HIV and Aging in the Era of ART and COVID-19: Symposium Overview

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HIV and Aging in the Era of ART and COVID-19 Inter-CFAR Symposium

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Antiretroviral therapy (ART) has altered the clinical environment of HIV, shifting the traditional focus on AIDS-induced opportunistic infections and cancers to one in which the most common morbidities and causes of death differ little from those seen in noninfected adults. The primary distinction is that these conditions, which include cardiovascular diseases, declining physical function, neurocognitive and neuropsychiatric disorders, and alterations in body composition, first manifest in people living with HIV (PLWH) approximately 5–10 years earlier than HIV-uninfected individuals.1–3 The accelerated aging in HIV has now been further complicated by the emergence of SARS-CoV-2 infection and postacute COVID syndrome (PACS). Exploring the linkages—and points of difference—between these 2 viral conditions, while promoting multidisciplinary collaboration among researchers to identify new perspectives on HIV and aging, was the aim of “HIV and Aging in the Era of ART and COVID-19 inter-CFAR symposium.”

The symposium started with a keynote address by Dr. Steven Deeks entitled, "The impact of viral infections on long-term health." In his keynote presentation, Dr. Deeks maintained that persistent viral-mediated tissue damage along with alterations in inflammation and immune function are common observations in PLWH, and these findings, which led to the introduction of ART, suggest that viral persistence, even in the absence of replication, is deleterious and contributes to various comorbidities, including a hypercoagulable state and coronary artery disease.4,5 Studies of HIV persistence may be particularly applicable to SARS-CoV-2 infection because SARS-CoV-2 RNA is detectable in autopsy tissues weeks after acute infection and can be identified in gut tissue for at least 6 months.6 In this study, too, the evidence indicates that inhibiting viral persistence is associated with a lower risk of disease, and ongoing research is exploring the extent to which antiviral therapy during acute COVID-19 prevents long-term disease, especially because immune dysregulation and inflammation have been shown to produce serious adverse outcomes, such as longer hospitalization and death.7,8 Although current vaccines seem to reduce viral burden and, therefore, the severity of infection, their effectiveness in preventing long-term complications of COVID-19 remains to be established. Thus, the mechanistic overlaps between the 2 conditions, which include viral persistence, the etiology of virus-associated comorbidities, immune dysfunction, and inflammation, are informing SARS-CoV-2 pathogenesis studies and disease management for patients.

The identification of PACS, the subset of people with acute SARS-CoV-2 infection who develop long-term morbidities, is of particular resonance regarding HIV. At present, the data on the mechanistic features and treatment of PACS are limited, and as a result, the condition remains poorly defined.9 Nevertheless, it seems reasonable to expect the manifestations of PACS to be similar to those seen in patients recovering from other acute viral infections. Furthermore, although HIV and SARS-CoV-2 are fundamentally different infections—the former is chronic and latent, whereas the latter is acute and resolved—and their long-term complications are distinct, the mechanisms are related and, as a consequence, the most efficacious therapies for HIV infection may have utility in COVID-19 (eg, antiviral drugs to treat persistent infection and immunomodulators and anticoagulants for more severe disease).10 Well-designed and carefully performed proof-of-concept interventional studies, drawn partly from previous HIV research, are determining the precise mechanisms involved in SARS-CoV-2 pathogenesis and the appropriate management strategies to address them.
SESSION 1: THE BASIC SCIENCE OF INFLAMMATION, METABOLISM, AND EPIGENETICS IN AGING: DEFINING THE EFFECTS OF HIV ON AGING

Metabolic Control of T-Cell Aging

T-cell aging is a degenerative process involved in many immune-mediated diseases. Reviewing the landmark findings of her group in models of rheumatoid arthritis (RA), Cornelia M. Weyand reported that in successful T-cell aging, the number of naïve cells, repertoire diversity, and activation thresholds are maintained. By contrast, in diseases such as RA, which are characterized by maladaptive T-cell development, protective immune responses decline, whereas proinflammatory pathways are triggered. As a consequence, the host is rendered susceptible to chronic tissue damage. In fact, when naïve T cells from patients with RA were compared with those from healthy controls, the former had telomere lengths similar to those from healthy individuals who were more than 20 years older.\(^\text{11}\) In RA and most autoimmune illnesses, the breakdown of self-tolerance and production of autoimmune antibodies precedes disease onset, which suggests that the chronic rewiring of the immune system occurs over time. T cells, which are primary players in inflammatory lesions and supporters of B-cell autobody production, have high metabolic requirements and depend on bioenergetics and biosynthetic plasticity to support their functioning. It is now clear that T cells from healthy people and patients with RA use different metabolic pathways. For instance, because of misplaced energy-sensing enzymes, such as activated protein kinase, T cells from patients with RA are unable to balance catabolic and anabolic processes, thereby shunting glucose away from glycolysis and Adenosine triphosphate (ATP) production toward the pentose phosphate pathway. In so doing, lipogenesis is upregulated, inducing increased motility and tissue invasiveness.\(^\text{12}\)

Another major contributor to the bioenergetic failure of T cells in autoimmune diseases such as RA, Weyand contended, is the DNA repair nuclease MRE11A, which accumulates around the site of telomeres. This protein is reduced in T cells from patients with RA, and this deficiency reduces mitochondrial oxygen consumption and ATP production. The ensuing loss of function leads to the leakage of mitochondrial DNA into the cytosol, triggering inflammasome assembly, the activation of caspase-1, pyroptotic cell death, loss of tissue homeostasis, and profound tissue inflammation. Notably, restoration of MRE11A expression restores mitochondrial fitness and protects tissue from the effects of local inflammation.\(^\text{13}\) A review article on the metabolic complication of B cells in aging and HIV contributed by Dr. Frasca has been included in this supplement.

HIV, Aging, Clinical Cohorts, and Comorbidities Research

Although the introduction of ART has reduced mortality, PLWH experience high rates of comorbidities, multimorbidity (>1 major chronic illness), and steeper functional decline (10–15 years earlier) compared with uninfected controls. As Heidi Crane observed, this conflation of poor outcomes increases rates of hospitalization and death and the prevalence of geriatric syndromes such as frailty and falls.\(^\text{14}\) For these reasons, future research should emphasize the health span of PLWH, rather than just mortality, the aim of which should be to better understand how to prevent comorbidities and determine the best approaches to assess and manage the increasingly complex needs of these patients.

Tracing the history of clinical cohort development, which has evolved with advances in information technology, Crane charted the path from early HIV collaborations of Center for AIDS Research (CFAR) in the mid-1990’s to contemporary multicohort HIV research partnerships, which broaden the geographic distribution and increase the sample size, both of which, among other benefits, permit the detection of rare events. For example, the CFAR Network of Integrated Clinical Systems has 8 sites with approximately 35,000 PLWH older than 18 years in HIV care, whereas the North American AIDS Cohort Collaboration on Research and Design partners with 200 sites in the United States and Canada and draws on a patient pool of more than 200,000 from 20 different cohorts. The knowledge gleaned from these—and other—international cohort collaborations has yielded 3 core lessons: the need for careful adjudication of measurements to accurately identify discrete comorbidities in aging PLWH populations; a cautious use of composite outcomes, as evidenced by the differences in cardiovascular disease (CVD) events stemming from the presence of distinct biomarkers; and the importance of using contemporary data when evaluating research findings, including such changes as have emerged in ART and nucleoside reverse transcriptase inhibitor classes over time.\(^\text{15}\) Doing so allows the possibility of charting the life-course trajectory of PLWH when interpreting research findings. In this supplement, Dr. Crane has contributed an article detailing her talk related to this topic.

Why do Older Folks With COVID-19 Have Worse Outcomes?

Although it is now uncertain why the elderly persons fare worse with the disease, Michael Saag explored the biological factors driving the pathogenic trajectory of COVID-19, the immune considerations necessary to interpret disease severity, and future treatment options. What is clear is that death rates vary by age and sex, so that older individuals, especially men and those older than 80 years, have an elevated risk of mortality.\(^\text{16}\) Predisposing conditions, such as cardiovascular disease, diabetes, and obesity, along with race and ethnicity, also increase the likelihood of death. But most important, aging is associated with immunosenescence, the aged-related impairment of the immune response. Because SARS-CoV-2 protective immunity requires a rapid innate immune response, including, primarily, interferons (IFNs) and, secondarily, specific antiviral adaptive immune cells, older individuals are placed at higher risk because of their impaired upregulation of IFN-stimulating genes and suboptimal adaptive B-cell–mediated and T-cell–mediated responses.\(^\text{17}\) These considerations are critical when considering viral load at the time of infection: those with a lower load tend to produce an early and robust IFN response, rapid
viral clearance, and, as a consequence, mild disease. By contrast, individuals with a high viral load, including older hosts, experience a delayed IFN response and associated lymphopenia and immunosuppression, extended viral persistence, destructive tissue inflammation, and severe disease, including multiorgan failure, disseminated intravascular coagulation, and death. Understanding the trajectory of disease has clarified patient management and treatment choice, Dr. Saag added.

**SESSION 2: GEROSCIENCE AND SENOLYactics: Potential for Clinical Trials in Aging PLWH**

**NAD Metabolism and Aging**

Sirtuins are a family of nicotinamide adenine dinucleotide (NAD+)-dependent deacetylase (SIRT1-7) implicated in aging dynamics. Recent research, Eric Verdin pointed out, demonstrates that SIRT1 and SIRT3 activities decrease during senescence due to downregulation of these factors, causing a host of deleterious health and life span effects, including increased stress responses, chronic inflammation, impaired lipid metabolism, and diminished DNA repair. Furthermore, decreased levels of SIRT1 and SIRT3 are now known to be a byproduct of reduced NAD+ in vital tissue. The focus of much current study, including that conducted by Verdin’s group, is on identifying the mechanism of NAD+ decrease and the means to correct it.

Shaping our understanding of NAD+ metabolism and the biological mechanisms of aging has been the identification of several key pathways that contribute to the reduced release of NAD+ during the aging process. In addition to the sirtuins, the poly (ADP-ribose) polymerases, which are vital to the process of DNA repair, and the immune molecules CD38 and CD157, which contribute to cell adhesion, signal transduction, and calcium signaling, serve to regulate NAD+ levels in tissue. Competition between these enzymes diminishes NAD+; increased polymerase activity and CD38 activation, which occurs during the aging process, siphon off NAD+, thereby preventing the sirtuins from exerting their seroprotective effects.

In this regard, Dr. Verdin reviewed a body of ongoing research examining the role of CD38 in NAD+ metabolism. These studies were prompted by the recognition that, in mouse models, levels of the ectoenzyme increase, whereas concentrations of NAD+ decrease, in resident macrophages of adipose tissue during aging. Of particular interest was the finding that in CD38-knockout mice, NAD+ levels persisted as the animals grew older. Contributing to the robust expression of CD38 in these macrophages is the presence of the senescence-associated secretory phenotype (SASP), which is characterized by the release of high levels of inflammatory cytokines, immune modulators, growth and hemostatic factors, reactive metabolites, and proteases. In sum, Verdin argued, the emerging evidence suggests a model of aging, in which senescence leads to inflammation, increased CD38, and reduced NAD+ expression, and, most importantly, contributes to both metabolic inefficiency and sirtuin dysfunction. The linkage of these pathways also provides the first evidence of why chronic inflammation is deleterious to the aging host. Dr. Montano has contributed a research article linking NAD levels in skeletal muscle and physiologic frailty and coinfection in PLWH.

**Developing Drugs That Target Fundamental Aging Processes**

The aging of the global population, in which nearly 70%–80% of individuals aged 65 years and older have at least 2 chronic diseases, requires a new approach to medical care. Can we treat aging itself, Laura Niedernhofer asked, thereby preventing, delaying, or ameliorating multiple debilitating, chronic, and degenerative diseases, while avoiding polypharmacy and reducing escalating health care costs? She identified multiple and interconnected pillars of aging, among them macromolecular damage, epigenetics, inflammation, metabolism, adaptation to stress, proteostasis, stem cell dysfunction, and cellular senescence. Therapeutic interventions targeting any of these pillars will improve the status of them all.

In particular, cellular senescence is now considered a causal agent of aging, not merely a consequence of getting older. Evidence from transgenic animal models demonstrates that deleting p16-positive senescent cells actually improved all-cause mortality, thereby extending health span. The complex SASP in which senescent cells are expressed overlaps with cellular alterations characteristic of autoimmune diseases, chronic infection, and inflammation. Potent triggers of senescence, including mitotic, epigenetic, nucleolar, and oxidative stress, along with DNA damage and mitochondrial dysfunction, also affect these and other hallmark conditions of aging. However, no specific markers of cellular senescence have as yet been identified.

Research in Ercc1 hypomorphic mice has led to the description of a library of drugs that can be classified as either senomorphic (ie, those that modify SASP but do not alter senescent cell number) and senolytic (improve both SASP and cell number). Antipoptotic pathways also are upregulated in senescent cells, and this discovery led to the identification of the first senolytics, dasatinib and quercetin, which are nonspecific, and BCL2 inhibitors such as navitoclax, which are more selective. These first-generation agents, which also include curcumin, HSP90 inhibitors, cardiac glycosides, and aspirin, have since been followed by various vaccines, toxin-loaded nanoparticles, immunomodulators, and cell-based therapies. All these pharmaceuticals increase the clearance of senescent cells, and, in mice models, improve physical function and lifespan in old age. Dr. Niedernhofer concluded that senotherapeutics have the potential to prevent, attenuate, and reverse age-related disease, loss of tissue homeostasis, stem cell dysfunction, and frailty.

**The W5 of Geroscience-Guided Trials and HIV Care**

At the interface of HIV and geriatric medicine and the emerging field of geroscience stand a series of questions with...
important implications for the conduct of future clinical trials and patient care. These questions, George Kuchel observed, might be considered the 5 Ws:

- Why assume that geroscience-guided trials should work?
- Who might benefit the most?
- When during one’s life with HIV should this approach be taken?
- What approaches might be the most promising?
- Where will the studies be done and who will design and lead them?

Part of the difficulty in linking the aforementioned medical specialties stems from a disconnection between the traditional, linear view of disease pathogenesis in geriatric medicine and HIV and the contemporary, multifactorial perspective used in geroscience, which more accurately describes the development of common chronic diseases and geriatric syndromes. In this new perspective, a predisposing risk factor triggers a precipitating risk factor, which then causes a decline in function and the emergence of clinical disease. This etiology is further affected by considerations such as lifestyle choices, behavior, and social and economic considerations, all of which shape the individual’s ability to function and remain independent. Although these risk factors contribute independently to the development of comorbidities in older adults, a number of them are shared. For example, individuals with dysfunctional lower extremities are much more likely to have upper extremity weakness, and both can precipitate a variety of geriatric syndromes, including urinary incontinence, falls, and functional dependence. Interventions targeting these shared risk factors can improve functional domains and prevent the onset of multiple geriatric syndromes.

Thus, in designing geroscience-guided clinical studies targeting HIV populations, Kuchel endorsed a multifaceted strategy. Study designers should partner with the right collaborators (especially those with expertise in HIV medicine, geroscience, geriatric medicine, and functional outcome measurements); determine the relative incidence of comorbidities over time between PLWH and those without HIV; confirm that the proposed agent is likely to be tolerated by the population in question; validate the preclinical evidence to support its use in targeting functional outcomes that are both meaningful to patients and families; and demonstrate the treatment has the potential to improve resilience and time to disease. Although many of these measures remain to be fully described, the emergence of geroscience creates novel opportunities for a host-directed therapeutic approach that has the prospect of improving outcomes, reducing chronic pathology and comorbidities that lead to frailty and disability, and promoting the development of immunological memory to protect against disease relapse. An article coauthored by Drs. Niedernhofer and Kuchel is included in this supplement.

Aging With Grace for PLWH

One of the notable biological features of aging is gut permeability, a phenomenon induced by translocations in the microbiota, the presence of viruses such as cytomegalovirus and HIV, environmental agents, host factors, and diet, all of which can contribute to the so-called inflammatory aging in the digestive tract. Jean-Pierre Routy described his research into the role of the fungal polysaccharide beta-D-glucan (BDG), a biomarker for microbial translocation and gut integrity, which is elevated in HIV and cytomegalovirus. Along with lipopolysaccharides, BDG can increase inflammation and the immune activation of macrophages, natural killer and dendritic cells, neutrophils, and B cells, thereby contributing to disease progression, further gut damage, inflammation, and premature aging. Early ART initiation can downregulate circulating levels of BDG, suggesting that the fungal antigen presents a potential therapeutic target to prevent non-AIDS-related comorbidities.

Another compelling line of study involves growth differentiation factor (GDF)-15, a stress-responsive cytokine produced by intestinal cells and known to suppress food intake. Notably, GDF-15 induction is another benefit of metformin therapy, and its use seems to reduce body weight independently of glycemic control. In that study, the cytokine also was a marker of increased NADH-reductive mitochondrial stress and dysfunction, seemingly paradoxical, which can be explained by the concept of hormesis, a dose–response phenomenon characterized by a low-dose stimulation, a high-dose inhibition, and an ideal exposure called eustress. In this framework, metformin produces eustress, contributing to its long-term utility as an antiaging therapy, despite its initial induction of GDF-15 and associated negative effects on mitochondrial biology. The article by Dr. Routy on this subject is included in this supplement.

SESSION 3: COVID-19 OUTCOMES: WHAT IS DIFFERENT IN PERSONS AGING WITH HIV VERSUS PERSONS AGING WITHOUT HIV

Got Anything for this Cough?

Might ARTs be repurposed to treat COVID-19? In his review of emerging COVID-19 therapies, Davey Smith explored how pharmacotherapy for HIV and aging might be recruited for use in the fight against the SARS-CoV-2 infection. As the field has advanced dramatically since the presentation, we provide a very brief overview. Lopinavir and other repurposed antiviral drugs did not show a survival benefit in hospitalized patients in 2 signal studies, but other mechanistic targets of infection may offer antiviral therapeutic opportunities. Potential approaches include passive immunization; using treatments such as convalescent plasma were initially considered beneficial in hospitalized older patients and those with comorbidities. Administration of monoclonal antibodies (mAbs), for example, a cocktail of casirivimab and imdevimab significantly reduced the mean viral load in COVID-19 patients relative to controls. Similar results were reported for bamlanivimab in early-phase disease, with patients also showing a favorable symptomatic response, and for a combination of bamlanivimab and etesevimab. Of note, mAb cocktails are likely to be more effective against new SARS-CoV-2 variants, and in the
future, noninfusion modes of administration will probably produce better uptake.

Using Systems Serology to Define Age-Dependent Correlates of SARS-CoV-2

A cytokine storm contributes to, and marks, the pathogenesis and pathophysiology of severe COVID-19. As Galit Alter mentioned, the storm differs by sex and age.40 Men, especially those who are older, tend to have lower antibody levels, a greater inflammatory response, and, therefore, worse outcomes. This hyperinflammatory reaction is caused by an autoimmune-like response, in which antibody-coated viruses circulate in the lungs and bind with innate immune cells, thereby forming immune complexes that drive inflammation. Within the context of infection, the diverse range of immune activities engaged in by antibodies (eg, cytokine secretion, phagocytosis, enzyme degranulation, and apoptosis) allows them to serve as molecular beacons, offering the innate immune system a set of instructions to eliminate antibody-coated targets. Systems serology is a means to profile these antibody interactions within the broad immune system, thereby helping to identify the patterns of activity that distinguish protective from nonprotective responses and which populations do better or worse.

The initial serology findings, especially those relating to age, are provocative. Although SARS-CoV-2 infection is highly prevalent in children, there is limited evidence of serious disease. In fact, the antibody response profiles of children and adults with mild disease are similar, Alter reported. By contrast, adults with severe disease have a very different pattern of humoral response because they produce excess levels of IgM at the outset of infection, along with elevated concentrations of such antibodies as IgG1. Phagocytotic, chemotaxic, and antibody-dependent cytotoxic processes are also upregulated. However, the key difference between the 2 profiles seems to be the dramatically higher release of nucleocapsid and spike-specific IgA in older adult patients and those with serious disease, which contributes to neutrophil, monocyte, and macrophage activation; amplified cytokine secretion (including the production of IL-1 beta, IL-6, IL-18, and TNF-alpha, the critical biomarkers of the early cytokine storm), secondary proinflammatory responses; and, as a consequence, severe tissue damage and respiratory distress.41 Age also is associated with a distinct functional hormonal response, one that in older adults is directed toward immune complex–driven activities and higher degrees of IgG3, IgA, and IgA-Fc receptor binding.42 In short, IgA responses track with enhanced disease severity in adults, driving a robust inflammatory response that contributes to the pathophysiology of COVID-19.

Resilience and Frailty in PLWH During the COVID Era

For people living in the 21st century, the COVID pandemic has been an unprecedented stressor, one that produces varying effects in the vulnerable, including PLWH. One way to assess vulnerability, Giovanni Guaraldi argued, is to compare frailty, the reduction in homeostatic reserves that raises the risk of negative outcomes, with resilience, the ability to adapt to significant physical or psychological life stressors. A recent study described the relationship between the 2 health conditions in PLWH to identify the different phenotypes that affect quality of life (QoL) and intrinsic capacity, the composite of all physical and mental resources individuals can draw on during their lives.43 Using a variety of validated physical and psychological assessment tools, including the 37-item frailty index and the 25-item Connor Davidson Resilience Scale (CD-RISC-25), the investigators found that, of the 575 PLWH who participated in the study and completed the CD-RISC-25 questionnaire, 79.3% was nonresilient.43 Significant contributors to this outcome were HIV duration and loneliness. No association was identified for age, HIV-specific biological correlates (ie, CD4/CD8 cell count), or the presence of comorbidities. Four different phenotypes emerged in this study: frail/nonresilient, fit/nonresilient, frail/resilient, and fit/resilient. During the COVID-19 crisis, the first category yielded the poorest outcomes because the duration for recovery from health events was the longest. Overall, resilience tended to diminish during times of extreme stress. Taken together, the findings indicate that frailty and resilience should be evaluated in PLWH to identify vulnerable individuals and deliver the appropriate health interventions. Details of the study conducted by Dr. Guaraldi is contained in the article contributed by him to this supplement.

Community and Advocates Panel

Concerns of the possible impact of COVID-19 on aging HIV-infected people were addressed by a panel that included community advisory board members representing national CFARs, including Miami, Washington DC, UPenn, and NATAP, and was moderated by Dr. Michael Saag and Dr. Suresh Pallikkuth. Discussions in this session were guided by the following specific questions.

- How has living with HIV and any other comorbidities (or concerns about potential comorbidities) affected you during the current pandemic?
- What do you look for in a physician for your HIV care?
- People who are aging often experience conditions such as cardiovascular disease, cancer, and age-related memory loss, but these tend to affect PLWH at an earlier age. What has been your experience with these kinds of aging conditions?
- Health equity and access to quality care are a National CFAR priority. How do you think that the CFARs can make more of a difference in achieving these goals?
- How do you keep up with knowing what new treatment options are available to you?

Members shared their concerns that COVID-19 has changed everyone’s lives, including the lives of PLWH. The community and advocates panel identified several unique ways that COVID-19 has changed the lives of PLWH. They noted that PLWH are concerned about the added effect of COVID-19, a highly contagious disease, relative to their reduced immune systems due to HIV. Panelists related that just when they believed their health was stable taking medications for HIV and...
other medications for their chronic conditions, another serious and highly contagious threat emerged. They indicated that they are thankful for the vaccine but unsure of its effects on PLWH. The new variants also are an important concern, and PLWH do not believe safe from them—even if vaccinated. The panel identified increased use of telehealth, which has provided better access to both physical and mental health care, as a positive outcome of the pandemic.

Selected posters were prerecorded and delivered over 3 minutes each. The Miami CFAR mentoring team conducted a mentoring session on the second day for the junior investigators to offer advice on the path to independence through pilot awards, K awards, and ultimately achieving NIH R funding. In this interactive mentoring session, the mentoring team discussed their own trajectory of success as a model and advised the participants about the potential resources and opportunities. There were 47 participants who joined the online virtual mentoring session.

CONCLUDING REMARKS

The 2-day symposium achieved its goals of participant registration and received high ratings for the content, organization, and delivery. The webinar had more than 300 registered attendees. Attendance over the 2 days averaged more than 130 unique views from the federal government, the University of Miami, other outside UM institutions, the Florida Department of Health, and industry. We hope this symposium supplement assists readers in their understanding of the field and guides investigators in their research.

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