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REVIEW ARTICLE

HIV-1 Infection and the Aging of the Immune System: Facts, Similarities and Perspectives

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During infection with the human immunodeficiency type-1 virus (HIV), the immune system has to cope with the exposure to an unexpected number of different and new antigens that are generated by continuous mutations of the virus. This phenomenon causes a profound derangement of the immune response, which is similar to that defined immunosenescence, a complex remodeling, whereby clonotypical immunity deteriorates, and ancestral and innate immunity is largely preserved. Either in HIV+ patients or in elderly individuals, the lifelong chronic antigenic stress, along with the involution of the thymus, causes the accumulation of memory/effector T cells and the exhaustion of naïve T cells. Furthermore, in both these conditions a chronic inflammatory status exists in the aging process, which has been defined as "inflammaging" and is characterized by an enhanced production of proinflammatory cytokines. In this review, we will underline the similarities that exist between immunological changes present during the physiological aging process and HIV infection.

1. Introduction

In the last few years, it became more and more evident that studies on immunological changes that occur during human aging (globally defined: "immunosenescence") and those coping with the infection by the human immunodeficiency virus type-1 (HIV) have several points in common (immunological changes due to the infection with a different virus, such as HIV-2, will be not discussed here). The observation that age-related changes in immune function are often due to a chronic antigenic stimulation has suggested to HIV researchers to concentrate on the consequences of this phenomenon. On the other side, immunogerontologists have learned that if the chronic immune stimulation that follows a viral infection is reduced, as in the case of the use of a highly active antiretroviral therapy (HAART), some immunological changes, such as those of the memory T-cell compartment, can be delayed.[1]

An additional point of contact between the studies on HIV infection and those on immunosenescence comes from the observation that the age of HIV+ patients is progressively increasing because of different reasons—including the moment of the first contact with the virus, the late recognition of the infection, and the possibility to use potent drugs acting on different mechanisms of the infection—and that are collectively defined "HAART". Thus, it is now crucial to understand how and why the immune system ages more rapidly in patients with HIV infection, and what can be done to delay this phenomenon.

Thus, aging and immunosenescence have in common several features, among which the shrinkage of the T-cell repertoire, the accumulation of oligoclonal expansions of memory/effector cells directed toward infectious agents, the involution of the thymus and the exhaustion of naïve T cells, and finally a chronic inflammatory status called inflammaging. Here we will discuss some of the basis of such common immunological changes, pointing out those parts that are worth of more detailed investigation.

2. Epidemiology Reveals the Dimension of the Problem

The Joint United Nations Programme on HIV/AIDS and World Health Organization estimate that among 40 million people living with HIV/AIDS in the world, approximately 2.8 million are >50 years. In the United States, more than 15% of new HIV infection or AIDS cases reported to the Center for Disease Control and Prevention in the year 2005 were persons aged 50 years and above, whereas 2% of new diagnoses were in patients more than 65 years of age.[2,3] Present epidemiologic data in all western countries show changes in the demography of the HIV+ population as a result of growing awareness, implementation of prevention strategies, and

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the availability of HAART, which has resulted in dramatically increasing life expectancy and the quality of life among patients with HIV infection.[4] As a consequence, nowadays there are many more individuals infected by HIV of older age than those before 25 years.[5] Similarly, in western countries, also the number of elderly individuals is dramatically increasing, whereas the birth rate decreases. These demographic trends are causing a relevant increase in the age-associated diseases, a phenomenon that is forcing immunologists to unprecedented efforts to better understand how immune senescence occurs, and to limit the development and progression of these diseases.

As the HIV+ population ages, the rate of newly detected infections in the elderly people rises. Indeed, it has been predicted that, in the United States, more than one-half of all individuals infected by HIV will be >50 years by 2015.[1] Thus, as far as the immune system is concerned, the effects of the infection will overlap with those of aging *per se*.

3. The Natural Course of HIV-1 Infection

Most of the HIV transmissions mainly occur across a mucosal surface such as the anorectal or vaginal mucosa, or by a parenteral way, such as the exchange of infected needles among intravenous drug users. HIV is an enveloped retrovirus belonging to lentiviruses family,[6] which specifically targets and infects cells expressing the CD4 molecule, i.e., T-helper lymphocytes, monocytes, macrophages, and dendritic cells. Binding of the viral envelope glycoprotein 120 to the CD4 molecule and to the chemokine receptors CCR5 or CXCR4 that are present on the cell surface allows the infection. Once inside the cell, the viral enzyme reverse transcriptase transcribes viral RNA to DNA, then the integration into the host cell genome occurs, and finally the host cellular mechanisms are used to produce viral progeny.[7,8]

The clinical course of HIV infection can be schematically divided into three stages. The first stage, i.e., the acute infection, is characterized by widespread viral dissemination, which is arrested within 1–4 weeks with the induction of an efficient host cellular immune response that causes the resolution of the clinical symptoms associated with primary infection. This response is often accompanied by a marked drop in the number of circulating CD4+ T cells, and by a high production of the virus, as detected by the presence of a relevant number of viral copies in the patient's plasma. Such an acute viremia is associated with a massive activation of CD8+ T cells, most of which are specific for the virus. The CD8+ T cell response is thought to be important in controlling the production of the virus, which first peaks and then declines. This decline allows an increase in CD4+ T cell count.[9] A good antiviral response driven by CD8+ T cells has been associated to a slower disease progression and a better prognosis, though it is not able to eliminate the virus.[10] From a clinical point of view, during acute infection (usually 2–4 weeks postexposure) most individuals develop an acute syndrome that is very similar to influenza or mononucleosis, whose main symptoms may include fever, lymphadenopathy, pharyngitis, rash, myalgia, and mouth and esophageal sores. During this syndrome, a massive activation of the immune system is accompanied by a high tendency to apoptosis of the activated cells.[11–16]

Patients infected by HIV enter a period of clinical latency, defined chronic stage of HIV-1 infection, whose duration depends on many factors, including age. Indeed, age influences the course of HIV-1 infection: the probability of seroconversion to HIV decreases with age, but also the mean CD4+ T cells decrease with age, and the time from HIV-1 infection to the development of AIDS is shorter.[5,17,18] During the chronic infection, HIV is active within lymphoid organs, where large amounts of virus become trapped in the follicular dendritic cells network. The surrounding tissues that are rich in CD4+ T cells may also become infected, and viral particles accumulate both in infected cells and as free virus.

The latter stage of HIV-1 infection is AIDS, characterized by the development of opportunistic diseases that is caused by the failure of the immune system, which is in turn caused by the dramatic CD4+ T cells decline and the raise in viral activity.[18]

4. Accelerated Aging in HIV-1 Infection

Increasing evidence is suggesting that patients infected by HIV experience similar immunological changes as older uninfected individuals,[4] and indeed aging and HIV infection are associated with overwhelming changes in immunity and host defense, with striking similarities (summarized in Table 1).[19–23] It has been postulated that immune activation and inflammation play a crucial role in promoting a gradual age-related decline of the functionality of the immune system, leading to the so-called "immunosenescence". These two phenomena are thought to occur because of the chronic stimulation of the immune system, because of the presence of chronic or persistent infections that are not eradicable, such as that induced by cytomegalovirus or herpes viruses.

In the case of HIV infection, whose eradication is at the moment the "Holy Grail" for immunologists and infectivologists, the persistence of the virus causes immune activation and continuous inflammation. Indeed, not only viral antigens exert a strong pressure on the immune system, but they also change continuously because of the high rate of mutations that is the characteristic of HIV. In turn, this causes continuous modifications of the epitopes that the immune system has to recognize, and thus a relevant number of new cells have to be produced to cope with the new antigens. Unfortunately, the fate of these cells, which are actually directed towards antigens that are no longer present in the organism simply because they have mutated, is anergy or apoptosis. This phenomenon occurs during all the course of the infection, and mimics the accelerated replicative senescence of T cells that progressively accumulate during the normal course of human aging.[24]

5. Immunologic Response in HIV+ Elderly Patients

It has been shown that HIV infects thymocytes, reducing the functionality of the organ, namely its capacity to produce naïve T lymphocytes.[25] Qualitative T-cell alterations have been well reported in HIV+ individuals, and include: accumulation of highly differentiated CD8+ or CD4+ T cells, a reduced capacity to proliferate, short telomere length, changes in the capability to produce some types of cytokines, and an increased susceptibility to activation-induced cell death.[26] Rare patients, who are able to better control viral replication, defined long-term nonprogressors have HIV-specific CD8+ T cells that retain a strong capacity to proliferate upon antigenic stimulation and that present polyfunctional capacities in terms of cytokine production,[27,28] and have a low tendency to undergo apoptosis.[29]

Physiological aging is characterized by a progressive involution of the thymus, and resultant thymic volumes are significantly lower in persons >45 years as compared with younger persons.[30] The production of naïve T cells further declines, and thymic output becomes minimal after the age of 55,[17] even if signs of thymic activity (in terms of production of the T-cell receptor rearrangement excision circles—defined TREC—and their presence in peripheral blood lymphocytes) can be found also in persons aged >100 years.[31] Increased age is then associated with diminished T cell functionality,[32] reduced naïve T cell populations,[33] progressive enrichment of terminally differentiated T cells with shortened telomeres, and fewer numbers of properly functional CD8+ cytotoxic T cells.[3,34] Since these changes are very similar to those caused

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Table 1 Similar alterations of some cellular functions are present during aging and HIV-1 infection. Relationships between immunological changes present during aging and HIV infection that cause inflammation or "inflammaids".

	Aging	HIV-1 infection	Ref.
Innate immunity			
Macrophages	Functional decline of macrophages Impaired production of cytokine, chemokine	Resistant to cytopathic effect induced by HIV-1 Impaired phagocytosis, intracellular killing, chemotaxis, and cytokine production	66–69
Myeloid and plasmocytoid dendritic cells	Number of myeloid DC declines Decreased levels of CD34+ precursors High levels of circulating monocytes High expression of CD80 and CD86 Impaired ability to produce IL-12 under stimulation	Reduced levels of plasmacytoid and myeloid dendritic cells (direct correlation with CD4+ cell count, inverse correlation with viral load) HAART significantly increases plasmacytoid dendritic cells	70–73
Adaptive immunity			
B lymphocytes	Polyclonal activation Hypergammaglobulinemia Activation of resting B cells Decrease of naive B cells Increased IgG, IgM, IgA production	Polyclonal activation Hypergammaglobulinemia Activation of resting B naive Decrease of naive B cell Increase amounts of IgG, IgM, IgA	59–65
T lymphocytes	Diminished thymic production of naive T cell Increase of activated T cell High levels of CD28−/CD57+ T cells (senescent phenotype) Clonal exaustion	Diminished thymic production of naive T cell Increase of activated T cell High levels of CD28−/CD57+ T cells (senescent phenotype) Clonal exaustion	31–45
T regulatory cells	Increased levels of memory Treg cells Decreased levels of naive Treg cells	Increased levels of memory Treg cells Decreased levels of naive Treg cells	46–50
Th17 cell in GALT	Depletion of Th17 cells	Depletion of Th17 cells	51–58

DC = dendritic cells; GALT = gut-associated lymphoid tissue; HAART = highly active antiretroviral therapy; HIV = human immunodeficiency type-1 virus; IL = interleukin; Th17 = T helper 17; Treg = regulatory T cells.

by the presence of the virus, the progression of HIV infection in elderly patients may be more pronounced: elderly patients infected by HIV have lower count of CD4+ and functional CD8+ T cells if compared with their aged-matched controls or to younger HIV-1-infected patients.[17]

CD8+ cytotoxic T lymphocytes control HIV replication as they kill virus-producing infected cells. They exert a strong effect in determining the initial viral set point,[35] which is related to the trend of the course of the whole infection,[36] and indeed this is well demonstrated also by the different ability of Class I major histocompatibility complex molecules to present viral antigens to CD8+ T cells and the related genetic polymorphisms.[37] It is possible to hypothesize that in elderly persons infected by HIV, viral load is higher than that in younger patients[38] for the reason that elderly patients fail to control infection from the very beginning, essentially because of a deficit in CD8+ T cell functionality and number. Hence, HIV infection could compound, or be synergistic with, the effects of aging on the human immune system.[24]

6. Altered T Cell Homeostasis

As mentioned before, the intrathymic production of T cells diminishes with time in elderly patients infected by HIV, because of either atrophy or direct infection of the thymic precursors and thymocytes.[31] As HIV persists in the host, the immune system continues to be challenged and immune activation and inflammation become more and more generalized.[39] The infection alters the homeostatic control of the production of T-cell precursors, which leads to the progressive loss of naïve and memory T cells. As a consequence, naïve CD4+ and CD8+ T cells (that are typically CD45RA+, CCR7+) are reduced in patients infected by HIV and in elderly HIV-1-negative individuals as compared with HIV-negative young controls, with proportional increase in terminally differentiated effector T cells (CD45RA+, CCR7−). Moreover, CD4+ and CD8+ central memory T cells (CD45RA−, CCR7+) can be reduced in individuals infected by HIV as compared with older seronegative donors. The degree of activation of CD8+ T cell (that typically express HLA-DR and CD38) is almost always higher in HIV-1-infected patients as compared with HIV-1-negative older and younger controls.[5]

Like aging, HIV infection is characterized by high levels of antigen-experienced T cells that do not express CD28 and express CD57.[40] This subpopulation is a key predictor of immune incompetence: highly differentiated T cells (CD28−, CD57+) are approaching end-stage senescence: this subpopulation is not longer able to produce interleukin (IL)-2 and demonstrates a decline in proliferative capacity, associated with a shortening of telomere length.[41]

CD28, expressed on T cells, provides co-stimulatory signals that are required for T-cell activation. CD28 is the receptor for B7.1 (CD80) or B7.2 (CD86), that are expressed on different types of antigen presenting cells;[42,43] after binding, CD28 transduces downstream survival and proliferation signals including induction of IL-2 and its receptor, telomerase activation, stabilization several cytokines mRNAs.[5,44] Thus, the loss of expression of CD28 alters both B-cell and T-cell response by inhibiting the helper activity of CD4 T cell as far as B-cell proliferation and antibody production are concerned.[45] The mechanism for the accelerated loss of CD28 expression during HIV infection and its significance in the progression to AIDS remains to be elucidated. In HIV+ patients and elderly people, the majority of CD8+ cells are CD28−, whereas less than 10% CD4+ T cells loose this molecule.[21] It has also been reported that the expression of CD28 on CD4+, but not CD8+, T cells is a significant predictor of the progression to AIDS.

According to some authors, CD57 expression defines better than CD28 the proliferative defect of CD8+ T cells after *in vitro* stimulation.[40] Accordingly, the frequency of senescent CD8+ T cells (that are CD28−, CD57+) is higher in HIV-infected as well as in elderly healthy individuals as compared with seronegative young donors.[40]

7. Effect of Aging on Regulatory T Cell Frequency in HIV-1 Infection

Regulatory T cells (Tregs) are a subpopulation of CD4+ T lymphocytes that inhibits T cell activation, proliferation, and function. Tregs are characterized by high expression of CD25 (the alpha-chain of the receptor for IL-2), expression of Forkhead P3 transcriptional factor (FoxP3) and the lack of expression of CD127.[46] Unfortunately, the identification of these cells by flow cytometry is always

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incomplete, and several papers do not identify Treg in a correct manner. As a result, a high number of data are difficult to understand—if not completely wrong.

Naïve Tregs do not express CD45R0 antigen, are directly derived from thymus, target self-antigens and are resistant to apoptosis. Memory Tregs are CD45R0+, are generated in peripheral tissues from naïve T cells after exposure to antigen, are activated and apoptosis-prone.[47] Deficiency in the number or function of Treg is associated with autoimmune disease, whereas increased Treg frequency is present in certain cancers and chronic infections.[48]

As far as the number of Treg in aging and HIV infection is concerned, it has to be immediately underlined that in the literature data are quite heterogeneous, especially because of the different markers used to identify Treg. According to some authors,[49] it seems that memory Tregs increase in HIV infection, whereas naïve Tregs tend to diminish. Furthermore, Treg percentage is increased in older HIV+ population and may play a role in the accelerated disease progression seen in older persons infected by HIV-1,[49] even if a possible effect of the virus on age-related changes in Treg cannot been excluded. On the other hand, others studies suggest that the progression of the infection, and not aging *per se*, drives the expansion of Treg that was found in elderly patients infected by HIV.[50]

In any case, studying the alterations in Treg functionality remains quite complex, and it is likely that these cells would play a different role (and thus would be detectable or active in a diverse manner) in different moments of the infection.

8. Changes in Gut-associated Lymphoid Tissue

The gut-associated lymphoid tissue (GALT) is an important site for early viral replication and severe CD4+ T cell depletion during HIV-1 infection.[51] A rapid dysfunction of the intestinal epithelial barrier is observed during acute HIV-1 infection and coincides with the loss of CD4+ T cells. Such loss also involves CD4+ cells defined T helper 17 (Th17), a family of CD4+ T cells able to exert a variety of functions.[52] GALT lymphocytes are the primary target cells of HIV during mucosal transmission, and GALT is the first tissue where a profound CD4+ T cell depletion occurs. Normally, the percentage of Th17 cells is higher in GALT than in peripheral blood or other tissues[51] and, despite HAART, CD4+ T cell reconstitution remains deficient in the gastrointestinal tract; furthermore, the reduced number of Th17 cells is hardly reconstituted after HAART.[53] Th17 cells produce several cytokines, including IL-17, IL-21, IL-22, IL-26, and tumor necrosis factor-alpha, and generate a rapid response to microbial pathogens at mucosal site.[54] Successively, Th17 cells stimulate the intestinal epithelium to produce antimicrobial molecules (like mucin and defensins) and induce chemokine expression, along with the production of granulocyte colony-stimulating factor, for the recruitment of neutrophils, monocytes, and eventually lymphocytes to the site of infection. Th17, through the production of IL-17A, induces the renewal of intestinal epithelial barrier by triggering cellular signals like claudins that ultimately produce tight junction, and facilitate helper T cell functions.[55] Thus, at the mucosal level, Th17 cells are a crucial linker between innate and adaptive immunity.[56]

During HIV-1 infection, microbial translocation is associated with chronic immune activation: progressive depletion of Th17 CD4+ T cells in the gut results in loss of barrier integrity, causing gut leakiness and translocation of microbial products and eventually microbes into circulation.[57] In turn, this phenomenon provokes and maintains the massive immune activation. Unfortunately, the physiological consequences of mucosal Th17 depletion have not yet been fully explored[56] and further data are needed to fully understand the mechanisms and the possible intervention strategies.

Also the effect of aging on GALT is poorly understood but, as suggested by clinical evidence, there may be age-related changes in GALT as well.[58] Indeed, the aged immune system fails to control gut-derived antigens mainly because of the dysfunctional thymic output and the lack of maintenance of an intact naïve T cell repertoire.[5] Hence, during lymphophenic condition such as aging and chronic viral infections, keeping an efficient gut mucosal defense is extremely difficult.

9. Altered B-cell Function and Antibody Production

Although HIV-1 does not directly target B lymphocytes, during HIV-1 infection the number of B cells is reduced and their function is impaired. HIV+ patients display follicular hyperplasia in secondary lymphoid organs with changes in the architecture of germinal centers, whose integrity is crucial for the development of high affinity antibodies against T cell-dependent antigens. The abnormalities of B cells in Patients infected by HIV include polyclonal activation, hypergammaglobulinemia, autoimmune phenomena, defective response to antigen stimulation, and occurrence of AIDS-related lymphomas.[59] The loss of the appropriate interactions between fully competent T lymphocytes and B cells in the germinal centers might be the basis for the impairment of B-cell responses during HIV-1 infection.[60]

Although nearly all individuals infected by HIV produce antibodies against several HIV antigens, only a few display an efficient antiviral activity, such as the neutralization of viral particles, and in any case the neutralizing response appears only several months after infection,[61] when relevant and often-irreversible damages to the immune system had already occurred. A baseline high activation of resting naïve B cells persists in HIV+ individuals even during HAART.

With HIV infection, as well as during the aging process, the number of memory B cells may vary, the quality of the B-cell response may worsen and the naïve B-cell repertoire decreases.[3,62] Recent studies have reported that the expression of CD27, a molecule expressed by somatically mutated peripheral memory B lymphocytes, is decreased in HIV infection. In the peripheral blood of healthy individuals, memory B lymphocytes represent about 40% of the total B-cell pool, whereas this subset is reduced to about 20% in HIV+ patients.[63] In persons infected by HIV and elderly individuals, the clinical evidence of B-cell dysfunction, such as an increased risk of infection such as pneumonia (due to *Streptococcus pneumoniae*), is well evident.[64] Finally, both older and HIV+ individuals exhibit elevations in total serum levels of IgG and IgM, along with changes in Ig classes and subclasses,[65] whereas total IgA serum levels are higher only in patients with AIDS.[39]

10. Innate Immune Response in HIV-1 and Aging: Alterations of the Monocyte/macrophage System and Dendritic Cells

The senescence of the innate immune system is an extremely complex phenomenon, and studies are difficult also because innate immunity cells are spread in almost every tissue and organ, and play a variety of roles. Natural killer cells, monocytes, macrophages, plasmacytoid dendritic cells, and neutrophils are crucial elements that are functionally impaired during HIV-1 infection, and whose activity can change during pathological or physiological aging.[5,66–73] Monocyte/macrophages are resistant to the cytopathic effect of HIV and can persist alive throughout the course of infection as long-term stable viral reservoirs that are capable of producing virus, and thus allowing the dissemination to tissues.[74] Indeed, infectious virus can be recovered from peripheral blood monocytes obtained from patients receiving HAART, who have an undetectable viremia.[75] Following infection, effector functions performed by monocyte/macrophages, including phagocytosis,

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intracellular killing, and chemotaxis and cytokine production, are also impaired.[74,76,77] Such defects contribute to the pathogenesis of AIDS allowing the reactivation of the virus, that further impairs CD4+ T cell response, and also facilitating the development of opportunistic infections.[78]

In HIV+ patients, a defective phagocytic capacity for opportunistic pathogens by cells of macrophage lineage has been largely documented, but the mechanism whereby HIV-1 impairs phagocytosis has been not clarified in detail.[79] As monocyte and macrophages contribute considerably to cytokine and chemokine production, it is not surprising that cytokine profile is altered during almost all stages of the infection and is associated with increased production of inflammatory cytokines, Th2 cytokines, beta-chemokines by cells of macrophage lineage.[80]

These changes are similar to those observed in elderly people.[81–85] In fact, as a person ages, the adaptive immune system shows a functional decline in ability to respond to new pathogens whereas serum levels of some cytokines (typically, those with proinflammatory activity) are elevated.[86] Despite age-associated increases in cytokines, the function of aged macrophages is decreased: toll-like receptor expression and function decline, wheras there are elevated levels of activated nuclear factor-kB (NFkB),[87] whose activation by means of toll-like receptor stimulation results in the production and the secretion of proinflammatory cytokines.[88]

Furthermore, in elderly persons infected by HIV, who display a chronic inflammation because of their age, age-associated defects in innate immunity are exacerbated by the infection, and viral clearance is further compromised. This clearly increases the persistence of viral antigens in the organism, and further drives immunosenescence,[5] which is in turn accelerated by the immunological impairment caused by HIV.

11. Inflammaging and Inflammaids

The term "Inflammaging" has been coined a few years ago to explain the fact that, in humans, physiological aging is accompanied by a low-grade and chronic and systemic up-regulation of the inflammatory response, and that the underlining inflammatory changes are common to most age-associated diseases.[89] The inflammatory *scenario* that characterizes inflammaging constitutes a highly complex response to internal and environmental stimuli (like chronic infections) mediated mainly by the increased circulating levels of proinflammatory cytokines. Inflammaging is a consequence of "macrophaging",[90] i.e., a hyperactivity of macrophages producing proinflammatory cytokines.

Inflammaging is influenced by unfavorable genetic polymorphisms and epigenetic alterations, may slowly damage one or several organs, and lead to an increased risk of frailty together with the onset of age-related chronic diseases. Interestingly, different tissues (adipose tissue and muscle), organs (brain and liver), immune system and even ecosystems (such as the gut microbiota) can give relevant contributions to the age-related inflammation, and offer different targets for interventions. It is easy thus to note that the factors that play a role in causing the aforementioned alterations are well present, also during HIV infection. For example, alteration in the permeability of the intestinal tract can either modify the microbiota, or cause a constant activation of the immune system,[40,57] which is very similar to that observed during aging.

Thus, taking into account the changes that occur during HIV infection, and their striking similarity to what happens during immunosenescence (Figure 1), it is possible to define as “inflammaids” the immunological situation that is characterized by a massive activation of either the natural immune system (with a relevant production of proinflammatory cytokines) or the adaptive immune system (with the induction of a massive cellular activation).

12. Therapy for HIV Infection and the Problem of Side Effects

HAART consists of a combination regimen, usually including a minimum of three antiretroviral agents, typically from at least two different classes. At present, six classes of antiretroviral agents are available: (1) protease inhibitors , which are able to inhibit the viral protease (that has to cleave viral proteins into functional components); (2) nucleosidic or nucleotidic reverse transcriptase inhibitors, which block the viral RNA to DNA transcription process by substituting in chain-terminating nucleosides in the DNA chain;

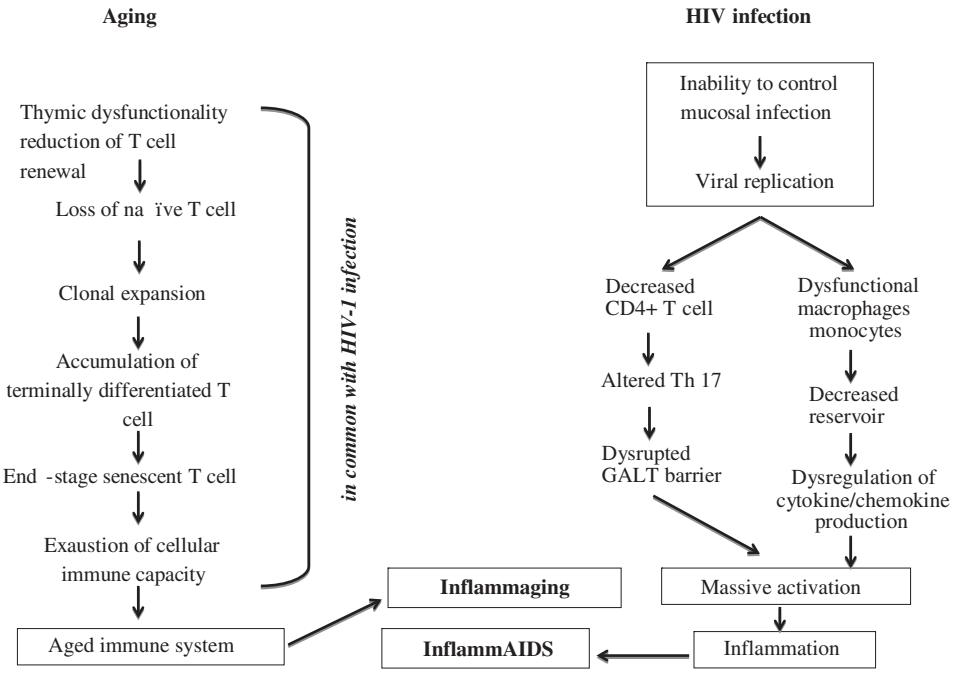

Figure 1 Relationships between immunological changes present during aging and HIV infection that cause inflammation or “inflammaids”.

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(3) non-nucleosidic reverse transcriptase inhibitors, which change the conformation of the reverse transcriptase enzyme; (4) fusion inhibitors, which block the fusion of HIV-1 with the host cell at the initial point; (5) entry inhibitors, which can block the entry of HIV-1, for example by blocking the cell-surface co-receptor CCR5; (6) integrase inhibitors, which prevent the integration of the viral DNA into host genome.

Combination therapy for HIV infection is required because, thanks to the presence of an extremely high frequency of mutations, the virus can quickly develop resistance to one agent if it is given as monotherapy; with combination of drugs, the virus takes longer time to develop resistance to the entire regimen.[2] In other words, should a viral subspecies emerge with a mutated protein that cannot be inhibited by a single compound, a drug with a different mechanism of action can intervene and block the virus. Using different drugs renders highly unlikely that a single virus harbors all the mutations required for escaping all classes of drugs. Unfortunately, this may occur in patients who have received a suboptimal treatment with different drugs for long periods.

The complex relationship between HIV-1 infection, HAART, aging and treatment of a multitude of comorbidities makes the comprehensive care of elderly patients infected by HIV a challenging clinical effort. If treatment guidelines are available for the management of HAART for naïve patients (of undefined age), there are no specific treatment guidelines presently available that focus on management in the elderly adults infected by HIV.[3] This has an extraordinary importance, considering the age-related changes in several districts of the organism. Hepatic mass, blood flow, and metabolism decrease with age;[91] the age-related decrease in renal mass, blood flow, tubular secretion, and glomerular filtration can lead to drug accumulation and result in drug toxicity.[92]

Patients infected by HIV appear to have higher prevalence of the metabolic syndrome.[93,94] Drug-induced metabolic changes, that include derangement of lipid and glucose metabolism, along with older age, have been associated with increased risk of cardiovascular disease and myocardial infection.[95]

Age-related changes in body composition can also influence drug pharmacokinetics by altering drug volume of distribution.[96,97] Some interesting data suggest that elderly HIV+ patients receiving HAART experience more adverse events than younger ones.[98] However, few drug trials involving elderly populations have been performed, and almost nothing is known about drug interactions in elderly HIV+ individuals.[3] Thus, additional research is urgently needed to determine the efficacy and safety of antiretroviral therapy in the elderly patients.

13. HAART, Virologic Suppression, and CD4 T Cell Counts in Elderly HIV+ Patients

Contrasting data exist on the influence of age on virologic suppression and CD4+ T cell restoration in HAART-treated patients. Furthermore, it is not clear whether the level of CD4+ T cell required for initiation of the therapy should be different in elderly HIV+ patients.

It has been demonstrated that the degree and the speed of immune recovery and CD4+ T-cell restoration are reduced in elderly patients[99] and that younger age may favor CD4 cell restoration because of a more preserved thymic mass and functionality.[100] In other studies, older patients tended to achieve better virologic control compared with younger patients, possibly because of better HAART adherence.[101,102]

It has been shown that, although elderly individuals present a more severe HIV-1 infection, they can achieve the same viro-immunological success as the younger individuals under HAART.[103] Accordingly, a more recent study showed that CD4 cell counts were not significantly different from those of younger patients after 3 years of HAART.[102] Considering the effect of age on HIV-1 progression and mortality in the HAART era, some data indicate that, despite the good rate of virologic suppression, which is expected because the plasma concentrations of the drugs are always in the range of efficacy for suppressing viral activity, elderly patients had an increased risk of death and new opportunistic infections, compared with younger patients.[104]

Concerning the earliest period of the use of HAART, data on the importance of the patient's age are difficult to interpret, and they yield mixed results probably because of the few patients enrolled in the studies, the different drugs used in the HAART regimen, or even because studies has not been adjusted for adherence or for comorbidities.[3,103,105–107] In fact, clinical trials often exclude elderly patients because of multiple medical problems, and especially because of the use of other, nonantiviral therapeutic regimens by these patients. Future studies, based on selected populations of elderly patients, eventually taking well-defined therapies, are needed to better understand and characterize the immunological response in HAART patients.[2]

14. Conclusions

HIV infection, through a continuous process of both direct and indirect immune activation, might accelerate the aging or decay of the immune system. A relatively young HIV+ adult might exhibit some of the immune characteristics displayed by an uninfected, healthy individual even 3 times older.[4]

Activation and inflammation occur in both HIV infection and aging, and both conditions share a common detrimental pathway that lead to early immunosenescence. This includes direct or indirect activation of the adaptive immune system and of innate immune cells.[5] Thymic dysfunctionality, loss of thymic mass, reduction of T cell renewal, exhaustion of cellular immune capacity, inability to control mucosal dysregulation, loss of Th17 cells, and impaired function of monocyte/macrophages are the major characteristic of immunological aging and HIV-1 infection. Thus, the accelerated aging caused by HIV is a huge problem in these years, characterized by the efficacy of HAART, and it is necessary study cohorts of elderly people infected by HIV to better understand the management of elderly persons living with HIV, and to increase the quality of their life.

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