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REVIEW ARTICLE

Frailty in People Aging With Human Immunodeficiency Virus (HIV) Infection

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The increasing life spans of people infected with human immunodeficiency virus (HIV) reflect enormous treatment successes and present new challenges related to aging. Even with suppression of viral loads and immune reconstitution, HIV-positive individuals exhibit excess vulnerability to multiple health problems that are not AIDS-defining. With the accumulation of multiple health problems, it is likely that many people aging with treated HIV infection may be identified as frail. Studies of frailty in people with HIV are currently limited but suggest that frailty might be feasible and useful as an integrative marker of multisystem vulnerability, for organizing care and for comprehensively measuring the impact of illness and treatment on overall health status. This review explains how frailty has been conceptualized and measured in the general population, critically reviews emerging data on frailty in people with HIV infection, and explores how the concept of frailty might inform HIV research and care.

Keywords. HIV; frailty; aging; risk assessment; geriatric assessment; chronic infectious disease; chronic viral illness.

AGING WITH HIV INFECTION

Effective therapies have transformed human immunodeficiency virus (HIV) infection into a chronic illness [1]. As people with HIV live longer, aging-related challenges are arising. Despite complete suppression of viral load and immune recovery, HIV-positive individuals are more vulnerable to poor health than HIV-negative individuals [2]. This vulnerability is characterized by higher risk of several common, age-related health problems, even after adjustment for established risk factors. These conditions, termed HIV-associated non-AIDS (HANA), include cardiovascular disease, osteoporosis, metabolic disorders, hepatic and renal diseases, and some cancers, as well as age-associated immunologic changes and chronic inflammation [3–5]. Each involve different physiological systems and etiologies yet are all strongly age-associated in the general population. While HANA conditions are more common among HIV-positive individuals who are older, have more severe HIV disease, and who have longer duration of antiretroviral treatment and toxicity, these factors do not completely explain differences in risk and survival [1, 4, 6].

Among people without HIV, aging and the accumulation of age-related health problems are also highly heterogeneous processes. Although people generally accumulate health problems with age, individuals of the same age can experience very different levels of health. Geriatricians introduced the term "frailty" to describe this variability. Frailty represents the cumulative effects of age-related deterioration in multiple physiological systems and homeostatic mechanisms, resulting in greater vulnerability to stressors [7, 8]. Frail individuals often present with nonspecific health complaints, fluctuating disability, falls, and delirium and are at higher risk for multiple adverse outcomes, including longer

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hospital stays, postoperative complications, poor responses to vaccination, functional decline, and death [7].

With the accumulation of multiple health problems, it is likely that many people aging with HIV may be identified as frail [9]. The concept of frailty could provide a useful tool to measure and communicate the complexity of aging and vulnerability in people living with HIV, inform the development of therapies, and guide the delivery of care. This review explains how frailty has been conceptualized and measured in the general population, critically reviews emerging data on frailty in people living with HIV, and explores how applying the concept of frailty to research and care might benefit people living with HIV.

FRAILTY IN THE CONTEXT OF HIV

Investigators have begun investigating frailty among people with HIV to identify individuals more vulnerable to disease progression and death and to measure the effects of illness and treatment on health status [1, 10, 11]. However, frailty is not yet well understood in the context of the highly active antiretroviral therapy (HAART) era, where most HIV-positive individuals now experience significant immune recovery, undetectable HIV viral load, and primarily HANA clinical manifestations [1, 2]. Neither CD4 count nor viral load appear to be useful surrogate markers of vulnerability in this immune-reconstituted population, whereas frailty is strongly associated with HANA conditions and disability [12, 13] and might be a more sensitive indicator of health changes [6, 9, 14]. Age-related and HANA conditions have been associated with both immune activation (eg, soluble CD14 and CD163, $CD16^+$ monocytes, $HLA\text{-}DR^+/CD38^+$ $CD8^+$ T cells) and immune senescence markers (eg, terminally differentiated $CD45RA^+CCR7^-$ $CD4^+$ T cells), as well as inflammatory circulating cytokines (eg, interleukin 6, tumor necrosis factor α [TNF-α]) [1, 9, 15, 16]. Frailty is associated with both CD4 count and viral load [17], yet relationships between frailty and markers of immune senescence and activation among HIV-positive individuals have not been established. Although the clinical spectrum of HIV disease differs whether individuals experience immune deficiency or immune activation, frailty might emerge in the context of both profiles. A hypothetical representation of the association between frailty, HANA, and immune system dysregulation is depicted in Figure 1. Causal pathways between these factors are not yet understood, in part because most studies investigating HANA or frailty in HIV have been cross-sectional.

DEFINING FRAILTY

While "frail" is commonly used to describe vulnerable older adults, there is no consensus on the best way to define and identify frailty systematically [7]. Two conceptual models inform most approaches to frailty: the phenotype model and the cumulative deficit model [7]. The phenotype views frailty as a clinical syndrome arising from a "cycle of frailty" composed of chronic undernutriton, sarcopenia, and weakened strength and exercise tolerance. It suggests that frailty pathophysiology is distinct from aging or other disease processes [19]. Other factors, such as cognitive impairment, have been suggested as further phenotypic characteristics of frailty [7].

The cumulative deficit model (first proposed by members of our group) views frailty as a state of vulnerability, rather than a syndrome. It suggests that frailty arises from the cumulative effects of nonspecific age-related health deficits and does not have a unique pathophysiology but rather is related to the aging process [20]. As people accumulate health deficits and homeostatic mechanisms begin to fail, those who are frail exhibit excessive changes in health in response to even minor further insults [7]. Under this model, frailty has been proposed to describe the overall health state of an individual and therefore serve as an integrative marker of biologic aging, as opposed to chronological age [8, 9].

Studies applying both frailty models have identified associations between increasing severity of frailty and age-related deterioration in multiple systems, including immunosenescence and chronic inflammation [21, 22], which may be particularly relevant in people with treated HIV [4, 5, 15, 16].

MEASURING FRAILTY

Multiple measures exist to identify and measure frailty. Some are based on clinical judgment or a single item (eg, walking speed), but most scales assess multiple domains of age-related health and grade frailty by counting the number of deficits individuals have acquired [23]. One commonly used scale, based on the frailty phenotype [24], identifies frailty by the presence of 3 deficits out of 5 specific measures originating from the Cardiovascular Health Study (an existing prospective cohort study): self-reported unintentional weight loss >10lbs or recorded weight loss ≥5% in a year, measured slow walking speed, measured weak grip strength, self-reported exhaustion (3-4 days per week or most of the time), and low activity/energy expenditure (assessed by Minnesota Leisure Time Questionnaire) [25]. The frailty phenotype scale has been widely applied and extensively validated in its ability to identify people at increased risk for a range of adverse outcomes [7, 19].

Another commonly used scale, the "frailty index," counts the number of deficits individuals have accumulated out of various health measures and presents them as a proportion [20, 26]. In contrast to the phenotypic approach, any measure can be included in a frailty index if it is generally related to age and poor health, and if the group of items covers multiple physiological systems. When at least 30 items are included, the proportion of deficits accumulated appears more informative than the specific nature of those deficits. Though the effect of each individual deficit may be small, their cumulative effects can be large.

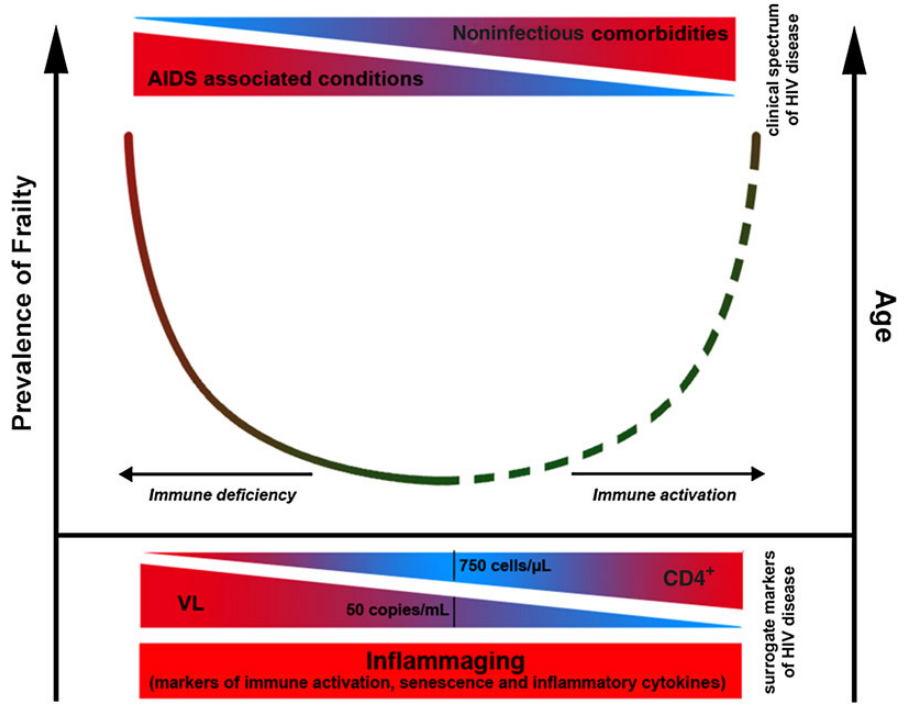

Figure 1. Hypothetical association between frailty prevalence, HANA conditions, and immune system dysregulation. Presented at 4th International Workshop on HIV and Aging, 30–31 October Baltimore, MD [18]. Abbreviations: HANA, HIV-associated non-AIDS; HIV, human immunodeficiency virus.

This reinforces the notion that health problems in the same individual rarely arise independently from one another [7, 8, 26]. Each frailty index can make use of different available measures, including functional limitations, comorbidities, cognition, and affect [26]. This approach has been operationalized clinically using data from comprehensive geriatric assessments and routine medical records [7].

Many other frailty scales exist, often including more items than the 5 specified by the frailty phenotype but fewer than the 30 suggested by the frailty index [23]. By counting health deficits across multiple physiologic systems, frailty scales are each able to identify individuals vulnerable to adverse outcomes and to do so better than chronological age alone [7, 23]. Although scales differ in the number and nature of deficits they count, people who have accumulated more deficits are more likely to be vulnerable and therefore more likely to be frail [27]. Different scales also demonstrate remarkable consistency in characteristics, including the nonlinear relationship between frailty severity and age, greater frailty in women than same-aged men, and higher risk of death in men than women of equal frailty [27].

However, as they include different criteria, frailty scales vary in ability to predict outcomes and in operational feasibility in different settings [23]. Frailty scales that include more measures can more sensitively grade vulnerability and track improvement and decline and are less likely to overlook individuals who have accumulated diverse deficits in health; they might, however, be relatively cumbersome to construct [23, 28]. Parsimonious scales can be quicker to apply but often require specific measures (eg, grip strength measured by dynamometer) and might overlook people with different health problems. Modifications to such scales are common, especially replacing performance-based measures (eg, walking speed) with self-reported measures (eg, reported difficulty walking), or using different criteria for performance-based measures (eg, loss of >10lbs in past year vs loss of >5% of body weight in past 6 months), yet the validity of such modifications is unknown [23].

MEASURING FRAILTY IN HIV-POSITIVE INDIVIDUALS

All published studies of frailty in HIV infection use frailty scales composed of a limited number of specific health measures, following the phenotype approach (Table 1). For instance, analyses of the Multicenter AIDS Cohort Study (MACS) used a frailty scale based on 4 self-reported deficits: weight loss, exhaustion, impaired physical activity, and difficulty walking [29]. One study used a single measure of unexpected weight loss to define frailty [40]. No published studies of frailty in people with HIV have used the cumulative deficit/frailty index approach, or scales based on clinical judgment.

Table 1. Deficits Included in Different Frailty Scales Applied to People Living With HIV

Study	Setting	Inclusion Criteria	Description and Scoring	Deficits Included in Frailty Scale
Based on frailty phenotype scale:				
Multicenter AIDS Cohort Study (MACS) [before 2007][17, 29, 30] (USA)	Urban, community-based cohort of men who have sex with men (MSM)	Age 18+; no clinical AIDS	Considered frail if 3 or more deficits present	1. Weight loss: 'Since your last visit (6 mo ago), have you had unintentional weight loss of at least 10 pounds?' 2. Exhaustion: 'During the past 4 wks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)?' 3. Low activity: 'Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?' 4. Slowness: 'Does your health now limit you in walking several blocks?'
Multicenter AIDS Cohort Study (MACS) [2007 and later] [13] (USA)	Urban, community-based cohort of MSM	Age 18+; either HIV–, or HIV+ receiving ART	Considered frail if 3 or more deficits present	1. Weight loss: 'Since your last visit have you had unintended weight loss of at least 10 pounds?' 2. Exhaustion: 'During the past 4 wks, as a result of your physical health, have you had difficulty performing your work or other activities (for example, it took extra effort)? 3. Low activity: 'Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?' 4. Slowness: Timed 4 m walk 5. Weakness: Grip strength measured with dynamometer
Women's Interagency HIV Study (USA) [31]	Urban, community-based HIV-positive female cohort in five cities	Age 13+; receiving ART; participants with 'missing limbs, prostheses, paralysis, or assistive devices' were excluded from walking speed and grip strength tests and assigned missing values	Considered frail if 3 or more deficits present	1. Weight loss: ≥10 pounds in past year, self reported and confirmed by physical exam 2. Exhaustion: 'based on responses to two items from the CES-D scale' 3. Low activity: A modified version of the Minnesota Leisure Time Activities Questionnaire 'capturing intensity and duration of 18 activities that range from work to child care' 4. Slowness: Timed 4 m walk 5. Weakness: Grip strength measured with dynamometer
Onen et al [12] (USA)	Urban, outpatient clinic convenience sample	Age 18+; participants with any pain, arthritis, tendonitis, or carpal tunnel syndrome were excluded from grip test and assigned missing values; participants with missing limbs, paralysis, or needing assistive device were excluded from walking speed test and assigned missing values.	Considered frail if 3 or more deficits present	1. Weight loss: >10 pounds in past year or ≥5% of previous year's body weight, unintentionally, based on clinic records 2. Exhaustion: Answering 'occasionally (3–4 d)' or 'most of the time (5–7 d)' to either 'How often have you felt that everything you did was an effort' or 'How often have you felt that I could not 'get going'' 3. Low activity: Answering 'yes, limited a lot', when asked 'whether their health limits vigorous activities such as running, lifting heavy objects' 4. Slowness: Timed 15 ft walk, stratified by gender and height 5. Weakness: Grip strength measured with dynamometer, stratified by gender and body mass index

Table 1 continued.

Study	Setting	Inclusion Criteria	Description and Scoring	Deficits Included in Frailty Scale
AIDS Linked to the IntraVenous Experience (ALIVE) Study [32] (USA)	Urban, community-based cohort of persons with a history of injecting drugs	Age 18+; history of injecting drugs	Considered frail if 3 or more deficits preset; 'prefrail' if 1 or 2 deficits present	1. Weight loss: ≥5% of body weight since last visit (ranged from 5 to 12 mo), based on physical exam 2. Exhaustion: Answering 'moderate' or 'most of the time' to either 'During the past week, I felt everything I did was an effort' or 'During the past week, I could not get going' 3. Low activity: Answering 'limited a lot', when asked 'Does your health now limit the kinds or amount of vigorous activities you can do, like lifting heavy objects, running, or participating in strenuous sports?' 4. Slowness: Timed 4 m walk; deficit assigned to lowest 20% of participants stratified by gender and height 5. Weakness: Grip strength measured with dynamometer; deficit assigned to lowest 20% of participants stratified by gender and body mass index
Ianas et al [33] (USA)	Urban, outpatient clinic convenience sample	Age 18+	Considered frail if 3 or more deficits present	1. Weight loss: ≥10 pounds in past year, unintentionally, based on physical exam 2. Exhaustion: Answering '3 to 4 d' or 'most of the time' to either 'How often in the last week did you feel that everything was an effort' or '. . . I could not get going.' 3. Low activity: Weighted score of kilocalories expended per week as measured by Minnesota Leisure Time Activity Questionnaire 4. Slowness: Timed 15 ft walk, stratified by gender and height 5. Weakness: Grip strength measured with dynamometer, stratified by gender and body mass index
Pathai et al [34] (South Africa)	Urban, community-based HIV-positive cohort	Age 30+; no opportunistic infections or symptoms of tuberculosis; participants with pain or arthritis of dominant hand were excluded from grip strength test and assigned missing values; participants with paralysis or needing assistive device were excluded from walking tests and assigned missing values.	Considered frail if 3 or more deficits present	1. Weight loss: >10 pounds in past year, or ≥5% of previous year's body weight, unintentionally, based on clinic records 2. Exhaustion: Answering 'occasionally (3–4 d)' or 'most of the time (5–7 d)' to either 'How often have you felt that everything you did was an effort' or '. . . that I could not 'get going'' 3. Low activity: Answering 'yes, limited a lot', when asked 'whether their health limits vigorous activities such as running, lifting heavy objects.' 4. Slowness: Timed 6 m walk, stratified by gender and height 5. Weakness: Grip strength measured with dynamometer, stratified by gender and body mass index
Erlandson et al [15, 35, 36] (USA)	All individuals receiving care for HIV-1 infection at an outpatient clinic at a U.S. academic medical center	Age 45–65; taking effective ART for at least 6 mo; at least one clinic visit with plasma HIV RNA <48 copies/mL, and no visit with plasma HIV RNA >200 copies/mL in prior 6 mo	Considered frail if 3 or more deficits present	1. Weight loss: ≥4.5 kg in past year, or ≥5% of previous year's body weight, unintentionally, self reported and verified by records when available 2. Exhaustion: 3-4 times per week of feeling 'everything I do is an effort' or 'sometimes I just cannot get going.' 3. Low activity: Self-report of being 'limited a lot' in vigorous physical activities on the SF-36 questionnaire 4. Slowness: Timed 4.5 m walk, stratified by gender and height 5. Weakness: grip strength measured with dynamometer, stratified by gender and body mass index

Table 1 continued.

Study	Setting	Inclusion Criteria	Description and Scoring	Deficits Included in Frailty Scale
Sandkovsky et al [37] (USA)	Participants recruited for a pilot clinical trial at a US academic medical center	Age 20–40 or 50+; English speaking; on stable ART for 12 wks or not anticipating initiating ART for 6 wks; no intercurrent acute infection, active psychiatric illness, active neurologic disease, current delirium or intoxication, active drug or alcohol overuse, or pregnancy	Considered frail if 3 or more deficits present	1. Weight loss: >10lbs unintentional weight loss (time period unspecified) 2. Exhaustion: Fatigue Severity Scale score >36 3. Low activity: POMS activity scale score <2 4. Slowness: Timed Gait Test (10 yards × 2) >11 s 5. Weakness: Grip strength >1 SD below mean
Based on other frailty scales:				
Shah et al [38] (USA)	Urban, hospital based HIV clinic outpatients	Age 50+; receiving antiretroviral therapy for 3+ mo and continuing; able to ambulate without assistive devices; no AIDS-defining illnesses for 6 mo; no 'severe cardiopulmonary illness, severe anemia, significant orthopedic or neuromuscular impairments, renal failure, cirrhosis, significant cognitive or sensory impairments, untreated depression, unstable manic or psychotic disorder, or active malignancy'	Considered frail if two or more deficits present	1. Physical Performance Test score of 18 to 32 2. Peak oxygen uptake of 11 to 18 mL/kg per minute 3. Difficulty with one activity of daily living (ADL) or two or more instrumental ADLs (IADLs)
Ruiz et al [39] (USA)	20 patients selected from outpatient clinic program	Participants had identified problems in multiple health domains	Considered severely frail if 3 or more deficits present; moderately frail if 2 deficits present; mildly frail if 1 deficit present	1. Limitations with basic activities of daily living 2. Limitations with instrumental activities of dialing living 3. 'nutrition' 4. 'cognitive' 5. 'hearing and visual screening' 6. 'depression' 7. 'mobility problems'
Talukdar et al [40] (India)	All patients newly diagnosed with HIV infection at tertiary care hospital in Kolkata from 2008 to 2012	Age 50+	Considered frail if unexpected weight loss	1. Unexpected weight loss
Veterans Aging Cohort Study - Virtual Cohort [41] (USA)	All HIV-positive US military male veterans receiving care in the Veterans Health Administration system, enrolled between 1997 and 2009	Men	Items are summed for a continuous score	1. Age 2. CD4 count 3. Hemoglobin 4. FIB-4 (a measure of liver fibrosis): (years of age × AST)/platelets in 100/L × square root of ALT) 5. Estimated glomerular filtration rate: $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 1.21$ if Black 6. Hepatitis C status

Abbreviations: ART, antiretroviral therapy; HIV, human immunodeficiency virus.

A recently introduced measure of health status in people aging with treated HIV, the Veterans Aging Cohort Study (VACS) index, has also been proposed to measure frailty [41]. The VACS index is a prognostic tool made up of both traditional HIV-related factors, including CD4 count and viral load, as well as hepatitis C coinfection, liver fibrosis (FIB-4), hemoglobin,

estimated glomerular filtration rate (eGFR), race, and age. Investigators have considered adding measures to the index, including inflammatory markers D-dimer and soluble CD14 [42]. As the VACS index is a measure of multisystem deterioration and vulnerability, we included it as a frailty scale. However, the VACS index differs from other frailty measures as it was designed to predict mortality and includes chronological age and race [43]. Most frailty scales do not include age, as they intend to describe biological age-related changes independent from chronological age, and most do not include race, because they instead incorporate markers of individual physical and mental health.

Further work is needed to determine the best approach to measure frailty in people aging with HIV. It is important to consider the intended use and setting for a frailty scale, whether as a brief screening tool or as a comprehensive evaluation, for use in the community, hospital, or long-term care. Some scales that have been used to identify frailty in people with HIV might not be appropriate for those who are very frail or immobile, as they include measures of physical performance (eg, walking speed [12, 31–35]) or apply exclusion criteria based on disability or comorbidities. One study using a modified version of the frailty phenotype scale in an HIV clinic excluded 19% of participants because time constraints prevented assessment of grip strength and walking speed [12], and another excluded participants requiring an assistive device to walk [38].

Table 2. Summary of Factors Associated With Frailty Among HIV-positive Individuals on Antiretroviral Therapy

Age [12, 13, 17, 32–34]
HIV-related measures
Longer time since diagnosis [12]
Lower current CD4 count [12, 13, 31–34, 44]
Lower nadir CD4 count [12]
Low CD4/CD8 ratio [31]
Detectable viral load [13, 32]
Longer duration of HAART [13]
Protease inhibitor-containing HAART regimen [12]
Comorbidities
Hepatitis C coinfection [33]
Low BMI [12, 34]
High BMI [38]
Lipodystrophy [38]
Diabetes [13]
Kidney disease [13]
Depressive symptoms [12, 13, 32]
Cognitive impairment [12, 45]
Inflammation [6]
Weak upper and lower extremities [42]
History of falls [36]
Social factors
Lower education [12, 13, 32]
Current unemployment [12, 35]
Low income in past year [12]

Abbreviations: BMI, body mass index; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus.

EPIDEMIOLOGY OF FRAILTY IN HIV INFECTION

Before the introduction of HAART in 1996, men in the MACS study who seroconverted were 9 times more likely to be identified as frail (via a modified frailty phenotype) during at least 1 study visit than men who remained uninfected (13.9% vs 1.5% prevalence) [29]. Risk for frailty increased nonlinearly with age and with duration of HIV infection [29]. Frailty was also associated with CD4 count <350 cells/mm^3, viral load ≥50 000 copies/mL, and AIDS [29].

With the introduction of HAART, the prevalence of frailty appeared to decrease. Among MACS participants, frailty decreased from 8% in 1994–1995, when <0.1% of participants received HAART, to 5% in 2000–2005, when almost 70% were on HAART [17]. Among participants presenting with AIDS, frailty prevalence decreased from 24% to 10% [17]. However, from 2007–2011, when grip strength was added to the MACS frailty scale, 25% of all participants were identified as frail during at least 1 study visit [13]. Here the use of different scales complicates comparison of estimates between studies [7, 23].

Among individuals on HAART, multiple factors have been associated with frailty in cross-sectional studies, using different frailty scales (Table 2). Some are traditional HIV measures, including lower current CD4 cell count (measured continuously [12, 13] and categorically, as <500 cells/mm^3 [34], <350 cells/mm^3 [32], <200 cells/mm^3 [33], and <100 cells/mm^3 [31]), lower nadir CD4 count [12], CD4/CD8 ratio ≤0.29 [31], detectable viral load [13, 32], history of AIDS [13], and longer time since diagnosis [12], as well as hepatitis C coinfection [33], low body mass index (BMI) [12, 34], high BMI [38], lipodystrophy [38], depressive symptoms [12, 32], 1-year history of multiple falls [36], and lower cognitive performance [12]. HIV-positive individuals who are frail are also more likely to have lower socioeconomic status, no more than high school education [12, 32], current unemployment [12, 35], and income <$10 000 in the prior year [12]. Among people who inject drugs, those with advanced HIV disease (defined as CD4 <350 cells/mm^3 and detectable viral load) are more likely to be frail than uninfected individuals, whereas those without advanced HIV disease are not more likely to be frail [32]. Frail HIV-positive individuals are also more likely to have been on HAART for longer duration [13] and on a protease inhibitor-containing HAART regimen and less likely to be on a non-nucleoside reverse transcriptase inhibitor-containing regimen; this disparity is not explained by differences in adherence or successful viral suppression [12]. Frail HIV-positive individuals are also more likely than

the nonfrail to have been hospitalized in the past year and to have longer hospital stays [12].

Also in cross-sectional studies, markers of inflammation (interleukin-6, D-dimer, and soluble CD14) are more strongly correlated with VACS index scores than an index comprised only of age, CD4 cell count, and viral load [6]. VACS index scores are also associated with upper and lower extremity strength [46] and cognitive impairment [45]. Although VACS index scores were suggestive of an association with 1-year history of multiple falls in 1 study, this was not statistically significant [36]. As falls are a common outcome identified among frail HIV-negative older adults [7], further research is needed to assess whether the VACS index is measuring frailty or a different but related construct, including some common components.

Two longitudinal analyses of frailty in people with HIV have been published, both from the MACS cohort. One report included data from before 2007 [17] and the second data from 2007 to 2011 [13]. Each report used a different modification of the frailty phenotype scale (Table 1), which complicates comparisons between the 2 time periods. In both studies, likelihood of presenting as frail at a later study visit was associated with lower CD4 count and no greater than high school education [13, 17]. Some risk factors for frailty identified in pre-2007 data were not replicated in the second analysis (eg, white, non-Hispanic ethnicity [17]), and other risk factors were assessed in only 1 study. In pre-2007 data, the association between frailty and low CD4 count was identified independently of low viral load (<400 copies/mL) and hepatitis B and C coinfection. Participants with high viral load (>50 000 copies/mL) were also significantly more likely to become frail [17]. In the analysis of data from 2007 to 2011, participants with detectable viral loads were not more likely to become frail than those with undetectable viral loads, but participants with depressive symptoms, diabetes mellitus, and kidney disease were more likely to become frail [13]. Also in the 2007–2011 data, HIV-positive participants with a history of AIDS had higher odds of becoming frail than HIV-negative participants, whereas HIV-positive participants without history of AIDS did not have higher odds [13].

As frailty represents an integrative marker of health and vulnerability, and the severity of frailty can worsen or improve over time [47], more longitudinal research is needed. In particular, risk factors for frailty among HIV-positive individuals aging with high CD4 counts and undetectable viral loads have not been identified. This will be critical as this profile represents many HIV-positive persons currently ageing successfully with treated HIV infection [1–3, 9].

FRAILTY AND HEALTH OUTCOMES IN HIV INFECTION

The clinical importance of frailty is often noted as its ability to describe individuals more vulnerable to adverse health outcomes [7]. To date, knowledge is limited regarding the prognostic characteristics of frailty in people with HIV. In 1 sample of people who inject drugs, having HIV or being frail was associated with 3-fold higher likelihood of death, whereas both having HIV and being frail increased the risk 7-fold compared to those with neither [32]. In the MACS study, the presence of frailty prior to HAART initiation decreased time to AIDS or death [30]. The prevalence of frailty at baseline was 8%; 36% of people who frail at baseline developed AIDS or died, whereas 16% of people who were not frail developed AIDS or died [30].

Although assessments of outcomes related to frailty in people with HIV are limited, multiple prospective studies have evaluated outcomes in relation to the VACS index. Higher VACS index scores are associated with all-cause mortality [6, 43], coronary heart disease-related mortality [48], and fragility fractures, suggesting that the index might indeed measure frailty as well [41]. Compared to CD4 count and viral load, VACS index scores had better predictive ability for mortality among HIV-positive individuals with viral load <500 copies/mL and those age ≥50 years [42, 43].

FUTURE DIRECTIONS: FRAILTY AND HIV CARE

While early data have identified the feasibility and usefulness of measuring frailty in people aging with HIV, the implications of incorporating frailty concepts into HIV care are unknown. The ultimate question will be whether recognizing frailty assists in the clinical management of patients with HIV who are frail. Even when immunologically stable, people with HIV accumulate a variety of health problems, and each individual problem likely cannot characterize overall vulnerability. As people with HIV live longer, many will survive to such an age that they might be frail in spite of –not because of –the disease. Models of care need to adapt to this changing paradigm, and principles of frailty management may be useful [49]. A challenge in the management of any patient with complex needs is that many clinical interventions are intended to help people with only 1 problem, and such interventions can do harm in people who have many problems [7]. Interdisciplinary assessment and care can improve clinical outcomes for people who are frail, and screening for frailty among patients with complex needs has been found to be both feasible and useful in primary care settings [7]. Future studies should investigate comprehensive assessments and frailty screening in the delivery of care to people aging with HIV.

Healthy aging with HIV may be promoted by early interventions among those who are at risk for becoming frail. As frailty is associated with lower CD4 count, and risk appears to decline once individuals begin HAART [17, 33], early antiretroviral treatment might delay or reduce the severity of frailty. In longitudinal studies, some older HIV-negative adults show improvement in

frailty status over time and not simply progressive decline [47]. Frailty might be an especially dynamic process in people with HIV, particularly in younger people with greater physiologic reserve and greater opportunity to improve [32–34]. However, contributions of long-term antiretroviral treatment and toxicity to frailty are unknown. Characteristics of frailty and opportunities for intervention should be investigated among the increasing proportion of treated HIV-positive individuals who demonstrate high CD4 counts and undetectable viral loads.

Evidence is also unavailable regarding effective interventions for HIV-positive people who are already frail. Much of the evidence for the care of frail HIV-positive people is necessarily based on trials performed on younger and fitter people. Although some medical interventions developed in fit populations are less effective, or even dangerous, in people who are frail, others can continue to have important benefits. Although some treatments provide smaller risk reductions in people who are frail, the high absolute risk for poor outcomes with frailty might make this smaller benefit worthwhile [7]. People aging while receiving HAART are also at high risk of polypharmacy and related adverse outcomes, and people who are frail are likely most vulnerable [50]. Better understanding of optimal prescribing for frail patients on HAART is needed.

CONCLUSION

The increasing life spans of people with HIV reflect enormous treatment successes and present new challenges related to aging. Although some people with HIV live to older ages with relatively few health problems, others accumulate multiple problems earlier in life. Risk for HANA conditions and other adverse outcomes vary significantly between individuals, and are not fully explained by age, HIV disease severity, or duration of antiretroviral treatment and toxicity. With the accumulation of multiple health problems, it is likely that many people aging with HIV may be identified as frail. Emerging data suggest frailty might be a feasible and useful integrative marker of multisystem vulnerability in people aging with HIV. As people with HIV live longer and with more complex health and social care needs, the concept of frailty could be useful for identifying vulnerable individuals, for organizing care and for comprehensively measuring the impact of illness and treatment on overall health status.

SEARCH STRATEGY

We searched Cochrane Library, CINAHL, PubMed, Embase, PyschINFO, and Google Scholar using the terms “frail” or “frailty” along with “human immunodeficiency virus” or “HIV.” Additional papers were identified from reference lists of retrieved articles, Google Scholar linking of articles citing retrieved articles, and personal libraries of the authors.

Notes

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Potential conflicts of interest. J. F. has received consulting fees from Theratechnologies, Inc, and has received payment for lectures from Viiv Canada, Gilead Canada, and Abbott Canada. With colleagues, K. R. has applied to various Canadian government schemes to commercialize a version of a frailty index based on a Comprehensive Geriatric Assessment, and a company called Videx Canada was incorporated for this purpose. At present Videx Canada no longer exists. The version of the frailty index presented here was not the one that Videx aimed to commercialize. Videx Canada played no role in the preparation of this manuscript. K. R. was associated with Videx Canada but received no funding while it existed. All other authors report no conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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