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CONFERENCE SUMMARY

Current Considerations for Clinical Management and Care of People with HIV: Findings from the 11th Annual International HIV and Aging Workshop

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Abstract

The number of people with HIV (PWH) aged 50 years or older continues to steadily increase. The convergence of age- and HIV-related complications in these individuals presents a challenge for both patients and clinicians alike. New findings continue to emerge, as numerous researchers evaluate the combined impact of these two factors on quality of life, physiological systems, and mental health in PWH. Since its first occurrence in 2009, the International Workshop on HIV and Aging has served as a multidisciplinary meeting to share basic biomedical data, clinical trial results, treatment strategies, and epidemiological recommendations, toward better understanding and outcomes among like-minded scientific professionals. In this article, we share a selection of key findings presented in plenary talks at the 11th Annual International Workshop on HIV and Aging, held virtually from September 30, 2020 to October 2, 2020. We will also address the future directions of HIV and aging research, to further assess how the aging process intersects with chronic HIV.

Keywords: neuroscience, aging, HIV, antiretroviral therapy, clinical outcomes

Introduction

People at least 50 years or older make up more than 50% of people living with HIV (people with HIV [PWH]) in the United States.[1] Improvement in antiretroviral therapy (ART), increased life-expectancy of PWH, as well as new infections in older age groups are all partially responsible for this phenomenon, but the end result is the inevitable intersection of age-related, disease-related, as well as treatment-related symptoms.[2–6] Prior studies have estimated that some

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physiological systems may be phenotypically ''aged'' up to 10 years in PWH compared with HIV-uninfected people,[7–9] including vasculature,[10–12] bone and connective tissue,[13,14] central nervous system structure function,[15–19] and metabolism.[20–22] The degree to which these different systems are affected varies, and although some researchers have proposed a compounding effect of age and HIV,[18,23,24] others have instead concluded that these processes are impacting aging PWH at the same time, but independently.[4,5,25,26] The Annual International Workshop on HIV and Aging was created in 2009 to address these questions, sharing findings from a multidisciplinary group of scientists spanning from geneticists and basic science investigators to epidemiologists and clinicians. The workshop has three goals: (1) to stimulate and guide research that will enable better treatment methods and strategies for older PWH; (2) to encourage young investigators to engage in research and clinical care of older PWH; and (3) to foster collaborations among investigators, clinicians, advocates, and PWH.

As the spread of the COVID-19 virus changed many aspects of life in the year 2020, the 11th Annual International HIV and Aging Workshop was held virtually for the first time. Despite the altered format, the meeting was a successful one, featuring a collection of presentations focusing on several key factors that can reduce quality of life in aging PWH: changing recommendations for ART in older adults with HIV, effects of the virus and treatments on dental health, skeletal muscle and adipose tissue, increased risk of bone fractures or frailty, and neuropathologies in central and peripheral systems (see Table 1). In addition, three early stage programs to coordinate geriatric care at a relatively earlier life point in PWH (relative to people without HIV) were also presented, with suggestions for more widespread implementation of similar programs at other clinics and hospitals. This review will summarize a collection of the plenary talks from the meeting. For more information about the conference proceedings, details can be found on the conference website: https://academicmedicaleducation.com/hiv-aging-2020

ART Adherence and Pharmacokinetics in Older Adults with HIV: Where to Go in the Next Decade

Dr. Jose Castillo-Mancilla, MD

The physiological changes that are associated with aging—such as an increase in body fat, a decrease in free water, and the reduction in renal and hepatic functions[27–30]—have a significant impact on the absorption, distribution, metabolism, and excretion (i.e., pharmacokinetics) of ART. These changes could alter drug efficacy and lead to increased toxicity, which may be accentuated by the accumulation of non-HIV/AIDS-related comorbidities in older adults.[29,31] However, the data on the pharmacokinetic and clinical impact of these aging-induced changes remain conflicting, with some studies demonstrating a significant influence of age on the pharmacokinetics of some ART,[32–38] whereas others demonstrated no effect,[39–47] with the limitation that most of these studies focused on PWH who were younger than 65 years.[27,30] Similarly, data on the influence of aging on adherence to ART are also conflicting, as some reports have identified higher or similar adherence to ART in old versus young adults with HIV,[48–51] whereas others have observed an inverse association between aging and adherence,[52] possibly driven by polypharmacy[53,54] (i.e., ≥5 medications in a regimen) or cognitive impairment.[55] In this context, the ideal method to best quantify and monitor ART adherence in older adults with HIV also remains unknown.[30] This has limited our understanding of the clinical applicability of novel adherence measures—such as pharmacologic biomarkers and new digital technologies—in this population.

Along with the conflicting data and knowledge gaps surrounding aging, adherence, and pharmacokinetics, the interplay with clinically significant HIV-related outcomes—such as viral suppression, inflammation, and toxicity—remains vastly unexplored. For example, although several studies have demonstrated that 100% adherence to ART may not be necessary to sustain viral suppression,[56–59] a growing body of literature has identified adverse consequences of this forgiving suppressive versus complete ''adherence gap'' as it relates to higher residual inflammation, immune activation, and coagulopathy.[60–65] Unfortunately, whether this association is enhanced or blunted in older PWH remains unknown, which potentially may leave these older PWH on less effective treatments, or regimens prone to more age-related side effects. Comparatively, higher ART exposure in aging adults could also lead to higher toxicity, which may result in end-organ or functional toxicity over prolonged periods of high drug exposure. To date, the ideal balance between ART forgiveness and toxicity in older adults with HIV has not been studied, and none of the available ART guidelines in adults provides any age-specific recommendations about dosing or regimen selection in this population.[66–68] The quickly growing population of PWH older than the age of 50 necessitates future inquiry into metabolic and pharmacokinetic changes that may affect ART regimens in these patients, and how these factors may change long-term outcomes and successful viral suppression in their later years.

As the research agenda on aging and HIV evolves in the next decade, the optimization of ART in older adults through a better understanding of ART pharmacokinetics and ART adherence will be paramount.[30] Future studies should particularly focus on identifying ART regimens with the most favorable pharmacokinetics (i.e., minimal toxicity and drug interactions) and on understanding the biological and clinical consequences of ART forgiveness in this population. This includes the potential evaluation of dose modification studies to minimize over-exposure while maintaining viral suppression. Similarly, identifying the most informative adherence measure in the aging population will allow for a more robust implementation of interventions to improve adherence and improve clinical outcomes.[30] Finally, novel ARTs, including long-acting injectable, implantable, and oral drugs, will need to be evaluated in older adults (including those older than 65 years) to generalize their applicability in this expanding population.

The Effects of HIV, ART, and Aging on Muscle and Adipose Tissue

Dr. Jordan E. Lake, MD, MSc

Aging, HIV, and ART are associated with changes in muscle and adipose tissue and the development of cardiometabolic disease,[69,70] but the intersection of these is not fully understood. Both HIV and ART can contribute to a proinflammatory environment and immunologic dysregulation, posing an increased risk of physiological consequences

and negative clinical outcomes, particularly as age progresses. Proposed mechanisms include PPAR-γ (peroxisome proliferator-activated receptor gamma) suppression, glucocorticoid receptor activation, altered lipid and glucose metabolism,[71–75] stimulation of the renin angiotensin system by HIV and ART [protease inhibitors (PIs), in particular],[76,77] and low penetration of ART into adipose tissue, contributing to a persistent HIV reservoir in this tissue.[78] Virus effects on muscle and fat are independent of virologic suppression. Other ART effects on muscle and adipose tissue include subcutaneous adipose tissue lipoatrophy, visceral adipose tissue accumulation, generalized weight gain, fatty muscle infiltration, reduced muscle aerobic capacity and increased muscle oxidative stress, mitochondrial dysfunction, and disruption of lipid or glucose metabolism.[79–81] In addition, increased inflammatory and cardiovascular complications can impact several other crucial physiological systems in aging PWH, such as neurological function, metabolism, and affecting quality of life and maintenance of general health as they age.

Aging is also associated with generalized weight gain, increased adipose tissue, loss of muscle mass, skeletal muscle mitochondrial dysfunction, and other tissue-level disturbances. The combination of HIV, ART, and aging effects on adipose tissue and muscle are overlapping, likely causing greater accumulation of deficits compared with aging people without HIV. Further study is needed to understand the mechanistic intersections between aging, HIV, and ART, and will be particularly necessary to reduce morbidity and mortality in PWH, optimizing current and future health care in these more vulnerable individuals. Future inquiries should address how different ART drug classes affect adiposity and cardiovascular risk factors in these aging adults, to ensure that these potentially interacting mechanisms can be managed clinically.

Fatty Liver and Implications for Frailty in Aging PWH

Dr. Giada Sebastiani, MD

Despite improved life expectancy and ongoing decrease in HIV/AIDS-related mortality, liver diseases have still increased 10-fold in the post-ART era.[82,83] Recent studies suggest that PWH are at higher risk for non-alcoholic fatty liver disease (NAFLD), a condition when fat accumulates in liver cells, without alcohol consumption. NAFLD is an umbrella term encompassing two pathological and clinical entities that present with diverse prognostic implications, nonalcoholic fatty liver or simple steatosis, and nonalcoholic steatohepatitis (NASH) characterized by liver fat and necrotic-inflammatory changes. Without intervention, NAFLD can progress to NASH, significant scarring (fibrosis), and liver cirrhosis, eventually resulting in end-stage liver complications, including ascites, encephalopathy, and hepatocellular carcinoma.[84,85] Liver fibrosis has been identified as one of the most important predictors of mortality in aging PWH.[83,86,87]

Risk for liver disease progression among people without HIV but with NAFLD is affected by multiple metabolic factors (obesity, insulin resistance, and menopause) as well as patient-related factors (age/gender, excessive alcohol/drug use, lifestyle). However, the progression of liver disease in the aging population of PWH is complicated by the additional risk posed by disease-related factors (HIV-1 viral load) and prolonged ART use (which can lead to lipodystrophy and/or hepatotoxicity). HIV mono-infection has been associated with a more rapid progression of liver pathology to severe hepatic steatosis compared with HCV co-infected PWH,[88] and NAFLD has been shown to be a significant predictor of frailty[89] and metabolic/cardiovascular conditions.[90] On comparison of multiple available studies evaluating the predictive validity of many of these co-factors for NAFLD in PWH,[88,91–95] the most common predictor variables were weight or body mass index (BMI) and hemoglobin A1C. Taken together, this collection of evidence suggests that weight management may alleviate risk factors for cardiovascular, metabolic, and hepatic comorbid conditions in PWH. Indeed, a weight loss of >10% of the body weight can improve all features of NAFLD, including hepatic steatosis, NASH, and liver fibrosis.[96]

Examining adjunctive treatment options, we have also shown that vitamin E is a promising treatment for NASH in PWH.[97] In a 24-week phase 4 single-arm trial, vitamin E decreased the proportion of participants with severe steatosis, increased the proportion with no evidence of steatosis, and significantly reduced ALT by week 12 of the study. Tesamorelin may also reduce histological markers of liver damage (hepatic fat fraction and ALT) and decrease the progression rate of steatosis.[98] Switch from efavirenz to raltegravir was associated with decreased liver steatosis by $\sim$30% over 48 weeks among PWH with hepatitis C co-infection.[99] These data should be cautiously interpreted in light of recent evidence linking integrase inhibitors with weight gain.[100] Use of ''d-drugs'' should be avoided, and lipid neutral regimens should be considered in patients at risk of or with NAFLD.[101]

In summary, liver pathology associated with chronic HIV mono-infection can be approached with a three-part plan to reduce the severity of NAFLD and prevent progression to NASH and liver fibrosis: (1) lifestyle changes to reduce cardiovascular and metabolic factors that may exacerbate the risk of severe liver damage, (2) additional pharmacotherapy to alleviate an early stage existing liver pathology, and (3) revision of ART regimen to minimize therapy-related liver damage.

Should We Still Care About Bone? Screening, Treatment, and TDF vs. TAF

Dr. Michael Yin, MD

Both HIV and ART have negative effects on bone mineral density (BMD),[102–104] with the greatest bone loss occurring during the first 1–2 years after initiation of ART.[105] Atraumatic fractures occurring at the spine, hip, and wrist are the most important clinical consequences of decreased BMD and bone strength, but they are usually not observed in PWH until they are older. However, children and young adults with perinatal HIV have evidence of decreased BMD and disrupted bone structure by high resolution computed tomography (CT), and they may have fractures earlier and more frequently as they age.[106,107] Newer antiretrovirals such as integrase strand transfer inhibitors (INSTIs) and tenofovir alafenamide fumarate (TAF) have less negative effects on BMD than tenofovir disoproxil fumarate (TDF) and ritonavir-boosted PIs.[108,109] Switching from TDF to abacavir

or INSTIs or from PIs to INSTIs results in a 1%–3% increase in BMD over 1 year.[110] This is an effective strategy for mitigating risk in patients who have low bone density or are at an increased risk of falls and fracture. It is important to note that the impacts of HIV, antiretrovirals, and other factors (nutrition, hormones, and lifestyle) on BMD are cumulative; therefore, it still makes sense to screen for osteoporosis with dual-energy X-ray absorptiometry (DXA) in PWH older than age 50. It remains uncertain whether earlier initiation of ART and widespread use of newer ART regimens will decrease fracture risk among PWH on the population level over time.

Falls and Fractures in HIV: Prevention and Treatment

Dr. Todd Brown, MD, PhD

Bone fractures are a preventable cause of decreased functioning and quality of life of PWH. Among PWH, DXA screening is recommended for men age 50 years and older, and for postmenopausal women.[111] The World Health Organization Fracture Risk Assessment Tool (FRAX; www.shef.ac.uk/FRAX) has been found to underestimate fracture risk in PWH.[112,113] Indeed, subclinical vertebral fractures can be discovered in patients with spinal x-rays who do not meet criteria for osteoporosis by FRAX.[114,115] To prevent osteoporosis, ART switching is recommended to avoid regimens, including the nucleoside reverse transcriptase inhibitor (NRTI) tenofovir[116] or PI medications[117] in high-risk individuals.

To treat osteoporosis in PWH, the antiresorptive [bisphosphonate, selective estrogen receptor modulators (SERMs), denosumab, and hormone replacement therapy] and the anabolic therapies [parathyroid hormone (PTH)/parathyroid hormone related-protein (PTHrP) analogs and romosozumab] are available medications. Patients at a higher risk of osteoporosis should also incorporate lifestyle changes, including, but not limited to, at least 1,200 mg daily of calcium, vitamin D supplementation to a target serum level of 20 ng/mL, smoking cessation, alcohol reduction, weight-bearing exercise, and discontinuation of medications associated with osteoporosis such as corticosteroids.[118] There has been a decline in the use of bisphosphonates due to side effects and poor adherence, though these agents are still considered first-line therapy for osteoporosis.[119] Denosumab may be associated with an increased risk of infection,[120] which could be of greater concern in individuals with a low CD4 count. For severe osteoporosis, the PTH/PTHrP analogs or romosozumab are used, with no specific caveats for use in PWH.

Ultimately, however, *fall prevention* is fracture prevention. To prevent falls, clinicians should assess fall risk, as well as evaluate sedative use, cognitive and sensory impairments, neuropathy, lower-extremity disability, weakness, and frailty, all of which can contribute to fall risk. Physical therapy for strength and balance is also recommended, in conjunction with environmental modification, such as enhancing lighting and reducing trip hazards where possible. Lastly, behavioral changes such as avoiding sedative medications, wearing appropriate footwear, and avoiding hazardous walking surfaces can all decrease the risk of falls and fractures in PWH.

Oral Health with Aging: Periodontal Disease and Dementia

Dr. Angela R. Kamer, DDS, MS, PhD

The accumulation of amyloid beta plaques (Aβ) is a central feature of Alzheimer's disease (AD) and occurs in cognitively normal people, years before cognitive symptoms.[121] However, the risks and mechanistic pathways resulting in brain amyloidosis are not fully understood, although converging evidence points toward the hypothesis that inflammatory and dysbiotic conditions could promote brain amyloidosis. Periodontal disease is a peripheral, chronic, inflammatory, and dysbiotic condition affecting more than 50% of the elderly[122–124] resulting from the interaction between the dysbiotic bacteria and the host immune response. Clinically, periodontal disease is characterized by significant inflammation (erythema, bleeding, and deep pockets around the teeth) and clinical attachment loss, signifying structural damage to the surrounding tissue.

Periodontal bacterial dysbiosis is characterized by a disruption in the balance between periodontal and healthy bacteria.[122] Subgingival environment (under the gum line) in periodontal disease is enriched in gram-negative bacteria triggering local[125–127] and systemic inflammation.[128] Up to 700 species colonize the subgingival biofilm and among them, several bacteria are enriched in periodontal disease (*Tenerella forsythus*, *Porphyromonas gingivalis*, *Treponema denticola*, *Prevotella sps*, and others such as *Porphyromonas endodontalis* and *Fretibacterium* fastidiosum),[129–134] whereas others are enriched in periodontically healthy people (i.e., species of *Rothia*, *Corynebacterium*, *Veillonella*, *Actinomyces*, *Streptococcus*, and *Capnocytophaga*).[132,133] In the presence of periodontal disease, periodontal bacteria particularly get access to the systemic circulation and induce pathology at distant sites. Periodontal disease-derived bacteria have been also identified in the brain, which may impact neurological health and function, particularly in older adults or those aging with comorbid chronic diseases, such as HIV.

We and others have shown that periodontal disease is associated with increased risk of cognition dysfunction, dementia, and AD (review by Kamer *et al.*[135]). Moreover, animal and clinical studies have shown that periodontal disease was able to induce AD pathology, including amyloid pathology.[135–138] We hypothesized that periodontal disease with its inflammatory and dysbiotic burden can promote Aβ brain accumulation. In line with this presumption, we have shown that in cognitively normal subjects, clinical measures of periodontal disease (such as clinical attachment loss) were associated with higher 11-C PiB radio tracer retention in the brain in Positive Emission Tomography (PET) studies (indicating higher amyloid load).[136] Further, we hypothesized that periodontal microbial dysbiosis is also associated with amyloidosis. Subgingival bacterial composition was assessed by using 16S ribosomal RNA (rRNA) sequencing in amyloid negative and amyloid positive subjects.

We found consistent differences in the microbial taxa between the amyloid positive and amyloid negative groups expending over multiple taxonomic ranks. For example, at the species level, using linear discriminant analysis effect size (LEfSe) we found *Prevotella oris*, *P. endodontalis*, and *F. fastidiosum* to be enriched in the amyloid positive group and *Corynebacterium matruchotii* and *Actinomyces* species

to be enriched in the amyloid negative group. Importantly, the bacterial taxa associated with amyloid positivity are bacteria known for their association with periodontal disease whereas the bacteria taxa associated with amyloid negativity are known for their association with periodontal health. Although *P. gingivalis* was not found to be significant between the two groups, we found a similar trend, with increased frequency and abundance in the amyloid positive group. In conclusion, our studies have demonstrated that clinical periodontal disease as well as periodontal microbial dysbiosis is associated with biomarkers of brain amyloidosis. Though this current study focused only on periodontal microbes in older adults with and without amyloid burden, these results have important implications for clinical management in those vulnerable to age- or disease-related impacts on brain function. A better understanding of the interplay between periodontal bacterial species and amyloid burden may be an opportunity for preventative measures to improve dental health, potentially decreasing the impact of age-related increases in amyloid and subsequent symptoms of dementia. For instance, if the combined effects of age, periodontal disease, and amyloid burden can potentially be mitigated in those at the highest risk for complications, future studies may be able to contribute to improved overall health outcomes, before these symptoms are significant enough to impact daily life and functioning.

Eye Disease and HIV

Dr. Douglas Jabs, MBA, MS, MD

Age-related macular degeneration (AMD) is the leading cause of vision loss and blindness in people older than 65 years of age in the United States and the third leading cause of vision loss worldwide.[139,140] AMD can be staged as early (small retinal drusen), intermediate (large drusen or multiple medium-sized drusen), or late (either neovascular AMD or geographic atrophy). Visual loss occurs with late-stage AMD, and people with intermediate-stage AMD are at a high risk for progression to late-stage AMD.[141] The Longitudinal Study of the Ocular Complications of AIDS (LSOCA) was a prospective cohort study of people with HIV (PWH) in the era of modern ART. Prior studies indicated that PWH but without ocular opportunistic infections (OIs) had an increased risk of cataract at younger ages and had retinal vascular calibers compatible with those seen in HIV-uninfected people 11–24 years older, suggesting accelerated/accentuated aging in the eye of people with AIDS. The LSOCA cohort had baseline and 5- and 10-year follow-up photographs permitting the evaluation of participants for AMD. Photographs were evaluated at a centralized Reading Center by graders masked as to clinical features of participants. The primary outcome was intermediate-stage AMD.

Evaluation of baseline photographs among 1,825 participants without ocular OIs revealed a 4.1-fold increased age- and gender-adjusted prevalence of AMD when compared with that seen in a cohort of people without HIV, evaluated using similar methodology. Risk factors for AMD in the LSOCA cohort included age and smoking (also a risk factor for AMD in people without HIV). Evaluation of follow-up photographs revealed a 1.75-fold increased race/ethnicity- and gender-adjusted incidence of AMD compared with a cohort of people without HIV, evaluated with similar methodology. Smoking was a risk factor for incident AMD. Neither use of ART nor any specific antiretroviral drugs were associated with AMD in either the prevalent or incident analysis. Plasma inflammatory biomarkers at baseline, including C-reactive protein (CRP), interleukin (IL)-6, interferon-γ inducible protein (IP)-10, soluble CD14 (sCD14), soluble CD163 (sCD163), kynurenine/tryptophan (KT) ratio, and intestinal fatty acid binding protein (I-FABP), were evaluated for their relationships to AMD and mortality.

There was a borderline association of elevated baseline levels of IL-6 and prevalent AMD. Prevalent AMD (at baseline) was associated with an increased mortality (hazard ratio = 1.48, $p = .04$). Increased baseline levels of CRP, IL-6, IP-10, and sCD14 each also were associated with increased mortality. In the multiple cox regression of mortality, elevated levels of the biomarkers CRP, IL-6, and IP-10 remained associated with increased mortality, but AMD no longer was significantly associated. Step-wise variable selection of mortality on AMD demonstrated that it was the biomarker levels that attenuated the association of AMD with mortality and suggested interrelationships among AMD, systemic inflammation, and mortality. These data inform on the aging eye in PWH and potentially on the pathogenesis of AMD in people without HIV. Increased inflammation burden associated with HIV infection is a well-characterized complication even in virally suppressed PWH, affecting multiple physiological systems. Maintaining health of the visual system in aging PWH is a crucial future research focus, particularly to understand the biological mechanisms that underlie the accelerated changes in ocular health as a consequence of aging with HIV.

Neuropathy in Aging PWH

Dr. Ronald Ellis, MD, PhD

Neuropathy and neuropathic pain are among several HIV-related conditions that have stubbornly resisted improvement with virally suppressive ART.[142,143] The clinical characteristics of neuropathy in the era of modern ART have evolved, as has our understanding of its pathophysiology and potential interventions. We recently evaluated signs of distal sensory polyneuropathy (DSP) and self-reported distal neuropathic pain (DNP) at baseline and 12-year follow-up in a cohort of community-dwelling PWH at six research centers.[144] Of the 254 participants with a mean baseline age of 43.5 years, DSP prevalence increased from 25.7% to 43.7%, and 24.3% of those who were initially pain-free developed incident neuropathic pain at 12 years. Baseline risk factors associated with a lower risk of incident DNP were being employed and having a lower BMI. Factors previously seen to be associated with DSP and DNP in pre-ART cohorts, such as low CD4 and detectable viral load, were not significantly predictive of incident DSP and DNP in this cohort. Participants with neuropathic pain at follow-up had significantly worse quality of life and greater dependence in activities of daily living than those who remained pain-free.

The factors we observed to protect against DNP—having a lower BMI and being employed—might have clinical significance. Thus, BMI is a plausible surrogate for vascular risk factors that can contribute to peripheral nerve injury, so lifestyles that promote healthy body weight might protect from the development of DSP and DNP. Being employed

might be a surrogate for other salutary factors that promote better overall health status. At the same time, new insights into pathophysiology, such as the role of muscarinic cholinergic constraint on mitochondrial biogenesis and neurite outgrowth, raise the possibility of enhancing peripheral nerve regeneration using muscarinic antagonists.

Monitoring of PWH Older Than 50

Dr. Marta Boffito, MD, PhD

PWH aged 50 years or older in long-term follow-up at Chelsea and Westminster Hospital in London have the opportunity of attending a dedicated ''Over 50 Clinic.'' This clinic enables the ongoing assessment of targeted screening tests in PWH to best define their clinical utility and cost-effectiveness. Improved knowledge on HIV and aging through such methods has and will facilitate clearer screening guidelines for aging PWH and development of future care pathways, particularly in community and primary care settings. In our 10-year experience, numerous PWH older than 50 years of age were found to have numerous clinical conditions, detected by targeted screening, including clinically significant drug–drug interactions. Importantly, PWH who are affected by multimorbidity are likely to also be vulnerable to polypharmacy. The latter may lead to drug–drug interactions with toxic clinical outcomes. People aging with HIV have been shown to be at a higher risk for drug interactions between ARTs and non-ARTs, and between non-ARTs and other non-ARTs.[145] Further, the central nervous system is very sensitive to drug-related toxicities and the permeability of the blood–brain barrier increases with age.[146] This can result in sedation, cognitive impairment, and dementia among older PWH. In this regard, different tools have been implemented to estimate the anticholinergic risk such as the Anticholinergic Cognitive Burden scale and Anticholinergic Risk Scale. However, the use of these tools is not widely implemented in aging PWH.[147] In the Over 50 Clinic, all PWH do undergo depression and memory screening.

As cardiovascular disease (CVD) is more common in PWH than people without HIV due, in part, to HIV-1 infection and certain antiretrovirals (ARVs), all PWH older than 50 years of age also undergo CVD risk assessment. Importantly, however, several intervention studies have indicated that regular assessment of these patients can mitigate the risk through early intervention,[148] such as management of hypercholesterolemia, hypertension, and diabetes, and lifestyle modification, including smoking cessation. Coronary artery calcium (CAC) scoring can be useful in the risk assessment of PWH with a high risk of CVD,[149] in addition to the traditional cardiovascular risk (CVR) calculators such as the Framingham Risk Score.

Patients at our clinic also undergo bone health review, which requires screening using regular bone DXA scan and FRAX score measurement in PWH to ensure interventions are implemented to avoid osteoporosis deterioration and increased bone fracture risk. Finally, the clinic has served to improve liaison with primary care and closer working relationships with other specialties (e.g., cardiology, psychology), including speedy referral to a separate co-specialty clinic run by HIV providers and experts in care of the elderly, where frailty is assessed in depth and management plans are discussed.

Important limitations include lack of longer-term follow-up, particularly with regard to CVD and neurocognitive assessment. However, data from the Over 50 Clinic are reviewed regularly to increase general knowledge and learn to prevent negative health outcomes. Most of the assessments performed are recommended in consensus guidelines, and numerous cases where a serious condition may have remained otherwise undetected (e.g., prostate cancer, virological failure because of a drug interaction, myocardial infarction, *etc.*) have been observed. The majority of patients reacted positively to the clinic, particularly as many do not routinely access their primary care physician; however, this model may not be applicable in settings where the HIV provider is the primary provider.

Geriatric HIV Consultation Clinic at Zuckerberg San Francisco General Hospital

Dr. Meredith Greene, MD

The Golden Compass program is based at San Francisco General Ward 86 clinic, and it is designed to administer aging services to PWH starting in at age 50. For the development of the Golden Compass program, focus groups with patients, providers, and staff led to the program name and services highlighted on the framework of the compass points. The program includes an embedded cardiologist and geriatrician, dedicated pharmacy, and social work support and the Compass points include (1) Heart and Mind (Northern Point), including a cardiology clinic, cognitive assessments, and brain health classes; (2) Bones and Strength (Eastern Point), focused on bone health, fall and functional assessments; (3) Network and Navigation (Southern Point) focused on addressing isolation, linkage to community programs; and (4) Dental/Hearing/Vision (Western Point), addressing screening and linkage to these services.

The initial evaluation from the first 1.5 years of the program was also presented, which was conducted by using the Reach-Effectiveness-Adoption-Implementation-Maintenance (RE-AIM) framework. An implementation science evaluation framework was specifically chosen to help organize findings in a way that program components could be adapted to other settings. In terms of reach, 200 patients participated in the first year and a half of the program. Adoption, defined at the provider level, was high with 85% of providers in the clinic having referred at least one patient to the geriatrics clinic and 60% referring at least one patient to the cardiology clinic. Effectiveness focused on early outcomes such as satisfaction and acceptability with services. Overall satisfaction was high, with >90% of providers and patients satisfied with services. Medication, mobility, and cognitive assessments were particularly valued and in interviews, colocation of services was noted to be an important component of implementation. In addition, at this same conference, effectiveness data on prescribing outcomes from the program were presented, showing a statistically significant reduction in potentially inappropriate medications.

Lessons learned in the initial implementation included that framing ''aging services,'' especially geriatric consults, remained a challenge despite attempts to avoid ''aging'' or ''geriatric'' in the program name. In addition, acknowledging

it takes time to develop and implement programs and that determining the most appropriate outcome evaluations will be important for the field. Planned expansions of screenings and educational offerings were discussed, including the impact of COVID-19 on service delivery and the need to find ways to bridge the digital divide for patients.

Integrating Geriatric Assessments into HIV Care

Dr. Sarah Schmalzle, MD

HIV clinics are finding a need to incorporate geriatric principles into the comprehensive care of PWH to appropriately address the changing demographics and needs of aging PWH. Major models of care trialed thus far in HIV clinics have included establishing referral channels to geriatric specialists, colocating geriatricians in HIV clinics, educating HIV providers in geriatric principles, and developing or linking to home or community-based programs to enhance geriatric care.[150] Herein, we initiated a grant-funded demonstration project, titled ''Strengthening Therapeutic Resources for Older patients Aging with HIV'' (STRONG) to integrate comprehensive geriatric assessment into an urban HIV clinic in Baltimore, Maryland, USA.

In the planning phase, patient listening sessions and provider input sessions were conducted to identify medical and other needs of people aging with HIV, social work staff were trained in geriatric principles, HIV providers took an HIV-aging knowledge test and needs assessment survey, and nurses and social workers took a quiz on age bias. A multidisciplinary team reviewed available validated geriatric screening instruments in the domains of mental health, cognition, physical functioning, and quality of life to determine the most feasible set of assessments to use. Volunteer patients were used to test the draft screening instruments for length and comfort with the assessments. Final assessments chosen included: patient health questionnaire 9, general anxiety disorder 7, Montreal cognitive assessment, short physical performance battery, older Americans resources and services, Fried frailty phenotype, ''Determine'' nutritional assessment, and patient-reported outcomes measurement information system global health assessment. A sociodemographic questionnaire was developed to address aspects of living and aging with HIV not captured in standard instruments, including questions on personal HIV history, stigma, loss, HIV disclosure, support systems, relationships, caregiving responsibilities, substance use, housing, employment, financial stability, community engagement, advanced care planning, and health care utilization.

A pharmacist reviewed medical records to identify opportunities for medication optimization, including outside medications not reconciled with local medication list, medications last prescribed or refilled greater than 1 year earlier, and missing or duplicate medications. A review of potential drug interactions and Beers list medications was conducted. Patients with issues identified above or with recent hospital discharge or detectable HIV-1 RNA were offered an appointment with a pharmacist. A physician or nurse practitioner conducted a medical chart review to evaluate for the presence of and guideline-conducive screening for age-related comorbidities (low BMD, atherosclerotic CVD risk, renal and liver disease, diabetes, hypertension, hyperlipidemia, and breast, colon, cervical, and anal cancer). The PWH older than the age of 50 were recruited to participate in the STRONG demonstration project, including in-person geriatric assessments and STRONG sociodemographic questionnaire completed by and with assistance of graduate research assistants. The patients were incentivized with a $25 gift card and were offered follow-up appointments to review results with their HIV specialist and a clinical pharmacist. Each patient's medical team was notified of all results, with suggested resources for areas identified as deficient.

Factors critical to successful implementation were the multidisciplinary team of experts involved and early inclusion of and input from both patients and multiple disciplines, which allowed the project to be constructed to address clear unmet needs. Patients participating in the listening sessions and the demonstration project reported back that they felt that the project was important; continued listening sessions/support groups were requested by participants. Many patients appeared to appreciate the partial anonymity of doing the assessments and questionnaires with a new person (rather than a member of their medical team), and the extended time to share their personal stories. Even patients with long-standing relationships with multiple team members revealed additional key details in their sociodemographic questionnaires, leading to impactful interventions.

It is expected that the project will improve the general awareness of geriatric principles, assessments, and resources among clinic staff and providers, and will lead to several quality improvement projects to address identified needs. An increase in visit volume and subspecialty referral is also expected; in our clinic this was seen in appointments for HIV providers, pharmacists, nutritionists, social workers, employment counselors, housing coordinators, substance abuse counselors, and partners at the school of law for advanced directives. The key challenge to a project of this magnitude includes sustainability after grant funding no longer covers the cost of research assistants and patient incentives. Additional hurdles include duration of time to conduct assessments and to review results with patients, patient referral fatigue, lack of local resources to adequately and quickly address all identified deficiencies, and competing priorities in a population with significant socioeconomic struggles.

Government Partnerships

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Government partnerships are helping us reconfigure practices as the COVID-19 epidemic has forced a change in the way we provide patient care. The quantity of educational content and technical assistance in support of older PWH has changed significantly. Recently, the NYS AIDS Institute's (AI) Medical Care Criterion Committee posted a Guidance for Addressing the Needs of Older Patients in HIV Care (https://www.hivguidelines.org/hiv-care/aging-guidance/#tab_2); the AI is also providing support for a joint subcommittee (consumers and providers) on HIV, Aging, and Long-term Survivors. Currently, this committee is helping to develop and publicize a statewide survey (based at Syracuse University, Maria T. Brown, PhD, Primary Investigator) regarding the needs of older PWH and long-term survivors, and recommendations for meeting those needs. New York City is creating a train-the-trainers program and resource guide for clinical sites and is sponsoring a Request for Proposals to create a clinical program modeled on San Francisco's Golden

Table 1. Summary of Problems and Suggested Solutions for People Aging with HIV

Clinical topic	*Current challenges to care*	*Recommendations for future studies*
ART Adherence and Pharmacokinetics	Decreased efficacy, increased toxicity, decreased adherence, polypharmacy	Optimized regimens designed for older patients: balanced between side effects, toxicity, and efficacy
Muscle and Adipose Tissue in PWH	Increased inflammation, weight gain and visceral adipose deposition, reduced aerobic capacity/increased oxidative stress in muscle tissues, altered lipid metabolism, establishment of persistent viral reservoir	Improved understanding of mechanistic interactions between HIV, ART, and Aging, future inquiry into ART therapies with better penetration of muscle/adipose tissue, preventative measures to strengthen muscles/reduce body fat with age
Fatty Liver and Frailty	Increased risk of NAFLD, leading to liver fibrosis and cirrhosis	Lifestyle changes to reduce cardiovascular and metabolic factors that may exacerbate risk to liver, pharmacotherapy to alleviate early stage existing liver pathology, Revision of ART regimen to minimize therapy-related liver damage
Bone Mineral Density	Significant impact to bone density associated with initiation of ART	Development of or switching to newer ART therapies (i.e., integrase strand transfer inhibitors) with less effects on bone density, consistent medical screening of bone density
Falls and Fractures	Increased risk of osteoporosis, underestimation of fracture risk in PWH	Switching to regimens that avoid tenofovir or protease inhibitors, improved screening techniques to improve diagnostic accuracy in PWH, therapeutic medications and health supplements to support bone health (anti-resorptive and anabolic therapies, also calcium, vitamin D), physical and environmental modifications to improve fall prevention
Periodontal Health and Dementia	Periodontal disease can trigger inflammation and tissue damage that may allow microbes to enter systemic circulation and cause pathologies in other body systems, potentially affecting amyloid burden and Alzheimer's risk	Consistent dental screening and cleaning to maintain dental health, particularly in older PWH, monitoring of amyloid burden from middle age, particularly in those with other diseases that cause inflammation (such as PWH)
Ocular Disease and Inflammation	Increased risk of age-related macular degeneration and cataracts in PWH, with symptoms occurring roughly 11–24 years earlier	Screening for retinal health and visual impairments regularly, treatment strategies to alleviate HIV-related inflammation
Neuropathy	Neuropathy develops in up to 45% of PWH over the lifespan, despite effective viral suppression via ART	Maintenance of a healthy body weight, decrease cardiovascular risk factors, determine the underlying biomechanisms that may contribute to distal nerve damage, develop and evaluate novel treatments to encourage neurite outgrowth and potential regeneration of affected nerves
Clinical Geriatric Assessment of PWH over 50	Increased risk and earlier experience of age-related dysfunctions in PWH is not adequately assessed or captured until they reach 50–65, when symptoms are much more significant than uninfected individuals	Development of clearer guidelines for assessing age-related symptoms in PWH, establishment of HIV-specific norms for assessment of cognitive, physiological, and biological markers of aging in primary care settings, implementation of standard geriatric assessments starting at an earlier age

ART, antiretroviral therapy; NAFLD, non-alcoholic fatty liver disease; PWH, people with HIV.

Compass initiative. At the federal level, Health Resources and Services Administration (HRSA) is promoting partnerships between its Geriatric Workforce Enhancement Programs and HIV/AIDS Bureau Ryan White programs (https://www.hiv.gov/blog/ryan-white-and-hivaids-aging-awareness-day). This year it has sponsored webinars on caring for older PWH, published technical assistance guides, and hosted a 2-day virtual technical expert panel to ''discuss methods of creating health care environments and health care teams adequately structured to care for people aging with HIV.''

Despite the increase in support at all levels and the funding of demonstration practices in academic medical centers, roadblocks to care for older PWH include (1) continued siloing of efforts: Information already gathered from town halls and webinars must be widely disseminated, and we must determine how to get the best value from new outreach; (2) the risk of

losing the message about HIV/aging amid the focus on *Ending the HIV Epidemic* programs; and (3) the challenge of meeting the needs of clinical sites of all sizes and all regions, translating what we have learned from grant-supported transformative academic programs for older PWH into practical ideas that resource-limited local programs can use.

Conclusions

In the 11 years since its founding, the Annual HIV and Aging Meeting has committed itself to being a platform for the sharing of multidisciplinary data and innovations in the management, care, and research of comorbidities in older PWH. The speakers at this year's conference provided a breadth of expertise, including metabolic, dental, cognitive, and treatment-related considerations that should be taken into account to support ongoing quality of life for aging PWH. In this article, we summarized a collection of the key plenary speakers from the 2020 meeting, with an emphasis on the prevention of complications before they occur, instead of treating them afterward. The physiological, medical, and psychological changes experienced by those people aging with HIV present a complicated collection of disruptions that are not always applied equally among different body symptoms. Some show clear evidence of accentuated interactions between the effects of advancing age and chronic HIV infection,[17,18,151,152] whereas others argue that aging and HIV are co-occurring, but independent processes.[153–155] In addition, the inherent heterogeneity of HIV infection and treatment from patient to patient can further complicate clinical decisions regarding the optimal combination of approaches to address individual concerns as well as mitigate potential side effects.

As we each continue our research on these important and interrelated topics, several unanswered questions remain. For instance, the implementation of earlier geriatric medical care for PWH is still in its infancy, despite several decades of evidence that age-related complications affect this population at an earlier stage than in the uninfected. Many of these other comorbidities experienced by PWH can also be complicated as much by the treatments as by the disease itself, and research continues to solve these and other important questions. However, the 11th annual HIV and Aging Meeting was a successful platform to discuss and enrich our understanding of these topics, and it encourages further inquiry at every level of care: patients, community advocates, providers, researchers, and trainees.

Authors' Contributions

A.R. Kamkwalala was responsible for the outlining and preparation of the initial draft. A.R. Kamkwalala, A.G., U.R., and A.M. were responsible for revisions and editing. J.C.-M., J.E.L., G.S., M.Y., T.T.B., A.R. Kamer, D.A.J., R.J.E., M.B., M.G., S.S., and E.S. were each responsible for the writing and initial editing of their individual sections.

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J.E.L. has served as a consultant to Merck, ViiV, and Theratechnologies. G.S. has acted as speaker for Merck, Gilead, Abbvie, Novonordisk, Novartis, and Pfizer; served as an advisory board member for Pfizer, Merck, Novartis, Gilead, Allergan, and Intercept; and has received unrestricted research funding from Merck and Theratec. T.T.B. has served as a consultant to ViiV Healthcare, Gilead Sciences, Merck, Janssen, and Theratechnologies. M.B. has received travel and research grants from and has been advisor for Janssen, Roche, ViiV, Bristol-Myers Squibb, Merck Sharp & Dohme, Gilead, Mylan, Cipla, Teva, and Novavax. M.G. receives grant support from Gilead. K.M.E. receives grant support from Gilead and has served as a consultant to ViiV Healthcare and Theratechnologies.

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