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# Mechanisms of immune ageing in HIV

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## Abstract

Massive CD4<sup>+</sup> T-cell depletion as well as sustained immune activation and inflammation are hallmarks of HIV-1 infection. In recent years, an emerging concept draws an intriguing parallel between HIV-1 infection and ageing. Indeed, many of the alterations that affect innate and adaptive immune subsets in HIV-infected individuals are reminiscent of the process of immune ageing, characteristic of old age. These changes, of which the presumed cause is the systemic immune activation established in patients, likely participate in the immuno-incompetence described with HIV progression. With the success of antiretroviral therapy, HIV-seropositive patients can now live for many years despite chronic viral infection. However, AIDS-related opportunistic infections have given way to chronic diseases as the leading cause of death since HIV infection. Therefore, the comparison between HIV-1 infected patients and uninfected elderly individuals goes beyond the sole onset of immunosenescence and extends to the deterioration of several physiological functions related to inflammation and systemic ageing. In light of this observation, it is interesting to understand the precise link between immune activation and ageing in HIV-1 infection to figure out how to best care for people living with HIV.

**Keywords :** HIV, ageing, immunosenescence, inflammation

## 28 **Introduction**

29 The prevalence of Human Immunodeficiency Virus (HIV) infections among people over 50 years old  
30 is rapidly increasing. According to data from the Dutch AIDS Therapy Evaluation in the Netherland  
31 (ATHENA) cohort, the proportion of HIV-infected people aged 50 and older is expected to increase  
32 from 28% in 2010 to 73% in 2030 (1). Indeed, HIV-infected patients can now live for years despite the  
33 chronic presence of the virus, thanks to the development of antiretroviral therapy (ART) (2).  
34 Individuals on ART are more likely to experience serious non-acquired immunodeficiency syndrome  
35 (AIDS) events, which occur with higher prevalence at earlier ages than in the general population. This  
36 observation results in the emergence of an intriguing parallel between HIV-1 infection and ageing:  
37 many of the alterations that affect innate and adaptive immune cell subsets in HIV-infected individuals  
38 are reminiscent of the process of immune ageing, characteristic of old age. These changes likely  
39 participate in the decline of immune competence and the deterioration of several physiological functions  
40 related to inflammation and systemic ageing (3). As a result of HIV-1 infection, the leading cause of  
41 death has changed from AIDS-related opportunistic infections to chronic diseases. Indeed, even among  
42 patients who respond well to antiretroviral medication, there is an increasing occurrence of  
43 comorbidities that are not related to HIV but are characteristic of the situation observed in old age with  
44 an inflammatory pathogenesis, such as cardiovascular disease, cancer, renal failure, liver disease,  
45 osteopenia and osteoporosis, as well as neurocognitive impairment (4), (5). In addition, antiretroviral  
46 medication toxicity accumulates over time, causing clinically meaningful metabolic abnormalities and  
47 organ damage. Of note, older HIV-infected individuals are at greater risk of polypharmacy, frailty, and  
48 other age-related conditions (6). The increased prevalence of these comorbidities could be explained by  
49 chronic low-grade inflammatory phenotype (inflammaging) due to HIV-1 infection in addition to viral  
50 coinfections, ART toxicity, residual HIV replication, and lifestyle factors. In this review, we focus only  
51 on the mechanisms of immune ageing in HIV-1 infection, which is the most common type of HIV  
52 infection (almost 95% of all infections).

## 53 **1. Summary of HIV pathogenesis**

54 A fundamental event in the HIV-1 pathogenesis is the infection of the CD4<sup>+</sup> T-cell pool (Figure 1).  
55 During primary infection, HIV-1 is able to infect CD4<sup>+</sup> T-cells extensively, in particular activated  
56 memory CCR5-positive cells (7). At this stage, the anti-HIV immunity is not mounted yet, so that viral  
57 replication and spreading remain uncontrolled. Viremia increases to reach peak levels, while the  
58 immune response ascends, in particular HIV-specific CD8<sup>+</sup> T-cells, which terminate the acute phase.  
59 However, the damage has been done, leading to the establishment of HIV-1 latent reservoir, rooting  
60 itself in its host, with an extensive viral replication and the massive depletion of CD4<sup>+</sup> T-cells, in  
61 particular from mucosal lymphoid tissues (8). This has immediate consequences on the unity of the  
62 mucosal surfaces, and microbial translocation occurs.

63 Then, considerable immune activation takes place, which is multicausal and lasts throughout the course  
64 of the infection. First, the immune response against HIV-1 itself ensues, and aims at controlling the  
65 virus, despite persisting replication and emergence of variants that can escape both humoral and cellular  
66 responses. The immune system has also to cope with other persisting pathogens (like Cytomegalovirus,  
67 CMV), whose reactivation may be enhanced by the substantial loss of CD4<sup>+</sup> T-cells (9). HIV proteins  
68 can also directly induce cellular activation through the binding of the envelope protein gp120 to CD4  
69 or co-receptors, or with the protein Nef which is able to induce lymphocyte activation directly or  
70 through the infection of macrophage. Last but not least, translocation of microbial products leads to  
71 systemic activation of monocytes and lymphocytes. As a consequence, levels of proinflammatory  
72 cytokines increase notably. In addition, immune activation promotes HIV replication, thus establishing  
73 a vicious cycle (10).

74 Systemic immune activation leads to considerable cellular turnover, senescence and apoptosis, which  
75 represent a massive challenge for the immune system in terms of cellular renewal in order to maintain  
76 homeostasis. Overtime, the consequence is the development of immunosenescence and a progressive  
77 decline of regenerative capacities (down to the level of hematopoietic progenitors). In parallel, the  
78 constant production of proinflammatory cytokines leads to inflammation-related disorders such as

79 osteoporosis, atherosclerosis, neurocognitive deterioration, frailty or cardiovascular disease. With the  
80 exhaustion of primary resources, naïve T-, B- and Natural Killer (NK)-cells disappear and highly  
81 differentiated oligoclonal populations accumulate. Optimal anti-HIV immunity cannot be maintained  
82 and the CD4<sup>+</sup> T- cell pool cannot be replenished, resulting in the collapse of the immune system's ability  
83 to control pathogens, hallmark of AIDS.

84 The development of immunosenescence is determined by the very physiological defense function of  
85 the immune system. The normal ageing process is characterized by low grade, recurrent immune  
86 activation and inflammatory activity, which eventually leads to immunosenescence. Through the  
87 induction of persistent, sustained immune activation, HIV-1 infection could be considered as a model  
88 of accelerated immunosenescence and systemic ageing (Figure 1). During this process, the immune  
89 system burns itself quickly, as the source of its exhaustion (i.e. the virus) cannot be eliminated.

90

## 91 **2. Immune system alterations with ageing and HIV**

92 Alterations of the immune system are characteristic of immune ageing caused by advanced age and  
93 probably contribute to the decline of immune function in people living with HIV (PLWH). Although  
94 ageing and HIV-1 infection both affect immune function, there are differences in both myeloid and  
95 lymphoid cell alterations in the peripheral blood. Indeed, advanced HIV-1 disease results in a profound  
96 decline of peripheral blood myeloid cells, which is not seen with normal ageing. As with ageing, HIV-  
97 1 disease affects lymphocyte subsets in a significant way, even though the most affected lymphocyte  
98 subsets differ. For instance, CD4<sup>+</sup> T-cell loss is most profound in HIV-1 infection, but other lymphocyte  
99 subsets are functionally altered as well (11). Finally, it was observed in PLWH that their T cell  
100 proliferative capacity and their delayed hypersensitivity decreased, while their apoptosis increased,  
101 however, these changes were not related to age (12). Below, we discuss the multiple ageing-like  
102 alterations that occur in the different cellular compartments of the immune system.

103

104

## 105 **2.1 Immune resources**

### 106 ***Bone marrow***

107 The bone marrow is a critical developmental niche for CD34<sup>+</sup> hematopoietic stem cells (HSCs) that  
108 gives rise to the myeloid and lymphoid cells required for innate and adaptive immunity. Under normal  
109 circumstances, the percentage of marrow space occupied by the hematopoietic tissue declines from 90%  
110 at birth to a level of approximately 50% at 30 years of age and 30% at 70 years of age. This decreased  
111 cellularity observed with ageing is reflected anatomically by a reduction in lymphoid mass with an  
112 increase in fat or fibrosis and results in skewing of all peripheral blood subsets. Due to similar  
113 histoarchitectural deterioration of lymphoid tissue during HIV infection, several studies reported a  
114 variety of hematological abnormalities in the bone marrow of PLWH, such as anemia, dysplasia and  
115 leukopenia (13), even in treated patients (14). It has also been reported defective cytokine and  
116 chemokine productions by bone marrow cells (15). Similarly, decreased Interleukin (IL)-2 levels and  
117 elevated Tumor Necrosis Factor (TNF)- $\alpha$ , Macrophage Inflammatory Protein (MIP)-1 $\alpha$ , MIP-1 $\beta$  and  
118 RANTES levels, as well as defective bone marrow clonogenic activity were observed before treatment  
119 compared with non-HIV-infected control subjects (16).

120

### 121 ***Hematopoietic cells***

122 In addition to the microenvironmental changes occurring in lymphoid tissue during HIV infection,  
123 defects in the formation of blood components (hematopoiesis) have been pinpointed since HSCs from  
124 PLWH present functional alterations (17). Both elderly people and patients progressing towards AIDS  
125 have decreased numbers of circulating CD34<sup>+</sup> hematopoietic progenitor cells (HPCs), and their  
126 remaining CD34<sup>+</sup> cells present functional alterations such as reduced clonogenic potential (18). Among  
127 CD34<sup>+</sup> HPCs from these individuals, cells with lymphoid precursor capacity are drastically reduced,  
128 and the ability to produce T lymphocytes is impaired in *in vitro* culture assays (19). Age-related declines  
129 in the hematopoietic system are thought to be one of the main factors underlying immune degeneration  
130 in the elderly and are likely to contribute to accelerated immune ageing in PLWH. ART partially  
131 restores the HPCs compartment and hematopoiesis, together with the recovery of all immunocompetent

132 cell pools (18). A study reveals that the recovery of CD4<sup>+</sup> T-cells following ART initiation was  
133 correlated with HPCs proliferation, which indicates that bone marrow-derived HPCs are crucial for  
134 reconstituting the immune system during HIV infection (20). Studies have shown that CD34<sup>+</sup> cells can  
135 sustain both active and latent HIV infection *in vitro* and *in vivo* (21). As a result of infection of these  
136 cells, HIV leads to anemia and hematopoiesis dysfunction, which also creates a long-lasting, stable viral  
137 reservoir that can lead to residual plasma viral infection in ART-treated individuals (22).

138

### 139 *Thymus*

140 The thymus is a primary lymphoid organ where T-cells differentiate into self-tolerant CD4<sup>+</sup> and CD8<sup>+</sup>  
141 lymphocytes which migrate to populate the peripheral lymphoid tissues. The thymus produces new  
142 T-cells throughout life but has no self-renewing ability and requires replenishment and recruitment of  
143 progenitors derived from the bone marrow. Thymic involution, characterized by the loss of thymic  
144 function and size with age (23), can also be caused by HIV-1 infection, which induces structural and  
145 functional changes leading to immune senescence (13).

146 The reduced generation of naïve T-cells associated with normal thymus ageing or with diseases linked  
147 to chronic inflammation such as HIV, result in reduced T-cell specificity, peripheral T-cell imbalances,  
148 and a higher risk of infection (24). Both ageing and HIV infection cause T-cells to switch from naïve  
149 to more differentiated cells with transitional or effector memory phenotypes (25). Moreover, infection  
150 with HIV causes irreversible damage to the thymus, which is partly responsible for the inability to  
151 produce naïve T-cells. PLWH can recover functional thymic mass after its degradation induced by the  
152 virus with the use of ART. In addition, it has been shown that patients with larger thymic sizes are able  
153 to maintain higher CD4 counts and thymocyte production after five years of ART (26).

154

## 155 **2.2. Innate immunity**

### 156 *Natural Killer cells*

157 NK cells are subdivided into three subsets: the cytokine producing CD56<sup>++</sup> CD16<sup>-</sup> subset, the cytotoxic  
158 CD56<sup>+</sup> CD16<sup>+</sup> subset, and a minor CD56<sup>-</sup> CD16<sup>+</sup> NK cell subset with poor antiviral activity. NK cell

159 subset distribution and function are altered with ageing or HIV infection (27). In both contexts, a gradual  
160 loss of CD56<sup>++</sup> NK cells is observed, likely caused by limited production of its precursors, along with  
161 an expansion of CD56<sup>-</sup> CD16<sup>+</sup> NK cells (28), (29). This expansion has been suggested to be a  
162 mechanism to maintain overall NK cell homeostasis in PLWH by compensating the loss of CD56<sup>+</sup> NK  
163 cells (27). The presence of an expanded CD56<sup>-</sup> NK cell population among HIV viremic individuals has  
164 been associated with significantly reduced spontaneous NK cytolytic activity as compared with that of  
165 aviremic individuals or healthy donors (30).

166 With age or throughout the course of HIV infection, the characteristics of predominant CD56<sup>+</sup> NK cells  
167 are also altered. There is indeed evidence of an accumulation of mature CD57<sup>+</sup> CD56<sup>+</sup> CD16<sup>+</sup> NK cells  
168 with ageing (in particular in CMV seropositive donors) (31), (32). In addition, CD56-NK cell expansion  
169 has also been attributed to high viral loads, as both parameters are strongly correlated, except when the  
170 virus is suppressed (33). In HIV patients, their functionality is impaired with a decreased ability to  
171 eliminate virus-infected target cells and to interact with other cellular components of the adaptive  
172 immune system (34), (35). Additionally, chronic HIV infection results in impaired NK cell cytotoxicity  
173 and cytokine secretion as well as the inability to respond to Interferon (IFN)- $\gamma$  and to produce high  
174 amounts of IFN- $\gamma$  and TNF- $\alpha$  (36). These alterations are found even in treated patients (37). The  
175 diversity of NK cells, which may affect immune surveillance, also changes after HIV-1 infection and  
176 ageing (38,39). Even after successful therapy, the recovery of NK cell function, as IFN- $\gamma$  production  
177 (40) and repertoire expression may remain impaired (39,41). However, a direct comparison between  
178 PLWH and elderly individuals is difficult to establish since their respective CD56<sup>+</sup> cell subsets have  
179 been characterized according to either phenotype, function or repertoire. A deeper understanding of the  
180 relationship between HIV-1 infection and ageing will require further studies of CD56<sup>+</sup> NK cells.

### 181 *Monocytes*

182 Monocytes can be classified into three main subpopulations: classical CD14<sup>++</sup> CD16<sup>-</sup> that expresses  
183 CD62L, CCR2 and low levels of CX3CR1, intermediate CD14<sup>++</sup> CD16<sup>+</sup> that lacks CD62L or CCR2  
184 but expresses CX3CR1 and secretes high level of TNF- $\alpha$  in response to Toll-like receptors, and  
185 non-classical CD14<sup>+</sup> CD16<sup>++</sup> which are CCR2<sup>low</sup> CX3CR1<sup>high</sup>. PLWH display several phenotypic



186 and functional changes that are similar to those observed within the elderly. Although there are  
187 relatively few changes in the absolute numbers of monocytes, the distribution of these cells is altered,  
188 characterized by a marked decrease in classical monocytes and an increase in intermediate and non-  
189 classical monocytes in older or HIV-infected patients (42,43). Infection increases CD16<sup>+</sup> monocytes,  
190 which correlate with viremia, T cell activation, and IL-6 plasma levels. Patients who do not take therapy  
191 or discontinue treatment have an expanded number of these cells. On the other hand, patients who are  
192 on effective ART exhibit the same level of expression of CD16 as uninfected controls (44).  
193 Monocytes from elderly or PLWH produce proinflammatory cytokines, are CD38, CD69, CD11b,  
194 HLA-DR and CD86 positive, and have decreased CD62L expression, which are all characteristics of  
195 activated cells (45). The expression of CD69 and HLA-DR in HIV-infected patients correlates well with  
196 plasma lipopolysaccharide (LPS) levels, an indicator of microbial translocation (46). Moreover, plasma  
197 levels of soluble CD163 and CXCL10 which are markers associated with monocyte activation, also  
198 increase with both age and HIV-1 infection (42,47). These biomarkers of monocyte activation are only  
199 partially normalized upon ART mediated viral suppression (42), indicating that such changes may  
200 contribute to the increased risk of inflammatory age-related diseases in treated HIV-positive patients  
201 (47).

202

### 203 **2.3. Adaptive immunity**

204 Adaptive immunity alteration with age is a major source of morbidity and mortality in the elderly, and  
205 these changes can be also found in HIV. Indeed, ageing and HIV-1 infection are associated with the  
206 accumulation of CD8<sup>+</sup> T-lymphocytes lacking CD28 (48,49) and end-stage senescent cells (CD57<sup>+</sup>  
207 cells) (50,51). Similarly, a decrease in CD4<sup>+</sup> and CD8<sup>+</sup> naïve T-cell counts is described both in ageing  
208 and HIV-1 infection. Interestingly, the frequency of naïve T-cells is a good indicator of the  
209 immunological age of individuals, and its gradual decline is associated with the progression of HIV-1  
210 infection (52). Considering that adaptive immunity requires specific naïve T-cells to be activated,  
211 changes of this compartment may impact the ability of PLWH to initiate new robust immune responses.

212 For instance, as with uninfected elderly, PLWH respond less well to influenza vaccination (53) or to  
213 neo-antigen priming capacity (54).

214 Chronic cellular activation which results in the accumulation of highly differentiated T-cells, is often  
215 related to chronic replication of HIV, as well as other persistent viruses, in particular CMV in  
216 co-infected patients. The immune system does activate T lymphocytes that are specific for viruses,  
217 which eventually lose CD28 expression, and instead display CD57 (50), (55). In PLWH, the  
218 accumulation of CD28/CD57<sup>+</sup> T-cells is usually considered as a marker of immunosenescence. In  
219 combination with HLA-DR expression, an indicator of T cell activation, this marker of  
220 immunosenescence can be used as a score of immune activation and senescence. This score correlates  
221 with the clinical state of PLWH and was significantly associated with the raise of non-AIDS related  
222 comorbidities (kidney disease, diabetes, cardiovascular events, degenerative central nervous system  
223 disorders, and cancer) in treated patients younger than 60 years old (56). Patients who are initiating  
224 ART do not see their CD28/CD57<sup>+</sup> T-cell count decrease, even with good CD4<sup>+</sup> T-cell recovery (52).  
225 Furthermore, it has been found that adaptive immune activation and immune senescence markers  
226 increase in ageing HIV-infected patients, however they are not reliably associated with non-AIDS-  
227 defining morbidity and mortality, contrary to markers of innate immune activation and inflammation  
228 (57,58). Indeed, CD4/CD8 ratio has been shown to be a prognostic marker for non-AIDS defining  
229 events among long-term virologically suppressed PLWH (59) and correlates with non-AIDS morbidity  
230 (60,61) as well as risk of cancer (62,63). Thus, measurement of the CD4/CD8 ratio may serve as an  
231 adequate surrogate for the HIV reservoir since this ratio was associated with integrated levels of HIV-  
232 DNA in peripheral blood cells (64). Similarly, an inverse correlation is demonstrated between CD4/CD8  
233 ratio and the frequency of CD4 T-cells carrying HIV-proviral DNA (64). More knowledge is needed  
234 regarding the impact of specific ART regimens (65) and the simultaneous treatment of coinfections,  
235 such as cytomegalovirus which is known to lower CD4/CD8 ratio through the accumulation of CMV-  
236 specific CD8 T-cells (66).

237 Altogether, immune exhaustion observed during HIV-1 infection occurs at different levels: functional,  
238 clonal and global and likely plays an important role in the onset of disease progression.

239

### 240 **3. HIV-related mechanisms**

#### 241 **3.1. Immune activation and other co-infections**

242 A major contributor of immune activation in PLWH is the recurrent stimulation of immune cells that  
243 directly recognize HIV components. Continued exposure of cells to viral replication can lead to their  
244 functional and clonal exhaustion. Moreover, systemic inflammation due to activation of the innate  
245 immunity is another major issue in HIV-1 pathogenesis (67). This is reinforced by the fact that HIV-  
246 mediated depletion of CD4<sup>+</sup> T-cells can disrupt the normal phenomenon of immune surveillance in  
247 mucosal lymphoid tissues, resulting in the abundant release of microbial products and pro-inflammatory  
248 mediators. In addition, HIV-mediated depletion of CD4<sup>+</sup> T-cells and inflammatory environment result  
249 in the reactivation of latently integrated forms of persistent viruses (Epstein-Barr Virus (EBV), Herpes  
250 Simplex Virus, CMV, Hepatitis B and C Viruses, human papillomavirus), which HIV seropositive  
251 patients are commonly infected with. Among these chronic viral infections, the most notable is CMV  
252 infection. As a result of CMV co-infection, CMV-specific CD8<sup>+</sup> T-cells are associated with immune  
253 senescence (68), clonal expansion and homeostatic changes (69). These attributes are hallmarks of the  
254 immune risk phenotype (70), leading to chronic low-grade inflammation that negatively impacts health  
255 (71). Despite the suppression of HIV-1 replication by ART, PLWH exhibit premature  
256 immunosenescence (67,72,73).

#### 257 **3.2. Inflammation, mitochondrial dysfunction and oxidative stress**

258 A direct consequence of immune activation is the increase of NF- $\kappa$ B levels, which enhances the  
259 transcription of integrated virus, and thus the production of new virions that will infect new targets. A  
260 vicious circle is therefore established during which HIV-1 replication promotes immune activation, and  
261 immune activation promotes HIV-1 replication. The release of pro-inflammatory mediators participates  
262 also to this gear: the synergic action of IL-6 and IL-1 $\beta$  and TNF- $\alpha$ , can lead to T cell activation (10) and  
263 can promote microbial translocation (74).

264

265 Under normal physiological conditions, reactive oxygen species (ROS) like H<sub>2</sub>O<sub>2</sub> have vital roles in  
266 signal transduction cascades to reversibly oxidize/reduce protein cysteine thiol groups as molecular  
267 on/off switches. As a result of immune activation, both found in HIV infection and ageing, ROS are  
268 released into the cells (75), which lead to over-oxidation and irreversible changes in protein structure  
269 and function (76). This can cause mitochondrial DNA damage due to its proximity to free radical  
270 sources and the relative lack of a protein scaffolding. Thus, mitochondrial DNA mutations lead to  
271 impaired mitochondrial protein synthesis, which has an adverse effect on oxidative phosphorylation, a  
272 process that eventually leads to premature cell ageing (77,78). The biological process to remove these  
273 accumulated damaged proteins stimulates inflammatory responses leading to a chronic inflammatory  
274 state and tissue injury (79,80). Compared to age-matched controls, HIV-infected men have reduced  
275 activity levels of skeletal oxidative enzymes, including dehydrogenase and citrate synthase by 38% and  
276 77%, respectively (81). The rate of acyl-coA synthase and carnitine palmitoyltransferase I oxidation is  
277 not significantly different between HIV-infected men and controls. However, skeletal muscle oxidative  
278 stress is significantly higher (H<sub>2</sub>O<sub>2</sub> by 1.4 fold and oxidized cardiolipin by 1.8 fold). Therefore, the  
279 progressive mitochondrial dysfunction contributes to accelerate ageing in highly energy-demanding  
280 organs like heart, skeletal muscle, kidney, liver, and brain (82). Even in clinically stable HIV-infected  
281 treated patients, mitochondrial functions are disrupted (83). Of note, ART regimen differentially  
282 impacts on mitochondrial dysfunction, as reviewed by Schank *et al.* (84), highlighting the toxicity of  
283 treatment on cellular senescence.

284

### 285 **3.3. Intestinal dysbiosis**

286 As HIV-1 causes a substantial loss of CD4<sup>+</sup> T-cells, especially in mucosal lymphoid organs where the  
287 majority of CD4<sup>+</sup> T-cell pools are located, the diverse immunological components constituting the gut's  
288 mucosal barrier can be disrupted leading to microbial translocation from the gastrointestinal tract to the  
289 systemic immune system (85). Measures of immune activation are directly linked with plasma LPS  
290 levels which are significantly increased in HIV-1 infection (86). LPS is known to induce production of  
291 a range of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-6 and IL-1 $\beta$  by stimulating peripheral

292 macrophages and dendritic cells. Therefore, a proinflammatory state can be established due to systemic  
293 activation and the differentiation of lymphocytes and monocytes.

294 Studies evaluating microbiome composition, diversity, and function in HIV-1 infection suggest changes  
295 in the gut microbiome as it can be observed with ageing, exemplified by an increase in facultative  
296 anaerobes with inflammatory properties and a decrease in obligate anaerobes that play critical roles in  
297 maintaining intestinal homeostasis and in regulating host immunity. Indeed, recent studies have  
298 documented that enteric bacterial communities in people living with HIV (PLWH) are different when  
299 compared to individuals without HIV infection (reviewed by Vujkovic-Cvijin *et al.* (87)). In both  
300 ART-treated and in treatment-naïve infected patients, a dysbiotic fecal microbiome in PLWH was  
301 characterized by greater abundance of *Prevotella* with concurrent depletion of some *Bacteroides*  
302 species, higher abundance of *Proteobacteria*, and lower abundance of obligate anaerobes including  
303 butyrate-producing bacteria (88). Nevertheless, a recent report highlights that age and HIV interact to  
304 shape the fecal microbiome in ART-treated, older adults (89). In this study, the authors showed that  
305 HIV and age were independently associated with distinct changes in the fecal microbial communities.  
306 Immune dysfunction is associated with these changes, and treatment with ART only partly restores  
307 microbiota diversity (90). Additional studies that identify both HIV and age effects on gut bacterial  
308 communities and their metabolic products in the setting of comorbidities will help to identify functional  
309 pathways which could be targeted to improve clinical outcomes.

310

### 311 **3.4. Metabolic disorders**

312 Key metabolic pathways include glycolysis, the tricarboxylic acid cycle, the fatty acid oxidation, the  
313 pentose phosphate pathway, the fatty acid synthesis and amino acid metabolism (particularly  
314 glutaminolysis), with various fuel sources utilized to produce the intermediates required for each  
315 pathway. Variation of immune cell metabolic programming that affects these pathways may thus result  
316 in change of immune function.

317 In the last decade, an increasing number of studies, reviewed by Butterfield *et al.* (91), have examined  
318 the immunometabolic dysfunction characteristic of HIV-1 infection. As summarized by Asier Sáez-

319 Ciri3n (92), the metabolic pathways of CD4+ T-cells and macrophages determine their susceptibility to  
320 infection, the persistence of infected cells and the establishment of latency. Immunometabolism also  
321 shapes immune responses against HIV-1. Briefly, HIV-1 infection alters immunometabolism by  
322 increasing reliance on aerobic glycolysis for energy and productive infection and repurposing oxidative  
323 phosphorylation machinery for immune cell proliferation and survival.

324 The relationship between immunometabolism and HIV-1 pathogenesis is complex and represents a new  
325 area of research with many issues still to be addressed, in particular if we consider that  
326 immunometabolism is likely an important mediator in associated age-related disease (93). According  
327 to Moore *et al.*, the prevalence of metabolic syndromes among the United States adults has increased  
328 by more than 35% from 1988-1994 to 2007-2012, rising from 25.3% to 34.2% (94). The pathogenesis  
329 of metabolic disorders among PLWH includes various components: genetic and environmental host  
330 factors as well as immunologic and inflammatory responses intrinsic to HIV-1 infection (95). It is  
331 becoming increasingly clear that the immune and metabolic systems are closely inter-connected and  
332 play a critical role in the maintenance of immune homeostasis, linking to several aspects of the aging  
333 process and associated chronic inflammatory conditions (96,97). Immune cells sense and respond to  
334 exogenous metabolic signals (98), including fatty acids, free cholesterol, sphingosine-linked fatty acids,  
335 products of lipid metabolism, amino acids and microbial derived-metabolites. Metabolic alterations,  
336 such as increased visceral adiposity, altered circulating lipid composition and accumulation of lipids in  
337 primary lymphoid organs have been observed in both older adults and PLWH. Of note, cholesterol is  
338 critical for HIV replication, as both HIV entry into and exit from the target cells occur through  
339 cholesterol enriched regions of the plasma membrane, called lipid rafts (99). Therefore, impairment of  
340 cellular cholesterol metabolism and overabundance of lipid rafts may be a common factor driving  
341 pathogenesis of HIV-associated comorbidities.

342 Recent studies in PLWH with diabetes mellitus or cardiovascular disease have identified an association  
343 with elevated T-cell and monocyte glucose metabolism, respectively. Immunometabolic dysfunction  
344 has also been observed in PLWH in frailty and additional studies suggest a role for immunometabolism  
345 in non-AIDS defining cancers and neurocognitive disease (91).

346 A combination of HIV infection itself and its effects on gut permeability, which can lead to bacterial  
347 translocation, may cause accelerated atherosclerosis and a decrease in high-density lipoprotein (HDL)  
348 levels (100). Additionally, activated monocytes and proinflammatory T-cells may play a role in changes  
349 in vascular structure and function that can result in coronary plaque development (6). Moreover, the  
350 prevalence of obesity increases with age, and HIV-positive older adults also have an increase in visceral  
351 adiposity, partly as a result of antiretroviral medication (101), (102). However, studies have shown that  
352 traditional lipid measurements (low-density lipoprotein, high-density lipoprotein, and total cholesterol)  
353 cannot precisely evaluate dyslipidemia to accurately predict cardiovascular risk in PLWH without  
354 taking into account CD4 lymphocyte count and exposure to ART (103) (104). Noteworthy, both HIV  
355 and ART may have a role in the development of metabolic disorders; these adverse effects are more  
356 common in women, people in high BMI, and older people. Also that protease inhibitors are the most  
357 deleterious class of drugs causing metabolic disorders (105).

358

### 359 **3.5. DNA damage and Epigenetics**

#### 360 *Telomere length shortening*

361 Age-related DNA damage tends to alter the genome randomly, however telomeres (which are tandem  
362 repeats of DNA sequence TTAGGG located at each end of chromosome) appear to be more vulnerable  
363 to age-related degradation (106). The failure of DNA polymerase to duplicate the extreme 5' end of the  
364 lagging strand of DNA causes telomere length to decrease with each cell division. Telomere length  
365 shortening is a typical marker of cellular senescence and is widely used to determine an individual's  
366 biological age. It is estimated that peripheral blood mononuclear cells (PBMCs) lose about 50 base pairs  
367 of telomeric DNA per year, and this loss doubles in HIV-1 patients even with ART (107). In a  
368 longitudinal follow-up over 3 to 9 years, telomere length of total PBMCs from PLWH was shown to  
369 shorten at an increased rate compared to age-matched seronegative individuals (108). This telomere  
370 shortening occurred primarily in CD8<sup>+</sup> T-cells, with minimal or no variation observed in CD4<sup>+</sup> T-cells  
371 (109). This faster telomere erosion in PBMCs and T-cells indicated an accelerated immunological  
372 ageing process associated with HIV-1 infection. However, it should be noted that in these studies,

373 telomere length was measured mainly by assessing PBMCs or subsets of T-cells like CD8 or CD4.  
374 Shortening of B cell telomeres in PLWH has also been documented, supporting findings of  
375 hyperactivation during HIV-1 infection (110).

376

### 377 *Epigenetics*

378 Epigenetic changes are changes to phenotypes or gene expression resulting from modifications other  
379 than modifications in the underlying DNA sequence. These alterations may be retained by the cell  
380 throughout its lifespan or may be passed to future generations for germline cells (111). DNA  
381 methylation is one of the most well characterized epigenetic changes (112), and can serve as an indicator  
382 of the cumulative effects of epigenetic maintenance (113). During ageing, epigenetic alterations in  
383 response to both exogenous and endogenous factors (114), result in an abnormal chromatin condition,  
384 genomic instability, and accumulation of DNA mutations (115). The age-related DNA methylation  
385 pattern changes, leading to a global decrease in methylation with hypermethylation of some promoter  
386 regions. Histone modifications and changes in DNA methylation near telomeric regions correlate with  
387 telomere attrition and cellular senescence (116). In addition, these epigenetic changes are associated not  
388 only with activation of inflammatory genes (117), but also with the occurrence of age-related  
389 pathologies such as cancer, dementia, and atherosclerosis (118), (119). Thus, the epigenetic clock could  
390 be a useful biomarker for detecting premature ageing due to HIV-1 infection (120).

391 Methylome-wide analysis of chronic HIV-1 infection in patients receiving ART revealed an average  
392 ageing advance of 4.9 years, leading to a 19% increase in mortality (121). This sub study of a clinical  
393 trial (comparing ritonavir-boosted darunavir with either raltegravir or tenofovir disoproxil fumarate and  
394 emtricitabine) was conducted in ART-naive PLWH. They analyzed whole blood samples from 168  
395 study participants both before they started treatment, and after two years on ART. The study compared  
396 the treated participants to 44 age- and sex-matched control participants without HIV. The authors found  
397 that, compared to those without HIV, ART-naive PLWH showed higher mean epigenetic age  
398 acceleration. The study observed no significant differences in the impact of ART on epigenetic ageing  
399 between treatment regimens. Among participants with HIV-1 at baseline, the study observed



400 dysregulation of DNA methylation-based estimated leucocytes, or white blood cells, toward more  
401 differentiated T-cell phenotypes and proinflammatory subsets. This dysregulation was corrected to  
402 some degree by long term ART (121).

403 Importantly, the cellular epigenetic machinery plays an important role in chronic infection with HIV-1  
404 (122). First, epigenetic mechanisms are heavily involved in regulating transcriptional silencing of the  
405 proviral-derived DNA burden. Secondly, this tight regulation is crucial since transcriptional activity of  
406 intact proviral genomes in reservoir cells results in viremic rebound with serious clinical consequences.  
407 Last, infection with HIV-1 also appears to modify the epigenetic landscape of infected and bystander  
408 immune cells. This signature of infection, whether directly or indirectly associated to the proviral load,  
409 could thus be an important cofactor in developing HIV-1-associated comorbidities (123). For example,  
410 two main *loci* have been identified as contributing to the genetic contribution to human lifespan : *APOE*  
411 encoding *apolipoprotein E* which is involved in lipoprotein metabolism, cognitive function and immune  
412 regulation (124) and *forkhead box O3A (FOXO3A)* involved in apoptosis and oxidative stress (125).  
413 The *apolipoprotein E4 (APOE4)* allele is associated with decreased cognitive performance, premature  
414 brain ageing, and atrophy in HIV-infected individuals over 60 years of age. HIV-associated  
415 neurocognitive disorders, including dementia, are more prevalent in *APOE4* carriers, suggesting that  
416 this gene may contribute to age-related cognitive decline (126).

417 For a curative therapy of HIV-seropositive patients, a combination of antiretroviral drugs with  
418 epigenetic modifying compounds have been suggested for the transcriptional reactivation of HIV-1  
419 latency. These epigenetic drugs include histone deacetylase inhibitors (HDACI), histone  
420 methyltransferase inhibitors (HMTI), histone demethylase inhibitors, and DNA methyltransferase  
421 inhibitors (DNMTI).

422

### 423 **3.6. Extracellular vesicles (exosomes)**

424 Exosomes are the main actors of intercellular communications: these nanoparticles are secreted by  
425 almost all cell types and contain lipids, cytokines, growth factors, messenger RNA, and different non-  
426 coding RNA, especially micro-RNAs (mi-RNAs). Exosomes' cargo is released in the neighboring

427 microenvironment but is also expected to act on distant tissues or organs. Evidence has increasingly  
428 shown that exosome-derived mi-RNAs are key regulators of age-related diseases, and their involvement  
429 in longevity is becoming a promising issue. For instance, mi-RNAs such as mi-RNA-21/ 29/ 34  
430 modulate regeneration and tissue functionality by targeting various tissues and involving different  
431 pathways which might interfere with long life expectancy (127). Despite, substantial changes to  
432 extracellular vesicles with age, it is not clear whether these changes represent a cause or effect of aging  
433 or associated comorbidities (128). On the contrary, the role of exosome in HIV infection is critical since  
434 this pathway releases intracellular material and exchanges material and information between cells. As  
435 such, exosomes play an important role in AIDS progression and affect the occurrence, development,  
436 and outcome of HIV through multiple mechanisms (such as cell-to-cell transmission and interaction  
437 with HIV molecules and receptor cells), recently reviewed by Chen *et al.* (129).

438

#### 439 **4. Long-term consequences comorbidities**

440 If we consider that increased immune activation and long- term chronic inflammation are major players  
441 in the aging process in the general population, it is obvious that these processes are more prevalent in  
442 PLWH, even when the infection is well controlled. Therefore, PLWH will be more prone to prematurely  
443 develop age-related diseases.

444 It is established that a high level of immune activation has been related to a poor CD4 cell recovery  
445 during treatment. Of importance, the occurrence of several non-AIDS-related comorbidities has been  
446 clearly linked to the presence of immune depletion, as indicated by a low CD4 cell count (130). As  
447 expected, age and male gender were found as independent predictors of polypathology by comparing  
448 PLWH to the general population, but Guaraldi *et al.* found also that a nadir CD4 cell count < 200  
449 cells/mm<sup>3</sup>, was related to the occurrence of several comorbidities. This could be explained by persistent  
450 low-grade viral replication in the reservoirs which could thereby participate in local inflammation and  
451 tissue-related complications (131). Finally, the authors found ART to be an independent risk factor for  
452 polypathology. Thymidine–nucleoside reverse-transcriptase inhibitors are associated with  
453 mitochondrial dysfunction, cell senescence, and lipodystrophic phenotype (132,133) whereas some

454 ritonavir-boosted PIs induce prelaminA accumulation, oxidative stress, inflammation, and cell  
455 senescence *in vitro* (134), all alterations associated with aging.

456 In addition to all the factors related to the virus and the treatment, a number of environmental factors  
457 could also prematurely induce aging in PLWH, such as sedentary lifestyle, low-nutrition diet, smoking  
458 or drug use.

459 A cross sectional comparison of over 500 HIV-infected patients (median viral load of 50 copies/ml,  
460 CD4 count >500 cells/ $\mu$ l and 95% on ART for greater than 10.5 years) with 500-age matched controls  
461 showed that PLWH had a higher number of age associated non communicable comorbidities  
462 (AANCCs). In addition, the number of AANCCs in each 5 years stratum in the HIV-infected patients  
463 resembled those of the controls who were 5 years older (135). In a retrospective study comparing PLWH  
464 with matched counterparts, HIV-infected subjects had significantly more comorbidities, such as bones  
465 fractures due to osteoporosis (6.4% vs 2.1%,  $p < 0.001$ ), acute renal failure (0.5% vs 0.2%,  $p = 0.045$ ),  
466 chronic renal disease (4.3% vs 2.4%,  $p < 0.001$ ) and cardiovascular disease (12.8% vs 10.4%,  $p = 0.006$ )  
467 (136). Since HIV-positive individuals are at high risk of developing non-HIV-1 related diseases, a  
468 specific follow-up of PLWH will be necessary in particular to assess the risk linked to polymedication  
469 (137).

470

#### 471 **4.1. Frailty**

472 The well-known frailty phenotype in geriatrics is characterized by the loss of functional homeostasis,  
473 which causes individuals to be unable to effectively recover from various stressors and is associated  
474 with poor health outcomes, including excessive mortality (138). PLWH may become frail due to the  
475 cumulative effect of comorbidities and ART. According to Piggott *et al.*, 5–19% of cohorts were frail  
476 or exhibited frailty-like symptoms despite effective antiretroviral therapy (139). Moreover, frail  
477 individuals are more likely to suffer from comorbid conditions such as cardiovascular disease or  
478 cognitive impairment (140). In a Multicenter AIDS Cohort Study, individuals ageing with HIV-1  
479 infection showed greater declines in gait speed and grip strength (141). In addition, the risk of frailty  
480 was higher after prolonged HIV-1 infection and was strongly predicted by the peripheral CD4<sup>+</sup> T-cell

481 count (142).

482

#### 483 **4.2. Sarcopenia**

484 Despite adequate treatment with ART, PLWH may exhibit a physiopathological process associated with  
485 ageing called sarcopenia, which involves a reduction in muscle strength, muscle quality and physical  
486 performance as well as an increased risk of falls, physical disability and premature death (143).  
487 Increased muscle protein catabolism, muscle fat accumulation (144) or low protein intake and  
488 vitamin D deficiency (145), among others can also lead to sarcopenia. Physical activity, however, can  
489 improve muscle mass and function and reduce chronic inflammation, which may protect against or  
490 partially reduce sarcopenia (146). Few data exist regarding the prevalence of sarcopenia in PLWH,  
491 although, similar to other chronic diseases, this syndrome occurs more frequently and at a younger age  
492 than in the general population. It has been proposed that metabolic changes and immune activation by  
493 HIV-1 are major factors involved in the development of sarcopenia in patients on ART (147). PLWH  
494 and controls experienced similar rates of muscle loss over a 5-year study period (148), although  
495 sarcopenia increased over a 7- to 10-year follow-up period for HIV-infected individuals older than 50,  
496 with sarcopenia progressing more rapidly in women than men (149).

497

#### 498 **4.3. Osteoporosis**

499 PLWH are more likely to suffer from osteopenia and osteoporosis (47.5% and 23% respectively),  
500 although the mechanism and consequences of these changes are not fully understood (150). Activation  
501 of the immune system and inflammation in PLWH can affect the expression and regulation of  
502 immunological factors involved in bone remodeling (151), even with effective ART. During an  
503 inflammatory process, cytokines such as TNF- $\alpha$  are produced, increasing the expression of Receptor  
504 Activator of Nuclear Factor  $\kappa$ B Ligand (RANKL), which causes bone resorption by osteoblasts (152).  
505 Activating inducible nitric oxide synthesis by cytokines such as TNF- $\alpha$  and IL-1 inhibits the function  
506 of osteoblasts *in vitro* and leads to osteoblast apoptosis (153). Furthermore, ART drugs such as tenofovir  
507 or protease inhibitors may adversely affect bone mineral density (154).

508

#### 509 **4.4. Cardiovascular disease**

510 The prevalence of cardiovascular disease has been found to double in PLWH. Patients with HIV-1 have  
511 nearly two-fold greater risk of heart disease than their uninfected counterparts. Moreover, the risk of  
512 developing the disease will likely continue to rise as PLWH are ageing (155). Aside from traditional  
513 cardiovascular risk factors (such as smoking), other factors including chronic HIV-1 viremia, ART, co-  
514 infection with CMV, chronic inflammation, innate immune activation, the microbiome and microbial  
515 translocation may be involved in the pathogenesis of cardiovascular disease in PLWH (156). HIV-1  
516 induces endothelial dysfunction and early atherosclerosis by altering signaling pathways through gp120  
517 or Tat proteins, or by activating monocytes that release cytokines (157). Oxidized lipids may also  
518 contribute to atherosclerosis by disrupting nitric oxide signal transmission, promoting endothelial  
519 activation, and influencing adhesion molecules, which play a role in leukocyte homing. Following the  
520 inflammation, biomarkers are released, such as VCAM-1, fibrinogen, D-dimer,  
521 C-Reactive Protein (CRP), selectins, IL-6, and TNF, which make the patient more likely to suffer from  
522 coronary artery disease and heart failure, including myocardial infarction, stroke and sudden cardiac  
523 death (158), (159). Subclinical atherosclerosis in PLWH while on ART appears to be associated with  
524 monocyte markers CD11b and CX3CR1 (160), suggesting a critical role for monocytes in promoting  
525 cardiovascular disease. Of note, the physiopathology of cardiovascular disease in  
526 HIV-infected individuals is complex, combining both traditional risk factors as well as ART-related  
527 factors (161).

528

#### 529 **4.5. Chronic kidney diseases**

530 Acute renal failure and chronic kidney disease are more common in PLWH than in the general  
531 population (162). Immune activation has been proposed as one of the main reasons whereby HIV-  
532 infected individuals with suppressed immune systems have more kidney disease (163). It has been  
533 shown that HIV-1 can infect renal epithelial cells through the transfer of virions occurring *via* a CD4-  
534 independent mechanism and induce changes, especially in renal tubular cells (164). The interaction with

535 renal epithelial cells leads to the release of cytokines (IL-6 and IL-8) and chemokines (CXCL-1,  
536 CXCL-2 and CXCL-8) from renal tubular cells, which contributes to exacerbating inflammation. Even  
537 though ART is associated with a lower incidence of severe renal events, specific classes of antiretroviral  
538 drugs may negatively impact kidney function (165).

539

#### 540 **4.6. Cognitive impairment**

541 The combination of HIV, inflammation, and stress is believed to be important factors leading to  
542 impaired cognitive function (166). Neurocognitive impairment affects approximately half of all HIV-1  
543 patients, and is potentially due to chronic inflammation or damage sustained before starting ART (167).  
544 During an inflammatory state, cellular damage is triggered both in PLWH and in the elderly, including  
545 the expression of IL-6 and CRP, which are associated with cognitive decline and in addition to an  
546 elevated risk of dementia (168). Furthermore, blood-brain barrier dysfunction is common among PLWH  
547 despite ART (169). In older PLWH, there are a number of mechanisms through which chronic HIV  
548 disease alone or in combination with ART and other co-morbidities (e.g.: drug use, HCV) might be  
549 contributing to HIV-associated neurocognitive disorder. This includes 1) overlapping mechanisms  
550 between HIV and ageing (e.g.: decreased proteostasis, DNA damage, chronic inflammation,  
551 epigenetics, vascular), which could lead to accelerated cellular ageing and neurodegeneration and/or 2)  
552 enhancing pathways involved in Alzheimer's disease (AD) or AD-related dementias (e.g: triggering  
553 amyloid  $\beta$ , tau, or  $\alpha$ -synuclein accumulation) as suggested by Mackiewicz *et al.* (170).

554

#### 555 **Conclusion & Perspectives**

556 PLWH are increasingly reaching old age, where they have to face the dual burden of managing their  
557 disease and the ensuing process of accelerated ageing. As a consequence, their quality of life is affected,  
558 and they are facing decreased energy availability and increased chronic inflammation. HIV infection  
559 causes immunological alterations that parallel those that occur in physiological ageing, exhibiting a  
560 striking similarity between ageing and HIV infection. Through elevated chronic immune activation,

561 PLWH exhibit innate and adaptive immunosenescence. Although many ageing-like alterations can be  
562 identified in HIV-infected patients, it is necessary to keep in mind that some factors are specific to each  
563 condition. Thus, no sign of viral reactivation with persistent viruses such as CMV or EBV was found  
564 in elderly. In addition, different lifestyles and/or environments impact on the evolution and the  
565 physiopathology of HIV-1 infection and ageing. Noteworthy, as a result of successful ART, HIV-  
566 infected geriatric patients are now living longer, leading to an emerging vulnerable population.  
567 Therefore, the question is how to best care for them. Surprisingly, in a recent study based on a highly  
568 selected geriatric HIV population, HIV-1 infection does not seem to have an additional impact on age-  
569 related inflammation and immune disorder, suggesting that HIV-patients are well taken care of and  
570 monitored (171). It is therefore encouraging to observe that prevention and treatment of comorbidities  
571 could have limited both immune activation and inflammation in the ageing HIV population. Briefly,  
572 these strategies (summarized in Figure 2), aim at:

- 573 - **preventing immune activation** with the use of ART and anti-inflammatory molecules;  
574 prevention of bacterial translocation by impacting on gut mucosa integrity or on microbiota  
575 composition; treatment of inter-current infections such as herpesviruses and reduction of  
576 metabolic abnormalities.
- 577 - **enhancing regenerative capacity** where the use of hormones, cytokines or anti-ageing  
578 therapies is explored.

579 So far, trials have been empiric. To validate these potential therapeutic options, other clinical trials need  
580 to be performed on large cohorts of PLWH.

581

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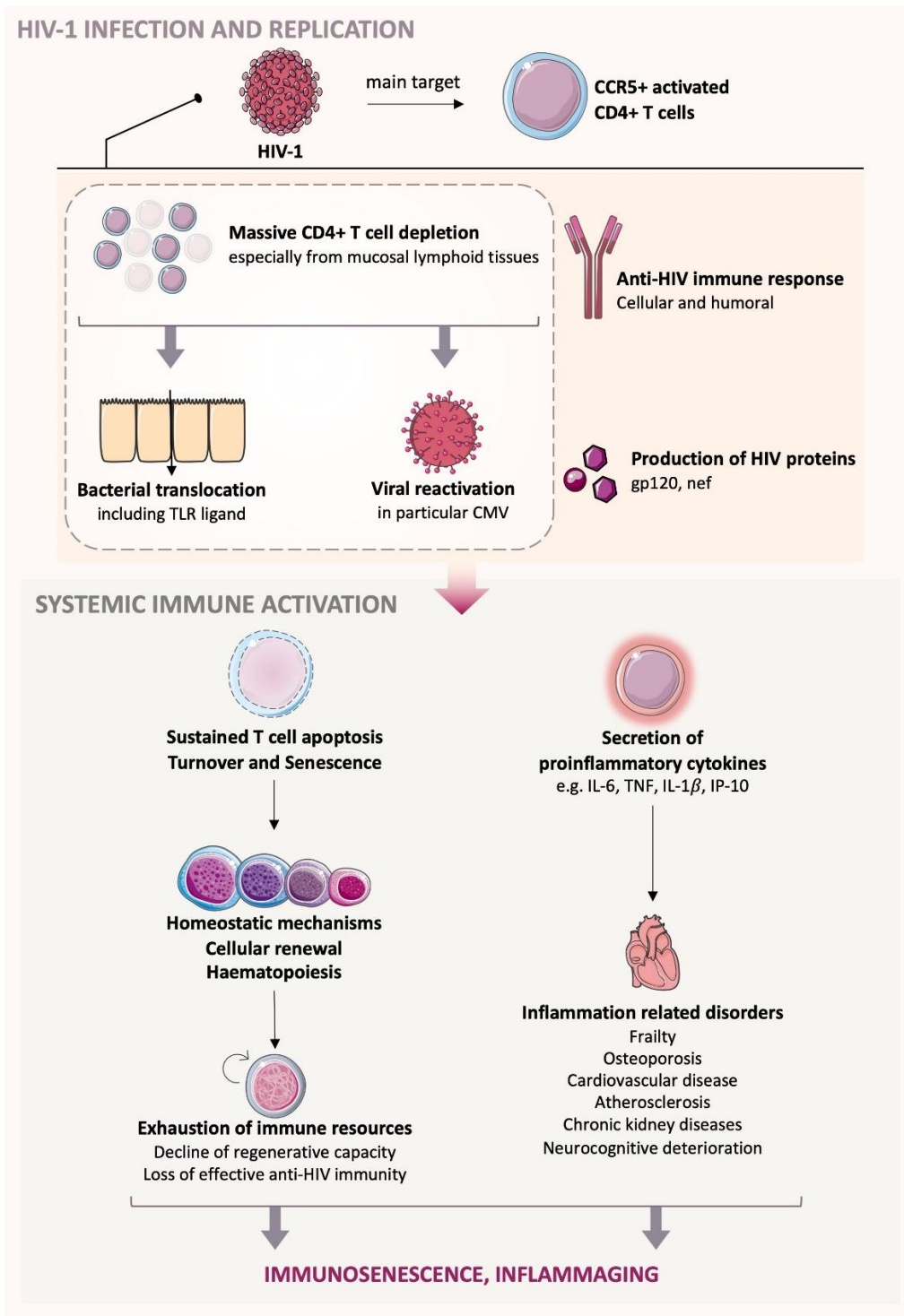
1278 **Figure Legend**

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**Figure 1. HIV pathogenesis: a model of accelerated immunosenescence.**



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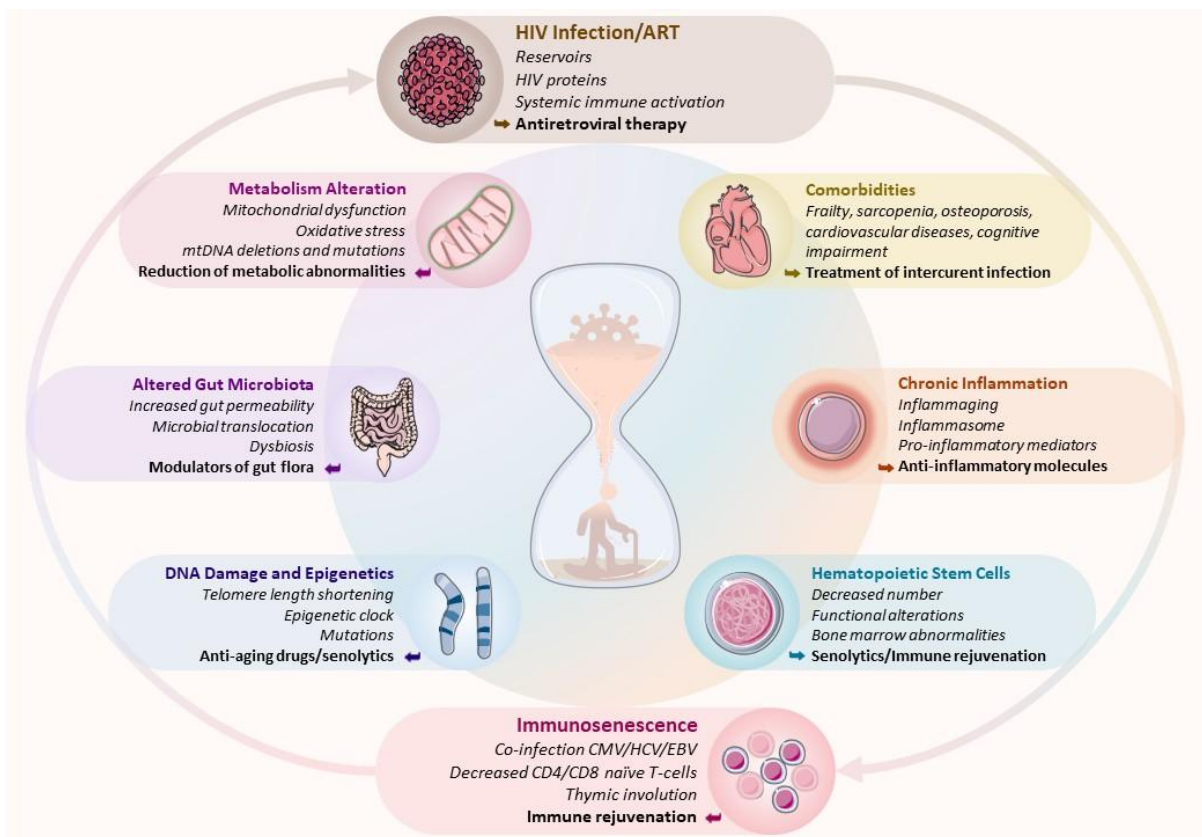
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1286 **Figure 2. Similarities between physiological ageing and HIV-related premature ageing.** On various  
 1287 levels, HIV infection can cause premature ageing that mimics or emphasizes physiological ageing. As  
 1288 indicated, several strategies are actually explored to limit immune activation and/or restore immune  
 1289 resources such as:

- 1290 - Antiretroviral Therapy (ART (172), (173))
- 1291 - Anti-inflammatory molecules (Nonsteroidal anti-inflammatory drugs (NSAIDs) (174);  
 1292 Glucocorticoids (175); Prednisolone (176); Hydroxychloroquine (177); Curcumin (178))
- 1293 - Modulators of gut flora (prebiotics/colostrum (179); Rifaximin (180); Probiotics (181), (182))
- 1294 - Treatment of intercurrent infection (Valganciclovir (183) ; Valacyclovir (184); Acyclovir  
 1295 (185))
- 1296 - Reduction of metabolic abnormalities (Rosuvastatin (186); Atorvastatin (187); Iovastatin (188);  
 1297 Sitagliptin (189))
- 1298 - Immune rejuvenation (IL-2 (190); Bone marrow transplantation (191); Thymus transplantation  
 1299 (192); Growth hormone (193); IL-7 (194))
- 1300 - Anti-aging drugs/senolytics (195); Quercetin (196); Rapamycin (197); Everolimus (198);  
 1301 Metformin (199), (200), (201); HDAC inhibitors (202,203); Telomerase activator (TAT2)  
 1302 (204)).



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