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Current Challenges and Solutions for Clinical Management and Care of People with HIV: Findings from the 12th Annual International HIV and Aging Workshop

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Abstract

People with HIV on combination antiretroviral therapy (ART) have longer life expectancy and are increasingly experiencing age-related comorbidities. Thus, aging with HIV has become a central issue in clinical care and research, which has been particularly challenging with the intersection of the ongoing coronavirus (COVID)-19 pandemic. Since 2009, the International Workshop on HIV and Aging has served as a multidisciplinary platform to share research findings from cross-disciplinary fields along with community advocates to address critical issues in HIV and aging. In this article, we summarize the key oral presentations from the 12th Annual International Workshop on HIV and Aging, held virtually on September 23rd and 24th in 2021. The topics ranged from basic science research on biological mechanisms of aging to quality of life and delivery of care under the COVID-19 pandemic. This workshop enriched our understanding of HIV and aging under the COVID-19 pandemic, identified challenges and opportunities to combat the impact of COVID-19 on HIV communities, and also provided updated research and future directions of the field in order to move HIV and aging research forward, with the ultimate goal of successful aging for older people with HIV.

Keywords: HIV, aging, COVID-19, biological mechanism, quality of life, delivery of care

Introduction

Globally, there are more than 5.7 million people with HIV who are older than 50 years, which has increased from 8% of the population in 2000 to 16% in 2016.[1] This trend is more prominent in western and central European and north America.[1] For example, this age group currently comprises more than half of all adults with HIV in the US,[2] and will reach an estimated 75% by 2030.[3] With an increasing burden of comorbid and geriatric conditions among people with HIV, aging with HIV is at the forefront of clinical care and research. Many unanswered questions related to the mechanisms, treatment, and prevention of complications of aging among people with HIV still remain.

The 12th Annual International Workshop on HIV and Aging was held on September 23rd and 24th in 2021 via a virtual platform due to the ongoing coronavirus (COVID)-19 pandemic caused by SARS-CoV-2. Over the past year, our knowledge of the COVID-19 pandemic has also increased dramatically; thus several presentations touched on the pathogenesis or impact of COVID-19 on older adults, especially in the setting of HIV. The COVID-19 pandemic has created many challenges for older adults, especially people who are immune compromised, including those with HIV. Although barriers to care during the COVID-19 pandemic have been discussed in prior workshops,[4] older and vulnerable people with HIV have experienced negative impacts of the COVID-19 pandemic on health and well-being.[5] The COVID-19 pandemic has brought forth unprecedented and unforeseen global healthcare challenges, including delivery of healthcare for vulnerable populations, and living with HIV under oppression, marginalization, and multiple layers of racial discrimination. Novel ways to deliver healthcare have evolved rapidly over the past 18 months including telehealth to ensure ongoing HIV-healthcare during the COVID-19 pandemic, and many of these were woven into this year's presentations.

Herein, we summarize the key oral presentations from the Workshop and the recent developments in research pertaining to issues in HIV and aging. Presentations focused on topics including immune senescence, inflammation and thrombosis, and COVID-19 vaccine efficacy in older adults and people with HIV. Presentations also delved into neurologic complications of COVID-19 and cognitive impairment in aging people with HIV; the impact of oppression and structural forms of racisms impacting the quality of life among aging

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people with HIV; the effect of sleep deprivation, frailty and resilience; and how to enhance the delivery of care for older people with HIV. This summary is not a comprehensive review of issues related to HIV and aging, but, rather, a selection of timely and important issues related to aging with HIV, including special considerations for people with HIV in the context of the COVID-19 pandemic and potential therapeutic targets.

Role of Immunosenescent Cells in the Aging Process

Darren J. Baker, PhD

Treatment of HIV, particularly if begun early enough, can be viewed as a triumph of modern medicine. What was once considered a terminal diagnosis is now manageable if people have access to active antiretroviral therapies. These people are increasingly living longer lives. This improved life expectancy results in people with HIV that are subsequently experiencing a variety of age-related conditions, including cancer, osteoporosis, and cardiovascular diseases.[6] The molecular underpinnings for this are not fully understood because of the inherent complexities: the role of unfavorable social determinants of health, intrinsic rates of aging effects, impacts of long-term drug treatments, and the chronic inflammatory state that is characteristic of treated HIV infection can all contribute to onset of age-dependent pathology. To this end, recent work has demonstrated that HIV infection can impact the rate of epigenetic aging,[7] which could influence onset of clinical aging.

Among the key aging mechanisms relevant to HIV is the contribution of senescent cells to biological aging and age-related diseases. Senescent cells, which are stably growth-arrested and produce a bioactive secretome,[8] arise in response to a variety of intrinsic and extrinsic stresses, including extended passage in culture, telomere attrition/damage, excessive oncogene activation, tumor suppressor loss, proteotoxic damage, and unresolved DNA damage.[9] Importantly, inactivating a cell's ability to engage in senescence arrest promotes the development of cancer, thus highlighting an important biological pathway that needs to be intricately investigated. Using genetically-engineered mouse models, we have demonstrated that senescent cells accumulate quickly in prematurely-aged mouse models, and that their subsequent attenuation or elimination can impact their health[10, 11] and also positively influence aging in otherwise normal mice.[12] Our observation

that senescent cells can be safely removed without causing negative effects, at least in laboratory mice, opened the possibility that influencing the accumulation of senescent cells may impact various diseases of aging. Importantly, mouse models prone to osteoporosis[13] and cardiovascular diseases[14, 15] have been shown to accumulate senescent cells; targeting these cells for removal offers a possible disease-modifiable intervention. Much recent effort has focused on developing tools to safely intervene against senescent cells in the absence of genetically-engineered animal models. Elimination of these cells through senolytic drugs[16] or attenuation of the proinflammatory secretome through senomorphic drugs[9] shows great promise for clinical trials.

Many recent studies have suggested that senescent cells accumulate prematurely in people with HIV[17]. Although there is not a great understanding for the burden or cause of these cells, theoretically senescence-modifying strategies might decrease the burden of premature aging complications in people with HIV. Use in clinical trials would clearly require that senescence-modifying therapies be both safe and well tolerated in among individuals with weakened immune systems. Until these are demonstrated, the best strategy for decreasing complications of aging remains a healthy lifestyle of optimal diet coupled with appropriate levels of physical activity.[18]

Biological Mechanism: Inflammation, Thrombosis, & COVID-19

Russell P. Tracy, PhD, DABCC, FAHA

Many viral infections, including HIV and SARS-CoV-2 infection, impact the health of the host in several ways beyond the direct infection and killing of host cells. Two such ways include autoreactive antibody production and thrombosis. With respect to thrombosis, HIV infection is a prime example.[19] The thrombin generation marker D-dimer strongly predicts poor outcomes in people with HIV, as it does in those with other viral infections such as SARS-CoV-2, influenza, hepatitis, and cytomegalovirus.[20] Possible mechanisms, which may vary depending on the virus and the extent of the infection, include a) endotoxemia caused by a viral-induced breakdown in gut barrier function,[21] b) procoagulant imbalance in the pro- and anti-coagulant factor profile in blood caused by interferon-mediated, anti-viral alterations in protein synthesis in the liver,[22] c) chronic, persistent endothelial damage caused by either direct viral infection or as yet unclear secondary effects,[23] and d)

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procoagulant autoreactive antibodies, such as anti-phospholipid antibodies, caused by a breakdown in tolerance,[24] possibly due to the virally-mediated induction of B cell maturation outside of tolerance-regulating germinal centers.

The production of autoreactive antibodies has been particularly impactful in SARS-CoV-2 infection. Autoantibodies have been identified to phospholipid/coagulant factor complexes (causing thrombosis), interferons (particularly IFN-alpha2A, limiting interferon-mediated antiviral effects), cytokines (limiting innate and adaptive responses to SARS-CoV-2), sACE2 (the virus' primary receptor and major component of the blood pressure-regulating Renin-Angiotensin-Aldosterone System), and many other antigens. [25, 26] The complete repertoire is unknown, and the overall impact of autoreactive antibody production in different viral infections remains to be elucidated.

COVID-19 Vaccine Effectivity in Aging Populations and Immune Protection

George A. Kuchel, MD, FRCP, AGSF

Age represents the major risk factor for hospitalization or death following exposure to the SARS-CoV-2 virus. For example, when compared to 18-29-year-olds, individuals who are 65-74 have a 5-fold increase in risk of hospitalization and 90-fold increase in risk of death, while in those 85 years and older, these risks increase to 13-fold and 630-fold, respectively.[27] However, chronological age alone cannot be used to guide prognosis and treatment given remarkable heterogeneity in the ability of older adults to overcome this infection. Frailty is a common geriatric syndrome that is associated with enhanced risk of future disability and death. Frailty is a state of decreased reserves, resulting in increased vulnerability to adverse outcomes when exposed to stressors,[28] and frailty status has been shown to provide additional information beyond age on the probability of survival in older adults hospitalized with COVID-19.[29] Moreover, the presence of multiple chronic diseases, obesity, and male sex also need to be considered as important risk factors which may individually and collectively contribute to accelerating the rate of biological aging and associated declines in multiple facets of immune responses.[30, 31]

With aging, the immune system experiences a variety of changes and functional declines that become apparent when the system is challenged with pathogens, especially

when these are novel or unfamiliar to the individual.[32, 33] Infection with SARS-CoV-2 presents challenges to older adults in terms of both innate and adaptive immunity, as well as the required coordination between these different arms of the immune response.[25] There is considerable evidence that protein-based influenza vaccines provide less than optimal protection in frail older adults, which is especially evident at the level of cell-mediated immunity.[34] However, to date, the use of COVID-19 vaccines using mRNA technology has been very encouraging, with evidence of robust responses in antibody levels even among frail or disabled nursing home residents.[35-37] Nevertheless, there is some evidence that neutralization of live SARS-CoV-2 declines with aging,[36] and more work is needed to establish the degree of clinical protection in these highly vulnerable individuals. These uncertainties, combined with the fact that during future pandemics, older adults may remain vulnerable to novel pathogens while new vaccines and other pathogen-specific therapeutics are being developed, have raised interest in the study of geroscience-guided therapies.[38, 39] Interventions such as metformin,[38] and senolytics such as fisetin[39, 40] or others are increasingly being examined for their ability to decrease the onset and progression of chronic diseases. By targeting biological aging they may help improve outcomes in older adults by improving immune resilience, irrespective of the specific pathogen involved.[38]

COVID-19 Vaccines, HIV and Aging

Kathryn E. Stephenson, MD, MPH

Note: some references have been updated with data made available after the conference.

People living with HIV present with a similar spectrum of COVID-19 symptoms as people without HIV, but HIV infection has been shown to be a risk factor for progression to severe disease.[41-46] There are characteristics common to people with HIV that may drive the increased risk of COVID-19 diagnosis[47] and progression to severe disease.[48, 49] For example, people with HIV are more likely to be Black or Latinx, which are both populations disproportionately affected by COVID-19 due to a combination of interrelated factors, including structural elements (e.g., the fact that these populations are more likely to live in multi-family households, work essential jobs without access to remote options, and be

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exposed to racism) and the parallel increased rate of significant co-morbidities that also increase COVID-19 risk.[50, 51] There is also increased exposure to congregate settings among people with HIV. Perhaps most importantly, the immune status of people with HIV, namely, whether an individual is at an advanced stage of HIV disease or has a low CD4 count, is a driver of increased risk for severe COVID-19.[52-54] Despite these differences in risk for progression to severe disease, treatment of COVID-19 for people with HIV is no different than treatment for the general population, and antiretroviral therapy should be continued without adjustment. For people with HIV who do not meet the CDC's definition of "moderately or severely immunosuppressed", prevention recommendations are similar to those for the general population (e.g., vaccination, monoclonal antibody therapy, avoiding crowded indoor spaces, and the use of masks when indicated).

COVID-19 vaccination is the mainstay of prevention of COVID-19 for people with HIV. At the time of this conference, about 2000 people with HIV had been included in trials of major vaccines including the Pfizer, Moderna, Janssen/J&J, AstraZeneca, and Novavax vaccines. Most of these were enrolled in the Janssen/J&J trial, which recruited heavily in South Africa. In general, people with HIV in these trials had well-controlled disease, and people with HIV were ineligible if they were severely immunocompromised (e.g., CD4 cell count <200/μl). In these trials, there were no safety signals or unusual concerns. Though the sample sizes were too small for an efficacy analysis by HIV status, efficacy is assumed to be the same as the general population based on comparable immune responses. For example, two studies of the AstraZeneca vaccine examined immune responses in people living with and without HIV and found no differences in antibody concentration.[55, 56] Additional studies of the Pfizer and Moderna vaccines also found that immune responses were similar between people living with and without HIV.[57, 58] The caveat to these analyses is that severely immunocompromised people with HIV were excluded from these trials, so immune responses in individuals with a low CD4 cell count are unknown. Currently, CDC recommends that everyone, including people with HIV, get a booster shot when they are eligible.[59] In data published after this conference, vaccination and boosting was shown to be effective at preventing SARS-CoV-2 infection in people living with HIV even in the setting of additional variants (e.g., Delta) that were circulating through December 31,

2021, though people with HIV had an increased risk of breakthrough infections.[47] Recognizing that vaccine recommendations are very dynamic, people with HIV should always enquire if they are eligible for supplemental immunization or additional boosters, especially if they are moderately to severely immunocompromised (due to advanced HIV or other comorbidities). In general, only one COVID-19 vaccine study specifically addressed both HIV status and age. In a single-arm open-label trial of the AstraZeneca vaccine in two HIV clinics in London, UK, investigators found that there was no difference in immune responses when stratified by age.[56] However, further age-specific data in people with HIV are limited and this needs further study.

Neurologic Complications of COVID-19

Scott Letendre, MD

People with COVID-19 commonly have neurologic complications.[60, 61] The most severe ones include delirium, stroke, seizure, encephalomyelitis, and demyelinating polyneuropathy, which can be life-threatening, and tend to occur in people with more severe COVID-19 disease.[62-64] These severe complications increase the risk of mortality, but even if patients survive they may have persistent sequelae. Fortunately, these more severe complications do not occur frequently. Less severe complications are more common and include anosmia/hyposmia, ageusia/hypogeusia, and headache. The persistence of these non-life-threatening complications varies between individuals, with some having loss of taste or smell or cognitive and mood symptoms, and some describing a non-specific “brain fog” that persists for months and longer.[65] Findings to date support that the pathogenesis of many of these complications is likely related to the combination of robust immune and endothelial responses to SARS-CoV-2.[62, 66, 67] Vulnerability to these acute and post-infectious complications is likely affected by age, immunocompromising conditions, like HIV, and other factors.[68, 69] For example, younger people appear to be more likely to have neuropsychiatric complications, while older people are more likely to have cerebrovascular complications.[70] Expression of the cellular receptor for SARS-CoV-2, ACE2, can be upregulated by HIV infection,[71] older age,[72] and aging-related diseases, including Alzheimer’s Disease.[73] The extent of ACE2 expression in the central and peripheral systems has not been clearly linked to the risk for neuropsychiatric

complications from COVID-19, but these and other findings[66] support an additional biological basis for inter-individual variability in their incidence. Regarding HIV, a review of 25 studies of people with HIV[74] found that about two-thirds of those with COVID-19 had mild to moderate symptoms, the most common being fever and cough. Similar to people without HIV, people with HIV who died were more likely to be older and have multimorbidity with conditions like diabetes mellitus and chronic lung disease.[74] However, other studies suggest that people with HIV who were hospitalized with COVID-19 were much younger than people without HIV who were hospitalized with COVID-19 (median 56 vs. 74 years) and had a nearly 70% higher hazard of mortality.[75] The substantial impact of the pandemic on communities and resources highlights the importance of protecting vulnerable people with HIV by ensuring access to housing, counseling and social interaction, and medical care, including a secure supply of ART.[76] A multifaceted approach is needed to protect vulnerable older people with HIV from these and other stressors. In addition, research is needed to understand the interactions between COVID-19 and the cognitive and mood disorders that occur more frequently in people living with HIV than in the general population.

Cognitive impairment in Aging PLWH

Bruce Brew, MBBS, DMedSci, DSc, FRACP FAAN & Lucette A, Cysique, PhD

With an almost normal life expectancy, people living with HIV are at increased risk for cognitive impairment,[77] augmented potentially by a persistent state of low-grade inflammation despite effective cART and an increasing burden of comorbidities, especially vascular disease.[78, 79] Additionally, there is the potential for long-term cART neurotoxicity and drug-drug interactions.[80] Advancement in this field is best underpinned by the following manifestations of cognitive impairment that, importantly, are not mutually exclusive: 1) Premature: occurring *before* the normal age-related decline in cognition, suggesting that earlier medical services will be needed,[81, 82] 2) Accentuated: greater *severity* of cognitive decline than normal age, suggesting that more services are needed, and 3) Accelerated: greater *progression* of cognitive decline compared to normal cognitive aging[83] underpinned by accelerated brain aging, suggesting that more services are needed with faster implementation.[84] Further, in regard to studying cognition in people living with

HIV, collection and analyses of data should take into account the age-duration effect (age + duration of HIV disease), the suppression-duration effect (time virally suppressed), and age-suppression-duration effect.[85]

The evidence of cognitive impairment in aging people with HIV relates to both real world data[86, 87] and observational studies.[81] The most recent, most comprehensive, and only systematic review is that by Aung et al 2021.[81] Methodological limitations across studies were found to be numerous. For example, many studies were underpowered: for 80% power to observe a small-to-medium effect size, 350 individuals are needed to demonstrate premature impairment, 1050 for accentuated aging, and 230 for accelerated aging.[81] Other limitations of many existing studies include a lack of age-matched HIV-negative controls, clinical heterogeneity, suboptimal representation of people with HIV aged ≥50 years, variable virological control, and limited follow-up (4.7 years was the longest). Moreover, the age-duration effect was commonly not included or inadequate (disease duration <12 years) and suppression-duration effect was not included. For premature aging, there have been 20 studies, only three of which were longitudinal; nine of the 20 were positive. Accentuated aging was addressed by two studies, both negative. Accelerated aging was noted in three of four studies. In general, there seems to be a signal for more pronounced cognitive impairment in aging people with HIV, though the precise details require further study.

Despite some mixed results in small studies, large studies show increased signals for premature, accentuated, or accelerated cognitive aging in people with HIV[77] especially when brain imaging and multimorbidity[88] data are also considered.[89] Identification of mild neurocognitive deficit in the past should also serve to flag patients at risk in clinics.[90] Targeted screening should be considered in all ≥50 years old, especially those with multiple comorbidities or demographics associated with increased risk.[85] The uptake of computerized cognitive screening enhanced with brief mood and an activities of daily living questionnaire, easy to administer by non-specialist staff [91, 92] or self-administered[93] would assist in identifying individuals at risk of cognitive decline for early interventions, management and differential diagnosis and associated treatment. In addition, such screenings would facilitate monitoring for any cognitive decline.[94] Implementation

research in real world settings is needed now to develop HIV aging care that targets cognitive and brain health and improves quality of life in aging people with HIV. Future studies should also consider complex socio-determinants factors including history traumas, assess the impact of hormones particularly in women (e.g., menopause) and include markers of successful biological aging.

Aging, Coping, and Living with HIV in the Context of Oppression

Sannisha K. Dale, PhD and Chelsie Wallen, Psy.D.

The majority of people with HIV in the US are Black, Latinx, and those that identify as lesbian, gay, bisexual, transgender, queer, etc. (LGBTQ+). Among the 1.2 million people in the US living with HIV, 40% are Black, 22% are Latinx, and 62% are gay or bisexual men.[2] The disproportionate impact of HIV on these communities reflects oppression and marginalization including racism, heterosexism, and cisgenderism, which continue to negatively impact individuals as they live and age with HIV.[95-97] Further, oppression and structural factors drive poverty, HIV criminalization, mass incarceration, unstable housing, food insecurity, unemployment, neighborhood deprivation, and lack of access to healthcare and transportation.[98, 99] Most people with HIV face intersectional discrimination and stigma[100-102] meaning that their lives are impacted by intersecting and overlapping systems of oppression, and many of these issues impact their day to day lives. Facing these struggles on an ongoing basis has consequences in terms of both mental and physical health.[103-107]

Research indicates that older people with HIV are more likely to experience mental health difficulties, cognitive impairment, negative life events, anxiety, and stress.[108] For instance, there is a higher prevalence of depression and a higher prevalence of post-traumatic stress disorder (PTSD) diagnoses and recent trauma among people with HIV.[109, 110] The prevalence of depression, PTSD and recent trauma also differ by gender, race/ethnicity and HIV acquisition risk group among people with HIV.[111-114] These mental health struggles may be exacerbated or caused by oppression. Our work among Black women living with HIV has found that oppression targeting race, gender, and HIV status that manifests in the form of both daily microaggressions (subtle) and more macro acts of

discrimination is linked to increased barriers to HIV care, depression, post-traumatic stress disorder, and suicidality.[115-118]

Further, discrimination and stigma faced by people with HIV can also result in elevated levels of stress hormones such as cortisol which impacts inflammation and places individuals at risk for other health issues.[119] For instance, a study by Carter and colleagues found that, among African Americans, the experience of racial discrimination between the ages of 10-15 was later related to depression and accelerated aging at the cellular level as they got older.[120]

Oppression may also impact the physical and mental health of older people with HIV via behaviors not optimal for health. For instance, oppression may result in skipping a medical appointment with a provider who made a stigmatizing or microaggressive comment. Taking out one's HIV medication bottle may come with the risk of unintended HIV disclosure and thereby negatively affect adherence. Ongoing barriers linked to structural oppression such as unstable housing, lack of transportation, poverty, food insecurity, and inadequate access to competent care may also negatively impact engagement in care when people with HIV are unable to travel to medical appointments, cannot have a meal to avoid potential medication side-effects, have no home to store their medication, face stigma or judgement from care providers, and/or need to prioritize trying to fulfill basic needs (housing, food) over HIV care. Similarly, mental health struggles (e.g., depression, PTSD) resulting from oppression may make it difficult for people with HIV to practice self-health-care behaviors such as taking medication and attending appointments, and research has shown that depression and PTSD are linked with lower medication adherence and engagement in care, and higher morbidity, among people with HIV.[110]

With ongoing oppression and mental and physical health struggles, people living and aging with HIV need public health interventions to create better conditions to help them thrive. Policies are needed to decrease racism, heterosexism, cisgenderism, HIV stigma, and poverty and create access to affordable housing, food, transportation, and competent care for physical and mental health struggles. In the absence of better policies and interventions, many people with HIV are utilizing coping strategies to help them thrive. These strategies include seeking social support, attending therapy, partaking in self-care

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(religious practices, music, cooking, writing, arts and crafts), getting adequate sleep and physical activity, and volunteering or activism.[100, 121] People living and aging with HIV continue to be resilient, but changes at the structural level are urgently needed.

Effect of Sleep Deprivation

Ken M. Kunisaki, MD, MS

Sleep is a fundamental physiologic process and critical to maintaining optimal human health. Like many other human physiologic processes, sleep changes with aging. The U.S. National Institutes of Aging recognizes this phenomenon and provides aging-specific sleep information on its website for the public,[122] although this information is directed towards general sleep health rather than specific sleep disorders. The terminology of 'sleep health' is distinguished from 'sleep disorders', where sleep health includes characteristics of sleep such as Regularity, Satisfaction, Alertness, Timing, Efficiency, and Duration (the so-called RU-SATED sleep dimensions[123]), rather than specific sleep disorders (e.g., insomnia, sleep apnea) that have specific diagnostic criteria.

Many studies have quantified aspects of sleep health in people with HIV using the Pittsburgh Sleep Quality Index (PSQI) a 24-item questionnaire where scores of ≥5 points indicate poor sleep quality.[124] Multiple studies have shown a very high prevalence of abnormal PSQI scores in people with HIV, ranging from 46%-80%.[125-133] Excessive daytime sleepiness, as assessed by the Epworth Sleepiness Score, has also been shown to be highly prevalent in people with HIV, ranging from 19%-47% in various studies.[129, 132, 134-137] Whether aging affects sleep quality more in people with HIV than in people without HIV remains unclear, but even younger people with HIV have a high prevalence of poor sleep quality. Reasons for poor sleep quality in people with HIV are myriad and might include factors ranging from antiretroviral treatments (e.g., efavirenz, dolutegravir), a higher prevalence of substance use (e.g., alcohol, opiates, amphetamines), mental health challenges (e.g., depression, anxiety), and social determinants of health (e.g., poverty, safety, stigma). Additional HIV-specific factors that could affect sleep in people with HIV include central nervous system viral persistence, heightened systemic inflammation, and/or so-called inflammaging; these etiologic pathways require further research and remain important knowledge gaps at this time.

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People with HIV have long been described as having a high prevalence of insomnia, but much of this research has relied on the PSQI, which is an instrument not designed or validated for insomnia diagnoses, leading to a systematic review in 2014 being unable to find any studies to estimate insomnia prevalence in people with HIV.[138] More recently, two studies used the validated Insomnia Severity Index (ISI) and reported a high prevalence of insomnia in people with HIV. In a cohort of 321 people with HIV and 188 seronegative controls from seven sites in the UK and Ireland, insomnia prevalence by ISI was high in people with HIV and did not differ by older or younger age (21% in people with HIV >50 years old, 23% in people with HIV 18-50 years old), though the people with HIV had far higher prevalence of insomnia compared to seronegative controls (adjusted odds ratio 5.26 [95%CI: 2.2.to 12.9]; p<0.001).[139] Another study of 103 people with HIV at a single site in the US found an ISI-based insomnia prevalence of 35%.[140] In both studies, the presence of insomnia was strongly related to worse patient-reported quality of life, highlighting the clinical relevance of insomnia. The studies also reported that only 8%-26% of these study participants with insomnia had reported ever being diagnosed or treated for insomnia, suggesting substantial under-diagnosis of this highly treatable condition. Ongoing studies are evaluating the efficacy of cognitive behavioral therapy for insomnia (CBT-I) in people with HIV, since CBT-I is the primary treatment of insomnia; however, CBT-I has not been well validated in this population, which may need more tailored CBT-I approaches.

In addition to insomnia, one of the most common sleep disorders is obstructive sleep apnea (OSA). Common risk factors for OSA are older age and obesity, which are both increasingly common among people with HIV. Studies objectively assessing for OSA (e.g., with physiologic testing rather than based on OSA risk factors or administrative data) in people with HIV are few, but they have arrived at widely discrepant estimates of OSA prevalence, ranging from 6% to 72%,[137, 139] for reasons that remain unclear. However, these studies importantly found no difference in OSA prevalence between people with HIV and seronegative individuals, while another study found no difference in endotypes of OSA between people with HIV and seronegative individuals.[141] Combined, these emerging data suggest that people with HIV may not be uniquely predisposed to OSA and standard approaches to case finding, diagnosis, and treatment of OSA in people with HIV may suffice. Therefore, people with HIV can currently be assessed for usual risk factors for OSA

(e.g., older age, high body mass index, hypertension) and symptoms (e.g., daytime sleepiness, loud snoring, witnessed apneas) in decisions about whether to refer for sleep apnea testing. While OSA pathogenesis and risk may not differ by HIV status, general population data show that OSA is associated with heightened risk and severity of common HIV-associated comorbidities of aging, such as cardiovascular disease, cognitive impairment, and metabolic disease. Therefore, in older people with comorbid HIV and OSA, the presence of OSA (and treatment of OSA) could potentially impact cardiovascular, cognitive, or metabolic health outcomes. However, robust data are lacking and this is an area in need of further research.

Frailty and resilience in people living with HIV during the COVID era: two complementary constructs?

Giovanni Guaraldi, MD & Jovana Milic, MD, PhD

The COVID-19 pandemic represents a unique model of generalized stress that may impact people with HIV who may be at heightened risk for severe physical and psychological vulnerability compared to the general population. We have described this vulnerability using two complementary constructs, frailty and resilience, that together depict the reduction (or ability to avoid reduction) of homeostatic reserves of an individual in relation to stressors and aging. People with HIV may have lower resilience and increased risk of transitioning to frailty, and are thereby at increased risk of adverse outcomes.[142] In this study of 575 people with HIV, frailty was assessed in 2019, prior to the onset of COVID pandemic by using a validated 37-Item frailty index (FI) ranging from 0 to 1. FI score was categorized as fit (<0.25) or frail (>0.25).[143, 144] Resilience was assessed using the Connor Davidson resilience scale (CD-RISC-25) that ranges between 0–100. Resilience was defined as CD-RISC-25 score >75.7.[145, 146] Four frailty-resilience phenotypes were built: “fit/resilient”, “fit/non-resilient”, “frail/resilient” and “frail/non-resilient”.

The impact of the COVID-19 pandemic on people with HIV is evidenced by an increase in frailty prevalence from 3.2% in 2019 to 7.6% in 2021.[147] We also sought to describe how the concept of resilience was related to frailty: among 575 (72%) people with HIV attending the Modena HIV Metabolic Clinic who completed an electronic questionnaire, we identified 4 different phenotypes according to frail/fit and resilience/non-resilience

status. Using health-related quality of life (HRQoL) assessed with EQ-5D-5L as an outcome, the "frail/non-resilient" (OR=5.21, 95% CI: 2.62-10.33) and "fit/non-resilient" (OR=5.48, 95% CI: 2.8-10.74) phenotypes were associated with suboptimal HRQoL after adjustment for age, sex, time since HIV diagnosis, and nadir CD4.[148] Resilience is complementary to frailty in the identification of clinical phenotypes with different impacts on HRQoL. The combination of frailty and resilience among people with HIV can identify vulnerable individuals in order to prioritize urgent health interventions.[148]

Telehealth in Clinical Settings Since COVID

Alan Winston, MD

The COVID-19 pandemic has thrown unprecedented and unforeseen global healthcare challenges. One of these challenges is the delivery of healthcare for medical conditions other than COVID-19. Novel ways to deliver healthcare have evolved rapidly over the past 18 months.

Modern HIV care involves not only the diagnosis of HIV infection, commencing the optimal antiretroviral regimen to suit an individual with HIV and ensuring virological suppression, but also ensuring optimal HRQoL for people with HIV. This paradigm is often known as the four 90s[149] and focuses on three treatment targets (90% of individuals being diagnosed with HIV, being on treatment, and being virologically suppressed), but also on a fourth 90 ensuring optimal HRQoL and management of non-infectious co-morbidities in people with HIV.

The advent of telehealth, either via a video or telephone platform, has permitted ongoing HIV healthcare to ensue during the COVID-19 pandemic. Quite appropriately, questions have been raised regarding the ability of telemedicine to provide holistic care and to cover the fourth 90 whereby healthcare focuses not just on virological and immunological success, but also on HRQoL and patient-reported outcomes (PRO).[150] In a recent review of the European AIDS Clinical Society's (EACS) guidelines on monitoring for people with HIV, many screening tools for QoL, PRO, and the presence of non-infectious comorbidities can be successfully undertaken via telehealth[2]. While these initial data are reassuring and telemedicine may provide more flexibility for future healthcare

attendances, information and research is urgently required on several aspects of telemedicine including patient acceptability (with specific focus on older individuals and vulnerable population), the frequency of face-to-face phlebotomy visits required to ensure maintenance of virological suppression and safety of antiretroviral therapies are monitored, the impact of retention in HIV care, and importantly the impact on future HIV clinical research. Ongoing training will be required for healthcare professionals managing people with HIV, and ongoing work is required to determine the optimal screening tools to be delivered via telehealth, which may differ from the optimal screening tools traditionally utilized for face-to-face medical consultations.

Conclusions

The 12th Annual International Workshop on HIV and Aging 2021 discussed a wide variety of timely and important research issues in the intersection of HIV, aging and COVID-19, that ranged from basic science research on biological mechanisms of aging to quality of life and delivery of care under the COVID-19 pandemic. The discussions and presentations conveyed the current understanding of the complexity of interaction between HIV and biological aging and the challenges created by COVID-19 for traditional HIV care. Innovative care models are needed and will require interdisciplinary teamwork from researchers, clinicians, patients, and community partners. Overall, three broad research priorities surrounding the intersection of COVID-19 and HIV emerged: (1) understanding immune senescence in elderly people with HIV; (2) investigating factors impacting the quality of life of aging people with HIV; and (3) enhancing the delivery of care for older people with HIV. This workshop also provided the most updated research and future direction of the field in order to move the HIV and aging research agenda forward, with the ultimate goal of successful aging for older people with HIV.

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Authors' Contributions

X.Y. and J.D.L were responsible for the outlining and preparation of the initial draft. K.M.E. was responsible for supervision. X.Y., J.D.L, E.S., D.J.M., J.M., and K.M.E. were responsible

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