Biologic aging, frailty, and age-related disease in chronic HIV infection

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Purpose of review
Effective therapies have transformed HIV infection into a chronic disease, and new problems are arising related to aging. This article reviews the aging process, age-related deficit accumulation and frailty, and how these might be affected by chronic HIV infection.

Recent findings
Aging is characterized by acceleration in the rate of unrepaired physiologic damage an organism accumulates. HIV infection is associated with many factors that might affect the aging process, including extrinsic behavioral risk factors and co-infections, and multiple intrinsic factors, including intercellular communication, inflammation, and coagulation pathways. Whether each factor affects the aging process, they likely result in an increase in the risk of adverse health outcomes, and so give rise to frailty, likely with several clinical manifestations.

Summary
Age-related deficit accumulation is influenced by both the background or environmental rate of insults an organism sustains and the efficacy of intrinsic damage control and repair mechanisms. Both processes are likely affected in people living with HIV infection.

Keywords
aging, frailty, health status, HIV, older adults

INTRODUCTION

Effective therapies have transformed HIV infection into a chronic disease, and many HIV-positive people with access to treatment are living to near-normal life expectancies [1,2▪]. With this success, new challenges arise related to aging with HIV and its lifelong treatment. People living with HIV exhibit higher rates of many age-related health problems, including cardiovascular disease, certain cancers, cognitive and renal impairment, bone demineralization, and age-related immune dysregulation [3]. In consequence, a contested theory has emerged that this might represent a form of 'accelerated' or 'premature' aging [4]. The purpose of this review is to discuss what aging is, its relationship with health, disease, and frailty, and how these might be affected by chronic HIV infection.

BIOLOGIC AGING AND CHRONOLOGIC AGE

On average, as people grow older they are more likely to die. They also become more and more likely to experience health problems, including disease, mobility and functional limitations, and cognitive impairment. This trend can be described as acceleration in the rate of unrepaired damage an organism sustains, which characterizes aging and helps differentiate it from the concept of chronological age. This is classically described by the Gompertz law of mortality [5]: that is, the key to distinguishing age from aging is that the latter results in an increase in the hazard rate – which occurs, for example, each year after age 15 but which falls from the perinatal months to the early teenage years. Accelerating hazard rates have been observed across species [6].

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KEY POINTS

- Aging is characterized by acceleration in the rate of unrepaired physiologic damage an organism accumulates.
- This phenomenon is influenced by both the background or environmental rate of insults an organism sustains and the efficacy of intrinsic damage control and repair mechanisms.
- Both of these are likely affected in people living with HIV infection, as illustrated by differences in extrinsic and social risk profiles as well as altered cellular and intercellular processes.
- Heterogeneity in the aging process can be assessed and measured through the concept of frailty.
- Patterns of aging, deficit accumulation, and frailty in HIV infection are not yet well established, but could add valuable perspectives to understanding aging with HIV disease.

Hallmarks of aging

Aging happens, even among the fittest and healthiest of us. This damage is largely intrinsic, representing the byproducts of lifelong metabolic processes at cellular and subcellular levels. Current understanding describes various 'hallmarks' of aging, which have been reviewed elsewhere [7▪▪]. These processes are complex, but in general terms, a well accepted view is that aging is characterized by an accumulation of near-random damage throughout the life course, which appears to also occur consistently within telomeres [8,9], dysfunction in the mechanisms that stabilize and guide protein folding [10], and DNA and posttranslational epigenetic changes [11]. Compensatory mechanisms initially repair or mitigate this damage, but can cause further damage when they are chronically activated or engaged; these include mitochondrial dysfunction, leading to accumulation of reactive oxygen species (ROS) and less efficient ATP generation [12], and cellular senescence, arresting cellular growth after a finite number of divisions [7▪▪]. Both primary and compensatory mechanisms contribute to the exhaustion of stem cells and regenerative potential of tissue with age, and also alter intercellular communication, leading to a progressive proinflammatory state at older ages [7▪▪].

Inflammaging

The observation of this chronic proinflammatory state has given rise to the 'inflammaging' hypothesis of aging [7▪▪,13]. Like other characteristic processes of aging, inflammaging has multiple potential contributory sources, including the tissue damage and accompanying inflammatory response, pathogens and problematic host cells not fully cleared by the immune system, and senescent cells with a propensity to secrete proinflammatory cytokines [13,14]. Chronic inflammation causes or is exacerbated by multiple age-related diseases, including obesity, type II diabetes, and atherosclerosis, which in turn might lead to the more rapid accumulation of further deficits [13].

Inflammation and age-related immune system dysfunction have been particularly implicated in the greater prevalence of age-related health problems observed in people aging with treated HIV infection [14]. Higher levels of biomarkers of inflammation (IL-6), altered coagulation (D-dimer), and monocyte activation (sCD14) have been observed among HIV-positive individuals with CD4 depletion and ongoing virus replication, compared with HIV-negative individuals [15]. Data from the Strategies for Management of Antiretroviral Therapy (SMART) trial showed significantly greater IL-6 and D-dimer increases among people randomized to receive interrupted, CD4-guided antiretroviral therapy (ART) compared with those randomized to receive continuous ART, and that IL-6 and D-dimer were strongly associated with all-cause mortality [16]. Further SMART data identified higher rates of cardiovascular, renal, and hepatic disease in the interrupted-treatment group [17]. Proposed mechanisms between chronic inflammation and the greater risk for specific age-associated diseases observed in HIV infection have been reviewed in detail elsewhere [14,18–20].

Age-related damage and repair

As damage goes unrepaired and accumulates with aging, further damage becomes more likely. The dominant view of cellular aging is that subcellular, cellular, and intercellular damage progress to deficits at the level of tissue and organs (which might be identified by laboratory or imaging tests before they become clinically apparent), and eventually at higher level functions, including functional dependence, falls, immobility, and cognitive impairment [21▪▪]. The mechanisms of this scaling process are complex and not yet fully understood, but the notion that health problems make an individual more likely to develop further health problems is a plausible one [22]. Problems in one physiological system also contribute to vulnerability in others, and though the individual effects of a deficit can be small their cumulative effects can be large [23,24▪]. This is characteristic of the 'atypical' disease

presentation often seen in frail older adults. In a common example, a frail older adult with bacterial pneumonia might present with falls and without the cough, fever, or elevated leukocytes seen in younger, fitter adults with bacterial pneumonia [25].

It is important to recall this damage is largely intrinsic, and as a byproduct of living it is experienced throughout the life course. For this damage to become a deficit, it must go unrepaired. The involvement of maintenance and repair mechanisms throughout the aging process has been noted [7▪▪,26,27]. Such repair mechanisms contribute to the complex and stochastic nature of damage and deficit accumulation [28▪▪]. They also suggest that change with aging is not always deteriorative, improvement is also possible [29,30].

Alternative accounts of cellular aging

More recent work on aging has revealed processes other than widespread age-related deficit accumulation in cells. A great body of evidence points to an important role for cellular senescence, in which cells undergo irreversible growth arrest. Senescent cells exhibit features notable in the deficit accumulation account: extensive gene-expression changes, increased cell size and protein content, and changes in cell and organelle shape [31]. Originally understood as a protective response to potentially oncogenic events, such as telomere shortening, DNA damage and mutations, protein aggregation, and increased ROS, senescent cells instead have a 'senescence-associated secretory phenotype' (SASP) that elaborates a variety of factors that promote not only low-level chronic inflammatory damage, but also cancer [31]. Importantly, then, the accumulation of senescent cells might be implicated in tissue damage associated with aging (sometimes otherwise viewed as too little cellular activity) and with cancer (being too much cellular activity) [32].

One account of how cellular aging comes about sees it not as a matter of accumulated random damage, but rather the result of cell programs gone awry. The mammalian target of rapamycin pathway in particular is implicated: it responds to a variety of nutrients, so that aging is a byproduct of specific metabolic processes in a so-called hyperfunction theory of aging [33,34].

Heterogeneity in aging processes

No matter what the mechanism, how individuals age is influenced by the background or environmental rate of insults, the efficacy of their intrinsic damage control and recovery mechanisms, and interactions between the two [28▪▪]. These processes are also influenced by extrinsic factors experienced throughout the life course. For example, in Canadian [35] and Chinese [36] cohorts, smokers accumulated more deficits at a given age than nonsmokers. European residents who were born in low-income or middle-income countries accumulated more deficits than native-born Europeans of the same age [37].

People living with HIV infection often experience high rates of such environmental insults, including smoking, alcohol and drug use, co-infections, and psychosocial stressors, as well as the cumulative toxic effects of long-term antiretroviral use [3,15,38]. These same factors likely also influence damage control and repair mechanisms, as might the natural history of the virus itself. This is illustrated in part by altered intercell communication observed in HIV infection, characterized by the chronic inflammatory and hypercoagulable state described above, as well as mitochondrial dysfunction [39]. Emerging data further reinforce the importance of this interaction between the rate of insults and the efficacy of damage repair mechanisms in chronic viral infection [19]. Cytomegalovirus (CMV) infection, for example, remodels the immune system, but its effects on poor health (and its role as an independent risk factor for mortality) are not demonstrable until older ages when other deficits accumulate [40]. CMV co-infection has also been implicated in the hyperinflammatory state observed in HIV-positive individuals who respond to antiretroviral treatment [41,42].

AGING, DEFICIT ACCUMULATION, AND FRAILTY

Although aging happens to everyone, not everyone ages the same way. Indeed, two people of the same age might experience very different levels of health. This variable risk of poor health in people of the same age is known as 'frailty' [21▪▪]. Frailty is recognized as a condition of increased vulnerability to stressors, associated with an impaired homeostatic response and increased likelihood of multiple adverse health outcomes, including falls, delirium, disability, and death [21▪▪]. Homeostatic mechanisms normally decline with aging, so that the notion of greater decline relative to other people of the same age is key; even so, it is the case that at some static, uncommonly high age (notionally in the 10th decade) all older adults are frail, in the sense of being at some very high risk of adverse health outcomes. This is commonly manifested when a relatively small insult can result in a disproportionately negative response [21▪▪]. In consequence, a great deal of effort has gone into identifying who

is in the risk state before adverse consequences occur. Counting deficits is one useful way to quantify frailty [25,43▪]. As people accumulate health deficits and become frailer, they are both more likely to accumulate further health deficits (i.e. an acceleration in the hazard rate) and more likely to experience changes in health state (e.g. from independent to dependent, mobile to immobile, lucid to delirious, or alive to dead) [21▪▪].

Frailty as a syndrome or a state

Many tools exist to assess frailty, and these different tools count different groups of health deficits [43▪]. They differ especially in being informed by two contrasting conceptual models: the frailty phenotype and the frailty index [21▪▪]. The frailty phenotype views frailty as a clinical syndrome, originating in a 'cycle of frailty' comprised of undernutrition, sarcopenia, and weakness and impaired exercise tolerance [44]. To operationalize this, the frailty phenotype in effect counts five specific health deficits: unintentional weight loss, impaired grip strength and walking speed, fatigue, and decreased activity levels [45]. An individual is frail if they exhibit three of these five health deficits. This approach suggests that the pathophysiology of frailty is distinct from aging or other disease processes.

The frailty index (first proposed by members of our group) views frailty as a state, rather than a specific syndrome, representing the cumulative effects of multiple nonspecific health deficits that might arise through the aging process [46]. The approach is very robust, and remarkably, as long as enough items are counted, appears to lead to comparable results even when different items are included in different versions of the frailty index. In other words, a frailty index can include any variable measuring an age-related health deficit, as long as at least around 30 are selected which cover a range of physiological systems [47]. Each deficit should be associated with adverse health outcomes and with age, have a prevalence of at least 1%, and not become universal with age. For each selected variable, an individual should be assigned 1 if a deficit is fully expressed and 0 if a deficit is absent. For intermediate values (e.g. 'good' or 'fair' self-rated health), individuals can be assigned relevant fractions (e.g. 0.33, 0.66, etc.) although it is not necessary to do more than dichotomize [48]. By calculating the proportion of deficits an individual has accumulated out of the total number of items measured, this assesses the severity of frailty. Other scales often include more health variables those specified by the frailty phenotype, and fewer than the generally 30 or more used in the frailty index approach [49▪].

Many frailty scales demonstrate ability to grade vulnerability and to do so better than chronological age alone. Even so, different scales vary in their prognostic abilities and operational feasibility [49▪]. The frailty phenotype has been extensively studied and widely validated for multiple adverse health outcomes. It appears to be insensitive to changes in frailty severity and relatively nonspecific (especially in relation to comorbidities, such as cancer, parkinsonism, or musculoskeletal disorders, which might influence the presence or absence of the specific criteria). Additional items have been proposed to make up an expanded frailty phenotype, including affect and cognition [50,51]; on the other hand, some have proposed removing items so as to simplify the phenotype [52].

The frailty index has been widely applied across different populations, using different sets and different numbers of variables [29]. Consistent findings include that frailty index values increase nonlinearly with age after age 50 (by 3% with each year of age, on a log scale), and there appears to be an upper limit to deficit accumulation (around about 0.7) beyond which survival is not possible. Because at least 30 health variables are required, this might make it less convenient to apply in some settings. Clinically, frailty indexes have been created using electronic medical records [53] and comprehensive geriatric assessments (CGAs) [54,55▪,56,57].

Frailty in people aging with HIV infection

Data on frailty in people with HIV are rapidly emerging from cohort and clinical studies. Reports to date use frailty scales that count a limited number of age-related health deficits; most are based on the frailty phenotype [58,59▪▪,60]. Although methodological differences in the frailty scales used limit meaningful comparisons of frailty prevalence estimates between studies, some consistent findings reinforce the notion of frailty quantifying heterogeneity in the aging process. Similar to findings in HIV-negative individuals, frailty levels are higher in HIV-positive individuals with less formal education [61,62▪,63▪▪], who are unemployed or who have lower incomes [61,64], or who have comorbidities not included in the frailty scale, including diabetes [63▪▪], kidney disease [63▪▪], depressive symptoms [61,62▪,63▪▪], hepatitis C co-infection [65], and markers of chronic inflammation (IL-6, D-dimer, and sCD14) [66].

Frailty is positively associated with traditional markers of HIV disease and vulnerability, including current and nadir CD4 count [61,62▪,63▪▪,65,67–69], and presence of a detectable viral load [62▪,63▪▪]. Among a cohort of people who inject drugs,

HIV-positive participants with advanced HIV disease (defined as CD4 <350 cells/μl and detectable viral load) were more likely to be frail than HIV-negative participants, whereas HIV-positive participants without advanced HIV disease were not more likely to be frail [62▪]. One longitudinal analysis of the Multicenter AIDS Cohort Study (MACS) from 2007 to 2011 found that HIV-positive participants with a history of AIDS were more likely to become frail than HIV-negative participants, whereas HIV-positive participants with no history of AIDS were not [63▪▪].

Limited data exist on frailty in relation to outcomes in HIV infection, and further work is needed. In a cohort of people who inject drugs, being HIV-positive or being frail was each associated with three times higher odds of death, whereas being both HIV-positive and frail was associated with seven times higher odds [62▪]. In the MACS, participants who were frail before starting ART had shorter time to AIDS or death [70].

Of particular interest is the widely investigated Veterans Ageing Cohort Study (VACS) index. The VACS index was originally developed to assess health status and predict death in people with chronic HIV infection, and has recently been proposed as a frailty measure in this population [59▪▪]. The index includes traditional HIV-related measures, including CD4 count and viral load, other deficits including hepatitis C virus co-infection, liver fibrosis, hemoglobin, kidney function, as well as race and age.

Data from studies employing the VACS index can help illustrate the association between deficit accumulation, frailty, and the emergence of age-related disease across multiple physiological systems. VACS index scores are associated with multiple health problems common with aging and frailty: inflammation (IL-6, D-dimer, and sCD14) [66], distal muscle weakness [71], fragility fractures [59▪▪], cognitive impairment [72▪], coronary heart disease-related mortality [73], and all-cause mortality [66,74▪].

Notwithstanding these points of similarity, the VACS index differs from frailty measures developed in HIV-negative populations, as it includes chronological age and race [74▪]. Most frailty scales do not include age as a variable, as they intend to describe the cumulative effects of multiple biological age-related health changes, including the possibility of improvement [75]. Most frailty scales also do not include race, which obviously does not change with age. Although it can reasonably be argued that as a measure of vulnerability, frailty scales could include all variables which improve the prediction of adverse outcomes, different patterns have been observed between the accumulation of social deficits [76] and general health deficits [43▪,76]. The VACS index also includes variable weightings derived from the VACS study to optimize its prognostic abilities. Weighting of deficits is uncommon in frailty scales, as variable weights derived from one sample can limit generalizability to other populations [49▪]. Even so, as described above, the VACS index has identified vulnerability for outcomes in addition to death, including many collinear with frailty, and its variable weightings have demonstrated notable stability in validation datasets [74▪].

How best to measure frailty in people living with HIV?

In the current highly active antiretroviral treatment era, in which most HIV-positive people with access to therapy experience long-term immune reconstitution and suppression of viral load below detectable levels, which frailty scale is best or most informative has not been established [58]. This is not surprising, as there is also no consensus on which frailty scale is best to use in geriatric practice in general [49▪]. The best frailty scale to use might also depend on the setting in which it is used, whether as a convenient screening tool to signal a need for follow-up or as a more comprehensive evaluation.

Special considerations might apply to those aging with HIV infection, however, as HIV-positive and HIV-negative people might experience characteristically different risk profiles with age. Perhaps scales measuring frailty in people aging with HIV should include measures of behavioral risk factors for illness, of chronic viral co-infections, or of surrogate laboratory measures known to be influenced by HIV infection. Although these factors might contribute to vulnerability in people aging with HIV, this might represent something else in addition to the frailty that has been identified in HIV-negative older adult populations in geriatric medicine. Here, the frailty index approach might prove useful. As noted, a frailty index can be comprised of many different variables that assess age-related health, and deficits can be included or excluded as long as there are at least around 30 included that meet the few stated criteria. No published studies have yet evaluated the frailty index among people aging with HIV.

CONCLUSION

Aging, characterized by acceleration in the accumulation of unrepaired health deficits over time, is influenced by both the rate of insults an organism sustains and the efficacy of damage maintenance and repair mechanisms. Both of these processes are

likely affected in complex and heterogeneous ways among people aging with HIV infection. Differences in aging can be assessed and quantified by counting these deficits, through the concept of frailty. Patterns of aging, deficit accumulation, and frailty are not yet well understood in HIV infection, and this perspective may add to understanding about aging and age-related disease in this population.

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None.

Conflicts of interest

K.R. assigned copyright of a frailty instrument called the Clinical Frailty Scale to Dalhousie University. Several prior publications indicated that K.R. intended to commercialize two frailty measures, but this is no longer the case. When people write to ask for permission to use the scale, they are asked not to modify and commercialize the instruments. If they are doing it for a commercial research organization, Dalhousie has a fee schedule that they follow for any such instrument. T.D.B. reports no conflicts of interest.

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