Frailty and Common Geriatric Syndromes in the Aging HIV Population

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Disclosure Statement
In accord with the disclosure policy of the Harvard Medical School as well as standards set forth by the Accreditation Council on Continuing Medical Education, speakers, I, my spouse or partner, do not have any relationship to companies producing pharmaceuticals, medical equipment or devices.
Learning Objectives

1. Learn the definition of primary and secondary frailty
2. Assessment of Frailty
3. Relationship between HIV, frailty and other Geriatric Syndromes
4. Potential approaches to prevention of frailty
Demographics
Disability & Age

Percentage of adults aged ≥18 years reporting disability

![Bar graph showing the percentage of adults aged 18-44, 45-64, and ≥65 reporting disability, with bars indicating the percentage for men and women.](Image)
What is Frailty?

• Frailty has long been considered synonymous with disability and co-morbidity, to be highly prevalent in old age and to confer high risk for falls, hospitalization, and mortality

• It is becoming recognized that frailty may be a distinct clinical syndrome with a biologic basis

• The frailty process appears as a transitional state in the dynamic progression from robustness to functional decline. During this process, total physiological reserves decrease, and become less likely to be sufficient to maintain and repair the aging body
What is Frailty?

- Longitudinal studies have demonstrated that slow gait, fatigue, exhaustion, anorexia, unintentional weight loss and reduced muscle strength should all be considered as major symptoms of frailty.

- At the stage of frailty, clinicians can easily distinguish frail from nonfrail older adults using factors such as appearance (consistent or not with age), nutritional status (thin, weight loss), subjective health rating (health perception), performance (cognition, fatigue), sensory/physical impairments (vision, hearing, strength), and current care (medication, hospital).
What is Frailty?

- The process of “becoming frail” is silent and insidious. A better understanding of these clinical changes and their underlying mechanisms, beginning with the pre-frail state, may confirm the impression held by many geriatricians, that increasing frailty is distinguishable from aging, and in consequence is potentially reversible.
Definition of Frailty

- Frailty is a clinical syndrome of dysregulated energetics, with definable clinical manifestations that become apparent when physiologic dysregulation reaches a critical threshold.

- Frailty has recognizable causes at the level of both altered physiology and potentially altered genetic, cellular, and molecular processes—[hormonal & cellular changes: GH, IGF-1, IL-6, DHEAS, CRP, apoptosis, decreased amino acid use in muscle repair].

- A validated frailty syndrome is manifested when multiple components are present: (1) weakness, (2) low energy / exhaustion, (3) slowed walking speed, (4) low physical activity, and (5) weight loss.
Table 1. Scoring Systems to Assess Frailty in Older Adults

Cardiovascular Health Study (CHS) Index - Fried Criteria

Frail = 3 of the following findings present
Pre-frail = 1 or 2 of the following findings present

- Weight loss (≥5 percent of body weight in last year)
- Exhaustion (positive response to questions regarding effort required for activity)
- Weakness (decreased grip strength)
- Slow walking speed (>6-7 seconds to walk 15 ft)
- Decreased physical activity. Males expending <383 kcals/week and females <270 kcal/week in physical activity.

(For reference - walking 4 miles in 1 hour = 300 kcal)
Frailty Components

Age-Related Anatomical Changes

A - Loss of height
B - Increased AP diameter of chest
C - Kyphosis
D - Protruding abdomen
E - Increased hip flexion
F - Increased knee flexion
G - Flattening of foot arch

Kyphosis

Sarcopenia

Oropharyngeal Dysphagia

Baroreceptor Dysfunction
Frailty Cycle

Fig 2. The frailty cycle $\text{VO}_2 =$ volume of oxygen utilisation. Reproduced with permission from The McGraw-Hill Companies.²
Primary & Secondary Frailty

• **Primary**: loss of muscle mass is a central component and a key predictor of clinical manifestations of this syndrome

  – Predictors of loss of muscle mass and strength with aging include anabolic factors such as testosterone and IGF-1, amount of physical activity, nutritional intake (protein, vitamin D, etc.) and age

• **Secondary**: inflammatory diseases independently predict frailty potentially through inflammation and/or their effect on cardiopulmonary function (heart failure, COPD, arthritis, HIV)
Secondary Frailty
HIV-Associated

There are studies to support that:

1. HIV-associated inflammation and immune activation may be partly responsible for early aging in people with HIV

2. HIV is associated with increased frailty risk

• We need to integrate geriatric principles into the clinical care of our newly aging HIV population
Secondary Frailty
HIV-Associated

• Frailty in HIV leads to decreased physiological reserve, and accumulation of deficits that are associated with an increased susceptibility to undesirable outcomes such as loss of function, loss of independence, falls, worsening mobility, possibly ending up in a hospital or an institution.

• Though most studies have focused on physical frailty (physical weakness, muscle wasting, not being able to do activities of daily living), these impairments often co-exist and interact with cognitive and immune frailty as well (including depression & dementia).
Secondary Frailty
HIV-Associated

A number of HIV-related issues may increase frailty risk:

1. How long a person has been HIV positive
2. When they started antiretroviral therapy (ART)
3. Adherence to treatment
4. Medications they are taking
5. CD4 T-cell count now or at their lowest point (nadir) before starting treatment
6. Viral load both in plasma and in cerebrospinal fluid (CSF)
7. Co-infections, such as cytomegalovirus (CMV) or hepatitis C
Secondary Frailty
HIV-Associated

A number of HIV-related issues may increase frailty risk:

8. Other medical and physiological factors can also increase risk, such as other medications being taken, cardiovascular health, liver and kidney function, cancer, body weight and composition, and lifestyle issues such as smoking, diet, and levels of physical activity.
Secondary Frailty
HIV-Associated

- Recent data suggest that all these factors probably work together to increase the risk of frailty for people living with HIV

- Recent report from the Multicenter AIDS Cohort Study, following 1946 men found significantly higher prevalence of frailty among HIV positive compared to HIV negative individuals (12% versus 9%, respectively) that began to be apparent at the age of 50 and persisted into later life
A cross-sectional study enrolled 155 HIV positive people aged 50 or older (median age 57), all with an undetectable viral load on ART:

1. Frailty was observed in 9% of the participants, but "pre-frailty" was observed in 56% of the cohort, higher than seen in the national HIV negative population.

2. Other geriatric syndromes were also common: 26% were at risk of falls and 25% had urinary incontinence.

3. 25% reported that they had difficulty with more than 1 basic ADL (self-care tasks such as bathing, using the toilet, feeding or clothing oneself).

4. 47% reported difficulty with more than 1 instrumental ADL (higher level tasks such as shopping, housekeeping, managing accounts, food preparation, taking medications, using the telephone, or transportation).

M Greene, V Valcour, Y Miao, et al.
HIV and Other Geriatric Syndromes

• Whether HIV itself or the comorbidities associated with it are most responsible for frailty and other geriatric symptoms is unclear, but it is widely agreed that inflammation related to HIV, other infections such as CMV, and chronic conditions or lifestyle factors plays a major role in driving more rapid aging and increased morbidity and mortality.

• HIV itself can have lasting effects on immune activation that persist despite treatment & CD4 count normalization – one example is imbalance in CD4/CD8 ratios: HIV positive people with low CD4/CD8 ratios continue to be at higher risk of serious non-AIDS events and death regardless of absolute CD4 counts.
The term *Failure to thrive* is used in older adults with decreased functional status, along with:

1. Protein-energy undernutrition
2. Loss of muscle mass (sarcopenia)
3. Problems in balance & endurance
4. Decreased cognitive function
5. Depression
Frailty – Clinical Syndrome

• Increased vulnerability to stressors such as extremes of heat and cold, acute infection or injury, or stress of hospitalization or surgery

• Delayed recovery from illness

• Increased risk of falls, functional impairment & death

• Diminished homeostatic reserve (linked to frailty) – referred to as *homeostenosis* – is one of the major characteristics of aging

• Decreased hand-grip, FEV-1, sit-to-stand
Frailty
**Frailty Index**

<table>
<thead>
<tr>
<th>Table 1. Frailty Criteria</th>
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<td><strong>Shrinking (weight loss)</strong></td>
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<td><strong>Decreased grip strength (weakness)</strong></td>
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| **Exhaustion** | Exhaustion was measured by responses to the following 2 statements from the modified 10-item Center for Epidemiological Studies—Depression scale: 

&ldquo;I felt that everything I did was an effort&rdquo; and &ldquo;I could not get going.&rdquo; Subjects were asked, &ldquo;How often in the last week did you feel this way?&rdquo; Potential responses were: 0 = rarely or none of the time (&lt;1 day); 1 = some or a little of the time (1–2 days); 2 = a moderate amount of the time (3–4 days); and 3 = most of the time. Subjects answering either statement with response 2 or 3 met the criteria for exhaustion. |
| **Low activity** | Physical activities were ascertained for the 2 weeks before this assessment using the short version of the Minnesota Leisure Time Activities Questionnaire, and included frequency and duration. Weekly tasks were converted to equivalent kilocalories of expenditure, and individuals reporting a weekly kilocalorie expenditure in the lowest 20th percentile for their gender (men, &lt;383 kcal/week; women, &lt;270 kcal/week) were classified as having low physical activity. |
| **Slowed walking speed** | Slowness was measured by averaging 3 trials of walking 15 feet at a normal pace. Individuals with a walking speed &lt;20th percentile, adjusted for gender and height, were scored as having slow walking speed. Men met criteria if height and walk time were $\leq 173$ cm and $\geq 7$ seconds, or $>173$ cm and $\geq 6$ seconds, respectively. Women met criteria if height and walk time were $\leq 159$ cm and $\geq 7$ seconds, or $>159$ cm and $\geq 6$ seconds, respectively. |

Each criterion is scored with a 0 or 1.
68 year-old man presents with weight loss of 10 lb over 18 months (7% of body weight). Feels everything he does is an "effort," and has begun using his arms to lift himself from the chair. Physical examination is significant for slow, steady gait. Depression screening is negative. CBC, BUN, creatinine, electrolytes, TFTs & LFTs are normal. Frailty is diagnosed. Which of the following is most likely to prevent further decline in function?

A. The use of antidepressants
B. Increased social interaction
C. Combined resistance-training & walking exercise program
D. Protein supplements with meals
E. The use of appetite stimulants
Figure 1. The cycle of frailty (Adapted from Fried LP, et al. J Gerontol 2001).
Interventions to Reduce Frailty

1. Exclude any modifiable precipitating causes of frailty, including causes that are treatable or environmental

2. Improve the core manifestations of frailty, especially physical activity, strength, exercise tolerance, and nutrition

3. Minimize iatrogenic complications during hospitalization or surgery (infections, medication adverse effects, dehydration)
Interventions to Reduce Frailty – Interdisciplinary Approach

- PT / OT: balance (Tai Chi), resistance training (prevent fatty sarcopenia)
- Nutritional support: frequent small meals (5/day), protein supplements; check albumin, prealbumin & cholesterol levels
- Adequate hydration
- Good oral care – treat periodontitis
- Screen for oropharyngeal dysphagia – adjust diet (thickened liquids)
- Screen for depression / cognitive impairment, late-life paranoia
- Early mobilization
- Review medications: digitalis, NSAIDs, SSRI are associated with anorexia
Summary

- Frailty can make day-to-day living more difficult for people living with HIV.
- Reduction in frailty-associated functional capacity is associated with a lower quality of life.
- Among aging people with well-controlled HIV, better performance on the 400-meter walk, faster chair rise, and greater physical activity were associated with both higher physical and mental quality-of-life scores.
- Targeted exercise programs to increase physical activity and improve speed and power should be evaluated as interventions to improve quality of life for HIV-positive people on ART.
Summary

- One study showed a 12-week exercise program which consisted of 3 x 60 minute walks per week at 65%-75% of maximum heart rate, either with or without 30 minutes of circuit training (the "walk" and "strength-walk" groups) resulted in:

1. Significant improvement in performance and in all strength exercises, as well as in body mass index, waist and hip circumferences, and total and LDL cholesterol levels
2. Significant reductions in the inflammation biomarkers D-dimer, IL-18, IL-6, and myostatin (inhibits muscle differentiation)

- Programs incorporating moderate exercise may be beneficial, at least for less active people with HIV; need to better define types of exercise needed, duration, and intensity
Questions