Chronic HIV Infection and Aging: Application of a Geroscience-Guided Approach

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Abstract: The ability of virally suppressive antiretroviral therapy use to extend the life span of people with HIV (PWH) implies that the age of PWH will also increase. Among PWH, extended survival comes at a cost of earlier onset and increased rates of aging-associated comorbidities and geriatric syndromes, with persistent inflammation and immune dysregulation consequent to chronic HIV infection and to antiretroviral therapy use contributing to an overall decrease in health span. The geroscience hypothesis proposes that the root causes of most aging-related chronic diseases and conditions is the aging process itself. Hence, therapeutically targeting fundamental aging processes could have a greater impact on alleviating or delaying aging-associated comorbidities than addressing each disease individually. Extending the geroscience hypothesis to PWH, we speculate that targeting basic mechanisms of aging will improve overall health with age. Clinical features and pathophysiologic mechanisms of chronic diseases in PWH qualitatively resemble those seen in older adults without HIV. Therefore, drugs that target any of the pillars of aging, including metformin, rapamycin, and nicotinamide adenine dinucleotide precursors, may also slow the rate of onset of age-associated comorbidities and geriatric syndromes in PWH. Drugs that selectively induce apoptosis of senescent cells, termed senolytics, may also improve health span among PWH. Preliminary evidence suggests that senescent cell burden is increased in PWH, implying that senescent cells are an excellent therapeutic target for extending health span. Recently initiated clinical trials evaluating senolytics in age-related diseases offer insights into the design and potential implementation of similar trials for PWH.

Key Words: geroscience, hallmarks of aging, senotherapeutics, chronic HIV infection, HIV and aging

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INTRODUCTION

Routine use of virally suppressive antiretroviral therapy (ART) has extended the life span of people with HIV (PWH) so that it now approaches that of the general population. The Centers for Disease Control and Prevention estimates that more than 50% of Americans living with HIV in 2018 were aged 50 years or older.[1] With rising ART access throughout the world, the global number of older PWH will continue to increase.[2,3] Improvements in life span have been accompanied by changing patterns of morbidity among PWH. Although deaths and illness from AIDS and opportunistic infections have declined, older PWH experience both earlier onset and increased rates of certain age-associated comorbidities, including cardiovascular disease (CVD), neurocognitive disorders, diabetes, kidney disease, liver disease, reduced bone mineral density, and non–AIDS-defining malignancies.[4–6] PWH also exhibit geriatric syndromes, such as frailty, declines in physical function, and functional disabilities at younger ages than people without HIV.[7] The disproportionately greater prevalence of aging-related comorbidities in PWH extends across both resource-rich and limited care settings.[8,9] Thus, despite improvements in *life span*, older PWH face significantly reduced *health span* (ie, the period of life free from aging-related chronic diseases and disabilities) compared with the general population.

Although the pathophysiologic mechanisms that underlie excess burden of age-associated diseases among PWH remain incompletely understood, qualitative parallels with biological aging processes are noted. Debate exists as to whether excess burden of age-associated diseases among PWH represents *accentuated* aging in which chronic viral infection, HIV disease processes, and/or ART therapy exacerbate chronic non-HIV age-associated conditions and thereby increase their prevalence at every age or rather

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represents a form of *accelerated* aging through shared underlying fundamental aging mechanisms.[10] Accentuated and accelerated aging may be organ- and disease-specific among PWH. Current approaches to alleviate age-related conditions in HIV have met with limited success,[11,12] so that novel approaches are needed. The geroscience hypothesis postulates that targeting fundamental aging processes will delay the onset and progression of multiple age-related disorders with a single intervention. Herein, we propose that current studies in geroscience conducted among older adults without HIV could help guide the evolution of a novel and potentially transformational paradigm for preventing, delaying, and/or attenuating age-related phenotypes seen in PWH.

INFLAMMAGING

In the general population, inflammaging, or the chronic low-grade, sterile inflammation that occurs with advancing age, represents one common feature of biological aging and has been linked to various chronic diseases of aging.[13] Chronic inflammation and immune activation are also linked to increases in age-related comorbidities among PWH.[11] Even with long-term ART use, systemic levels of immune activation and inflammation remain elevated in PWH compared with people without HIV. Elevations in levels of biomarkers of inflammation, such as interleukin-6 (IL-6), C-reactive protein (CRP), soluble tumor necrosis factor-α, soluble CD163, and sCD14, have been associated with onset of age-associated diseases in PWH.[14,15]

Both common aging pathways and processes specific to HIV and its treatment contribute to excess chronic inflammation in PWH.[10] Some known drivers of chronic inflammation in the general population are enriched among PWH. For example, rates of tobacco smoking, recreational drug use, sedentary lifestyle, poor diet, and chronic coinfections, such as cytomegalovirus (CMV) and hepatitis B and C virus, are increased among PWH.[11] Microbial dysbiosis is also associated with heightened inflammation and age-associated diseases in the general population and is increased among PWH.[16] Early in HIV infection, there is a loss of gastrointestinal tract integrity that persists even after ART initiation. As a result, ongoing dysbiosis and microbial translocation contribute to persistent inflammation even among virally suppressed PWH.[17] The contribution of the HIV reservoir (ie, HIV persistence despite ART use) to chronic inflammation and immune activation is not well understood. Although HIV T-cell reservoir size does not correlate with systemic inflammatory markers,[18] monocytes and macrophages are also viral targets and have an HIV-induced proinflammatory profile[19] that ART does not completely abrogate.[20,21] Although ART initiation reduces systemic inflammation through HIV suppression, certain antiretroviral therapies may contribute to inflammation. Older generations of nucleoside reverse transcriptase inhibitors (NRTIs) and protease inhibitors were associated with untoward alterations in metabolic and lipid profiles as well as with mitochondrial toxicity.[22] Abacavir use has also been associated with increased CVD risk and platelet activation.[23,24] More recently, integrase strand transfer inhibitors use has been linked to weight gain.[25] Although ascertainment of metabolic ramifications of integrase strand transfer inhibitor–associated weight gain comprise areas of active investigation, obesity in general contributes to chronic inflammation[26] regardless of HIV serostatus as well as to increased senescent cell burden.[27,28] Although inflammaging is a phenomenon common to PWH and HIV-uninfected people who has been linked to age-associated disease, comparisons of inflammatory pathways and potential mediators by HIV serostatus are an area of ongoing study.

Targeting inflammatory pathways to attenuate age-related disease among PWH has met with limited success to date. Clinical trials of both aspirin[29] and low-dose methotrexate[30] failed to demonstrate lower biomarkers of inflammation levels among PWH. However, a 10-person pilot study of canakinumab, an IL-1β antagonist, did demonstrate reductions in biomarkers of inflammation and monocyte activation.[31] A larger trial to evaluate effects of canakinumab on markers of inflammation and CVD is underway (NCT02272946), although the agent's high cost and potential for immunosuppression remain a concern. Statin use has had some beneficial effects on markers of inflammation[32]; REPRIEVE (NCT02344290), an ongoing, large, randomized clinical trial, will examine the effects of pitavastatin use on CVD and inflammation in PWH who are without clinical indications for statin use. Because the Janus kinase (JAK) signal transducer and activator of transcription pathway is implicated in the proliferation of the HIV reservoir, there has been considerable interest in using JAK inhibitors to modulate levels of inflammation as part of a functional cure strategy among PWH. However, in a clinical trial among PWH, ruxolitinib only led to a modest decrease of sCD14 and a nonsignificant change in IL-6 levels.[33] Interestingly, JAK inhibitors can inhibit the proinflammatory secretory phenotype of senescent cells in vitro and in vivo.[34] In aged mice, ruxolitinib treatment reduced inflammation and improved metabolic function.[35] For none of these investigative interventions have reductions in adverse clinical events been observed.

Efforts to target drivers of chronic inflammation in PWH have also only met with modest success. Interventions targeting microbial translocation with the use of probiotics,[32] sevelamer,[36] and rifaxmin[37] failed to reduce levels of markers of inflammation. Treatment of chronic CMV coinfection with valganciclovir in PWH reduced markers of T-cell activation,[38] although long-term toxicity is a limitation of this approach. A new trial will assess the effect of the antiviral letermovir, which is better tolerated, on levels of chronic inflammation in PWH who also have asymptomatic CMV infection (NCT04840199). Although several studies evaluating anti-inflammatory interventions among PWH are ongoing, a broader approach targeting more fundamental biological mechanisms of aging may provide new insights into and therapeutic strategies to address age-related phenotypes observed in this population.

THE GEROSCIENCE APPROACH

The geroscience hypothesis posits that therapeutically targeting fundamental mechanisms of aging will have a

significantly greater impact on overall human disease burden than successfully curing any one individual disease. Research into the biology of aging has led to the identification of hallmarks or "pillars" of aging that represent the varied mechanistic drivers of aging physiology.[39] These include impaired adaptation to stress, increased burden of damaged macromolecules and organelles, epigenetic alterations, mitochondrial dysfunction, inflammation, impaired proteostasis, loss of stem/progenitor cell function, altered metabolism, and increased senescent cell burden. Although historically viewed as distinct types of biological processes, growing evidence demonstrates that these aging hallmarks are intricately linked to one another,[40] suggesting that improving one hallmark will improve the others. The overarching premise of adapting the geroscience approach to PWH is that interventions targeting biological aging processes, postulated to delay the onset and progression of pathologies attributable to biological aging (Fig. 1A), will similarly impact aspects of age-associated morbidities that can be attributed to HIV (dark green arrow in Fig. 1B) as well as those attributable to both HIV and aging in PWH (light green arrow in Fig. 1B).

Several studies have begun to describe the hallmarks of aging in PWH. Epigenetic alterations in DNA methylation patterns, histone modification, and chromatin remodeling accompany aging and have been associated with age-associated diseases in the general population.[41,42] Studies measuring the "epigenetic clock" among PWH revealed that untreated HIV infection increases (hastens) DNA methylation age.[43] ART treatment only moderately improves epigenetic age so as to diminish the latter's differences with chronologic age in PWH.[44] However, whether epigenetic changes serve as accurate biomarkers of age-related disease or treatment efficacy in PWH remains uncertain.

In the general aging population, telomere attrition has also been associated with aging and multiple age-related disease conditions.[45] Shorter telomere length has been observed in PWH compared with age-matched people without HIV.[46,47] Shorter leukocyte telomere length is also associated with CVD in PWH.[48] Some studies indicate that NRTIs inhibit telomerase activity,[49] although this has not been a consistent finding.[46] Further work is needed to understand how the dynamics of telomere attrition across tissue types differ by HIV serostatus among older adults, and how telomere attrition is linked to age-related diseases in PWH.

A progressive decline in mitochondrial function accompanies aging. Mitochondrial dysfunction is linked to reduced muscle function, cardiorespiratory fitness, and cognitive function in PWH.[50,51] Use of early NRTIs were associated with mitochondrial alterations[52]; use of more recent NRTIs, such as abacavir and tenofovir, also can have mitochondrial effects.[53] Further research is needed to examine contemporary ART's effect on mitochondrial function and age-related disease in PWH.

Growing interest exists in characterizing cellular senescence among PWH as a promoter of inflammaging and assessing whether it can be therapeutically targeted as it has been in non-HIV aging populations.[13] Cellular senescence is a state of essentially irreversible proliferative arrest driven by excessive replication, oncogene activation, and different types of stresses, including telomere shortening, DNA damage, high serum glucose, increased reactive oxygen species, infections, and protein aggregation.[54] Senescence is mediated by upregulation of the cell cycle regulators, $p16^{INK4a}$/Rb and/or $p53/p21^{CIP1}$, and it can be amplified by a number of mediators and pathways, including ataxia-telangiectasia–mutated kinase, IκB kinase/nuclear factor-κB, JAK/SAT, GATA binding protein 4, and mechanistic target of rapamycin (mTOR).[55] A significant percent of senescent cells (SnCs) demonstrate increased secretion of proinflammatory ILs, chemokines, growth factors, proteases, receptors, metabolites, lipids, noncoding nucleotides, extracellular vesicles, and certain extracellular matrix components and modifiers, which collectively have been termed the senescence-associated secretory phenotype (SASP).[56] In younger mammals, the SASP serves to stimulate the immune

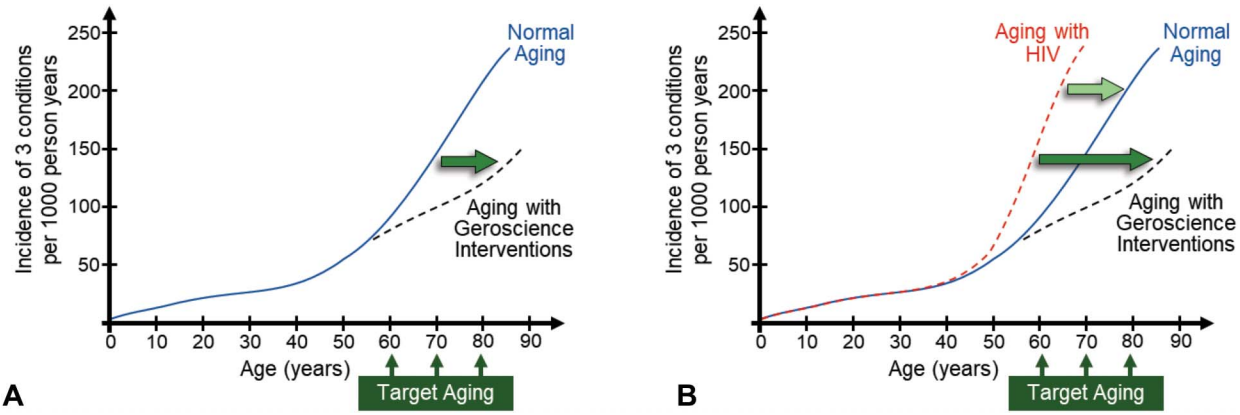

FIGURE 1. HIV as an additional consideration in geroscience-guided approaches for delaying onset and progression of multiple chronic diseases. Geroscience interventions target biological aging processes to delay the onset and progression of pathologies attributable to biological aging (A). The premise of adapting a geroscience-guided approach to PWH is that such interventions will similarly impact facets of age-associated morbidities that can be attributed to HIV (dark green arrow in B) as well as those attributable to both HIV and aging in PWH (light green arrow in B).

system to clear SnCs. However, if SnCs are not cleared, they can exert deleterious paracrine and systemic effects through proinflammatory SASP. Some SnCs also demonstrate increased cytoplasmic mitochondrial DNA, cytoplasmic chromatin fragments, and/or increased expression of the Line-1 retrotransposon, which can activate cytoplasmic DNA sensing cyclic-GMP-AMP synthase/stimulator of interferon gene (cGAS/Sting) and/or Toll-like receptor 9 (TLR9) pathways to induce senescence and thereby exacerbate the SASP.[57] Because the cGAS/Sting and TLR9 pathways have evolved to sense viral double-stranded RNA and DNA, it is possible that senescence may represent a cell fate mechanism to limit viral replication and spread.

SnCs accumulate with age in different tissues and at sites of pathology in multiple age-related diseases and conditions, including pulmonary fibrosis, osteoarthritis, osteoporosis, atherosclerosis, Alzheimer disease, and even preeclampsia.[54] The genetic depletion of SnCs in conjunction with transplantation of SnCs has established that SnCs not only accumulate with aging in numerous mammalian models but also can drive aging phenotypes and disease.[58–60] In addition to aging and disease, the SASP of SnCs, including senescent immune cells, can contribute to loss of resilience to pathogen exposure.[61] Importantly, SnCs-induced SASP is further exacerbated by pathogen-associated molecular patterns and damage-associated molecule patterns through the stimulation of TLRs, leading to the spread of senescence and tissue damage.[61] In aged mice, the SASP following pathogen exposure leads to an increased risk of cytokine storm, with increased morbidity and mortality. Increases in the SASP with age and disease can also impede immune function, further reducing resilience to pathogen exposure and the ability of the immune system to clear SnCs. We have termed this the "Threshold Theory of SnC Burden," which hypothesizes that once SnC burden reaches a certain point, SnCs are not cleared by the immune system fast enough to keep pace with the rate of formation of new SnCs.

There is growing evidence linking cellular senescence, accelerated aging, and chronic HIV infection. HIV infection and ART therapy are associated with increased cellular senescence both in vitro and in human studies.[15,62,63] Chronic HIV infection and certain ART regimens are postulated to lead to oxidative stress, mitochondrial dysfunction, and inflammation, thus generating physiologic stress that drives cellular senescence. In addition, levels of SASP biomarkers are associated with multimorbidity in PWH.[64] However, better characterization of SnCs and SASP profiles that contribute to and are associated with age-related conditions in PWH is needed to identify mechanisms and potential biomarkers for therapeutic interventions.

PHARMACOLOGIC GEROPROTECTORS

Geroprotectors are drugs that target fundamental mechanisms of aging. Table 1 provides a list of current geroscience-guided clinical trials that use geroprotectors. Figure 2 illustrates these compounds' target pillars of aging. Recently, multiple types of senotherapeutics have been identified; these are geroprotectors that target SnCs. They include senolytics, which selectively kill SnCs, and senomorphics, which attenuate the pathological SASP and/or improve organelle function. The first senolytics identified were the combination of dasatinib and quercetin (D + Q), followed by fisetin, heat shock protein 90 inhibitors, and B-cell lymphoma 2 (BCL-2) family inhibitors. Senolytic use has positive effects on health span and life span in numerous mouse models of disease, frailty, and old age. An advantage of senolytics is that they can be administered intermittently, every few weeks or months, to yield a therapeutic impact, thus limiting toxicity.

Several senolytics are Food and Drug Administration-approved anticancer drugs or natural products, lending themselves to rapid translation to exploit their senolytic properties in noncancer populations. D + Q, fisetin, UBX0101, an inhibitor of the p53-MDM2 interaction, and the BCL-X_L inhibitor UBX1325, are currently being studied in more than a dozen clinical trials. In an open-label, phase-1, pilot study of participants with diabetic kidney disease (NCT02848131), D + Q reduced expression of senescence markers in adipose tissue, and SASP factors in the blood.[65] In an open-label study of intermittent D + Q treatment in people with idiopathic pulmonary fibrosis (NCT02874989), there was an improvement in physical function and a trend toward reduction in certain serum SASP proteins.[66] D + Q is being studied in clinical trials targeting Alzheimer disease (NCT04063124; NCT04785300; NCT04685590), skeletal health (NCT04313634), and treatment of adult survivors of childhood cancers (NCT04733534). The senolytic natural flavonoid fisetin is currently being evaluated in clinical trials as a treatment for chronic kidney disease (NCT03325322), skeletal health (NCT04313634), frailty (NCT03675724), and osteoarthritis (NCT04210986), whereas the BCL-2 family inhibitor UBX1325 is being evaluated for macular edema (NCT04537884). Although findings from these clinical trials have not yet been reported extensively, taken together, preliminary results suggest target engagement with limited toxicity in humans.[65,66]

To date, no clinical trials employing senotherapeutics to target age-related diseases have been undertaken in PWH. Several senolytics have been explored as part of investigational HIV cure strategies because some senotherapeutic agents have an impact on the HIV viral reservoir.[15] The Bcl-2 inhibitor venetoclax reduces the HIV reservoir in vitro following reactivation and homeostatic proliferation.[67] In a small study of men with HIV and chronic myeloid leukemia, dasatinib decreased HIV reservoir size and proviral reactivation.[68] These early clinical data provide additional support for investigation of senotherapeutic agent use in PWH.

Diverse compounds have been evaluated for potential geroprotective effects. These include metformin, which is a senomorphic[69] possessing other pleiotropic effects relevant to the hallmarks of aging including reducing oxidative stress, mTOR signaling, and DNA damage, impacting mitochondrial energetics, and it potentially possesses some senolytic activity.[70–72] The Targeting Aging through Metformin (TAME) clinical trial is being developed to test the hypothesis that metformin can delay the development or progression of age-related chronic diseases—such as heart disease, cancer, and dementia.[73] Rapamycin and rapalogs, such as everolimus,

TABLE 1. Current Clinical Trials Implementing the Geroscience Approach

Candidate Geroprotector	Trial	Indices	1 Outcome	2 (3) Outcomes	Sponsor
Metformin Antihyperglycemic	TAME	Age-related comorbidities	Incidence of age-related disease	Physical and cognitive function; geriatric syndromes	
Targets: AMPK Complex I cAMP GPDH Microbiome	**NCT03309007**	Prediabetes	LC3 autophagy score		U NM
	NCT02432287	≥60 yrs old	Transcriptome SKM and adipose tissue	Insulin sensitivity and secretion	AE CoM
	NCT02308228	≥65 yrs old	Type 2 myofiber diameter	CT-SKM hypertrophy; strength, DXA lean mass; insulin sensitivity	UAB
	NCT04264897	40–75 yrs old	Insulin sensitivity; complex I activity	Glucose monitoring; HbA1c	OMRF, NIA
	NCT03451006	≥60 yrs old	Frailty, balance, standing from chair, gait speed	Serum IL-6, MMP, PAI, MCP-1, Activin	Mayo Clinic
	NC03861767	Surgery patients	Hospital-free days	ICU admission; re-operation; readmission DVT, PE, infection; organ failure; hospital stay; mortality; discharge site; survival	UPMC
	NCT03713801	63–90 yrs old	Antibody response to PCV13	Immunophenotypes	UTHSCSA
	NCT03072485	≥55 yrs old	Transcriptome skin	Wrinkle score	Stanford U
	NCT03996538	≥65 yrs old	Granzyme B and IFNγ in PBMC after flu vaccine	Antibody titer, T-cell GLUT expression and O_2 consumption, frailty	UConn
NR NAD^+ source	**NCT03818802**	65–80 yrs old	VO_2 max; 6 min walk, SPPB, CTX SKM respiration and gene/protein expression	Serum glucose, insulin, cholesterol, HbA1c; OGTT	Mayo clinic
	NCT04907110	65–80 yrs old	Myofiber O_2 consumption	VO_2 max, 6-min walk; SKM NAD^+, p-MRS; MRI; DXA, PRO quality of life; CMP, cycling energy expenditure, indirect calorimetry during sleep, exercise efficiency	Maastricht U (NL)
	NCT04990869	≥60 yrs old COPD	Sputum IL-8	Blood NAD^+, IL-6, IL-10, TNF-α, CRP, MMP-9 (metabolomics PBMCs; RNAseq nasal epithelium; DNAme PBMC)	U Copenhagen (DK)
	NCT04407390	≥70 yrs old COVID-19	Need for O_2	Mortality, sepsis, circulatory failure, days in hospital, blood NAD^+	U Copenhagen (DK)

TABLE 1. (*Continued*) Current Clinical Trials Implementing the Geroscience Approach

Candidate Geroprotector	Trial	Indices	1 Outcome	2 (3) Outcomes	Sponsor
NMN NAD^+ source	**NCT04228640**	40–65 yrs old	Blood NAD^+; 6 min walk; BP; pulse pressure; PRO;	Adverse events, CMP, lipid profile (BMI, HOMA)	EffePharm LTD
	NCT04823260	40–65 yrs old	Blood NAD^+/NADH, 6 min walk, PR health, telomere length	Safety, tolerability (BMI; HOMA, biologic age Ai 3.0 calculator)	Abinopharm, Inc.
	NCT04685096	40–65 yrs old ♀	Wrinkles, eye bags, dark circles, relaxed features	PRO on skin	Seneque SA
	NCT05040321	55–85 yrs old AD	CSF (NMN)	CSF (NMN metabolites); MRI (brain NAD^+); PBMC [NAD^+]; serum HbA1c, IGF1, T3, IL-6, TNFα; urinary F2-isoprostane (CSF Aβ; cognition; ADL; neuropsych symptoms)	Brigham and Women's
	NCT03151239	Cardiometabolic function 55–75 yrs old	SKM insulin sensitivity	Liver and adipose insulin sensitivity, fat mass; triglycerides, BP, plasma glucose, FFA, NAD^+	Washington U
	NCT04571008	Glucose metabolism disorders; 45–75 yo	SKM insulin sensitivity	Glucose tolerance	Washington U
	NCT04903210	HTN 18–65 yrs old	Flow-mediated dilation, baPWV	BP, PBMC NAD^+, sleep quality, adverse events	Sun Yat-Sen U (China)
Rapamycin mTOR inh.	**NCT04488601**	50–85 yrs old	DXA–visceral fat	Bone density, lean mass, adverse events, CBC, CMP, serum IGF-1, HbA1c	AgelessRx UCLA
+metformin, D+Q, fisetin, glucosamine, NR, resveratrol	**NCT04994561**	Aging	Adverse events; DXA, BP, MMP-9; HOMA-IR; epigenetic clock		Vitality in Aging Research Group, Inc.
	NCT01649960	≥60 yrs old	Frailty	PRO quality of life, mitochondrial DNA copy #; senescent preadipocytes	Mayo Clinic
	NCT02874924	70–90 yrs old	T-cell number	Physical performance, cognitive function, ECG, MRI diastolic filling	UTHSCSA
RTB101	**NCT04584710**	≥60 yrs old COVID-19	Time from positive SARS-CoV-2 test or exposure to first treatment	eDiary to measure compliance and symptoms, safety, tolerability, infection, hospitalization, death	Restorbio Inc; NIA
	NCT00891696	Sarcopenia	SKM protein synthesis	p-mTOR levels	UT Galveston
D+Q Senolytic D targets: BCR/Abl Src c-Kit Ephrin-R	NCT02874989	IPF	Inflammatory makers in skin, BP, BW, HR, CBC, lipid panel, HbA1c, CMP, CRP, IL-6 SASP, p16		Wake Forest U, Mayo Clinic
	NCT02652052	BMT survivors	Frailty		Mayo Clinic
vs. fisetin	NCT04733534	Cancer survivors	Walking speed, $p16^+$ $CD3^+$ PBMC	Safety, tolerability	St. Jude's

(*continued on next page*)

TABLE 1. (*Continued*) Current Clinical Trials Implementing the Geroscience Approach

Candidate Geroprotector	Trial	Indices	1 Outcome	2 (3) Outcomes	Sponsor
	NCT02848131	CKD	# SnCs in skin, fat, blood	Senescent MSCs, MSC function; frailty index, GFR	Mayo Clinic
vs. fisetin	NCT04313634	Skeletal health ≥70 yrs old	CTX-I, P1NP		Mayo Clinic
	NCT04063124	AD	CSF (D+Q)	CSF Tau, Aβ, IL-6, p16, gait, MoCA	UTHSCSA; Mayo
	NCT04785300	AD	Safety and tolerability		Mayo Clinic
	NCT04685590	AD	Adverse events	SASP, CD3 SnC, CDR-SB, ADAS-Cog, PET	Wake Forest U, Mayo Clinic
	NCT04946383	≥40 yrs old	Epigenetic age	DNAme Illumina 850K epic array	TruDiagnostic
Quercetin Senolytic Q targets: PI3K Serpines Other Kinases	NCT0398927	COPD	8-Isoprostane IL1b and IL-8 in BAL, serum CRP and SP-D	(Quercetin) in blood and lungs	Temple U
	NCT01708278	COPD	FEV1%, CBC, CMP		U Michigan
	NCT01376011	Cerebral blood flow 18–75 yrs old	Blood HIF-1, VEGF, EPI, NOS, MCA blood flow	Cognition	Brigham and Women's
Plus fish oil, cinnamon, pomegranate; green and black tes; lipic acid, reseveratrol; curcumin; sesamin; acetyl-L-carnitine	**NCT01752868**	40–60 yrs old	Carotid-femoral pulse wave		Washington U
	NCT0437779	COVID-19	PR COVID, death	Morbidity	Orbiteratec (Turkey)
	NCT04861298	COVID-19	PCR test for SARS-COV-2; PR symptoms	Hospitalization, CRP, LDH, ferritin, CBC	University (Pakistan)
	NCT04853199	COVID-19	Efficacy in treating	Death, hospitalization	Hospital (Tunisia)
	NCT05037240	COVID-19	Prevention of infection		Institute (Italy)
	NCT04907253	CAD	CRP, ANGPTL2 at surgery	Endothelial relaxation, scRNAseq and bulkSeq to measure SnC in endothelium	Montreal Heart Institute
	NCT03943459	CAD progression	Serum SIRT-1 and end-glycation products		Institute (Brazil)
	NCT01839344	Type II diabetes	GTT	AUC, RHI	Bastyr U
	NCT00065676	Type II diabetes; obesity	Glucose absorption		NIDDK

TABLE 1. (*Continued*) Current Clinical Trials Implementing the Geroscience Approach

Candidate Geroprotector	Trial	Indices	1 Outcome	2 (3) Outcomes	Sponsor
Fisetin Senolytic Neuroprotective Antihyperglycemic Inflammatory Cancer Parasitic Viral Bacterial Neovascularize Provasodilator Immune stim. Proteostasis Targets: mTOR Wnt ERK IκBα PI3K TSC1-TSC2	NCT04476953	COVID-19	Serious adverse events, SPO_2/FiO_2	CoV severity status	Mayo Clinic
	NCT04771611	COVID-19	Serious adverse events	Long Hauler syndrome	Mayo Clinic
	NCT04537299	COVID-19 in nursing homes ≥65 yrs old	Change in COVID-19 severity		Mayo Clinic
	NCT03675724	Frailty ≥70 yrs old	Decrease in serum SASP		Mayo Clinic
	NCT03430037	Frailty ≥70 yrs old	6-min walk; gait speed		Mayo Clinic
	NCT04210986	Knee OA 40–80 yrs old	Adverse events, CMP	Blood SASP and CTX-II, PBMC SnC, 6 min walk, timed up-and-go, fast 40-m walk; kinematics, stair climbing, isokinetic dynamometry, PRO pain, knee function, MRI cartilage, need steroids, time to alternative Rx	Steadman Philippon Research Inst
	NCT04770064	Knee OA 35–80 yrs old	CMP	Pain, OA index, sit/stand, MMP-3, CTX-II (adherence; need for steroids)	Brigham and Women's
	NCT03325322	Diabetics and CKD 40–80 yrs old	Serum SASP, CRP, MSC function including migration	Fried frailty, GFR, proteinuria, adverse events	Mayo Clinic
	NCT02741804	MCI ≥55 yrs old	Retinal scan–amyloid	Cognitive test, dx of dementia, MRI, FDG-PET, CMP, BP, HbA1	Cedars-Sinai
+ Losartan	NCT04815902	Knee OA 40–85 yrs old	Adverse events	Above + BMAC, urine CTX-II, synovial fluid content	Above + NIAMS
vs other natural products	NCT02909686	Gulf war illness 39–65 yrs old ♂	Disease severity	PRO pain, fatigue, mood, cognition, dermatologic conditions, respiratory and GI symptoms	UAB
+ Other natural products = Glaucocetin	NCT04784234	Open angle glaucoma 40–80 yrs old	Visual field	PR quality of life	Wills Eye
UBX1325 Senolytic Target: Bcl-xL	NCT04537884	DME, neovascular age-related macular degeneration ≥50yo	Ocular and systemic safety and tolerability	Plasma [UBX1325]	Unity Biotechnology Inc
	NCT04857996	DME ≥18 yrs old	Ocular and systemic safety and tolerability	Above + SD-OCT-macular changes, edema, visual acuity, anti-VEGF rescue	

Column 1 indicates the therapeutic intervention and its mechanism of action. Column 2 indicates the ClinicalTrials.gov identifier. Bold font indicates the trial identified searching the clinical trials database by disease outcome-aging and the name of the therapeutic. Data collected September 11, 2021.

Aβ, Amyloid beta; AD, Alzheimer disease; ADAS-Cog, Alzheimer Disease Assessment Scale-Cognitive subscale; ADL, activities of daily living; AMPK, AMP-activated protein kinase; ANGPTL2, angiopoietin like 2 protein; AUC, area under the curve; BAL, bronchoalveolar lavage; baPWV, brachial-ankle pulse wave velocity; BMAC, bone marrow aspirate concentrate; BMI, body mass index; BMT, bone marrow transplant; BP, blood pressure; BW, body weight; CAD, coronary artery disease; cAMP, cyclic adenosine monophosphate; CBC, complete blood count; CDR-SB, clinical dementia rating scale sum of boxes; CKD, chronic kidney disease; CMP, complete metabolic profile including serum electrolytes, liver function tests, renal function tests ± tumor lysis syndrome panel; COPD, chronic obstructive pulmonary disease; CSF, cerebrospinal fluid; CT, computerized tomography; CTX, C-terminal telopeptide of type I collagen; a marker of cartilage turnover; DME, diabetic macular edema; DNAme, DNA methylation; DVT, deep vein thrombosis; DXA, dual-energy x-ray absorptiometry–scan to measure bone density and body composition; ECG, electrocardiogram; FEV, forced expiratory volume; FFA, free fatty acids; GFR, glomerular filtration rate; GLUT, glucose transporters; GPDH, glycerol-3-phosphate dehydrogenase; GTT, glucose tolerance test; HbA1c, hemoglobin A1c; HIF-1, hypoxia-inducible factor 1; HOMA, homeostatic model assessment; a measure of pancreatic β-cell function; HR, heart rate; HTN, hypertension; ICU, intensive care unit; IFN, interferon; IGF-1, insulin-like growth factor-1; IPF, idiopathic pulmonary fibrosis; LC3, light chain 3; MCA, middle cerebral artery; MCP-1, monocyte chemoattractant protein-1; MMP, matrix metalloproteinase; MoCA, Montreal Cognition Assessment; MRI, magnetic resonance imaging; MSC, mesenchymal stem cell; NMN, Nicotinamide mononucleotide; NOS, nitric oxide synthase; NR, Nicotinamide riboside; OA, osteoarthritis; OGTT, oral glucose tolerance test; PAI, plasminogen activator inhibitor-1; PBMC, peripheral blood mononuclear cells; PCV13, pneumococcal conjugated vaccine; PE, pulmonary embolism; PET, positive emission tomography; P1NP, amino-terminal propeptide of type 1 collagen; a serum marker of bone turnover; PR, patient reported; p-MRS, phospho-magnetic resonance spectroscopy; PRO, patient reported outcomes; RHI, reactive hyperemia index; scRNAseq, single-cell RNAseq; SD-OCT, spectral domain optical coherence tomography; Short Physical Performance Battery; SKM, skeletal muscle; SP-D, surfactant protein; SpO2/FiO2, oxygen saturation to fraction of inspired oxygen ratio; a predictor of acute respiratory distress syndrome; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

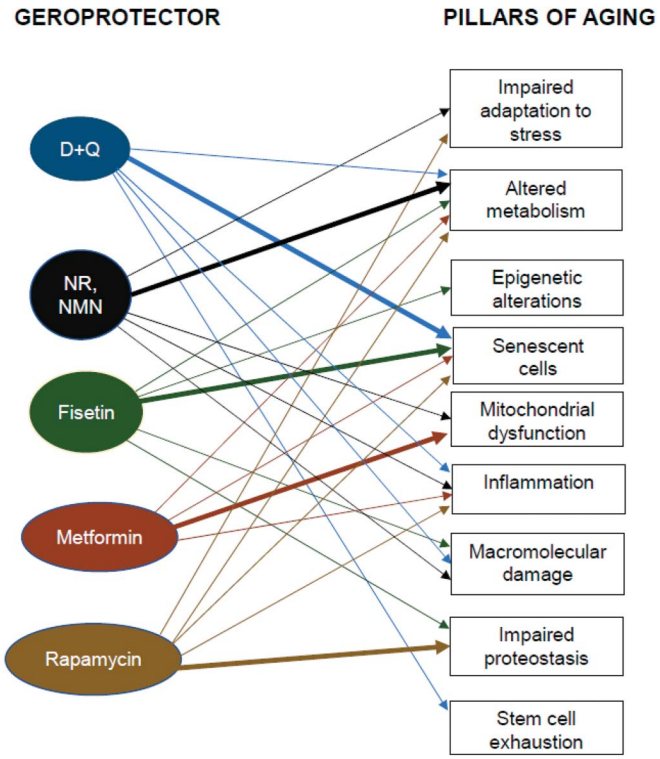

FIGURE 2. Geroprotector effects on the pillars of aging. The hallmarks or "pillars" of aging represent fundamental mechanisms of biologic aging. Geroprotectors are drugs that target these aging processes. This figure depicts geroprotectors that are currently being studied in ongoing geroscience-guided clinical trials and each agent's target pillars of aging. Bold arrows indicate the geroprotector's primary target; thin arrows indicate secondary targets and effects. NR, nicotinamide riboside; NMN, nicotinamide mononucleotide.

sirolimus, or tacrolimus, which inhibit mTOR, are also senomorphic SASP inhibitors.[69] Their use extends health span and life span in experimental animals.[74,75] Because decreased cationic nicotinamide adenine dinucleotide (NAD^+) can lead to increased oxidative stress and metabolic dysfunction,[33,76] the NAD^+ precursors, nicotinamide mononucleotide, and nicotinamide riboside, may offset the decline of NAD^+ with aging, and their use appears to alleviate some age-related phenotypes.[77,78] SnCs can promote accumulation of the leukocyte ectoenzyme, CD38, which degrades NAD^+ and is may be the key driver of age-related declines in NAD^+[77,79]; consistent with this, senolysis leads to reduction in CD38 activity. Of note, CD38 is overexpressed among PWH and is associated with $CD4^+$ and NAD^+ depletion iH.[80,81] 17α-estradiol is a nonfeminizing estrogen that is present in mammals of both genders.[82,83] 17a-estradiol levels decline with age and its replacement therapy; extends life span, reduces metabolic dysfunction, and improves some neurodegenerative diseases in mice.[84–86] Sirtuin agonists, eg, the polyphenol resveratrol, have antioxidant and anti-inflammatory properties.[87] Ketogenic diets and ketone bodies can reduce adipose mass and obesity and might hold promise for alleviating age- and infection-induced morbidities.[88,89] Dietary modifications, such as caloric restriction (CR), compressed eating, or intermittent fasting (IF), may be effective against some age-related diseases and syndromes.[90–92] IF consists of alternating feeding schedules, whereas CR limits calorie intake without malnutrition. Both reduce oxidative stress and inflammation.[92,93] IF and CR inhibit the mTOR pathway and promote autophagy, both of which are linked to inflammation and aging.[94,95] Whether combining these interventions and thereby targeting different but interlinked hallmarks of aging can exert salutary effects that are less than additive, additive, or synergistic remains to be ascertained.

Several histone deacetylase inhibitors have been tested for their impact on the HIV reservoir without substantial success. However, the histone deacetylase inhibitor panobinostat reduces CRP and IL-6 in PWH on suppressive ART.[96] The mTOR inhibitor, sirolimus, reduces markers of T-cell cycling, and in one clinical trial, it somewhat reduced the HIV reservoir in PWH.[97] In a small study of metformin in PWH, there was a reduction in mTOR activation/phosphorylation as well as colonic $CD4^+$ T-cell infiltration.[98] Such preliminary results involving diverse investigative interventions provide support for exploring whether geroscience approaches can be of benefit among PWH.

CONSIDERATIONS FOR GEROSCIENCE-GUIDED CLINICAL TRIALS IN PWH

Advances in geroscience-based approaches and therapeutics offer a novel paradigm for addressing age-related disease in chronic HIV infection. The growing population of older PWH requires a new focus upon evaluating interventions aimed at reducing multimorbidity, improving health span, and promoting resilience. Because many of the same clinical features and pathophysiologic mechanisms of chronic diseases that are operative in older adults without HIV are also observed and have an accelerated rate among PWH, we speculate that geroscience-based interventions can promote healthy aging in PWH. Ongoing geroscience-based trials in the general aging population like TAME can guide the approach to such studies, but it must also be informed by unique challenges that chronic HIV infection presents. In this section, we will use the classic 5 Ws (Who, What, When, Where, and Why) to provide a framework for key considerations in designing geroscience-guided trials for PWH (summarized in Table 2).

First, we must consider why we assume that geroscience-guided approaches should work in PWH. Common chronic diseases associated with aging and geriatric syndromes have multifactorial etiologies, including lifestyle, behavioral, social, and economic factors.[99] Biological aging is a major and modifiable risk factor for such chronic diseases and for geriatric syndromes. Therefore, the presence of multiple chronic diseases can amplify the impact of biological aging.[39] PWH exhibit an earlier onset of many of these chronic conditions and an excess burden of multimorbidity.[100] As we have described, HIV-infection and ART can directly impact pillars of aging. Other known drivers of biological aging are also enriched in PWH, including tobacco

TABLE 2. Summary of the "5 Ws" to Consider for Geroscience-Guided Trials in PWH

The 5 Ws	Considerations in PWH	Areas for Further Research
Why assume that geroscience-guided approaches would work?	Geroscience interventions target biological aging processes to delay the onset and progression of pathologies attributable to biological aging.	How do biological aging processes in PWH differ across age-associated morbidities and from observations in older populations without HIV?
	PWH have earlier onset and excess burden of age-related morbidities.	How do biomarkers of aging correlate with chronic disease of aging and geriatric syndromes among PWH?
	HIV infection and ART are linked to biological aging. Known drivers of biological aging are also accentuated among PWH.	
Who might benefit most?	Risk stratification using demographic characteristics, lifestyle factors, comorbidities, and functional status can guide participant selection depending on outcome of interest.	Can biomarkers of aging risk stratify PWH for adverse outcomes?
		How does SARS-CoV-2 coinfection impact biological aging in PWH?
When during a PWH's life to intervene?	PWH have earlier onset of comorbidities associated with aging.	How does the onset and time course of risk factors associated age-related disease compare between PWH and people without HIV?
	Whether an intervention is aimed at preventing or treating age-related disease will affect its timing and effectiveness	
What interventions are the most promising?	Targeting upstream pillars of aging on biological aging pathways may have the greatest impact.	How do particular pillars of aging relate to specific age-related diseases?
	Senotherapeutics represent a promising approach to reduce or delay age-related comorbidities among PWH.	What is the safety profile of geroprotectors in PWH?
		Are there drug–drug interactions between geroprotectors and ART?
	Lifestyle interventions are a promising nonpharmacologic intervention.	What is role for combination therapies and/or multimodal interventions?
	Selection of outcomes is key and dependent on trial goals	
Where will such studies take place?	Multidisciplinary collaborations between teams with expertise in HIV and geriatric medicine are essential.	How can these interventions be adapted for and implemented in resource limited settings?

use, recreational drug use, depression, socioeconomic disparities, and chronic coinfections. As a result, geroscience-based approaches have the potential to mitigate the risk of both common and HIV-specific drivers of aging. Additional studies are needed to further characterize biological aging processes in PWH and how they may differ across age-associated morbidities and may be distinct from observations in older populations without HIV. To avoid further delays in design and initiation of geroscience-guided clinical trials in PWH, biomarker studies offer a starting point for this process. For example, measuring the SnC burden in PWH compared with age-matched older adults without HIV or with matching comorbidity burden will further characterize cellular senescence in PWH and also enable power analyses to estimate sample size for future interventional clinical trials.

Who might benefit most from and when during one's life with HIV to administer a geroscience-based intervention are additional considerations for such clinical trials in PWH. The effectiveness of the intervention will differ depending on whether it is applied as primary or secondary prevention against age-associated disease, that is, before or after at least one major specific age-related clinical event(s) has occurred.[101] To feasibly measure age-related outcomes of interest, eligible participants should also be at an increased risk of comorbidities. Although chronic HIV itself increases the risk of early onset of age-related diseases, additional selection criteria will clearly need to be considered depending on the clinical outcomes to be studied. Such factors might include age and BMI thresholds (eg, older than 50 years in PWH), risk factors that accentuate aging (eg, substance use, obesity, sedentary lifestyle), impairment in certain functional outcomes (eg, prefrailty, gait speed, cognitive function), intermediate metabolic factors (eg, prediabetes), or risk stratification by levels of systemic inflammatory markers or biomarkers of biological aging. Better discernment of how risk factors for the development of age-related disease may differ by HIV serostatus might further guide participant selection. Understanding how the ongoing COVID-19 pandemic impacts long-term health outcomes in PWH is an important area for future research.[102] How SARS-CoV-2 coinfection, particularly Post-Acute Sequelae of SARS-CoV-2 infection or long COVID, and pandemic-incited disruptions in HIV care impact diseases of aging in PWH remains unknown but could be an important consideration for geroscience-guided interventions.

We must also evaluate which of the geroscience therapeutic approaches might be the most promising in terms of impacting target pillars of aging and outcomes of interest. Targeting hallmarks of aging that are further upstream on biological aging pathways (eg, cellular senescence rather than inflammation) may have a broader impact on chronic disease and geriatric syndromes. Improved understanding of how particular pillars of aging are associated with specific age-related diseases among PWH could guide personalized interventions or possibly reveal a common target.

Such improved ascertainment can also guide selection from among available geroprotective agents. The success and favorable safety profiles of senolytics evaluated in recent clinical trials among people without HIV as well as evidence that SnC burden plays a role in age-related disease in PWH support the contention that senotherapeutics represent a promising approach to reduce or delay age-related comorbidities among PWH. Combinations of geroprotectors that target multiple pillars of aging might also be considered. However, it is paramount to assess HIV-specific adverse events and potential drug–drug interactions with ART for any selected geroprotector regimen. Clinical interventions that involve persistent viral reactivation or additional immunocompromise, regardless of other geroprotective effects, would be unacceptable. Because lifestyle factors are also associated with hallmarks of aging, nonpharmacologic strategies, such as exercise-based or dietary interventions, might also be considered. Multimodal interventions combining a geroprotector with lifestyle interventions may have benefits.

Appropriate selection of outcome measures is also key in clinical trials guided by a geroscience approach. To demonstrate that an intervention has an effect on aging, end points should include measures of time to occurrence of one of the collection of possible disease end points rather than focusing on a specific mechanistic pathway. Targeted disease end points should share few risk factors other than age, avoiding overlapping pathogenic mechanisms. A possible approach is to group primary clinical outcomes into distinct causative or risk factor pathways, such as atherosclerosis and CVD, cancers, dementias, diabetes, and all-cause mortality. Secondary outcomes could include functional aging outcomes or disability. For example, the TAME trial includes a primary clinical outcome of time to incidence of age-related disease (myocardial infarction, stroke, congestive heart failure, cancer, dementia/cognitive impairment, or death) with secondary functional aging outcomes of decline in mobility or cognitive function.[70] Factors related to overall resilience and intrinsic recovery or repair capacity, such as vaccine responses or time needed to recover from acute stressors like surgery, might also be considered.[103]Given that geroscience-guided therapeutic trials usually require several years of follow-up for adequate numbers of clinical end points to be observed, levels of carefully selected biomarkers can provide intermediate evidence that an intervention is impacting aging biology. The Biomarkers Workgroup from the TAME trial recently outlined a conceptual framework for selection of blood-based biomarkers in geroscience-guided clinical trials.[104] This group posited that biomarkers selected must be feasible and reliably measurable in a clinical trial setting, represent biologic aging processes, have robust and consistent associations with mortality risk and trial clinical/functional end points, and be responsive to interventions that affect aging biology. Based on these criteria, they selected IL-6, tumor necrosis factor-α receptor I or II, high-sensitivity CRP, growth-differentiating factor 15, insulin, insulin-like growth factor 1, cystatin C, N-terminal B-type natriuretic peptides, and hemoglobin $A1_C$[104]. Similarly, before initiating a geroscience-guided trial clinically involving PWH, further research is needed to identify and validate appropriate aging biomarkers for this population. Clinical researchers must be cognizant that certain biomarkers and many disease risk prediction tools underperform in PWH.[105] Furthermore, additional necessary considerations for trials involving PWH include assessing relationships between selected biomarker levels on HIV viral reservoir, circulating viral load, and immune function.

Finally, we must consider where will these studies will be done and who will lead them. Efforts to design, implement, and analyze findings of geroscience-guided studies will require multidisciplinary investigative efforts that bring together expertise from geroscience, HIV clinicians and clinical trialists, virologists, immunologists, and pharmacologists. As the population of PWH continues to age globally, it will also be essential to understand how to adapt and implement successful geroscience-guided interventions in resource-limited settings.

In conclusion, although modern virally suppressive ART has dramatically extended the life span of PWH, novel approaches are urgently needed to address significant gaps in health span by HIV serostatus that persist globally. The geroscience hypothesis offers a framework to conceptualize mechanisms contributing to and therapeutic targets for age-related comorbidities in PWH. We offer considerations for rapid development of geroscience-guided clinical research trials in PWH. The time has come to refocus HIV care beyond longevity and comorbidity management to include the goals of successful healthy aging.

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