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The Silent Epidemic – Frailty and Aging with HIV

Amanda L. Willig, PhD, RD, **Edgar T. Overton, MD**, and **Michael S. Saag, MD**
Division of Infectious Diseases, School of Medicine, at the University of Alabama at Birmingham

Abstract

As the number of older adults with HIV increases, this population is experiencing an increased risk for frailty. While there is no single definition or diagnostic criteria for frailty, it is generally recognized as an accumulation of deficits in functional capacity and ability to perform activities of daily living. Frailty may be present in up to half of older adults living with HIV, and is associated with significant morbidity and mortality risk in this group. Frailty in HIV can either be transient, and linked to the status of HIV infection, or resemble a more typical gradual decline in functional capacity. Frailty risk in HIV may be exacerbated by mitochondrial dysfunction, chronic inflammation, and oxidative stress. Several tools have been developed and adapted to assess different domains of frailty, yet medical treatment of this condition can be complex and should consider management of polypharmacy as well as nutrition and exercise interventions. However, few concrete strategies have been developed to prevent or treat frailty in the context of HIV infection. This review summarizes what is currently known about the prevalence, diagnosis, and management of frailty among older adults living with HIV.

INTRODUCTION

The introduction of antiretroviral therapy (ART) was a revolutionary advancement in HIV care that demonstrably expanded the life expectancy of people living with HIV (PLWH). As the number of older adults with HIV increases, this population is experiencing greater morbidity[1-5] compared to age-matched HIV-negative groups. Frailty, characterized by decreased functional capacity and reduced ability to perform basic activities of daily living, represents both a manifestation and a contributor to complications in the aging HIV epidemic.[6] Accumulated deficits in functional capacity exacerbate the risk for disability and disease burden and decrease an individual's ability to recover from health challenges. As such, frailty will have a critical impact on clinical care and health outcomes in HIV infection. This article summarizes the recent literature regarding the impact of frailty on aging with HIV infection.

What is frailty?

Frailty is a clinically recognizable condition manifested by physical weakness and vulnerability due to age-associated declines in physiologic reserves, to the point that the ability to cope with acute or chronic stressors is impaired. No single set of defining criteria

Corresponding Author: Amanda Willig, University of Alabama at Birmingham, Center for AIDS Research, 845 19th Street South, BBRB 203, Birmingham, AL 35294. Telephone 205-975-5464; Fax 205-934-1640; mandyrd@uab.edu.

exists to diagnose frailty; rather it is considered as a pathology distinct from aging or other chronic diseases. However, the “frailty phenotype model” is a commonly used method to investigate frailty in geriatrics and HIV infection. Fried and colleagues define frailty as meeting three out of five criteria: unintentional weight loss, self-reported fatigue, low physical activity levels, weakness (measured by hand grip strength), and slow walking speed.[7] Those adults with one or two phenotypic deficits are considered “pre-frail”. Frail older adults do not all experience the same symptoms but rather experience a range of negative health outcomes. Frailty prevalence ranges from 4-59% and varies greatly between countries or geographic locations, is more prevalent in women than men, and is associated with lower income and poor general health.[7-9] The significant impact of frailty on clinical care and health outcomes of older adults has resulted in a call by some clinicians to consider frailty as “the sixth vital sign” in geriatric care.[10]

Frailty in HIV infection

Frailty has become widely recognized among middle-aged and older adults with HIV. One of the first studies of frailty in HIV estimated that 4.4% of participants were frail in a retrospective analysis of HIV-positive men in the Multicenter AIDS Cohort Study (MACS).[4] The MACS frailty assessment was based on self-report questions of three out of four criteria: unplanned weight loss, exhaustion, low physical activity level, and slow walking speed. Investigators have since confirmed that the condition is prevalent in 4-10% of all PLWH[11] and up to half of PLWH >50 years of age.[12,13] Kooij et al. investigated frailty prevalence in HIV-positive versus HIV-negative adults aged 45 and over in the AGEhIV Cohort Study and reported a higher prevalence of frailty with HIV infection at all ages.[14] The negative consequnces of frailty include increased falls, excess hospitalization risk, and higher mortality.[15-17] Indeed, Piggott et al. showed that frailty predicts mortality risk in PLWH, and that frailty and HIV infection have independent and interactive effects on mortality.[18]

Furthermore, frailty is associated with significant morbidity among PLWH, as a key contributor to depression, decreased ability for self-care, and poor quality of life.[7,15,19,20] PLWH diagnosed as frail report higher levels of food insecurity and difficulty performing activities of daily living compared to those pre-frail or not frail.[21] Guaraldi and colleagues evaluated the performance of a 37-item frailty index in the Modena HIV Metabolic Clinic cohort.[22] Higher frailty index score was associated with increased risk for incident multimorbidity (>2 comorbid chronic diseases), including cardiovascular disease, hypertension, type 2 diabetes, chronic kidney disease, chronic obstructive pulmonary disease, cirrhosis, cancers, or osteoporosis. Frailty also has been associated with cognitive impairment in older adults with HIV.[16,17] Collectively, these studies highlight the wide-ranging clinical impacts of frailty and the importance of understanding the etiology and potential interventions for frailty in the context of HIV infection.

Mechanisms of frailty in HIV

A constellation of biological, environmental, and HIV-specific factors contribute to frailty in PLWH. This population now has a higher prevalence of obesity and cardiometabolic disease risk, which can impact frailty risk.[23,24] Older adults with HIV also present at varying HIV disease stages that impact frailty risk differentially. Some PLWH have lived with the virus for several decades and used older, more toxic pharmaceutical/antiretroviral therapy (ART) regimens. Still others have been diagnosed with HIV prior to age 50 and prescribed newer ART regimens. Finally, an expanding number of older PLWH are diagnosed after age 50. These individuals may have been infected for a longer period prior to diagnosis. As such, an understanding of the mechanisms underlying declines in functional capacity is critical to develop interventions for individuals aging with HIV.

HIV infection increases frailty risk—Among the general population, aging persons experience a steady, albeit variable, decline in functional capacity until a threshold is passed, and frailty is manifest.[7,25] However, frailty in PLWH can either mirror this steady decline, or be more transient in nature. Frailty is associated with low CD4+ T-cell count and high HIV viral load. Strikingly, some PLWH experience a reconstitution of functional capacity and immune reconstitution with controlled, indicating some degree of reversibility.[26,27] Frailty in the general population is associated with sarcopenia (decrease in muscle mass and quality);[28] however, Rees et al. report that frailty in HIV is not always directly related to sarcopenia.[29] Using Fried's frailty criteria this group compared performance in 23 frail versus 99 non-frail PLWH. Frailty was associated with exhaustion, depression, and low physical activity levels rather than measures of grip strength and muscle mass.

Systemic Inflammation—Chronic systemic inflammation, mitochondrial damage, and oxidative stress may also contribute to frailty in HIV infection. Chronic systemic inflammation can result in a feedback mechanism whereby inflammation causes mitochondrial damage, which induces oxidative stress and more persistent inflammation.[30-34] Known as "InflammAging", levels of inflammatory biomarkers are elevated in populations of frail, older PLWH, and higher levels of IL-6, TNF-alpha, and c-reactive protein (CRP) have specifically been linked to frailty and consequent morbidity and mortality.[35-40] Several inflammatory biomarkers, notably IL-6 and sTNFR-1 and -2, are independently associated with poor physical function and low muscle mass in HIV-infected cohorts.[41,42] However, Wallet et al. recently reported that elevated levels of sCD14, CRP, and IL-6 in PLWH were not associated with performance on a frailty assessment.[43] Chronic cytomegalovirus (CMV) infection is highly prevalent in HIV infection and may contribute to frailty in PLWH by causing clonal T-cell expansion to a terminally differentiated, senescent phenotype.[44] This T-cell expansion process leads to a state of persistent immune activation and adaptive immune exhaustion with excess systemic inflammation. However, conflicting results have been reported regarding the association of CMV with frailty.[45,46]

Mitochondrial dysfunction and frailty—Lower mitochondrial DNA copy number is associated with a 31% increased frailty prevalence and higher mortality in HIV-negative adults aged ≥ 45 years.[47] Investigators have not identified the mechanism by which these changes occur, but mitochondrial function (or bioenergetics) may decline with age and time on antiretroviral therapy,[48-52] and mitochondrial damage that impacts overall function is likely a key contributor to frailty in older PLWH.[53] Earlier generations of ART were highly toxic to mitochondria; however, newer ART regimens are significantly less "mito-toxic." Despite reduced toxicity, ART use remains independently associated with increased basallevel energy requirements.[54] Similar to the general population, mitochondrial function is also inversely correlated with high body fat percentage in women with HIV, suggesting a role for excess adiposity in HIV-related mitochondrial dysfunction.[55,56] Additional research is needed to identify the best approaches to combat mitochondrial dysfunction and frailty in HIV. Exercise improves mitochondrial number and function, as demonstrated by a significant effect of resistance training on mitochondrial function.[57] Optimal strategies must be both impactful for mitochondrial function and feasible for the majority of PLWH.

Oxidative Stress—Age-related diseases and HIV infection are independently associated with oxidative stress and failure of mitochondrial quality control.[58-60] For example, HIV-1 gene products, such as Tat, can induce mitochondrial damage and mtDNA depletion thus promoting oxidative stress.[60] In treated HIV, the mitochondrial toxicity of ART medications contributes to oxidative stress and a persistent inflammatory state.[61] This oxidative stress shifts lipid composition to a more atherogenic profile that causes persistent inflammation. Oxidized LDL (oxLDL) are proinflammatory lipid molecules that contribute to aging-related diseases,[62] are increased in HIV-infected patients, and are correlated to measures of vascular disease.[63-65] These pro-atherogenic lipid particles also contribute to declines in muscle function and the development of frailty. In contrast, Collerton et al. was unable to confirm an association of oxidative stress with frailty in HIV-uninfected adults aged 85+.[40] Additional research into unique contributors to frailty in PLWH at different life stages will thus be essential as PLWH continue to experience gains in life expectancy.

Measuring and diagnosing frailty in clinical settings

Several tools have been developed to measure and diagnose frailty. However, no standardized tool is universally accepted. Frailty can be assessed according to phenotypic tests that measure physical deficits in certain domains. Other groups have computed frailty “index” scores, which count the number of deficits a person has accumulated in many domains, including functional limitations, cognitive assessment, comorbidities, and laboratory data. Theou et al. evaluated the ability of eight frailty scales to predict all-cause mortality in the Secondary Analysis of the Survey of Health, Aging and Retirement in Europe (SHARE) studies.[66] They reported that the scales varied widely in ability predict mortality in the eleven countries included, and clinical utility depended greatly on which aspects of frailty were being captured. Additionally, some phenotypic assessments may require space or equipment that is not typically available in a clinical setting to test functional and cognitive deficits. Here we present a summary of commonly used frailty scales in studies of PLWH, and provide a more comprehensive list of frailty scales in Table 1. More work is needed to determine which frailty tools best capture the phenotype of frailty among PLWH.

As previously described, The Fried Frailty Phenotype uses five criteria (weight loss, exhaustion, physical activity, hand grip strength, walking speed) to classify participants as not frail, pre-frail, or frail and has been used in several studies of PLWH.[7] The Short Physical Performance Battery (SPPB) includes subjective and objective criteria for diagnosing frailty.[67] Participants are assessed based on balance, gaid speed (4-meter walk), and leg strength (5-repitition chair stand). Scores range from 0-12; poor performance (frail) ranges 0-6, moderate performance (pre-frail) from 7-9, and good performance (not frail) 10-12. Greene et al. reported that an SPPB score ≤10 in the AIDS Linked to IntraVenous Experience (ALIVE) study was associated with a 2.52-fold increase in mortality risk. Compared to HIV-negative participants, having both HIV and an SPPB ≤10 was associated with a 6-fold increase in mortality risk.[68,69]

A 7-item frailty index was developed from the Veterans Aging Cohort Study (VACS). The VACS Index considers age, CD4+ count, HIV-1 viral load, hepatitis C coinfection, and biomarkers of organ system injury.[70] It is associated with baseline frailty status and 5-year mortality in PLWH, with baseline frailty status assessed using the Fried Frailty Pheontype.[70,71] A 30-item frailty index refined by Guraldi et al predicts survival and cardiometabolic disease risk in the Modena HIV Metabolic Clinic Cohort.[22] The index includes biomarkers of organ function, behavioral traits including alcohol consumption and physical activity, and chronic diseases such as osteoporosis and kidney disease.

Interventions to prevent or treat frailty

Frailty has a complex etiology that requires a multidisciplinary framework for treatment. Few interventions have been investigated in the context of HIV infection and aging adults. As such, there are no guidelines for the medical management of frailty in HIV once an individual is identified as pre-frail or frail.

Managing Polypharmacy—Medications can contribute to frailty risk through direct side effects or drug-drug interactions, but these relationships have predominately been studied in HIV-negative populations. Polypharmacy, defined as the use of greater than five prescription medications, was associated with 1.77 greater odds of frailty in the French SIPAF study of HIV-negative older adults. Investigators also reported independent and interactive effects of frailty and polypharmacy on mortality risk.[72] Jamsen et al. similarly identified an association between polypharmacy and frailty in men >70 years of age.[73] Greene and colleagues reported that a median of thirteen medications and supplements used for 89 PLWH aged 60 and over, with most being non-ART. Excluding ART, 66% of participants met criteria for polypharmacy.[74] This finding suggests that polypharmacy is an area in need of further research in the setting of HIV-related frailty.

Exercise—Exercise is an accepted intervention to combat frailty[75,76] and improve cognitive function[77,78] in HIV-uninfected older adults, but data regarding the benefits of exercise among older PLWH is limited. Several studies demonstrate decreased systemic inflammation,[79-81] gains in strength and cardiorespiratory fitness among PLWH younger than 50 years,[82-89] and improvements in self-efficacy, self-reported quality of life and overall health.[87,90-92] Jaggers et al. reported that 6 weeks of increased physical activity decreased perceived stress, depressive symptoms, and fatigue in PLWH aged 18 and older,[90] indicating that such benefits are possible for older PLWH. Gains in physical strength and decreased systemic inflammation have been reported from both laboratory and home-based exercise interventions in younger adults with HIV.[83,85] Souza et al. found that twice-weekly resistance training was associated with equivalent improvements in strength, lipid levels, and glycemic control in a small sample of HIV-infected and HIV-negative men older than 60.[93]

However, published studies have not included a frailty assessment as an outcome of interest in older PLWH. Thus, current physical activity guidelines for older adults with HIV are based on evidence from studies of (i) younger PLWH and (ii) uninfected older adults.[94] These guidelines emphasize that total time spent in one exercise bout should be limited to prevent adverse effects on immune function despite a paucity of data on which to base this recommendation. It remains unclear what type of exercise, and at what dose, is most appropriate and feasible to treat and/or prevent frailty in older adults with HIV. Targeted dose-response exercise trials among older PLWH are desperately needed to bridge the gap between diagnosis of frailty and effective, validated treatment options.

Nutrition—There is a paucity of data regarding appropriate nutrition interventions to prevent or treat frailty in HIV. In the HIV-uninfected population, inadequate caloric and protein intake is associated with frailty and sarcopenia.[95,96] Smit et al. identified an association between food insecurity and frailty, and a trend of lower calorie/protein intake in frail PLWH, in a small sample of women over age 45 living with HIV.[21] HIV infection increases predicted caloric requirements by 10-30% in PLWH; therefore, older adults with HIV may require more calories than typically recommended for age and weight to maintain functional status.[97,98] Protein requirements in HIV have been estimated at 1.0-1.4 grams/kg body weight to preserve lean mass and 1.5-2.0 grams/kg to build lean mass.[99] However, no studies have directly evaluated protein requirements in adults with HIV during the ART era, or whether protein supplementation can minimize frailty among older PLWH. A Mediterranean diet pattern and supplementation with vitamin D (U-shaped association with frailty), selenium, and omega-3 fatty acids have all been investigated in relation to frailty among older adults.[100-103] Nonetheless, few clinical trials have assessed the impact of these dietary factors on frailty. Whether these dietary interventions or other dietary patterns/ micronutrients are effective to address frailty in the context of HIV infection remains unknown. Additional research is needed to clarify nutritional guidelines for PLWH.

Conclusions

Frailty is a highly prevalent condition among older PLWH that requires a multidisciplinary approach for prevention and care. Several critical barriers limit our ability to effectively address frailty. Validated tools to accurately diagnose frailty that can be consistently implemented in the clinical setting need to be codified. Medications can also contribute to frailty risk, particularly in the setting of polypharmacy, a common prescribing pattern in HIV clinics. The dose/type of exercise or dietary interventions required to sustain adequate functional capacity has not been delineated. Research is needed to show whether exercise regimens that can be implemented in “real-world” settings produce health benefits equivalent to those of controlled laboratory-based interventions. Older PLWH often report co-morbid symptoms of fatigue and depression, and clinicians must take these factors into consideration when developing frailty prevention/treatment programs. Finally, different types of intervention may be required depending on the reasons an individual is classified as frail (for example, HIV-related laboratory values versus poor grip strength or walk time). We are currently unable to predict which individuals will respond to a physical activity or nutrition intervention; thus more work remains to fully integrate personalized medicine into frailty treatment for HIV. Our charge is clear: provide data for interventions to improve functional capacity and quality of life and decrease the manifestations of frailty among the aging HIV populations.

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Table 1

Commonly utilized tools for frailty assessment

Frailty Tool	Item No.	Criteria	Classification
Phenotype Assessments			
FRAIL Scale[104]	5	Self-reported deficits in **F**atigue, fitness (**R**esistance and **A**erobic), **I**llness, and **L**oss of weight	1-2: Pre-frail ≥3: Frail
Fried Frailty Phenotype[7]	5	Self-reported weight loss, exhaustion, physical activity Performance on grip strength, walking speed	1-2: Pre-frail ≥3: Frail
Short Physical Performance Battery[67]	3	Performance on tests of balance, gait speed, chair stand	0-3: Severe limitations 4-6 Moderate limitations 7-9: Mild limitations 10-12: Minimal limitations (*subscales can be scored*)
Gérontople Frailty Screening Tool[105]	5	Self-reported social support, weight loss, fatigue, mobility Performance on gait speed test	If at least one deficit identified, clinician judgment of frailty: yes/no
Index Assessments			
Frailty Index[106,107] (frequently adapted)	30 minimum	Proportion of acquired deficits in strength, mobility, balance, nutrition, medical diagnoses, medication count, activities of daily living, social support	Score Range: 0-1 <0.25: Not frail/Pre-frail ≥0.25: Frail
Clinical Frailty Scale[108]	-	Single score selected based on provider's clinical judgment	1: Very fit; 2: Well 3: Well, with treated comorbid disease 4: Apparently vulnerable 5: Mildly frail 6: Moderately frail 7: Severely frail
Veterans Aging Cohort Study Frailty Index (VACS)[70]	7	Scored risks by age, CD4+ count, HIV-1 viral load, Hepatits C co-infection, fibrosis-4 levels, e-glomerular filtration rate	Score Range: 0-164 Higher Score = greater mortality and frailty risk