AIDS RESEARCH AND HUMAN RETROVIRUSES
Volume 35, Number 11-12, 2019

DOI: 10.1089/aid.2019.0130

Harvard HIV and Aging Workshop: Perspectives and Priorities from Claude D. Pepper Centers and Centers for AIDS Research

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Abstract

People aging with HIV (PAWH) infection experience greater impairments in physical and cognitive function, in addition to higher rates of peripheral comorbid conditions (e.g., renal failure, diabetes, bone fracture, hypertension, cardiovascular disease, polypharmacy, and multimorbidity). While multifactorial drivers, including HIV infection itself, antiretroviral therapy-related toxicities, disparities in care, and biobehavioral factors, likely contribute, there remains an overarching question as to what are the relevant age-related mechanisms and models that could inform interventions that promote health span and life span in PAWH? This workshop was convened to hear from experts on the biology of aging and HIV researchers studying PAWH to focus on advancing investigations at the interface of HIV and Aging. In this study, we summarize the discussions from the Harvard Center for AIDS Research and Boston Claude D. Pepper cosponsored workshop on HIV and Aging, which took place in October 2018.

Keywords: HIV, aging, immune activation, frailty

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Introduction

In October 2018, an HIV and Aging workshop at Harvard Medical School was held to bring together basic and clinical experts working at the interface of HIV and the biology of aging, as well as National Institutes of Health (NIH) leadership. Specific emphases included the role(s) of community, the biology of aging, HIV and aging, biomarker discovery, methods, and alignment with NIH priorities. This workshop reflects an ongoing robust collaboration between the Harvard University Centers for AIDS Research (HU CFARs) and the Boston Claude D. Pepper Older Americans Independence Center (aka ''Boston Pepper Center'').

The CFARs, initially founded in 1988, have made substantial advances in HIV-related basic, clinical, and biobehavioral research, but have, until very recently, lacked focused resources or expertise in aging biology, clinical phenotypes, or functional measures. Initially founded in 2003, the Pepper Centers (currently 14 throughout the United States) have advanced research into the causes, mechanisms, prevention, and treatment of functional decline with age. Pepper Center investigators in the context of geroscience have developed and refined multiple measures of physical function, as well as defined phenotypes and mechanisms of aging and disability. Multimorbidity, functional decline, and disability have typically been research domains of geriatrics and gerontology. However, assessment tools developed in the context of geriatric populations may not be optimal in the context of chronic HIV infection and aging.

Collaborations between centers of aging and cohorts or centers of HIV, such as CFARs and Pepper Centers, are uniquely positioned in their complementary expertise to accelerate improvements in the health span of people aging with HIV (PAWH). While effective antiretroviral therapy (ART) is allowing PAWH to live near normal life spans, they nevertheless experience earlier onset of functional and cognitive decline and are at greater risk for age-related comorbidities, including cardiovascular disease (CVD) and cancers that substantially reduce quality of life (QoL) compared to uninfected people.

This workshop leveraged national expertise from multiple Pepper Centers and CFARs, as well as local expertise from Harvard Medical School and affiliated hospitals, the Boston Pepper Center, and the Paul F. Glenn Center for the Biology of Aging, with the singular purpose of accelerating investigation at the interface of HIV and aging.

Overview of Workshop Presentations

The workshop was organized into five sessions, with opening comments from the Director of the Boston Pepper Center (Shalender Bhasin) and the Director of the HU CFAR (Bruce Walker), followed by a community panel discussion led by Bisola Ojikutu (panel: Julia Tripp, Jeff Webb, Julie A.Womack) that discussed gaps and challenges remaining in people living with HIV (PWH).

The first session focused on the biology of aging with five speakers (David A. Sinclair, Michael B. Schultz, Ram Miller, James Mitchell, William J. Evans). David A. Sinclair and Michael B. Schultz presented data supporting the therapeutic potential of nicotinamide adenine dinucleotide (NAD)-boosting molecules in the context of inflammation and aging and potential relevance for NAD in HIV infection.[1] Ram Miller summarized recent and ongoing interventional approaches that target aging and senescence, including senescence pathways (e.g., rapalogs and mTOR, IGF1),[2,3] efforts to reduce immunosenescence and enhance immune function,[4–6] and senolytic agents that target senescent cells.[7,8] James Mitchell discussed research on adaptive responses to genotoxic stress, including effects of DNA damage and repair effects on energy metabolism, in models of premature aging. Data were summarized indicating that loss in subcutaneous fat due to adaptive changes in energy metabolism is a common feature in segmental aging phenotypes and may be driven by cellular senescence[9,10] and inflammation.[11] Interestingly, fat loss associated with premature aging may, in part, be an adaptive beneficial response to DNA damage to maintain energy balance. A better understanding of which aging-related changes are primary versus adaptive is essential for targeted antiaging strategies.[12,13] William J. Evans discussed sarcopenia as an age-related loss of skeletal muscle mass.[14–18]

The second session focused on studies related to HIV and aging with four speakers (Amy Justice, Kristine M. Erlandson, Monty Montano, Jennifer Schrack). Amy Justice summarized data on the elevated use of multiple medications (i.e., polypharmacy) in PWH compared to uninfected individuals.[19] The utility of the Veterans Aging Cohort Study (VACS) index as a measure of mortality risk and physiologic frailty was discussed, as well as the potential for frailty to confound measures of adverse outcomes in the context of polypharmacy.[20] Kristine M. Erlandson summarized recent data on physical function and frailty in PWH, with an emphasis on distinguishing impairment, functional limitations, and disability in relation to frailty.[21] Summary data were presented indicating that impairments are more pronounced among PAWH compared to uninfected[22–24] and that exercise at a high intensity may improve muscle strength in PAWH.[25] Monty Montano discussed whether aging with HIV is accelerated or asynchronous (i.e., some but not all features of aging present). Summary data were presented on preclinical risk for functional deficits that appear prematurely but occur asynchronously with other stereotypical features of aging. Summary data were presented on emerging deficits in function in middle-aged PAWH.[26,27] Jennifer Schrack discussed energy expenditure and aging and presented data that profiled HIV-related decline in aerobic capacity with age and increasing burden of multimorbidity on energy reserves and metabolism.[24,28,29] Summary data indicated that PWH have higher resting metabolic rates, slower peak and usual walking speed, lower aerobic capacity, and lower physical activity (PA).

The third, fourth, and fifth sessions focused on biomarkers, research methods, and NIH initiatives. In the third session Paola Sebastiani described genomic and proteomic biomarkers of aging and led a panel discussion (panel: Kathy Anastos, Lishomwa Ndhlovu, Savita Pahwa). Data on centenarians were summarized that described compression of morbidity associated with signatures composed of genetic variants. The possibility of *a priori* prediction based on interaction of variants with environment was discussed.[30,31] In the fourth session, Marco Pahor described the measurement of geriatric outcomes and led a panel discussion (panel: Susan Cu-Uvin, Richard T. D'Aquila, Nicholas T. Funderburg, Alice S. Ryan, Raymond Yung). Geriatric outcomes of

Table 1. HIV and Aging Priorities of the NIH

NIA

With the growing population of aging individuals living with HIV on cART, many studies on HIV/AIDS are relevant to NIA's mission to support and conduct genetic, biological, clinical, behavioral, social, and economic research on aging. Example topics include: Interactions among aging-related genetic, molecular, and cellular changes with HIV risk, infection, and pathogenesis; Interactions among HIV/AIDS, other diseases, social structural variables, and population aging (including in low-income areas to understand how individual, interpersonal, social, structural, and other factors contribute to physical, psychological, and economic well-being); interactions among HIV infection, treatment, and development or progression of cognitive decline, dementia, and other disabilities in older adults; and interactions of HIV infection and treatment with other aging-related diseases, conditions, and syndromes and ''geriatric'' approaches to assessment and management of older adults with HIV. The NIA also described a significant interest in support for early clinical investigators offered through the Grants for Early Medical/Surgical Specialists' Transition to Aging Research (GEMSSTAR) program for junior faculty physicians or dentists interested in a research career bridging their specialty and aging, which can be applied to HIV studies.

NCI

NCI as a participating institute seeks to foster research studies to help understand how aging in the presence of chronic HIV infection affects the risk, spectrum, and biology of cancer (AIDS-defining and non-AIDS-defining cancers). Recent data indicate an increase in the non-AIDS-defining cancers that is driven to a large extent by the growth and aging of the HIV/AIDS population. Aging is by itself a key factor promoting the development of many cancers, and there are a lack of data on the interplay between aging, HIV, long-term exposure to antiretroviral drugs, and other factors promoting cancer development in the aging population. In addition, there is little understanding of the interplay between host factors and immune perturbations that occur in aging and how these interactions affect cancers that are mostly seen in older people (e.g., Kaposi's sarcoma and Merkel cell carcinoma).

NIAAA

Patterns of alcohol use among HIV-infected individuals are associated with increased morbidity and mortality from multiple causes. Research priorities for NIAAA include the impact of alcohol use and its interaction with HIV and antiretroviral medications in both causing and adapting to accelerated disease progression. Alcohol may cause increased inflammation, and the accumulation of toxicities results in organ and tissue damage impacting the gut, liver, and brain. Research should address the development of interventions for health care providers to screen for early signs of these conditions, and preventive interventions should be developed, tested, and implemented to ameliorate the interaction of current or past acute and chronic use of alcohol on patient frailty and associated health outcomes over the life span.

NIAMS

NIAMS is interested in studies that investigate the effects of HIV infection and/or antiretroviral therapy on musculoskeletal and skin tissues and diseases. Proposed research should focus on chronic diseases and conditions in older adults and/or arising in the context of long-term HIV infection and/or antiretroviral therapy. Mechanistic ancillary studies that leverage existing HIV/AIDS cohorts and clinical trials are encouraged.

NIDCR

NIDCR is interested in research that investigates the effects of HIV infection and treatment on dental, oral soft and hard tissues, and salivary glands. Specifically, changes in these tissues with relation to aging adults and premature aging of oral tissues in chronic and acute HIV infections are of high priority.

NIDA

NIDA strongly encourages new interdisciplinary collaborations on a wide range of issues focused on HIV in aging high-risk, substance-abusing populations, including those with multiple infections (e.g., HIV and HCV).

NIMH

NIMH's overarching angle in HIV and aging is interdisciplinary, conceptually grounded HIV research studies in behavioral/clinical science research, and basic/clinical neuroscience research of older adults.

NINDS

CNS. Research to define and elucidate novel mechanisms of pathogenesis that are driving neurocognitive decline at the intersection of HIV-associated neurodegenerative processes and aging-associated CNS diseases.

NHLBI

NHLBI supports research on the prevention and treatment of heart, lung, blood, and sleep disorders. As the population of individuals living with HIV/AIDS ages, the interplay of the viral infection, antiretroviral therapies, and complicating chronic conditions becomes increasingly important. For this initiative, NHLBI is interested in basic, epidemiologic, clinical translational, and interventional studies, as well as implementation science research on topics such as, but not limited to: Elucidating the impact of accelerated senescence, HIV, and antiretroviral therapy on the pathogenesis of HIV associated cardiovascular (e.g., heart failure) and lung diseases (e.g., chronic obstructive pulmonary disease, pulmonary hypertension, and pulmonary fibrosis); Understanding the changes in hematopoiesis that occur with HIV infection, including changes in the hematopoietic stem cells and the stem cell niche; Developing stem cell strategies as a means to cure HIV infection; Understanding the impact of disordered sleep and sleep-disordered breathing on cardiovascular and pulmonary disease risks and exploring strategies to reduce these risks; Investigating interventions aimed at reducing HIV-related heart, lung, and blood diseases by modifying or eliminating more traditional risk factors such as smoking, metabolic disturbances, hypertension, and coagulation abnormalities; and Developing strategies for novel biomarkers or other measures to detect subclinical HIV-related heart, lung, and blood diseases and strategies to mitigate the manifestation of clinical disease.

cART, combination antiretroviral therapy; CNS, central nervous system; NCI, National Cancer Institute; NHLBI, National Heart Lung and Blood Institute; NIA, National Institute on Aging; NIAAA, National Institute on Alcohol Abuse and Alcoholism; NIAMS, National Institute of Arthritis and Musculoskeletal and Skin Diseases; NIDA, National Institute on Drug Abuse; NIDCR, National Institute of Dental and Craniofacial Research; NIMH, National Institute of Mental Health; NINDS, National Institute of Neurological Disorders and Stroke.

interest included measures of physical function, cognitive function, body composition, patient-reported outcomes (PROs), falls, and estimates of cost effectiveness, and exercise as medicine.[32–38] The fifth and final session focused on NIH support for HIV and aging research. The speaker Basil Eldadah described the view from the National Institute on Aging (NIA) and led a panel discussion [Geraldina Dominguez/National Cancer Institute (NCI), Gallya Gannot/ National Institute of Dental and Craniofacial Research (NIDCR), Leia Novak/ National Heart Lung and Blood Institute (NHLBI)] on initiatives and emerging opportunities (Table 1). The following sections in this review reflect a summary of major themes of discussion across the sections, as well as conversations emerging from the community panel discussion.

HIV and aging geroscience

This thematic reflects views from the experts on the biology of aging and HIV researchers studying PAWH to evaluate whether there is a discrepancy in chronological age (the time after birth) versus biological age (pathological factors and functional status in reference to chronological peers).[39] Discussions were centered on molecular factors and pathways that influence or drive biological aging. There was a consensus in the need to distinguish chronological age from biological age and to develop assessment tools and biomarkers to reflect differences in life histories.

In addition to higher rates of peripheral comorbid conditions (e.g., renal failure, diabetes, bone fracture, hypertension, CVD, and multimorbidity),[40] PAWH appear to experience greater impairments in physical and cognitive function, with development of impairment in activities of daily living and frailty seen at younger than expected ages in multiple cohorts.[41] For example, in the Multicenter AIDS Cohort Study, the percent of visits with a frailty phenotype dramatically increases at ages >50 among men aging with HIV compared to uninfected men,[22] and despite effective ART, the decline in gait speed and grip strength was greater in men aging with HIV infection.[24,42] While multifactorial drivers, including HIV infection itself, ART-related toxicities, disparities in care, and biobehavioral factors, likely contribute,[43] an overarching question is how PAWH may differ from aging in people without HIV, and what are the relevant mechanisms and models that could inform interventions?

Based on multiple nonhuman models and more recently human studies of biological aging, there has been substantial progress in identifying genes and pathways that influence the pace of aging. Evidence exists for biological mediators that accelerate aspects of aging, such as in progeroid syndromes, leading to what can be characterized as a shortened life span due to premature presentation of a distinct subset of biological alterations more often seen in older individuals. There are also studies showing decreases in the pace of aging that compress morbidity, increasing life span and longevity.[30,44] Efforts to measure differences in the pace of aging in humans have contrasted chronological age with biological age, defined as a set of variably defined biomarkers with expected normative values for a given chronological age.[45,46] Divergence in these two measures of aging can suggest pathology. Implicit in the concept of accelerated aging is the expectation that clinical conditions of aging (i.e., frailty and cognitive decline) appear at earlier ages. While it is unlikely that one or even a few genes or pathways fully explain the rate of biological aging, there is a convergence in biological phenotypes, often described as the pillars of aging.[47] These pillars, or processes of damage accumulation or dysfunction, develop subclinically before overt clinical evidence for functional compromise.[42]

As increasing numbers of PAWH make it to retirement age and beyond, and before disability designation, they are facing the dual burden of managing their disease and an apparently accelerated aging process. Many of the manifestations of this dual burden are subclinical, but still greatly affect QoL, such as decreased energy availability and increased chronic inflammation. The question is whether our understanding of the aging process can help people with HIV age more slowly. Data presented at the recent HIV and Aging workshop at Harvard Medical School suggest that the field of aging biology may be able to inform the treatment of those afflicted with HIV long term. Work from David Sinclair's laboratory and others is focused on the metabolite NAD^+, whose levels fall during aging and in various disease states. Restoration of NAD^+ levels improves DNA repair, mitochondrial function, and endurance capacity and reduces inflammation. For example, aged mice given a NAD^+ precursor for 2 months improved blood flow to their muscles allowing them to run 50% further.[48] The underlying mechanisms driving the long-term effects of chronic infection and of aging may be shared. Therefore, a better understanding of the effects of this molecule on aging and inflammatory pathways may yield profound benefits for the health of those with HIV and other chronic diseases.

Immune dysregulation: inflammation, activation, vaccine response

Inflammation is a common driving feature of both HIV disease and biologic aging (where it is termed inflammaging) and is considered to be an underlying factor in many comorbid conditions. Another feature ascribed to HIV infection is premature immune senescence leading to impaired immunity, similar to that observed in biologic aging. Overall, an improved understanding of the events leading to these age-related complications will inform additional therapeutic measures to reduce these morbidities. Although not specifically discussed in detail in the presentations of this workshop, generalized activation and upregulation of activation markers (i.e., HLA-DR and CD38) are well documented on lymphocytes in HIV infection and aging. Ongoing and future studies using more sophisticated profiling of surface proteins, cell signaling molecules, and molecular signatures will be critical to define mechanistic and prognostic biomarkers in HIV and biologic aging.

In old age, as well as in HIV infection, the risk for contracting influenza infection is high. Thus, seasonal influenza vaccination is recommended for aging individuals and for PWH, even though effectiveness of the vaccine for clinical protection is variable. Influenza vaccination can serve as a useful tool to assess immune competence by analysis of immune response to vaccine antigens. The cohort FLORAH (FLu Responses Of people in relation to Age and HIV), in which PWH and uninfected participants were grouped by age

as young (<40 years), middle aged (40–59 years), or elderly (≥60 years) and all PWH were on combination antiretroviral therapy (cART) with plasma viral load (VL) of <50 copies/mL, was recently used to address these questions. Serum antibody responses postvaccination showed the best responses (frequency and magnitude) in young uninfected participants, whereas a high proportion of old uninfected participants, as well as PWH of all age groups, were vaccine nonresponders (VNR).[49] Defects of B cells[50] and monocyte/macrophages[51] and association of inflammation and immune activation with VNR status[52] were also described. Interestingly, there was also a profound deficiency of influenza-specific and total peripheral T follicular helper (pTfh) cells in VNR and their pTfh cells exhibited markers of immune activation. Attempts to improve pTfh function by measures such as high dose vaccines and strategies that decrease inflammation could potentially improve influenza vaccine responses and clinical efficacy.

Epigenetics

Several recent studies have demonstrated the utility of measuring the biological rate of aging using DNA methylation levels.[53] DNA methylation profiles reflect dynamic epigenetic mechanisms used by cells to control gene expression and regulate cellular phenotypes. DNA methylation can be used to define cell types and deconvolute heterogenous cell populations and also regulate viral persistence. In the context of HIV and aging, DNA methylation of specific genomic loci across tissues and blood has provided valuable information about the biological age status of HIV infected persons and delivered unique insight to potential biological epigenetic mechanisms of ''accelerated aging'' compared to their age matched uninfected counterparts.[54] Additional insights indicate that ART does not restore age-apparent DNA methylation configurations. Furthermore, we have recently utilized DNA methylation profiling of specific immune cell populations and identified host cell type specific immune-epigenetic signatures that distinguish older PWH with cognitive impairment from those with normal cognition relative to population specific norms.[55] These data indicate the utility of DNA methylation and other potential epigenetic mechanisms to monitor the development and progression of age-related comorbidities in this vulnerable population.

Unique and composite biomarkers

There is a growing effort within the HIV field to identify phenotypes and/or biomarkers that may predict clinical adverse events, including fractures or cardiovascular events, and if these profiles may be unique to PWH or PAWH. For example, inflammatory cytokines, including IL-6 and IL-1β, or the monocyte/macrophage markers sCD14 and sCD163 have been linked to CVD risk in both HIV+ and HIV− individuals, but the mediators that likely drive increased levels of these markers may or may not be different in these populations (low level HIV replication, ART toxicities, increased dysbiosis and microbial translocation, altered lipid profiles, smoking, and lifestyle choices).

Composite serologic biomarkers are promising to predict disease development. Recently 19 serum biomarkers were evaluated in over 5,000 participants enrolled in the Long-Life Family Study (LLFS) to generate biomarker signature of aging. The biomarkers included results from ordinary blood test such as white blood cell counts or HA1C and well-established biomarkers of inflammation like IL6 or IGF1, biomarkers of physical functions like DHEA, and biomarkers of kidney functions like creatinine levels. One signature was characterized by lower than average inflammatory markers and predicted better survival and decreased risk for type 2 diabetes and CVD compared to individuals with normative molecular aging. Other signatures predicted reduced survival and higher risk for aging-related diseases. The biomarker signatures and their predictions were replicated in comparable data from the Framingham Heart Study.[30] Serum proteins have also been more generally associated with aging and longevity. Some 4,785 proteins measured in serum of 224 centenarians, offspring, and controls from the New England Centenarian Study using a high-throughput Somascan platform revealed that a substantial number of proteins change with aging. These two analyses suggest that signatures of multiple biomarkers can be useful to track various aging patterns and that there are many so-far unknown circulating proteins in serum that track aging and could lead to more specific and sensitive biomarker profiles of aging and longevity.

Defining mechanisms and biomarkers for inflammaging

A key point emphasized in the workshop was the need for future research to better understand mechanistically how the combination of immune senescence and inflammaging overlaps to influence the outcome of HIV infection/AIDS in older adults. Although we generally think of immune senescence as a ''decline'' in immune response to pathogens, the chronic low-grade inflammation that occurs in aging also interacts with HIV (and potentially other coinfections such as cytomegalovirus (CMV) that can further promote inflammation and CVD as HIV patients grow older. Obesity in aging is known to occur in middle age and older, and PAWH also have increased visceral adiposity, in part, as side effects of some antiretroviral drugs. There is a growing appreciation that traditional lipid measurements (low-density lipoprotein, high-density lipoprotein, and total cholesterol) may inadequately capture dyslipidemia and CVD risk in PWH receiving ART.[56] Members of the Funderburg group[57,58] and others[59] have recently reported substantial differences in lipid classes and lipid species in PWH and uninfected populations, even when traditional lipid measurements between these groups were not different. These advanced lipid analyses have also linked alterations in the lipidome to inflammation, monocyte activation, and atherosclerosis. How these processes interact to contribute to the high morbidity and mortality in older HIV/AIDS patients is currently poorly understood. Another important aspect of inflammaging is the contribution of age-related gut microbiota to the systemic inflammation in old age. We need to understand the interplay between altered gut microbiota in HIV/AIDS and aging, including the role that age-associated remodeling of the intestinal barrier plays in systemic inflammation in older HIV/AIDS patients.

Future studies need to take advantage of ''pattern recognition'' approaches using technological advances (mass spectrometry multilevel omics, etc.) that can shed light on unique and overlapping profiles of metabolic changes, immune activation and inflammation, and functional outputs, which may

inform the underlying mechanisms of comorbid events in PWH and uninfected individuals. While ART has extended the expected life spans of PAWH, ART-related toxicities remain a concern, even with modern regimens. Understanding the consequences of ART exposure, including effects on mitochondrial function and advanced lipidomic and metabolic profiles, should be explored. Until we gain a better understanding of the underlying mechanisms that lead to comorbidities (or identification of biomarkers that predict nascent complications in advance of clinical events), implementation of successful therapies will remain elusive.

Geriatric Research Methods

This thematic reflects views expressed related to methods and approaches used to evaluate physical decline in PAWH. Discussion was centered on the utility of geriatric assessments and they being adapted to younger PAWH. There was consensus in the need to develop better tools for measuring loss in mass and function. It was unclear whether existing assessments need to be adapted as disease-specific assessments for PAWH.

Measuring muscle mass, physical performance, and frailty outcomes are particularly useful for characterizing and assessing intervention effects in older populations with HIV. Tests such as the Short Performance Physical Battery, 400-meter walk, 6-minute walk distance, grip strength, Berg Balance, and others are relatively easy to conduct, whereas measurement of fitness (VO_2peak), muscular isokinetic strength, gait biomechanics, and cellular and molecular biology in tissue are more difficult but provide a wealth of information in this population.

Measuring skeletal muscle loss in PAWH

Muscle loss commonly found in aging populations may be further compounded by HIV status. Low muscle mass and function (prevalence of sarcopenia) in PWH is high ($\sim$25%),[60,61] and PWH suffer from muscle loss leading to impaired physical function and ultimately to mobility disability.[62] Furthermore, some report that this may also differ by sex.[63,64] The rate of decline in muscle mass over a 5-year study period was similar in PWH and controls,[64] yet the frequency of sarcopenia increased over a 7- to 10-year follow-up in PWH older than 50 years with the progression of sarcopenia greater in women than men.[63] Standardized physical performance measures allow early detection and assessment of physical function impairments, as well as assess the effects of interventions aimed at averting physical decline and preventing mobility disability. Going beyond traditional research regarding muscle mass in PWH, we can learn more about the skeletal muscle specifically cellular and enzymatic activity changes that transpire with the use of skeletal muscle biopsies. In terms of mitochondrial markers, older male PWH have reduced oxidative enzyme activity compared to age-matched controls with 38% and 77% lower β-hydroxy acyl-CoA dehydrogenase (β-HAD) and citrate synthase activities, respectively.[65] Other key enzymes of fatty acid oxidation, acyl-coA synthase, and CPT-1 are not different between male PWH and controls, but skeletal muscle oxidative stress is increased (H_2O_2 by 1.4 fold and oxidized cardiolipin by 1.8 fold). The importance of these findings is further demonstrated as low oxidative enzyme activity and high oxidative stress, which are related to fitness or VO_2 peak perhaps suggesting that these tissue changes may contribute to the accelerated age-associated reduction in aerobic capacity in HIV. This research is one example of the mitochondrial changes in skeletal muscle in HIV-infected adults. However, there is limited information on skeletal muscle (using muscle biopsies) in HIV+ women, highlighting a clear research deficit for future studies.

Sarcopenia has been described as the age-associated decrease in skeletal muscle mass. However, virtually every study of sarcopenia has measured lean body mass or fat free mass (LBM, FFM) rather than muscle mass, specifically. In a number of published sarcopenia studies, LBM or FFM is referred to as muscle mass, leading to an incorrect assumption that measuring LBM or FFM is an accurate measure of muscle mass. As a result, the data on the effects of changes in LBM or FFM in older populations on outcomes such as functional capacity, disability, and risk of injurious falls have been inconsistent resulting in the conclusion that muscle mass is only weakly related to these outcomes. The D3-creatine (D3Cr) dilution provides a direct and accurate measurement of creatine pool size and skeletal muscle mass.[16,66] A subject ingests a capsule with a tracer dose of D3Cr, which is absorbed and actively transported into all muscle cells. Creatine is turned over through conversion to creatinine and excreted in urine allowing a single urine sample to be used to assess D3-creatinine enrichment and determine total body creatine pool size and muscle mass ($\sim$98% of total body creatine is found in muscle). In a recent study in older men [>80 years, Osteoporotic Fractures in Men (MrOS) cohort], D3Cr muscle mass was associated with functional capacity and risk of injurious falls and disability, while assessments of LBM or appendicular lean mass (aLM) by dual energy X-ray absorptiometry (DXA) were only weakly or not associated with these outcomes.[17] In this study many of the factors associated with frailty such as slow walking speed, low PA, and low strength were strongly associated with D3Cr muscle mass, but not DXA lean mass. Inaccurate measurements of muscle mass by DXA and other methods have led to inconsistent results and potentially erroneous conclusions about the importance of skeletal muscle mass in health and disease. PWH over 55 often have a higher burden of functional impairment and physical frailty,[21,67] although some have speculated that sarcopenia is not an important factor in HIV associated frailty.[68] The assessment of skeletal muscle mass using the D3Cr dilution method in prospective cohort studies in PWH may reveal sarcopenia as a powerful risk factor for low levels of PA, weakness, risk of falling and hip fracture, and disability.

Methods for measuring physical function

Gait speed. Slow gait speed is an independent predictor of morbidity, disability, institutionalization, and mortality.[32,33] Assessments of gait speed include the 6-min and 400 m endurance walking tests,[69] and the 4 m at usual pace, which is a measure of functional performance.[70–72] Moreover, the inability to walk 400-m[73] or gait speed <1.0 or <0.8 m/s.

The short physical performance battery. The short physical performance battery (SPPB) score includes the 4-m

walk, tandem stand test, and 5-time chair rises, providing an excellent assessment of lower extremity function,[74] and is a strong predictor of future disability. It is particularly useful in lower functioning persons.[75] Clinically meaningful changes in physical performance measures have been defined and are used as target outcomes in clinical trials.[76,77] For example, the Lifestyle Interventions and Independence for Elders (LIFE) study found that, compared with health education, a structured PA intervention significantly improved the SPPB score and 400 m speed in a clinically meaningful manner[78] and also prevents the onset of major mobility disability.[34] In the T-Trial, supplemental testosterone improved self-reported mobility measure, as well as the 6-minute walk distance. These data show that the standardized physical performance measures are modifiable in older adults with various interventions.

Free-living PA. Changes in physical function with aging have been linked to the onset and progression of disease,[32,79] as well as increased risk of disability and death.[32,75,80] Recent evidence has supported the use of physical function measures among PWH to help distinguish differences in ''normal'' versus ''accelerated'' aging by HIV serostatus.[21,24,42,81] PWH have shown accelerated rates of decline in both grip strength and gait speed, with greater risk of reaching clinical thresholds of ''weakness'' and ''slowness''[24,42] and eventual frailty.[22,82] Yet to truly disentangle the mechanisms contributing to these accelerated rates of decline, a better understanding of the preclinical physiological underpinnings is warranted. Measures of laboratory-based energy expenditure—from resting to peak exertion—and free-living PA using accelerometers have been utilized in the general aging population to differentiate variations in energy utilization and PA by health status[28,83–85] and subsequent resilience to functional decline with aging.[86–88] Application of such measures to PWH may help identify new opportunities for earlier intervention in the spectrum of functional capability, preserving mobility and reducing risk for frailty and disability.

Application of geriatric assessment of frailty to HIV

PAWH who have mitochondrial dysfunction, potentially due to HIV infection and/or ART, as well as impaired peripheral oxygen uptake or oxygen diffusion capacity, often have lower testosterone, increased prevalence of neuropathy, and elevated self-reported fatigue. A clinical consequence of these underlying biological processes is frailty, which is elevated in PWH. Frailty reflects a vulnerability to stressors and is most commonly defined by either a phenotype (frailty phenotype of slowness, weakness, shrinking, fatigue, and low activity)[89] or a burden of health deficits as comorbid conditions (frailty index).[90] Multiple prior studies have found that physical function impairments and frailty may occur in both an accelerated and accentuated manner among PWH compared to uninfected controls.[22,24,42,91,92] Among older adults, assessments of frailty and physical function provide a measure of ''biologic'' aging that may differ considerably from chronologic age in PWH. Factors that may be relevant to the disconnect include comorbidities, chronic inflammation, social stressors, and resiliency.

Incorporation of frailty assessments can inform care in multiple ways: (1) early identification of impairments, so that earlier interventions can prevent decline in physical function. The intervention that has been shown to be most effective in improving physical function and preventing frailty is PA. Several studies have shown that exercise or PA improves measures of strength or exercise endurance in younger populations of PWH,[93,94] with recent studies by our group and others also demonstrating improvements in physical function outcomes, such as time to rise from a chair and 400-m walk.[25,95–99] PAWH have an excellent physical function response to exercise, similar to if not greater than uninfected controls.[25] (2) Frailty assessment can guide clinical care decisions. A frail or markedly impaired individual with multiple comorbidities is likely to experience more risk than benefit with interventions such as cancer screening; this information can inform discussions on goals of care.[100] (3) Physical function measures can be incorporated into interventions in HIV-related studies to determine the clinically relevant impact. For example, a recent study of a senolytic agent among older adults with pulmonary hypertension found an improvement in physical function markers, but not markers of inflammation.[101] Ultimately, physical function or frailty assessments may serve as a more clinically relevant ''biomarker'' with a clear target for intervention and impact on clinical decision making in PAWH.

Physiologic frailty and polypharmacy in people aging with and without HIV infection

Polypharmacy typically begins when an individual is on five or more medications. It is of general concern because it is strongly associated with poor health outcomes, and rates doubled from 1999 to 2011.[102] For those aging with HIV, polypharmacy is of particular concern because it typically occurs 10 years earlier than for those aging without HIV infection,[19] PAWH have a greater burden of physiologic frailty, and antiretroviral medications interact with a number of common nonantiretroviral medications.[103]

The study of polypharmacy, however, and how its associated harms might be mitigated is challenging. Observational studies are limited due to concerns regarding confounding by indication or channeling bias.[104] One approach that holds some promise is careful adjustment using an established prognostic index such as the VACS Index 2.0.[105] By adjusting for physiologic effects of multimorbidity we may begin to disentangle indications for multiple medications (multimorbidity) from adverse effects of polypharmacy.

Preclinical decline and asynchronous aging in HIV

Among those younger or middle aged with HIV infection, a current challenge in HIV care is identifying preclinical cues for risk of functional decline as they grow older. Ideally, studies on preclinical risk would be comprehensive and obtain concurrent physical function, immune, and muscle phenotyping to gain mechanistic insight into potential drivers of functional decline and potential accelerated age-related pathways. One such study discussed in the workshop, the MATCH cohort study, is composed of asymptomatic PAWH and uninfected controls, all 50–65 years of age, recruited from the Boston metropolitan area. In this cohort, there were modest deficits in gait speed, stair climb power, without

deficits in leg power or strength among PWH compared to age-matched seronegative controls. Histological assessment of muscle fiber type did not reveal differences or increased size variability (both of which are expected with muscle aging[106]). There was an unexpected increase in internalized muscle nuclei that are more often seen with a more advanced age.[107] Also observed were reduced levels of nuclear PGC-1α, suggesting compromised bioenergetic pathways, potentially influencing exercise tolerance. Collectively, certain features of aging were present but not others, suggesting asynchronous or segmented aging, rather than an accelerated pace of biological aging pathways. Provocatively, among male participants in the MATCH cohort, there were minimal differences in gait speed, despite elevated fatigue. However, using accelerometry in a follow-up study, volitional gait speed by activity tracker was significantly reduced compared to the uninfected participants.[26,27] Consistent with this observation, male PWH spent significantly more time in the lowest quartile of PA compared to the seronegative controls.[26]

Collectively, asymptomatic PWH on effective ART were characterized by subclinical deficits in physical function, greater levels of fatigue and estimated mortality risk (by the VACS Index), elevated inflammation and immune activation, and increased skeletal muscle internalized nuclei with decreased PGC-1α. Differences by HIV serostatus on volitional but not laboratory-based gait measures and activity profiles characterized by more time spent at lower activity levels suggest potential limits on functional reserve. These data suggest that activity profiles may be useful as presymptomatic digital biomarkers of functional decline. Future studies should distinguish the trajectory of aging in PWH compared to aging without HIV and seek to identify biological and biobehavioral risk factors apparent before clinical presentation of physical function impairment or frailty.

Priorities in HIV and Aging as Identified by the Community

This thematic reflects patient reported priorities and health care disparities. Discussion was centered on racial and ethnic disparities, gender, and support services. There was consensus that more emphasis needs to be placed on PROs and QoL, given increasing life span of PAWH.

Racial and ethnic disparities

In the United States, ~47% of PWH are 50 years and older, the majority of whom are Black/African American or Latino.[108] Black and Latino individuals living with HIV have higher rates of HIV-related morbidity and mortality than older adults of other racial and ethnic groups.[108] Among non-HIV-infected Black and Latino individuals, higher rates of functional decline and disability with aging have been documented.[109,110] Among Black and Latino PWH, aging is further complicated by HIV-related stigma resulting in limited social engagement, social isolation, and depressive symptoms.[111,112] These factors, in addition to well-described demographic and structural challenges faced by aging Black and Latino PWH (e.g., poverty, unstable housing, and suboptimal neighborhood resources), lend themselves to a patient-centered, community-engaged understanding of aging. Future research directions identified through the panel discussion regarding racial/ethnic disparities include:

(1) According to the CDC, fewer Black PWH had sustained virologic suppression, which can adversely affect their health outcomes and pose a risk for HIV transmission to others. The racial/ethnic differences in sustained virologic suppression were present across all sex, age, and transmission categories.[108] What more needs to be done to promote racial and ethnically targeted retention in care, adherence, reduce structural barriers etc., among older individuals living with HIV to overcome these persistent findings?
(2) Black and Latino individuals over 50 years old are, respectively, 13 and 5 times more likely to receive an HIV diagnosis than are White Americans. What is driving this disparity? Underestimation of personal risk, increased biologic vulnerability (among women increased risk for HIV during penetration potentially due to differential rates in vaginal and cervical thinning that occurs during menopause), greater availability of sexual partners through the internet, or less focus on older populations in prevention efforts?
(3) Has the gender disparity in life expectancy (described below) differentially impacted women by race or ethnicity? In an analysis of data from the Women's Interagency HIV Study (WIHS), Murphy *et al.*[113] noted that Black women were twice as likely as white women to experience adverse HIV clinical outcomes, specifically death from AIDS even after adjusting for multiple potential confounding characteristics, including illicit drug use, depressive symptoms, and adherence. Additional studies confirming these findings and examining structural factors and behavioral and potentially biologic factors that were not explored in this analysis should be undertaken.

Gender disparities

One of the key areas of research in the context of HIV and aging needs to be women aging with HIV. Obviously, this includes gynecologically-focused concerns such as the management of human papillomavirus (HPV) and when to stop screening for breast and cervical cancer. However, there are other areas that are of equal importance that are considered less often when discussing women's health.

Since 2006, highly effective ART in once-daily formulations has led to improved survival among PWH. Life expectancy, however, has not improved equally in men and women: a growing body of research suggests that HIV+ men live longer. This is in marked contrast to the general population where women live longer than men. In a 2017 study of HIV+ and uninfected men and women in British Columbia, at age 20 years, the life expectancy of women living with HIV (WLWH) was 5 years less than men living with HIV (29 vs. 34 years; $p < .001$). The uninfected women in the study, however, lived for almost 5 years longer than the uninfected men.[114] While this is the most dramatic evidence of how WLWH are disadvantaged in terms of life expectancy relative to men, it is not a unique finding. This finding suggests that there are a number of important research gaps that need to be addressed. First, we need to understand what

the most common causes of mortality among WLWH are. In particular, we need to explore the role that domestic violence plays in early death among women. In the WIHS, French *et al.* found that between 1995 and 2004, the most common cause of non-AIDS-related death among study participants (all women) was trauma and self-harm. Contributing factors included the high prevalence of depressive symptoms, physical abuse, and the ongoing vulnerability associated with poverty and substance abuse.[115] In contrast, the ART Cohort Collaboration (ARTCC), in a study that was primarily (73%) men, found that violent death (7.8%) was the fourth most common cause of death behind non-AIDS malignancies (11.8%), non-AIDS infections (8.2%), and CVD (7.9%).[116]

We also need to understand whether this difference in survival is the result of disparities in access to care between men and women? Research out of Kaiser suggests that men have significantly greater linkage to HIV care, ART prescription, and viral suppression than women in 2010–2011, but these differences in linkage to care did not persist.[117]

Substance use may also be an important contributor to earlier death in WLWH relative to men. We know that an equivalent amount of alcohol has a more negative impact on women than on men.[118] We also know that alcohol has a more negative impact on PWH than on uninfected comparators.[119] A key question is whether there is an interaction between alcohol use and HIV that makes alcohol particularly dangerous for WLWH. Similar questions need to be asked about smoking. As trends in injection drug use change with the increase in opioid use will we note higher increases in new HIV infection among men and women? We know that women who use drugs are faced with multiple issues, which enhance their vulnerability to HIV, including sex work, stigma, discrimination, and violence.

Multimorbidity and polypharmacy may also have differential impacts on women versus men. Research from the ALIVE cohort suggests that WLWH have higher rates of multimorbidity than men.[120] There is ample evidence to suggest that pharmacokinetics are different in women than in men. We need to understand whether these differences contribute to an increased risk of adverse events and thus to a shorter life expectance in WLWH compared with men. Comparisons need to be made both in non-antiretroviral (ARV) medications and in ART.

In addition to issues related to life expectancy, women in the general population do less well than men on issues of health-related QoL. Specifically, women experience higher rates of falls, disability, frailty, and functional disability than men. So not only do we need to work to lessen gender disparities in terms of life expectancy, we also need to work with our patients to determine how best to optimize QoL and to be sure that QoL for WLWH is on par with that of men.

Need for holistic comprehensive care

Even though many PWH who are over 50 years old are virologically suppressed, there are many psychosocial, mental health, and comorbid medical issues that have led to reductions in QoL. According to PWH who participated in the community panel, HIV is not at the top of their hierarchy of concerns. Psychosocial issues include isolation, fear of rejection, and persistent stigma (homophobia, HIV related stigma, both perceived and enacted), particularly within communities of color. Mental health issues include depression, anxiety, posttraumatic stress disorder, and cognitive decline. Medical issues (discussed elsewhere during the meeting) include diabetes, hypertension, and cancer, as well as many other illnesses associated with aging. Thus, there is a desire for more holistic comprehensive care that includes HIV, but not to the exclusion of these other important concerns.

Holistic comprehensive care should include services that are often deemed to be ancillary but are central to QoL for PAWH. Care should include behavioral and cognitive diagnostic screenings and educational workshops on topics such as smoking cessation and cardiovascular health. Social interaction should be facilitated given the overwhelming isolation that PAWH experience. People may no longer see HIV as a major health issue, but stigma associated with living with HIV can be detrimental and lead to isolation and depression. Some people living with HIV of all ages are fearful of socializing due to stigma. In addition, among older individuals living with HIV survival fatigue can foster isolation and lack of socialization. The weight of stigma and the feeling of being forgotten can be agonizing. Development of a positive and uplifting media campaign focused on how PAWH are actually living might be useful. One panelist described the concept of ''hope literacy,'' which is just as important as ''health literacy.'' Social engagement and one-on-one interaction with other PAWH may help to facilitate wellness and ''hope literacy.'' In addition, panel members discussed the need to seek input from PAWH in regard to the development of research questions, clinical trial/research design, and the dissemination of study findings. Researchers should be encouraged to visit with PWH in their own communities to learn about the issues that they truly face. This action would demonstrate that older individuals living with HIV are valued.

Priorities for HIV and Aging Studies as Identified by the NIH

The closing session was convened to hear perspectives of NIH program staff on NIH priorities related to HIV and aging. Discussion centered on program announcements and multifactorial comorbid conditions in PAWH. There was consensus that multiple opportunities exist but that more needs to be done to harmonize efforts across institutes and study sites.

In the early 1980's, multiple NIH institutes began to sponsor HIV/AIDS research. By 1985, NIAID was the lead NIH sponsoring institute. However, because HIV/AIDS is a multiorgan, multisystem disease, research priorities quickly exceeded the mission of any one institute. More recently, there has been a substantial investment in aging research programs by the NIA. Past program announcements have included Program Announcement Reviewed by an Institution (PARs) and Request for Applications (RFAs) investigating a broad range of studies directly related to aging and HIV, including: Multidisciplinary Studies of HIV/AIDS and Aging; Pathogenesis of Age-Related HIV Neurodegeneration; as well as investigator-initiated mechanisms. Multiple institutes contribute to support CFARs, of which HIV & Aging is a major research focus, and NIH also supports studies through the

Multicenter AIDS Cohort Study (MACS)/Women's Interagency HIV Study (WIHS) Combined Cohort Study. A brief description of HIV-related interests expressed by NIH institutes presenting at the workshop is shown in Table 1.

Conclusions

While dramatic advances have been simultaneously made in the biology of aging and in HIV treatment, there remains the need to identify mechanistic drivers of biological aging in the context of HIV infection. Furthermore, there remains a need to develop muscle mass and function assessment tools and biomarkers that reflect differences in the trajectory of life histories among PAWH compared to uninfected persons. Finally, more emphasis needs to be placed on patient-reported outcomes and QoL, as well as increased awareness of geriatric approaches, and the inclusion of input from PAWH when developing research priorities going forward.

Acknowledgments

The authors thank Drs. Geraldine Dominguez (NCI), Basil Eldadah (NIA), Gallya Gannot (NIDCR), and Leia Novak (NHLBI) for their participation in the workshop and helpful comments on the article.

Author Disclosure Statement

K.M.E. has served as a consultant for Gilead and ViiV. D.A.S. is a founder, equity owner, board member, advisor to, director of, consultant to, investor in, and/or inventor on patents licensed to Vium, Jupiter Orphan Therapeutics, Cohbar, Galilei Biosciences, GlaxoSmithKline, OvaScience, EMD Millipore, Wellomics, Inside Tracker, Caudalie, Bayer Crop Science, Longwood Fund, Zymo Research, EdenRoc Sciences [and affiliates Arc-Bio, Dovetail Genomics, Claret Bioscience, Revere Biosensors, UpRNA and MetroBiotech (an NAD booster company), and Liberty Biosecurity], and Life Biosciences [and affiliates Selphagy, Senolytic Therapeutics, Spotlight Biosciences, Animal Biosciences, Iduna, Immetas, Prana, Continuum Biosciences, Jumpstart Fertility (an NAD booster company), and Lua Communications]. D.A.S. sits on the board of directors of both companies. D.A.S. is an inventor on a patent application filed by Mayo Clinic and Harvard Medical School that has been licensed to Elysium Health; his personal royalty share is directed to the Sinclair laboratory. For more information see https://genetics.med.harvard.edu/sinclair-test/people/sinclair-other.php All other authors report no disclosures.

Funding Information

This work was supported by the following grants from the National Institutes of Health: M.M. was supported by the NIA (R21 AG055415), the NIAID (R01 AI08541), and the Boston Older Americans Independence Center (P30 AG031679). K.M.E. was supported by the NIA (K23 AG050260 and R01 AG054366). D.A.S. was supported by the Glenn Foundation for Medical Research and grants from the NIH (R37 AG028730, R01 AG019719, and R01 DK100263). R.K.R. was supported by the NIAID (R01 AI120828) and NIDCR (R01 DE026014). The Harvard University Center for AIDS Research (P30 AI060354) provided logistical and organizational support for workshop.

References

1. Gomes AP, Price NL, Ling AJ, *et al.*: Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell 2013; 155:1624–1638.
2. Barzilai N, Crandall JP, Kritchevsky SB, Espeland MA: Metformin as a tool to target aging. Cell Metab 2016;23: 1060–1065.
3. Lamming DW, Ye L, Sabatini DM, Baur JA: Rapalogs and mTOR inhibitors as anti-aging therapeutics. J Clin Invest 2013;123:980–989.
4. Mannick JB, Del Giudice G, Lattanzi M, *et al.*: mTOR inhibition improves immune function in the elderly. Sci Transl Med 2014;6:268ra179.
5. Mannick JB, Morris M, Hockey HP, *et al.*: TORC1 inhibition enhances immune function and reduces infections in the elderly. Sci Transl Med 2018;10:449. DOI: 10.1126/scitranslmed.aaq1564
6. Pawelec G: Age and immunity: What is ''immunosenescence''? Exp Gerontol 2018;105:4–9.
7. Childs BG, Gluscevic M, Baker DJ, *et al.*: Senescent cells: An emerging target for diseases of ageing. Nat Rev Drug Discov 2017;16:718–735.
8. Miller RR, Roubenoff R: Emerging interventions for elderly patients—The promise of regenerative medicine. Clin Pharmacol Ther 2019;105:53–60.
9. Baker DJ, Perez-Terzic C, Jin F, *et al.*: Opposing roles for p16Ink4a and p19Arf in senescence and ageing caused by BubR1 insufficiency. Nat Cell Biol 2008;10: 825–836.
10. Baker DJ, Weaver RL, van Deursen JM: p21 both attenuates and drives senescence and aging in BubR1 progeroid mice. Cell Rep 2013;3:1164–1174.
11. Karakasilioti I, Kamileri I, Chatzinikolaou G, *et al.*: DNA damage triggers a chronic autoinflammatory response, leading to fat depletion in NER progeria. Cell Metab 2013;18:403–415.
12. Brace LE, Vose SC, Stanya K, *et al.*: Increased oxidative phosphorylation in response to acute and chronic DNA damage. NPJ Aging Mech Dis 2016;2:16022. DOI:10.1038/npjamd.2016.22
13. Mitchell SJ, Madrigal-Matute J, Scheibye-Knudsen M, *et al.*: Effects of sex, strain, and energy intake on hallmarks of aging in mice. Cell Metab 2016;23:1093–1112.
14. Evans WJ: What is sarcopenia? J Gerontol A Biol Sci Med Sci 1995;50:Spec No. 5–8.
15. Evans WJ, Hellerstein M, Orwoll E, Cummings S, Cawthon PM: D_3-creatine dilution and the importance of accuracy in the assessment of skeletal muscle mass. J Cachexia Sarcopenia Muscle 2019;10:14–21.
16. Clark RV, Walker AC, O'Connor-Semmes RL, *et al.*: Total body skeletal muscle mass: Estimation by creatine (methyl-d3) dilution in humans. J Appl Physiol (1985) 2014;116:1605–1613.
17. Cawthon PM, Orwoll ES, Peters KE, *et al.*: Strong relation between muscle mass determined by D_3-creatine dilution, physical performance, and incidence of falls

and mobility limitations in a prospective cohort of older men. J Gerontol A Biol Sci Med Sci 2019;74:844–852.
18. Schaap LA: D_3-creatine dilution to assess muscle mass. J Gerontol A Biol Sci Med Sci 2019;74:842–843.
19. Edelman EJ, Gordon KS, Glover J, McNicholl IR, Fiellin DA, Justice AC: The next therapeutic challenge in HIV: Polypharmacy. Drugs Aging 2013;30:613–628.
20. Justice AC, Gordon KS, Skanderson M, *et al.*: Non-antiretroviral polypharmacy and adverse health outcomes among HIV-infected and uninfected individuals. AIDS 2018;32:739–749.
21. 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;11:279–290.
22. Althoff KN, Jacobson LP, Cranston RD, *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;69:189–198.
23. Oursler KK, Sorkin JD, Smith BA, Katzel LI: Reduced aerobic capacity and physical functioning in older HIV-infected men. AIDS Res Hum Retroviruses 2006;22: 1113.
24. Schrack JA, Althoff KN, Jacobson LP, *et al.*: Accelerated longitudinal gait speed decline in HIV-infected older men. J Acquir Immune Defic Syndr 2015;70:370–376.
25. Erlandson KM, MaWhinney S, Wilson M, *et al.*: Physical function improvements with moderate or high-intensity exercise among older adults with or without HIV infection. AIDS 2018;32:2317–2326.
26. Hale TM, Guardigni V, Roitmann E, *et al.*: Middle-aged men with HIV have diminished accelerometry-based activity profiles despite similar lab-measured gait speed: Pilot study. JMIR Mhealth Uhealth 2019;7:e11190.
27. Tran T, Guardigni V, Pencina KM, *et al.*: Atypical skeletal muscle profiles in human immunodeficiency virus-infected asymptomatic middle-aged adults. Clin Infect Dis 2018;66:1918–1927.
28. Fabbri E, An Y, Schrack JA, *et al.*: Energy metabolism and the burden of multimorbidity in older adults: Results from the Baltimore Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci 2015;70:1297–1303.
29. Schrack JA, Jacobson LP, Althoff KN, *et al.*: Effect of HIV-infection and cumulative viral load on age-related decline in grip strength. AIDS 2016;30:2645–2652.
30. Sebastiani P, Thyagarajan B, Sun F, *et al.*: Biomarker signatures of aging. Aging Cell 2017;16:329–338.
31. Sebastiani P, Thyagarajan B, Sun F, *et al.*: Age and sex distributions of age-related biomarker values in healthy older adults from the long life family study. J Am Geriatr Soc 2016;64:e189–e194.
32. Studenski S, Perera S, Patel K, *et al.*: Gait speed and survival in older adults. JAMA 2011;305:50–58.
33. Newman AB, Simonsick EM, Naydeck EM, *et al.*: Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. JAMA 2006;295:2018–2026.
34. Pahor M, Guralnik JM, Ambrosius WT, *et al.*: Effect of structured physical activity on prevention of major mobility disability in older adults: The LIFE Study randomized clinical trial. JAMA 2014;311:2387–2396.
35. Groessl EJ, Kaplan RM, Castro Sweet CM, *et al.*: Cost-effectiveness of the LIFE physical activity intervention for older adults at increased risk for mobility disability. J Gerontol A Biol Sci Med Sci 2016;71:656–662.
36. Trombetti A, Hars M, Hsu FC, *et al.*: Effect of physical activity on frailty: Secondary analysis of a randomized controlled trial. Ann Intern Med 2018;168:309–316.
37. Cesari M, Vellas B, Hsu FC, *et al.*: A physical activity intervention to treat the frailty syndrome in older persons-results from the LIFE-P study. J Gerontol A Biol Sci Med Sci 2015;70:216–222.
38. Katz PP, Pate R: Exercise as medicine. Ann Intern Med 2016;165:880–881.
39. Karasik D, Demissie S, Cupples LA, Kiel DP: Disentangling the genetic determinants of human aging: Biological age as an alternative to the use of survival measures. J Gerontol A Biol Sci Med Sci 2005;60:574–587.
40. Guaraldi G, Orlando G, Zona S, *et al.*: Premature age-related comorbidities among HIV-infected persons compared with the general population. Clin Infect Dis 2011; 53:1120–1126.
41. Sheppard DP, Iudicello JE, Bondi MW, *et al.*: Elevated rates of mild cognitive impairment in HIV disease. J Neurovirol 2015;21:576–584.
42. Ferrucci L, Cooper R, Shardell M, Simonsick EM, Schrack JA, Kuh D: Age-related change in mobility: Perspectives from life course epidemiology and geroscience. J Gerontol A Biol Sci Med Sci 2016;71:1184–1194.
43. Guardigni V, Montano M: The demographic shift in HIV: The aging HIV patient. Infect Dis Special Ed (IDSE) 2018:77–83.
44. Harkema L, Youssef SA, de Bruin A: Pathology of mouse models of accelerated aging. Vet Pathol 2016;53:366–389.
45. Belsky DW, Caspi A, Houts R, *et al.*: Quantification of biological aging in young adults. Proc Natl Acad Sci U S A 2015;112:E4104–E4110.
46. Levine ME: Modeling the rate of senescence: Can estimated biological age predict mortality more accurately than chronological age? J Gerontol A Biol Sci Med Sci 2013;68:667–674.
47. Lopez-Otin C, Blasco MA, Partridge L, Serrano M, Kroemer G: The hallmarks of aging. Cell 2013;153:1194–1217.
48. Das A, Huang GX, Bonkowski MS, *et al.*: Impairment of an endothelial NAD(+)-H_2S signaling network is a reversible cause of vascular aging. Cell 2018;173:74.e20–89.e20.
49. Pallikkuth S, De Armas LR, Pahwa R, *et al.*: Impact of aging and HIV infection on serologic response to seasonal influenza vaccination. AIDS 2018;32:1085–1094.
50. Rinaldi S, Pallikkuth S, George VK, *et al.*: Paradoxical aging in HIV: Immune senescence of B cells is most prominent in young age. Aging 2017;9:1307–1325.
51. George VK, Pallikkuth S, Pahwa R, *et al.*: Circulating inflammatory monocytes contribute to impaired influenza vaccine responses in HIV-infected participants. AIDS 2018;32:1219–1228.
52. de Armas LR, Pallikkuth S, George V, *et al.*: Reevaluation of immune activation in the era of cART and an aging HIV-infected population. JCI Insight. 2017;2:e95726. https://doi.org/10.1172/jci.insight.95726.
53. Bocklandt S, Lin W, Sehl ME, *et al.*: Epigenetic predictor of age. PLoS One 2011;6:e14821.

54. Horvath S, Levine AJ: HIV-1 infection accelerates age according to the epigenetic clock. J Infect Dis 2015;212: 1563–1573.
55. Corley MJ, Dye C, D'Antoni ML, *et al.*: Comparative DNA methylation profiling reveals an immunoepigenetic signature of HIV-related cognitive impairment. Sci Rep 2016;6:33310.
56. Bowman E, Funderburg NT: Lipidome abnormalities and cardiovascular disease risk in HIV infection. Curr HIV/AIDS Rep 2019;16:214–223.
57. Belury MA, Bowman E, Gabriel J, *et al.*: Prospective analysis of lipid composition changes with antiretroviral therapy and immune activation in persons living with HIV. Pathog Immun 2017;2:376–403.
58. Bowman ER, Kulkarni M, Gabriel J, *et al.*: Altered lipidome composition is related to markers of monocyte and immune activation in antiretroviral therapy treated human immunodeficiency virus (HIV) infection and in uninfected persons. Front Immunol 2019;10:785.
59. Zhao W, Wang X, Deik AA, *et al.*: Elevated plasma ceramides are associated with antiretroviral therapy use and progression of carotid artery atherosclerosis in HIV infection. Circulation 2019;139:2003–2011.
60. Pinto Neto LF, Sales MC, Scaramussa ES, da Paz CJ, Morelato RL: Human immunodeficiency virus infection and its association with sarcopenia. Braz J Infect Dis 2016;20:99–102.
61. Wasserman P, Segal-Maurer S, Rubin DS: High prevalence of low skeletal muscle mass associated with male gender in midlife and older HIV-infected persons despite CD4 cell reconstitution and viral suppression. J Int Assoc Provid AIDS Care 2014;13:145–152.
62. Hawkins KL, Brown TT, Margolick JB, Erlandson KM: Geriatric syndromes: New frontiers in HIV and sarcopenia. AIDS 2017;31(Suppl 2):S137–S146.
63. Echeverria P, Bonjoch A, Puig J, *et al.*: High prevalence of sarcopenia in HIV-infected individuals. Biomed Res Int 2018;2018:5074923.
64. Yarasheski KE, Scherzer R, Kotler DP, *et al.*: Age-related skeletal muscle decline is similar in HIV-infected and uninfected individuals. J Gerontol A Biol Sci Med Sci 2011;66:332–340.
65. Ortmeyer HK, Ryan AS, Hafer-Macko C, Oursler KK: Skeletal muscle cellular metabolism in older HIV-infected men. Physiol Rep 2016;4:e12794. DOI: 10.14814/phy2 .12794
66. Shankaran M, Czerwieniec G, Fessler C, *et al.*: Dilution of oral D_3-creatine to measure creatine pool size and estimate skeletal muscle mass: Development of a correction algorithm. J Cachexia Sarcopenia Muscle 2018; 9:540–546.
67. Branas F, Jimenez Z, Sanchez-Conde M, *et al.*: Frailty and physical function in older HIV-infected adults. Age Ageing 2017;46:522–526.
68. Rees HC, Meister E, Mohler MJ, Klotz SA: HIV-related frailty is not characterized by sarcopenia. J Int Assoc Provid AIDS Care 2016;15:131–134.
69. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories: ATS statement: Guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;166:111–117.
70. Simonsick EM, Montgomery PS, Newman AB, Bauer DC, Harris T: Measuring fitness in healthy older adults: The Health ABC Long Distance Corridor Walk. J Am Geriatr Soc 2001;49:1544–1548.
71. Rolland YM, Cesari M, Miller ME, Penninx BWJH, Atkinson H, Pahor M: Reliability of the 400-meter usual pace walk test as an assessment of mobility limitation in older adults. J Am Geriatr Soc 2004;52:972–976.
72. Guralnik JM, Branch LG, Cummings SR, Curb JD: Physical performance measures in aging research. J Gerontol 1989;44:M141–M146.
73. Fielding RA, Rejeski WJ, Blair SN, *et al.*: The Lifestyle Interventions and Independence for Elders (LIFE) Study: Design and methods. J Gerontol A Biol Sci Med Sci 2011; 66:1226–1237.
74. Cesari M, Kritchevsky SB, Newman AB, *et al.*: Added value of physical performance measures in predicting adverse health-related events: Results from the Health, Aging and Body Composition Study. J Am Geriatr Soc 2009;57:251–259.
75. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB: Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med 1995;332:556–561.
76. Kwon S, Perera S, Pahor M, *et al.*: What is a meaningful change in physical performance? findings from a clinical trial in older adults (the LIFE-P study). J Nutr Health Aging 2009;13:538–544.
77. Perera S, Mody SH, Woodman RC, Studenski SA: Meaningful change and responsiveness in common physical performance measures in older adults. J Am Geriatr Soc 2006;54:743–749.
78. Pahor M, Blair SN, Espeland M, *et al.*: Effects of a physical activity intervention on measures of physical performance: Results of the Lifestyle Interventions and Independence for Elders Pilot (LIFE-P) study. J Gerontol A Biol Sci Med Sci 2006;61:1157–1165.
79. Rosso AL, Sanders JL, Arnold AM, *et al.*: Multisystem physiologic impairments and changes in gait speed of older adults. J Gerontol A Biol Sci Med Sci 2015;70:319–324.
80. Guralnik JM, Simonsick EM, Ferrucci L, *et al.*: A short physical performance battery assessing lower extremity function: Association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol 1994;49:M85–M94.
81. Erlandson KM, Allshouse AA, Jankowski CM, *et al.*: Comparison of functional status instruments in HIV-infected adults on effective antiretroviral therapy. HIV Clin Trials 2012;13:324–334.
82. Desquilbet L, Jacobson LP, Fried LP, *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;62:1279–1286.
83. Ruggiero C, Metter EJ, Melenovsky V, *et al.*: High basal metabolic rate is a risk factor for mortality: The Baltimore Longitudinal Study of Aging. J Gerontol A Biol Sci Med Sci 2008;63:698–706.
84. Schrack JA, Knuth ND, Simonsick EM, Ferrucci L: ''IDEAL'' aging is associated with lower resting metabolic rate: The Baltimore Longitudinal Study of Aging. J Am Geriatr Soc 2014;62:667–672.
85. Schrack JA, Zipunnikov V, Goldsmith J, *et al.*: Assessing the ''physical cliff'': Detailed quantification of age-related differences in daily patterns of physical activity. J Gerontol A Biol Sci Med Sci 2014;69:973–979.

86. Schrack JA, Leroux A, Fleg JL, *et al.*: Using heart rate and accelerometry to define quantity and intensity of physical activity in older adults. J Gerontol A Biol Sci Med Sci 2018;73:668–675.
87. Schrack JA, Simonsick EM, Ferrucci L: The energetic pathway to mobility loss: An emerging new framework for longitudinal studies on aging. J Am Geriatr Soc 2010; 58(Suppl 2):S329–S336.
88. Schrack JA, Zipunnikov V, Simonsick EM, Studenski S, Ferrucci L: Rising energetic cost of walking predicts gait speed decline with aging. J Gerontol A Biol Sci Med Sci 2016;71:947–953.
89. Fried LP, Tangen CM, Walston J, *et al.*: Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001;56:M146–M156.
90. Jones DM, Song X, Rockwood K: Operationalizing a frailty index from a standardized comprehensive geriatric assessment. J Am Geriatr Soc 2004;52:1929–1933.
91. Piggott DA, Muzaale AD, Mehta SH, *et al.*: Frailty, HIV infection, and mortality in an aging cohort of injection drug users. PLoS One 2013;8:e54910.
92. Greene M, Covinsky K, Astemborski J, *et al.*: The relationship of physical performance with HIV disease and mortality. AIDS 2014;28:2711–2719.
93. O'Brien KK, Tynan AM, Nixon SA, Glazier RH: Effectiveness of Progressive Resistive Exercise (PRE) in the context of HIV: Systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis 2017;17:268.
94. O'Brien KK, Tynan AM, Nixon SA, Glazier RH: Effectiveness of aerobic exercise for adults living with HIV: Systematic review and meta-analysis using the Cochrane Collaboration protocol. BMC Infect Dis 2016; 16:182.
95. Souza PM, Jacob-Filho W, Santarem JM, Zomignan AA, Burattini MN: Effect of progressive resistance exercise on strength evolution of elderly patients living with HIV compared to healthy controls. Clinics (Sao Paulo) 2011; 66:261–266.
96. Souza PM, Jacob-Filho W, Santarem JM, Silva AR, Li HY, Burattini MN: Progressive resistance training in elderly HIV-positive patients: Does it work? Clinics (Sao Paulo) 2008;63:619–624.
97. Zanetti HR, Cruz LG, Lourenco CL, Neves Fde F, Silva-Vergara ML, Mendes EL: Non-linear resistance training reduces inflammatory biomarkers in persons living with HIV: A randomized controlled trial. Eur J Sport Sci 2016; 16:1232–1239.
98. Hand GA, Phillips KD, Dudgeon WD, William Lyerly G, Larry Durstine J, Burgess SE: Moderate intensity exercise training reverses functional aerobic impairment in HIV-infected individuals. AIDS Care 2008;20:1066–1074.
99. Ogalha C, Luz E, Sampaio E, *et al.*: A randomized, clinical trial to evaluate the impact of regular physical activity on the quality of life, body morphology and metabolic parameters of patients with AIDS in Salvador, Brazil. J Acquir Immune Defic Syndr 2011;57(Suppl 3):S179–S185.
100. Walston J, Buta B, Xue QL: Frailty screening and interventions: considerations for clinical practice. Clin Geriatr Med 2018;34:25–38.
101. Justice JN, Nambiar AM, Tchkonia T, *et al.*: Senolytics in idiopathic pulmonary fibrosis: Results from a first-in-human, open-label, pilot study. EBioMedicine 2019;40: 554–563.
102. Kantor ED, Rehm CD, Haas JS, Chan AT, Giovannucci EL: Trends in prescription drug use among adults in the United States from 1999–2012. JAMA 2015;314:1818–1831.
103. Tseng A, Szadkowski L, Walmsley S, Salit I, Raboud J: Association of age with polypharmacy and risk of drug interactions with antiretroviral medications in HIV-positive patients. Ann Pharmacother 2013;47:1429–1439.
104. Schottker B, Saum KU, Muhlack DC, Hoppe LK, Holleczek B, Brenner H: Polypharmacy and mortality: New insights from a large cohort of older adults by detection of effect modification by multi-morbidity and comprehensive correction of confounding by indication. Eur J Clin Pharmacol 2017;73:1041–1048.
105. Tate JP, Sterne JAC, Justice AC: Albumin, white blood cell count, and body mass index improve discrimination of mortality in HIV-positive individuals. [Miscellaneous Article] Source: AIDS 2019;33:903-912. DOI: 10.1097/QAD.0000000000002140
106. Lexell J, Taylor CC: Variability in muscle fibre areas in whole human quadriceps muscle: Effects of increasing age. J Anat 1991;174:239–249.
107. Cristea A, Qaisar R, Edlund PK, Lindblad J, Bengtsson E, Larsson L: Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells. Aging Cell 2010;9:685–697.
108. Crepaz N, Dong X, Wang X, Hernandez AL, Hall HI: Racial and ethnic disparities in sustained viral suppression and transmission risk potential among persons receiving HIV Care—United States, 2014. MMWR Morb Mortal Wkly Rep 2018;67:113–118.
109. Chinn JJ, Hummer RA: Racial disparities in functional limitations among Hispanic women in the United States. Res Aging 2016;38:399–423.
110. Thorpe RJ, Jr., Koster A, Kritchevsky SB, *et al.*: Race, socioeconomic resources, and late-life mobility and decline: Findings from the Health, Aging, and Body Composition study. J Gerontol A Biol Sci Med Sci 2011;66: 1114–1123.
111. Lichtenstein B, Laska MK, Clair JM: Chronic sorrow in the HIV-positive patient: Issues of race, gender, and social support. AIDS Patient Care STDS 2002;16:27–38.
112. Shacham E, Rosenburg N, Onen NF, Donovan MF, Overton ET: Persistent HIV-related stigma among an outpatient US clinic population. Int J STD AIDS 2015;26: 243–250.
113. Murphy K, Hoover DR, Shi Q, *et al.*: Association of self-reported race with AIDS death in continuous HAART users in a cohort of HIV-infected women in the United States. AIDS 2013;27:2413–2423.
114. Hogg RS, Eyawo O, Collins AB, *et al.*: Health-adjusted life expectancy in HIV-positive and HIV-negative men and women in British Columbia, Canada: A population-based observational cohort study. Lancet HIV 2017;4: e270–e276.
115. French AL, Gawel SH, Hershow R, *et al.*: Trends in mortality and causes of death among women with HIV in the United States: A 10-year study. J Acquir Immune Defic Syndr 2009;51:399–406.

116. Antiretroviral Therapy Cohort C: Causes of death in HIV-1-infected patients treated with antiretroviral therapy, 1996–2006: Collaborative analysis of 13 HIV cohort studies. Clin Infect Dis 2010;50:1387–1396.
117. Horberg M, Hurley L, Klein D, *et al.*: The HIV care cascade measured over multiple time periods varies by age and gender. ID Week, Philadelphia, PA, October 8–12, 2014.
118. Tuchman E: Women and addiction: The importance of gender issues in substance abuse research. J Addict Dis 2010;29:127–138.
119. Justice AC, McGinnis KA, Tate JP, *et al.*: Risk of mortality and physiologic injury evident with lower alcohol exposure among HIV infected compared with uninfected men. Drug Alcohol Depend 2016;161:95–103.
120. Salter ML, Lau B, Go VF, Mehta SH, Kirk GD: HIV infection, immune suppression, and uncontrolled viremia are associated with increased multimorbidity among aging injection drug users. Clin Infect Dis 2011;53:1256–1264.

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