Ageing with HIV

Biological ageing with HIV infection: evaluating the geroscience hypothesis

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Although people with HIV are living longer, as they age they remain disproportionately burdened with multimorbidity that is exacerbated in resource-poor settings. The geroscience hypothesis postulates that a discrete set of between five and ten hallmarks of biological ageing drive multimorbidity, but these processes have not been systematically examined in the context of people with HIV. We examine four major hallmarks of ageing (macromolecular damage, senescence, inflammation, and stem-cell dysfunction) as gerodrivers in the context of people with HIV. As a counterbalance, we introduce healthy ageing, physiological reserve, intrinsic capacity, and resilience as promoters of geroprotection that counteract gerodrivers. We discuss emerging geroscience-based diagnostic biomarkers and therapeutic strategies, and provide examples based on recent advances in cellular senescence, and other, non-pharmaceutical approaches. Finally, we present a conceptual model of biological ageing in the general population and in people with HIV that integrates gerodrivers and geroprotectors as modulators of homeostatic reserves and organ function over the lifecourse.

Introduction

Advances in antiretroviral therapy (ART) have enabled people with HIV to live longer and healthier lives than individuals diagnosed in the earlier years of the HIV pandemic. However, life expectancy and disease-free years of people with HIV variably differ compared with people without HIV, for reasons that include earlier treatment and traditional risk factors across cohorts. The Centers for Disease Control and Prevention estimate that 50% of people with HIV are older than 50 years, and account for 70% of total deaths among people with HIV. The primary causes of death for people with HIV who have access to combination ART are non-communicable diseases such as cancer, cardiovascular disease, and neurocognitive impairment. Older people with HIV also have deficits in physical function, frailty-related syndromes, and many other non-communicable diseases that limit their quality of life. Notably, the prevalence of age-related comorbidities has been found to be considerably higher in people with HIV than in people without HIV across a range of cohorts, including those in Brazil, Italy, and the USA. Efforts to explain this disproportionate comorbid burden in people with HIV have proposed that HIV infection accelerates or accentuates ageing independent of traditional risk factors, without specifying an association between mechanisms of ageing and disease susceptibility. Regardless of whether lifespan (ie, a person’s length of time alive) can be increased through evidence-based interventions, most health-care spending occurs at the end of life owing to a high prevalence of age-related conditions. Improving healthspan (ie, the part of a person’s life during which they are generally in good health) is therefore proposed to have a greater effect on wellbeing and economic indicators for a given population.

The geroscience hypothesis postulates that a discrete set of biological processes creates a global susceptibility to diseases that leads to multimorbidity. Geroscience emerged from key advances in the biology of ageing, including the discoveries that biological ageing is influenced by evolutionarily conserved pathways that are modifiable, and that a discrete set of biochemical mechanisms (termed pillars or hallmarks) drive multiple age-related conditions. Of the five to ten overlapping processes that have been described extensively in the literature, given the constraints of space and scope we have focused on four in this Series paper—macromolecular damage, senescence, inflammation, and stem-cell dysfunction—in the context of people with HIV. Innovations in measuring the rate of biological ageing in relation to chronological age include biomarkers for age-correlated changes in immune function, DNA methylation patterns, and the plasma proteome. Because of the disproportionate burden of comorbidities

Key messages

- Large gaps exist in our understanding of the effect of HIV on the ageing process, even though age-related conditions seem to be more common, and occur at an earlier age, in people with HIV than in people without HIV infection.
- Although many hallmarks of biological ageing appear to be dysregulated in people with HIV, there is a need to precisely define the effect of HIV infection and therapy on the molecular processes defined by geroscience as gerodrivers and geroprotectors.
- Models of ageing that integrate and better define measures of reserve and resilience are needed to holistically define the ageing process and to counterbalance and leverage advances in identifying drivers of ageing.
in people with HIV, and the framing of the biology of ageing as a condition of increasing multimorbid risk owing to loss in homeostatic control of key biological processes, in this Series paper we explore whether advances in the biology of ageing and geroscience inform pathogenesis and provide insight into the management of people with HIV, and, reciprocally, how understanding HIV infection dynamics has informed the science of ageing.

Macromolecular damage
DNA damage and genomic instability
The maintenance of genome stability is continuously challenged by extrinsic and intrinsic destabilising factors that contribute to genomic instability (eg, point mutations, insertions and deletions, or rearrangements of large genomic fragments). Characteristic features of genomic instability are telomere dysfunction, epigenetic alterations, proteostatic stress, and compromised mitochondrial function.

Several mechanisms related to HIV infection can lead to DNA damage and genomic instability. For example, a deficiency in DNA damage response has been observed both in latently infected cells and from exposure to nucleoside reverse transcriptase inhibitors. Long-term HIV-related psychosocial and behavioural stressors, through excessive stimulation of glucocorticoid signalling or sympathetic nervous system (adrenergic) signalling, increase oxidative stress and inflammation, which, in turn, promote DNA damage and genomic instability.

Although there is good evidence for genomic instability in people with HIV, the link between genomic instability and age-related outcomes in people with HIV is less clear. Although new technologies (eg, next-generation sequencing technology) offer the opportunity to survey human genomes, including ageing-related and infection-related genetic damage and genomic instability, the benefits of these technologies are currently limited by an incomplete understanding of the link between ageing-related genetic mutations and clinical outcomes.

Telomere attrition
Analysis of telomere length across multiple tissue types indicates that a shortening of telomere length is generally positively correlated with age in most tissues and in blood cells. Telomere attrition has been associated with multiple disease conditions. However, although knowledge of telomere attrition derived primarily from in-vitro and in-vivo studies suggests that telomere length is a hallmark of ageing, data from epidemiological and clinical studies show such strong linkage between telomere length and characteristics of ageing that causation and correlation cannot yet be differentiated. In the context of chronic, treated HIV infection, shorter telomere length has been documented in the blood cells of people with HIV than in people without HIV, and shorter blood telomere length has been linked to increased cardiovascular risk in people with HIV. Telomere length is also shorter in the lung epithelia of people with HIV than in people without HIV, possibly increasing risk of lung disease.

Although there is evidence for excessive loss of telomere length in people with HIV, and associations of telomere attrition with disease progression, whether incremental declines in telomere length disproportionately increase the risk of disease onset, disease severity, and multimorbidity is unclear. In addition, whether the dynamics of the shortening of telomere length across tissue types in people with HIV differ from age-related declines in people without HIV is also not clear. Finally, more research is needed on the mechanistic links between telomere attrition and physical and neurocognitive function in people with HIV.

Loss of proteostasis
Under normal and stress conditions, protein homeostasis (the equilibrium between protein synthesis and degradation) is maintained by two primary protein-clearance mechanisms: the ubiquitin–proteasome system and autophagy-mediated proteinolysis. Proteostasis declines with ageing, and, conversely, the maintenance of proteostasis increases lifespan. Various non-communicable diseases are associated with impaired protein homeostasis. For example, altered proteostasis and proteotoxicity are linked to diabetes, neurodegenerative conditions, cardiovascular disease, and sarcopenia. Notably, chaperone-mediated autophagy declines with ageing and brain pathology, and, by contrast, mice with preserved chaperone-mediated autophagy have increased lifespan and reduced frailty. Evidence is also emerging that the loss of regulated autophagy affects other hallmarks of ageing, including senescence and stem-cell function.

HIV infection and viral proteins disrupt the autophagy process in various cell types, including macrophages, T cells, microglia, and astrocytes. Notably, HIV-associated neurocognitive disorder is increasing in prevalence among people with HIV despite treatment, and could be due to accentuated brain ageing, or alert chaperone-mediated autophagy that prematurely degrades essential cellular machinery in neurons leading to neurodegeneration, or both. Also, mitophagy is impaired in primary neurons when exposed to the HIV proteins gp120 and Tat.

Although there is clear evidence for deficits in proteostasis in many age-related diseases that disproportionately affect people with HIV, more data are needed that link proteostasis to health-related outcomes, quality of life, multimorbidity, and resilience, by comparing carefully matched people ageing with HIV to people ageing without HIV.

Mitochondrial dysfunction
Human ageing is linked to a progressive decline in mitochondrial function, which is characterised by the accumulation of mutations and deletions in mitochondrial...
DNA (mtDNA), mitophagy, reduced cellular energy production, and a mitochondrial-dysfunction-associated senescence phenotype. Mitochondrial dysfunction preferentially affects tissues with high energy demands, such as the brain, skeletal muscle, and heart, adversely affecting healthspan. Perturbations to this energetic pathway appear to be amplified by inflammation and reactive oxygen species and linked to age-related non-communicable disease.

Earlier nucleoside reverse transcriptase inhibitors were known inhibitors of mtDNA polymerase γ. The consequent accumulation of mtDNA mutations in skeletal muscle and decreased oxidative phosphorylation are well established and represent the earliest evidence of advanced ageing in people with HIV. Evidence from current nucleoside reverse transcriptase inhibitors shows that mitochondrial function might be affected in other cell types, such as renal cells. Abacavir and tenofovir have been shown to decrease the quantity of mtDNA in adipocytes, but only tenofovir decreased oxidative phosphorylation activity. Despite scarce information on other current ART, mitochondrial dysfunction shows the need for research into ageing that specifically focuses on people with HIV, so that the additive effects of ART can be considered.

Mitochondrial dysfunction in people with HIV adversely affects physiological determinants of healthspan. There is accumulating evidence for deficits in skeletal muscle bioenergetics based on deficits in PGC-1α in muscle and reduced skeletal muscle oxidative phosphorylation, which correlates with low cardiorespiratory fitness. Cognitive dysfunction manifested as HIV-associated neurocognitive disorder provides evidence for the direct effects of HIV on mitochondrial function in people with HIV in whom a plasma HIV RNA load is undetectable but virally encoded proteins are expressed in the brain and linked to mtDNA mutations and oxidative damage. Similarly, in people with HIV who have not received ART, numerous virally encoded proteins are implicated in mitochondrial-facilitated apoptosis of CD4 lymphocytes and disrupted mitochondrial biogenesis.

**Cellular senescence and inflammation**

The accumulation of senescent cells with ageing occurs asymmetrically across organ systems and contributes to age-related diseases. Clearance of senescent cells increases lifespan in mouse models. Notably, multiple hallmarks of ageing are influenced by cellular senescence, including inflamming, mitochondrial dysfunction, and stem-cell exhaustion. Inflamming, which was originally considered to be a non-infection, age-related, low-grade inflammation, might both be driven in part by senescence and be a component of the senescence-associated secretory phenotype. Inflamming is exacerbated by multiple factors, including dysbiosis (imbalance of the intestinal microbiota composition) and the associated release of microbial products into the circulation (microbial translocation), and various other stressors that increase risk for many age-related diseases.

The prevalence of age-related comorbidities remains higher in people with HIV than in the general population, which could be due partly to cellular senescence and consequent inflammation. Although there are no universal biomarkers for senescence, a composite score for cellular biomarkers has been associated with multimorbidity in a cohort of people with HIV. Notably, chronic exposure to pathogenic antigens (ie, cytomegalovirus or HIV) drives expansion of T cells into a state of replicative senescence (eg, elevated CD28 and decline in CD57) that is similar to, but distinct from, cellular senescence. People with HIV continue to have chronic low-grade inflammation compared with people without HIV, despite controlled viremia; for example, people with HIV who are on effective ART show persistent elevations in interleukin-6 (IL-6), TNF, soluble CD14, soluble CD163, C-reactive protein, and MCP-1 concentrations in peripheral blood compared with people without HIV.

This observed HIV-associated inflammation is linked to adverse functional outcomes. The contribution of age-related inflammation in compartments and tissues other than peripheral blood remains unclear, as is how inflamming pathways and their associated morbidity risks differ between people ageing with and without HIV.

People with HIV have more exaggerated loss in thymic function than do people without HIV of similar age, and thymic function has been linked to geriatric syndromes such as frailty. However, the mechanistic links between age-related functional decline in lymphoid organs, the emergence and spread of senescent immune cells, and consequent multimorbidity in people with HIV remains unclear.

**Stem-cell exhaustion**

Stem cells reside in most tissues and range from unipotent (eg, muscle stem cells) to multipotent (eg, haematopoietic stem cells), with lineage and cell differentiation outcomes largely influenced by the epigenome, external stimuli, and stress response (eg, to injury). The regenerative potential of stem cells is generally associated with tissue turnover rates and markedly declines with ageing, with characteristic loss in lineage specificity, loss of self-renewal capacity, onset of cellular senescence, and accumulation of damage (eg, proteotoxicity). For example, with ageing, stem-cell function in blood skews towards the myeloid lineage, skeletal muscle repair declines, and neurogenesis in the brain declines. Chromatin modifications that limit stem-cell function have been observed in brain and muscle.

In the context of HIV infection, loss in stem-cell functionality is evident across the range of stem-cell regenerative potentials. For example, loss of haematopoietic progenitors (CD34) and naive T cells is observed, resulting in outcomes that are possibly
linked to systemic immune activation and inflamming. Impaired neurogenesis has been linked to cognitive impairment in transgenic mice. Evidence for loss of intermediate stem-cell regenerative potential is indirect. For example, there is evidence for premature expression of an ageing signature in skeletal muscle and deficits in bioenergetic capacity that reflect ageing profiles in intermediate stem-cell regenerative potential is indirect. For example, there is evidence for premature expression of an ageing signature in skeletal muscle and deficits in bioenergetic capacity that reflect ageing profiles in skeletal muscle and deficits in oxidative phosphorylation, brain mitochondrial DNA mutations and oxidative damage, and disrupted mitochondrial biogenesis and deficits in intervention studies in patients who were not treated with ART for loss in stem-cell regenerative potential in skeletal muscle and impaired mesenchymal stem cells.

We have summarised the relevance of geroscience hallmarks to HIV, and biomarkers for measuring changes in these hallmarks (table 1).

Can the geroscience hypothesis be reframed to include both gerodrivers and geroprotectors in the general population and in people with HIV?

In the previous sections of this Series paper, we have summarised several discrete biochemical mechanisms of ageing that represent hallmarks of the geroscience hypothesis and can be considered as gerodrivers (figure). The clinical phenotype of ageing in the context of chronic HIV infection is a higher prevalence of traditional risk factors for cardiovascular, neurocognitive, malignant, metabolic, liver, and kidney diseases. There are also unique host–environmental interactions for people with HIV that can alter the typical clinical manifestations that are associated with age-related diseases. Notably, the loss in immunological homeostasis, a broadly recognised feature of HIV infection, ultimately leads to changes in the intestinal mucosa, persistent systemic inflammation, tissue fibrosis, and disruption of neoplastic surveillance mechanisms, thereby providing a fertile landscape for inflammatory conditions, malignancies, and autoimmune conditions. Loss of crosstalk between multiple other conditions. Loss of crosstalk between multiple other organs (figure B) is also likely to promote asynchronous ageing. There are two prominent hypotheses that provide explanations for differences in the ageing trajectory between individuals that are potentially relevant for people with HIV. The first hypothesis, compression of morbidity, is based on the observation that individuals without HIV who reach the age of 100 years (in the absence of HIV infection) have longer lifespans and a later onset and progressive decline in health before death. This observation contrasts with individuals who do not reach this age, who have variable onset of comorbidities and progressive decline in health before death. Both models of ageing could be relevant to people with HIV. As discussed in previous sections and reviews, people with HIV have an accelerated onset and increased age-adjusted burden of multimorbidity, making them ideal populations to comparatively analyse ageing mechanisms that prevent compression of morbidity and decelerated ageing in future studies.

### Table 1: Hallmarks for biological ageing, associated biomarkers, and relevance for HIV infection

| Biomarkers and approaches | HIV-specific references |
|---------------------------|-------------------------|
| Genetic damage and genomic instability | Genome stability (next-generation sequencing) |
| Telomere attrition | Telomere loss in blood, association of telomere loss with cardiovascular risk and lung disease |
| Loss of proteostasis | Disruption of autophagy in multiple cell types, neurodegeneration, and mitophagy in primary neurons |
| Mitochondrial dysfunction | Deficits in PGC-1α in skeletal muscle and reduced oxidative phosphorylation, brain mitochondrial DNA mutations and oxidative damage, disrupted mitochondrial biogenesis and deficits in intervention studies in patients who were not treated with ART |
| Epigenetic changes | Aberrant methylation in immune modulation, accelerated epigenetic age, and influence of ART |
| Senescence | Multimorbidity and senescence, and replicative senescence |
| Inflammation | Persistent elevation in IL-6, TNF, soluble CD14, soluble CD163, CRP, and MCP-1; and association with adverse functional outcomes |
| Stem-cell exhaustion | Loss in regenerative potential of haematopoietic progenitors (CD34+) and loss of naive T cells, impaired neurogenesis, indirect evidence for loss in stem-cell regenerative potential in skeletal muscle, clonality in haematopoietic stem cells, and impaired mesenchymal stem cells |

MIDAS=mitochondrial dysfunction-associated senescence. SASP=senescence-associated secretory phenotype.
A crucial counterbalance to physiological decline with ageing under the geroscience hypothesis is the notion of healthy ageing, which is defined as a composite of reserves and capacities that promote recovery, adaptation, and psychosocial growth over the lifecourse. Physiological reserves are conceptualised as the energy available for metabolic homoeostasis and other energy-consuming activities such as physical activity and health maintenance.

Figure: Cascade and crosstalk conceptual model
(A) Cascade model. During biological ageing, total organ physiological function (the size of the pool) declines over the lifecourse as a result of exposure to stressors (e.g., injury, chronic high blood pressure, oxidative stress, environmental toxicity, and structural determinants such as stigma), concomitant with an increase in the multimorbidity burden. Gerodrivers accelerate this process, whereas geroprotectors are postulated to attenuate and ideally reverse the process.

(B) Organ crosstalk model. HIV and age-related decline in reserve and capacities that counteract stressors result in a loss of organ crosstalk and homoeostasis. As an illustrative example, the expansion of a senescence phenotype with the deposition of senescent cells in distal organs could in trans result in dysfunction and disruption of interorgan communication and loss of homoeostasis. Geroprotectors are postulated to increase resilience in response to stressors and maintain homoeostatic pools.

SASP = senescence-associated secretory phenotype.
and organ homeostasis. Efforts to operationalise healthy ageing, although ongoing, have gained traction with the introduction of two related constructs, resilience and intrinsic capacity, which measure multiple functional domains including mobility, cognition, psychology, vitality, and sensory capacities. The interplay between resilience and intrinsic capacity as a counterbalance to age-related deficit accumulation and vulnerability to stressors is an understudied area of research in geroscience that is advancing as a result of studies of geriatric conditions in people with HIV.

Hallmarks of ageing are inter-related and can be modifiable, which raises the possibility of delaying ageing at a person-centred level and increasing healthspan in people with HIV. For example, environmental protective factors, lifestyle changes, and pharmacological interventions can change trajectories of ageing and could be termed geroprotectors (figure). Successful ageing, a biopsychosocial model that integrates biological, psychological, and social determinants of functional independence, has been associated with several resilience factors such as a strong self-concept of cognition, strong perception of social relationships, well developed emotional regulation, and positive coping skills among middle-aged people living with HIV infection. Lifestyle changes (eg, smoking cessation, physical activity, dietary changes, healthy sleep, and alcohol abstinence) increase healthspan through multiple ageing mechanisms. Smoking cessation substantially reverses smoking-associated DNA methylation markers, and could change the outcomes of smoking-associated comorbidities. Physical activity appears to preserve telomere length and to favourably modulate ageing.

Integrative and comprehensive measures of biological ageing under the geroscience hypothesis have recently attracted substantial attention. However, few studies have applied biological ageing as a person-centred holistic measure in uninfected people or in people with HIV. Furthermore, future studies are needed to develop and operationalise strategies that promote resilience and capacity, to identify HIV-specific ageing protective factors and behaviours, to apply ageing-attenuating (gero-protective) medication treatments that are calibrated for ageing in people with HIV, and to gain a better understanding of how and which interventions can address the apparent balance of gerodrivers and geroprotectors. A summary of current limitations in geroscience and opportunities in HIV research is presented in table 2.

Can we leverage insights from diagnostic and therapeutic approaches based on geroscience to identify new approaches in HIV care?

Regarding diagnostics, although there are biomarkers in use or being tested for each hallmark of ageing, there is currently no composite score or biological signature that captures all the relevant biological processes to provide a holistic understanding of biological ageing either in the general population or in the nested population of ageing people with HIV. Nevertheless, taken individually, there is substantial utility in biomarker discovery (table 1). Various epigenetic changes, including DNA methylation, histone modifications, and chromatin remodelling, are associated with the ageing process and are linked to other hallmarks of ageing. For example, members of the sirtuin family of NAD-dependent deacetylases have been evaluated in relation to epigenetic reprogramming and biological ageing. Methylation alterations associated with HIV infection have been linked to genes involved in immune modulation. Horvath and Levine reported an increase in epigenetic age among approximately 5 years in blood and 7 years in brain in people with HIV compared with uninfected people. Subsequently, Esteban-Cantos and colleagues reported a smaller age acceleration. The role of ART in defining epigenetic age among people with HIV has also been investigated. Several studies have shown that differences in epigenetic age between people with HIV and uninfected people are reduced with ART. A better understanding of how mechanisms of ageing are linked to epigenetic signatures would facilitate the use of these measures scientifically and clinically. There is also a need to evaluate the effects of ART on the homoeostatic balance of gerodriver and geroprotective mechanisms that affect ageing trajectories in people with HIV.

Composite scores for ageing that attempt to assess multiple domains (ie, both deficits and resilience factors) include the comprehensive geriatric assessment (CGA), physiological and deficit-based scores for frailty as a phenotype, multimorbidity, and intrinsic capacity. Apart from the CGA, the frailty phenotype, and the Veterans Aging Cohort Study Index, these approaches are yet to be applied to people with HIV and adapted or calibrated for healthy ageing trajectories among people with HIV. There is some progress in the clinical use of the CGA, which often includes geriatric referral and geriatric syndrome assessments. Newer approaches that incorporate artificial intelligence and machine learning to omic and dataset methods in infection and integrative medicine, although early in development, appear promising.

None of the composite scores currently capture all the relevant biological processes to provide a holistic understanding of biological ageing either in people with HIV or in the general population. Also, although there is some progress in the use of comprehensive assessments in people with HIV, there remains a need for composite measures that capture distinct trajectories of functional ability and reserves, intrinsic capacities, and resilience with ageing in people with HIV and in the general population (figure). There is an increasing number of therapeutic strategies based on geroscience that could be useful in the context of HIV and ageing. These include dietary, exercise, and biobehavioural (a conceptual model that includes...
behavioural and biomedical components) interventions, senolytics, and senomorphics. Discussing each approach is outside the scope of this Series paper, but as an illustration we will discuss current approaches based on senescence (senolytic and senomorphic). Senolytic approaches promote the clearance of senescent cells through apoptosis by B-cell lymphoma 2 (Bcl-2) inhibitors or Bcl-2 homology 3 (BH3) mimetics, signalling-pathway inhibitors (such as heat-shock proteins, p53, histone deacetylase, and kinases), and mitochondria targeting (tamoxifen). For example, when quercetin (a plant flavanol with senolytic activity that inhibits the Bcl-2 pro-survival pathway) was combined with dasatinib (a tyrosine kinase inhibitor) in people with idiopathic pulmonary fibrosis it was found to be safe and showed some improvement in physical function.131

Senomorphic approaches do not clear senescent cells but block the proliferation of a senescence-associated secretory phenotype, and include compounds with mTOR or JAK1 and JAK2 inhibitory activity.

A distinct advantage of senolytic compounds for people with HIV might be the potential effect on the HIV viral reservoir, which can contribute to residual chronic inflammation. As a result, several of these agents have been explored as curative therapy for HIV infection. Venetoclax is a Bcl-2 antagonist that, through selective elimination of HIV-infected cells by reversing the intrinsic ability of HIV to block apoptotic pathways, has shown a reduction of the HIV viral reservoir in vitro following reactivation132 and homoeostatic proliferation.133 Several histone deacetylase inhibitors have been tested in people with HIV to reverse latency, with the expectation that such treatment would lead to a reservoir decline, known as the kick-and-kill strategy. Although some studies have shown a transient increase in viral RNA, no effect on the reservoir has been observed despite bearing the cost of an increase in T-cell activation.134 Fimepinostat (Curis, Lexington, MA, USA) is a newer histone deacetylase inhibitor that induces potent latency reversal but decreases T-cell activation ex vivo.135 Panobinostat has also been shown to reduce concentrations of C-reactive protein and IL-6.136 The use of senomorphic compounds as an approach to reduce senescence-associated secretory phenotype

| Limitations and opportunities               |
|---------------------------------------------|
| Overall limitations                        |
| Genoscience does not yet fully incorporate strategies for accessing reserve, measures of resilience, intrinsic capacity, stress response adaptive mechanisms, from cell function to holistic person-centered response; it does not provide a disease-specific roadmap of inter-relations between hallmarks; and progressive loss in physiological integrity as a hallmark is ill-defined and lacks testable insight. |
| Specific geroscience hallmarks              |
| Genome instability                         |
| Identify genomic markers associated with HIV infection and ageing-related outcomes in people with HIV |
| Telomere attrition                         |
| Understand the mechanisms of cell-type-specific telomere alteration because of HIV infection |
| Loss of proteostasis                        |
| Understand the link between proteostasis decline and HIV comorbidities, such as HIV-associated neurocognitive disorder |
| Mitochondrial dysfunction                  |
| Link age-related mitochondrial dysfunction with HIV treatment, polypharmacy, and the onset of comorbidities |
| Cellular senescence and inflammation        |
| Better understand how the mechanisms of inflammation in chronic HIV infection contribute to immune-cell senescence |
| Stem-cell exhaustion                       |
| Investigate whether ART affects stem-cell decline in specific organs |
| Additional mechanistic limitations          |
| Transcriptional drift                      |
| Transcription becomes instable and drifts with ageing, with increased transcriptional noise and accumulation of genetic errors |
| Segmental progenia                          |
| Inadequate inclusion of segmental progenia phenotypes in which ageing pathways are engaged asynchronously |
| Other relevant ageing factors               |
| Healthy ageing constructs                  |
| Physical and cognitive reserve, resilience, and intrinsic capacity | Identify hallmarks of healthy ageing, operational measures of reserve, resilience, and intrinsic capacity in people with HIV, compared with uninfected people |
| Environmental stress and resilience         |
| Substance use and misuse                   |
| Understand the effects of substance misuse (eg, tobacco, cocaine) on ageing in people with HIV |
| Psychological and physiological stress     |
| Understand the role of hypothalamic-pituitary-adrenal dysfunction in people with HIV under physical and psychological stress conditions |
| Nutrition and physical activity            |
| Understand the effects of nutrition and physical activity on geroscience hallmarks and derive interventions tailored to people with HIV that change the trajectories of ageing |
| Subpopulations of people with HIV          |
| Co-infection of HIV with hepatitis C virus, hepatitis B virus, and SARS-CoV-2 | Models for understanding multimorbidity and chronic inflammation |
| Elite control of HIV infection, longevity with HIV infection | Models for understanding successful immune ageing and consequent increases in lifespan |

Table 2: Limitations of and opportunities for geroscience in HIV research
concentrations in people with HIV is another major area under investigation. In addition to lowering lipid concentrations, statins can reduce autophagy through the mTOR pathway and block the upregulation and binding of intercellular adhesion molecules, among other effects. As an example, treatment with rosuvastatin for 1 year resulted in a reduction in D-dimer, IL-8, and IL-12 concentrations. Based on these and other data, REPRIEVE (NCT02344290), the largest randomised trial to date in HIV research, is examining the cardiovascular and anti-inflammatory benefits of pitavastatin for people with HIV who would not otherwise receive a statin. Results from this study are expected in 2023.137 Additionally, the mTOR inhibitor sirolimus reduced the percentages of cycling Ki67, CD4, and CD8 T cells, PD-1 and CD8 T cells, and CCR5 and CD8 T cells but did not affect the viral reservoir.138 Janus kinase inhibitors have been studied in vitro and ex vivo and shown to reduce inflammation and the HIV reservoir.139 In the randomised trial ACTG A5336,140 concentrations of IL-6 were not reduced, but concentrations of other biomarkers of inflammation, immune activation, and microbial translocation decreased significantly for people with HIV receiving ruxolitinib, a Janus kinase inhibitor approved for myelofibrosis. Incidentally, Bcl-2 concentrations were also significantly reduced for patients on the study drug, suggesting combined senomorphic and senolytic activity. In LILAC,141 a single-arm study of metformin for people with HIV but not diabetes, there was a reduction in CD4 T-cell infiltration in the colon, and mTOR activation and phosphorylation. Finally, the targeting ageing with metformin (TAME) trial142 will be the first trial with age-related multimorbidity as an outcome in people uninfected with HIV, and should provide insights for future trials in people with HIV.

Other non-pharmacological interventions have shown variable effects on inflammation, ageing, and frailty. Exercise and physical activity have been studied extensively in the general population and in people with HIV. Beyond the obvious benefits of increasing muscle mass, cardiovascular endurance, and strength, there have been mixed effects on inflammatory biomarkers.143–145 Although some data are available,146 further studies are needed to evaluate mitochondrial function and ageing in people with HIV in different contexts (eg, with interventions such as calorie restriction, stress reduction, and exercise). Approaches modifying the diet and microbiome that involve probiotics might lower concentrations of D-dimer but did not affect the microbiome.146 Nutritional interventions, although scarce, appear to be the most effective at reducing frailty when combined with exercise,147 although few studies have examined the effects of micronutrient replacement or calorie restriction on inflammation in people with HIV. Mindfulness techniques and meditation interventions are actively being explored as methods to reduce psychological stress, improve mental wellbeing, and reduce biomarkers of inflammation. To date, studies have been positive regarding mental health improvement, but only a few have shown changes in immunological parameters.148,149,150

How has the HIV pandemic driven advances in ageing research and what gaps remain in geroscience-guided approaches?

Advances in geroscience are converging on the need to focus on reducing multimorbidity and improving healthspan. The disproportionate burden of multimorbidity for ageing people with HIV has been recognised as a key challenge in HIV management for over a decade. Although there has been substantial focus on improving the quality of life of people with HIV, our geroscience model supports future work to improve healthspan by increasing healthy ageing reserves and capacities that promote resilience.150,151

For 40 years, efforts to characterise the pathophysiology of HIV infection have driven key advances in understanding inflammation associated with elevated CD38 concentrations152 and a loss of immune homeostasis (as we discussed), with the eventual recognition of the transcription factor NF-κB as a major driver of inflammation and biological ageing.153,154 Of gut dysbiosis and persistent inflammation,155 and of links between inflammation, immune activation, and cognitive stress.156,157 Measuring changes in inflammatory profiles with geroscience-driven interventions for people with HIV could be an effective cohort approach to quantifying improvements in healthspan and lifespan.158 An inflammation ageing clock that predicts multimorbidity, immune senescence, frailty, and cardiovascular ageing159 could be informative in intervention studies that enrol people with HIV at earlier ages.

We acknowledge that a single model cannot encompass ageing as a process, and that the crucial relationships and interactions across primary ageing (biological), secondary ageing (lifestyle), and tertiary ageing (comorbidity and coinfection) require integration. As a next step, we suggest that characterising the interaction of biology with geography, ancestry, sex, and structural and psychosocial factors (eg, socioeconomic status, stigma, and access to care) will be crucial to improve both health and healthcare delivery (eg, adherence and access to ART, and its off-target effects) and to understand how these interacting
factors contribute to the increased risk of adverse outcomes and potential long-term complications (eg, chronic fatigue) in HIV infection, and of co-infection. Notably, in SARS-CoV-2 infection, older people are at increased risk of adverse outcomes owing to a dysregulation of the inflammatory response.

In conclusion, we provide a conceptual model of biological ageing with HIV, informed by geroscience, that attempts to integrate hallmarks from the literature (figure). As shown in figure A, the model is reminiscent of a cascade waterfall with a series of descending water pools that decrease in size as homeostatic levels (ie, capacity) of organ function and reserve become diminished in response to a life history of exposure to stressors, concomitant with increases in multimorbid burden. Gerodrivers that represent the major hallmarks of ageing accelerate this process by driving a loss in protective mechanisms, whereas geroprotectors are postulated to attenuate and ideally reverse this process by promoting mechanisms that favour homeostatic reserves and organ function (as we discussed before; figure A). Furthermore, HIV and age-related declines in reserve and capacities that promote resilience to stressors drive loss in homeostatic organ crosstalk and compromised homeostatic levels (ie, capacity) that result in asynchronous organ and physiological ageing. Notably, the study by Lee and colleagues supports a broad role for immune system resilience as a homeostatic geroprotector. To illustrate the dynamic role of gerodrivers and geroprotectors in biological ageing, we provide an example wherein we speculate that the expansion of a senescence phenotype with deposition of senescent cells in trans results in dysfunction and disruption of interorgan communication, reducing reserve, resilience, and physiological homeostasis (figure B). Although asynchronous senescence-driven ageing has been shown in mice, a similar process in people with HIV has not yet been established.

Going forward, carefully conducted clinical studies, which are designed to ensure equal access to care and treatment for all and which interrogate geroprotector and gerodriver pathways with targeted interventions, will be crucial to inform pathogenesis, diagnosis, and therapeutic management for people with HIV in resource-poor settings, and indeed in the general population. As mused in Joni Mitchell’s song, “Both Sides Now”, she notes that with life, “well something’s lost, but something’s gained, in living every day”. The time has come for geroscience to advance our understanding beyond a focus on decline to include those gains that are key to successful ageing, and in so doing, leverage the profound progress made in our efforts to combat HIV/AIDS.

Contributors

MM conceptualised the work. MM, YVS, VCM, and KKO searched the literature. All authors wrote, reviewed, and edited the manuscript. MM and VCM prepared the figure and KKO assisted with preparing the figure.

Declaration of interests
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