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

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.

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 (daranavir-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) coinfecions (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,
HIV infection compared with the uninfected indicates a steeper early mortality. The mechanisms by which HIV induces pre-functional decline in HIV-positive individuals 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. Skeletal muscle aging in HIV infection compared with the uninfected indicates a steeper decline in mitochondrial function and increases in skeletal muscle central nuclei, as well as pathways related to senescence (eg, p21/Cip1, p16INK4a, transforming growth factor-beta and inflammation). 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, these features are not apparent in middle-aged PAWH. 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, B cells, CD8 T cells, and regulatory T cells (for review see Tidball). 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. A key gap in knowledge is a better understanding of this cross talk and how HIV may dysregulate coordinated immune-muscle homeostatic mechanisms.

### 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. Functional decline in HIV-positive individuals is associated with early mortality. The mechanisms by which HIV induces premature functional aging, and how this differs from aging in the uninfected, remain largely unknown. Skeletal muscle aging in HIV infection compared with the uninfected indicates a steeper decline in mitochondrial function and increases in skeletal muscle central nuclei, as well as pathways related to senescence (eg, p21/Cip1, p16INK4a, transforming growth factor-beta and inflammation). 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, these features are not apparent in middle-aged PAWH. 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, B cells, CD8 T cells, and regulatory T cells (for review see Tidball). 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. 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. With inflammmaging, 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. We and others have shown that biomarkers for inflammation are upregulated.

### Table. Comorbidities in People Aging With HIV

<table>
<thead>
<tr>
<th>Comorbid Condition</th>
<th>Screening Methods</th>
<th>Recommendations</th>
<th>Antiretroviral Drugs With Additional Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases&lt;sup&gt;15,59&lt;/sup&gt;</td>
<td>Risk calculation scores (eg, Framingham, ASCVD); dyslipidemia screening</td>
<td>Stop smoking; aerobic exercise; treatment of risk factors (dyslipidemia, diabetes, hypertension)</td>
<td>ABC, LPV/r, DRV/r</td>
</tr>
<tr>
<td>Bone abnormalities&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Fracture risk calculation (FRAX score); DXA</td>
<td>Exercise; vitamin D and calcium supplementation</td>
<td>TDF</td>
</tr>
<tr>
<td>Kidney diseases&lt;sup&gt;61&lt;/sup&gt;</td>
<td>eGFR; urinary albumin/protein ratio</td>
<td>Cardiovascular risk prevention; HCV coinfection treatment</td>
<td>TDF</td>
</tr>
<tr>
<td>Liver diseases&lt;sup&gt;62&lt;/sup&gt;</td>
<td>US; US elastography; HBV and HCV screening</td>
<td>Treatment of HBV and HCV; HBV vaccination; lifestyle intervention</td>
<td>First-generation NRTI and NNRTI</td>
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<tr>
<td>Neurocognitive and psychiatric disorders&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Neurocognitive evaluation; Patient Health Questionnaire-9 for generalized anxiety disorder</td>
<td>Antiretroviral drugs with high CNS penetration effectiveness score; treatment of depression or anxiety</td>
<td>EFV, DTG&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Malignancies&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Oncology screening tests (cervical and anal PAP test)</td>
<td>ART continuation during antineoplastic treatment</td>
<td>-</td>
</tr>
<tr>
<td>Frailty&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Physical functioning test</td>
<td>Exercise; treatment of HIV</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> 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. 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. Also shared are declines in the ratio of naïve-memory CD4 and CD8 T cells, as well as increases in senescent CD28-negative and CD57-positive T cells and decreases in telomere length. 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.

The Table on page 79 shows comorbid conditions, screening, recommendations, and potential drug contraindications.

### Treatment-Related Complications

Treatment algorithms that consider age are of increasing importance. With aging there are often attenuated immune recovery and response to immunotherapies, 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. 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 dysfunction. 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. 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, 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. Conversely, no changes in raltegravir exposure were found in PAWH older than 60 years of age. Complications from ART regimens include TDF-related bone and kidney toxicity, 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; 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. 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.

Furthermore, zidovudine and the PI boosters ritonavir and cobicistat should be avoided during cancer chemotherapy and concomitant medications that 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. However, because biomarker expression levels are often interrelated, they can be affected by population composition and cohort-specific variables. HIV infection modifies expression of multiple aging-associated biomarkers, 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. 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). 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, underscoring the need for HIV testing in older 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.

Self-efficacy refers to people’s confidence in their capacity to perform a specific task. Targeting self-efficacy in the HIV-positive population to promote healthy behavior has been explored. 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, studies demonstrate a low proportion (3%-4%) of HIV testers among people over 50 years of age. 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.

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 pre-symptomatic 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


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