REVIEW

Frailty in people with HIV: a geriatric syndrome approach to aging with HIV

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Purpose of review

Older persons with HIV (OPWH) are at risk of earlier onset of age-related comorbidities and common geriatric syndromes, notably frailty. The purpose of this review is to provide an update on recent developments related to frailty in OPWH, particularly as they relate to common co-occurrence of frailty with other geriatric syndromes which have an adverse impact on health outcomes.

Recent findings

Recent studies reliably demonstrate that frailty co-occurs with other geriatric syndromes due to common biologic risk factors. They often have an equal or greater impact on mortality and quality of life (QoL) compared to age-related comorbidities. Frailty is potentially reversible and risk factors for progression to or regression from a state of frailty have been identified. Importantly, HIV and Aging care centers have been initiated based on proven geriatric-based principles and frail OPWH should be referred. The role of agism and stigmatization are identified as contributors to states of frailty.

Summary

Recent findings focus on the important role geriatric syndromes especially frailty play in determining QoL in OPWH and this has led to efforts to operationalize frailty screening methods and to develop appropriate management protocols to limit or delay the impact of frailty on health.

Keywords

aging, frailty, geriatric syndromes, HIV, interdisciplinary care, quality of life

INTRODUCTION

The life expectancy of people with HIV (PWH) has significantly increased over the past four decades as a result of advances in combination antiretroviral therapy (cART). Recent estimates show that for PWH who are virally suppressed, life expectancy is nearly the same as for those without HIV [1,2]. However, additional years are not necessarily spent in good health. Since the introduction of the 4th 90 [improving quality of life (QoL) and supporting healthy aging in PWH] as a new target for the UNAIDS 90–90–90 framework, it is evident that successful management of HIV must address health needs of this aging population beyond viral suppression [3,4]. Focusing on healthy aging among PWH marks a significant shift in the way HIV care is approached in the current era and emphasizes the importance of improving both quantity and quality of life. It is recognized that health is affected by a multitude of factors and does not merely represent an absence of disease, reflecting an individual's multidimensional state of wellness and functional capacity [5].

With this understanding, it is not surprising that frailty has become the topic of significant interest in the field of HIV. In the past 5 years, there have been several important reviews on the topic [6–8].

These papers emphasize that increased frailty risk in PWH is driven by factors unique to the population, including HIV-related inflammation, immune dysfunction, and cART side effects, especially related to several earlier regimens. They also stress that frailty management must go beyond simple medical interventions, incorporating psychosocial support and lifestyle modifications (such as exercise and nutrition) to improve outcomes. This is particularly true because frailty is a geriatric syndrome, rather than a distinct disease entity, caused by interrelated biological, environmental, and

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KEY POINTS

- Frailty is associated with impaired quality of life (QoL) and increased mortality in older persons with HIV (OPWH).
- Frailty is associated with increased immune activation in OPWH.
- Frailty often occurs concurrently with other common geriatric syndromes in OPWH which together impact functional status and QoL to a similar extent as age-related comorbidities.
- Risk factors which promote development of frailty and reversal of frailty are identified.
- OPWH who screen positive for frailty should be referred to an HIV-Aging center for assessment and management.

lifestyle factors that are shared across other geriatric syndromes.

This review explores frailty as a geriatric syndrome and its growing significance in older people with HIV (OPWH). By examining recent evidence, we emphasize the importance of assessing frailty as a means to gauge functional capacity, quality of life, and overall well being in OPWH. This multidimensional approach offers a better understanding of how to support OPWH, ensuring interventions are tailored to the individual's functional needs.

DEFINING FRAILTY AS A GERIATRIC SYNDROME

Frailty is a condition marked by vulnerability to physiologic and environmental stressors, resulting in greater susceptibility to adverse outcomes including falls and impaired mobility, loss of independence, disability, polypharmacy, cognitive impairment and mortality [9]. Although there is a significant overlap between frailty, comorbidities and disabilities, frailty can occur in the absence of either [10]. Frailty therefore offers a more nuanced and multidimensional way to assess aging, particularly for OPWH who experience a higher prevalence and earlier onset of frailty [11], by emphasizing how well an individual can cope with the stresses of aging, illness, and treatment.

It is important to recognize that frailty does not occur in isolation and PWH often experience a constellation of geriatric syndromes [12]. Geriatric syndromes are a group of clinical conditions commonly seen in older adults that do not fit into specific disease categories and are caused by a combination of physical, psychological, and social factors [13]. They may be associated with functional decline and can have a profound impact on an individual's ability to live independently and maintain a good QoL. Common geriatric syndromes include but are not limited to cognitive impairment, sarcopenia, falls, depression, malnutrition, sensory deficits and polypharmacy. As frailty shares many risk factors with these conditions, they should be considered when assessing and managing frailty in OPWH.

FRAILTY AND ITS RELATIONSHIP WITH OTHER GERIATRIC SYNDROMES

Several recent studies have explored the complex interaction between frailty and other geriatric syndromes in OPWH. Makinson and colleagues evaluated the link between neurocognitive impairment and frailty among OPWH over 70 enrolled in the French ANRS EP66 SEPTAVIH cohort [14]. They found an association between low cognitive performance and risk of frailty/prefrailty but not HIV-related factors such as history of AIDS, $CD4^+$ T cell count or $CD4^+/CD8^+$ ratio. They attributed this correlation to underlying mechanisms and confounders that link these two conditions, including inflammation, oxidative stress, sarcopenia and depression. Practically, cognitive decline may impair a person's ability to manage daily activities, leading to reduced physical activity, poor medication adherence, and difficulty managing comorbidities – all of which can accelerate frailty. Conversely, frailty itself, often characterized by a decline in physical strength, endurance, and overall resilience, can lead to an increased vulnerability to cognitive decline through social isolation, reduced physical activity, nutritional deficiencies, and concurrent mental health problems.

Polypharmacy, especially medications with anticholinergic toxicity, can potentiate the interaction between frailty and cognitive impairment, as well as falls. In the UK POPPY study, a cohort of OPWH over 50, prescription of anticholinergic medications was identified in 28% of participants and was associated with increased odds of both frailty and recurrent falls [15▪]. A systematic review and meta-analysis (10 studies with a sample size of 7755 individuals) examined the association between frailty and adverse health outcomes among PWH (mean age of 49 years) [16]. The authors found a significant association between frailty and injurious falls as well as all-cause mortality, highlighting the need for early screening and fall prevention strategies, such as physical rehabilitation, strengthening exercises, and environmental modifications.

Depression has been implicated in multiple studies evaluating frailty in PWH. The relationship between depression, frailty and resilience is complex and interrelated, as highlighted by a recent study by Meng and colleagues [17], which revealed that the association between resilience and frailty was mediated by depression. Depression had a particularly strong impact on psychological frailty, which may be a reflection of impaired motivation, increased social isolation, reduced QoL and increased risk of cognitive dysfunction. On the other hand, frailty can contribute to development of depression in response to physical limitation, loss of independence and social isolation. Sensory deficits such as visual and hearing impairment, common in PWH [18] can compound the challenges faced by individuals with frailty and depression, exacerbating self-perception of disability and contributing to social withdrawal and isolation. Furthermore, sensory deficits can make it harder for individuals to navigate their environment, increasing the risk of falls and injuries.

Taken together, these studies contribute to the growing evidence for the interconnected nature of frailty and other geriatric syndromes in PWH. A recent cross-sectional study evaluated the prevalence of 9 geriatric syndromes (polypharmacy, visual or hearing impairment, cognitive impairment, physical disability, frailty/prefrailty, falls, depression and incontinence) among OPWH aged ≥50 years in Mexico [19▪▪]. A quarter of participants (26.4%) had at least three coexisting geriatric syndromes, 17.6% had five or more, while only 1.6% had no geriatric syndrome. Higher number of geriatric syndromes was associated with worse clinical profiles, independently of age. Branas *et al.* assessed four geriatric syndromes (falls, depression, cognitive impairment, and risk of malnutrition) among OPWH aged ≥50 years enrolled in the Spanish FUNCFRAIL cohort [20▪]. A total of 65% of participants had multimorbidity (≥3 comorbidities), at least one of the evaluated geriatric syndromes and/or were frail. A significant proportion were found to have a geriatric syndrome and/or frailty without presence of multimorbidity (26.5%), which was independently associated with increased risk of reduced QoL and mortality. This study highlights that the coexistence of frailty and other geriatric syndromes can occur in the presence or absence of significant comorbidity. Overall, there is compelling evidence supporting the inclusion of routine screening for geriatric syndromes, including frailty, in clinical practice for OPWH.

COMMON RISK FACTORS AMONG GERIATRIC SYNDROMES IN PEOPLE WITH HIV

HIV-1 infection has been linked to chronic immune activation and exhaustion, which contributes to an "accelerated aging" phenotype [21]. Despite initiating effective cART, residual immune dysfunction and chronic inflammation persists, which is increased by delayed treatment initiation. Older adults are more likely to experience delays in HIV diagnosis for several reasons, but are in fact most likely to benefit from early treatment initiation as they may already be experiencing some age-related comorbidities and immune dysfunction [22,23]. Multiple studies have identified shared risk factors and biomarkers for frailty and other geriatric syndromes, including immune activation, chronic inflammation, oxidative stress, age-related comorbidities, and adverse effects of cART [6,7]. Researchers have explored potential mechanisms and treatment targets for increased risk of frailty and other geriatric syndromes among PWH. Sultana and colleagues proposed that inhibiting the Kynurenine pathway, which has been implicated in several age-related disorders including neurodegeneration, osteoporosis, sarcopenia and inflammation, may help improve musculoskeletal health in PWH [24]. The pathway is upregulated in PWH even when effective cART has been initiated, with evidence pointing towards gut dysbiosis in the context of HIV infection as a major driver of this effect. Zhang and colleagues evaluated T cell responses to cytomegalovirus (CMV) in men with treated HIV and those without HIV enrolled in the Multicenter AIDS Cohort Study (MACS) [25,26]. They identified an impaired response to CMV among PWH (lower magnitude of total T cell response and lower polyfunctionality of CD4 and CD8 T cell responses), which may contribute to more frequent CMV reactivation and higher burden of inflammation.

Recent studies have also identified social vulnerability, low socioeconomic status and stigma to be significant contributors to frailty and other geriatric syndromes [27–29]. These intersecting societal and psychological factors can lead to lack of resources and access to medical care, isolation, loneliness and other mental health issues. Conversely, strong social networks, interventions targeting HIV, frailty, and age-related stigma, along with better access to financial and housing support, can serve as protective factors and should be considered in the prevention and management of frailty in OPWH.

FRAILTY TRAJECTORIES

Longitudinal studies, such as those conducted with the ACTG HAILO cohort and the French multicenter SEPTAVIH study, have identified several frailty trajectories including both worsening and improvement of frailty status [30▪▪,31]. In the ACTG HAILO cohort of PWH (mean age 51 years), 8% of participants experienced worsening frailty, while 9% had an improvement. Older age, female sex, presence of select comorbidities (cardiovascular disease, diabetes, depression) and behavioral characteristics (low level of physical activity, alcohol use, smoking) were associated with fluctuating frailty trajectories. In the SEPTAVIH study of OPWH (median age 73 years), transitions in frailty status were more common (worsened in 18% of participants and improved in 14% over one year). Older age, lower nadir $CD4^+$ cell count and diabetes were associated with worsening frailty status, while female sex was associated with improvement from prefrailty to non-frailty. These studies highlight the dynamic nature of frailty. Addressing modifiable factors associated with frailty progression is crucial for frailty prevention and management efforts.

FRAILTY MEASUREMENT TOOLS

Despite significant interest in frailty among PWH there is no gold standard tool for identifying frailty. Two instruments have been by far the most commonly studied in PWH, the Fried frailty phenotype (FP) and the frailty index (FI) [32,33]. The FP focuses on physical frailty and is characterized by presence of 3 or more of the following criteria: unintentional weight loss, weakness, low physical activity, exhaustion and slow gait. Although it is well characterized and validated in multiple populations, it can be challenging to implement in the clinical setting given the need for a hand-grip dynamometer, space to assess gait speed and average time of 10 min required for completion [34]. The FI is based on a model of accumulation of deficits, which considers a broad range of possible factors including diseases, laboratory abnormalities, activities of daily living and results of a clinical evaluation. Given its continuous nature, the FI is more sensitive to change but requires a comprehensive evaluation across multiple health domains. It can be easily determined if an electronic health record is accessible [35]. Although there is some overlap between the two measures, they can yield different results when determined in the same cohort.

Given the challenges with these tools, there are ongoing efforts to improve frailty screening in PWH. Ruderman and colleagues evaluated a self-reported modified FP with PWH enrolled in the CNICS cohort [36]. This consisted of 4 self-reported criteria, which correctly classified 94% of participants as frail or not frail compared to the standard FP, but had a lower sensitivity (62%). The improved feasibility of a self-reported measure may support its use in clinical practice when measurement of strength and gait speed are not possible or practical. Other frailty metrics used in OPWH include the Clinical Frailty scale [37] and the FRAIL scale as recommended by EACS [38].

STIGMA IMPLICATIONS

It has been well recognized in multiple studies that HIV stigma and discrimination significantly impact the QoL of PWH, leading to emotional, social, and psychological challenges [39▪,40–42]. Stigma can arise from negative beliefs, attitudes, and judgments about self and others based on HIV status, often resulting in social exclusion, rejection and marginalization. As people age with HIV, they are encountering new forms of stigma, particularly related to older age [42]. Ageism can manifest as negative attitudes or beliefs about individuals due to their age and may result in unfair treatment in social interactions and healthcare settings. Clinicians also need to be particularly aware of the unintended impact a frailty label can have on an individual's self-perception and access to resources and treatments.

FRAILTY MANAGEMENT

In order to be effective, frailty prevention and management strategies need to reflect the multifactorial nature of frailty, which requires a comprehensive evaluation of an individual's health status and risk factors. Multiple models of geriatric care for OPWH have been described with regional variability in clinical structure [43▪,44,45]. The first step involves screening for frailty and other geriatric syndromes and referring those identified to an HIV and aging specialist or center, where a locally adapted comprehensive geriatrics assessment (CGA) can be undertaken [43▪]. The CGA can inform targets for intervention which can be operationalized through the geriatric 5 M's (Mind, Mobility, Medications, Multicomplexity, Matters Most, as well as Modifiable Factors, as suggested for PWH) [46–48].

Studies evaluating specific interventions for prevention and management of frailty have yielded mixed results and it is unclear whether addressing some modifiable factors can prevent development of frailty [46]. The most effective intervention appears to be exercise, however, integrating routine exercise over the lifespan can be challenging [49–51]. Optimizing comorbidities and addressing other geriatric syndromes can be beneficial. Interventions that address social risk factors as well as HIV and aging stigma may also be beneficial [46].

CONCLUSION

Effective cART has turned HIV from an almost uniformly fatal infection in the 1980s into a manageable chronic illness for many PWH. However this nearly-normal survival has been associated with a significant burden on QoL due to the earlier onset of age-related comorbidities and, as is increasingly appreciated, by common geriatric syndromes, with frailty among the most notable [52]. Frailty impacts ability to maintain independence, and may serve as the canary in the coal mine for the possible presence of other geriatric syndromes which PWH are also at risk for. Awareness of these conditions, assisted by using reliable tools to screen for frailty, is actively coupled with the operationalization of inter-disciplinary programs responsive to the real-life needs of OPWH. It has always been a basic truism of HIV care that responsive partnerships between the various care-provider communities focusing on PWH leads to better outcomes. As the HIV story continues to evolve this remains an important sign-post to remember.

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Conflicts of interest

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