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Current Challenges and Solutions in Research and Clinical Care of Older Persons Living with HIV: Findings Presented at the 9th International Workshop on HIV and Aging

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Abstract

In the era of effective antiretroviral therapy, the number of older people with HIV (PWH) is increasing, and those aging with HIV are experiencing an increasing burden of age-associated comorbidities. Life expectancy among older PWH is approaching that of demographically comparable HIV-uninfected (HIV-) adults. With this changing demographic of PWH come new challenges for researchers and clinicians in how to identify, address, and manage the complex interplay of treated HIV infection and aging-associated factors. In response to these challenges, the annual International Workshop on HIV and Aging was initiated in 2009 as a multidisciplinary platform for scientific discourse on the research and clinical complications arising from the aging population of PWH. The multidisciplinary nature of the workshop has resulted in a wide range of topics addressed over the past 9 years, from basic mechanisms in aging and HIV pathogenesis, to epidemiology of aging within large cohorts, interventions, and implementation of clinical programs. Herein, we summarize the key topics discussed at the 9th Annual International Workshop on HIV and Aging 2018, including ''inflammaging,'' mitochondrial dysfunction, exercise interventions, HIV-associated neurocognitive impairment, metabolic dysfunction, menopause, and polypharmacy. In addition to recent developments in research and clinical care, we discuss open questions and future research directions required to better understand the interaction of HIV and aging.

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Introduction

The number of people with HIV (PWH) who are 50 years old and older is increasing due to early initiation and increased effectiveness of antiretroviral therapy (ART), which have greatly improved longevity of PWH. Currently, one-half of PWH in the United States are older than 50 years of age and life expectancy among ART-treated adults is approaching that of the general population.[1–4] Concurrently, the determinants of morbidity and mortality among PWH have shifted from AIDS-related opportunistic infections and neoplasms to complications of aging-related conditions, including neurocognitive impairment, kidney disease, liver disease, osteoporosis, cardiovascular disease, and frailty.[5–7] Furthermore, some of these aging-related conditions appear ~5 to 10 years earlier among PWH compared with demographically similar HIV-uninfected populations.[8] The increased frequency and earlier onset of some age-related conditions among PWH, may suggest a ''premature aging'' phenomenon.

Among PWH, premature aging remains a matter of debate given mixed research findings, lack of an agreed-upon definition and objective criteria, and the difficulty in obtaining a valid comparator group of HIV-uninfected persons. Even when HIV serostatus groups are demographically matched, PWH tend to have higher rates of biopsychosocial risk factors that impact age-related health outcomes than HIV-uninfected controls such as poverty, lower educational attainment, comorbid conditions (e.g., diabetes mellitus and depression), coinfections (e.g., chronic viral hepatitis), and substance use disorders (e.g., tobacco, alcohol, and illicit drugs).[9–11] In addition, risk for aging-related outcomes may be greater among older PWH due to less than optimal ART in the early years of the HIV epidemic, long-term toxicity of some ART, lack of consistent viral suppression over time, and the potential interactive or compounding effects of HIV and aging on mechanisms such as chronic inflammation.[5,12–14] Thus, the aging of PWH presents new challenges in how to address, manage, and treat the complex interplay of HIV and aging-associated factors, including medical comorbidities, polypharmacy, and psychosocial stressors, and how to develop the best models for clinical care and community support.

The increasing proportion of older (aged 50 years and older) adults living with HIV and the growing burden of age-associated comorbidities create a pressing need to understand the risk and protective factors of physical and mental illness among older PWH as well as strategies for prevention and treatment of these conditions. In response to this need, the annual International Workshop on HIV and Aging was initiated in 2009 as a unique platform for scientific exchange on the increasingly recognized difficulties encountered in the clinical care of, and research on, persons aging with HIV. The goals of the workshop are to (1) stimulate and guide research that will enable better treatment methods and strategies for older PWH, (2) encourage young investigators to engage in research and clinical care of older PWH, and to (3) foster collaborations among investigators working to understand HIV and aging. The workshop brings together experts in cross-disciplinary fields, including basic mechanisms of aging, HIV pathogenesis, clinical geriatrics, endocrinology, HIV biology, pharmacology, neurology, psychology, and social work, to address the multidisciplinary nature of HIV and aging.

The 9th Annual International Workshop on HIV and Aging was held on September 13 and 14, 2018 in New York, NY. Herein, we summarize the key oral presentations from the Workshop and the recent developments in research pertaining to these issues. This is not a comprehensive review of issues related to HIV and aging, but, rather, a selection of timely and important issues that reflect both unique mechanisms underlying aging among PWH and potential therapeutic targets.

Immunity and Aging: Impact of HIV Infection

Savita Pahwa, MD

Inflammation is a common feature of both HIV and biologic aging (where it is termed ''inflammaging''),[15–17] and is considered to be an underlying factor in many age-associated comorbidities. Premature immune senescence is another feature ascribed to HIV infection that is considered to be similar to the impaired immunity observed with aging. For example, in older age as well as in HIV infection, the risk for contracting influenza infection is high, but effectiveness of the influenza vaccine for protection against clinical influenza is variable. Influenza vaccination can serve as a useful tool to assess immune competence by analysis of immune response to the vaccine antigens.

We investigated responses to influenza vaccine in 151 PWH and 164 HIV-uninfected, healthy control participants grouped as young (<40 years), middle aged (40–59 years), and older (≥60 years) under the acronym ''FLORAH'' (FLu Responses Of people in Relation to Age and HIV). All PWH were receiving ART with a plasma HIV-1 viral load of <50 copies/mL. Participants were classified as vaccine responders based on greater than or equal to fourfold change in serum antibody titers postvaccination compared with prevaccination levels, while those who failed to achieve this change were classified as vaccine nonresponders. Young controls had the highest frequency of and most robust vaccine responders, whereas a high proportion of older controls were vaccine nonresponders. In contrast, among PWH, vaccine nonresponders were present in all age groups. The detrimental effect of HIV was most evident in the young age group wherein the PWH showed the maximum difference from controls with lower antibody titers and a higher frequency of vaccine nonresponders.[18] Older PWH and older controls both showed age-associated immune decline. A vaccine nonresponders state was commonly associated with increased inflammation and immune activation at prevaccination.[19]

To further understand the cellular basis of these antibody responses, we investigated a subset of circulating CD4 T cells known as peripheral (p) T follicular helper cells (Tfh). The pTfh share functional and some phenotypic characteristics of Tfh cells that are found in germinal centers of lymph nodes. The interaction of germinal center Tfh cells and germinal

center B cells is critically important for the generation of antibody responses to pathogens and vaccines. Study of circulating pTfh and circulating B cells provides a noninvasive means to investigate aspects of T–B cell interaction involved in antibody response. We investigated pTfh in project FIND (*FI*nding *N*ovel *D*eterminants of Flu responses), a substudy of 103 FLORAH participants, consisting of roughly equal numbers of vaccine responders and vaccine nonresponders, grouped by age as younger (<40 years, 20 PWH and 18 uninfected controls), and older (≥60 years, 30 PWH and 35 uninfected controls).[20] We compared blood samples in PWH and controls in both influenza vaccine responders and nonresponders. Samples were compared at prevaccination and postvaccination. In brief, younger controls who were vaccine responders had greater numbers of pTfh cells prevaccination that expanded postvaccination and expressed predominantly the intracellular cytokine interleukin (IL)-21[20] that is critical for pTfh and B cell functions. The pTfh also expressed inducible costimulator, a molecule that interacts with its ligand on B cells to promote B cell function. In contrast, among vaccine nonresponders, regardless of age, the pTfh cells were lower at prevaccination, failed to expand postvaccination, and exhibited a much different cytokine response. This pTfh response in vaccine nonresponders comprised interluekin-2, a cytokine known to inhibit Tfh, and induction of inflammatory cytokines, tumor necrosis factor alpha, and interluekin-17 as well as expression of the inhibitory molecule, programmed cell death protein 1. Vaccine nonresponder status in PWH was also often associated with defects of B cells[21] and of monocyte/macrophages.[22]

We conclude that an impairment of serologic response to influenza vaccine in vaccine nonresponders is associated with greater inflammation and immune activation at prevaccination and can manifest at any age in PWH. This state is associated with cellular immune impairment, in which the pTfh play a major role. We speculate that high dose vaccines can circumvent inadequacies of pTfh, and strategies that decrease inflammation may reverse the IL-2/IL-21 axis in favor of interluekin-21, with improved influenza vaccine responses in older age and in PWH.

Mitochondrial Dysfunction and Aging

Brendan Payne, PhD

There is a wealth of data linking mitochondrial dysfunction to human aging, but our understanding of the mechanisms involved has evolved in recent years. For example, the mitochondrial free radical theory of aging that suggested a ''vicious-cycle'' of mitochondrial DNA mutations and oxidative damage has been largely disproved.[23] Instead, mitochondrial DNA mutations exist at fairly static levels over the human lifespan, but stochastically undergo clonal expansion within individual cells during aging.[24] Nucleoside/Nucleotide Reverse Transcriptase Inhibitor drugs may cause lasting mitochondrial dysfunction in PWH through an effect on clonal expansion.[25] Currently, investigators are attempting to understand the subcellular processes that drive clonal expansion.[26] We now recognize that mitochondrial dysfunction in aging is important, not only in postmitotic tissues with high energy demands (muscle, neurons), but also in replicative tissues through an effect on the maintenance of stem cell function.[27] Future research is needed to determine the clinical relevance of this effect among PWH with treated HIV infection.

One key question is, ''How might mitochondrial dysfunction in aging be ameliorated?'' Most therapies under current investigation aim to increase mitochondrial biogenesis. Multiple signaling pathways can affect mitochondrial biogenesis, but most converge through peroxisome proliferator-activated receptor gamma coactivator 1-alpha, the so-called master regulator of mitochondrial biogenesis. Recently, there has been much interest in manipulating the NAD^+/NADH ratio (the ratio of oxidized to reduced nicotinamide adenine dinucleotide). This nutrient-sensing pathway regulates mitochondrial biogenesis via peroxisome proliferator-activated receptor gamma 1-alpha. NAD^+ can be supplemented and results in increased longevity in mice. Interestingly, this effect seems to be mediated at least, in part, by rescuing mitochondrial function in stem cells.[28]

Human trials of NAD^+ supplementation are ongoing in a variety of conditions. The intervention for which the most *in vivo* data exist, however, is exercise, with multiple human and animal studies indicating that mitochondrial function can be improved with exercise. Nevertheless, a recent study has suggested that there is a partial ''metabolic block'' to exercise response in older persons that is characterized by reduced conversion of adenosine diphosphate (ADP) to adenosine triphosphate (ATP).[29] We examine *in vivo* mitochondrial function in skeletal muscle by phosphorus magnetic resonance spectroscopy (31P-MRS) in 24 PWH and 24 age-matched, uninfected healthy controls. We demonstrated that PWH had elevated ADP/ATP ratio, suggesting that this metabolic block may also exist in PWH.[30] Exercise studies are underway in people aging with HIV and will determine whether there are metabolic barriers to improving mitochondrial function in this population.

Preclinical Biomarkers for Functional Decline in HIV and Aging

Monty Montano, PhD

In addition to the higher rates of peripheral comorbid conditions (e.g., renal failure, diabetes, bone fracture, hypertension, cardiovascular disease, and multimorbidity),[31] older PWH appear to experience greater impairments in physical and cognitive function, with development of impairment in activities of daily living (ADLs) and frailty in multiple cohorts.[32] For example, in the Multicenter AIDS Cohort Study (MACS), the percent of visits with a frailty phenotype dramatically increases at ages older than 50 years among PWH compared with HIV-uninfected men,[33] despite effective ART. Similarly, declines in gait speed and grip strength were observed in the MACS among men with HIV, beginning between ages 50 and 60 years.[34,35] While multifactorial drivers, including HIV infection itself, ART-related toxicities, social inequities, and biobehavioral factors likely contribute,[36] an overarching question is how aging in PWH may differ from aging in people without HIV?

A current challenge is whether there are preclinical cues for risk of functional decline in the context of persons with treated but chronic HIV infection. Ideally, studies on preclinical risk would obtain concurrent physical function, immune and muscle phenotyping and mechanistic insights into drivers of functional decline, and potential accelerated aging.

The *M*uscle and *A*ging in *T*reated *C*hronic *H*IV (MATCH) Cohort had begun to address this challenge (NCT03011957). The MATCH Cohort is composed of 170 asymptomatic men and women living with HIV and HIV-uninfected controls, all 50–65 years of age, recruited from the Boston metropolitan area. All PWH have an HIV-1 RNA below the limit of detection and CD4+ T cell counts above 350 cells/mm^3.[37] Functional assessment was performed and included gait speed, leg strength and power, predicted metabolic equivalents, and stair climb power. Multiple additional parameters were measured, including fatigue, the Veterans Aging Cohort Study (VACS) Index, and skeletal muscle computed tomography (CT) scans. Blood and skeletal muscle (vastus lateralis) were obtained to assess immune profiles and immunohistochemistry (muscle only).

In MATCH, we observed modest deficits in gait speed, stair climb power, predicted metabolic equivalents, without deficits in leg power or strength among PWH compared to age-matched, HIV-uninfected controls. We also observed elevated systemic immune activation (cluster of differentiation 38 [CD38], human leukocyte antigen-DR subtype [HLA-DR] expression on T cells) and inflammation (serum C-reactive protein [CRP], soluble CD14, soluble CD163) but not serum IL-6 among PWH compared to control participants. CT scans did not reveal expected declines in skeletal muscle density, typically seen with increasing age, among PWH compared to control participants of similar age. Similarly, histological assessment of muscle fiber type did not reveal differences or increased size variability (both of which are expected with muscle aging[38]). Provocatively, however, we observed an unexpected increase in internalized muscle nuclei that are typically diagnostic of acute injury or advanced age.[39] Also, we observed reduced levels of nuclear Peroxisome proliferator-activated receptor-gamma coactivator-1 alpha (PGC-1α), suggesting potential downstream effects on exercise tolerance. Notably, while aging among HIV-uninfected persons has generally been associated with declines in fast-twitch muscle fibers and increased size variability,[38,40] these features were not evident in PWH,[37] despite the earlier than expected presence of internalized nuclei and reduced PGC-1α. This complex phenotype may suggest that PWH experience an asynchronous aging, wherein some, but not all, features of aging become evident prematurely and display dysregulated expression. Partial expression of age-related phenotypes that occur prematurely or that are accelerated has been referred to as segmental progeria (aging).[41] However, the premature and dysregulated expression observed in PWH may be more consistent with an asynchronous aging. The timing, levels, and cross-regulation of hallmarks of aging in PWH compared with the uninfected therefore remain unclear and warrant further study.

An additional finding was that, among male participants in the MATCH cohort, we did not detect differences in gait speed, despite elevated reports of fatigue. This prompted a pilot accelerometer study wherein we collected activity tracker data (Withings Pulse Ox) for 3 consecutive weeks.[42] Interestingly, in this substudy of men living with HIV compared with HIV-uninfected controls, we observed significant differences in average volitional gait speed by activity tracker, but not laboratory-based assessment,[42] (similar to results from the larger cohort).[37] We also observed that the men with HIV spent significantly more time in the lowest quartile of physical activity compared with the uninfected controls.

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 in men 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 and indicate 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.

Translating Exercise into the Community with Adults Aging with HIV

Kelly K. O'Brien, PhD, PT

A common comorbidity experienced by older PWH is disability defined as any physical, cognitive, mental, emotional, and social health-related challenges, including uncertainty worrying about future health, experienced by an individual.[43] Disability can be episodic in nature, characterized by unpredictable periods of wellness and illness, and exacerbated or alleviated by extrinsic contextual factors (stigma, social support) or intrinsic contextual factors (multimorbidity, age, coping strategies).[43,44] Rehabilitation, such as physical therapy and occupational therapy, has a role in addressing episodic disability experienced by PWH.[45] However, in Canada, few PWH access formalized rehabilitation services.[46,47] A Canadian web-based survey found that PWH tend to adopt independent living strategies such as adopting positive attitudes and beliefs and a healthy lifestyle, in which to address their disability.[48]

Exercise is one rehabilitation living strategy that may be adopted by PWH. Systematic review evidence indicates that performing aerobic exercise, resistive exercise, or a combination at least three times per week can lead to benefits of physical and mental health, specifically cardiopulmonary fitness, weight and body composition, strength, and quality of life for PWH.[49,50] Nevertheless, the extent to which PWH engage in exercise or physical activity varies, with results of systematic reviews documenting inactivity in 19%–73% of PWH ($n=24$ studies; mean age range: 33–47 years)[51] and less than 50% achieving physical activity guidelines ($n=24$ studies; mean age range; 37–58 years).[52] Among a sample of 21 older PWH, mean age 66 years with an undetectable viral load in the United States, participants engaged in 35 min of moderate to viogorous physical activity per week.[53] Barriers to physical activity among PWH can be multifactorial, including pain, depression, competing life priorities, and episodes of illness.[54] Among the 55 correlates of physical activity examined in this systematic review ($n=45$ studies), older age was associated with lower levels of physical activity in 6 of 10 included studies.[54] Overall, it is unclear the extent to which PWH are achieving the physical activity guidelines of 150 min of moderate to vigorous intensity

aerobic activity per week with 2 days of muscle and bone strengthening.[55]

Community-based exercise can offer an alternative strategy to enhance physical activity within a self-management framework. Our team in Toronto, Canada, is examining the effectiveness of a community-based exercise intervention on health and disability outcomes for PWH.[56] Eighty PWH initiated a 6-month exercise intervention composed of thrice weekly exercise sessions involving a combination of aerobic, resistive, neuromotor, and flexibility activity, supervised weekly by a fitness instructor.[56] Results will help to establish feasible, sustainable, and accessible interventions to enhance physical activity and healthy aging among PWH, and practical recommendations for physical activity among PWH have recently been published.[57]

In the meantime, multimorbidity, episodic disability, readiness to engage in exercise, and accessibility to fitness centers are key considerations when implementing and prescribing community-based exercise with PWH.[58,59] Furthermore, clinicians should consider the terms ''exercise'' versus ''physical activity'' as a continuum of activity and health-promoting behavior.[60] Physical therapy has a key role in promoting physical activity among PWH. In the *Framework of Physical Therapy Role in HIV Care*, deBoer *et al.* highlight the role of rehabilitation as multidimensional, focused in physical, social, and psychological (mental and emotional) areas of health.[61] Physiotherapists can offer goal-oriented and person-centered approaches while considering the influence the potentially episodic nature of HIV, stigma, aging, multimorbidity, social isolation, resource security, and competing priorities (e.g., housing, food insecurity) may individually or collectively have on one's ability, preferences, or priority for engaging in physical activity.[61]

In summary, as PWH live longer, the role for rehabilitation will increase, as the need to prevent or mitigate episodic disability among those aging with HIV continues to grow. The Canada-International HIV and Rehabilitation Research Collaborative (CIHRRC) is a network of researchers, clinicians, PWH and representatives from community organizations working to translate evidence and identify new and emerging priorities in the field (cihrrc.hivandrehab.ca).[62] Future research should examine the nature and extent of episodic disability, determine the effectiveness of rehabilitation interventions, and models of care, while advancing the development and use of patient-reported outcomes in the field.[63] Disciplines of HIV, rehabilitation, primary care, and geriatric medicine are well positioned to partner in collectively addressing these research priorities to provide timely, appropriate, and effective care to optimally address disability and promote healthy aging with PWH.

Aging Considerations in HIV-Associated Neurocognitive Impairment

Leah H. Rubin, PhD, MPH

Impairments in neurocognitive function persist in the era of effective ART. Approximately 30%–60% of PWH will develop neurocognitive impairment, with the majority acquiring milder forms of impairment, at some point during their lifetime.[64] Therefore, it becomes important to understand the patterns, mechanisms, and predictors of neurocognitive impairment especially as people age because, in its severe forms, neurocognitive impairment can impact daily functioning or quality of life.

Standard neuropsychological testing batteries are typically used to assess neurocognitive function. The presence of impairment in two or more domains in those living with HIV has been termed HIV-associated neurocognitive disorders (HAND). Enthusiasm for the term HAND is mixed given the large heterogeneity in the pattern of neurocognitive impairment and age-related neurocognitive changes.[65,66] Understanding the heterogeneity of neurocognitive impairment becomes important as we work toward identifying the underlying pathophysiology of neurocognitive impairment and developing targeted interventions to improve neurocognitive impairment.

Impairment in the cognitive domain of declarative memory may be particularly important as PWH continue to age because it is common in HAND[64,66] and it is a defining characteristic of Alzheimer's disease and its precursor, amnestic mild cognitive impairment. Declarative memory relies on hippocampal and prefrontal function and, in the context of HIV, has been shown to be impacted by the stress hormone, cortisol, and inflammation. In studies conducted in the Women's Interagency HIV Study (WIHS), we found that both hippocampal and prefrontal function are impaired in midlife women living with HIV versus HIV-uninfected women[67] and, in a pharmacologic challenge study, we found that hormonal mechanisms (hypothalamic-pituitary-adrenal axis) and inflammation[68,69] may contribute to the hippocampal-prefrontal function that underlies declarative memory. In support of this notion, strong scientific evidence supports the role of myeloid-specific activation (e.g., serum levels of sCD163 and sCD14) and microglia[70] in declarative memory[71,72] and in hippocampal and prefrontal function.[73]

There are a host of additional predictors that may contribute to or exacerbate age-related neurocognitive impairment in the context of HIV. These predictors include mental health factors (e.g., depressive, anxiety, and stress-related symptoms),[74] cardiovascular risk factors (e.g., arterial stiffness),[75] metabolic factors (e.g., insulin resistance),[76] menopause,[77] substance abuse,[78–80] low educational attainment,[81,82] sensory impairment,[83] and neurotoxic effects of nonantiretroviral drugs.[84] Many of these factors increase with age and intervening on a number of these factors may improve cognitive aging among PWH.

Metabolic Dysfunction, Aging, and Cognition

Norman J. Haughey, PhD

One factor that may play an instrumental role in neurocognitive dysfunction with aging is metabolic dysfunction. In the general population, aging is associated with increased likelihood of metabolic dysfunction. In both men and women, metabolic rate decreases and percentage of body fat increases with age. In particular, nutrition- and aging-related chronic microinflammation is linked to the increased hypothalamic cellular network dysfunction, which participates in the development of metabolic syndrome. Metabolic syndrome components include abdominal obesity, hypertension, dyslipidemia, and insulin resistance.[73] Metabolic syndrome is associated with greater risk of type-2 diabetes mellitus and atherosclerosis.[85]

Importantly, the presence of HIV infection increases the likelihood of metabolic syndrome development. Research has identified several mechanisms explaining the effects of HIV infection on metabolic syndrome. First, metabolic syndrome may develop as a possible complication of combination ART, especially regimens that include protease inhibitors.[85] Second, HIV infection may itself be a contributing factor via immune dysregulation and chronic low-level inflammation.[73] Furthermore, PWH who suffer from metabolic syndrome or metabolic syndrome components experience increased likelihood of neurocognitive impairment.[85,86] For example, a study by Sattler *et al.*[87] found that abdominal obesity was associated with neurocognitive impairment, and research by Valcour *et al.*[76,88] linked higher *insulin resistance* to a greater degree of neurocognitive impairment among PWH. The impaired brain insulin signaling and brain glucose metabolism connected to insulin resistance may be the underlying mechanisms contributing to neurocognitive impairment. In particular, increased aerobic glycolysis, one of the pathways of glucose metabolism, was found to be associated with cognitive decline among PWH.[89] Conversely, a shift to anaerobic glycolysis may lead to improvements in cognitive outcomes.[89] It is important to note that glycolysis is a modifiable factor; anaerobic glycolysis can be promoted through exercise and intranasal delivery of insulin. Past and ongoing human intranasal insulin trials examine its safety and efficacy in improving cognitive outcomes among the general population as well as PWH.[90,91]

Considerations for Women Living with HIV During Menopause

Sharon Walmsley, FRCPC, MD, MSc

Dramatic shift in hormones that occurs with aging may contribute to impairments in physical and neurocognitive impairment, and these changes in hormones may manifest as unique differences in clinical manifestations among men and women. Despite the fact that the Canadian Surveillence Report estimated that about 20% of new HIV infections are diagnosed in women older than the age of 50 years;[92] older women are infrequently tested for HIV because of (1) lack of perceived risk, (2) failure to discuss risk factors, (3) fear of partner violence, and 4) attribution of symptoms to depression, aging, or menopause.[93–96] Due to the increased lifespan of PWH in the post-ART era, more women with HIV are experiencing menopause. Menopause is thought to occur earlier in women with HIV than in the general population, but early menopause may also be a consequence of malnutrition, smoking, depression, substance, use and other psychosocial factors that are disproportionately present in women with HIV.[97] Although the hormonal changes associated with menopause are not thought to impact CD4 cell count or HIV-1 viral load, they can increase the risk of age-associated comorbidities such as osteoporosis, heart disease, and stroke.[98] Given that, the perimenopausal period may represent a period of increased risk for these comorbidities, practitioners should evaluate ART to ensure that the agents are not contributing to comorbidity risk (e.g., abacavir and cardiovascular disease and tenofovir and renal disease). Menopausal symptoms are also thought to be more frequent in women with HIV and have been associated with increased rates of anxiety, depression, and sexual function dissatisfaction.[99]

The use of hormone replacement therapy is controversial in the general population. The beneficial effects of hormone replacement therapy on menopausal vasomotor symptoms and on the rates of hip fracture and colon cancer need to be balanced against the small increased risk of stroke, cardiovascular disease, breast cancer, deep vein thrombophlebitis, and pulmonary embolism. Hormone replacement therapy can cause adverse effects such as breast tenderness and can impact adherence to other medications. However, the studies of the risks of hormone replacement therapy are confounded by the dose, route, and timing of therapy, and there are no studies of hormone replacement therapy in women living with HIV. Concerns have been raised about the additive risk of hormone replacement therapy, HIV and ART on cardiovascular disease and stroke, and deep vein thrombophlebitis.[100] If required for management of vasomotor symptoms, hormone replacement therapy should be prescribed early in the menopausal period, for as short a period as possible, and in the lowest dose possible. In addition, clinicians need to consider drug interactions with ART when prescribing hormone replacement therapy, especially non-nucleoside reverse transcriptase inhibitors and protease inhibitors whose induction or inhibition of cytochrome p450 enzymes might impact drug levels of the replacement therapy.

Polypharmacy and Inappropriate Prescribing in Older PWH

Catia Marzolini, PharmD, PhD

The management of HIV infection is becoming more challenging as older PWH experience age-related chronic comorbidities[101] leading to polypharmacy (defined as the use of ≥5 concurrent medications) and a related higher risk for drug–drug interactions.[102] While polypharmacy is highly prevalent among older adults without HIV, the risk is likely even greater among PWH. Polypharmacy has been shown to be highly prevalent in older PWH, ranging from 43% up to 94%,[103–106] and is linked to an increased risk for hospitalization or mortality.[105] Similarly, inappropriate prescribing appears to be frequent in older PWH and more commonly observed in patients treated with a large number of comedications.[106] A study comparing prescriptions among PWH and age-matched HIV-uninfected older individuals demonstrated a higher prevalence of medication-related problems in PWH.[103] These findings suggest that HIV specialists may be less familiar with geriatric prescribing and highlight the need for educational programs in geriatric medicine principles.

ARTs are recognized to be among the therapeutic agents with the highest potential for drug–drug interactions as these drugs can be both a perpetrator and a victim of drug–drug interactions. Common mechanisms of drug–drug interactions involve inhibition or induction of drug metabolism enzymes or drug transporters by ART leading to toxicity or loss of efficacy of coadministered drugs. On the contrary, comedications commonly used in older individuals (e.g., antacids or mineral supplements) can interfere with the absorption of certain ARTs, thereby compromising their efficacy. Selected drug–drug interactions of interest in aging PWH are represented in Table 1.[107–110]

With increasing age, medication-related problems go beyond the issue of drug–drug interactions. The presence of age-related comorbidities increases the risk of drug–disease

Table 1. Selected Drug–Drug Interactions of Interest in Older People with HIV

Drug class	*ART*	*Comments/recommendations*
Antacids H2-receptor blockers Proton pump inhibitors	Atazanavir Rilpivirine	Solubility of ART decreases as pH increases. • Antacids, H2-receptor blockers: separate drug intake. • Proton pump inhibitors: contraindicated.
Antacids Mineral supplements (iron, calcium, magnesium)	Bictegravir Dolutegravir Elvitegravir/c Raltegravir	Integrase inhibitors form a complex with divalent cations at the level of the gastrointestinal tract thus reducing their absorption. Administration recommendations: • BIC: 2 h before antacid (fasted); simultaneous with mineral suppl. (fed). • DTG: 2 h before or 6 h after antacids or mineral suppl. • EVG/c: separate by 4 h from antacids or mineral suppl. • RAL: not recommended with aluminium and magnesium antacids. Coadministration possible with calcium carbonate antacid but only with RAL b.i.d. Separate by 4 h from mineral suppl. (only RAL b.i.d. can be used).
Corticosteroids[a]	Boosted PI Elvitegravir/c	Inhibition of steroids metabolism increases the risk of Cushing syndrome. Risk is not limited to oral administration but may also occur after topical, ocular, intra-articular or intrathecal administration of steroids. • Budenoside, fluticasone, triamcinolone, mometasone: contraindicated.
Antidepressants[a]	Boosted PI Elvitegravir/c	Tricyclic antidepressants are not recommended in elderly due to peripheral (constipation, orthostatic hypotension) and central (sedation, confusion, delirium) anticholinergic side effects. • Avoid regardless of ART.
Benzodiazepines[a]	Boosted PI Elvitegravir/c	Benzodiazepines should be avoided as elderly have an increased sensitivity and consequently are at increased risk of cognitive impairment, delirium, and falls. • Midazolam, triazolam: contraindicated. • Other benzodiazepines: use at the lowest dose and for a short duration.
Vitamine K antagonists[a]	Boosted PI Elvitegravir/c	DDIs with boosted regimens can be managed by close INR monitoring. • Dose adjustments may be needed when switching pharmacokinetic booster as ritonavir has inducing properties on cytochromes whereas cobicistat does not.
Direct acting anticoagulants[a]	Boosted PI Elvitegravir/c	Substrates of cytochromes and/or transporters and therefore direct acting anticoagulants are subject to significant DDIs. Their anticoagulant effect cannot be measured routinely and data on management of DDIs are limited. • Avoid with boosted regimens.
Antiplatelets[a]	Boosted PI Elvitegravir/c	• Aspirin: no DDIs with ARTs. • Clopidogrel: boosted regimens alters antiplatelet effect. Coadministration is not recommended, use alternatives. • Prasugrel: boosted regimens do not alter antiplatelet effect. Coadministration with boosted regimens is possible. • Ticagrelor: contraindicated as boosted regimens may substantially increase ticagrelor concentrations and the related risk of bleeding.
Calcium channel inhibitors[a]	Boosted PI Elvitegravir/c	Inhibition of metabolism is expected to increase calcium channel inhibitors concentrations and thereby the hypotensive effect. • Start at a lower dose and titrate based on response to therapy. A 50% dose reduction may be considered for amlodipine.
Statins[a]	Boosted PI Elvitegravir/c	Can significantly increase the exposure of some statins and the related risk of rhabdomyolysis. • Simvastatin, lovastatin: contraindicated. • Other statins: start with low dose and titrate to effect. Use of standard dose is possible with pitavastatin.
Antidiabetics[a]	Boosted PI Bictegravir Elvitegravir/c Dolutegravir	• Sulfonylureas: potential increase in concentrations with boosted regimens, monitor effect and reduce sulfonylureas dose if needed. • Metformin: DTG>BIC increase metformin exposure. Consider adjusting metformin dose when starting DTG. With BIC: no need to adjust dose in patients with normal renal function otherwise close monitoring is advised. • Saxagliptin: maximal daily dose: 2.5 mg. • Exenatide, linagliptin, liraglutide, sitagliptin, vildagliptin: no DDIs.

(*continued*)

Table 1. (Continued)

Drug class	*ART*	*Comments/recommendations*
Cancer drugs[a]	Boosted PI Elvitegravir/c	Multiple cancer drugs are metabolized by cytochromes and therefore are subject to significant DDIs leading to toxicities. Limited data to guide DDIs management. • Favour ARTs with a low potential for metabolic DDIs when possible.
Nonsteroidal anti-inflammatory drugs	TDF	Coadministration may increase the risk of nephrotoxicity. • Avoid long-term use and perform close monitoring of renal function.
Hormone replacement therapy[a]	Boosted PI Elvitegravir/c	Can increase the exposure of progestins. The clinical significance of this increase in terms of overall risk of deep vein thrombosis, pulmonary embolism, stroke, and myocardial infarction is unknown. Hormone replacement therapy should be used at the lowest effective dose and for the shortest duration consistent with treatment goals and risks for individual women.

[a]Non-nucleoside reverse transcriptase inhibitors such as efavirenz, etravirine, and nevirapine can lower some comedications.
ART, antiretroviral drug; BIC, bictegravir; c, cobicistat; DDI, drug–drug interaction; DTG, dolutegravir; EVG/c, elvitegravir/cobicitat; INR, international normalized ratio; PI, protease inhibitor; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.

interactions, whereby a medication prescribed for therapeutic use can cause medical harm due to an existing condition in the patient (e.g., prescription of corticosteroids can aggravate existing diabetes). Another issue includes age-related physiological changes that impact drug pharmacodynamics and pharmacokinetics, thus predisposing older persons to inappropriate prescribing or incorrect dosing and consequently to adverse drug reactions.[111] The latter can initiate a prescribing cascade, whereby an adverse drug event is misinterpreted as a novel medical condition resulting in more medications being used to treat side effects of other medications. Prescribing cascade contributes to polypharmacy and, in turn, increases the risk of drug–drug interactions or inappropriate prescribing and consequently adverse drug reactions, thus leading to a vicious circle. Furthermore, medication errors can be magnified due to patient-related communication problems as a result of deficits in vision, hearing, or cognition and/or due to care coordination or communication issues among health care providers.

The adverse health outcomes associated with polypharmacy and inappropriate prescribing should promote interventions to minimize this risk such as (1) *complete medication reconciliation*, (2) *periodic medication review* to ensure appropriate indication, dosing and treatment duration and to check for drug–drug interactions or drug–disease interactions (Beers and STOPP/START criteria allow checking for inappropriate prescribing),[112,113] and (3) *medication prioritization* according to the risk, benefit, and preference for a given patient. The medication prioritization intervention highlights the issue of the applicability of treatment guidelines, mostly developed for a single disease, to multimorbid older individuals. Applying a single disease treatment model may result in care that is impractical or harmful (e.g., a tight glycemic control can expose elderly to hypoglycemia), whereas a patient-centered treatment model may provide improved care.[114] In this context, de-prescribing, or the process of dose reduction or stopping of medications that may be harmful or no longer effective, has gained increasing attention as a means to reduce inappropriate polypharmacy in older adults.[115]

Comprehensive Geriatric Assessment

Alison A. Moore, MD, MPH, FACP, AGSF

The care of older PWH is becoming increasing complex as HIV providers are being asked to manage an increase in comorbidities, polypharmacy, increases in drug resistance, and toxicity, and changes in pharmacokinetics as kidney and renal function diminish with age. It is clear that these complications necessitate a more individualized, multidimensional approach to care of older PWH. Many new models of care are being proposed, including geriatric consultation, novel approaches to integrating specialty medicine into HIV care, implementation of the comprehensive geriatric assessment, as well as other routine geriatric screenings and practices.[116–120]

Although approaches to caring for older PWH differ, they generally embrace some if not all of five key components, known as the 5 Ms of geriatrics.[121] The 5 Ms include the following: (1) *What Matters Most:* knowing and acting upon each person's own health outcome goals and care; (2) *The Mind:* understanding a person's neurocognitive functioning, including assessment of dementia, depression, and delirium; (3) *Mobility:* identifying impairments in gait and balance, implementing an individualized fall prevention program and creating an environment that promotes mobility; (4) *Medications:* optimal prescribing, including adjusting doses, and deprescribing to reduce polypharmacy, adverse medication reaction effects, and medication burden; and (5) *Multicomplexity*: identifying and managing multimorbidity and complex biopsychosocial situations. By incorporating the 5 Ms into routine clinical care of older PWH, providers and patients can together develop a comprehensive plan for prevention, treatment, and rehabilitation, which is often accomplished using an interdisciplinary team and standardized instruments for assessment.

Standard instruments are available to assess each of 5 Ms. *Matters Most* may be assessed through advance care planning tools, including Prepare for your Care,[122] The Conversation Project,[123] and Physician's Order for Life Sustaining Treatment (POLST).[124] To quickly assess the *Mind*, cognitive impairment or dementia can be initially screened through

simple clinical tools at the bedside such as the Mini-Cog™,[125] the Montreal Cognitive Assessment (MoCA),[126] or the International HIV Dementia Scale, or screening batteries comprised of traditional neuropsychological tests.[127] The depression component of the mind domain is commonly screened for using the Patient Health Questionnaire-9 (PHQ-9).[128] *Mobility* assessment should include an assessment of falls, in addition to tests of gait speed and balance such as the Timed Up and Go (TUG),[129] the Tinetti Gait and Balance Test,[130] and the Short Physical Performance Battery.[131] *Medication tools* (further detailed above) to assess polypharmacy/inappropriate drugs include the American Geriatrics Society Beers Criteria and the STOPP/START criteria.[113] *Multicomplexity* incorporates functional status and multimorbidity, with functional implications assessed through measures such as the ADLs needed for self-care and Instrumental ADLs needed for independent community living. The VACS Index[132] provides an assessment of the severity of underlying disease and risk for mortality. Other frailty measures such as the Fried frailty phenotype[133] summarize an individual's vulnerability to additional stressors, often highly influenced by the degree of multicomplexity. Overall, the concept of multicomplexity or multimorbidity considers the benefit versus harm of additional treatment, medication, or interventions based on a patient's current health status and goals of care, rather than strictly adhering to disease-specific guidelines.[134] In summary, distilling the discipline of geriatrics down to five key components allows development of novel, feasible, and individualized models of care for older PWH that ultimately enhances implementation and dissemination of best practices.

Conclusions

The 9th Annual International Workshop on HIV and Aging 2018 discussed and showcased a wide variety of timely and important research issues in the field of HIV and Aging that spanned from neural and behavioral mechanisms and risk factors for aging-related impairments to potential therapeutic avenues and models of care. A key takeaway from the discussions and presentations was that understanding how HIV impacts and interacts with biological aging processes is complex and will require innovative interdisciplinary teamwork from researchers, clinicians, patients, and community partners. Overall, three broad research priorities emerged: (1) understanding biological and neurological mechanisms behind aging with HIV to better inform targeted and efficacious treatments and regimens for HIV; (2) investigating feasible and sustainable interventions to promote better daily function and health outcomes for PWH; and (3) enhancing clinical experience and treatment for older PWH, including women and vulnerable subpopulations.

Impaired immune responses to vaccines, underlying mitochondrial dysfunction, alternations in skeletal muscle, metabolic dysfunction, and the age-associated changes in hormones, particularly among women, were highlighted as important mechanisms influencing the aging process among PWH. These underlying mechanisms will guide the creation of new, targeted, therapies (e.g., medication, gene, and behavioral) aimed at improving health-related outcomes and overall function. Therapies and interventions should be considered both for their potential biologic relevance, as well as their feasibility of long-term sustainable uptake among PWH. For example, intranasal insulin trials are being tested to mitigate neurocognitive impairment seen with individuals with metabolic syndrome and HIV, and community-based physical activity interventions to promote healthy well-being for PWH experiencing episodic disability are being developed.[56] Physical actictivy interventions show therapeutic promise, but is accompanied with multifactorial barriers, including pain, depression, social isolation, stigma, and competing life priorities that may impact one's ability to sustain a physical activity regimen, especially in community settings.[54,58,59] In terms of improving clinical experience and treatment for older PWH, talks highlighted the importance of investigating preclinical biomarkers, conducting comprehensive, and geriatric-specific assessments of health, and addressing key interactions between HIV and biological processes such as menopause to improve care. Talks also informed challenges and solutions related to the progression of other aging-based comorbidities and issues such as polypharmacy, frailty, and Alzheimer's disease. Future research in these areas will help provide targeted treatment, promote a patient-centered treatment model, and provide essential training and guidance for HIV specialists who may be less familiar with geriatric medicine.

This workshop summarized the current and future direction of the field; however, it is clear that more research is needed, not only at the individual-level but also from a cohort population-level perspective. Previous research from MACS has begun to inform the field on frailty phenotypes within the context of HIV. Through large multisite cohorts such as the MACS, the WIHS, CNS HIV Antiretroviral Treatment Effects Research (CHARTER), and the National NeuroAIDS Tissue Network (NNTC), we can conduct needed complex, longitudinal investigations and begin to discern differences in aging with and without HIV. There is also a need for longitudinal cohort studies of PWH with sociodemographically matched control groups. The current evidence remains insufficient to determine if HIV infection leads to either accelerated or accentuated aging given that, in observational, epidemiological studies, PWH might differ from uninfected controls with respect to behavioral and lifestyle factors (e.g., smoking, alcohol, drug use) and viral coinfections (e.g., hepatitis C), which place PWH at higher risk of age-associated comorbidities.[9] Studies with appropriately matched HIV-uninfected control groups will provide more robust evidence and confirm the impact of HIV on the incidence of age-associated comorbidities.

Understanding the intricacies of HIV and aging at both the individual and population levels with appropriate comparison participants and research designs is necessary for both horizontal and vertical advances in HIV treatment and clinical practice. Finally, despite clear epidemiologic evidence that psychosocial differences between older PWH and HIV uninfected persons exist,[14] very little remains known of the impact of factors such as loneliness, social isolation, resilience, wisdom, mental health, and substance use on older PWH.[135–138] Recent work confirms that understanding how psychosocial factors interact with aging (both negatively and positively) and developing novel solutions to address negative factors are a major community priority.[139,140] By taking a biopsychosocial approach to HIV and aging-related research, we can gain holistic insight into the clinical challenges that

will ultimately translate into clinical care that promotes better health outcomes and well-being for PWH.

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