The Demographic Shift in HIV: The Aging HIV Patient

Although there is substantial enthusiasm for the development of HIV vaccines,[1,2] a remaining challenge is the treatment of people who are infected and under the care of a clinician. The introduction of effective combination antiretroviral therapy (cART) dramatically increased life expectancy in people aging with HIV (PAWH).[3] In developed countries, a growing percentage of PAWH are soon to be older than 50 years, due to a longer life expectancy and to acquiring HIV infection later in life.

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As the HIV-infected population ages, there is an increased risk for noncommunicable diseases (NCDs) that persist as chronic conditions affecting a patient's health and life. Multiple comorbidities affecting multiple organ systems have been identified in PAWH, increasing the risk for cardiovascular disease (CVD), bone loss, renal and liver dysfunction, various cancers, and geriatric syndromes that include cognitive and functional impairment. These comorbidities impinge on the quality of life and longevity of PAWH, and will require additional medical care that will significantly burden health care resources.[4]

Despite effective cART in those for whom treatment is available, inflammation and immune activation remain elevated compared with their uninfected counterparts.[5,6] Many of the NCDs that occur in HIV-infected people arise prematurely, prompting the characterization of chronic HIV infection in the modern era as a "premature" or "accelerated aging" condition.

To effectively care for PAWH, there is a critical need to address bidirectional effects of HIV and aging to better understand how aging with HIV differs from aging in the uninfected, as well as to develop effective and targeted interventions improving the health span of PAWH.

This review is directed toward the infectious diseases community, including physicians and practitioners caring for patients with HIV, and researchers engaged in HIV clinical research. We discuss features of aging with and without HIV infection, including epidemiology, comorbid conditions, and geriatric syndromes (eg, the decline in cognitive and physical function), as well as "inflammaging," a term coined to describe chronic, low-level inflammation among all aged populations, not just those with HIV.

Epidemiology

According to CDC estimates,[7] the age distribution of PAWH in the United States is shifting toward older individuals who are predominantly ethnic and racial minorities and more often men. In 2016, the number of PAWH older than 55 years of age rose 80%, whereas the total number of PAWH older than 13 years of age rose only 15%, indicating a dramatic shift in the age distribution of the epidemic. The epidemic also disproportionately affects nonwhite races and ethnicities. Among those PAWH older than 55 years of age in the United States, the prevalence in blacks (1,270 per 100,000) is nearly 8-fold higher than in whites (159 per 100,000) and nearly 4-fold higher in Hispanics (647 per 100,000) than whites. Also, in 2016, men accounted for most infections (77%) among those older than 55 years of age.

Multimorbidity

As PAWH age, their risk for comorbidities increases, partly due to age-associated risk factors, risk associated with HIV infection, and potential complications due to ART. The onset of comorbidities is often earlier than in those without HIV infection, increasing the lifetime of medical care and shifting comorbid treatment approaches to a younger demographic.[8] Most of these comorbidities—CVD, bone abnormalities, liver, renal, and neurocognitive—are exacerbated by persistent inflammation and immune activation. Furthermore, alteration of the intestinal epithelium, due to incomplete restoration of mucosal immunity, can lead to a "leaky gut" with translocation of bacterial products into the bloodstream that potentially drive chronic immune activation and inflammation.[9] Alterations of the gut microbiome occur with aging independently but also with HIV infection. Of note, some studies suggest a link between changes in the microbiome, inflammation, and comorbidities with evidence for microbiome restoration with treatment.[10-12]

Cardiovascular Disease

Multiple studies indicate that PAWH are at higher risk for complications related to cardiovascular health. For example, the risk for acute myocardial infarction was estimated to increase 1.5 times in HIV-positive individuals in the Veterans Aging Cohort Study.[13] Traditional cardiovascular risk factors—smoking, low activity level, dyslipidemia, hypertension, and diabetes—are more prevalent, and their onset is earlier in the HIV-infected population.[14] Cardiovascular risk persists despite effective ART and is often linked to chronic immune activation and inflammation.[9]

In 2016, the number of people with HIV older than 55, rose by **80%**, compared with just **15%** for those older than 13.

Of those over 55, the prevalence in blacks was **8-times higher,** and Hispanics **4-times higher** than whites.

In addition, men accounted for **77%** of people with HIV over 55.

Source: CDC

Bone Abnormalities

Reduced bone quality is becoming increasingly important in PAWH.[15] Risk for bone fracture in PAWH is estimated to be nearly 3 times more likely when compared with the uninfected. These events likely are related to altered bone morphology, decreased bone mineral density (BMD), and consequent osteopenia and osteoporosis. There are many risk modifiers for bone loss and reduced BMD in HIV infection, including smoking and alcohol abuse, low body weight, menopause, vitamin D deficiency, direct effects of ART, and persistent immune activation and inflammation. Whether bone loss with ART is related to immune reconstitution, which can drive bone resorption,[16] remains unclear. Some regimens appear to have direct effects on bone quality (eg, tenofovir disoproxil fumarate [TDF]-containing regimens). For example, the NEAT001/ANRS143 trial showed a greater loss in BMD in those patients who started a nucleoside reverse transcriptase inhibitor (NRTI)-sparing regimen (darunavir-ritonavir [DRV/r] plus raltegravir) compared with those taking DRV/r plus tenofovir-emtricitabine after 48 weeks of therapy.[17]

Renal and Liver Disease

Kidney disease in PAWH is a common condition (prevalence of 3.5%-9.7% for renal disease stage ≥3) and may be linked to HIV infection itself, systemic immune activation, hepatitis coinfection, and ART regimen (eg, TDF).[18] Also, non-alcoholic fatty liver disease (NAFLD) is a common comorbidity in HIV-infected people (13%-55% among ART-treated patients) that is likely related to the aging process and metabolic dysregulation by HIV-associated chronic inflammation and immune activation. This condition needs specific therapeutic approaches, as 10% to 15% of NAFLD progresses to non-alcoholic steatohepatitis and liver cirrhosis. Furthermore, HIV-infected patients have a higher prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) coinfections (5% and 30%, respectively) that tend to progress to cirrhosis more often and more rapidly over time.[19]

Malignancies

Although Kaposi sarcoma (KS) and non-Hodgkin lymphoma (n-HL) have dramatically decreased with effective ART, the burden of all cancers continues to increase, partly due to the longer life expectancy in PAWH, with AIDS-defining cancers (eg, KS, n-HL, cervical cancer) remaining stable in the last 2 decades and non–AIDS-defining cancers (eg, lung, anal, liver) increasing remarkably. Several malignancies in HIV-positive individuals are virus-related cancers: KS (human herpesvirus 8), anal, penile, gynecologic, and oral cancers (HPV); and liver cancer (HBV, HCV).[20]

Neurocognitive Decline

The prevalence and severity of HIV-associated cognitive impairment are likely to increase as the HIV-infected population ages.[21,22] Estimates indicate that nearly 50% of all HIV-positive patients have some level of cognitive impairment (mild,

moderate, or severe). In one study, HIV-associated dementia in older adults with HIV was 3 times more likely than in younger adults.[23] Age as well as stroke and cerebrovascular diseases—whose incidence is increasing—represent major risk factors for neurocognitive decline. HIV can enter the brain and infect astrocytes and microglial cells, contributing to neuroinflammation. Viral replication in the brain may persist despite viral suppression in peripheral blood, leading to progressive neuronal damage. The combined effect of HIV infection, neuroinflammation, and aging might accelerate neurodegenerative syndromes,[9] although there is evidence that some neurocognitive functions tend to improve after ART initiation.[24]

Functional Decline

Frailty has been defined as a clinical state of increased vulnerability to stressors resulting from aging-related decline in reserve and function. A frailty-related phenotype has been operationalized in the HIV population and is characterized by low grip strength, low energy, slowed walking speed, low physical activity, and/or unintentional weight loss. Frailty is more common in HIV-positive individuals compared with uninfected adults older than 50 years of age. The level of frailty has been associated with increased inflammatory markers and immune activation.[25] Functional decline in HIV-positive individuals is associated with early mortality.[26,27] The mechanisms by which HIV induces premature functional aging, and how this differs from aging in the uninfected, remain largely unknown.[28] Skeletal muscle aging in HIV infection compared with the uninfected indicates a steeper

decline in mitochondrial function[29,30] and increases in skeletal muscle central nuclei,[31-33] as well as pathways related to senescence (eg, p21/Cip1, p16INK4a,[34,35] transforming growth factor-beta[34,35]) and inflammation.[36] Although aging in the uninfected is associated with declines in the proportion of fast-twitch glycolytic muscle fibers to slow-twitch oxidative muscle fibers and increased variability in muscle fiber size,[37,38] these features are not apparent in middle-aged PAWH.[31] Thus, some but not all features of classic aging are observed prematurely with HIV infection, at least in the few studies where data are available. Multiple studies demonstrate that normal muscle maintenance relies on cross talk with multiple leukocytes, including monocytes,[39] B cells,[40] CD8 T cells,[41] and regulatory T cells[42] (for review see Tidball[43]). For example, muscle regeneration is linked temporally to polarization of macrophages that transition from a pro-inflammatory bias (ie, M1) to an anti-inflammatory bias (ie, M2) during myogenesis.[39] A key gap in knowledge is a better understanding of this cross talk and how HIV may dysregulate coordinated immune-muscle homeostatic mechanisms.

Inflammaging

Aging in the absence of infection is accompanied by a chronic low-grade inflammation that has been termed inflammaging.[44] With inflammaging, there is a progressive increase in blood concentrations of several inflammatory biomarkers (eg, C-reactive protein [CRP], tumor necrosis factor [TNF], interleukin-6 [IL-6]) that can occur in the absence of overt infection.[44] We and others have shown that biomarkers for inflammation are upregulated

Table. Comorbidities in People Aging With HIV

Comorbid Condition	Screening Methods	Recommendations	Antiretroviral Drugs With Additional Risks
Cardiovascular diseases[13,59]	Risk calculation scores (eg, Framingham, ASCVD); dyslipidemia screening	Stop smoking; aerobic exercise; treatment of risk factors (dyslipidemia, diabetes, hypertension)	ABC, LPV/r, DRV/r
Bone abnormalities[60]	Fracture risk calculation (FRAX score); DXA	Exercise; vitamin D and calcium supplementation	TDF
Kidney diseases[61]	eGFR; urinary albumin/protein ratio	Cardiovascular risk prevention; HCV coinfection treatment	TDF
Liver diseases[62]	US; US elastography; HBV and HCV screening	Treatment of HBV and HCV; HBV vaccination; lifestyle intervention	First-generation NRTI and NNRTI
Neurocognitive and psychiatric disorders[63]	Neurocognitive evaluation; Patient Health Questionnaire-9 for generalized anxiety disorder	Antiretroviral drugs with high CNS penetration effectiveness score; treatment of depression or anxiety	EFV, DTG[a]
Malignancies[64]	Oncology screening tests (cervical and anal PAP test)	ART continuation during antineoplastic treatment	-
Frailty[65]	Physical functioning test	Exercise; treatment of HIV	-

[a] Due to their high CNS penetration, these drugs can lead to CNS adverse effects.

ABC, abacavir; **ART,** antiretroviral therapy; **ASCVD,** atherosclerotic cardiovascular disease; **CNS,** central nervous system; **DRV/r,** darunavir-ritonavir; **DTG,** dolutegravir; **DXA,** dual-energy x-ray absorptiometry; **EFV,** efavirenz; **eGFR,** estimated glomerular filtration rate; **FRAX,** Fracture Risk Assessment Tool; **HBV,** hepatitis B virus; **HCV,** hepatitis C virus; **LPV/r,** lopinavir-ritonavir; **NNRTI,** non-nucleoside reverse transcriptase inhibitor; **NRTI,** nucleoside reverse transcriptase inhibitor; **TDF,** tenofovir disoproxil fumarate; **US,** ultrasound

with aging.[46-49] Drivers of chronic low-grade inflammation may include dysfunctional mitochondria, leading to excess oxidative stress, endotoxemia due to loss of integrity of intestinal mucosa, gut microbiome dysregulation, and an increase in the senescence-associated secretory phenotype in PAWH. When compared with the uninfected, and despite effective ART, HIV infection is associated with comparative increases in circulating IL-6, TNF, sCD14, sCD163, CRP, and monocyte chemoattractant protein-1.[28,31,49-53] Also shared are declines in the ratio of naive-to-memory CD4 and CD8 T cells, as well as increases in senescent CD28-negative and CD57-positive T cells[28,54] and decreases in telomere length.[55,56] However, compared with aging in the uninfected, HIV is associated with increases in both CD38-positive and human leukocyte antigen-DR+ (HLA-DR+) T cells, whereas only HLA-DR appears to increase with age in the uninfected.[57,58]

The Table on page 79 shows comorbid conditions, screening, recommendations, and potential drug contraindications.[59-67]

Treatment-Related Complications

Treatment algorithms that consider age are of increasing importance. With aging there are often attenuated immune recovery and response to immunotherapies,[66] as well as a greater risk for serious non–AIDS-related complications. Even in the uninfected, aging of the immune system is a major risk factor for increased morbidity and mortality.[67,68] No preferred regimens are as yet recommended for older individuals per se, but their parameters should be carefully evaluated: For example, NRTI dosage adjustments are required with renal disfunction.[69]

Aging is associated with pharmacokinetic-relevant physiologic variations (eg, gastric changes, volume of distribution alterations, and liver function deterioration) that might influence the pharmacokinetics and pharmacodynamics of antiretroviral drugs.[70] Retrospective studies did not demonstrate major pharmacokinetic changes in adults aged between 20 and 60 years, but a few studies have been conducted in adults older than 60 years of age. While a promising new therapy, the effective concentration of dolutegravir has been shown to be significantly higher in patients older than 60 years of age compared with younger adults,[71] as a possible expression of difference in absorption and a reasonable cause of more common side effects (eg, insomnia), which often lead to discontinuation in those older than 60 years of age.[72] Conversely, no changes in raltegravir exposure were found in PAWH older than 60 years of age.[73] Complications from ART regimens include TDF-related bone and kidney toxicity,[74] cardiovascular effects from protease inhibitor (PI)-based regimens (for induced dyslipidemia) and abacavir (platelet activation has been hypothesized), and metabolic and liver effects (early NRTIs and nonnucleoside reverse transcriptase inhibitors). These complications are more common in the elderly; thus, drug safety and accuracy should be monitored.

Polypharmacy is common in older patients with HIV[72]; therefore, there is a greater risk for drug–drug interactions (DDIs) between antiretroviral drugs and concomitant medications that should be considered.

The potential for DDIs should be evaluated regularly, especially when starting or switching ART and concomitant medications. Statins are largely used in aging PAWH, as dyslipidemia is an emergent issue that affects cardiovascular risk and may have major interactions with PIs. The ongoing REPRIEVE trial is now assessing the effect of a newer statin (pitavastatin) that is free from DDIs on HIV-positive individuals without known CVD over time.[75] With the advent of the new direct-acting antivirals, HCV is now curable in more than 90% of adults, despite age and HIV status. However, interactions with ART have to be considered before starting anti-HCV treatment.[76] Furthermore, zidovudine and the PI boosters ritonavir and cobicistat should be avoided during cancer chemotherapy for DDI-associated risks. Fixed-dose combinations for the treatment of HIV (mainly once daily) are recognized to improve adherence and may be preferable in the elderly with comorbidities and polypharmacy.

Biomarkers and Clinical Indexes

Biomarker development to distinguish aging versus aging with HIV infection is needed and will be critical for efforts to assign risk of geriatric health outcomes in PAWH. Multiple biomarkers have been identified that are associated with aging in the absence of HIV infection.[49] However, because biomarker expression levels are often interrelated, they can be affected by population composition and cohort-specific variables.[75] HIV infection modifies expression of multiple aging-associated biomarkers,[28,31,49,51-53] so the challenge will be to translate from expression into risk groups for geriatric outcomes to risk profiles for individuals, in the context of aging with HIV infection. Composite biomarker panels (eg, the Veterans Aging Cohort Study Index and Frailty Index) are in use in PAWH.[78-81] The current challenge is how to implement these biomarker panels at the individual patient level, and how best to monitor directional changes associated with adverse health outcomes in populations.

Screening and Management

Current management of elderly people with HIV mirrors the approaches in the management of those without HIV: evaluation of the risk for and early diagnosis of comorbidities (eg, CVD, bone abnormalities, and cognitive decline), managing polypharmacy and DDIs, and consideration of social issues (eg, isolation).[14] However, the risk for comorbidities and severity in individuals with HIV is higher than in those without infection. Therefore, attention to life history of the patient and screening approaches (by means of calculated index scores, questionnaires,

and biomarker and diagnostic tests) as well as treatment and prevention strategies is recommended for PAWH (Table).

Individuals who are older when diagnosed with HIV more often present with concurrent AIDS than people diagnosed at earlier ages,[82] underscoring the need for HIV testing in older

Figure. Conceptual model of aging with HIV infection.

HIV, structural determinants (eg, societal, social inequities), and biobehavioral factors interact to drive progression of comorbid conditions and are exacerbated by antiretroviral and comorbid drug treatment effects as well as age- and HIV-associated inflammation and immune activation. The collective burden of these subclinical conditions over time reduces physiologic reserve and resilience, leading to impairment in physical and cognitive function, ultimately reducing QOL and the health span.

NCDs, noncommunicable diseases; **QOL,** quality of life

adults in primary care settings: Data from the CDC indicate that in 2016, 17% of newly diagnosed patients were older than 50 years of age. Social determinants for infections later in life include general lack of understanding and recognition of HIV in older adults by the health care system, as well as by the older group of people at risk for HIV infection itself.

Indeed, health care professionals are less likely to suspect a diagnosis of HIV and AIDS in symptomatic and asymptomatic older men and women than in younger people. However, older people do not recognize the risk for HIV to themselves mostly because of the stigma associated with HIV that has been ascribed only to certain social subgroups of the population, namely, gay men and injection drug users, by an inaccurate social view.[83]

Self-efficacy refers to people's confidence in their capacity to perform a specific task.[84] Targeting self-efficacy in the HIV-positive population to promote healthy behavior has been explored.[85] Establishing whether self-efficacy influences or is associated with health span in PAWH may provide a potential avenue for targeted behavioral intervention.

Although the CDC recommends screening for HIV in all health care settings for individuals aged 13 to 64 years,[86] studies demonstrate a low proportion (3%-4%) of HIV testers among people over 50 years of age.[87,88]

Late presentation (ie, CD4 count <350 cells/mcL or AIDS at HIV diagnosis) is disproportionately more common in older people. Furthermore, late diagnosis is associated with a rapid progression of the disease and complicates the management of HIV infection and comorbid conditions.[87]

Concluding Remarks

Although under effective cART, PAWH experience a different aging progression when compared with uninfected individuals (Figure). A deeper insight into the interplay between HIV, the development and presentation of comorbidities, and the aging process will be necessary to optimize quality of life and health span in PAWH. Given the premature onset of geriatric syndromes, new diagnostic and therapeutic algorithms will be important for presymptomatic diagnosis and the implementation of prevention strategies. Patient engagement will be critical for effective care and should include assessment of structural determinants, including access to educational resources about aging-related risks and screening tests and a solid relationship between patients and their physicians. As increased awareness of HIV risk in the elderly grows, as well as the rollout of educational programs targeting people over 50 years of age, the hope is that new infections can be prevented or discovered early in the course of infection and before advanced disease onset.
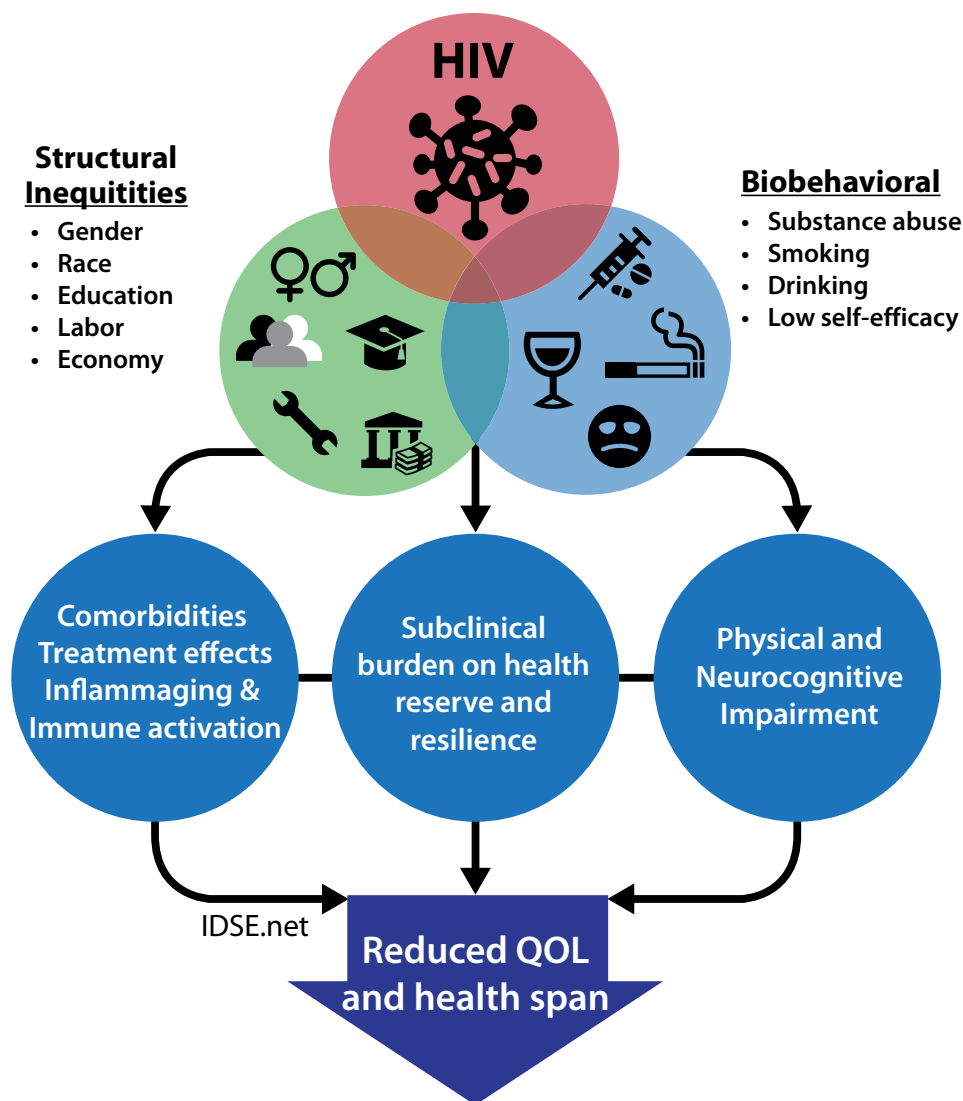
References

1. Barouch DH, Tomaka FL, Wegmann F, et al. Evaluation of a mosaic HIV-1 vaccine in a multicentre, randomised, double-blind, placebo-controlled, phase 1/2a clinical trial (APPROACH) and in rhesus monkeys (NHP 13-19). *Lancet*. 2018;392(10143):232-243.

2. Pavlakis GN, Felber BK. A new step towards an HIV/AIDS vaccine. *Lancet*. 2018;392(10143):192-194.

3. Wada N, Jacobson LP, Cohen M, et al. Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984-2008. *Am J Epidemiol*. 2013;177(2):116-125.

4. Mills EJ, Barnighausen T, Negin J. HIV and aging—preparing for the challenges ahead. *N Engl J Med.* 2012;366(14):1270-1273.

5. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*. 2013;39(4):633-645.

6. Nixon DE, Landay AL. Biomarkers of immune dysfunction in HIV. *Curr Opin HIV AIDS*. 2010;5(6):498-503.

7. CDC. NCHHSTP AtlasPlus. www.cdc.gov/nchhstp/atlas/index.htm. Updated 2017. Accessed August 8, 2018.

8. 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(11):1120-1126.

9. Nasi M, De Biasi S, Gibellini L, et al. Ageing and inflammation in patients with HIV infection. *Clin Exp Immunol*. 2017;187(1):44-52.

10. Desai SN, Landay AL. HIV and aging: role of the microbiome. *Curr Opin HIV AIDS*. 2018;13(1):22-27.

11. Presti RM, Handley SA, Droit L, et al. Alterations in the oral microbiome in HIV-infected participants after antiretroviral therapy administration are influenced by immune status. *AIDS*. 2018;32(10):1279-1287.

12. Villanueva-Millan MJ, Pérez-Matute P, Recio-Fernández E, et al. Differential effects of antiretrovirals on microbial translocation and gut microbiota composition of HIV-infected patients. *J Int AIDS Soc*. 2017;20(1):21526.

13. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med*. 2013;173(8):614-622.

14. Wing EJ. HIV and aging. *Int J Infect Dis*. 2016;53:61-68.

15. Hileman CO, Eckard AR, McComsey GA. Bone loss in HIV: a contemporary review. *Curr Opin Endocrinol Diabetes Obes*. 2015;22(6):446-451.

16. Ofotokun I, Titanji K, Vunnava A, et al. Antiretroviral therapy induces a rapid increase in bone resorption that is positively associated with the magnitude of immune reconstitution in HIV infection. *AIDS*. 2016;30(3):405-414.

17. Bernardino JI, Mocroft A, Mallon PW, et al. Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001/ANRS143 randomised trial. *Lancet HIV*. 2015;2(11):e464-e473.

18. Abraham AG, Althoff KN, Jing Y, et al. End-stage renal disease among HIV-infected adults in North America. *Clin Infect Dis*. 2015;60(6):941-949.

19. Guaraldi G, Lonardo A, Maia L, et al. Metabolic concerns in aging HIV-infected persons: from serume lipid phenotype to fatty liver. *AIDS.* 2017;31 suppl 2:S147-S156.

20. Yarchoan R, Uldrick TS. HIV-associated cancers and related diseases. *N Engl J Med*. 2018;378(22):2145.

21. Bonnet F, Amieva H, Marquant F, et al. Cognitive disorders in HIV-infected patients: are they HIV-related? *AIDS*. 2013;27(3):391-400.

22. Heaton RK, Clifford DB, Franklin DR Jr, et al. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER study. *Neurology*. 2010;75(23):2087-2096.

23. Valcour V, Shikuma C, Shiramizu B, et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. *Neurology*. 2004;63(5):822-827.

24. Engel T, Raffenberg M, Marzolin C, et al. HIV and aging - perhaps not as dramatic as we feared? *Gerontology*. 2018:1-11. doi: 10.1159/000489172

25. Erlandson KM, Ng DK, Jacobson LP, 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):228-237.

26. Erlandson KM, Allshouse AA, Jankowski CM, et al. Risk factors for falls in HIV-infected persons. *J Acquir Immune Defic Syndr*. 2012;61(4):484-489.

27. Greene M, Covinsky K, Astemborski J, et al. The relationship of physical performance with HIV disease and mortality. *AIDS*. 2014;28(18):2711-2719.

28. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med*. 2011;62:141-155.

29. Payne BA, Wilson IJ, Hateley CA, et al. Mitochondrial aging is accelerated by anti-retroviral therapy through the clonal expansion of mtDNA mutations. *Nat Genet*. 2011;43(8):806-810.

30. Camacho-Pereira J, Tarrago MG, Chini CCS, et al. CD38 dictates age-related NAD decline and mitochondrial dysfunction through an SIRT3-dependent mechanism. *Cell Metab*. 2016;23(6):1127-1139.

31. 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(12):1918-1927.

32. Cristea A, Qaisar R, Edlund PK, et al. Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells. *Aging Cell*. 2010;9(5):685-697.

33. Valdez G, Tapia JC, Kang H, et al. Attenuation of age-related changes in mouse neuromuscular synapses by caloric restriction and exercise. *Proc Natl Acad Sci U S A*. 2010;107(33):14863-14868.

34. Carlson ME, Suetta C, Conboy MJ, et al. Molecular aging and rejuvenation of human muscle stem cells. *EMBO Mol Med*. 2009;1(8-9):381-391.

35. Kusko RL, Banerjee C, Long KK, et al. Premature expression of a muscle fibrosis axis in chronic HIV infection. *Skelet Muscle*. 2012;2(1):10.

36. Oh J, Sinha I, Tan KY, et al. Age-associated NF-kappaB signaling in myofibers alters the satellite cell niche and re-strains muscle stem cell function. *Aging (Albany NY)*. 2016;8(11):2871-2896.

37. Evans WJ, Lexell J. Human aging, muscle mass, and fiber type composition. *J Gerontol A Biol Sci Med Sci.* 1995;50(Spec No.):11-16.

38. Lexell J, Taylor CC. Variability in muscle fibre areas in whole human quadriceps muscle: effects of increasing age. *J Anat*. 1991;174:239-249.

39. Saclier M, Yacoub-Youssef H, Mackey AL, et al. Differentially activated macrophages orchestrate myogenic precursor cell fate during human skeletal muscle regeneration. *Stem Cells*. 2013;31(2):384-396.

40. Long KK, Pavlath GK, Montano M. Sca-1 influences the innate immune response during skeletal muscle regeneration. *Am J Physiol Cell Physiol*. 2011;300(2):C287-C294.

41. Zhang J, Xiao Z, Qu C, et al. CD8 T cells are involved in skeletal muscle regeneration through facilitating MCP-1 secretion and Gr1(high) macrophage infiltration. *J Immunol*. 2014;193(10):5149-5160.

42. Burzyn D, Kuswanto W, Kolodin D, et al. A special population of regulatory T cells potentiates muscle repair. *Cell*. 2013;155(6):1282-1295.

43. Tidball JG. Regulation of muscle growth and regeneration by the immune system. *Nat Rev Immunol*. 2017;17(3):165-178.

44. Franceschi C, Capri M, Monti D, et al. Inflammaging and anti-inflammaging: a systemic perspective on aging and longevity emerged from studies in humans. *Mech Ageing Dev*. 2007;128(1):92-105.

45. 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-S9.

46. Howcroft TK, Campisi J, Louis GB, et al. The role of inflammation in age-related disease. *Aging (Albany NY)*. 2013;5(1):84-93.

47. Peters MJ, Joehanes R, Pilling lC, et al. The transcriptional landscape of age in human peripheral blood. *Nat Commun*. 2015;6:8570.

48. Pilling LC, Joehanes R, Melzer D, et al. Gene expression markers of age-related inflammation in two human cohorts. *Exp Gerontol*. 2015;70:37-45.

49. 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(11):e189-e194.

50. Margolick JB, Bream JH, Martinez-Mazo O, 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):407-417.

51. Martin GE, Gouillou M, Hearps AC, et al. Age-associated changes in monocyte and innate immune activation markers occur more rapidly in HIV infected women. *PLoS One*. 2013;8(1):e55279.

52. Sandmand M, Bruunsgaard H, Kemp K, et al. High circulating levels of tumor necrosis factor-alpha in centenarians are not associated with increased production in T lymphocytes. *Gerontology*. 2003;49(3):155-160.

53. Seidler S, Zimmermann HW, Bartneck M, et al. Age-dependent alterations of monocyte subsets and monocyte-related chemokine pathways in healthy adults. *BMC Immunol*. 2010;11:30.

54. Duggal NA, Pollock RD, Lazarus NR, et al. Major features of immunesenescence, including reduced thymic output, are ameliorated by high levels of physical activity in adulthood. *Aging Cell*. 2018;17(2). doi: 10.1111/acel.12750

55. Rizvi S, Raza ST, Mahdi F. Telomere length variations in aging and age-related diseases. *Curr Aging Sci.* 2014;7(3):161-167.

56. Srinivasa S, Fitch KV, Petrow E, et al. Soluble CD163 is associated with shortened telomere length in HIV-infected patients. *J Acquir Immune Defic Syndr*. 2014;67(4):414-418.

57. 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(20). pii: 95726. doi: 10.1172/jci.insight.95726

58. Qin L, Jing X, Qiu Z, et al. Aging of immune system: immune signature from peripheral blood lymphocyte subsets in 1068 healthy adults. *Aging (Albany NY)*. 2016;8(5):848-859.

59. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. *J Infect Dis*. 2010;201(3):318-330.

60. McGinty T, Mallon P. Protecting bone in long-term HIV positive patients receiving antiretrovirals. *Expert Rev Anti Infect Ther*. 2016;14(6):587-599.

61. Naicker S, Rahmanian S, Kopp JB. HIV and chronic kidney disease. *Clin Nephrol*. 2015;83(7 suppl 1):32-38.

62. Department of Health and Human Services. Guidelines for the use of antiretroviral agents in adults and adolescent living with HIV. www.aidsinfo.nih.gov/guidelines. Accessed August 7, 2018.

63. Letendre S. Central nervous system complications in HIV disease: HIV-associated neurocognitive disorder. Topics in antiviral medicine. *Top Antivir Med*. 2011;19(4):137-142.

64. Silverberg MJ, Chao C, Leyden WA, et al. HIV infection and the risk of cancers with and without a known infectious cause. *AIDS*. 2009;23(17):2337-2345.

65. Greene M, Justice AC, Covinsky KE. Assessment of geriatric syndromes and physical function in people living with HIV. *Virulence*. 2017;8(5):586-598.

66. Collaboration of Observational HIV Epidemiology Research Europe (COHERE) Study Group, Sabin CA, Smith CJ, et al. Response to combination antiretroviral therapy: variation by age. *AIDS*. 2008;22(12):1463-1473.

67. Haynes L, Swain SL. Aged-related shifts in T cell homeostasis lead to intrinsic T cell defects. *Semin Immunol*. 2012;24(5):350-355.

68. Nikolich-Zugich J, Li G, Uhrlaub JL, et al. Age-related changes in CD8 T cell homeostasis and immunity to infection. *Semin Immunol*. 2012;24(5):356-364.

69. Soriano V. Update of the DHHS antiretroviral treatment guidelines. *AIDS Rev*. 2014;16(2):117-118.

70. Schoen JC, Erlandson KM, Anderson PL. Clinical pharmacokinetics of antiretroviral drugs in older persons. *Expert Opin Drug Metab Toxicol*. 2013;9(5):573-588.

71. Elliot ER, Wang X, Singh S, et al. Increased dolutegravir peak concentrations in people living with HIV aged 60 and over and analysis of sleep quality and cognition. *Clin Infect Dis*. [Epub May 16, 2018]. doi: 10.1093/cid/ciy426

72. Scott IA, Hilmer SN, Reeve E, et al. Reducing inappropriate polypharmacy: the process of deprescribing. *JAMA Intern Med*. 2015;175(5):827-834.

73. Vera JH, Jackson A, Dickenson L, et al. The pharmacokinetic profile of raltegravir-containing antiretroviral therapy in HIV-infected individuals over 60 years of age. *HIV Clin Trials*. 2015;16(1):39-42.

74. Okonkwo RI, Weidmann AE, Effa EE. Renal and bone adverse effects of a tenofovir-based regimen in the treatment of HIV-infected children: a systematic review. *Drug Saf*. 2016;39(3):209-218.

75. Gilbert JM, Fitch KV, Grinspoon SK. HIV-related cardiovascular disease, statins, and the REPRIEVE trial. *Top Antivir Med*. 2015;23(4):146-149.

76. Chan J, Chung RT. Perspectives on HCV: current therapeutic regimens and drug-drug interactions. *Clin Pharmacol Drug Dev*. 2017;6(2):147-163.

77. Cohen AA, Legault V, Fuellen G, et al. The risks of biomarker-based epidemiology: associations of circulating calcium levels with age, mortality, and frailty vary substantially across populations. *Exp Gerontol*. 2018;107:11-17.

78. 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(11):1279-1286.

79. Desquilbet L, Margolick JB, Fried LP, 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.

80. Guaraldi G, Brothers TD, Zona S, et al. A frailty index predicts survival and incident multimorbidity independent of markers of HIV disease severity. *AIDS*. 2015;29(13):1633-1641.

81. Justice AC, Modur SP, Tate JP, et al. Predictive accuracy of the Veterans Aging Cohort Study index for mortality with HIV infection: a North American cross cohort analysis. *J Acquir Immune Defic Syndr*. 2013;62(2):149-163.

82. Ellman TM, Seton ME, Warshafsky D, et al. A forgotten population: older adults with newly diagnosed HIV. *AIDS Patient Care STDS*. 2014;28(10):530-536.

83. Goodroad BK. HIV and AIDS in people older than 50. A continuing concern. *J Gerontol Nurs.* 2003;29(4):18-24.

84. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. *Psychol Rev.* 1977;84(2):191-215.

85. Corless IB, Wantland D, Kirksey KM, et al. Exploring the contribution of general self-efficacy to the use of self-care symptom management strategies by people living with HIV infection. *AIDS Patient Care STDS*. 2012;26(6):335-343.

86. Branson BM, Handsfield HH, Lampe MA, et al. Revised recommendations for HIV testing of adults, adolescents, and pregnant women in health-care settings. *MMWR Recomm Rep*. 2006;55(RR-14):1-17; quiz CE1-4.

87. Ford CL, Godette DC, Mulatu MS, et al. Recent HIV testing prevalence, determinants, and disparities among U.S. older adult respondents to the Behavioral Risk Factor Surveillance System. *Sex Transm Dis*. 2015;42(8):405-410.

88. Harawa NT, Leng M, Kim J, et al. Racial/ethnic and gender differences among older adults in nonmonogamous partnerships, time spent single, and human immunodeficiency virus testing. *Sex Transm Dis*. 2011;38(12):1110-1117.

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