Current HIV/AIDS Reports (2020) 17:226–236
https://doi.org/10.1007/s11904-020-00494-2

HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

Frailty in People Living with HIV

Julian Falutz[1]

Published online: 12 May 2020

Abstract

Purpose of Review Different factors contribute to the decreased overall long-term survival in treated people living with HIV (PLWH). This paper will review the state of physical frailty which limits successful aging in PLWH.

Recent Findings Identifiable events on the continuum from clinical normality to heightened risk of adverse health outcomes contribute to frailty. These center on chronic inflammation leading to destabilization of autoregulated physiologic systems challenged by environmental and biologic challenges. Frailty assessment can inform the profile of aging PLWH at increased risk of common age-related disorders and geriatric syndromes. Biologic and psychosocial risk factors promoting progression to and reversion from a dynamic state of frailty are being investigated, allowing for preventative interventions to be considered.

Summary Insights gained from studying frail PLWH will help adapt an interdisciplinary geriatric model of health care for selected PLWH. This will improve the health and well-being of aging PLWH.

Keywords Frailty · HIV · Aging · Chronic inflammation · Geriatric syndromes

Introduction

This paper will review the current status of the physical frailty syndrome in people living with HIV (PLWH). Other types of frailty, including social frailty [1] and cognitive frailty [2], are also being investigated in the general population. This review will focus on physical frailty.

The course of HIV infection has changed dramatically in less than a generation. HIV is now a chronic illness for most PLWH with consistent access to effective combination antiretroviral therapy (cART) [3]. Long-term survival approaches that of the general population, and is similar in an increasing minority of PLWH [4]. This, plus the increasing age of recent seroconverters, of whom 20% are older than 50 [5], has resulted in the mean age of PLWH in high-income countries to currently be in the 50's [4]. By 2030, 73% will be older than 50 and 39% older than 60 [6]. This will significantly impact the type of health care required to assure ongoing improvement in healthspan.

Despite cART-related benefits on health and quality of life (QOL), an increase in some common age-related conditions also occurs [7]. This may represent an accelerated aging phenotype, whereby the increased rate of complications occurs earlier than in a control group of the same age. This is supported by studies of DNA-methylation [8], telomere length [9], and immune-senescence [10]. An alternative explanation, termed accentuated aging [11••], postulates that these co-morbidities occur more frequently but at a similar age in PLWH. Incomplete cART-dependent control of HIV replication leads to immune activation and chronic inflammation which increases vulnerability to these conditions [12], as occurs in the elderly population [13]. A recent study in male PLWH using a 10 marker aging panel (MARK-AGE) interpreted age advancement of approximately 13 years compared with controls as consistent with accentuated aging [14•]. In contrast, an analysis of age-related diseases in PLWH and matched seronegative controls in Denmark showed that the age-standardized and relative risks of most conditions did not increase after HIV diagnosis [15].

This article is part of the Topical Collection on *HIV Pathogenesis and Treatment*

✉ Julian Falutz
julian.falutz@mcgill.ca

[1] Division of Geriatrics
Director, Comprehensive HIV and Aging Initiative
McGill University Health Centre
Montreal, Quebec, Canada

Geriatric Syndromes in PLWH

An increase in geriatric syndromes also occurs in older PLWH [16•]. These include frailty, polypharmacy, falls and impaired mobility, cognitive decline and mood disorders, sensory dysfunction (vision, hearing, smell), incontinence, and sarcopenia. Broadly, these conditions occur often in the elderly, do not fit into discrete disease categories, have multifactorial etiologies, nonspecific clinical presentations, typically involve multiple organ systems, and are challenging to manage [17•]. Frailty may be the most difficult to define, evaluate, and treat.

Frailty as a Geriatric Syndrome

Fundamentally, frailty represents a unique condition of increased risk. The word frailty is derived from the Latin word fragilis, meaning breakable. Fried promoted the concept that frailty was a complex syndrome in the elderly with manifestations distinct from concurrent disabilities or co-morbidities. This was operationalized as the Frailty Phenotype (FP) in a cohort of men and women older than 65 enrolled in the Cardiovascular Health Study (CHS) [18••]. Rockwood proposed an alternative view, the Frailty Index (FI), which considers frailty as a state determined by the interaction between diverse assets and deficits and predicts an older person's ability to function independently [19••].

Diagnosis, Epidemiology, and Outcomes of Frailty

Clinicians and investigators agree on its fundamental attributes and outcomes, although the ability to easily diagnose frailty is limited by the lack of a simple operational definition. At least 67 metrics with overlapping criteria have been developed [20]. Both the FP and the FI are used to diagnose frailty mostly in research rather than in clinical settings.

The FP is more commonly used and is diagnosed if any three of five predefined physical conditions exist: unintentional weight loss, self-reported exhaustion, weak hand grip strength, slow gait speed, and low physical activity [18••]. Persons with one or two conditions are pre-frail, while those without any are non-frail.

The FI is based on the age-related accumulation of diverse health deficits. The FI is calculated as the proportion of common health deficits an individual has from among a predetermined set of conditions, regardless of whether they are clinical signs, symptoms, physical, cognitive or social impairments, or specific laboratory tests and diagnoses. The risk of adverse outcomes correlates with an increasing FI. Although the continuous nature of the FI does not readily allow for a diagnosis of frailty, a FI > 0.25 generally identifies a state of frailty in older community-living persons [21]. A FI above 0.7 identifies an individual with multiple acute conditions with poor short-term prognosis. Importantly, the choice of deficits assessed is not fixed as long as certain basic criteria are met [22] although a minimum of 30 conditions are required.

While the FP may be easier to apply, as it utilizes three questions and two physical tests, the necessary evaluations are not routinely performed in the common clinic settings and require personnel trained to administer them. Conversely, although the FI may seem challenging to operationalize, it has greater precision to discriminate individual risk. It can also be easily determined if an electronic health record (EHR) is available [23].

Both models identify subgroups who are frail in the absence of disabilities or co-morbidities. Few studies have focused attention on this subgroup, the prevalence of which varies from 2 to 25% [18, 24, 25]. Importantly, both major models agree that frailty is a dynamic condition and may be reversible [26].

Both scores have been validated in diverse populations and predict similar outcomes. The prevalence of prefrailty and frailty in the originally described CHS cohort was about 57% and 7%, respectively, in subjects over 65, with more women than men being frail. The prevalence of being FP+ was about 30% in those older than 80 [18••]. The prevalence of frailty using the FI was 22% for persons living in the community older than 65 and more than 40% in those older than 85 [21]. In studies comparing the two scores, the correlation between them is 0.65 [27].

Other more accessible tools to diagnose frailty have been developed. These include the 9-point clinical frailty scale [28], the multidimensional Edmonton frail scale (EFS) [29], the 5 item FRAIL questionnaire [30], the combined patient derived and provider determined Gerontopole instrument [31], and self-administered scores [32], among others.

A recent meta-analysis showed that the most commonly used frailty metrics were all significantly associated with an increased risk of overall mortality, hospitalization and loss of independence, disability, referring to deficits in activities of daily living (ADLs) and instrumental activities of daily living (IADLs), as well as falls, fractures, and cognitive decline. Significantly, prefrailty was also associated with an increased risk of mortality, hospitalization, institutionalization, disabilities in either ADLs or IADLs, as well as falls and fractures [33•].

Biology of Frailty

General Population

A progressive loss of normal homeostatic processes in diverse physiologic systems occurring in response to environmental and biologic stressors leads to frailty. This results in adverse outcomes which can be characterized at the cellular, tissue, organ and whole person level [34]. Although these changes also occur in physiologic aging, a heightened degree of dysfunction is central to the development of frailty [35].

Immuno-senescence plays a key role, as determined by activation of the multiple cellular components of the innate immune system, plus changes in the adaptive immune system. This results in a chronic inflammatory state [36] characterized by reduced numbers of naïve T cells, an increase in terminally differentiated CD8+ and CD28− T cells and a low CD4+/CD8+ T-cell ratio [37]. Chronic CMV infection contributes to both immune-senescence and frailty [38]. The combination of immune features plus CMV seropositivity is referred to as the Immune Risk Profile (IRP) and increases risk of mortality in the very old [39, 40]. Interestingly most centenarians have a normal CD4/CD8 T cell ratio [41]. The term inflammaging encompasses the aging-related dysregulation between the innate and adaptive immune systems [42]. Triggers include accumulation of damaged cells and their impaired elimination, entry of microbial products into the circulation via an aging and leaky gastrointestinal tract alongside changes in the gut microbiome, accumulation of senescent cells secreting proinflammatory cytokines, increased activation of the coagulation system, impaired regulation of the complement cascade, and mitochondriopathies [43••].

Commonly determined serum markers of these processes include increased levels of proinflammatory cytokines, particularly C-reactive protein (CRP), interleukin 6 (IL-6), tumor necrosis factor alpha (TNF-α), and coagulation factors including fibrinogen, Factor VIII, and D-dimer [44]. A meta-analysis confirmed the increased levels of these markers in both frail and pre-frail elderly subjects [45].

Contributing hormonal changes include decreased insulin-like growth factor-1 levels, decreased testosterone and dehydroepiandrosterone-sulfate levels, and abnormalities in cortisol secretion characteristic of a chronic stress response [46]. An important consequence is sarcopenia, a geriatric syndrome characterized by progressive loss of muscle mass and power which occurs frequently in persons with physical frailty [47].

Other fundamental contributors include epigenetic changes [48], telomere shortening associated with the frailty phenotype [49], genetic regulation of fundamental biologic pathways controlling apoptosis, transcription and biosynthesis [50], and age-related body composition changes. These include abdominal obesity, itself contributing to chronic inflammation, and loss of lean muscle mass [51].

Persons Living with HIV

Several determinants of frailty in the elderly also occur in PLWH, including sarcopenia [52] and abdominal obesity. The latter is of multifactorial etiology including toxicities associated with several early generation antiretroviral drugs [53] but may occur even with recently introduced ones [54•]. Telomere changes [55], and both HIV [56] and drug induced mitochondrial dysfunction also occur [57]. The IRP profile has been identified in PLWH [58]. A persistently low CD4/CD8 ratio occurring in most treated PLWH has clinical implications [59•] and has been associated with frailty [60, 61].

Factors unique to PLWH include untreated HIV infection causing significant immune activation which improves but does not return to baseline with cART [62]. This is related to ongoing low-level HIV replication in lymphoid tissues and sanctuary sites, microbial translocation of bacterial products into the circulation via an imperfectly cART-restored gastrointestinal epithelium, and frequent coinfection with Hepatitis B, C, and CMV [63].

The Multicenter AIDS Cohort Study (MACS) demonstrated elevated levels of the immune activation markers CD8+/CD38+, CD8+/HLA-DR+, and IL-6 in frail subjects [64]. CRP was 50% higher in frail PLWH compared with non-frail subjects [65]. The association between frailty and increased proinflammatory cytokines, decreased-free testosterone, and dehydroepiandrosterone supports the multifactorial etiology of frailty [66]. However, important differences in the nature of immune dysregulation in the two populations were suggested by distinct interactions between CD4+ regulatory T cells (Tregs) in frail PLWH and controls [67]. A role for CMV as a cofactor was demonstrated in both PLWH and controls, although the highest IL-2 responses to CMV predicted frailty only in the controls [68].

Frailty Assessment in Aging PLWH

Frailty has been evaluated in non-elderly populations, including dialysis patients [69], and persons with collagen-vascular diseases [70]. A recent UK study found that between 3 and 5% of healthy, middle-aged persons were FP+ [71•]. Although concern has been raised whether frailty described in older persons can be adapted to younger populations using similar metrics, the clinical utility of these models is supported as they reliably predict similar outcomes. Similar issues have been raised in regard to PLWH, although reassurance was provided by the same distribution of abnormal FP parameters in both PLWH and controls [72].

Frailty in the Multicenter AIDS Cohort Study (MACS)

The MACS initially investigated similarities between frailty in the elderly and PLWH using a four-item adapted frailty-related phenotype (aFRP). In untreated, seropositive, Caucasian, college-educated men, with a mean age of 55, the prevalence of frailty, 3.4%, was similar to that of HIV seronegative males older than 65 from the same cohort [73]. An association between frailty and immuno-virologic parameters was demonstrated by an increasing risk of being FRP+ relative to a CD4 count < 500/mm^3 and an HIV viral load > 50,000 copies/mL [74]. The clinical consequences of frailty were shown by an increased risk of AIDS or death in treatment naïve PLWH starting cART [75]. Frailty, regardless of HIV status, occurred without concurrent co-morbidities. Risk factors included older age and non-Hispanic black ethnicity. Potentially manageable risks included a history of AIDS, cigarette smoking, hepatitis C infection, depression, diabetes, and kidney disease. Higher education was protective. Although frailty is dynamic, PLWH who became frail were more likely than controls to remain frail at follow-up. [76].

Other Studies Using the FP to Diagnose Frailty

The AIDS Linked to the Intravenous Experience (ALIVE) cohort showed that 12% of mostly male, African-American injection drug users with a median age of 49 were FP+. Risk factors for frailty included HIV infection, older age and female sex, while potentially controllable risks, as in the MACS, included advanced HIV disease, lower education, depression and multimorbidity. Being frail, regardless of HIV status, was a risk factor for overall mortality [77], all-cause hospitalizations, as well as chronic conditions such as psychiatric, cardiovascular, and pulmonary diseases [78].

Disability, determined as impairments in IADLs, was investigated in the HAILO (HIV Infection, Aging, and Immune Function Long-Term Observational Study) Cohort, a prospective, observational, long-term study of treatment naïve PLWH starting cART, with median age 51. The prevalence of pre-frailty and being FP+ was 37% and 6% respectfully. There was minimal overlap between frailty and disability, although 52% of frail PLH had at least 1 disability [79]. Frailty was associated with increased incidence of CVD, type II diabetes, and with increased mortality [80]. Modifiable risk factors for frailty including neurocognitive impairment, obesity, smoking, choice of initial cART (with NNRTI [non-nucleoside reverse transcriptase inhibitor]-based cART increasing risk of frailty), and level of education. Physical activity and moderate alcohol use were protective [81].

More seropositive women than men are FP+ [82, 83], as in the general population [84]. In the Women's Interagency HIV Study (WIHS), consisting of mostly low-income, African-American non-Hispanic women, most with secondary education and a mean age of 39, 17.3% of seropositives were FP+ versus 10.0% of uninfected women [85]. Impaired bone health is more common in FP+ PLWH [80, 86, 87]. Functional impairment, determined by reduced gait speed and poor performance on the Short Physical Performance Battery (SPPB), occurred in 20% and 55%, respectively, in a cohort of Spanish PLWH with a median age of 61, of whom 51% were pre-frail and 15% were FP+ [61]. In an analysis of mostly non-Caucasian Brazilian PLWH with a median age of 55, the 19% who were FP+ were more likely to have a poor quality of life determined using the 36-item Short Form Survey [82]. In a study of younger, treated PLWH in South Africa with a mean age of 41, 19.4% were frail using an adapted FP, compared with 13.3% of seronegative controls [83]. This finding in a low-income country highlights the economic burden and impact on healthcare delivery that frailty will have as the prevalence of aging PLWH increases in all regions.

Frailty Assessment of PLWH Using Other Metrics

Veterans Aging Cohort Study Index (VACS-I)

The VACS-I was developed as a multifactorial mortality index in HIV infected and uninfected American veterans using commonly available clinical and laboratory parameters in addition to standard HIV-related metrics. It is associated with increased risk of all-cause mortality, hospitalization, admission to intensive care units, physical functional status, cognitive decline, and increased markers of inflammation [88, 89]. Because these outcomes are similar to those in frail persons, it has also been considered as a frailty index [86], analogous to the deficit accumulation model [90]. A higher VACS-I was associated with being either pre-frail or FP+, although the baseline score could not predict change in frailty status [91]. The VACS-I also predicted hospitalization or mortality more accurately than an adapted FP. However, the prevalence of being FP+ in PLWH with undetectable HIV-RNA or in uninfected controls was similar, 2% and 2.8%, respectively [90].

Frailty Index

Frailty determined using the FI has been extensively studied by the Modena HIV Metabolic Clinic (MHMC) cohort. Using a 37-item-derived FI, which importantly did not include any HIV-related variables, the median FI was 0.30 in the cohort of treated, mostly male PLWH with a mean age of 46. The FI was a significant predictor of survival and development of new multimorbidity [92]. A further study showed that potentially modifiable personal, environmental and HIV-related factors were independent contributors to the FI [93]. The MHMC cohort also showed that CT determined-thymus size, an essential component of immune function in the general population, and of immune recovery in treated PLWH [94], was

inversely related to the FI, supporting the interaction between immunity and frailty [95]. An Australian study in males with a median age of 59, diagnosed as frail using the FI, found an independent association with sCD163, suggesting that the FI may identify frailty biomarkers [96].

Frailty and Other Clinical Conditions in PLWH

Several studies have shown an association between measures of abdominal obesity and being FP+, regardless of HIV status, [72, 97, 98] highlighting this as a potentially reversible lifestyle factor for frailty. Potentially treatable mild-to-moderate depression is diagnosed in about 50% of frail PLWH [99, 100], and occurs often in PLWH with neurocognitive impairment. Asymptomatic neurocognitive impairment (NCI) is a feature of aging PLWH [101]. Studies have investigated whether physical frailty is a risk factor for NCI in PLWH. A higher VACS-I, suggestive of frailty, predicted the presence of NCI in a cohort with a mean age of 41 [99] . The Italian MHMC cohort study found that a lower FI was associated with successful cognitive aging, defined as the absence of depression, cognitive, and functional impairment [102]. Participants in the HAILO study who were both FP+ and had NCI had an increased risk of adverse health events including falls, disability, and overall mortality [103]. Being FP+ has also been associated with NCI in PLWH in diverse geographic regions including China [98] and Mexico [104]. These consistent findings using different metrics support the emerging construct of cognitive frailty as an important condition in PLWH.

Studies Comparing Frailty Metrics in PLWH

As in the general population [105], studies have compared frailty classifications in PLWH. In a subgroup of the MHMC cohort with a mean age of 46, the VACS-I, compared with the FI, more accurately predicted 2-year but not 5-year mortality [92]. The FI was compared with the FP in a different subgroup of the MHMC cohort with a mean age of 54, of whom 52% were pre-frail and 3.1% were FP+. The FI had a greater association than the FP with baseline factors of age, nadir CD4 count and with adverse events including co-morbidities, falls, and disability [106]. Overall, it is premature to recommend a particular frailty metric as more reliable to use for all PLWH.

Screening for Frailty and Management Principles

Screening

Diagnosing an older individual as frail has relevance beyond simply identifying a condition associated with adverse outcomes. For example, frailty is an important risk factor for perioperative complications. Pre-habilitation clinics, where identified preoperative risks for postoperative morbidity can be modified, improve outcomes [107]. An interdisciplinary geriatric approach is increasingly recommended for selected aging PLWH, particularly those diagnosed as frail [108]. Other surrogates besides frailty can help to identify those PLWH who may benefit from a geriatric evaluation. These include polypharmacy, which is more common in PLWH compared to controls [109•], impaired functional status as determined by gait speed or the comprehensive SPPB, and the presence of geriatric syndromes. Although distinct conditions, important interactions occur in PLWH between frailty, functional status, and disabilities [110]. Both functional impairment and disabilities occur in PLWH [111], especially in those with concurrent geriatric syndromes [110]. A combination of immune parameters, (e.g., a low nadir CD4 count < 200, a 'plateau' CD4 < 500 on suppressive cART, and a CD4/CD8 ratio < 1.0) may also identify frail PLWH requiring a geriatric evaluation [60, 61].

Frailty is a dynamic state. In a study of over 300 treated PLWH over a 12-month follow-up period, most non-frail and pre-frail persons maintained their status, whereas most who were frail reverted to prefrailty [91]. Pre-frailty, occurring in 30–60% of PLWH, is important to identify, as it is also associated with adverse outcomes. Factors associated with progression to frailty in PLWH in the MACS have been described above. Only younger age was associated with reversion from frailty [76]. Guaraldi investigated predictors of frailty transition over 4 years in the MHMC Cohort. Baseline FI, female sex, duration of HIV infection and cART exposure, and smoking history independently predicted FI at follow-up [93].

At present, the clinical utility of geriatric referrals remains untested, and no guidelines are in place regarding which PLWH to refer. In the general population, persons older than 70 should be screened for frailty [112]. Based on data suggesting age-advancement of PLWH, it is reasonable to consider screening PLWH older than 50. The role of geriatricians as either expert consultants or as active members of the managing team is being clarified.

Management of Frail PLWH

An algorithm to identify PLWH who may benefit from an HIV-geriatrics assessment, including a Comprehensive Geriatric Assessment (CGA), has been proposed [113]. The goals of the CGA in the general population, in addition to assessing and managing multimorbidity and geriatric syndromes, are also to ensure follow-up with primary care providers and evaluating the impact of recommended interventions. The CGA has been evaluated in diverse clinical settings. Collectively, and accounting for logistic differences, the CGA improves quality of life, decreases the need for emergency

room visits and hospitalization, and maintains independence [114•]. However, outcomes in one type of setting (e.g., acute care unit) do not necessarily translate to a different one (e.g., community clinic) [115]. Importantly, the process of performing a CGA need not be uniform, while maintaining the recommended "5 M's" approach, assessing the following: mind and mood; mobility; medications; multimorbidity; and matters most (e.g., discharge from hospital, end-of-life planning) [116]. Rather than simply adopting the CGA model to PLWH, it is essential to determine how best to adapt it to this population. A modification applicable to PLWH has been recently been suggested [117•]. Various locally responsive models of providing care to older PLWH have been organized [118]. An early report reviewed the first 76 older PLWH (median age 67) referred to a dedicated academic geriatric-HIV clinic for a CGA on the basis of perceived need, but with no specific referral criteria. Adherence to recommendations was about 30% [119].

The general approach to managing frailty in the geriatric population includes specific recommendations arising from a CGA, exercise and appropriate rehabilitation interventions, nutritional support, and cognitive care. The long-term effectiveness of regular, multicomponent, long-duration exercise programs on reducing frailty remains to be established but a targeted approach is often successful [120]. PLWH with more impaired baseline functional status may achieve similar or greater improvements in exercise domains compared with controls [121]. Priorities for rehabilitation interventions to limit disability in PLWH have been established and early outcomes have been encouraging [122]. Sarcopenia, diagnosed most reliably by dual energy X-ray absorptiometry, is increasingly recognized in PLWH [123] and may respond to judicious exercise and nutritional supplements [124], awaiting the introduction of more specific pharmacotherapies.

cART reduces the prevalence of frailty [74]. A recent modeling analysis showed that the burden of frailty using the FI model has decreased in PLWH older than 50 over the past 10 years and is projected to decrease further from 26% to 7% between 2015 and 2030. However, frailty will increase from 43 to 52% in PLWH older than 75. This was interpreted as the "compression of frailty" in older age, a successful feature of current therapies [125]. These results support the current recommendations of the early diagnosis of HIV and prompt initiation of cART in older PLWH. A post hoc analysis of the START study showed that older PLWH were the main beneficiaries of early initiation of cART [126].

It is essential that the assessments and interventions discussed in regard to frailty in aging PLWH go beyond increasing survival and shift the focus to maintaining and improving functional status and QoL, as in the geriatric population. Quality of life represents an ongoing hurdle to fulfilling the proposed "fourth 90" of the UNAIDS 90-90-90 goals for PLWH [127]. The paradigm of successful aging emphasizes better understanding of physical, social, and cognitive resilience as well as the evolving interactions between HIV, frailty, and intrinsic capacity [128, 129].

Conclusions

Pre-frailty and frailty affect more than 50% of effectively treated older PLWH. These states represent the clinical expression of the multifactorial decline of normally coordinated biologic systems to maintain physiologic homeostasis. Regardless of the tools used to diagnose them, they are associated with an increased risk of adverse health outcomes which contribute to the overall reduced survival and QoL of PLWH.

Both pre-frailty and frailty are potentially preventable and reversible. Risk factors increasing progression to, and importantly, promoting reversion from frailty, are under investigation. Encouragingly, several are lifestyle related and amenable to prevention and change, which does not need to be financially burdensome. Just as early cART was the main driver behind turning HIV/AIDS from a fatal disease into a chronic condition, so current cART may also be a key factor in reducing the progression along the frailty continuum. The vital lessons learned in providing humane and effective holistic patient-centered care to the elderly can be adapted to meet the latest challenges to confront aging PLWH. These will surely be met with the same vigorous determination which has marked the last 40 years struggle against HIV.

Compliance with Ethical Standards

Conflict of Interest No potential conflicts of interest relevant to this article were reported.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Wallace LM, Theou O, Pena F, Rockwood K, Andrew MK. Social vulnerability as a predictor of mortality and disability: cross-country differences in the survey of health, aging, and retirement in Europe (SHARE). Aging Clin Exp Res. 2015;27(3):365–72. https://doi.org/10.1007/s40520-014-0271-6.
2. Ruan Q, D'Onofrio G, Sancarlo D, Greco A, Lozupone M, Seripa D, et al. Emerging biomarkers and screening for cognitive frailty.

Aging Clin Exp Res. 2017;29(6):1075–86. https://doi.org/10.1007/s40520-017-0741-8.

3. Deeks SG, Lewin SR, Havlir DV. The end of AIDS: HIV infection as a chronic disease. Lancet. 2013;382(9903):1525–33. https://doi.org/10.1016/S0140-6736(13)61809-7.
4. Wandeler G, Johnson LF, Egger M. Trends in life expectancy of HIV-positive adults on antiretroviral therapy across the globe: comparisons with general population. Curr Opin HIV AIDS. 2016;11(5):492–500. https://doi.org/10.1097/COH.0000000000000298.
5. Centers for Disease Control and Prevention. *HIV Surveillance Report,* 25, . 2013 Published Feb 2015.
6. Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Sighem A, et al. Future challenges for clinical care of an ageing population infected with HIV: a modelling study. Lancet Infect Dis. 2015;15(7):810–8. https://doi.org/10.1016/S1473-3099(15)00056-0.
7. Lerner AM, Eisinger RW, Fauci AS. Comorbidities in persons with HIV: the lingering challenge. JAMA. 2019. https://doi.org/10.1001/jama.2019.19775.
8. Gross AM, Jaeger PA, Kreisberg JF, Licon K, Jepsen KL, Khosroheidari M, et al. Methylome-wide analysis of chronic HIV infection reveals five-year increase in biological age and epigenetic targeting of HLA. Mol Cell. 2016;62(2):157–68. https://doi.org/10.1016/j.molcel.2016.03.019.
9. Leung JM, Fishbane N, Jones M, Morin A, Xu S, Liu JC, et al. Longitudinal study of surrogate aging measures during human immunodeficiency virus seroconversion. Aging (Albany NY). 2017;9(3):687–705. https://doi.org/10.18632/aging.101184.
10. Cohen J, Torres C. HIV-associated cellular senescence: a contributor to accelerated aging. Ageing Res Rev. 2017;36:117–24. https://doi.org/10.1016/j.arr.2016.12.004.
11.•• Pathai S, Bajillan H, Landay AL, High KP. Is HIV a model of accelerated or accentuated aging? J Gerontol A Biol Sci Med Sci. 2014;69(7):833–42. https://doi.org/10.1093/gerona/glt168. **This article introduces the key concepts of accelerated and accentuated aging in regards to the changing clinical profile of PLWH**.
12. Hunt PW. HIV and inflammation: mechanisms and consequences. Curr HIV/AIDS Rep. 2012;9(2):139–47. https://doi.org/10.1007/s11904-012-0118-8.
13. Fulop T, Larbi A, Witkowski JM, McElhaney J, Loeb M, Mitnitski A, et al. Aging, frailty and age-related diseases. Biogerontology. 2010;11(5):547–63. https://doi.org/10.1007/s10522-010-9287-2.
14.• De Francesco D, Wit FW, Burkle A, Oehlke S, Kootstra NA, Winston A, et al. Do people living with HIV experience greater age advancement than their HIV-negative counterparts? AIDS. 2019;33(2):259–68. https://doi.org/10.1097/QAD.0000000000002063. **This paper investigates the important issue of differentiating chronologic and biologic age in PLWH using a multifactorial metric being validated in the general geriatric population**.
15. Rasmussen LD, May MT, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, et al. Time trends for risk of severe age-related diseases in individuals with and without HIV infection in Denmark: a nationwide population-based cohort study. Lancet HIV. 2015;2(7):e288–98. https://doi.org/10.1016/S2352-3018(15)00077-6.
16.• Greene M, Covinsky KE, Valcour V, Miao Y, Madamba J, Lampiris H, et al. Geriatric syndromes in older HIV-infected adults. J Acquir Immune Defic Syndr. 2015;69(2):161–7. https://doi.org/10.1097/QAI.0000000000000556. **This important paper broadens the thinking of the emerging clinical profile of aging PLWH to include typical problems normally seen in much older persons**.
17.• Inouye SK, Studenski S, Tinetti ME, Kuchel GA. Geriatric syndromes: clinical, research, and policy implications of a core geriatric concept. J Am Geriatr Soc. 2007;55(5):780–91. https://doi.org/10.1111/j.1532-5415.2007.01156.x. **This is a landmark paper discussing geriatric syndromes**.
18.•• Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, et al. Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci. 2001;56(3):M146–56. https://doi.org/10.1093/gerona/56.3.m146. **This is the key paper presenting the concept of frailty as a biologic phenotype**.
19.•• Mitnitski AB, Mogilner AJ, Rockwood K. Accumulation of deficits as a proxy measure of aging. ScientificWorldJournal. 2001;1:323–36. https://doi.org/10.1100/tsw.2001.58. **This is the seminal paper discussing frailty as the accumulation of health deficits**.
20. Buta BJ, Walston JD, Godino JG, Park M, Kalyani RR, Xue QL, et al. Frailty assessment instruments: systematic characterization of the uses and contexts of highly-cited instruments. Ageing Res Rev. 2016;26:53–61. https://doi.org/10.1016/j.arr.2015.12.003.
21. Rockwood K, Song X, Mitnitski A. Changes in relative fitness and frailty across the adult lifespan: evidence from the Canadian National Population Health Survey. CMAJ. 2011;183(8):E487–94. https://doi.org/10.1503/cmaj.101271.
22. Searle SD, Mitnitski A, Gahbauer EA, Gill TM, Rockwood K. A standard procedure for creating a frailty index. BMC Geriatr. 2008;8:24. https://doi.org/10.1186/1471-2318-8-24.
23. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. Age Ageing. 2016;45(3):353–60. https://doi.org/10.1093/ageing/afw039.
24. Wong CH, Weiss D, Sourial N, Karunananthan S, Quail JM, Wolfson C, et al. Frailty and its association with disability and comorbidity in a community-dwelling sample of seniors in Montreal: a cross-sectional study. Aging Clin Exp Res. 2010;22(1):54–62. https://doi.org/10.1007/bf03324816.
25. Theou O, Rockwood MR, Mitnitski A, Rockwood K. Disability and co-morbidity in relation to frailty: how much do they overlap? Arch Gerontol Geriatr. 2012;55(2):e1–8. https://doi.org/10.1016/j.archger.2012.03.001.
26. Thompson MQ, Theou O, Adams RJ, Tucker GR, Visvanathan R. Frailty state transitions and associated factors in south Australian older adults. Geriatr Gerontol Int. 2018;18(11):1549–55. https://doi.org/10.1111/ggi.13522.
27. Rockwood K, Andrew M, Mitnitski A. A comparison of two approaches to measuring frailty in elderly people. J Gerontol A Biol Sci Med Sci. 2007;62(7):738–43. https://doi.org/10.1093/gerona/62.7.738.
28. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. CMAJ. 2005;173(5):489–95. https://doi.org/10.1503/cmaj.050051.
29. Rolfson DB, Majumdar SR, Tsuyuki RT, Tahir A, Rockwood K. Validity and reliability of the Edmonton frail scale. Age Ageing. 2006;35(5):526–9. https://doi.org/10.1093/ageing/afl041.
30. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. J Nutr Health Aging. 2012;16(7):601–8. https://doi.org/10.1007/s12603-012-0084-2.
31. Vellas B. Implementing frailty screening, assessment, and sustained intervention: the experience of the Gerontopole. J Nutr Health Aging. 2015;19(6):673–80. https://doi.org/10.1007/s12603-015-0505-0.
32. Bielderman A, van der Schans CP, van Lieshout MR, de Greef MH, Boersma F, Krijnen WP, et al. Multidimensional structure of the Groningen frailty Indicator in community-dwelling older people. BMC Geriatr. 2013;13:86. https://doi.org/10.1186/1471-2318-13-86.

33.• Vermeiren S, Vella-Azzopardi R, Beckwee D, Habbig AK, Scafoglieri A, Jansen B, et al. Frailty and the Prediction of Negative Health Outcomes: A Meta-Analysis. J Am Med Dir Assoc. 2016;17(12):1163 e1–e17. https://doi.org/10.1016/j.jamda.2016.09.010. **This paper reviews the evidence supporting the clinical consequences of both prefrail and frail states**.

34. Fedarko NS. The biology of aging and frailty. Clin Geriatr Med. 2011;27(1):27–37. https://doi.org/10.1016/j.cger.2010.08.006.

35. Yao X, Li H, Leng SX. Inflammation and immune system alterations in frailty. Clin Geriatr Med. 2011;27(1):79–87. https://doi.org/10.1016/j.cger.2010.08.002.

36. Hubbard RE, Woodhouse KW. Frailty, inflammation and the elderly. Biogerontology. 2010;11(5):635–41. https://doi.org/10.1007/s10522-010-9292-5.

37. Larbi A, Franceschi C, Mazzatti D, Solana R, Wikby A, Pawelec G. Aging of the immune system as a prognostic factor for human longevity. Physiology (Bethesda). 2008;23:64–74. https://doi.org/10.1152/physiol.00040.2007.

38. Wang GC, Kao WH, Murakami P, Xue QL, Chiou RB, Detrick B, et al. Cytomegalovirus infection and the risk of mortality and frailty in older women: a prospective observational cohort study. Am J Epidemiol. 2010;171(10):1144–52. https://doi.org/10.1093/aje/kwq062.

39. Olsson J, Wikby A, Johansson B, Lofgren S, Nilsson BO, Ferguson FG. Age-related change in peripheral blood T-lymphocyte subpopulations and cytomegalovirus infection in the very old: the Swedish longitudinal OCTO immune study. Mech Ageing Dev. 2000;121(1–3):187–201. https://doi.org/10.1016/s0047-6374(00)00210-4.

40. Wikby A, Ferguson F, Forsey R, Thompson J, Strindhall J, Lofgren S, et al. An immune risk phenotype, cognitive impairment, and survival in very late life: impact of allostatic load in Swedish octogenarian and nonagenarian humans. J Gerontol A Biol Sci Med Sci. 2005;60(5):556–65. https://doi.org/10.1093/gerona/60.5.556.

41. Strindhall J, Nilsson BO, Lofgren S, Ernerudh J, Pawelec G, Johansson B, et al. No immune risk profile among individuals who reach 100 years of age: findings from the Swedish NONA immune longitudinal study. Exp Gerontol. 2007;42(8):753–61. https://doi.org/10.1016/j.exger.2007.05.001.

42. Fulop T, Larbi A, Witkowski JM. Human Inflammaging. Gerontology. 2019;65(5):495–504. https://doi.org/10.1159/000497375.

43.•• Franceschi C, Campisi J. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci. 2014;69(Suppl 1):S4–9. https://doi.org/10.1093/gerona/glu057. **This paper presents the data supporting the role of chronic inflammation as a driver for age-related conditions**.

44. Singh T, Newman AB. Inflammatory markers in population studies of aging. Ageing Res Rev. 2011;10(3):319–29. https://doi.org/10.1016/j.arr.2010.11.002.

45. Soysal P, Stubbs B, Lucato P, Luchini C, Solmi M, Peluso R, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. Ageing Res Rev. 2016;31:1–8. https://doi.org/10.1016/j.arr.2016.08.006.

46. Clegg A, Hassan-Smith Z. Frailty and the endocrine system. Lancet Diabetes Endocrinol. 2018;6(9):743–52. https://doi.org/10.1016/S2213-8587(18)30110-4.

47. Landi F, Calvani R, Cesari M, Tosato M, Martone AM, Bernabei R, et al. Sarcopenia as the biological substrate of physical frailty. Clin Geriatr Med. 2015;31(3):367–74. https://doi.org/10.1016/j.cger.2015.04.005.

48. Jones MJ, Goodman SJ, Kobor MS. DNA methylation and healthy human aging. Aging Cell. 2015;14(6):924–32. https://doi.org/10.1111/acel.12349.

49. Haapanen MJ, Perala MM, Salonen MK, Guzzardi MA, Iozzo P, Kajantie E, et al. Telomere length and frailty: the Helsinki birth cohort study. J Am Med Dir Assoc. 2018;19(8):658–62. https://doi.org/10.1016/j.jamda.2018.05.011.

50. Ho YY, Matteini AM, Beamer B, Fried L, Xue QL, Arking DE, et al. Exploring biologically relevant pathways in frailty. J Gerontol A Biol Sci Med Sci. 2011;66(9):975–9. https://doi.org/10.1093/gerona/glr061.

51. JafariNasabian P, Inglis JE, Reilly W, Kelly OJ, Ilich JZ. Aging human body: changes in bone, muscle and body fat with consequent changes in nutrient intake. J Endocrinol. 2017;234(1):R37–51. https://doi.org/10.1530/JOE-16-0603.

52. Hawkins KL, Brown TT, Margolick JB, Erlandson KM. Geriatric syndromes: new frontiers in HIV and sarcopenia. AIDS. 2017;31(Suppl 2):S137–S46. https://doi.org/10.1097/QAD.0000000000001444.

53. Lake JE, Stanley TL, Apovian CM, Bhasin S, Brown TT, Capeau J, et al. Practical review of recognition and Management of Obesity and Lipohypertrophy in human immunodeficiency virus infection. Clin Infect Dis. 2017;64(10):1422–9. https://doi.org/10.1093/cid/cix178.

54.• Bakal DR, Coelho LE, Luz PM, Clark JL, De Boni RB, Cardoso SW, et al. Obesity following ART initiation is common and influenced by both traditional and HIV−/ART-specific risk factors. J Antimicrob Chemother. 2018;73(8):2177–85. https://doi.org/10.1093/jac/dky145. **This paper supports the growing concern about the association of currently recommended antiretroviral drugs and increased weight**.

55. Montejano R, Stella-Ascariz N, Monge S, Bernardino JI, Perez-Valero I, Montes ML, et al. Impact of nucleos(t)ide reverse transcriptase inhibitors on blood telomere length changes in a prospective cohort of aviremic HIV-infected adults. J Infect Dis. 2018;218(10):1531–40. https://doi.org/10.1093/infdis/jiy364.

56. Garrabou G, Lopez S, Moren C, Martinez E, Fontdevila J, Cardellach F, et al. Mitochondrial damage in adipose tissue of untreated HIV-infected patients. AIDS. 2011;25(2):165–70. https://doi.org/10.1097/QAD.0b013e3283423219.

57. Li M, Foli Y, Liu Z, Wang G, Hu Y, Lu Q, et al. High frequency of mitochondrial DNA mutations in HIV-infected treatment-experienced individuals. HIV Med. 2017;18(1):45–55. https://doi.org/10.1111/hiv.12390.

58. Ndumbi P, Gilbert L, Tsoukas CM. Comprehensive evaluation of the immune risk phenotype in successfully treated HIV-infected individuals. PLoS One. 2015;10(2):e0117039. https://doi.org/10.1371/journal.pone.0117039.

59.• Serrano-Villar S, Sainz T, Lee SA, Hunt PW, Sinclair E, Shacklett BL, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. PLoS Pathog. 2014;10(5):e1004078. https://doi.org/10.1371/journal.ppat.1004078. **This paper provides evidence that persistent immune dysregulation in PLWH despite effective cART is a risk factor for adverse health events**.

60. Guaraldi G, Zona S, Silva AR, Menozzi M, Dolci G, Milic J, et al. The dynamic association between frailty, CD4 and CD4/CD8 ratio in people aging with HIV. PLoS One. 2019;14(2):e0212283. https://doi.org/10.1371/journal.pone.0212283.

61. Branas F, Jimenez Z, Sanchez-Conde M, Dronda F, Lopez-Bernaldo De Quiros JC, Perez-Elias MJ, et al. Frailty and physical function in older HIV-infected adults. Age Ageing. 2017;46(3):522–6. https://doi.org/10.1093/ageing/afx013.

62. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW. Residual immune dysregulation syndrome in treated HIV infection. Adv Immunol. 2013;119:51–83. https://doi.org/10.1016/B978-0-12-407707-2.00002-3.

63. Hunt PW, Lee SA, Siedner MJ. Immunologic biomarkers, morbidity, and mortality in treated HIV infection. J Infect Dis. 2016;214(Suppl 2):S44–50. https://doi.org/10.1093/infdis/jiw275.
64. Erlandson KM, Allshouse AA, Jankowski CM, Lee EJ, Rufner KM, Palmer BE, et al. Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. J Infect Dis. 2013;208(2):249–59. https://doi.org/10.1093/infdis/jit147.
65. Margolick JB, Bream JH, Martinez-Maza O, Lopez J, Li X, Phair JP, et al. Frailty and circulating markers of inflammation in HIV+ and HIV- men in the multicenter AIDS cohort study. J Acquir Immune Defic Syndr. 2017;74(4):407–17. https://doi.org/10.1097/QAI.0000000000001261.
66. Erlandson KM, Ng DK, Jacobson LP, Margolick JB, Dobs AS, Palella FJ Jr, et al. Inflammation, immune activation, immunosenescence, and hormonal biomarkers in the frailty-related phenotype of men with or at risk for HIV infection. J Infect Dis. 2017;215(2):228–37. https://doi.org/10.1093/infdis/jiw523.
67. Zhang W, Nilles TL, Johnson JR, Margolick JB. Regulatory T cells, frailty, and immune activation in men who have sex with men in the multicenter AIDS cohort study. J Gerontol A Biol Sci Med Sci. 2015;70(12):1533–41. https://doi.org/10.1093/gerona/glv132.
68. Margolick JB, Bream JH, Nilles TL, Li H, Langan SJ, Deng S, et al. Relationship between T-cell responses to CMV, markers of inflammation, and frailty in HIV-uninfected and HIV-infected men in the multicenter AIDS cohort study. J Infect Dis. 2018;218(2):249–58. https://doi.org/10.1093/infdis/jiy005.
69. McAdams-DeMarco MA, Law A, Salter ML, Boyarsky B, Gimenez L, Jaar BG, et al. Frailty as a novel predictor of mortality and hospitalization in individuals of all ages undergoing hemodialysis. J Am Geriatr Soc. 2013;61(6):896–901. https://doi.org/10.1111/jgs.12266.
70. Rockwood MR, MacDonald E, Sutton E, Rockwood K, Baron M. Canadian scleroderma research G. frailty index to measure health status in people with systemic sclerosis. J Rheumatol. 2014;41(4):698–705. https://doi.org/10.3899/jrheum.130182.
71.• Hanlon P, Nicholl BI, Jani BD, Lee D, McQueenie R, Mair FS. Frailty and pre-frailty in middle-aged and older adults and its association with multimorbidity and mortality: a prospective analysis of 493 737 UK biobank participants. Lancet Public Health. 2018;3(7):e323–e32. https://doi.org/10.1016/S2468-2667(18)30091-4. **This paper provides evidence that frailty is not limited to the geriatric population**.
72. Kooij KW, Wit FW, Schouten J, van der Valk M, Godfried MH, Stolte IG, et al. HIV infection is independently associated with frailty in middle-aged HIV type 1-infected individuals compared with similar but uninfected controls. AIDS. 2016;30(2):241–50. https://doi.org/10.1097/QAD.0000000000000910.
73. Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, et al. HIV-1 infection is associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci. 2007;62(11):1279–86. https://doi.org/10.1093/gerona/62.11.1279.
74. Desquilbet L, Margolick JB, Fried LP, Phair JP, Jamieson BD, Holloway M, et al. Relationship between a frailty-related phenotype and progressive deterioration of the immune system in HIV-infected men. J Acquir Immune Defic Syndr. 2009;50(3):299–306. https://doi.org/10.1097/QAI.0b013e3181945eb0.
75. Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, et al. A frailty-related phenotype before HAART initiation as an independent risk factor for AIDS or death after HAART among HIV-infected men. J Gerontol A Biol Sci Med Sci. 2011;66(9):1030–8. https://doi.org/10.1093/gerona/glr097.
76. Althoff KN, Jacobson LP, Cranston RD, Detels R, Phair JP, Li X, et al. Age, comorbidities, and AIDS predict a frailty phenotype in men who have sex with men. J Gerontol A Biol Sci Med Sci. 2014;69(2):189–98. https://doi.org/10.1093/gerona/glt148.
77. Piggott DA, Muzaale AD, Mehta SH, Brown TT, Patel KV, Leng SX, et al. Frailty, HIV infection, and mortality in an aging cohort of injection drug users. PLoS One. 2013;8(1):e54910. https://doi.org/10.1371/journal.pone.0054910.
78. Piggott DA, Muzaale AD, Varadhan R, Mehta SH, Westergaard RP, Brown TT, et al. Frailty and cause-specific hospitalization among persons aging with HIV infection and injection drug use. J Gerontol A Biol Sci Med Sci. 2017;72(3):389–94. https://doi.org/10.1093/gerona/glw142.
79. Johs NA, Wu K, Tassiopoulos K, Koletar SL, Kalayjian RC, Ellis RJ, et al. Disability among middle-aged and older persons with human immunodeficiency virus infection. Clin Infect Dis. 2017;65(1):83–91. https://doi.org/10.1093/cid/cix253.
80. Kelly SG, Wu K, Tassiopoulos K, Erlandson KM, Koletar SL, Palella FJ. Frailty is an independent risk factor for mortality, cardiovascular disease, bone disease, and diabetes among aging adults with human immunodeficiency virus. Clin Infect Dis. 2019;69(8):1370–6. https://doi.org/10.1093/cid/ciy1101.
81. Erlandson KM, Wu K, Koletar SL, Kalayjian RC, Ellis RJ, Taiwo B, et al. Association between frailty and components of the frailty phenotype with modifiable risk factors and antiretroviral therapy. J Infect Dis. 2017;215(6):933–7. https://doi.org/10.1093/infdis/jix063.
82. Zeballos D, Lins L, Brites C. Frailty and its association with health related quality of life in older HIV patients, in Salvador. Brazil AIDS Res Hum Retroviruses. 2019;35(11–12):1074–81. https://doi.org/10.1089/AID.2019.0103.
83. Pathai S, Gilbert C, Weiss HA, Cook C, Wood R, Bekker LG, et al. Frailty in HIV-infected adults in South Africa. J Acquir Immune Defic Syndr. 2013;62(1):43–51. https://doi.org/10.1097/QAI.0b013e318273b631.
84. Bandeen-Roche K, Seplaki CL, Huang J, Buta B, Kalyani RR, Varadhan R, et al. Frailty in older adults: a nationally representative profile in the United States. J Gerontol A Biol Sci Med Sci. 2015;70(11):1427–34. https://doi.org/10.1093/gerona/glv133.
85. Gustafson DR, Shi Q, Thurn M, Holman S, Minkoff H, Cohen M, et al. Frailty and Constellations of Factors in Aging HIV-infected and Uninfected Women–The Women's Interagency HIV Study. J Frailty Aging. 2016;5(1):43–8. https://doi.org/10.14283/jfa.2016.79.
86. Womack JA, Goulet JL, Gibert C, Brandt CA, Skanderson M, Gulanski B, et al. Physiologic frailty and fragility fracture in HIV-infected male veterans. Clin Infect Dis. 2013;56(10):1498–504. https://doi.org/10.1093/cid/cit056.
87. Bregigeon S, Galinier A, Zaegel-Faucher O, Cano CE, Obry V, Laroche H, et al. Frailty in HIV infected people: a new risk factor for bone mineral density loss. AIDS. 2017;31(11):1573–7. https://doi.org/10.1097/QAD.0000000000001507.
88. Justice AC, McGinnis KA, Skanderson M, Chang CC, Gibert CL, Goetz MB, et al. Towards a combined prognostic index for survival in HIV infection: the role of 'non-HIV' biomarkers. HIV Med. 2010;11(2):143–51. https://doi.org/10.1111/j.1468-1293.2009.00757.x.
89. Justice AC, Freiberg MS, Tracy R, Kuller L, Tate JP, Goetz MB, et al. Does an index composed of clinical data reflect effects of inflammation, coagulation, and monocyte activation on mortality among those aging with HIV? Clin Infect Dis. 2012;54(7):984–94. https://doi.org/10.1093/cid/cir989.
90. Akgun KM, Tate JP, Crothers K, Crystal S, Leaf DA, Womack J, et al. An adapted frailty-related phenotype and the VACS index as predictors of hospitalization and mortality in HIV-infected and uninfected individuals. J Acquir Immune Defic Syndr.

2014;67(4):397–404. https://doi.org/10.1097/QAI.0000000000000341.
91. Escota GV, Patel P, Brooks JT, Bush T, Conley L, Baker J, et al. Short communication: the veterans aging cohort study index is an effective tool to assess baseline frailty status in a contemporary cohort of HIV-infected persons. AIDS Res Hum Retrovir. 2015;31(3):313–7. https://doi.org/10.1089/AID.2014.0225.
92. Guaraldi G, Brothers TD, Zona S, Stentarelli C, Carli F, Malagoli A, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. AIDS. 2015;29(13):1633–41. https://doi.org/10.1097/QAD.0000000000000753.
93. Brothers TD, Kirkland S, Theou O, Zona S, Malagoli A, Wallace LMK, et al. Predictors of transitions in frailty severity and mortality among people aging with HIV. PLoS One. 2017;12(10):e0185352. https://doi.org/10.1371/journal.pone.0185352.
94. Ho Tsong Fang R, Colantonio AD, Uittenbogaart CH. The role of the thymus in HIV infection: a 10 year perspective. AIDS. 2008;22(2):171–84. https://doi.org/10.1097/QAD.0b013e3282f2589b.
95. Guaraldi G, Franconi I, Milic J, Besutti G, Pintassilgo I, Scaglioni R, et al. Thymus Imaging Detection and Size Is Inversely Associated With Metabolic Syndrome and Frailty in People With HIV. Open Forum Infect Dis. 2019;6(10):ofz435. https://doi.org/10.1093/ofid/ofz435.
96. Yeoh HL, Cheng AC, Cherry CL, Weir JM, Meikle PJ, Hoy JF, et al. Immunometabolic and lipidomic markers associated with the frailty index and quality of life in aging HIV+ men on antiretroviral therapy. EBioMedicine. 2017;22:112–21. https://doi.org/10.1016/j.ebiom.2017.07.015.
97. Hawkins KL, Zhang L, Ng DK, Althoff KN, Palella FJ Jr, Kingsley LA, et al. Abdominal obesity, sarcopenia, and osteoporosis are associated with frailty in men living with and without HIV. AIDS. 2018;32(10):1257–66. https://doi.org/10.1097/QAD.0000000000001829.
98. Ding Y, Lin H, Liu X, Wong FY, Sun YV, Marconi VC, et al. Higher prevalence of frailty among a sample of HIV-infected middle-aged and older Chinese adults is associated with neurocognitive impairment and depressive symptoms. J Infect Dis. 2017;215(5):687–92. https://doi.org/10.1093/infdis/jix032.
99. Marquine MJ, Umlauf A, Rooney AS, Fazeli PL, Gouaux BD, Paul Woods S, et al. The veterans aging cohort study index is associated with concurrent risk for neurocognitive impairment. J Acquir Immune Defic Syndr. 2014;65(2):190–7. https://doi.org/10.1097/QAI.0000000000000008.
100. Onen NF, Patel P, Baker J, Conley L, Brooks JT, Bush T, et al. Frailty and Pre-Frailty in a Contemporary Cohort of HIV-Infected Adults. J Frailty Aging. 2014;3(3):158–65. https://doi.org/10.14283/jfa.2014.18.
101. Underwood J, Winston A. Guidelines for evaluation and management of cognitive disorders in HIV-positive individuals. Curr HIV/AIDS Rep. 2016;13(5):235–40. https://doi.org/10.1007/s11904-016-0324-x.
102. Wallace LM, Ferrara M, Brothers TD, Garlassi S, Kirkland SA, Theou O, et al. Lower frailty is associated with successful cognitive aging among older adults with HIV. AIDS Res Hum Retrovir. 2017;33(2):157–63. https://doi.org/10.1089/AID.2016.0189.
103. Erlandson KM, Perez J, Abdo M, Robertson K, Ellis RJ, Koletar SL, et al. Frailty, neurocognitive impairment, or both in predicting poor health outcomes among adults living with human immunodeficiency virus. Clin Infect Dis. 2019;68(1):131–8. https://doi.org/10.1093/cid/ciy430.
104. Zamudio-Rodriguez A, Belaunzaran-Zamudio PF, Sierra-Madero JG, Cuellar-Rodriguez J, Crabtree-Ramirez BE, Alcala-Zermeno JL, et al. Association between frailty and HIV-associated neurodegenerative disorders among older adults living with HIV. AIDS Res Hum Retrovir. 2018;34(5):449–55. https://doi.org/10.1089/AID.2017.0100.
105. Theou O, Brothers TD, Pena FG, Mitnitski A, Rockwood K. Identifying common characteristics of frailty across seven scales. J Am Geriatr Soc. 2014;62(5):901–6. https://doi.org/10.1111/jgs.12773.
106. Guaraldi G, Malagoli A, Theou O, Brothers TD, Wallace L, Torelli R, et al. Correlates of frailty phenotype and frailty index and their associations with clinical outcomes. HIV Med. 2017;18(10):764–71. https://doi.org/10.1111/hiv.12527.
107. Lee DJK, Mak MHW, Tan KY. Frailty in surgical preoperative evaluation and postoperative recovery. Curr Geriatr Rep. 2019;8:87–96. https://doi.org/10.1007/s13670-019-0278-0.
108. Singh HK, Del Carmen T, Freeman R, Glesby MJ, Siegler EL. From one syndrome to many: incorporating geriatric consultation into HIV care. Clin Infect Dis. 2017;65(3):501–6. https://doi.org/10.1093/cid/cix311.
109.• Greene M, Steinman MA, McNicholl IR, Valcour V. Polypharmacy, drug-drug interactions, and potentially inappropriate medications in older adults with human immunodeficiency virus infection. J Am Geriatr Soc. 2014;62(3):447–53. https://doi.org/10.1111/jgs.12695. **This important paper reviews the underappreciated risks of polypharmacy in PLWH**.
110. Greene M, Justice AC, Covinsky KE. Assessment of geriatric syndromes and physical function in people living with HIV. Virulence. 2017;8(5):586–98. https://doi.org/10.1080/21505594.2016.1245269.
111. Erlandson KM, Schrack JA, Jankowski CM, Brown TT, Campbell TB. Functional impairment, disability, and frailty in adults aging with HIV-infection. Curr HIV/AIDS Rep. 2014;11(3):279–90. https://doi.org/10.1007/s11904-014-0215-y.
112. Morley JE, Vellas B, van Kan GA, Anker SD, Bauer JM, Bernabei R, et al. Frailty consensus: a call to action. J Am Med Dir Assoc. 2013;14(6):392–7. https://doi.org/10.1016/j.jamda.2013.03.022.
113. Branas F, Ryan P, Troya J, Sanchez-Conde M. Geriatric-HIV Medicine: the geriatrician's role. Eur Geriatr Med. 2019;10(2):259–65 doi-prg-443.webvpn.fjmu.edu.cn/10.1007/s41999-018-0144-1.
114.• Pilotto A, Cella A, Pilotto A, Daragjati J, Veronese N, Musacchio C, et al. Three Decades of comprehensive geriatric assessment: evidence coming from different healthcare settings and specific clinical conditions. J Am Med Dir Assoc. 2017;18(2):192 e1–e11. https://doi.org/10.1016/j.jamda.2016.11.004. **This paper summarizes the evidence supporting the fundamental assessment and intervention tool employed by geriatricians**.
115. Garrard JW, Cox NJ, Dodds RM, Roberts HC, Sayer AA. Comprehensive geriatric assessment in primary care: a systematic review. Aging Clin Exp Res. 2019;32:197–205. https://doi.org/10.1007/s40520-019-01183-w.
116. Tinetti M, Huang A, Molnar F. The geriatrics 5M's: a new way of communicating what we do. J Am Geriatr Soc. 2017;65(9):2115. https://doi.org/10.1111/jgs.14979.
117.• Erlandson KM, Karris MY. HIV and aging: reconsidering the approach to management of comorbidities. Infect Dis Clin North Am. 2019;33(3):769–86. https://doi.org/10.1016/j.idc.2019.04.005. **This is an up-to-date review of the clinical issues in aging PLWH**.
118. Siegler EL, Burchett CO, Glesby MJ. Older people with HIV are an essential part of the continuum of HIV care. J Int AIDS Soc. 2018;21(10):e25188. https://doi.org/10.1002/jia2.25188.
119. Bitas C, Jones S, Singh HK, Ramirez M, Siegler E, Glesby M. Adherence to recommendations from comprehensive geriatric assessment of older individuals with HIV. J Int Assoc Provid AIDS Care. 2019;18:2325958218821656. https://doi.org/10.1177/2325958218821656.

120. Walston J, Buta B, Xue QL. Frailty screening and interventions: considerations for clinical practice. Clin Geriatr Med. 2018;34(1):25–38. https://doi.org/10.1016/j.cger.2017.09.004.
121. Erlandson KM, MaWhinney S, Wilson M, Gross L, McCandless SA, Campbell TB, et al. Physical function improvements with moderate or high-intensity exercise among older adults with or without HIV infection. AIDS. 2018;32(16):2317–26. https://doi.org/10.1097/QAD.0000000000001984.
122. O'Brien KK, Ibanez-Carrasco F, Solomon P, Harding R, Cattaneo J, Chegwidden W, et al. Advancing research and practice in HIV and rehabilitation: a framework of research priorities in HIV, disability and rehabilitation. BMC Infect Dis. 2014;14:724. https://doi.org/10.1186/s12879-014-0724-8.
123. Debroy P, Lake JE, Sim M, Erlandson KM, Falutz J, Prado CM, et al. Lean mass declines consistently over 10 years in people living with HIV on antiretroviral therapy, with patterns differing by sex. Antivir Ther. 2019;24(5):383–7. https://doi.org/10.3851/IMP3312.
124. Landers-Ramos RQ, Dondero KR. Exercise and protein supplementation for prevention and treatment of sarcopenia. Curr Geriatr Rep. 2019;8:202–9. https://doi.org/10.1007/s13670-019-00293-7.
125. Guaraldi G, Francesco D, Malagoli A, Zona S, Franconi I, Santoro A, et al. Compression of frailty in adults living with HIV. BMC Geriatr. 2019;19(1):229. https://doi.org/10.1186/s12877-019-1247-3.
126. Molina JM, Grund B, Gordin F, Williams I, Schechter M, Losso M, et al. Which HIV-infected adults with high CD4 T-cell counts benefit most from immediate initiation of antiretroviral therapy? A post-hoc subgroup analysis of the START trial. Lancet HIV. 2018;5(4):e172–e80. https://doi.org/10.1016/S2352-3018(18)30003-1.
127. Lazarus JV, Safreed-Harmon K, Barton SE, Costagliola D, Dedes N, Del Amo VJ, et al. Beyond viral suppression of HIV - the new quality of life frontier. BMC Med. 2016;14(1):94. https://doi.org/10.1186/s12916-016-0640-4.
128.• Woo J. Frailty, successful aging, resilience, and intrinsic capacity: a cross-disciplinary discourse of the aging process. Curr Geriatr Rep. 2019;8:67–71. https://doi.org/10.1007/s13670-019-0276-2. **This paper introduces current models to consider factors related to successful aging of the growing population of the elderly world-wide**.
129. Guaraldi G, Milic J. The interplay between frailty and intrinsic capacity in aging and HIV infection. AIDS Res Hum Retrovir. 2019;35(11–12):1013–22. https://doi.org/10.1089/AID.2019.0157.