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AIDS Rev. 2022;25:79-86

HIV and aging, biological mechanisms, and therapies: What do we know?

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Abstract

Aging, a time-dependent loss of physiological function, and its drivers are turning into a significant topic of research as the population's mean age increases. Epigenetic alterations, telomere shortening or dysfunction, mitogenic stress, oxidative stress, or accumulation of DNA damage can drive the cell to senescence: a permanent cell cycle arrest sometimes associated with a secretory phenotype and inflammatory consequences in the surrounding tissue. The amount of senescent cells grows over time in older organisms and may induce tissue inflammation and threaten overall tissue homeostasis, favoring aging. Senolytic and senomorphic therapeutics are an emerging approach to eliminate senescent cells or to block their secretory phenotypes respectively. Given that people living with HIV suffer non-AIDS comorbidities in a higher prevalence than the general population, aging is accentuated among them. Inflammation biomarkers may be helpful to assess prognosis or act as surrogate endpoints for studies of strategies focused on reversal of HIV-associated accelerated aging. This review summarizes the latest findings in aging and its major drivers, under the light of HIV infection. Since the number of older PLWH is currently rising, it will be of great importance to address and treat their age-related conditions, as well as to better decipher their biological mechanisms.

Keywords

Aging. HIV infection. Genomic instability. Cellular senescence. Telomeres. Senolytics.

Introduction

Aging is a time-dependent functional decline characterized by a progressive loss of physiological integrity and underlying major human pathologies[1]. Many factors contribute to it including genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, cellular senescence and stem cell exhaustion, and among others.

Accumulation of unrepaired or poorly repaired DNA lesions (i.e., genetic damage) is one of the most common

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Received in original form: 08-11-2021
Accepted in final form: 19-01-2022
DOI: 10.24875/AIDSRev.21000085

aging triggers. For example, telomeres become shorter as we age[2]. Telomeres protect DNA ends from fusing to each other and when they shorten. DNA molecules can fuse, initiating genome instability. This might potentially transform cells, thus signaling transduction pathways to respond by arresting cell proliferation and inducing apoptosis or senescence. Cellular senescence is a special form of permanent cell cycle arrest coupled to stereotyped phenotypic changes, which serves to prevent oncogenic transformation in mammals[3]. Nonetheless, accumulation of senescent cells over time might induce tissue inflammation and threaten overall tissue homeostasis.

Identifying and eliminating senescent cells or their deleterious effects using senolytics and/or senomorphics agents are emerging therapeutic strategies to overcome aging. Resistance to apoptosis, lack of immune clearance, senescent cells, and inflammation persistence are the main targets for these drugs[4].

Research on aging is becoming progressively important as the median population age increases. In this context, it is particularly relevant to consider the HIV-infected population. People living with HIV (PLWH), even in those with viral suppression and restored CD4 T-cell count, suffer non-AIDS comorbidities at a higher prevalence than expected in the general population. On top of that, chronic inflammation is associated with HIV infection. To assess the prevalence of comorbidities and inflammation in PLWH, novel biomarkers such as complement 5 protein (C5) and soluble urokinase-type plasminogen activator receptor (suPAR) are being tested. As the number of older PLWH significantly grows, age-related conditions and its underlying biological mechanisms are a topic of major concern.

Genes and genetic risk factors involved in aging

Immunological host response to HIV infection depends on some genetic factors, namely, CCR5 variants and HLA type, which are linked to resistance to infection, viral set-point, viral progression, and drug metabolism-related toxicity. However, new concerns are arising: non-AIDS comorbidities and aging[5].

Genomic background is a well-known risk predictor for comorbidities such as atherosclerosis and coronary artery disease (CAD)[6] but genetic prediction of osteoporotic fractures or obesity in HIV is weak[7]. On the other hand, chronic kidney disease risk and rapid progression of kidney dysfunction can be predicted quite accurately by genetic background – similar to predictions based on clinical risk scores[8]. Moreover, there is some consensus on that heritability of longevity is determined genetically by 20-35%[9].

However, how should we study biological mechanisms of aging and its genetics? Do genetic aging markers associate with the problems we mentioned above? Some potential aging markers are telomere length, DNA methylation (epigenetic clock), mitochondrial DNA copy number, and loss of Y chromosome. PLWH have significantly shorter telomeres than the non-infected population, and the shortening seems to occur rapidly during seroconversion[10]. Hopefully, antiretroviral treatment (ART) is showing some effect on attenuating/reversing this condition in longitudinal studies[11].

A few loci are associated with telomere length and longevity. On this matter, evidence from the Swiss HIV Cohort Study revealed that it might be possible to predict CAD using telomere length and through a polygenic risk score (PRS). Unfavorable genotypes were associated with higher CAD risk compared to a favorable genetic background. Moreover, when CAD PRS and longevity PRS are combined. A slight improvement in CAD prediction was obtained. This is an example of combining traditional, HIV related, and genetic risk factors[12].

Genome instability

There is considerable evidence that DNA damage causes cellular dysfunction that manifests as aging, regardless of eventual cell senescence or apoptosis[13]. DNA instability increases with age and it manifests with the accumulation of somatic mutations, especially in proliferative tissues, genome rearrangements, and chromosomal aberrations, which may affect gene expression. Mutations in genes of some DNA repair proteins result in premature aging phenotypes[14].

DNA damage agents are either of endogenous (replication stress, cell metabolism, and oxygen radicals) or exogenous (radiation, viral infection, and chemotherapy) origin, and they can generate a variety of DNA lesions. Among them, DNA double-strand breaks are the most deleterious and their repair pathways diminish their activity during aging[15]. When DNA damage occurs, the cell triggers a DNA damage response (DDR) that encompasses sensor proteins, delaying cell cycle to favor DNA repair. If DNA repair fails, the cell undergoes senescence or apoptosis

Cellular senescence

Cellular senescence is defined as a halt in proliferation accompanied by phenotype changes, although meta-

bolic activity continues. Therefore, senescence can be seen as a mechanism that prevents proliferation of cells that have suffered potentially oncogenic stress, such as epigenetic alterations, telomere dysfunction, mitogenic stress, oxidative stress, or accumulation of DNA damage. There are several signal transduction pathways responsible for the induction and active maintenance of this status. Both $p16^{INK4a}$/Rb (normally silenced by Polycomb repressive complexes) and $p53/p21^{CIP1}$ (activated by DDR), which converge on repression of CDK4/6, are in control of arresting the cell cycle at G1[16].

Senescent cells show enlarged and flattened shapes under the microscope. Detection of β-galactosidase is the most commonly used indicator of senescence, but the absence of proliferative markers such as ^{3}H Thymidine and Ki67 can be used to detect arrested cells; expression of $p16^{INK4a}$ and p53/p21 signaling proteins; and presence of senescent-associated heterochromatin foci. DNA-SCARS (DNA regions with chromatin alterations and damage markers such as 53BP1 and PML) and senescence-associated secretory phenotype (SASP) can all be used as senescence markers. Cells where senescence is owing to or accompanied by genomic damage or epigenomic perturbation express SASP and secrete pro-inflammatory cytokines, chemokines, growth factors, and proteases (for instance, IL-6, IL-1α, IL-8, monocyte chemoattractant protein 1, plasminogen-activated inhibitor 1, and plasminogen-activated inhibitor 2). This immunogenic secretome allows organisms to clear senescent cells with a local immune reaction that terminates the inflammatory response and allows repair of the damaged tissue[17]. The paracrine activities of senescent cells can be either beneficial or deleterious, depending on the physiological context[1].

Two main approaches can be addressed for identifying the contribution of senescent cells to age-related pathologies and the effects of their removal: (1) genetic systems based on suicidal genes[18]: These genes are under control of the $p16^{Ink4a}$ promoter and they are activated with a prodrug that is transformed into a cytotoxic drug only in p16 expressing cells[19]. This way, senescent cells are selectively killed. (2) Senolytic and senomorphic drugs. These are from a clinical view, an easier tactic to develop and will be discussed later.

Stem cells also undergo senescence, severely compromising their self-renewal and proliferative functions which are meant to restore tissue functionality[20]. Senescence of hematopoietic stem cells definitively contributes to immune decline with age. Some recent experiments have shown that removal of senescent cells rejuvenates hematopoietic stem cells and their number is re-established[21].

HIV is capable of modulating DDR as a way to facilitate long-term infection and viral persistence, and it is believed that viral reservoirs in latent cells are the main sources of extracellular soluble viral factors that cause inflammation, oxidative stress, and genomic instability[22]. These cells have shown impaired DDR and increased susceptibility to drug-inducing DNA damage. Nef and Tat proteins are known to drive pulmonary arterial hypertension by the expression of pro-survival and anti-apoptotic phenotype in pulmonary vascular bystander cells[22]. Viral protein Vpr triggers double- and single-stranded DNA breaks, leading to the recruitment of repair factors, and represses double-stranded DNA break repair[23]. However, scarce data are available about DNA damage repair efficiency in HIV infection. Altogether, biomarkers of genome instability can contribute to detection of aging and senescence in PLWH, thus helping to establish early strategies to reverse or delay the effects of accelerated aging in these patients.

Telomere shortening

Telomeres consist of 10-15kB of repetitive DNA sequences – the hexamer TTAGGG-coated by capping proteins at the ends of linear chromosomes, which are looped at each chromosome end (the so-called T-loop). Thus covering the end of each DNA molecule as the aglet at tip of the shoelaces prevents it from unraveling[2]. After multiple replication cycles, telomeres become so short that the T-loop can no longer be formed. Moreover, the ends of DNA molecules become uncapped and available to fuse with another uncapped or broken DNA end. Consequently, telomere shortening is an aging marker and a source of genome instability[1].

Telomere length and mortality are positively correlated, as it is with the prevalence of diseases[2] such as diabetes, cancer, pulmonary fibrosis, and depression. Causes of telomere erosion are physiological (aging and environment), iatrogenic (transplantation), and genetic (telomerase mutations)[24].

Human cells have a limited capacity for division, after which they die (Hayflick's limit)[25]. This happens between the 40th and 60th division cycle. However. some cells do not stop dividing during life (i.e., germ cells) highlighting the value of telomerases. Telomerases catalyzes the synthesis of the TTAGGG sequences at the end of the telomere, thus elongating the telomere.

In HIV infection, T-cells are constantly exposed to antigens by both HIV replication and microbial translocation, resulting in loss of naïve T cells[26]. Activated cells undergo clonal expansion in response to the persistent antigen, resulting in differentiation and accumulation of non-functional end-stage senescent cells.

It is well-known that PLWH has shorter telomeres than non-infected people. Moreover, recent studies yielded that this is equivalent to one decade of aging[27]. Viral load and CD4 T-cell count are also telomere length-related parameters. These changes are quite fast and, in fact, 13% of telomere length is lost after 3 months of HIV seroconversion[28].

The impact of ART on telomere length is positive[11], probably because the virus no longer replicates and/or T-cell phenotype shifts from highly differentiated to naïve. This is observed in long-time virologically suppressed people as well[29].

Since one of the telomerase components is a reverse transcriptase, the sequence of the template is already known. Some nucleosides used as ART can impair the function of the telomerase. Tenofovir and abacavir decrease telomerase activity by 29% and 10-14%, respectively, at therapeutic concentrations[30]. Shockingly, when combinations of therapies were tested, the raltegravir/darunavir group showed no significant changes while tenofovir/emtricitabine had increased telomere length[31]. Taken together, these results indicate that the overall ART effect is positive on telomere length and only when viral replication is controlled. The impact of ART on telomerase's reverse transcriptase can be elicited.

Epigenetic clocks

Other aging biomarkers are improved on ART, for instance the epigenetic clock. This tool can correlate epigenetic and chronological age. Its basis is cytosine-5 methylation within CpG dinucleotides, genomic regions that either get hypermethylated or hypomethylated with age. There are different ways to distinguish biological age using epigenetic clocks, being the most conspicuous way to look at deviations around the epigenetic-biological age regression line. Hence, the deviations above this regression line are known as epigenetic age acceleration, which refers to a more aged phenotype for the actual age of the person.

There are several epigenetic clocks, each one with its advantages and limitations. The one developed by Horvath[32] uses 353 CpGs in "multi-tissue" samples of children and adults and has an error of about 3.6 years. Hannum's clock assesses blood methylation profiles and predicts chronological age with 4.9 years of error. PhenoAge clock is related to morbimortality in the general population[33].

In PLWH, older epigenetic age correlates with low CD4 count (<200 cells/μL) and high viral load (100.000 copies/mL) and there is report of lower epigenetic age acceleration under ART. Albeit, they do not reach levels seen in HIV-uninfected people[34].

Novel biomarkers in HIV, inflammation, and aging

Chronic and even treated HIV infection is a state of unresolved inflammation. Factors that continue to trigger inflammation among treated individuals might imply the residual HIV replication. Other chronic infections include cytomegalovirus or hepatitis C infection, acute coinfections, commensals, dying cells, lymph node fibrosis, and intestinal bacterial translocation[35]. These signals stimulate innate or adaptive immune cells that release mediators such as cytokines, chemokines, and activators of coagulation and complement pathways.

Chronic inflammation leads to a higher risk of cardiovascular disease, renal disease, liver disease, osteoporosis, and neurocognitive disorders that associate with aging[36].

It is well-known that IL-6 and D-dimer are strong predictors of these defined "non-AIDS comorbidities" or death among virologically suppressed PLWH receiving continuous ART[37]. Despite this fact, these markers have not been implemented in the clinic. In addition. chronic inflammation is an elusive therapeutic target in treated PLWH. Therefore, it is necessary to develop new biomarkers with discriminatory prognostic value, especially in people with long-term or early treatment.

Recent unbiased plasma proteomics screening (SOMAscans) in a matched case-control study within a cohort of aging PLWH and seronegative controls (AGE_hIV Cohort Study. NCT01466582) yielded that immune pathways related to antiviral and cytokine responses, coagulation, and the complement activation pathway were the most enriched in PLWH[38].

The complement pathway represents an innate immune mechanism that can directly attack pathogens and recruit myeloid cells enhancing their phagocytosis. Antigen-specific antibodies and cytokines such as IL-6, IL-1β, and TNF can increase complement protein expression. All activation pathways (lectin, classical, and alternative) converge at the activation of C5 pro-

tein, which recruits other serum proteins and generates the membrane attack complex that can cause cytotoxicity.

Out of the enhanced complement components in PLWH, C5 is one of particular promising interest since it was enriched across subject groups and was associated with comorbidities. In this cohort, C5 did not correlate with other known HIV inflammation markers such as IL-6, D-dimer, and sCD14. However, none of those markers showed significant differences between PLWH and control groups. In contrast, C5 strongly correlated with C-reactive protein (CRP) and inflammatory biomarker that are known to activate the classical complement pathway through C1q. In the mentioned cohort, CRP levels showed that no significant differences between PLWH and seronegative groups were not associated with the prevalence of comorbidities. These results suggest that C5 might have a higher discriminatory value in treated cohorts of PLWH. Addition of suPAR strengthened the association of C5 with the prevalence of comorbidities suggesting a synergistic effect.

Although these markers might be novel in the HIV field, they have been broadly investigated in cardiovascular disease, outperforming classical biomarkers such as CRP, and also in diabetes, aging, kidney injury, and lipid abnormalities. On top of that, C5 is now being evaluated as a marker of subclinical atherosclerosis and has also outperformed CAC or CRP in predicting cardiovascular events.

Senolytic therapeutics

There is an active debate around if aging should be considered as a pathological process or as a natural phenomenon during the lifespan[39]. In any case, different trajectories can be drawn. Moreover, different authors are proposing accelerated or accentuated aging in PLWH, in comparison with non-infected individuals. This allows to propose therapeutical interventions for stopping or delaying senescence, which could eventually prevent the development of different types of cancer, repair damaged tissues, and decrease inflammatory-associated diseases, as we age 1) more DNA damage and senescent cells accumulate; 2) elimination of senescent cells by the immune system is less efficient; and 3) exhaustion of stem cells results in disrupted homeostasis. This leads to abnormal inflammation, recruitment of activated immune cells replicative failure, and fibrosis[3]. Therefore, we could differentiate "good" from "bad" senescence patterns at the cellular level in the same way, we can talk about "healthy" or "pathological" aging in patients and propose the elimination of senescent cells as a potential therapeutic target. The main difference between what we call "good" and "bad" senescence is persistence of senescent cells. In normal conditions, senescent cells are produced to regenerate damaged tissues or block development of tumoral cells. However, once the "biological aggression" has been overcome, senescent cells die, and disappear. In contrast, in the scenario of "bad senescence", apoptosis resistance is very high in senescent cells and they persist despite the stimuli are no more present. The long-term secretion by these persistent senescence cells of inflammatory cytokines as IL6 and the production of TGF-beta leads to persistent inflammation and fibrosis which are hallmarks of senescence[3].

Two types of drugs are used to treat senescence[40]: 1) *Senolytics* that destroy senescent cells, which acting through the induction of apoptosis and decreased cell survival (Dasatinib,Quercetin, and Navitoclax); and 2) *Senomorphics* that modify cell phenotype, usually by blocking senescent-associated chemokines (Ruxolitinib, Cortisol, and NDGA).

To estimate potential targets for senolytic approaches[4,] focus on "bad" senescence milestones is needed: Resistance to apoptosis, lack of immune clearance, senescent cell persistence, and chronic inflammation. Baar et al. investigated a way of triggering apoptosis in senescent cells[41]. They observed that p53-FOXO4 interaction led to death cell resistance and designed a peptide capable of breaking this linkage. Then, they studied its effect on cellular tissue and organismal level. Not only fewer senescent cells were seen, but also levels of IL-6 in the mice liver were lower with phenotypic improvement as a whole.

An interesting approach is given by Amor et al. who used chimeric antigen receptor T-cell therapy[42]. They were successful at eliminating cells that expressed urokinase-type plasminogen activator receptor, a widely induced senescence membrane protein *in vivo* and *in vitro*.

The model developed by Xu et al. is optimal for drug testing[43]. In this system, injection of a few senescent cells from an old mouse to a young mouse makes the latter acquire an aging-like phenotype. They tested the impact of Dasatinib plus Quercetin (D+Q) in this setting and their results yielded not only an improvement of senescent markers in mice, but a turnover in aging markers in human adipocytes culture, which leads to consider the D+Q combination as one of most anti-aging hopeful strategies.

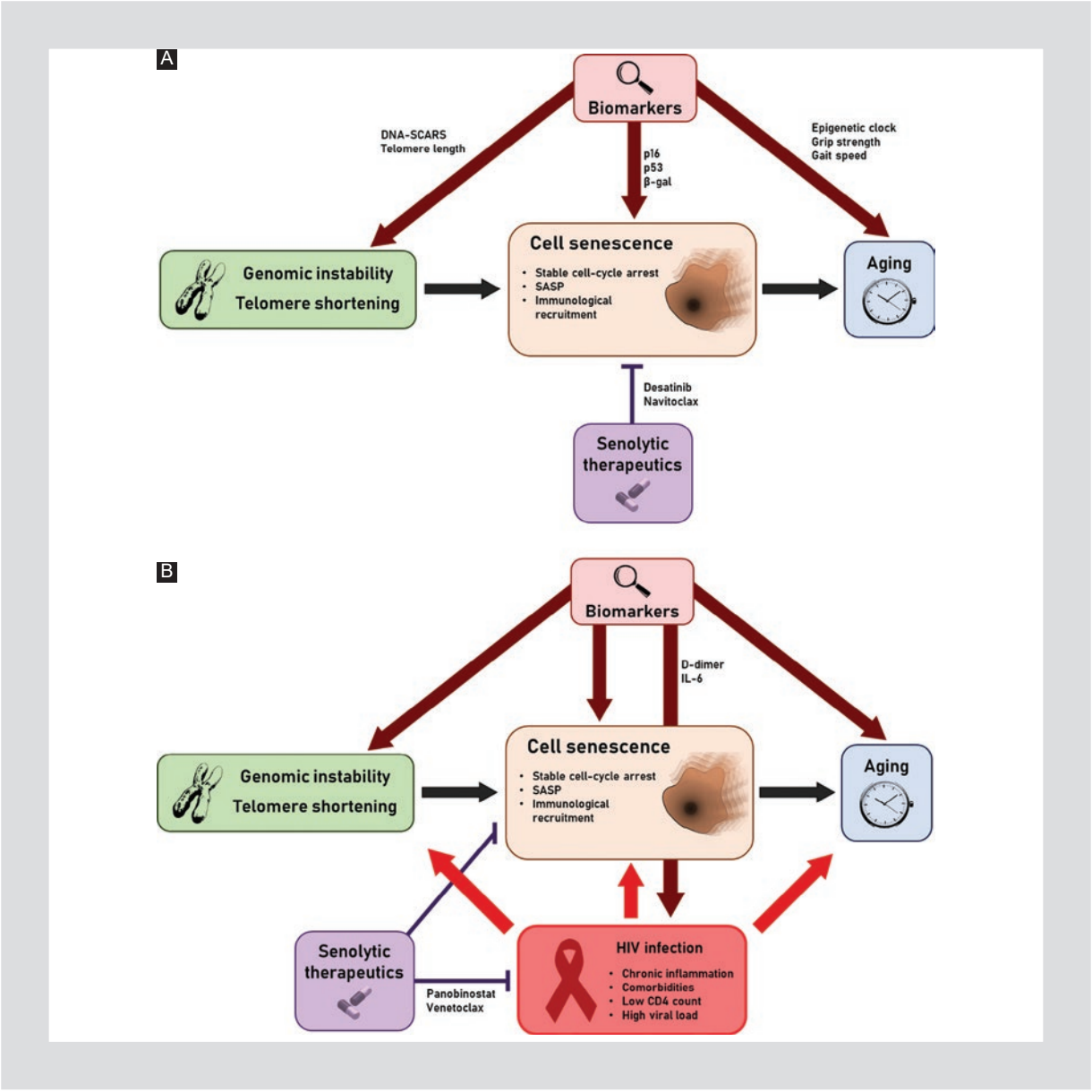

Figure 1. *Highlights of aging and its approaches.* **A:** *genomic instability and telomere shortening can lead to cellular senescence, one of major drivers of aging. These processes can be assessed by the use of several biomarkers. In order to treat aging, senolytic therapeutics can target senescent cells.* **B:** *in the context of HIV infection, chronic inflammation and prevalence of comorbidities accelerate/accentuate aging and its intrinsic mechanisms especially in people with low CD4 counts and high viral load. Classic inflammatory biomarkers like IL-6 and D-dimer and novel potential surrogate markers such as C5 and suPAR can be of high prognostic value. Senolytic therapeutics have shown great promise targeting both senescence and HIV infection.*

The pro-apoptotic drug Navitoclax, a BCL-XL/BCL-2 inhibitor that is being investigated to treat myelofibrosis, has shown to lower inflammatory cytokines and protects the heart from injury in a myocardial reperfusion mice model[44].

The field testing of senolytics is just beginning[45] and it is still unknown if these findings in animal models will translate to humans and its impact on chronic inflammation.

In particular, in PLWH, it is still need to confirm that the inflammatory pattern is due to senescent cells. Moreover, it is unclear how to differentiate true cell senescence from anergy, exhaustion, or terminal differentiation. More research is still needed to investigate what are the drivers of HIV-associated inflammation and/or senescence. Moreover, its potential role in the HIV infection curative strategy[46]. Panobinostat, a drug being tested in HIV cure trials, has been shown to di-

minish senescence parameters[47]. Selective BCL-2 antagonist Venetoclax lowers proviral DNA *in vitro* in mitogen-treated cultures[48]. Dasatinib is being proposed as a drug for reducing the HIV reservoir. It was recently found that it increases resistance to infection and probably enhances immunological status due to its action on NK and CD8 T-cells[49].

One potential concern when using senolytics is if their use could generate secondary effects due to the killing of "good" senescent cells and increase, for example, the risk of tumour development. This potential risk can be reduced if senolytics are administered in short cycles as it has been done in proof of concept trial. This strategy will destroy and clear predominantly persistent senescent cells during treatment period and will allow the generation of regular senescent cells once treatment is withdrawn[50].

Conclusions

Aging is a complex multifactorial process that requires multidisciplinary understanding, in particular, regarding its pathways and underlying biological, clinical, and social processes[9].

Untreated PLWH shows accentuated aging, particularly when viral load is high and CD4 count is low. ART produces partial reversion on aging biomarkers but more research is needed on the impact of different antiretroviral drugs in telomere length recovery. Interrupting or preventing cellular senescence can delay deterioration of health during aging. DDR components and C5 are promising biomarkers within this field.

Senolytic drugs may be the key to treating and preventing aging and are particularly interesting in PLWH as they can contribute to a decrease in inflammation and viral reservoirs.

Longitudinal studies will shed light the potential impact of different interventions. In the mean time, a more holistic approach to aging in HIV needs to stress the importance of lifestyle interventions such as smoking cessation, weight control, and exercise while prioritizing "*primun non nocere*" addressing the unwanted effects of polypharmacy and drug-drug interactions in this population (Fig. 1).

Conflicts of interest

Irini Sereti did her contribution as part of her US government official duties. Her work was supported by the Intramural Research Program of NIAID/NIH. The rest of the authors declare no competing financial or non-financial interests in relation to this review.

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