Perspective

Physical Function and Frailty in HIV

Aging is associated with declines in physical function that can be influenced by many factors, including HIV. These limitations may manifest as increased vulnerability to stressors, or frailty. Functional limitations and frailty can be used to guide clinical decisions, protect people from harm, and avoid strategies that are not likely to provide benefits. Such limitations could also serve as clinically relevant endpoints for some clinical trials. Interventions should ideally focus on early impairments that begin to occur in midlife, well before an individual becomes frail or experiences disabilities. Overall, physical activity is safe and effective in improving physical function, and counseling about physical activity should be a routine component of HIV care to increase the lifespan and healthspan of individuals with HIV. There are some promising pharmaceutical options, but more research is needed to determine the safety and long-term efficacy. This article summarizes an International Antiviral Society–USA (IAS-USA) webinar presented by Kristine M. Erlandson, MD, MS, on July 24, 2020. This webinar is available on demand at https://www.iasusa.org/courses/on-demand-webinar-2020-erlandson/.

Keywords: HIV, aging, disability, frailty, physical function

Aging is associated with declines in physical function. Peak performance is often seen in individuals in their 20s or 30s. Declines in physical function, including in muscle mass and strength, can be slow or rapid as individuals age and may be influenced by numerous factors, including activity level: physically active individuals may have slower physical declines than those who are less active. Clinicians can help patients maintain the highest level of function throughout their lifespans. Recognition of differences in function is key to individualizing how medical care should be provided and the implications of aging-associated physical decline for adults living with HIV.

Disability

Much of the model for characterizing the changes in physical function associated with aging stems from the classic disablement model, first conceptualized in the 1960s, that later formed the basis of the World Health Organization International Classification of Functioning, Disability, and Health.[1] This model assumes that there is an underlying pathology leading to 1) physical impairment that progresses to a 2) functional limitation that, ultimately, could lead to 3) disability (see Figure 1). Using this framework, impairment refers to a change in body function at the organ level. This impairment can be diagnosed during a physical examination or through imaging or laboratory tests (eg, vision or hearing impairment, osteopenia or osteoporosis, or loss of muscle mass). Limitations refer to decreased ability to do something because of the underlying impairment, and this can be assessed through performance-based measures (eg, performance of a 6-min walk), which may be more appropriate in research settings, or through individual self-report of daily functions, which may be preferred in the clinic setting.

The Centers for Disease Control and Prevention defines disability as "any condition of the body or mind (impairment) that makes it more difficult for the person with the condition to do certain activities (activity limitation) and interact with the world around them (participation restrictions)."[2] Importantly, disability is a social phenomenon and is highly dependent on what is expected of the individual

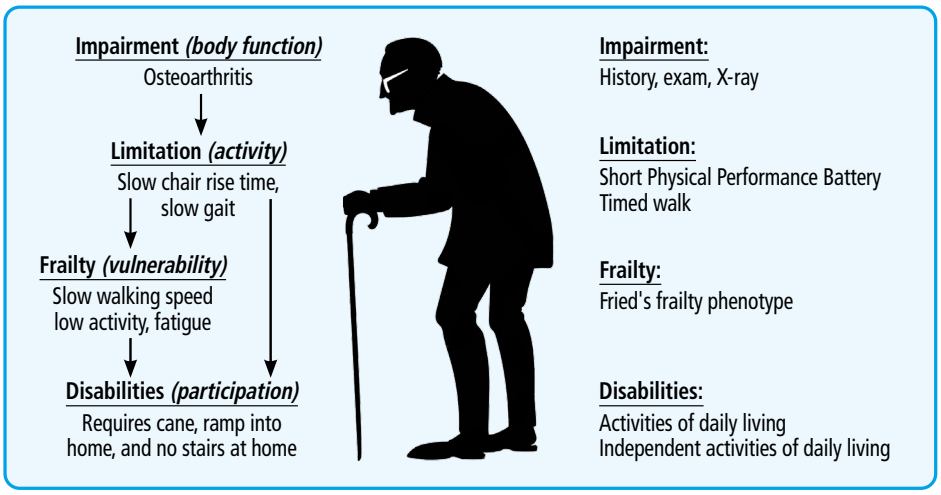

Figure 1. Impairment, limitations, frailty, and disability in an older individual with osteoarthritis. An individual may experience impairment in body function that is identified through history, exam, or imaging. These impairments in function may lead to limitations in activity that could be identified by self-report, or by slowed time on objective assessments such as a Short Physical Performance Battery. Over time, these activity impairments may result in disability if appropriate resources are not available and the individual cannot participant in usual activities. These concepts are related to, but distinct from frailty, which is a vulnerability to stressors and can be characterized through Fried's frailty phenotype or other measures. Adapted from Erlandson et al.[30]

Dr Erlandson is Associate Professor of Medicine at the University of Colorado in Aurora, Colorado.

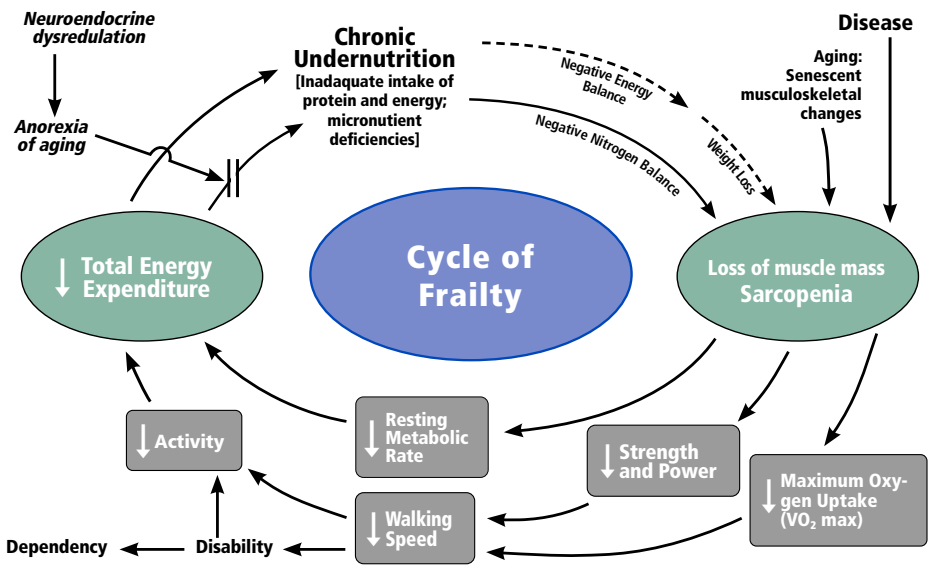

Figure 2. The cycle of the frailty phenotype. Underlying disease and senescent changes contribute to a loss of muscle mass. This loss of mass may impact strength (grip) and exercise endurance (fatigue), resulting in slower performance (gait). Slower gait and less endurance may contribute to less physical activity (activity). When combined with the loss in muscle mass, energy expenditure decreases, and appetite declines. Decreased caloric consumption may result in weight loss, which contributes to continued loss in muscle mass, perpetuating the cycle. Adapted from Fried et al.[3]

within their culture, what the individual expects of themselves, what resources are available to help them function in their community, and how their physical environment is set up for accessibility.

Frailty Assessments

Frailty is a separate but closely-related concept to disability, describing the vulnerability of an individual to stressors. When a health-related stressor, such as hospitalization, illness, or injury, occurs in individuals who are frail, they may not be able to "bounce back" to their baseline level of function, which is a pattern that may be repeated each time there is a new stressor.

One of the most common ways to describe frailty is with the frailty phenotype.[3] The frailty phenotype measures frailty by the presence or absence of 5 criteria: 1) slow gait or slowness, often measured via a 4-m walk; 2) weak grip, usually measured by a dynamometer; 3) low levels of physical activity, usually self-reported; 4) fatigue, usually self-reported; and 5) unintentional weight loss. For the frailty phenotype, which generally takes 5 to 10 minutes to assess, an individual is considered robust if they meet none of the above criteria, prefrail if they meet 1 or 2 of the criteria, and frail if they meet 3 or more of the criteria. Notably, some of these criteria can be attributable to factors or conditions other than frailty, such as fatigue caused by depression. The assessment occurs prospectively and may not be captured in a routine HIV clinic visit without prior planning.

The frailty phenotype attempts to define the components of the complex cycle of frailty (see Figure 2). Initially, factors such as senescent muscle changes, disease, and underlying comorbidities contribute to a loss of muscle mass. Loss of muscle mass affects exercise endurance (measured by maximum oxygen uptake [VO_2 max]), strength and power, and resting metabolic rate. Over time, decreased exercise endurance can lead to slow walking speed, which can lead to lower levels of physical activity, resulting in fewer calories burned. These decreases in energy expenditure can also suppress appetite, leading to chronic undernourishment, feedng back into loss of muscle mass and continuing the cycle.

Decreased strength and power and slow walking speed are also associated with increased mortality and poor outcomes in the general population. Of note, although frailty is related to and often overlaps with comorbidity and disability, it is not equivalent to these. Frailty can exist outside of comorbidity, and disability can exist without frailty.

Another way to define frailty is through the deficit accumulation model, also called the Frailty Index. This model considers variables that increase with age, but are not ubiquitous with age, and that are associated with health status. For example, most people will need corrective lens as they get older, and wearing eyeglasses is not associated with health status, so needing eyeglasses would not be a useful variable for the Frailty Index.

The Frailty Index measures frailty as the number of contributing variables an individual has, divided by the total number of variables assessed. The Frailty Index can be adapted for specific populations and can be measured retrospectively via chart review. The initial Frailty Index included 70 variables ranging across activities of daily living, physical function, mood, cognition, neurologic function, and cardiovascular, endocrine, and respiratory health.[4]

Similar to the Frailty Index, the VACS (Veterans Aging Cohort Study) Index uses routinely assessed laboratory-derived variables to predict mortality and morbidity in veterans with or without HIV. The VACS Index has been successfully applied to many populations within and outside of the Department of Veterans Affairs, nationally and internationally.

The Clinical Frailty Scale (Table 1) is a simplified version of the Frailty Index.[5] It employs a visual diagnosis of frailty using a 9-point scale, with 1 being Very Fit" and 9 being "Terminally Ill." The Clinical Frailty Scale has been utilized in many clinical settings as it is useful for quick assessment and appears to perform quite well in predicting frailty. Each of the tools that can be used to assess frailty, including those discussed above, has its own advantages and disadvantage (Table 2).

Table 1. The 9-Point Clinical Frailty Scale for Visual Determination of Frailty

Frailty Level[a]	Description
Very fit	Robust, energetic, and motivated Among the fittest for their age
Well	No active disease symptoms Less fit than "very fit" individuals Exercise or are very active occasionally or seasonally
Managing well	Medical problems are well controlled Not regularly active beyond routine walking
Vulnerable	Not dependent on others, but symptoms limit activities Feel "slowed down" or tired during the day
Mildly frail	More evident slowing Progressively need help performing some instrumental activities of daily living (eg, cooking, shopping, managing medications)
Moderately frail	Need help with all outside activities and keeping house Often need help with stairs, bathing, and dressing
Severely frail	Completely dependent for personal care Stable and not at high risk of dying (within next 6 months)
Very severely frail	Completely dependent Approaching end of life Would typically not recover from even minor illness
Terminally ill	Approaching end of life Life expectancy is less than 6 months

[a]In individuals with dementia, degree of frailty corresponds with degree of dementia: mild dementia includes forgetting the details of a recent event but remembering the event itself, repeating the same question or story, and social withdrawal; moderate dementia includes impaired short-term memory (past life events may be remembered) and the ability to perform personal care after prompting; severe dementia requires assistance to perform personal care.

Adapted from Waite et al.[5]

Assessing Physical Function Limitations

The Short Physical Performance Battery (SPPB) has been well validated in the geriatric literature, and there is growing evidence of its applications for individuals with HIV. The SPPB measures objective functional outcomes and requires only a chair, stopwatch, and enough space to complete a 4-m walk, which can easily be done in a clinic. It is a prospective assessment that takes approximately 5 to 10 minutes to complete. Of note, it does have a ceiling effect, meaning that categorical scoring is such that many participants have perfect scores, even in the presence of other mild impairments.

Crane and colleagues examined the feasibility of the SPPB by administering it across 3 HIV clinics.[6] In the study, 2 of the clinics administered the SPPB before or after a routine clinic visit, and one clinic required participants to return for a separate visit to complete the SPPB. Staff training to administer the SPPB took approximately 1 hour, and completion of the SPPB itself took approximately 7 minutes. The investigators concluded that it is feasible to implement the test without serious disruptions or injuries.

Another prospective assessment is the chair rise, which can be measured in a variety of ways, such as the time to complete 5 or 10 rises, or the number of chair rises an individual can complete in 30 seconds. This continuous scale produces less of a ceiling effect and can detect a range of values over a larger population; however, individuals with specific limitations, such as arthritis in the knees, may be unable to complete this assessment.

Weaker grip strength is associated with increased mortality, and grip strength is a component of frailty. Measuring grip strength requires a dynamometer, which must be regularly calibrated for accuracy, and individuals with specific limitations, such as arthritis in the hands, may have difficulty completing this assessment.

Completion of a 400-m or 6-min walk can be used to identify a higher level of physical endurance than shorter distances such as a 4-m walk. The 400-m walk or 6-min walk provide a continuous outcome (time or distance covered) and can help identify more subtle impairments in endurance or coordination. However, it requires more time and space than other assessment tools and may not always be a feasible option.

Questionnaires may also be used. These assessments are easy to standardize, can be completed in a variety of locations (eg, in a waiting room, by mail, or by telephone), and may be most appropriate as a brief screening to identify individuals with impairments. Of note, questionnaires are subjective and may not be as informative as an outcome for individuals in clinical intervention studies.

Frailty in Individuals With HIV

Many factors thought to contribute to the development of frailty in the general population are observed in people with HIV, including inflammation, changes in body composition markers, and neurocognitive impairment. Other factors that may contribute to frailty include socioeconomic factors, such as education level and health insurance, and modifiable risk factors, such as obesity, low level of physical activity, and smoking.

Some data have suggested that frailty occurs more commonly in people with HIV. In the AGEhIV Cohort Study (Cross-sectional Comparison of the Prevalence of Age-Associated Comorbidities and Their Risk Factors Between HIV-Infected and Un-infected Individuals), frailty was more common in people with HIV than in those without across nearly every age range.[7] In the MACS (Multicenter AIDS Cohort Study), which included men who have sex with men with and without HIV, prevalence of frailty was greater starting at age 50 years, and greater among older men with HIV than older uninfected controls.[8] The prevalence of frailty in other

Table 2. Advantages and Disadvantages of Tools Used to Measure Frailty

Test	Advantages	Disadvantages
Frailty phenotype	• Well-validated in geriatric literature and HIV literature	• Requires dynamometer • Overlaps with cognition/depression in HIV • Categorical • Subjective components • Prospective only
Frailty or Veterans Aging Cohort Study Index	• Easy to derive from labs • Can collect retrospectively	• No measure of physical function • More difficult to intervene (yes/no for each component)
Short Physical Performance Battery	• Well-validated in geriatric literature • Objective outcomes • Only requires chair and 4 meters of space	• Takes 5-10 min • Ceiling effects as the standard 12-scale exam • Prospective
4-meter walk	• Well-validated in older populations • Quick • Does not require equipment • Continuous outcome	• Requires some training to standardize across sites; space • Prospective
Chair rise time	• Easy/fast • Only requires chair • Continuous outcome • Less of a ceiling effect • Greatest impairment in HIV • Changes with intervention	• Patients with severe knee problems may be unable to complete • Prospective
Grip strength	• Associated with increased mortality	• Requires dynamometer with calibration • Impacted by arthritis
400-meter or 6-minute walk	• Higher level • Less of a ceiling effect • Continuous outcome • Identifies more subtle impairments	• Takes more time • Requires more space
Questionnaires	• Easy to standardize • Can be done in waiting room or by mail • Might be more appropriate as a brief screen	• Subjective • May not be amenable to interventions

populations with HIV varies depending on age, the definitions or measures of frailty used, and use of antiretroviral therapy.[7,9-18]

Interventions

The most effective intervention for frailty is physical activity or exercise, which when done consistently can improve physical function and reverse frailty over time.[19-25] However, questions remain about the appropriate level of exercise for individuals with underlying inflammation, or whose neuropathy or other pain could potentially be exacerbated.

In a study of 69 sedentary people with and without HIV aged 50 to 75 years, who had no contraindications to exercise, participants engaged in a supervised exercise program 3 days per week for 24 weeks.[26] Exercise started as 15 minutes on a treadmill and increased to 50 minutes over the course of the 24 weeks, and participants also completed 4 different resistance exercises. All participants completed 12 weeks of moderate-intensity exercise, and half the group was randomly assigned to increase to high-intensity exercise (high intensity based on their baseline measurements, VO_2 max, and strength) or continue moderate-intensity exercise for the next 12 weeks. All participants had improvements in their physical function after 24 weeks, and improvements were similar among individuals with and without HIV. Furthermore, individuals with HIV had statistically significantly greater improvements in 400-meter walk time, time to climb a flight of stairs, and VO_2 max. Overall, participants assigned to high-intensity exercise tended to have greater improvements in measures of strength, particularly among those with HIV. Improvements were also observed in components of frailty, and with an increase in lean mass and decrease in fat mass.

In addition to exercise, diet interventions may also help improve physical function. In a landmark study comparing the impact of a diet intervention in addition to an exercise intervention in older adults with obesity (without HIV), participants who had both diet and exercise interventions had the greatest improvement in their physical performance scores, followed by those who had exercise intervention only, and those who had diet intervention only, and those who had neither intervention.[27]

Beyond diet and exercise, some data suggests that a comprehensive geriatric assessment may have some benefit in reducing frailty. The comprehensive geriatric assessment ensures comprehensive, individualized care, rather than system-focused or guideline-driven care. A comprehensive assessment can

help identify care or medications that are no longer necessary, detect gaps in care or diagnoses (such as cognitive or hearing impairments), and can connect patients to appropriate resources (such as hearing aids, or home health), which ultimately may reduce frailty.

For individuals who cannot exercise or cannot exercise to the needed intensity because of substantial disability or other impairments, pharmacologic options may be appropriate and necessary. Testosterone has shown some benefit in improving muscle mass; few studies have shown a benefit of testosterone on muscle function, with added risk of cardiovascular disease.[28,29] Metformin and dasatinib are currently being studied in clinical trials of older adults without HIV as potential treatments for frailty, but more data are needed.

Summary

Functional limitations and frailty can provide a window into patient vulnerability and can be used to guide clinical decisions. Interventions for frailty should ideally focus on early impairments before an individual becomes frail. Overall, physical activity is safe and effective in improving physical function, and counseling about physical activity should be a routine component of HIV care. There are some promising pharmaceutical options, but more research is needed to determine the safety and long-term efficacy.

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