HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2020 March ; 15(2): 83–93. doi:10.1097/COH.0000000000000609.

Senotherapeutics for HIV and Aging

Matthew A. Szaniawski, **Adam M. Spivak**

University of Utah School of Medicine, Salt Lake City, Utah, USA

Abstract

Purpose of review—To summarize the state of chronic, treated HIV infection and its contribution to accelerated aging, and to evaluate recent research relevant to the study and treatment of aging and senescence.

Recent findings—Chronic treated HIV-1 infection is associated with significant risk of end-organ impairment, non-AIDS associated malignancies, and accelerated physiologic aging. Coupled with the chronologic aging of the HIV-1-positive population, the development of therapies that target these processes is of great clinical importance. Age-related diseases are partly the result of cellular senescence. Both immune and non-immune cell subsets are thought to mediate this senescent phenotype, a state of stable cell cycle arrest characterized by sustained release of pro-inflammatory mediators. Recent research in the field of aging has identified a number of 'senotherapeutics' to combat aging-related diseases, pharmacologic agents that act either by selectively promoting the death of senescent cells ('senolytics') or modifying senescent phenotype ('senomorphics').

Summary—Senescence is a hallmark of aging-related diseases that is characterized by stable cell cycle arrest and chronic inflammation. Chronic HIV-1 infection predisposes patients to aging-related illnesses and is similarly marked by a senescence-like phenotype. A better understanding of the role of HIV-1 in aging will inform the development of therapeutics aimed at eliminating senescent cells that drive accelerated physiologic aging.

Keywords

HIV-1; Aging; Senescence; Senolytic; Senotherapeutic

Introduction

Combination antiretroviral therapy (ART) has transformed HIV-1 infection from a lethal disease into a manageable chronic illness for those with access to therapy (1, 2). One result of this remarkable transformation is that a majority of people living with HIV-1 infection (PLWH) in the United States are now over age 50, a phenomenon that has been termed the "graying" of the HIV-1 epidemic (3). Individuals living with treated HIV-1 infection are at increased risk of aging-related diseases (4). This phenotype of chronic HIV-1 infection,

Correspondence to Adam M. Spivak, M.D., Division of Infectious Diseases, Department of Medicine, University of Utah School of Medicine, 30 North 1900 East, Room 4B319, Salt Lake City, UT 84132, USA, 801 587 1964, adam.spivak@hsc.utah.edu.

Conflicts of interest

none

often characterized as accelerated physiologic aging, is likely to exacerbate the clinical consequences of chronologic aging in this population.

Aging-related illnesses are driven in large part by cellular senescence, characterized by stable growth arrest and secretion of pro-inflammatory mediators (known as the Senescence-Associated Secretory Phenotype or SASP) (5, 6). While senescence is critical for preventing proliferation of damaged or pre-cancerous cells, it also leads to the persistence of inflammatory cells that are closely associated with diseases of aging (7, 8). Senescent cells are dependent on a variety of factors for survival that can be counteracted by a growing number of pharmacologic agents. These drugs, termed “senotherapeutics”, range in function from altering inflammatory profiles of senescent cells (“senomorphics”) to inducing targeted cell death (“senolytics”) (9). In this review, we highlight the current understanding of HIV and aging, emerging discoveries in aging research that directly address cellular senescence, and identify the potential for senotherapeutics to play a role in the context of chronic, treated HIV-1 infection.

Aging and HIV-1 Infection

Suppression of viremia by ART eliminates the development of opportunistic infections, however the immune system in aviremic HIV-1-infected individuals on ART reflects a state of persistent immune activation (10–12). T cell markers of activation (HLA-DR, CD38) and exhaustion (PD-1, CD57) are significantly elevated in patients with treated HIV-1 infection compared to uninfected individuals (13). There is a marked decrease in naïve $CD4^+$ and $CD8^+$ cells, an inverted CD4:CD8 cell ratio, increased frequency of activated monocytes, and increased pro-inflammatory cytokines including TNFα, IL-6 and IFNγ (12). Biomarkers of inflammation including C-reactive protein (CRP), d-dimer and soluble CD14 (sCD14) are all elevated in the plasma of HIV-1 infected patients on ART (14). These biomarkers of cellular activation and exhaustion are very similar to the phenotype observed in ‘inflamm-aging’ (15–17). Evidence for a direct link between senescence and HIV-1 infection has been demonstrated through evaluation of $p16^{INK4a}$, a biomarker of cellular senescence. In PBMCs isolated from ART-suppressed patients, $p16^{INK4a}$ levels are significantly elevated when compared to healthy, age-matched controls (18, 19). Thus, immune cells are important contributors to age-related diseases, and may themselves contribute to chronic inflammation through the process known as cellular senescence.

The cumulative effects of chronic inflammation contribute to a clinical syndrome known as frailty. Frail patients are at high risk of adverse clinical outcomes from aging-related conditions, and frailty is common among people living with treated HIV-1 infection (20, 21). As the population of PLWH continues to age, the prevalence of frailty in this population is increasing. The presence of frailty in PLWH has been linked to elevated levels of circulating pro-inflammatory mediators, such as IL-6 and CRP, which are highly associated with aging-related illness. Frailty is increasingly being considered an important HIV-associated, non-AIDS complication in PLWH (22–25), and serves as an independent predictor of the development of cardiovascular disease, diabetes mellitus, falls and mortality (24, 25).

The risk of developing cardiovascular disease (CVD), already the number one cause of mortality among the US population (26), is markedly elevated among PLWH (27–29) despite the ability of ART to suppress viral replication (30–32). There are mechanistic parallels between the increased CVD risk observed in aging and HIV-1 infection, and CVD is now the leading cause of morbidity and mortality in PLWH (33). Endothelial dysfunction is a major pathophysiologic driver of age-related CVD (34), which in turn is tightly associated with chronic immune activation (35–38). HIV-1-infected individuals on stable ART experience a state of chronic immune activation (14, 39), that has been shown to be associated with carotid plaque formation (40), carotid artery stiffness (41, 42) and arterial dysfunction (43, 44). The association between treated HIV-1 infection and CVD is independent of age, sex or tobacco use (27, 29).

Neurocognitive impairment is associated with both treated and untreated HIV-1 infection, and encompasses a spectrum of HIV-1-associated neurocognitive diseases (HAND) ranging in severity from dementia to more subtle loss of concentration, attention, and motor control (45, 46). While the more severe manifestations of AIDS dementia complex have improved dramatically with virologic control on ART, mild neurocognitive disorder and asymptomatic neurocognitive impairment persist and are now responsible for the majority of HAND (47). Approximately half of all PLWH experience some form of neurocognitive impairment, and it has been hypothesized that persistent inflammation despite ART or damage sustained prior to initiating ART may be responsible (48). This hypothesis is supported by the fact that in untreated HIV-1 infection, severity of dementia correlates not with the plasma viral load but rather with the presence of inflammatory markers and HIV-1 RNA in the CSF (47, 49, 50). Recent findings implicate macrophages as a cause of persistent central nervous system inflammation (51, 52), which helps explain the increased susceptibility of PLWH to microvascular disease, cognitive impairment, and frailty (53).

Can the physiologic aging phenotype in PLWH be ascribed to the concomitant chronological aging of this population? Immune activation, exhaustion and senescence in perinatally infected children provides strong evidence that the phenotype of advanced immunologic aging observed in chronic treated HIV-1 infection is largely uncoupled from chronologic age (54). Pathogenic age-associated changes in bone metabolism (55), renal (56, 57) and endocrine function (58) have all been well described in this population. Increased risk of non-AIDS related malignancies (59, 60), neuro-psychiatric conditions (61, 62) and premature cardiovascular disease (63, 64) in perinatally infected children and adolescents mirror observations in chronically infected adults (65). These risks are most pronounced in children and adolescents not taking ART, but remain significant despite viral suppression (66).

The drivers of the immune senescence of HIV-1

Untreated HIV-1 infection has long been recognized to result in persistent immune activation and a rapid-aging phenotype in $CD4^+$ and $CD8^+$ T cells (67), and myeloid cells (68). While ART is effective at suppressing virus replication, inflammation is known to persist (69) (Figure 1). The mechanisms governing chronic inflammation despite ART remain unclear, however a correlation exists between increased time-to-ART (or time with uncontrolled viral

proliferation) and increased post-ART inflammation (70, 71), suggesting that immunologic events occurring during the period of active viral replication prior to ART initiation dictate inflammatory outcomes long-term (72). This data is supported by the observation that elite controllers (EC), individuals who control HIV endogenously without ART, have lower levels of inflammatory markers than non-controllers (73). Further evidence demonstrating the ability of ART to reduce chronic, low-level inflammation and immune activation in ECs (74) supports a hypothesis in which HIV-associated inflammation is correlated with the degree of virologic control (75).

Despite the reduction in systemic inflammation after ART initiation (76), could years (or decades) of antiretroviral therapy contribute to the immune activation of treated HIV-1 infection? Over a decade ago, a large retrospective analysis identified an association between abacavir and increased cardiovascular risk (77). This finding has been replicated prospectively (78), and evaluation of cells from individuals taking abacavir demonstrates platelet activation (79). This off-target effect may contribute to vascular inflammation, atherosclerotic plaque formation and cardiac ischemia. However, other mechanisms are possible as well (80). More recently, accumulating evidence suggests that integrase inhibitors cause significant weight gain relative to other ART classes (81, 82). Both the mechanisms and clinical consequences of ART-associated weight gain are unclear at present (83). Beyond antiretroviral drugs themselves, the risks of poly-pharmacy and attendant drug-drug interactions among PLWH are increasing (84, 85). Despite the unquestioned benefit of ART on immune recovery, improvement in inflammatory markers and overall survival in PLWH, these are concerning signals of the cumulative effects of long-term ART that may contribute to the immune senescence of treated infection.

Comorbid conditions, particularly chronic viral co-infections, and chronic antigenic stimulation caused by microbial translocation from the gut appear to play important roles in immune senescence in PLWH. As reviewed by Dillon and Wilson in this issue, damage to the intestinal barrier is well-described in untreated HIV-1 infection (86) and results in translocation and systemic exposure to commensal bacteria, fungi, and viruses. The restoration of the peripheral T cell count in PLWH on ART is not accompanied by significant improvement in intestinal barrier integrity (87, 88), resulting in continued antigenic exposure, immune stimulation and exhaustion (89). Recent research suggests that this phenomenon may not be unique to HIV-1, but rather an acceleration of a pro-inflammatory process that has been associated with aging (90). Among PLWH, Hepatitis C virus (HCV) co-infection has been shown to result in activation and exhaustion of circulating $CD8^+$ T cells (91, 92) and NK cell dysfunction (93). Chronic infection with herpesviruses, including Epstein-Barr virus (EBV) and cytomegalovirus (CMV) have been closely associated with pathologic aging (94), and are frequent co-infections among PLWH (95). In a recent study of HIV-1-positive individuals on ART, the degree of T cell immune responses to CMV demonstrated a strong positive correlation with markers of systemic inflammation (21). The immune response to chronic CMV infection has been implicated in the development of immune senescence in both aging and HIV-1, though the specific mechanisms (and means to address them) remain to be fully elucidated (96).

The relationship between HIV-1 persistence despite ART (the HIV-1 reservoir) and the chronic immune activation and exhaustion of treated HIV-1 infection is not well understood. While reservoir size in T cells does not appear to be associated with systemic markers of inflammation (72), T cells are not alone in their ability to harbor HIV-1 despite ART (97, 98). Tissue macrophages are viral targets as well, and these cells are resistant to viral-induced cytopathic effects (99). The inflammatory profile of HIV-1-infected macrophages has been well-described ((100, 101) and reviewed in (102)). Recent evidence has shown that in vitro HIV-1 infection can induce senescence in microglia, suggesting that the virus itself may play an important and direct role in driving HIV-related comorbidities often associated with aging, particularly within the CNS (103). Monocyte activation and dysfunction is present in PLWH compared to HIV-negative controls and persists on ART (104). We have recently observed that HIV-1 infected macrophages develop a senescence-like phenotype, including depression of cell-cycle related genes concomitant with induction of SASP in both HIV-1 infected and bystander macrophages (unpublished data). Mounting evidence supports a role for macrophage-induced senescence in HIV-1 infection.

Cellular senescence as a driver of aging and aging-related diseases

Senescent cells are implicated as major drivers of aging-related diseases and frailty (105). Cellular senescence is characterized by stable cell cycle arrest, secretion of pro-inflammatory, pro-apoptotic, pro-fibrotic compounds (SASP) and resistance to apoptosis (106, 107). Initial descriptions of cell senescence did not identify it as pathogenic, but rather as a physiologic cellular program that was associated with embryogenesis, wound healing and tissue repair and served to limit proliferation of damaged or pre-cancerous cells (108). With increasing age however, senescent cells accumulate in tissues, creating a micro-environment that incites chronic immune activation and cell death among bystander cells, which in turn results in local or systemic dysfunction (109). Senescent smooth muscle and endothelial cells are present in blood vessels and atherosclerotic plaques and portend a risk of clinical cardiovascular disease (110, 111). Senescent astrocytes (112) and microglia (113) have been associated with the development of Alzheimer’s disease (114). Osteoarthritis, a chronic degenerative disease closely associated with aging, appears to be driven by senescent chondrocytes (115–117).

A mouse model in which senescent pre-adipocytes were infused into young syngeneic mice provides evidence of a causal role of senescent cells in aging-related disorders (118). Mice that received senescent cells developed dose-dependent, persistent deterioration of physical function relative to controls that received non-senescent pre-adipocytes, and demonstrated infiltration of senescent cells across multiple tissues. Smaller infusions of senescent cells into older mice resulted in significant decreases of both health- and life-span. In this model, senescent cells appear to be directly responsible for the observed pathogenic aging phenotype. Multiple lines of evidence now provide strong support for the hypothesis that cellular senescence is driving aging-related illness. Collectively, they raise a critical question: can these cells be targeted pharmacologically in order to ameliorate pathologic aging?

Targeting cellular senescence

The discovery that senescent cells are sufficient to drive pathogenesis in a number of animal models of disease, accumulate in tissues with chronological aging, and correlate with disease progression in a variety of age-related human conditions has spurred efforts to identify pharmacologic strategies to target senescence. A murine aging model has demonstrated that targeting of senescent cells results in increased health- and life-span (8). This discovery has given rise to pharmacologic strategies to directly counteract senescence by either killing senescent cells (senolytics) or modifying their phenotype (senomorphics) (Table 1) (5, 105).

The efficacy of senotherapeutics has been based on a wide range of mouse and in vitro models of human disease (109, 119–135). The first human trial of senolytics tested a combination of dasatinib (a tyrosine kinase inhibitor or TKI) and quercetin (a plant flavanol that targets BCL-2, insulin / IGF-1, and HIF1-alpha) in patients with idiopathic pulmonary fibrosis, and demonstrated that these compounds were safe, well-tolerated, and associated with improved physical function (136). Led by studies showing efficacy in animal models of aging (137, 138), the Targeting Aging with Metformin (TAME) Trial will examine metformin as a novel senotherapeutic. This new and rapidly developing field is identifying compounds capable of directly targeting processes underlying cellular senescence, and in so doing, aging itself (139).

Treatment of HIV-related aging with senotherapeutics

Can the immune senescence of treated HIV-1 infection be modified pharmacologically? Several lines of inquiry, including ongoing early phase clinical trials, seek to answer this question. Quercetin and fisetin are naturally occurring flavonoids shown to have senolytic activity. Fisetin has shown promise in vitro, though the senolytic mechanism of action remains unclear (140, 141). One study has demonstrated an anti-inflammatory effect of fisetin on microglial cells in vitro, suggesting a potential role for this natural product in the treatment of neuro-inflammation (142). Quercetin has inhibitory activity against several cellular kinases, and demonstrated targeted killing of senescent pre-adipocytes in vitro (107). Quercetin has shown synergistic activity with dasatinib in vitro (105), and this combination represents the current intervention strategy for pilot senolytic clinical trials (136, 143). With regard to HIV-1 infection, quercetin may also exhibit neuroprotective effects. Quercetin reduced ART-induced neuro-inflammation in a mouse model (144), and reactivated latent HIV-1 in vitro using an immortalized cell line (145).

Navitoclax and venetoclax are pharmacologic antagonists of BCL-2, an anti-apoptosis protein upregulated in senescent cells (121, 146). These compounds were originally designed for treatment of cancers in which BCL-2 is over-expressed (147, 148). Currently, Venetoclax is FDA-approved for chronic lymphocytic leukemia and acute myeloid leukemia, and this family of compounds has been investigated for their potential role as senolytics (119, 149). In a promising set of studies, venetoclax was shown to block proliferation of latently infected cells (150) and selectively induce apoptosis of latently infected cells upon viral reactivation in vitro (151).

The mechanistic target of rapamycin (mTOR) is a kinase active in innate and adaptive immune cells that governs cellular metabolism, growth and survival (152). While the mTOR inhibitor rapamycin is FDA-approved for chronic immunosuppression in organ transplant recipients, at lower dosing this drug has been shown to be immunostimulatory, boosting both anti-pathogen (153) and anti-tumor responses (154). Rapamycin is one of a few pharmacologic agents demonstrated to prolong the lifespan of a mammalian species (137, 155), a result that has been in part attributed to improved effector cell responses (156). A clinical trial administering everolimus, a rapamycin analog, along with the seasonal influenza vaccine demonstrated improved vaccine responses among elderly participants (157). Rapamycin was recently shown to modulate T cell exhaustion markers and responses to IL-7 and IL-15 in vitro (158). HIV-1-positive kidney transplant recipients who were treated with rapamycin were found to have smaller HIV-1 reservoirs than those taking other immunomodulatory agents (159), suggesting a role of the mTOR pathway in regulating viral persistence (160), and prompting two pilot clinical trials to evaluate the role of mTOR inhibition on reservoir dynamics using rapamycin (NCT02440789) and everolimus (NCT024298699). While full results are pending, these lines of evidence identify mTOR signaling as a high-yield target to ameliorate the immunologic dysfunction of chronic, treated HIV-1 infection.

Ruxolitinib is a janus kinase (JAK) 1 and 2 inhibitor that is FDA-approved for treatment of myeloproliferative disorders and has shown senolytic activity in mouse models (161). Ruxolitinib blocked HIV-1 replication in macrophages and diminished HIV-1-induced encephalitis in a mouse model (162). The same group has recently shown similar results using a different JAK inhibitor, baricitinib (163). JAK inhibition appears to perturb reservoir persistence (164). A randomized phase 2 clinical trial has recently been completed in which 60 participants living HIV-1 infection on ART received either ruxolitinib 10mg twice daily for five weeks (n=40) versus no treatment (n=20) [NCT02475655]. The drug was well tolerated and safe. IL-6 levels at the end of the intervention (week 5) compared to baseline were not significantly different in either group, though a statistically significant decrease in soluble CD14 was observed in the treatment group. Additional inflammatory, senescence or HIV-1 reservoir outcomes are not yet available, however these initial results show promise and future studies are warranted.

Panobinostat is a histone deacetylase inhibitor (HDACi) that is FDA-approved for the treatment of multiple myeloma (165). The senolytic activity of panobinostat is an area of active interest in oncology (166), particularly in the management of tumors that express senescence and anti-apoptotic markers (167). Histone deacetylation is a cellular mechanism for silencing gene transcription, and plays a role in HIV-1 proviral silencing (168). Several clinical trials have been conducted using HDAC inhibitors to perturb the HIV-1 latent reservoir in vivo (169, 170). In a sub-study of an HIV-1 eradication trial in which panobinostat was administered for eight weeks (171), c-reactive protein, IL-6 and circulating pro-inflammatory monocytes all significantly decreased at the end of the dosing period relative to baseline (172, 173). While HDAC inhibition appears to have a modest effect on reservoir perturbation, these drugs may play an important role in addressing HIV-1-induced senescence.

Tyrosine kinase inhibitors have not been used to target inflammation or senescence in HIV-1 infection in vivo, though pre-clinical evidence demonstrates promise. In vivo, the combination of dasatinib and quercetin decreased senescent cell burden in diabetic kidney disease (143) and improved physical function in patients with idiopathic pulmonary fibrosis (136). Dasatinib is known to inhibit proinflammatory functions of neutrophils as well as T cell activation and proliferation (174–177). We have recently shown that FDA-approved tyrosine kinase inhibitors including dasatinib enhances macrophage restriction of HIV-1 infection through activation of the restriction factor SAMHD1 (178). The Coiras and Alcami laboratories have observed similar viral restriction in T cells exposed to tyrosine kinase inhibitors including dasatinib, using peripheral blood mononuclear cells (PBMCs) obtained from patients receiving tyrosine kinase inhibitors for chronic myelogenous leukemia or CML (179). Whether dasatinib (and other tyrosine kinase inhibitors) will be capable of targeting senescent cells in the setting of HIV-1 infection remains an important unanswered question.

Knowledge gaps and key questions

There are significant gaps in knowledge regarding the nature of immune senescence in treated HIV-1 infection and its management. They include, but are not limited to, the following:

1. How does the ‘accelerated aging’ phenotype of treated HIV-1 infection differ from pathologic aging at a mechanistic level? Will this change as a younger cohort of PLWH who initiated ART earlier in the disease course and did not develop AIDS undergo chronologic aging?
2. While ART clearly diminishes the immune activation induced by viral replication, there are concerning signals that there may be a cumulative pro-inflammatory contribution of chronic therapy. Are there specific drug classes that potentiate this risk more than others? Does the weight gain associated with integrase-inhibitor-based ART increase the risk of metabolic and cardiovascular disease? Will the use of recently-approved two-drug regimens alter the chronic inflammation attributable to ART relative to current three- or four-drug regimens?
3. Are HIV-1 infected macrophages driving neuro-inflammation that results in HAND? If so, how can this be addressed?
4. The activity of senolytics have largely been tested in non-immune cells, including pre-adipocytes and fibroblasts. Do immune cells undergoing senescence have the same phenotype as these cells, and which of the senolytics discussed above (if any) will be most effective at targeting them?

Conclusion

Despite the suppression of viral replication by ART and consequent improvement in mortality, it has become clear that immunologic dysregulation persists in the form of chronic immune activation and immunologic aging in HIV-1-infected, ART-treated individuals. The

importance of developing strategies to address HIV-1 persistence, immunosenescence and serious pathophysiologic consequences including cardiovascular and metabolic diseases, non-AIDS-related malignancies and frailty in treated HIV-1 infection are underscored by the chronologic aging of the HIV-1 infected population in the United States. The rapidly advancing field of senotherapeutics holds great promise for a multitude of aging-related disease states including chronic treated HIV-1 infection.

Acknowledgements

The authors thank Vicente Planelles, Laura Niedernhofer, Paul Robbins, Kristine Erlandson, Beau Ances, and Alan Landay for insightful and thought-provoking discussions regarding senescence and HIV-1 infection.

Financial support and sponsorship

This work was supported in part by funding from the National Institutes of Health National Institute on Aging R03AG060192 (AMS) and the Infectious Diseases Society of America 2019 Grants for Emerging Researchers / Clinicians Mentorship (IDSA GERM; MAS).

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Key points

- The majority of PLWH are over age 50, exhibit advanced immunologic aging, and are predisposed to age-associated illness
- Cellular senescence is a major driver of pathologic aging
- In vivo and in vitro evidence has identified a contributory role of HIV-1 in cellular senescence
- Multiple strategies are being explored to pharmacologically target senescent cells for clearance
- Senotherapeutics improve health- and life-span in mouse models of disease and early trials in human patients, and hold great promise for treatment of HIV-1 immune senescence

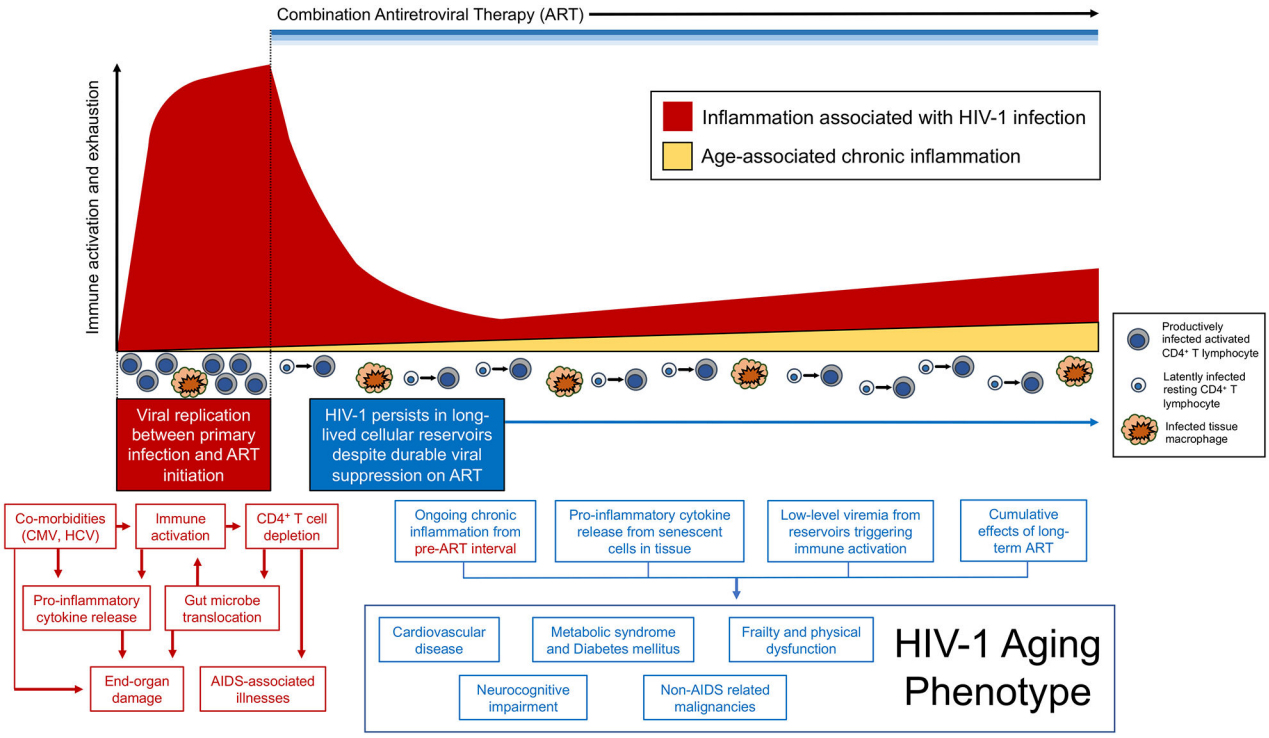

Figure 1. Mechanisms and Clinical Consequences of HIV-1-Associated Inflammation

Untreated HIV-1 infection is characterized by profound immune activation (shown in red above), triggered by ongoing viral replication and exacerbated by microbial translocation and co-morbid conditions. Immune activation accelerates T cell loss, resulting in progression to AIDS. ART eliminates this feed-forward system, however low-level inflammation and immune exhaustion persist and result in a phenotype of immune senescence and increased risk of aging-related illnesses (shown in blue above).

Table 1:

Investigational Senotherapeutics

Drug	Senotherapeutic Behavior	Mechanism(s) of Action	Clinical status	Tested in HIV-1 infection?	References
Dasatinib	Senolytic	Broadly active TKI	FDA approved for CML	Yes	143, 178, 179
Fisetin	Senolytic	PI3K/AKT/mTOR antagonist	Experimental	No	140
Quercetin	Senolytic	PI3K antagonist	Experimental	No	136, 143
Fenofibrate	Senolytic	PPARα agonist	FDA approved for hyperlipidemia	Yes	122, 123
Navitoclax (ABT-263)	Senolytic	BCL-2 antagonist	Experimental	No	121, 146
A1331852	Senolytic	BCL-XL antagonist	Experimental	No	141
A1155463	Senolytic	BCL-XL antagonist	Experimental	No	141
Venetoclax (ABT-199)	Senolytic	BCL-2 antagonist	FDA approved for CLL	Yes	150, 151
Piperlongumine	Senolytic	GSTP1 antagonist	Experimental	No	124, 125
Tanespimycin (17-AAG)	Senolytic	HSP90 inhibitor	Experimental	Yes	126–128
Radicilol	Senolytic	HSP90 inhibitor	Experimental	No	129
Geldanamycin	Senolytic	HSP90 inhibitor	Experimental	Yes	129, 130
FOXO4-related peptide	Senolytic	FOXO4 antagonist	Experimental	No	131
UBX0101	Senolytic	MDM2/p53 antagonist	Experimental	No	132
Panobinostat	Senolytic	HDAC inhibitor	FDA approved for multiple myeloma	Yes	172, 173
Metformin	Senolytic/ Senomorphic	AMPK agonist and glycerophosphate dehydrogenase (mGPD) inhibitor	FDA approved for T2DM	No	138
NBD Peptide	Senomorphic	IKK inhibitor	Experimental	No	133
Rapamycin	Senomorphic	mTOR inhibitor	FDA approved for immune suppression	Yes	158, 159
Everolimus	Senomorphic	mTOR inhibitor	FDA approved for immune suppression	Yes	158
Ruxolitinib	Senomorphic	JAK1/JAK2 inhibitor	FDA approved for myeloproliferative diseases	Yes	162, 164
KU-60019	Senomorphic	ATM Kinase inhibitor	Experimental	No	134
Mmu-miR-291a-3p	Senomorphic	TGFRB2 antagonist	Experimental	No	135