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Faces of Frailty in Aging with HIV Infection

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Abstract

Purpose of the Review—The number of adults who are aging successfully and have HIV-infection is increasing. More effective antiretroviral therapy (ART) regimens are preventing individuals infected with HIV from reaching end stages of the HIV infection and developing AIDS (Acquired Immunodeficiency Syndrome). However, even at lower viral loads, chronic HIV infection appears to have consequences on aging processes, including the development of frailty.

Recent Findings—Frailty is a term used to describe vulnerability in aging. Frailty indices such as the Fried Frailty Index (FFI), the Veterans Aging Cohort Study (VACS) index, and the CES-D, an index of emotional frailty, associate with or predict clinical outcomes and death. However, even among existing frailty definitions components require rigorous and consistent standardization. In the WIHS, we have shown that frailty does not exist in isolation, even in midlife, and we use frailty to predict death.

Summary—Frailty indices should be systematically used by health professionals to evaluate health and future risks for adverse events. Frailty prevention efforts, especially those with HIV infection, appear to be essential for ‘successful aging’ or aging without disability or loss of independence, and may prevent HIV transmission. Taking care of elderly people is one of the major challenges of this century, and we must expect and be prepared for an increase in the number of aging adults, some of whom are patients with many co-morbidities and HIV-infection.

Keywords

frailty; elderly; HIV; disabilities; assessment; prevention

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Compliance with Ethics Guidelines

All aspects of this review are compliant with ethical guidelines enforced by the State University of New York - Downstate Medical Center, USA and by Aix Marseille University, France.

Conflict of Interest

Marion Thurn and Deborah R. Gustafson have no conflicts of interest to declare.

Human and Animal Rights and Informed Consent

This article contains reference to human research studies, some performed by Dr. Gustafson. All studies cited or conducted within the WIHS are approved by ethical review boards at each WIHS site. The Brooklyn WIHS Institutional Review Board has reviewed and approved all data collection and analyses for the WIHS.

Introduction

Adults surviving past age 50 years with HIV infection are increasing at an exceptional and unprecedented rate. This occurs against the backdrop of an aging globe. The World Health Organization (WHO) reports that the number of people aged 60 years and older will increase from 900 million to 2 billion between 2015 and 2050 (a shift from 12% to 22% of the total global population).[1] In addition, between 2000 and 2015, AIDS-related deaths fell by 28%.[2] The availability of antiretroviral medications has played a major role in this demographic shift. In the USA, among people with HIV infection in 2013, 42% were age 50 years and older and 6% were age 65 years and older.[3] The HIV epidemic is a success story of successful treatment and subsequent survival in the 21st century. Adults infected with HIV (HIV+) are surviving longer successfully more than at any other time during the epidemic. While trying to cure HIV infection remains important, a priority is to also prevent further infections (there are about 50,000 new infections per year in the USA[3]) and newly occurring age-linked complications. Traditional aging outcomes, including frailty, are now routinely observed among those with HIV infection, even at mid-life, and must be addressed. Older HIV+ adults have specific health care needs at the intersection of the HIV-infection syndrome and commonly observed aging-related chronic diseases and deficits. Moreover, it appears that those with HIV infection present aging-related symptoms and co-morbidities similar to those found in uninfected older people, at younger ages. Thus, HIV-infection has been suggested to cause premature aging.[4–6] Understanding why and how the aging process may be disturbed is elemental to developing effective methods of prevention.

In this review, we explore aging in HIV infection from the standpoint of frailty, an aging syndrome, and through the specific lens of HIV infection among women. In so doing, we will describe types of frailty, the potential increased risk of early or premature frailty among women with HIV infection, and share results from the Women's Interagency HIV Study (WIHS) that have shed light on frailty in women with HIV infection. Finally, we will discuss some general ideas for moving forward with frailty as a dynamic, evolving research area.

Frailty definition and assessment methods

In traditional studies of aging, elderly people are classified into one of three categories: robust, frail and disabled[7] (see Figure 1). To be robust is to be without frailty or disability. Frailty is a vulnerability state characterized by impairments and limitations that might lead to disabilities. It represents the vulnerability that increases risk of negative health outcomes, loss of independence, and of mortality.[8] In contrast, being disabled means there are important deficits that restrict a woman from performing daily activities on her own. Whereas frailty seems to be reversible and sensitive to prevention, disability tends to be permanent and may lead to hospitalization, institutionalization and death. This classification is essential to evaluate health in aging populations and to provide appropriate health care. It is crucial to detect frail adults before they become disabled, and to apply active prevention measures of this irreversible state.

According to PubMed, frailty was first reported in 1956, in an article entitled 'Frailty of old age and bacterial allergy'.[9] Subsequent to initial, isolated reports, frailty as a health outcome

became consistently reported beginning in the late 1980s. Since then, varying definitions of frailty and essential components of frailty have been put forward. For example, frailty has been defined as a clinical syndrome[10] - a composite of physical symptoms, referred to as the Frailty Phenotype (FP)[11] - and the accumulation of deficits.[12,13] Underlying all definitions of frailty is the concept that to prevent the sequelae, which includes disability followed by death, the reversible frail state must be identified using a screening tool (see Table 1 for list of published frailty indices). Most geriatric indices and scales used in clinical practice to assess health in aging adults, do not assess frailty in its entirety, but can be used to assess selected components of the frail state.

The Fried Frailty Index (FFI), a physical frailty index, was validated in the Cardiovascular Health Study in 1998 and by Kiely in 2009. The FFI is a useful construct to predict poor quality of life, cognitive impairment, dementia and death.[14] The FFI is composed of five components: weakness, slowness, exhaustion, low physical activity and unintended weight loss[11]. Fulfilling at least three of the five components denotes frailty. However, the faces of frailty include emotional, social, cognitive, metabolic, and sensory frailty existing alongside physical frailty (see Figure 2), thus the FFI has been associated with other screening tools, such as the Center for Epidemiologic Studies Depression scale (CES-D scale).[5,15,16]

Ten years after introduction of the FFI, the first report on a validated Veterans Aging Cohort Study (VACS) index, specific for HIV+ adults, was published.[17] The VACS Index is a metabolic (biomarker-based) index with the following components: CD4 count, HIV-1 RNA, hemoglobin, fibrosis-4 (FIB4), estimated glomerular filtration rate (eGFR), and hepatitis C virus (HCV) co-infection. The VACS index predicts mortality in HIV+ and uninfected (HIV-) populations, and is associated with the FFI and death.[18,19]

HIV and Frailty: greater risk for aging adults with HIV-infection

Frailty and Morbidity

We have explored both cross-sectional and longitudinal analyses of frailty in the multicenter Women's Interagency HIV Study (WIHS). In cross-sectional WIHS analyses, we took a broad-based look at a variety of morbidities that may accompany HIV infection and co-occur and/or contribute to frailty and accelerated or more severe aging. We postulated that middle-aged HIV+ women may present as elderly due to accelerated aging or having more severe aging phenotypes occurring at younger ages and that this 'aging' phenotype is associated with a multidimensional constellation of factors. In other words, frailty does not occur in isolation.

To address our question, we engaged WIHS frailty measures collected among 2028 HIV+ (n=1449) and at risk HIV− (n=579) WIHS women, during mid-life (average age 39 years). At mid-life, we operationalized the FFI similarly to the Multicenter AIDS Cohort Study (MACS), which is composed of HIV+ and HIV− men.[15] With an age range of 50–64 years, MACS observed 12% frailty prevalence among HIV+ and 9% among HIV− men.[20] In contrast, using similar criteria in the WIHS, overall frailty prevalence was 15% (HIV+, 17%; HIV-, 10%) among women at mid-life. The WIHS Core battery provided FFI, HIV status, and constellations of variables representing demographic/health behaviors and aging-related

chronic diseases. A stepwise multivariable model suggested that HIV infection with CD4 count <200; age >40 years; current or former smoking; income ≤ $12,000; moderate vs low FIB-4 levels; and moderate vs high eGFR were positively associated with FFI. Low or moderate drinking was protective. Typical aging-related co-morbidities such as obesity, Type 2 diabetes, cardiovascular disease, and hypertension; as well as recreational drug use and self-reported or historically measured co-infections were not significantly associated with frailty in the final multivariate model. These results show that frailty is a multidimensional aging phenotype observed even in mid-life among women with HIV infection; suggest that the frailty constellation may change with age; and show that prevalence of frailty in HIV-infected WIHS women exceeds that for usual elderly populations.

Studies show that adults with HIV infection experience a prevalence of frailty equivalent to, and even greater than that observed in elderly.[16,20,21] The reason for this early manifestation of frailty may be a consequence of the HIV infection itself, suboptimal medication and control of infection early on, comorbid diseases (infectious or non-infectious)[21,22] and/or other lifestyle habits, such as smoking and substance use, which are more common among those with HIV infection.[23] Physical frailty may be due to the HIV-infection, itself. With a dropping CD4 cell count, the immune system is insufficient to protect against both infectious and chronic diseases such as cancer, cardiac diseases, and diabetes. Moreover, HIV-infection is accompanied by numerous symptoms that weaken the body, including pain, weight loss, fatigue or weakness.[24] Physical deterioration leads to vulnerability to diverse pathologies, which can lead to premature frailty among HIV-infected.

Frailty and Death

We are also predicting death by frailty indices within the WIHS. Why would multi-dimensional frailty indices be associated with mortality in adults with HIV infection? Throughout adult life, HIV infection is synergistic with adverse aging influences on the immune, vascular, reproductive, and central nervous systems, thereby intensifying the aging process.[25,26] Aging with HIV infection is associated with geriatric morbidities or syndromes, including frailty,[27] however these aging morbidities often occur earlier among those with HIV infection compared to uninfected individuals.[4,5,28] The question is whether HIV infection leads to more severe aging phenotypes, or accelerates their onset leading to earlier age of death, or is a cumulative marker of multiple morbidities.[29]

Several frailty indices have been used to predict mortality in women with HIV infection – the FFI, the VACS Index, and the CES-D score. Each index is considered a measure of frailty, since each worsens with age and denotes vulnerability.[17,21] For example, the FFI predicts death in elderly (65 years and older),[30] as well as in younger adult populations who may be at risk for premature or earlier aging, such as those with HIV infection.[18,31] Several HIV studies have found CES-D to be a significant “independent” predictor of mortality,[21,32–36] however do not consider measures of FFI and/or VACS in relation to death. The VACS index also predicts death, and in combination with the CES-D.[21,37] However, our analyses will differ from other studies, since we are evaluating all three indices together in the same model to see which one(s) are most relevant. No other study has included a simultaneous evaluation of these three primary mortality indices considered in

HIV research. This will be the first simultaneous evaluation of three common mortality indices in HIV infected adults reflecting physical, mental and biological aging and death.

Inclusion of the CES-D as an emotional frailty index and predictor of death originates from the incapacitating psychosocial conditions linked to HIV-infection and that lead to depressive symptoms, loneliness and isolation because of discrimination and stigmatization.[33] Hopelessness and helplessness, as well as anger, suicidal thoughts and feelings, and abandonment are also prevalent.[33] This profile may lead to cognitive frailty and premature aging. That HIV-infected adults might not be able to find or keep a job, contributing to a low socioeconomic status, also predisposes to the frailty phenotype.[20] Low income denotes a lack of resources to invest in health and disease prevention, which creates vulnerability to diverse negative health outcomes and complications.

Thus, in the WIHS we are simultaneously evaluating, among HIV-infected women on ART, the association of the VACS, FFI, and CES-D with death (both AIDS-and non-AIDS related). All indices are measured in mid-life (average age 39 years) and the follow-up evaluation time is approximately 8 years. This follow-up period is divided into short-term (within 0–3 years) and long-term (>3–8 years) deaths, since studies in elderly show that prediction of death may vary depending on the number of years between the exposure of interest and death.

At the time of this review, the median age of the WIHS participants is 50 years (see Table 2 for the age distribution of WIHS participants). Our ability to continue to explore risk and protective factors for healthful aging will continue given the solid foundation of over 20 years of follow-up of these women. Evaluating vulnerabilities in middle-aged HIV+ women is important to understanding the impact of HIV infection on mortality over the life course. This approach has been shown for other diseases of later-life.[38] Mid-life physical, biological and/or mental indicators against the background of HIV infection may be associated with earlier death.

With the increase in numbers of chronically HIV+ aging adults, it may be important to develop new indices to evaluate frailty that include components related to the infection. With the growing population of aging and HIV+ women in the world, a frailty index for HIV+ women would be an invaluable asset, as well as for the development of more precise and effective measures to prevent further disabilities.

Conclusions

Ideas for going forward

This overview of frailty among participants in the WIHS highlights the need for geriatricians and gerontologists to interact with younger ‘at risk’ populations, and assist in the formulation of best recommendations for frailty interventions to prevent early aging, excess morbidities and early death. In terms of preventing frailty, implementation of prevention measures should be adapted to the patient’s health, needs and motivation. Family and social networks should be assessed as well to determine support needs.

Some platforms have been created to assess frailty among populations without HIV infection, like the Platform for the Evaluation of Frailty and the Prevention of Disability, created in October 2011, in Toulouse, France. This innovative initiative permits physicians to screen frail patients, based on the Gérontopôle Frailty Screening Tool (GFST).[39] More platforms may be created in the years to come, in response to the current high public health demand in certain areas of the world to specifically screen for frailty due to the aging of the world's population.[1] Furthermore, medical practitioners should be aware of the frail condition and be able to detect frail patients, to be able to provide them with appropriate, symptom-specific care. Frailty risk assessment should be included in practitioner education, and be a part of the continuous training health-related professionals receive during their career.

For women with HIV infection, aside from typical components of the geriatric syndrome,[27] key modifiable factors associated with frailty, as identified in the WIHS[20,21] and other studies[13,15,28,31] are listed in Table 3. Sarcopenia,[40] aging-related changes in skeletal muscle, is especially of interest for measures of physical frailty. In addition, is the irony of coexisting excess vascular risk due to HIV treatment and the influence of vascular risk on mortality.[41–45] Since frailty is a syndrome, there are numerous paths for age-specific intervention. Both personalized medicine and public health approaches are necessary, since personalized medicine approaches are based on risk factor and health behavior profiles derived from population and community studies. Among women who are frail, depending on their age, there may be an opportunity to reverse frailty and/or lessen its impact on quality of life.

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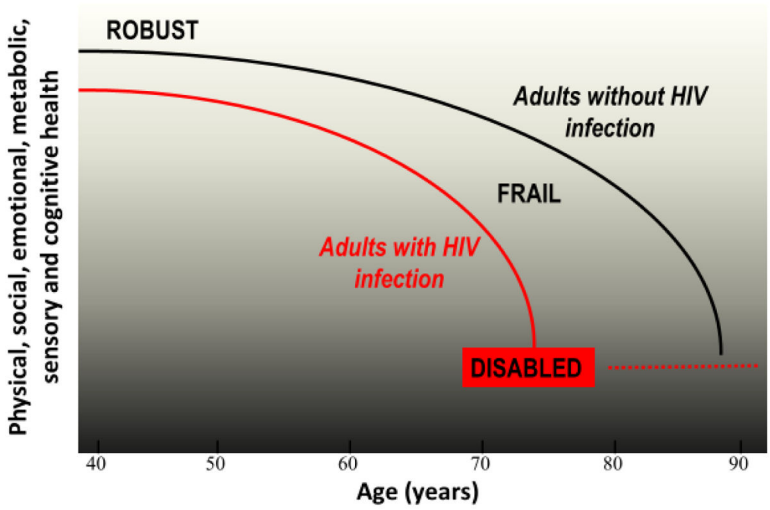

Figure 1.

Classification of elderly based on their health trajectory with aging. Adults living with HIV infection seem to follow the same path, albeit starting a lower level and declining at a faster rate than elderly without HIV infection, leading to earlier disability.

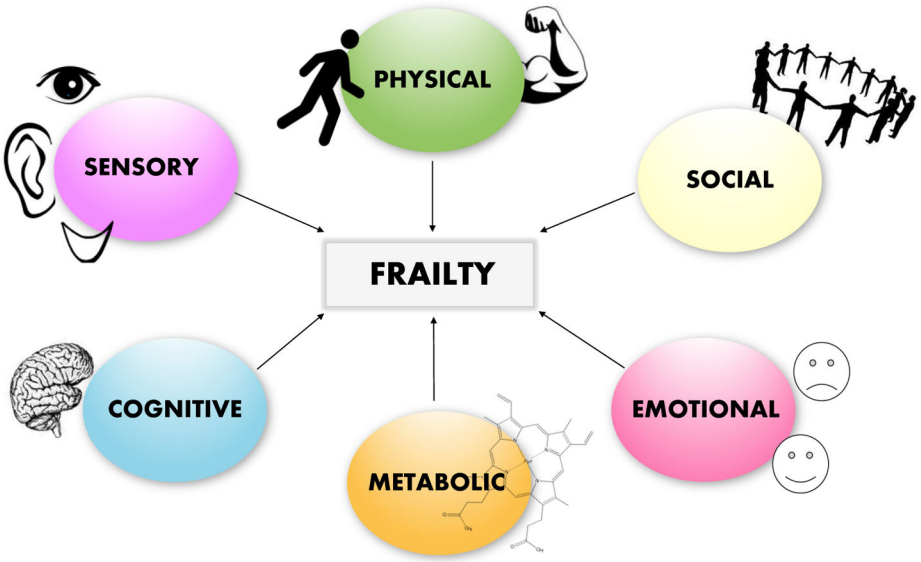

Figure 2.
The faces of frailty

Table 1

Frailty indices and selected geriatric scales assessing frailty components.

Frailty Indices	Year	Description
Strawbridge's questionnaire [46]	1998	Problems/difficulties in ≥ 2 functional domains (physical, nutritive, cognitive, and sensory)
Fried Frailty Index (FFI) [11]	2001	3 of 5 components: • Slowness • Grip strength • Weight loss • Exhaustion • Walking time
Frailty-Related Phenotype (FRP) [4]		4 components: • Physical shrinking • Exhaustion • Slowness • Low physical activity level
Rockwood - Clinical Frailty Scale [12]	2007	Combined symptoms, signs, diseases, and disabilities
Morley - FRAIL scale [47]	2012	Problems or difficulties in two or more functional domains (physical, nutritive, cognitive, and sensory
Vellas - Gerontopôle Frailty Screening Tool (GFTS) [39]	2013	7 components: Living alone Weight loss Fatigue Mobility Memory problems Gait speed Clinician evaluation of frailty
Examples of Geriatric Scales that Assess Components of Frailty		
Activities of Daily Living (ADL) [48]	1963	Tool permitting to describe the physical performance of an individual, with 6 fundamental daily activities people should be able to realize by themselves: eating, bathing, dressing, toileting, walking and continence.
Mini-Mental State Examination (MMSE) [49]	1975	30-point screen for global cognition
Center for Epidemiologic Studies Depression (CESD) scale [50]	1977	Screen for depression and depressive symptoms
Instrumental Activities of Daily Living (IADL) [51]	1984	Activities related to the capability to live independently in a community (housework, managing money)
Medical Outcomes Survey (MOS) [52]	1992	Items that assess quality of life including physical, mental and general health
CogScore [53]	1993	Cognitive screening tool for dementia
Short Physical Performance Battery (SPPB) [54]	1994	Objective assessment tool to evaluate lower extremity functioning in older persons.
Montreal Cognitive Assessment (MoCA) [55]	1996	Cognitive screening tool for cognitive impairment and dementia

Frailty Indices	Year	Description
Veterans Aging Cohort Study (VACS) index [37]	2001	Biochemical index including age, HIV-1 RNA, HCV co-infection, CD4, hemoglobin, FIB-4, eGFR
Patient Health Questionnaire 9 (PHQ-9) [56]	2007	Multipurpose tool to screen for depression and depression severity

Table 2

Age distribution in the WIHS as of 2016, reflecting survivors of the epidemic.

Age group years	N (%)
30–34	31 (1.9)
35–39	148 (9.2)
40–44	189 (11.8)
45–49	298 (18.6)
50–54	383 (23.9)
55–59	287 (17.9)
60–64	173 (10.8)
65–69	54 (3.4)
70 and older	40 (2.5)

Table 3

Avenues for intervention in HIV infection to reduce aging morbidities

- physical limitations
- immobility
- access and adherence to comprehensive medical care
- adherence to medications for control of HIV infection
- treatment of addictions (e.g., cigarette smoking, illicit drug use)
- polypharmacy
- control of vascular risk factors (e.g., hypertension, hyperlipidemias, obesity, sarcopenia)
- control of chronic diseases (e.g., cardiovascular disease, stroke, neuropathies)
- attention to mental health (e.g., cognitive impairments, depressive symptoms)
- gender-associated factors
- substance use and abuse
- partner abuse/domestic violence
- sociodemographic factors (e.g., income, education, food insecurity)