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"HIV and Aging in Special Populations: From the Mitochondria to the Metropolis"–Proceedings From the 2019 Conference

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Advances in the development of effective combination antiretroviral therapies (ART) have not only extended life expectancy of persons living with HIV (PLWH) but also introduced new health challenges as PLWH encounter older adulthood. As the proportion of PLWH

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older than 50 years continues to increase, both PLWH and providers may be unprepared to address the resultant complex physical, psychosocial, and biological needs that, in addition to HIV, include geriatric syndromes, chronic multimorbidities, polypharmacy, neurological conditions, and stigma. The needs for research and community resources to address these issues continues to grow.

With this context in mind, the “HIV and Aging: From Mitochondria to the Metropolis” conference series (R13AG047064) brings together experts from the fields of gerontology, geriatrics, and HIV every other year to foster collaboration and generate research related to HIV and aging, translate research findings to the community of PLWH, and enhance networking to increase the cadre of multidisciplinary professionals who conduct research related to HIV and aging. The 2019 conference was held in April 2019, in Atlanta, Georgia, USA, and focused on special populations aging with HIV. The aims were to assess the basis for functional wellness in special populations of older PLWH (e.g., women, lesbian, gay, bisexual, transgender, and queer [LGBTQ], persons who use substances) from biological/basic science, social and behavioral, and clinical perspectives and translate information and content into research and clinical care. This article presents a summary of the conference presentations.

Keynote Address

Charles Emlet, PhD, delivered the keynote address and highlighted findings from Aging with Pride: National Health, Aging, and Sexuality/Gender Study, the first federally funded, longitudinal study on the well-being of LGBTQ individuals and their families (www.age-pride. org). The study is grounded in the Health Equity Promotion Model and situated within the life course perspective (Fredriksen-Goldsen et al., 2014). In analyses comparing outcomes between 371 older LGBTQ men with HIV and 973 LGBTQ men without HIV, Emlet (2019) found several disparities. First, PLWH were more likely to be living below poverty level, have lower levels of education, and identify as ethnic/racial minorities. Second, PLWH were also more likely to be single/not partnered; have a history of drug addiction; have experienced the death of a same sex partner; have lower scores on measures of resilience, social support, and general health; and have more depressive symptoms. However, PLWH were more likely to have higher levels of social engagement in the LGBTQ community, which helped to alleviate disparities in poor general health and depressive symptoms.

Gerontology and Geriatrics Priority Areas

As suggested by the work of Emlet, older PLWH may have fragile social networks. Mark Brennan-Ing, PhD, and colleagues presented data from the Research on Older Adults with HIV study (Brennan et al., 2009; Karpiak & Shippy, 2006), which supported this assertion. Among a cohort of 914 PLWH, ages 50 years and older, 70% lived alone. Individuals who were socially isolated experienced more psychological distress and received less emotional support. People with social networks centered around friends, as opposed to family members, received support primarily from friends. Those with integrated social networks received support across both friends and family and received the highest level

of support from family. Additionally, 46% of the cohort had difficulty with at least one instrumental activity of daily living; 22% had difficulty with at least one personal activity of daily living; and 19% were in immediate need of caregiving. The presence of health challenges within the context of weak social networks presents a caregiving challenge for PLWH (Brennan-Ing, 2019).

Frailty is a common geriatric syndrome that increases vulnerability to adverse health outcomes and reduces capacity to recover from injury or insults. The Fried Frailty Phenotype (Fried et al., 2001) categorizes frailty in individuals who have three or more of the following features: weight loss, weakness (decreased grip strength), exhaustion, slow gait speed, and/or low physical activity. Frailty is prevalent in 4–10% of all PLWH and up to half of those older than 50 years (Desquilbet et al., 2009). Damani A. Piggott, MD, PhD (Piggott et al., 2020), presented findings from an epidemiological study, conducted by himself and colleagues, of frailty in people living with and without HIV and who are current or past injection drug users. Results showed that PLWH with frailty are at an increased risk for hospitalization and have seven times higher mortality risk compared with people without frailty and without HIV. Frailty was associated with socioeconomic disadvantage, depression, lower education, and comorbidities. Achieving virologic control early and maintaining it are also important contributors to less frailty. Using an inflammation index based on the expression of interleukin-6 and soluble tumor necrosis factor receptor-1, Piggott et al. (2020) demonstrated the detrimental activity of inflammation, showing a 22% reduction in frailty risk for every point reduction on the inflammation index.

Osteoporosis is another common geriatric concern, and a clinical update on bone health among PLWH was presented by Igho Ofotokun, MD, PhD (Ofotokun, 2019). Aging and HIV infection are both causes of osteopenia, which can lead to osteoporosis. However, the prevalence of both conditions is higher among older adults with HIV compared with older adults without HIV (Brown et al., 2015; Del Carpio-Cano et al., 2013; McComsey et al., 2010). Bone loss is affected by both HIV (through B cells) and ART (Li et al., 2007). In vitro and in vivo studies have demonstrated a dramatic increase in bone resorption with ART as early as 2 weeks after initiation (Ofotokun, Titanji, Vunnava, et al., 2016). A pilot study using a single dose of long-acting bisphosphonate (zoledronic acid) in persons with ART-induced bone loss showed no increases in bone resorption or gains in bone mineral density (Ofotokun, Titanji, Lahiri, et al., 2016).

Falls are prevalent among PLWH, in general, at a rate of about 30% annually and are associated with an increased risk for fractures and frailty (Erlandson et al., 2012). Susie Kim, MSW, MPH, and colleagues (Kim et al., 2019) examined falls in PLWH in relationship to alcohol or other substance use. Measures used in the study included the National Institute of Allergy and Infectious Diseases's AIDS Clinical Trials Group's fall history questionnaire, addiction severity index, and a physical performance battery. Analyses focused on differences between 163 PLWH (mean age, 54 ± 9 years) with and without falls in the past 6 months. Overall, 34% had a fall, and most who fell had more than one fall. Of those with a fall, 41% reported using a substance prior to a fall, with alcohol being the most commonly used substance, followed by marijuana.

For people aging with HIV, there is increasing focus on improving “health span” rather than lifespan (Niccoli & Partridge, 2012). That is, focusing not just on extending life but on extending healthy life. Accordingly, the field of geriatrics focuses not just on conditions associated with aging but on function as people age. Kevin High, MD (High, 2019), presented a new paradigm of approach that suggests that the key to addressing comorbidities associated with aging is to address the mechanisms related to aging. Related to epigenetics, DNA methylation may be the single best marker of age. With HIV, the epigenetic clock is accelerated in the brain by about 7 years and in the blood by about 5 years in virologically well-controlled patients (Horvath & Levine, 2015). In other words, among PLWH, methylation age exceeds chronologic age. Over time, this drives the accumulation of senescent cells. Senolytics therapy may be promising as an intervention to interrupt that pathway (Justice et al., 2019). Prevention and screening for comorbidities is also essential.

Topics Specific to Women and Transgender Individuals

Using 2018 data from the Women’s Interagency HIV Study (WIHS), Deborah Gustafson, PhD, and colleagues found that top causes of non–AIDS-related death among women with HIV (WWH) included cancers, overdose, trauma, cardiovascular disease, and liver disease. Women in the WIHS also showed high risks for cardiovascular disease due to lifestyle and other factors, such as hypertension and substance use history. Geriatric syndromes like sensory decline, sleep disorders, and risk for falls were also prevalent (Adimora et al., 2018).

Other analyses using WIHS data focused on risk factors for cognitive impairment among women aging with HIV. Findings showed indicators of adiposity, such as higher body mass index, greater waist circumference and waist-to-hip ratio, and higher leptin hormone levels, to be associated with better cognition in WWH, ages 50 years and older (McFarlane et al., 2017). These findings support other studies showing that adiposity in later life may have some protective effects on dementia (Backman et al., 2015; Gustafson et al., 2012). In contrast, findings from the Mayo Clinic Study of Aging showed that among women without HIV, higher plasma adiponectin levels were associated with poorer cognitive performance and greater odds of mild cognitive impairment (Wennberg et al., 2016). Greater clarity about the role of adiposity in cognitive outcomes, specifically among women aging with HIV, is needed (Gustafson, 2019).

Anna Rubtsova, PhD, and colleagues examined successful aging among women aging with HIV, defined as the capacity of older adults to thrive in the presence of age-related declines. Studies showed high levels of self-rated successful aging among older PLWH and that better mental and physical health are important for successful aging. However, studies have predominately represented male, White participants. Rubtsova et al. (2019) conducted the WIHS-FROST (From Surviving to Thriving) study with 523 women in the WIHS cohort (WWH and women without HIV) to examine correlates of self-reported successful aging. Adjusted models on the full sample showed significant main effects for personal mastery, optimism, resilience, social support, coping, and spirituality on successful aging. Interestingly, this model was not altered by HIV status.

Increasing numbers of WWH are experiencing menopause and its symptoms. From her previous research, Rebecca Schnall, RN, PhD, found that symptom burden tended to be higher in postmenopausal women compared with premenopausal women, but it is unclear whether menopause worsens the symptoms of living with HIV. Schnall and colleagues reported (Schnall et al., 2019, 2020) on a study of mostly Black/African American men (n = 25) and women (n = 75) with HIV, drawn from an HIV clinic in New York City. In both sexes, the most burdensome symptoms of living with HIV were fatigue, neuropathy, difficulty sleeping, muscle aches, and joint pain. Among women, these symptoms differed by the stage of menopause, where the highest burden scores were seen in premenopausal women. Women in perimenopause had the lowest symptom burden and were similar to men.

Vin Tangpricha, MD, PhD, presented on hormone therapy in older transgender PLWH (Tangpricha, 2019). It is estimated that there are more than 1.4 million transgender individuals in the United States, likely an underestimation because many registries only consider people who have had surgical sex reassignment as transgender (Centers for Disease Control and Prevention, 2017). Estimates from questionnaires suggest that approximately 1% of the US population are transgender (Flores et al., 2017). Transgender women bear a disproportionate burden of HIV with an estimated prevalence of up to 28%. Particularly, transgender women of color are at higher risk for HIV (Clark et al., 2017). This disparity is thought to be a consequence of increased vulnerability to discrimination, social stigma, barriers to health care, exclusion from employment, sex work as a means of support, and biologic factors related to potential interactions with hormone therapy (Grant et al., 2010; Martinez et al., 2020). Tangpricha reported that transgender women using hormone therapy are at an increased risk for elevated triglycerides and vascular thromboembolism, pulmonary embolism, and stroke. However, he noted that there appears to be no increase in the incidence of any cancer for transgender men or transgender women using hormone therapy (Maraka et al., 2017; Quinn et al., 2017).

HIV and Opioid Use

The opioid crisis in the United States has reached levels comparable to an epidemic, with around two million people affected, and the biggest reduction in life expectancy since World War II. PLWH are more likely to have chronic pain and receive opioid treatment to address pain (Justice et al., 2016; Ompad et al., 2016). Opioid use disorder (OUD) is related to cerebral dysfunctions in regions associated with executive dysfunction (e.g., problem solving, inhibition, motivation), learning, and memory. OUD also has cognitive effects on complex psychomotor functioning, attention/working memory, and visuospatial functions. Monica Rivera Mindt, PhD, ABPP-CN (Mindt, 2019), presented on studies that suggest that among people with OUD, medication-assisted treatment (MAT) with methadone or buprenorphine (BUP) improves cognitive function over time. BUP together with naloxone showed better outcomes compared with BUP alone, suggesting a synergistic effect (Arias et al., 2016; Scott et al., 2017).

Emma Klein, BA, and colleagues analyzed data from focus groups and personal interviews with patients and providers in opioid treatment programs (OTP) that included PLWH (Bender et al., 2019). Findings suggest that OTP providers had minimal training about

resources for aging patients. Findings also indicate that stigma was a barrier to accessing MAT and telling non-OTP providers about MAT use. Klein concluded that greater efforts to link patients with health providers and resources along with stigma reduction are required to overcome these limitations.

Chronic pain patients are very heterogeneous, but with regard to prescription opioids, they can be conceptualized as two groups: opioid-naive patients and legacy patients (i.e., those already prescribed opioids for chronic pain, often for a long time). The distinction is important because individuals in each group are subject to different risks, and as such, different treatment approaches need to be considered. Legacy patients may be at risk of leaving primary care and moving toward illegal opioid use if they lose access to prescription opioids, and so continued opioid prescribing may be an appropriate harm reduction approach, whereas for the opioid-naive patient avoiding initial prescription of opioids is imperative. Jessica Robinson-Papp, MD, and colleagues (Robinson-Papp et al., 2019) presented the TOWER model, a system for supporting HIV primary care providers in implementing the Centers for Disease Control and Prevention's Guideline for Prescribing Opioids for Chronic Pain. The model includes the use of an app that delivers a daily survey to patients about opioid-related risk factors, harms, and pain severity, as well as the implementation of a decision support tool for providers to use with patients.

Using data from the Veterans Aging Cohort Study, an ongoing, longitudinal study of more than 170,000 US veterans with and without HIV infection, Amy C. Justice, MD, PhD, and colleagues demonstrated that assessment of substance use, including opioid use, is more accurate with biomarker evaluation than self-report alone (Eyawo et al., 2018). These findings and the results presented above have important implications for future studies focusing on HIV and opioid use.

Neurocognition

Aging and HIV-infection are risk factors for neurocognitive decline, and cognitive aging is a major focus in HIV research (Clifford & Ances, 2013; Valcour et al., 2004; Walker & Brown, 2018). The presentation from Vir Singh, PhD, and colleagues (Singh et al., 2017) demonstrated in an animal model that the HIV-Tat protein negatively affects the expression of the sonic hedgehog homolog (SHH), a protein associated with the integrity of the brain–blood barrier. The downregulation of SHH induced by HIV-Tat causes infiltration of activated leukocytes in the brain, inducing immune inflammation and contributing to the insurgence of HIV-associated neurocognitive disorders. Future work will examine the role SHH mimetics could play in protecting against central nervous system complications associated with HIV infection.

Metabolic syndrome (MetS) among PLWH is associated with global neurocognitive deficits and is defined as having at least three of the following conditions: abdominal obesity, high triglycerides, low high-density lipoprotein cholesterol, higher blood pressure, and high fasting blood sugar (National Cholesterol Education Program Expert Panel on Detection, 2002). HIV increases the risk for MetS, and the prevalence among PLWH is estimated to be between 11% and 45% (Paula et al., 2013). The increased risk is partially due to

interactions with ART (Calza et al., 2017). Caitlin Pope, PhD, and colleagues (Pope et al., 2019) examined the effects of HIV serostatus and MetS on neurobehavioral disturbances (apathy, disinhibition, and executive dysfunction) in 215 participants with and without HIV. Findings show that PLWH and MetS had greater apathy and executive dysfunction. HIV status alone was associated with disinhibition.

Cancer and Cardiovascular Events

Keratinocyte carcinoma (KC) is the most common non–AIDS-related cancer in PLWH and includes basal cell and cutaneous squamous cell carcinomas (Burgi et al., 2005). Occurrences of KC is strongly associated with excessive sunlight exposure, male sex, older age, and skin type. All occurrences of KC in PLWH are considered high risk and thus warrant treatment that is more aggressive. Current guidelines of the American Academy of Dermatology and National Cancer Comprehensive Network recommend standard surgical excision and Mohs micrographic surgery for high-risk squamous cell and basal cell carcinoma (Kim et al., 2018a, 2018b). Howa Yeung, MD, and colleagues (Yeung et al., 2019) conducted a chart review among 3,353 veterans living with HIV from the Atlanta Veterans Administration Medical Center. They examined the occurrence of KC and its treatments. Of the 45 persons with KC lesions, 37.1% received conservative treatment despite guidelines recommending more aggressive treatment. Histologic subtype was not related to the type of treatment, but patients older than age 65 received more aggressive surgical treatment.

Oxidative stress induces a signaling cascade in endothelial cells starting with phosphorylation of the p90 subtype of the ribosomal s6 kinase (p90RSK). The consequences of this cascade are an increase in plaque formation through a reduced extracellular signal-regulated kinase 5 activity. Meera Singh, PhD, and colleagues (Singh et al., 2019) demonstrated that monocytes in PLWH are more sensitive to oxidative stress due to increased sensitivity of macrophages/monocytes to reactive oxygen species induced by ART drugs. Using both in vitro and in vivo models, they demonstrated that ART initiates a cycle of p90RSK activation/sensitization via increasing the production of reactive oxygen species in monocytes/macrophages. The main consequence of this increase is the inhibition of the nuclear factor erythroid 2–related factor 2and antioxidant response element transcriptional activity, which is known to accelerate vascular aging. New therapeutic approaches aimed at reducing p90RSK activity could be useful to prevent cardiovascular events. Also, (hydrogen peroxide) H_2O_2-induced p90RSK activation in $CD14^+$ monocytes obtained from participants could be used as a biomarker for the prediction of cardiovascular events.

HIV Prevention in Older Adults

Christina Chandra, BA, presented on *AIDSVu*, a web tool that monitors and visualizes HIV epidemiological data, such as geographical distribution and rate of new infections (www.aidsvu.org). Using *AIDSVu*, Chandra and colleagues (Chandra et al., 2019) examined new HIV diagnoses and use of preexposure prophylaxis (PrEP) in persons who lived in the Southeastern United States and Washington, DC, from 2012 to 2016. Results showed higher rates of new HIV diagnoses in men and Blacks in this age group with primary modes of

transmission being heterosexual contact and among men who have sex with men. Moreover, PrEP use was lower in the 55+ age group compared with younger individuals. Among people ages 55+, Washington, DC, had the highest rates of both HIV diagnoses and PrEP use, and as PrEP use increased during the period, HIV diagnoses also trended down in that age group. The results demonstrated the importance of continued HIV surveillance and lent evidence to the effectiveness of PrEP among older adults for HIV prevention.

Summary

The data presented on the special populations aging with HIV indicate both exciting strides and continued challenges for researchers, clinicians, and PLWH. Although PLWH can expect a lifespan comparable to their uninfected peers, efforts to improve the health span are crucial. Geriatric syndromes and conditions such as frailty, falls, cognitive impairment, bone loss, cancer, and cardiovascular disease are increasing concerns for PLWH. Many of these conditions are associated with lifestyle and inflammation occurring with aging; however, the increased risks from HIV-associated inflammation and treatments (i.e., ART) as well as lifestyle behaviors make the specific contributors to risk difficult to disentangle. These comorbidities occur at an earlier age for PLWH compared with HIV-uninfected individuals, which has implications for clinical screening guidelines that are designed with the general population in mind. Substance use, particularly opioid use, was a focus of many of the presentations, and studies demonstrated that substance use can exacerbate many of the comorbidities. Early ART treatment and viral control attenuates some of the negative health consequences of comorbid conditions, demonstrating the importance of continued HIV testing, surveillance, and linkage to care. As we enter the PrEP era of HIV prevention, PrEP use may be an effective tool to decrease HIV transmission among older adults, but uptake remains low. Therefore, health care providers should routinely ask older adults about their sexual activity and consider educating about and prescribing PrEP when risky behaviors are reported.

Stigma and health disparities contribute to negative outcomes, including being a barrier to receiving adequate health care. Sex and gender are important contextual factors to consider, particularly as women and transgender individuals may have unique needs (e.g., menopause, hormone replacement therapy) that are associated with different risks for comorbidities. Moving forward, geriatric models of care will need to be better integrated into HIV care, and attention should be paid to the implications for PLWH who are aging into their last decades of life with greater needs for caregiving.

Building on these themes, the next conference will address structural determinants of health that impact aging with HIV and expand to include international perspectives and those on the impact of COVID-19. It will be held virtually on April 14–15, 2021, and information can be obtained on our conference website: www.hiv-aging.org.

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Key Considerations

- Due to the effect of inflammation from HIV and antiretroviral therapy in addition to the inflammation associated with normal aging, PLWH are at risk for developing geriatric syndromes (e.g., frailty, falls, cognitive impairment) and chronic conditions (e.g., cardiovascular disease, metabolic syndrome, bone loss) at an earlier age.
- Multiple social and economic disparities were noted in older LGBTQ men with HIV compared with those who were without HIV infection.
- Integrated social networks composed of friends and family offer support from isolation for older PLWH.
- There is often a disconnect between self-reported substance use and objective measures, such as biomarkers.
- Older PLWH with chronic pain require different considerations for opioid use based on if they are beginning treatment for pain or have been on long-term opioid medications (legacy patients).
- Geriatrics and geroscience play an important role in both assessing functionality and improving the health span of older PLWH.