period compared with those who were HIV negative (29% vs 21%, respectively), and frailty was associated with the history of AIDS (another marker of advanced immune depletion).[10] The median age was 53.8 years (IQR 47.6–61.3) among frail participants compared with 50.5 years (IQR 44.6–56.9) among those considered nonfrail. In the cross-sectional analysis of 1781 women enrolled in WIHS, the prevalence of frailty among women living with HIV increased significantly as the CD4 count dropped, reaching 16.5% among those with a current CD4 count of less than 200 cells/mm^3.[11] It is possible that survivorship bias has contributed to the lack of association between CD4 nadir and frailty observed in our study. People living with HIV who did not survive into older age may have been more frail in the context of profound immunologic depletion and poorer CD4 count recovery. Another explanation of why our findings differ from those of earlier studies may be that depletion of the immune system (as indicated by CD4 nadir) can be reversed by modern antiretroviral therapy, while chronic low-grade inflammation persists and may be a greater contributor to frailty.

Prior studies have identified comorbidity as an important risk factor of frailty, which we did not observe when accounting for the total number of comorbidities present or for the presence of multimorbidity and severe multimorbidity. By contrast, frailty was associated with severe multimorbidity among 482 adults living with HIV attending the Modena HIV Metabolic Clinic in Italy (mean age 53.9 ± SD 6.9 years).[29] In the PBHN cohort, the presence of specific comorbidities (and certain combinations of comorbidities) was also associated with frailty.[26] In our analysis, we did not account for the type, severity, and duration of each illness, which may play a role in the pathophysiology of frailty and potentially explain the difference in our results.

We found an association between social vulnerability (not being in a relationship and loneliness) and frailty,

TABLE 2. Univariable and Multivariable Analysis for the Primary Outcome of Interest of Frailty

Characteristic	RR (95% CI)	aRR (95% CI)
Nadir CD4 count (per 100 cells/mm^3)	1.00 (1.00 to 1.00)	1.07 (0.93 to 1.22)
Age (per 10-year increment)	1.05 (0.70 to 1.57)	1.31 (0.81 to 2.11)
Women (ref = men)	1.46 (0.81 to 2.63)	1.17 (0.53 to 2.60)
Not in a relationship (ref = in relationship)	2.22 (1.28 to 3.85)	2.09 (1.01 to 4.30)
Loneliness (per 10-point increase in score)	1.30 (1.14 to 1.48)	1.25 (1.09 to 1.44)
Time since HIV diagnosis (per years)	1.01 (0.99 to 1.03)	1.01 (0.98 to 1.04)
Number of comorbidities (ref = 0)	1.07 (0.97 to 1.17)	1.04 (0.92 to 1.17)

aRR, adjusted risk ratio; RR, risk ratio.

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highlighting multiple potential ways social connections may be protective for persons aging with HIV (i.e. companionship, physical support, financial resources, nutrition). Another Canadian study of people living with HIV aged 50 years and older reported a high prevalence of loneliness (42%) among frail participants, arguing for the need to develop interventions that address loneliness.[17] A recent report on social isolation and loneliness in older adults from the National Academies of Sciences, Engineering, and Medicine found evidence from multiple studies on the association between lacking social connections and all-cause mortality.[30] The magnitude of the effect was comparable with or even greater than other well-established risk factors such as smoking and obesity. This is in keeping with the concept of social frailty and how being vulnerable to the loss of resources necessary to fulfill one's basic social needs can impact health outcomes. Sadly, many long-term HIV survivors, especially older men who have sex with men, have lost partners during the early days of the HIV epidemic, which has had a long-lasting impact throughout their life course.

As the aging HIV population grows, discussions around where and how people will age with HIV are becoming more important.[31] Recognizing that a large proportion of older adults living with HIV are single, divorced, or widowed (65% of our cohort); it is crucial to develop supports that would address loneliness in this population. This would allow people to age safely in their own homes and create opportunities to make supportive housing and long-term care facilities available and inclusive for persons living with HIV.

With the aging of the HIV population, most studies have evaluated persons aged 50 years or older. To our knowledge, this is the first study looking at frailty exclusively among people living with HIV over the age of 65 years, using the most commonly employed measure of Fried Frailty Phenotype. This increases our ability to make comparisons with the general population. However, our study has several limitations. It must be recognized that frailty is a dynamic process, with individuals transitioning between frailty states over time, which would not be captured using a cross-sectional analysis. A cross-sectional approach also limits our ability to establish causality but can provide insight into factors that are associated with frailty, whether as a contributor to or a result of frailty. As participants in the CHANGE HIV study complete repeat evaluations at 18-month intervals, we will be poised to examine frailty over time using longitudinal data from this cohort in the future. Furthermore, participants were recruited into the cohort from clinic sites, where they receive HIV care and were well enough to attend clinic in person, provide informed consent, and participate in lengthy study protocols. Inadvertently, this may underestimate prevalence of frailty among people aging with HIV by excluding individuals who are not engaged in HIV care, those who are homebound or admitted to a long-term care facility, and those with significant physical or cognitive impairment. Finally, although the makeup (90% men, 76% White) of the study cohort is reflective of the HIV epidemic evolution in Canada, our findings may not be generalizable to other populations of older adults living with HIV.

CONCLUSIONS

Overall, we found a frailty prevalence of 16.6% among people living with HIV in Canada who are 65 years and older. Although we did not identify an association between low nadir CD4 counts and frailty, loneliness and not being in a relationship were associated with a greater likelihood of being frail. Interventions aimed at reducing loneliness should be assessed in people living with HIV to determine whether this could prevent or reverse frailty and ultimately improve functional status and quality of life. In the interim, these variables should be recognized by clinicians as potential indicators of frailty risk.

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