Frailty: a new vulnerability indicator in people aging with HIV

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Abstract

Purpose To review the concept of frailty and its measurement, describe the existing data on frailty in people living with HIV, examine the limits of frailty as a marker of vulnerability in people living with HIV, and explore how frailty measurement could be incorporated into HIV care.

Methods Narrative literature review.

Results Frailty is an emerging marker of vulnerability that is increasingly being assessed among people aging with HIV. Which frailty measurement tool is best for people with HIV has not yet been established, and likely depends on clinical context. Evaluation of vulnerability should take into account social and structural factors. Frailty assessment can be incorporated into clinical care as a part of comprehensive geriatric assessment. Models of HIV–geriatric care are being established.

Conclusions As a group, people with HIV are aging and increasingly face multiple interacting age-related medical and social problems. It requires remarkable resilience to age successfully with HIV. The clinical care of people aging with HIV could benefit from a focus on frailty and related social vulnerability to better understand patients' needs and develop appropriate goals and care plans.

Keywords HIV · Aging · Frailty · Social vulnerability · Risk environment · Comprehensive geriatric assessment

Introduction

Modern antiretroviral therapies have transformed the course of human immunodeficiency virus (HIV) disease and the global HIV epidemic. For people who can access and regularly take medication, HIV has become a chronic, manageable condition [1]. People living with HIV who remain on lifelong treatment can now expect life expectancies comparable to people without HIV infection [2]. This is particularly true for those who retain healthy immune function with high CD4 cell counts and suppressed viral load on modern medication regimens [3].

As a consequence of this success, people living with treated HIV are now aging and so increasingly face age-related health challenges [4–6]. People aging with HIV are consistently found to have high rates of illnesses that are strongly associated with advanced age in general population cohorts, including cardiovascular, kidney, lung, bone, endocrine, and liver diseases [7, 8]. Geriatric syndromes such as cognitive impairment, falls, and incontinence are common among people with HIV aged 50 years and older [9]. The prevalence of these conditions may be higher among people living with HIV than among people without HIV of the same age. In longitudinal studies, aging-related declines in gait speed [10] and grip strength [11] appear to be accelerated in people with HIV.

Exactly why people with HIV may experience higher rates of aging-related diseases than people without HIV is attracting ongoing investigation [3]. Many factors contribute to increased risk, including those related to HIV disease and its treatment (e.g., CD4 count and viral load; adverse effects of HIV antiretroviral medications); to aging itself (e.g., chronic inflammation, cellular senescence); and to the social and personal environment [5]. Many of these factors are interacting. For example, more excess life years lost have

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now been attributed to smoking than to HIV infection itself among people living with treated HIV [12], and people with HIV are more likely to smoke if they have experienced poverty or social exclusion [13].

People tend to accumulate more health problems as they age. Even so, different people of the same age experience enormous variability in their overall health status, function, and vulnerability to poor health outcomes. This heterogeneity in the risk of adverse health outcomes among people of the same chronological age is how the statistical sense of “frailty” was first defined [14, 15]. If aging is defined as the time-dependent functional decline that affects most organisms, then conceived in this way, frailty is akin to summarizing biological aging, as opposed to chronological age [5, 15].

Frailty is an emerging framework for understanding and measuring age-related vulnerability among people aging with HIV who experience multiple interacting medical and social problems. Here we review the concept of frailty and its measurement, describe the existing data on frailty in people living with HIV, examine the limits of frailty as a marker of vulnerability in people living with HIV, and explore how frailty measurement could be incorporated into HIV care.

Frailty

Although most frailty research has focused on older adults, frailty can be measured across the life course [16, 17]. Frailty is strongly associated with advancing age, and older people tend to be frailer than younger people on average. This reflects the accumulation of unrepaired damage across the life course, as more insults are experienced with the passage of time and intrinsic repair mechanisms begin to deteriorate [18]. Whereas the severity of frailty on an average worsens with age, it can also stabilize or even improve over time [19]. The progression (or stability, or improvement) of frailty severity is affected by multiple factors, including differences in the rate of insults people experience from their environment, and differences in intrinsic repair capacity [18]. Protective factors include education, physical activity, and wealth, and some of the socioeconomic gradient in frailty has been explained by life course differences in health behaviors and cardiometabolic risk [20]. Diverse challenging life experiences have been associated with worsening frailty, including childhood hunger [21], childhood physical abuse and interpersonal violence [22] over the life course, and birth in low- and middle-income countries [23].

Frailty is strongly associated with multiple adverse health outcomes, including hospitalization, death, and placement in long-term care [15]. Frailty predisposes people to larger deteriorations in health after a stressor event, and may preclude returning to baseline functional status. Even so, the relationship between a given level of frailty and the risk of

an outcome is not uniform. It is interesting that people with the same degree of frailty experience different risks. For example, women consistently tend to be frailer than men of the same age, but are at relatively lower risk of death [15]. Among people with the same degree of frailty, those who are more socially vulnerable experience a much higher risk of death [24, 25]. Conversely, this varying risk amongst people of the same degree of frailty has also been explained by markers of variable resilience [26].

Measuring frailty

A patient's severity of frailty is commonly assessed in geriatric medicine as a part of comprehensive geriatric assessment and care planning, but a single best frailty measurement tool has not been identified. Many operational definitions of frailty and associated measurement tools are used in clinical practice [27, 28]. Most frailty measurement tools assess the severity of health deficits that a person has accumulated across multiple health domains over time [29]. This can be done by overall clinical judgment, for example with the Clinical Frailty Scale [30], or by counting the number of health deficits someone has accumulated out of a group of health variables, creating a frailty index [14, 31] (often based on a comprehensive geriatric assessment [32]). Some frailty measurement tools are designed to count the accumulation of a few specific health deficits, including the commonly used five-item Fried frailty phenotype [33] and FRAIL scales [34], and the 17-point Edmonton Frail Scale [35]. One frailty scale, the Veterans Ageing Cohort Study (VACS) Index, was specifically developed for and validated among people living with HIV [36]. Some frailty measurement scales have been designed to label people as “frail”, “pre-frail”, or “robust” or “not frail”, while others grade severity of frailty as a continuum [27, 29]. Frailty scales that incorporate more information and grade the severity of frailty may be more cumbersome to use, but tend to be more informative [27, 28] and may be automatically calculated when incorporated into electronic medical records [37]. Across different research studies, modifications to frailty measurement tools are common and significantly change their predictive properties [38].

Many frailty measurement scales comprise biological and clinical variables. Others include measurements of function or home care supports, as in a comprehensive geriatric assessment. Fewer frailty scales incorporate markers of social, economic, or structural vulnerability [39]. Frailty scales rarely specifically incorporate issues that may be more common among some people aging with HIV such as substance use, homelessness, food insecurity, or stigma-related social and economic exclusion. One common approach has been to assess the social and structural vulnerability factors

separately from frailty, and measure the severity of vulnerability in a “social vulnerability index” [24]; this may help to understand the variability in outcomes among people with the same degree of frailty.

The best frailty measurement tool in HIV care likely depends on its purpose and clinical context [40]. Some scales that incorporate measures of physical performance, such as gait speed or grip strength, may not be appropriate in those people who are more severely frail or too impaired to complete the task. The best simple screening test to identify those patients who might be frail would surely be different than the best comprehensive frailty measurement based on a comprehensive geriatric assessment. The best frailty measurement tools to use in HIV primary care, HIV specialists clinics, or HIV-geriatric consultation services have not yet been established [41, 42].

Frailty in people aging with HIV

Frailty has been identified and measured among people aging with HIV, using multiple different measurement tools [5, 9, 40, 43, 44]. Most of this work has been observational, chiefly in cross-sectional studies. One pilot pre–post intervention study among ten people living with HIV showed improvements in some aspects of the frailty phenotype with an exercise gaming intervention [45].

Similar to other age-related health conditions in people living with HIV, the incidence and severity of frailty have been associated with multiple factors related to HIV disease, individuals’ intrinsic biology, and social and structural environment [5, 43, 44]. Greater severity of frailty has been associated with increasing age, longer time since HIV diagnosis [46, 47], lower current [48, 49] and nadir [50] CD4 count, lower CD4/CD8 ratio [51], detectable viral load [52], and use of protease inhibitor-containing therapy regimens [46]. Other studies have identified an association between frailty and serum markers of inflammation and testosterone levels [53]. Co-morbid conditions including hepatitis C virus co-infection [54], diabetes [52], kidney disease [52], chronic obstructive pulmonary disease [55], pain [56], depression [51], obesity, sarcopenia [57], and osteoporosis [58] have also been associated with more severe frailty. Frailty has also been associated with behavioral, social, and structural factors in people aging with HIV, including smoking [49], injection drug use [59], lower education [48], unemployment [46], low income [46], and food insecurity [51].

Depending on the frailty framework that is used, or the question being asked, each of these co-factors or co-morbidities could either be incorporated into a frailty measurement tool or analyzed separately [59, 60]. Overall, the accumulation of more co-morbid diagnoses, laboratory abnormalities, and social and structural adverse conditions contribute to

more severe frailty and also to the lethality of a given level of frailty [5]. The more things that a person has wrong, the frailer and more vulnerable they tend to be. In longitudinal studies among people living with HIV, frailty has predicted multiple adverse outcomes including functional impairment [51], cognitive impairment [61], hospitalization [36, 62], fragility fractures [63], incident multimorbidity [59], cardiovascular mortality [64], post-liver transplant morbidity and mortality [65], and all-cause mortality [48, 49, 59].

Many recent studies have explored the relationship between frailty and cognitive impairment in particular among people aging with HIV. Cognition declines variably with age, and is associated with frailty and the accumulation of health deficits in both the general population and among people living with HIV [61, 66–69]. People living with HIV may suffer the long-term effects of HIV-associated neurocognitive disorder (HAND) as well as age-related cognitive decline and dementia [66]. In several recent studies of people aging with HIV, frailty was positively associated with concurrent cognitive impairment [67–70]. People with HIV and cognitive impairment who are also frail face increased risk of falls, disability, and death compared to those who are not also frail [66]. People with HIV who are frail may face more rapid cognitive decline than those who are not frail [61].

Why might people living with HIV experience a greater burden of frailty?

Compared to people without HIV, people living with HIV of the same age may experience a greater burden of frailty [71]. People living with HIV, as a group, tend to differ from people without HIV in many ways. Along with the virus and medication experience, and associated immune dysfunction and chronic inflammation, this includes higher rates of social, structural, and biological factors that may increase the rate of health insults, or diminish the body’s ability to repair insults, across the life course. These factors which are more common among people aging with HIV include experiences of poverty [72], food insecurity [73], racism and homophobia [74], homelessness [75], smoking [13], and HIV-related stigma, and social isolation. Many people living with HIV experience more than one of these factors simultaneously. In particular, people with HIV are more likely to belong to vulnerable “key populations” identified by UNAIDS, including men who have sex with men, sex workers, transgender people, and people who are incarcerated. These factors may influence vulnerability and the accumulation of deficits across the life course.

Investigating frailty among cohorts of socially and structurally vulnerable populations can be challenging, as at any given time people who are most vulnerable may die and cohorts can

only follow the survivors (who are inherently healthier). This is one explanation for why health disparities seem to diminish as people reach older ages [76]. The most vulnerable people are also less likely to participate in longitudinal studies.

Frailty and social vulnerability among people aging with HIV

Different frameworks exist to understand the relationship between frailty (capturing biomedical vulnerability) and actual risk of adverse outcomes. These may be particularly useful to explore in people living with HIV who are at higher risk of social and structural vulnerabilities that might not be captured in traditional frailty measurement scales. People who are frail and people living with HIV may also be more vulnerable to negative outcomes from policy focused on individual health behaviors without providing appropriate social supports or a focus on equity [24, 77].

One concept that has been explored in the general population is the relationship between frailty and social vulnerability with the risk of adverse outcomes [24]. This approach conceptualizes social vulnerability analogously to frailty, as an accumulation of social deficits that are more likely to occur with age (but not universally so) and also are affected by both intrinsic and extrinsic factors. The more socially vulnerable a person is, the more likely they are to experience adverse outcomes independent of their level of frailty [25]. A recent paper focused on protective social factors and resiliency (rather than vulnerability) demonstrated construct validity of a “protective factors index” in people with HIV [60].

Socioeconomic status, income, education, social supports, social isolation or exclusion, social cohesion, social capital, and social welfare policies all may have important effects on the risk of adverse outcomes among people who are frail [24]. These represent effects and potential interventions at different levels, from those focused on the individual to those focused on government or society more generally. Analytic frameworks used to investigate these levels of social influence on the health of older adults include “human ecology” and “social ecology” [24].

Social vulnerability may explain some of the relationship between frailty and adverse outcomes in people aging with HIV [78], and is being increasingly explored in this population.

Frailty and the “risk environment” in people aging with HIV

Approaches from HIV risk and prevention research may also be informative in trying to understand the vulnerability and frailty in people aging with HIV. The concept

of “risk environments”, as developed by Tim Rhodes, has been advanced to examine the risk of HIV acquisition and drug-related harm among people who inject drugs [77, 79]. It may be helpful in trying to understand the risk of age-related adverse outcomes among people with HIV who are frail.

A risk environment is the space (whether physical, social, economic, or policy) in which multiple factors interact to increase or decrease the chances of a harmful outcome [77].

The risk environment framework invites us to consider risk as more than simply related to intrinsic individual factors and to situate an individual’s risk within the social and environmental structures that surrounds them [77].

Micro risk environments can include factors related to perceived social norms, rules, values, the structure of social networks, and the local neighborhood context in which people live [77]. For people with HIV who are frail, this could include the nature of relationships with friends and family, taking into account the social norms leading to discrimination related to HIV status, sexual orientation, or substance use. The physical structure of residential neighborhoods, including walkability or safety, could determine physical activity levels, social engagement, and, therefore, be a mediator in the pathway between frailty and the risk of falls and death.

Macro risk environment may include factors related to policies and laws, systemic discrimination as it plays out in society at large, and social and material inequities [81]. For older adults living with HIV, this could include policies regulating the availability of safe housing for those with low incomes, or the provision of funding for medication or nutritious food supplements. These could affect the risk that someone developed sarcopenia and functional decline. Policies regarding the provision of home care could determine who is hospitalized or is placed in long-term care.

This framework may also be helpful in terms of understanding how to reduce the risk of adverse outcomes among people with HIV who are frail. “Enabling environments” could be established to reduce the risk of adverse outcomes among people who are frail.

To our knowledge, the risk environment framework has not been explored in the context of understanding the risk for aging-related harms in people aging with HIV, although a large body of work relates individual social and environmental factors to adverse health among older adults including related concepts of human ecology and social ecology [24]. This work is needed, and may be of particular relevance to understanding the health needs of people with HIV who are frail. Such an approach could inform designing of clinical and policy interventions to reduce the risks of aging-related harms in this group.

Incorporation of frailty into HIV care—the utility of frailty assessment

As more effective and tolerable antiretroviral medications have changed the natural history of HIV disease for people on treatment, clinical indicators of biological vulnerability have also changed. In the era before combination antiretroviral therapy, the HIV clinical focus was often on the prevention and treatment of opportunistic infections. As early antiretroviral therapies helped restore and maintain immune function, troubling metabolic side effects became a focus for HIV clinics. In the new era of HIV care, chronic diseases of aging, including cardiovascular disease, COPD, and chronic kidney disease have become a focus. Identification of frailty and related geriatric syndromes, and incorporation of this information into care planning are now emerging foci in HIV care [80].

Screening for frailty and geriatric syndromes in clinical care involves evaluating multiple domains of function, physical health, cognition, mental health, formal and informal care supports, and more. The focus of care can change from avoiding mortality to maximizing function and quality of life. Decisions to undertake referrals to multiple subspecialists for different disease diagnoses, or plans for appropriateness of specific interventions, can be assessed in the context of a patient's overall health, vulnerability, and goals.

In geriatric medicine, the most robustly studied method for accomplishing this is through comprehensive geriatric assessment (CGA). This usually involves assessing and creating management plans across multiple domains of health and function. This is often done in a multidisciplinary team. Practitioners then incorporate the CGA information and frailty assessment into decision-making and care planning.

As people living with HIV develop more aging-related problems, they are more often referred to subspecialists for individual disease management. There are few HIV–geriatric specific services to place individual chronic disease management in the context of CGA, frailty, and patients' overall goals. In a recent survey of HIV clinics in the UK, only 5 HIV clinics out of 102 had a clinician with specific training or a focus on aging [42]. Further, 23% of the clinics identified a need for a specific aging-related care service. While 68% of the clinics supported dedicated guidance for monitoring and assessment among older adults with HIV, 41% supported dedicated guidance on treatment [42].

The most recent update of the Italian HIV care guidelines includes a section on managing aging and frail patients with HIV, which generally recommends assessments for frailty and comprehensive geriatric assessment

(CGA) [6, 81]. The American Academy of HIV Medicine, the AIDS Community Research Initiative of America (ACRIA), and the American Geriatrics Society 2012 guidelines on managing older adults with HIV also speak generally to the utility of frailty and functional assessment [82]. A number of recent best-practice clinical review papers focus on assessing and managing age-related conditions in older people with HIV, including geriatric syndromes and frailty [83–85]. Important principles raised by this early literature include the importance of CGA in guiding care planning for people with HIV who are frail. Medication review, including potential interactions between multiple antiretroviral drugs and multiple drugs for age-related chronic health problems, may be a particular focus of these care models [4].

The best models for incorporating geriatric medicine principles into subspecialty medicine, including HIV care, have not yet been established but are an area of active investigation [41]. A few specialty geriatric–HIV services have been described. One HIV-aging service operates monthly with a geriatrician and HIV physician present in a joint clinic model [42]. Referral criteria are based on age and need, including multimorbidity and polypharmacy. The clinic offers comprehensive geriatric assessment and full medication review. A second HIV-aging service is a weekly clinic with an HIV physician and a nurse specialist with an interest in aging, without a geriatrician. Another program described in the literature consists of geriatricians providing weekly geriatric consultation within an HIV clinic, and attending discussions at interdisciplinary care rounds [80].

It is likely that different models of care are best based on the local resources, expertise, and identified need. Even within general geriatric medicine the evidence for specific care models incorporating comprehensive geriatric assessment into care planning is mixed, and this is also true for geriatric consultative or specialist services for specific health conditions [86]. This may be in part because the best outcome measures to identify when assessing the complex interventions have still not been established. Often the focus is on global measures of health-related quality of life, while individualized measures like Goal Attainment Scaling (GAS) may be more responsive or appropriate [87].

Conclusion

Initiatives aimed at meeting the “90–90–90” targets proposed by the WHO (that is 90% of the people with HIV diagnosed, 90% of those diagnosed on treatment, and 90% of those on treatment with a suppressed viral load) will eventually help to end the epidemic, and will also lead to even more people with HIV living to older ages.

As a group, people with HIV are aging and increasingly face multiple interacting age-related medical and social problems. It requires remarkable resilience to age successfully with HIV. As such, the clinical care of people aging with HIV could benefit from a focus on frailty and related social vulnerability to better understand patients' needs and develop appropriate goals and care plans.

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Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study formal consent is not required.

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