Immunosenescence and hurdles in the clinical management of older HIV-patients

Marco Ripa#, Stefania Chiappetta#, and Giuseppe Tambussi
Department of Infectious and Tropical Diseases, Ospedale San Raffaele, Milan, Italy

ABSTRACT
People living with HIV (PLWH) who are treated with effective highly active antiretroviral therapy (HAART) have a similar life expectancy to the general population. Moreover, an increasing proportion of new HIV diagnoses are made in people older than 50 y. The number of older HIV-infected patients is thus constantly growing and it is expected that by 2030 around 70% of PLWH will be more than 50 y old. On the other hand, HIV infection itself is responsible for accelerated immunosenescence, a progressive decline of immune system function in both the adaptive and the innate arm, which impairs the ability of an individual to respond to infections and to give rise to long-term immunity; furthermore, older patients tend to have a worse immunological response to HAART.

In this review we focus on the pathogenesis of HIV-induced immunosenescence and on the clinical management of older HIV-infected patients.

Introduction

The advent of highly active antiretroviral therapy (HAART) deeply improved HIV-infected people’s quality of life making possible for young patients with CD4 cell count > 350 cell/mcL to have a life expectancy similar to that of HIV negative individuals.1 Thanks to the prolongation of life expectancy due to HAART,1 the number of people with HIV infection older than 50 y increased during the last years in all Western Countries. According to last CDC report, in 2013 people aged 50 and over accounted for 18% of estimated HIV diagnoses, for 23% of estimated AIDS diagnoses and for 37% of deaths related to AIDS in the United States.2 In 2014, in Italy the 20% of new HIV diagnoses and the 10% of AIDS diagnoses were in people over 50 y old.3

The incidence of infectious and non-infectious comorbidities and overall mortality have been found to be higher in HIV infected patients compared with HIV-negative ones.4 Moreover the duration of HIV infection seems to be a stronger predictor of morbidity and non-infectious comorbidities compared with age at the diagnosis.4

The main problems with older people are the low perception of risk and the stigma of speaking about sex, even with people sexually active. These 2 factors make more difficult to achieve HIV diagnosis and consequently they cause a delay that can lead to a severe immune deficiency. The progression to AIDS is faster in older people5,6 mainly because of the immunosenescence due both to age and to HIV infection itself. Moreover, progression to AIDS or occurrence of non-AIDS related comorbidities can be only partially prevented with HAART.7

In this review we focus both on the pathogenesis of immunosenescence in HIV infected patients and on the main challenges involved in the clinical management of older HIV-patients.

Immunology of aging in HIV-infected patients

Immunosenescence and inflammation

Cellular senescence was first described by Hayflick as an irreversible cellular growth arrest following repeated cellular divisions, even in the presence of mitogenic stimuli (“replicative senescence”).8,11 In this status, cells continue to be viable but they cannot proliferate and this process is not reversible. Senescent cells are different both from terminally differentiated cells, which stopped cellular division as a part of their development program, and from quiescent cells, that have the possibility to re-enter the cellular
cycle following external stimulation. Cellular senescence is mainly mediated by p53/p21 and p16INK4a/retinoblastoma (Rb) tumor suppressor pathways. Different cellular stressors can trigger cellular senescence. In particular telomere shortening, due to consecutive cell divisions, is sensed by the cell as a DNA damage and drives a DNA-damage response (DDR) (“replicative senescence”). DDR together with hypoxia or accumulation of reactive oxygen species (ROS), can provoke “stress-induced senescence” mediated first by p53/p21 and followed, if stress is repeated, by p16INK4a pathways. Finally also the activation of oncogenes induces senescence (“oncogene-induced senescence”). (Fig. 1) As a matter of fact cellular-senescence was an anti-proliferative program to prevent damaged cells to replicate. An increased number of studies draw the attention to the reduction in telomerase length, which is a measure of the proliferation of each single cell, and to mitochondrial damage, which is able to increase oxidative stress and inflammatory pattern, as major drivers for senescence program in all individuals.

Senescence provokes a cascade of morphological and phenotypic changes in cells: a) increase in size and a flat morphology; b) upregulation of tumor suppressor genes and downregulation of cell-cycle promoting genes; c) production of senescence-associated secretory phenotype (SASP), which are inflammatory cytokines, growth factors and matrix metalloproteinases. In particular Effros et al found an increase in pro-inflammatory cytokines (interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]) and a reduction in antiviral interferon-γ (IFNγ) (released by CD8+ T-cells). The release of chemokines, activated cytokines and immune modulators (SASP) from senescent cells induces local inflammation attracting cells of immune system. Senescent cells can be removed by innate immune cells (especially macrophages) maintaining tissue homeostasis and restricting tumorigenesis, but they can also accumulate in tissue leading to cancer, aging and fibrosis. What drives this process leading to the clearance or not of senescent cells it is not well-known. It is supposed to depend both on the kind of trigger (which cell? In which context?) or on the ability of the immune system to get rid of senescent cells.

The term immunosenescence refers to age-related changes in both the innate and adaptive immune systems associated to morbidity and mortality and reduction in vaccines responses.

In older adults, these changes seem to be linked to pro-inflammatory pathway (Inflamm-Aging), even if the mechanism is not completely understood (cellular damage? endogenous activators? hormonal changes?). Main data of immunosenescence associated to increased mortality in elderly derive from OCTO/NONA cohorts (2 longitudinal studies in Swedish octogenarians or nonagenarians). In these studies the inversion of the CD4/CD8 ratio (less than 1) and the expansion of terminally differentiated cytotoxic T cells, associated to raised levels of pro-inflammatory cytokines and to seropositivity to cytomegalovirus (CMV), were linked to higher morbidity and mortality in healthy elderly individuals.

In HIV infection, both HIV-replication itself and viral coinfections induce immune stimulation and clonal expansion of T-cells. The immune activation results into differentiation and accumulation of nonfunctional senescent cells (CD28- T-cells) and into an inflammatory milieu which perpetuates premature aging. The higher level of inflammation in HIV individuals is measured by inflammatory biomarkers: in particular interleukin-6 (IL-6), C-reactive protein (CRP), D-dimer (DD), cystatin C-dimers and cystatin D-dimers. In HIV-infected individuals these biomarkers are higher than in uninfected adults. They have been studied in HIV patients during HAART and they remain elevated

![Figure 1](https://example.com/figure1.jpg)
despite suppressive therapy;\textsuperscript{7,18} moreover in SMART study IL-6 and DD values predicted both mortality and non-AIDS related events in HIV patients.\textsuperscript{13,18} Numerous factors are involved in the persistence of inflammation during HIV infection: a) ongoing HIV production; b) viral coinfections and microbial translocation; c) loss of T-regulatory cells; d) irreversible fibrosis of the thymus and lymphoid tissues and e) oxidative stress from smoking, obesity and HAART toxicities.\textsuperscript{7,13}

In spite of the benefit in survival due to HAART, event therapy itself may contribute to cellular activation and senescence. Some nucleoside reverse transcriptase inhibitor (NRTIs), as stavudine or zidovudine, inhibit mitochondrial synthesis causing the release of mitochondrial DNA and increasing oxidative damage.\textsuperscript{7,20} Rodriguez-Mora et al. found a direct HIV damage on mitochondrial DNA mediated by Tat, which was shown to polarize mitochondria and enhance the expression of metabolism-related proteins. According to this mitochondrial dysfunction, Rodriguez-Mora et al. supposed Tat to predispose cells to mitochondrial toxicities due to HAART.\textsuperscript{20} NRTIs were supposed to inhibit telomerase and consequently accelerate cellular aging.\textsuperscript{7,21} Protease inhibitors (PIs), especially indinavir, lopinavir and ritonavir, provoke fat redistribution which induces metabolic changes in adipocytes causing inflammation and mitochondrial alterations similar to NRTIs.\textsuperscript{22,23} Gallego-Escuredo et al. compared adipocyte differentiation after efavirenz and lopinavir/ritonavir treatment, finding that both efavirenz and lopinavir/ritonavir impaired human adipogenesis and increased the expression and secretion of inflammation-related cytokines, but the overall effects were greater with efavirenz.\textsuperscript{24} Contrarily maraviroc, a chemokine receptor CCR5 antagonist, does not alter adipocyte differentiation and seems to have anti-inflammatory properties exerted by inhibition of the expression and release of pro-inflammatory cytokines.\textsuperscript{25}

\textbf{Coinfections and pro-inflammatory pattern}

HIV itself, especially before the start of HAART, herpesviridae, in particular cytomegalovirus (CMV), and hepatitis viruses cause a prolonged stimulus to the immune system, reducing in particular the capability of proliferation of the T cells and depleting T-cells receptor (TCR) repertoire.\textsuperscript{7,8,26}

CMV causes a lifelong infection able to produce continuous antigenic stimulation thanks to most of viral proteins (751 unique CMV proteins) in infected cells.\textsuperscript{27} This antigen burden is responsible for a more restricted T-cells repertoire and cause the accumulation of terminally differentiated T-cells, a process called “memory inflation.” CMV infection provokes expansion of CD8- T-cell population both in CD8+ T-cells and in CD4+ T-cells, similarly to the physiologic alterations which happen to T-cell compartment in older patients.\textsuperscript{8,27,28} CMV stimulates high CD28-CD8+ T-cells response, higher than the CD28-CD4+, causing a reduced CD4: CD8 ratio, hallmark of immunosenescence.\textsuperscript{27,28} Shortening of telomere length in T-cell phenotype is also associated with CMV infection.\textsuperscript{27} In addition to the antigenic burden, CMV has developed numerous mechanisms to evade host surveillance as downregulation of HLA I and II of infected cells to escape recognition by CD4+, CD8+ and natural killers (NK). Finally the UL111.5A region of CMV genome encodes for an immunosuppressive interleukin homologous to IL-10. Thereby CMV is able to produce a state of immunosuppression producing a vicious circle in which CMV induces immunosuppression, which in turn facilitates CMV reactivation. This process is seen both in elderly people and in immunosuppressed patients, whether due to iatrogenic suppression as after bone marrow or solid organ transplantation or due to acquired causes as in HIV infection.\textsuperscript{27} Prevalence of CMV coinfection is estimate to be around 90–100% in HIV infected-people. HIV and CMV chronic infections and the consequent inflammation and immune activation, the perturbation of T-cell compartment associated to the supposed role of CMV as “smoking gun” in immunosenescence, make the double infection play a synergic role in accelerated aging.\textsuperscript{7,14,27,28}

Finally, HIV infection causes the depletion of CD4+ T-cells of gut-associated lymphoid tissue (GALT) both by HIV direct effect and by activation-induced cell death. The mucosa-associated damage, due to GALT depletion, promotes a persistent intestinal bacterial translocation which increases chronic inflammation.\textsuperscript{7,9,13,16} Soluble CD14 (sCD14) is an acknowledged biomarker of microbial products translocation. In particular sCD14 is expressed on the surface of monocytes and macrophages and it is released into circulation after its binding to LPS, which provokes monocytes/macrophages activation. sCD14 levels have been correlated with mortality in treated HIV patients.\textsuperscript{13,16}

\textbf{Thymic function and T-cells response}

T-cell development occurs in thymus, where bone marrow progenitor cells migrate to undergo positive selection (where T cells expressing a TCR that can recognize host MHC proteins on APCs are selected) and negative selection (where T cells recognizing autoreactive or “self” antigens are deleted) processes.

Thymus starts to involute during childhood and continues to involute in adults (at a rate of approximately 1–3% per year)\textsuperscript{29}; for this reason thymus-
dependent T-cell creation declines with aging reducing the number of naive T-cells. Under physiologic conditions, thymus releases immature lymphocytes termed “recent thymic emigrants” (RTEs) which maintain a stable pool of naive T-cells. Whether thymus activity is maintained in adulthood is debated but it is accepted that most (approximately 90% of CD4+ T cells) of T cells in older adults are generated from division of cells in the existing T-lymphocyte pool (as RTEs).

Consequently, in older adults, most T-cells appear to be antigen-experienced memory T-cells. In elderly people, the analyses of TCR repertoire revealed decreased diversity if matched with younger people. This finding in addition to developmental and signaling alterations alongside with age-related decrease in T-cell generation are all found in cells from older adults, which contribute to functional deficits. The altered signaling is fostered by the persistence of low quantity of pro-inflammatory cytokines and increased production of ROS, both characteristics of Inflamm-Aging. Moreover, the human T-cell compartment lose CD28 expression on CD8 T-cell during the shift from central to effector memory cells. CD28+ has a central role in the proliferation of CD8+ T-cells as one of the main co-stimulator of T+ cell response during the antigen presentation between APCs and T-cells (in conjunction with TCR recognition by peptide bound to host MHC proteins on APCs).

HIV infected more preferably CD31−central naive CD4+ T-cells than CD31+thymic naive CD4+ T-cells. The active proliferation of CD31−central naive CD4+ T-cells thereby provides a reservoir for HIV in humans. In HIV patients the CD31+thymic naive CD4+ cells depletion is more evident than in age-matched healthy controls: this process may explain at least part the reduced TCR repertoire and the consequent detrimental response to neoantigens (infections, cancer, autoimmunity, vaccinations). Moreover, in older HIV-infected patients (> 50 years) the compensatory increase of CD31−central naive CD4+ cells is also reduced compared both to age-matched controls and to younger HIV patients.

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Recent studies have reported that the senescence phenotype in both CD8 effector memory and CD4 T-cells is strongly associated with irregular signaling via the p38 MAP kinase. Altogether, the increased ROS, the skewed TCR repertoire and the loss of CD28 which occur in the aging process provoked an aberrant signaling, leading to immunosenescence, inflamms-aging and their adverse effects. Recent studies found that mTOR serine threonine kinase activity plays a role in T-cell activation and differentiation, in particular of naive CD4+ T-cells, leading toward Th1 or Th17 phenotypes. TCR/CD28 stimulation controls mTOR signaling pathway. Only few reports on T-cell mTOR in aging are available, based mainly on murine models. Recently, Arnold et al.
have reported that TCR stimulation provoked autophagy in human CD8+ T-cells, whereas autophagy was reduced in CD28-CR8+ cells, thus limiting their survival under antigen stimulation. These data strengthen the interconnection between TCR pathways and mTOR activity and the resulting possible relationship to immunosenescence.39

Kovaiou at al.40 studied CD4 subsets in healthy young and elderly volunteers finding increased CD27+CD28+ T-cells (naive and early-differentiated cells) in younger people, while elderly presented more frequently CD27-CD8- T-cells (fully differentiated cells) demonstrating that the aging process was linked to a shift of CD4 T-cells from naive and early-differentiated to late differentiated subset. To better differentiate these phenotypes, the authors measured the presence of cell-surface markers, in particular CD45RA, receptors involved in lymphocyte homing [CCR7] and intercellular adhesion and co-stimulation [CD11a] associated with the different cellular subset ability to produce perforin. As expected elderly volunteers showed decreased frequency of CD45RA+ cells (markers of naive cells) and increased number of CD11a++ cells compared with younger individuals. These data suggest that the CD27+CD28+CD4+ T-cells population is composed of 2 different phenotypes in the 2 groups of volunteers enrolled: a naive antigen-inexperienced subset in younger patients and an antigen-experienced cells of an early differentiation stage in elderly subjects. No differences were found in cytokine production (IL-2, IL-4 and interferon-γ) after in vitro stimulation in each CD4+ T-cell subset between the 2 population considered; whereas CD28-CD8+ T-cells are known to be unable to replicate and to produce IL-2. Finally the analysis of telomere length revealed a significantly shorter length in CD27-CD28-CD4+ cells when compared with CD27+CD28+CD4+ T-cells.40

While CD4+ naive T-cells decrease with age, memory CD4+ T-cells expand thanks to the continuous antigen presentation and to homeostatic proliferation.40-42 T lymphocytes with specificity for a particular pathogen can persist in the host for many years after the pathogen has been eliminated.43 CD8+ T lymphocytes can persist without re-exposure to antigen, either from exogenous sources or from antigen depots that might be maintained after the resolution of primary infection.43 Memory T-cells survive and undergo homeostatic proliferation in the absence of any MHC molecules. Memory CD8+ T lymphocytes specific for a viral pathogen diminish in frequency in the absence of IL-15 or if they do not express the IL-15 receptor. Memory CD4+ T-cell populations show a similar dependency on IL-7 and IL-15 signals. Despite these similarities, antiviral CD8+ memory T-cell populations typically persist at relatively constant levels over time, whereas virus-specific CD4+ memory T-cells decrease in frequency; this combination provokes a reduction in CD4:CD8 ratio that is enhanced both in aging and in HIV infection.26,29,38 Antigen persistence is required for long-term maintenance of CD4+ memory T-cells.53 Memory T cells can be divided into 2 main subsets, central memory (TCM; cells with high levels of CD62L and CCR7) and effector memory cells (TEM; cells with low levels of CD62L and CCR7, which actively expresses effector functions and traffics to peripheral rather than secondary lymphoid tissues), based on expression of homing and chemokine receptors involved in preferential trafficking to secondary lymphoid organs or peripheral sites, respectively.43,44 Several models of memory T-cell generation have been proposed, including the hypothesis that memory T-cells rapidly distinguish themselves from conventional effector T-cells during the primary immune response. Most data support the model of naive T-cells differentiating into effector T-cells, then further differentiating into memory T-cells. Comparison of the TCR repertoire of pathogen-specific effector and memory T-cells suggests that these 2 populations share a common ancestry. Memory T-cells appear to have expressed genes encoding effector proteins, further supporting the notion that memory T-cells derive from effector T-cells. During infection, at very early stages of the immune response, a subset of T-cells maintain the capacity to undergo more extensive proliferation.43

HIV-infected patients have several similarities to older people as increased memory cells proliferation compared with naive cells.16,40,45,46 In particular HIV-1 infection is related to: a) reduction of naive CD4+ and CD8+ T-cells and an increased frequency of memory CD8+ T-cells; b) alterations in expression of CD27 and CD28 in chronic HIV-1 infection (as with aging) regardless of age; c) significantly shorter telomere length of CD28-CD8+ T-cells and d) shift to a replicative senescent phenotype of CD28-CD8+ T-cells. The sum of these changes greatly limits the capability of the CD8+ T-cell compartment to perform an appropriate response against HIV-1 and other antigens. In elderly HIV-infected individuals both aging and HIV-1 infection itself play a role in the loss of naive CD4+ T-cells, enhancing the changes in CD8+ T-cell phenotypes and the consequent poorer outcome of these subjects.34 Allers et al. found an increased effector memory phenotype in older HIV patients associated to an increased inflammatory cytokines.6

The reduced CD4/CD8 ratio,47 the decreased expression of CD28, the shift from naive to central memory cells and the reduction of TCR repertoire is much more evident in HIV-infected patients before the introduction of HAART.8 However HAART is not able to normalize
The B-cell lineage generates a highly diverse repertoire of rearranged antigen receptor genes and there is evidence that diversity in large populations of B cells is substantially reduced with age and with changes in functional phenotype such as the geriatric syndrome of frailty. Chronic infection with Epstein-Barr virus or CMV also influence B-cell repertoire. Current studies on sequencing the repertoire of purified B-cells revealed evidence for age-related repertoire changes. Moreover many B-cell functions are dependent on T-cell help, the effects of aging on the B-cell lineage reflect both B-cell intrinsic changes and those resulting from altered T-B-cell interactions (reduced number of recognized antigens and reduced production of antibodies). Activation-induced cytidine deaminase (AID) expression on B-cells is a protein fundamental for the heavy chain class switching of B-cells and for somatic hypermutation. AID expression is reduced with age, so that in elderly patients there is a decreased proportion of B cells that underwent class switching and decrease in B cell responses to primary antigenic stimulation. Older people have increased proportion of memory B-cells than naive cells, with increased gene expression of TNF-α which is negatively correlated with proliferative responses.

In HIV-infected patients compared with age-matched controls, there is an increase in memory B-cells which are more activated, resulting in polyclonal production of immunoglobulins (Ig), in particular IgG and IgA isotypes. HIV-1 infection causes B-cell hyperactivation and exhaustion through the interaction of HIV-1 virions with CD21 (complement receptor 2) on mature B-cells and through indirect effects of HIV-1 infection (immune activation and follicular-helper T-cell dysfunction). B-cell hyperactivation in patients with HIV also leads to accumulation of activated mature (AM) B cells, exhausted “tissue-like” memory (TL) B cells, and immature transitional B cells, whereas resting memory (RM) B cells are depleted. Decreased CD21 expression on B cells (CD21low/-) is a marker of B-cell exhaustion which drives the spontaneous production of immunoglobulins and characterizes cells with decreased proliferative capacity (plasma blast). HIV-naive patients have higher values of CD21low/- compared with HIV patients in chronic therapy, nevertheless HAART cannot normalize B cells subpopulations.

**Innate response**

Neutrophils are short-lived cells that are among the first to reach the site of inflammation. Neutrophils use a great number of different mechanisms to phagocyte and kill pathogens. Phagocytosis, chemotaxis, generation of neutrophil extracellular traps, free radical production and apoptosis are modified by aging. These modifications seem to be related to changes in signalosome formation causing reduced cell responses. Moreover, even though the number of TLRs is not altered by aging, there is still an impairment in the trafficking of pathway-associated signaling molecules in the plasma membrane.

Several studies illustrate the increase of activated/inflammatory monocytes, in particular CD14+ CD16++, both in older people and in HIV positive patients. This “activated pattern” is confirmed by the expansion of CD11b expression and by the reduction of CD38, CD62L, and CD115 expression. Plasma levels of soluble CD163 (sCD163) and CXCL10, markers of innate immune activation, increase with age. Interestingly, also basal levels of IL-10, an anti-inflammatory cytokine, are higher in older than in younger individuals. Van Duin et colleagues registered a reduced production of IL-6 and TNF-α following TLR-1/2 stimulation. While in chronic HIV infection there is an increase in TLR-2 expression and consequent augmented release of pro-inflammatory cytokines.

Myeloid dendritic cells (mDC) are professional APCs with strong antigen-presenting properties able to influence immune activation through secretion of regulatory cytokines. TLR function of mDC changes in HIV-infected people depending on the stage of infection. While plasmacytoid dendritic cells (pDC) are APCs which can exert antiviral activities mainly by producing abundant amounts of interferon-α (IFN-α), pDC function usually decreases both in HIV patients and in older people. TLR function of pDC in chronic and primary HIV infection is related to IFN-α production and induction of NK cytotoxicity. The production of inflammatory cytokines, as IL6, IL2, TNF-α and type I interferon, is diminished in older adults compared with younger ones. NK cells are defined by the expression of CD56 (or N-CAM) and CD16, receptor for the Fc region of IgG (Fc-R-III). The major compartment
of peripheral blood NK cells is CD56dimCD16+ (90%) while CD56brightCD16−NK cells represent less than 10% of peripheral blood NK cells. Both these subsets have a high immunoregulatory capability due to cytokine and chemokine production in response to stimulation.62 There is a third compartment of dysfunctional NK cells, CD56−CD16+, also found in a small percentage in peripheral blood of healthy individuals, which is expanded in HIV and in hepatitis C virus infections.62 Changes in NK cells subset of elderly are associated with: a) increased numbers of NK in healthy elderly individuals, b) reduced frequencies of CD56bright NK cells and increase of CD56dimCD16+ NK cells.29,62 These changes drive to a reduction of cytotoxicity-activating receptors and a major susceptibility to infections, also mediated by the reduced ability to respond after stimulation.29,62 In HIV infection NK cells are supposed to have a central role in the complex net of interactions between immune and adaptive responses, as well reported in Scully and Alter’s recent paper.63

**Treatment of the aging HIV-infected patient**

Treatment of HIV infection in both patients diagnosed at an older age and in younger subjects with disease-related biologic senescence represent a challenge for the clinician. While the mechanisms behind aging in these 2 populations may be somewhat different, from the clinical point of view it is necessary to evaluate the patient not only on the base of the chronological age but also considering the biologic age. Nevertheless, elderly HIV-infected patients constitute a specific population in which both disease-related and physiologic mechanisms take place and the choice of treatment must be carefully aimed and tailored to address these issues.

Currently, international guidelines do not recommend specific regimens in older HIV patients, and treatment should be started regardless of CD4 T-cell count.64-68 (Table 1) Nevertheless, delaying HAART initiation in this population seems to be more harmful than in younger patients even at similar CD4 T-cell thresholds.69 Few large randomized studies enrolled patients >50 y old, so data regarding efficacy and tolerability of HAART in this special population is somewhat scarce, especially considering that by 2030 more than 70% of HIV-infected patients will be more than 50 y old.70

**Clinical outcome**

Works evaluating risk of AIDS and death in HIV-infected patients >50 y old showed a higher risk of progression even after adjusting for baseline CD4+ T-cell count, HIV-RNA and stage of disease.71-77 Interestingly, this finding is not explained by differences in virological response, as older HIV-infected patients tend to have a superior virological outcome when compared with younger patients.78-83 Some suggests that these finding may be linked with higher adherence in older patients,78,84-85 but other authors reported a higher risk of inadequate adherence in HIV patients who have other comorbidities and take other medications besides HAART.86-87

While virological response seems not to be influenced by age, at least biologically, older patients have lower CD4+ T-cell gain compared with younger persons,88-95 even when adjusted for antiretroviral therapy regimens. This is particularly relevant considering that lower CD4 T-cell counts are not only linked to HIV-related opportunistic infections and malignancies, but also lead to higher risk of non-AIDS-related comorbidities, adding to the already elevated risk conferred by age.96-108 Moreover, even after an adequate CD4 T-cell increase, the functionality of the immune system remains compromised compare with younger treated HIV+

| Guidelines          | DHHS 201664 | WHO 201665-66 | EACS 201667 | BHIVA 2015 (2016 INTERIM UPDATE)68 |
|---------------------|-------------|---------------|-------------|----------------------------------|
| **Recommendations** | ART is recommended for all patients regardless of CD4 T lymphocyte cell count (AI). ART is especially important for older patients because they have a greater risk of serious non-AIDS complications and potentially a blunted immunologic response to ART. | ART should be initiated in all adults living with HIV, regardless of WHO clinical stage and at any CD4 cell count (strong recommendation, moderate-quality evidence). | ART should always be recommended irrespective of the CD4 count with the possible exception of elite controllers with high and stable CD4 count. | We recommend standard criteria are used to determine when to commence antiretroviral therapy in older PLWH (1C). We recommend standard antiretroviral regimens are commenced in older PLWH (1C). |
| **Notes**           | Special attention to: adverse drugs events from ART and concomitants; drug-drug interactions concomitants | No specific recommendations for older HIV-infected patients. | No specific recommendations for older HIV-infected patients | Special attention to: non-infectious concomitant medications clinical pharmacology |

*Note: ART: antiretroviral therapy; PLWH: people living with HIV.*
patients.\textsuperscript{109-110} Finally, patients who are diagnosed with HIV at an older age have lower CD4 T-cells and less favorable prognosis comparable to younger patients.\textsuperscript{111}

The recent results from the START study\textsuperscript{112} highlight how an early treatment started with more than 500 CD4 T-cell was able to reduce the rate of serious AIDS and non-AIDS related events. In a cohort study following people living with HIV in the UK, life expectancy at the age of 35 was comparable to that of general population when optimal virological and immunological (i.e. >350 CD4 T-cell) response was achieved. The study showed that even when virological suppression was obtained, life expectancy was shorter for people with a lower CD4 T-cell count.\textsuperscript{113} Life expectancy at the age of 20 in HIV-infected patients compared with a non-infected cohort in the US was also recently analyzed.\textsuperscript{114} While the gap with uninfected population during 1996–2006 was 26 years, this value was reduced to 13 y in the period between 2007 and 2011. Interestingly, starting HAART with more than 500 CD4 T-cells further narrows the gap to 9 years, and patients who are not co-infected with hepatitis B or C, who do not smoke and have a current or past history of drug and/or alcohol abuse have a life expectancy at 20 y old just 6 y lower than uninfected subjects. These findings were also confirmed by other recent reports.\textsuperscript{115-119} In conclusion, while starting HAART in older HIV-infected patients is undoubtedly recommended, the poorer immunological response seen in this population represent a matter of concern and should be intensively investigated to increase life expectancy of elderly patients.

**Drug-drug interactions**

Currently, 6 different classes of antiretroviral drugs are approved for clinical use. Antiretrovirals belonging to the same class share similar metabolic pathways, but each drug has its own peculiar pharmacokinetic properties. Protease inhibitors (PIs) inhibit P-glycoprotein (P-gp), cytochrome P450–3A (CYP3A) and other isoenzymes belonging to the same family. Among this class, ritonavir is the most potent and it is currently used to increase plasma levels of other PIs, acting as a so-called booster. Cobicistat, an analog of ritonavir lacking antiviral activity, is a potent inhibitor of CYP3A and P-gp, but its effect is more specific and has no inducing properties. On the other hand, non-nucleoside reverse transcriptase inhibitors (NNRTIs) are inducers of CYP3A. Consequently, PIs usually carry the risk of increasing the concentration of drugs metabolized by CYP3A, while NNRTIs may lower plasma levels of such molecules. Finally, nucleoside reverse transcriptase inhibitors (NRTIs), integrase inhibitors (INIs) and maraviroc are not metabolized by the cytochrome system and therefore carry lower risk of drug-drug interactions.

Older patients are more likely to receive more drugs compared with younger HIV-infected people, and the risk of drug-drug interactions (DDI) is therefore higher in this particular setting.\textsuperscript{70,120-123} The clinician must face the challenge of selecting an appropriate HAART regimen in a naive HIV-infected elderly patient and to adapt an ongoing HAART according to concurrent medications in an aging patients already receiving antiretrovirals. Table 2 illustrate a brief summary of the most relevant interactions between first-line antiretrovirals and commonly prescribed drugs in the aging population.

**Cardiovascular medications**

Cardiovascular comorbidities are common among older patients; moreover, both HIV infection and certain antiretrovirals constitute a risk factor for cardiovascular events.\textsuperscript{124} Rivaroxaban, an oral anticoagulant which acts as a direct inhibitor of factor Xa, must not be co-administered with protease inhibitors and cobicistat, as the inhibition of CYP3A4 and P-gp may increase rivaroxaban plasma concentrations, leading to an increased bleeding risk. Moreover, a close international normalized ratio monitoring must be performed when PIs, cobicistat or NNRTIs (with the exception of rilpivirine) are prescribed in people receiving warfarin.

Amiodarone, propafenone, flecainide and lidocaine coadministration with PIs is contraindicated, as serum concentrations of these antiarrhythmics is increased leading to potential serious adverse events. Caution must also be used if using cobicistat.

Among anti-hypertensive medications and drugs used for heart failure, ivabradine, lercanidipine and ranolazine concentrations are increased by concomitant use of PIs or cobicistat, and co-administration should be avoided. Close monitoring is also required with dihydropiridine calcium-channel blockers. Conversely, efavirenz and nevirapine may reduce plasma concentrations of this class of anti-hypertensive.

Finally, digoxin levels may be increased by PIs and cobicistat, and frequent serum digoxin levels monitoring is therefore recommended, while patients already taking digoxin should have their dose halved. In patients receiving rilpivirine, plasma concentrations of this drug may also increase due to inhibition of intestinal P-gp.

Lipid-lowering agents are among the most prescribed medications in both general populations and people living with HIV. While simvastatin and lovastatin coadministration with PIs and cobicistat is contraindicated, other agents as rosuvastatin and atorvastatin may be used if dose-adjusted. Pravastatin and fluvastatin may be safely coadministered with PIs, while the interaction with cobicistat has not been fully evaluated yet.
Table 2. Interactions between first-line antiretrovirals and commonly prescribed drugs in aging population, extracted from68 and http://www.hiv-druginteractions.org/.

| Cardiovascular medications | DRV/r | RPV | DTG | EVG/COBI | RAL | ABC | FTC or 3TC | TDF or TAF |
|----------------------------|-------|-----|-----|----------|-----|-----|------------|------------|
| Atorvastatin               | ↑     |     |     | ↑        |     |     |            |            |
| Rosuvastatin               | ↑     |     |     | ↑        |     |     |            |            |
| Pravastatin                | ↑     |     |     | ↑        |     |     |            |            |
| Simvastatin                | ↑     |     |     | ↑        |     |     |            |            |
| Fluvastatin                | =     |     |     | ↑        |     |     |            |            |
| Calcium channel blockers – Dihydropiridine | ↑     |     |     | ↑        |     |     |            |            |
| Calcium channel blockers – Non-dihydropiridine | ↑     |     |     | ↑        |     |     |            |            |
| Metoprolol                 | ↑     |     |     | ↑        |     |     |            |            |
| Atenolol                   | =     |     |     | =        |     |     |            |            |
| Bisoprolol                 | ↑     |     |     | ↑        |     |     |            |            |
| Carvedilol                 | ↑/↓   |     |     | ↑        |     |     |            |            |
| Warfarin                   | ↑     |     |     | ↑/↓      |     |     |            |            |
| Rivaroxaban                | ↑     |     |     | ↑        |     |     |            |            |
| ACE-inhibitors             | =     |     |     | =        |     |     |            |            |
| Torasemide                 | ↓     |     |     | ↓        |     |     |            |            |
| Losartan                   | ↓     |     |     | ↓        |     |     |            |            |
| Other Angiotens-receptor blockers | =     |     |     | =        |     |     |            |            |
| Amiloride                  | =     |     |     | =        |     |     |            |            |
| Furosemide                 | =     |     |     | =        |     |     |            | E          |
| Torasemide                 | =     |     |     | ↑        |     |     |            |            |
| Spironolactone             | =     |     |     | ↑        |     |     |            |            |
| Doxazosin                  | ↑     |     |     | ↑        |     |     |            |            |
| Acetylsalicylate           | =     |     |     | =        |     |     |            |            |
| Amiodarone                 | ↑     |     |     | ↑        |     |     |            | E          |
| I伐bradine                 | ↑     |     |     | ↑        |     |     |            |            |
| Digoxin                    | ↑     |     |     | ↑        |     |     |            |            |
| Gastrointestinal medications |      |     |     |          |     |     |            |            |
| Metformin                  | ↑     | ↑   | ↑   | ↑        |     |     |            |            |
| Antacids                   | =     | D   | D   | D        | D   | =   | =          | =          |
| PPIs                       | =     | D   | =   | =        | E   | =   | =          | =          |
| H2 blockers                | =     | D   | =   | =        | E   | =   | =          | =          |
| Domperidone                | ↑     |     |     | ↑        |     |     |            |            |
| Neurologic and psychiatric medications |      |     |     |          |     |     |            |            |
| Ergot derivatives          | ↑     | ↑/E | ↑   | =        | =   | =   | =          | =          |
| Quetiapine                 | ↑     |     |     | ↑        |     |     |            |            |
| Citalopram                 | ↑     |     |     | ↑        |     |     |            |            |
| Paroxetine                 | ↓     |     |     | ↓/↑      |     |     |            |            |
| Sertraline                 | ↓     |     |     | ↑        |     |     |            |            |
| Fluoxetine                 | ↑     |     |     | ↑        |     |     |            |            |
| Duloxetine                 | ↑/↓   |     |     | ↑        |     |     |            |            |
| Venlafaxine                | ↑     |     |     | ↑        |     |     |            |            |
| Amitriptyline              | ↑     |     |     | ↑        |     |     |            |            |
| Mirtazapine                | ↑     |     |     | ↑        |     |     |            |            |
| Carbamazepine              | ↑     |     |     | =        |     |     |            |            |
| Lamotrigine                | ↓     |     |     | =        |     |     |            |            |
| Phenytoin                  | ↓/D   | D   | D   | D        | D   | D   | =          | =          |
| Diazepam                   | ↑     |     |     | ↑        |     |     |            |            |
| Triazolam                  | ↑     |     |     | ↑        |     |     |            |            |
| Miscellaneous medications  |      |     |     |          |     |     |            |            |
| Alfuzosine                 | ↑     |     |     | ↑        |     |     |            |            |
| Sildenafil                 | ↑     |     |     | ↑        |     |     |            |            |
| Prednisone                 | ↑     |     |     | ↑        |     |     |            |            |
| Coxiib                     | =     |     |     | =        |     |     |            |            |
| Acetaminophen              | =     |     |     | =        |     |     |            |            |
| Ibuprofen                  | =     |     |     | =        |     |     |            | E          |
| Diclofenac                 | =     |     |     | =        |     |     |            | E          |
| Codeine                    | ↑     |     |     | ↑        |     |     |            |            |
| Buprenorphine              | ↑     |     |     | ↑        |     |     |            |            |
| Fentanyl                   | ↑     |     |     | ↑        |     |     |            |            |
| Morphine                   | ↓     |     |     | ↓        |     |     |            |            |
| Tramadol                   | ↑     |     |     | ↑        |     |     |            |            |
| Oxycodone                  | ↑     |     |     | ↑        |     |     |            |            |
**Gastrointestinal medications**

Metformin is the first-line medication for people diagnosed with type 2 diabetes. Cobicistat may increase metformin levels thanks to the inhibition of MATE1 transporter, while rilpivirine may exert the same effect by inhibition of active renal secretion of metformin. Dolutegravir was also demonstrated to increase metformin concentrations, and a dose adjustment is required in case of coadministration.

Gastric pH-lowering agents must be used with caution with most antiretrovirals. Antacids and medications containing polyvalent cations must not be administered concomitantly with atazanavir, rilpivirine and integrase inhibitors. Proton-pump inhibitors must not be coadministered with rilpivirine, and should also be avoided in patients receiving atazanavir, especially unboosted. Finally, anti-H2 receptor antagonist should also not be administered concomitantly with PIs and rilpivirine. Domperidone, an anti-emetic metabolized by CYP3A4, must not be prescribed to patients receiving PIs or cobicistat, due to an increase concentration leading to higher risk of QT prolongation; caution should also be used when coadministered with NNRTIs.

**Neurologic and psychiatric medications**

Ergot derivatives, commonly used for migraine treatment, should not be used with PIs, cobicistat and NNRTIs because of increased concentrations of dihydroergotamine and ergotamine.

Most antipsychotic drug concentrations are increased if used with PIs and cobicistat, while dose should be adjusted with NNRTIs (with the exception of rilpivirine) because of risk of insufficient drug concentration. In particular, quetiapine carries the higher risk of interactions with PIs and should therefore not be coadministered. Benzodiazepines behave similarly, with risk of overexposure if coadministered with PIs and cobicistat and subtherapeutic levels with NNRTIs. Notably, midazolam and triazolam should not be prescribed to patients receiving these PIs, cobicistat and also efavirenz, because of high risk of overdosing.

Most anti-depressant interacts the same way with PIs, cobicistat and NNRTIs, with the former leading to higher levels and the latter to decreased concentrations of the coadministered drug.

**Miscellaneous medications**

Boosted PIs and cobicistat increase the concentration of steroid, both systemic and topical, leading to potential serious adverse events such as adrenal insufficiency or Cushing’s syndrome. On the contrary, NNRTIs, with the exception of rilpivirine, reduce the concentration of steroids.

Opioid analgesics, such as fentanyl, tramadol or oxycodone, show higher plasma levels when coadministered with PIs or cobicistat, while NNRTIs, again with the exception of rilpivirine, are able to decrease serum concentration of such molecules. Methadone has a remarkable behavior, as it is increased by PIs while cobicistat does not significantly alter plasma concentrations; nevirapine, rilpivirine and especially efavirenz reduce methadone levels in blood, while etravirine does not produce a substantial effect.

**Impact of aging on drug toxicity in HIV-infected patients**

Multiple factors affect drug absorption and metabolism in older patients. Increase in gastric pH, reduced gastric emptying and gastrointestinal motility associated with reduced splanchnic blood flow influence the absorption of antiretrovirals. Moreover, hepatic and kidney function are known to decline in aging patients, due respectively mainly to decreased activity of the cytochrome P450 system and reduced glomerular filtration and tubular secretion. Finally, the pharmacokinetics of prescribed drugs is also influenced by change in body composition which typically occurs in the elderly, such as increased in body fat and decrease in total body water. Special attention should then be made to adjust the dosage of antiretrovirals given these physiologic modifications occurring with age, as several works demonstrated an increase in drug-related adverse events in older patients.

**What to start**

The decision of an appropriate HAART should be made considering the higher frequency of comorbidities in older patients, which also leads to an higher risk of drug-drug interactions. A recent analysis of a French cohort showed that HIV-infected patients older than 75 y old had a similar rate of viral suppression but significantly more age-linked noncommunicable comorbidities, highlighting the need of a “targeted intervention” in aging HIV patients.

When choosing a first-line regime in older patients, antiretrovirals with an impact on pre-existing conditions or on potential age-associated comorbidities must be avoided. Moreover, a strict monitoring for potential toxicities and screening for age-related diseases must be constantly be performed. Several works described the issue of comorbidities in older HIV-patients, and a further analysis goes beyond the scope of this review. Regarding the choice of first-line antiretrovirals, in patients with renal impairment (i.e., an estimated creatinine clearance < 70ml/min) regimens containing both...
TDF and cobicistat should be avoided; moreover, TDF itself must be used with caution, adjusting the dosage if necessary. TDF should also be avoided in case of osteoporosis. In patients with cardiovascular disease ABC and combinations containing LPV/RTV should be avoided, and in subjects with dyslipidemia PI-based combinations, ABC, EFV and EVG/COBI must be used with caution. Finally, EFV should be avoided in patients with psychiatric comorbidities.

**New treatment strategies and immunotherapy in aging HIV patients**

Treating older patients with HIV constitutes a multi-faceted challenge which the clinician will face more and more commonly in next few years. Several novel approaches could be considered in the aging population, with the aim of selecting a regimen which could ensure effectiveness and long-term tolerability. Given the already mentioned issue of comorbidities and comedication, one should consider if drug toxicity burden in this particular population may be lowered by using alternative strategies. A possible key player in the immediate future will be the introduction of tenofovir alafenamide (TAF), a pro-drug of tenofovir, with a more favorable renal toxicity profile due to lower plasma levels achieved by higher cellular concentration in lymphoid cells, where TAF is converted in tenofovir diphosphate. The pharmacokinetics properties of this novel antiretroviral may be appealing in aging population.

In older patients class-sparing regimens are more difficult to introduce, as most of these strategies include PIs or ABC, which should be used with caution in patients with a high cardiovascular risk or dyslipidemia. A recently published study examined the efficacy of cabotegravir (a novel integrase inhibitor, which also has the possibility of being administered as a long-acting formulation) plus rilpivirine as a maintenance therapy, which could be an interesting option in aging population. Another possible approach may be based on dolutegravir dual-therapy. While the efficacy of dolutegravir mono-therapy has yet to be fully evaluated, ongoing pilot studies are showing promising results.

The immunological defects associated with immunosenescence need specific considerations, as they may potentially be targeted with immunotherapeutic intervention with either exogenous cytokine administration or by the use of other immune-based therapies.

Interleukin(IL)-2 and IL-7 were the most extensively studied cytokines in the context of HIV infection. IL-2 is a molecule primarily produced by CD4 T-cell; alongside its major role as T-cell proliferation promoter this cytokine act as a crucial molecule in immune system differentiation and development, influencing also cytokine secretion, T regulatory cells development, B and NK-cells replication. IL-2 production impairment was one of the first immunological defects described in HIV infection. Two randomized international trials evaluated the use of intermittent IL-2 administration in patients receiving HAART. While CD4 T-cell increase was substantial, there was no effect on clinical outcome (deaths, opportunistic infections). Moreover, patients receiving IL-2 had more frequent grade 4 side effects than patients receiving HAART alone. The somewhat paradoxical effect of IL-2 may be explained by the increase of distinct CD4+CD25+ expressing high level of FOXP3, defined as cytokine-induced naïve (CEN) T-cells, which could act as T regulatory cells with suppressor activity. IL-7 is another key cytokine which role is impaired in HIV infection, mostly thank to impairment of receptor signaling via CD127 (a component of IL-7 receptor [IL-7R]). IL-7 is crucial for T cell development and homeostasis thanks to its anti-apoptotic and co-stimulatory proliferative signals and in untreated patients with HIV infection high levels of IL-7 reflects a compensatory loop mechanism to contrast HIV-induced lymphopenia. A first phase I/IIa randomized dose-escalation trial showed that IL-7 treatment was able to provide a stable increase in CD4 T-cells in HAART-treated patients. The T-cell receptor diversity was shown to be broadened and thymic output was increased by IL-7 administration, possibly paving the way for an improvement of the immune function. Finally, IL-7 was well-tolerated with a favorable toxicity profile. Two subsequent phase II trials confirmed these findings, but a large proportion of patients developed anti-recombinant-human-IL-7 binding antibodies (including neutralizing antibodies in more than a third of the subjects), although without any impact on CD4 T-cell response. Finally, in an unrelated study aimed at evaluating a possible eradication strategy, IL-7 administration associated with HAART intensification was shown to induce an increase in HIV-DNA and in CD4 T-cell subsets harboring the majority of HIV reservoir (T central and transitional memory). This finding led to concerns regarding the expansion of HIV reservoir in patients treated with IL-7. Other cytokines are being explored as potential therapeutic tool in HIV. Another cytokine with a relevant role in HIV infection is IL-15, which physiologically influences the host defense against intracellular pathogens but also regulates T, B and NK-cells survival. In HIV infection, the injection of IL-15 enhanced the survival and effector function of HIV-specific CD8+ T-cells and, when exogenously increased by administration of a IL-15 coding plasmid, was shown to be a potent adjuvant by stimulating CD8 T-cell response and longevity as well as increasing IFNγ.
Finally, IL-21 is a cytokine involved in CD8 T-cell proliferation and activation and controls the differentiation of naïve CD4 T-cell in Th17 cells; this molecule is defective in SIV-infected rhesus macaques and this deficit is associated with Th17 cell depletion. In untreated rhesus macaques with SIV infection the administration of IL-21 led to an increase in the cytotoxic potential of T cells without enhancing cellular activation and in HAART-receiving animals drove a reduction of immune activation and a restoration of intestinal Th17 and Th22.

Another issue related to chronic HIV infection is represented by the interplay of immune senescence and immune activation. Theoretically, approaches aimed at reducing immune activation may prove to be beneficial in breaking the vicious circle of chronic inflammation and immunological dysfunction. Chloroquine and its derivate hydroxychloroquine are 2 antimalarial drugs which are also used in autoimmune diseases such as systemic erythematous lupus thanks to their immune modulatory activities. These molecules mainly acts on different TLRs (especially TLR9 and TLR4) and are able to decrease proinflammatory cytokine release such as IL-6, IL-18 and TNFα. Several works explored the use of chloroquine or hydroxychloroquine in HIV-infected patients in HAART-treated and HAART-naïve patients, showing contrasting results. In some studies this molecule was shown to reduce immune activation markers (i.e., IL-6, TNF-α and LPS) and CD8 T-cells expressing CD38+HLA-DR+ and Ki-67, while other researchers found no effect on immune activation.

A possible target is also represented by TNF itself, which may be antagonized by several molecules currently in use for rheumatologic diseases. A study in rhesus macaques showed that adalimumab, a human anti-TNF monoclonal antibody, was able to reduce infiltration of polymorphonuclear cells into the T-cell zone of lymphoid tissues, diminishing also lymphoid tissue fibrosis; nevertheless, no effect on plasma immune activation was proven. Interestingly, a very recent case report described the efficacy of infliximab, another anti-TNF monoclonal antibody, in treating immune reconstitution inflammatory syndrome in HIV-patients coinfected with tuberculosis, possibly highlighting the efficacy of this approach to control excessive immune activation.

Another molecule whose immune-regulatory properties were tested in HIV infection is cyclosporine, which inhibits nuclear factor of activated T-cells (NFAT) reducing T-cell activation and proliferation. However, while an initial report in early HIV infection suggested a possible immunological benefit, other studies showed no substantial benefit. Moreover, mycophenolic acid (an inhibitor of T-cell proliferation which block the synthesis of guanosine nucleotides acting as an inhibitor of the enzyme monophosphate dehydrogenase) and rapamycin (which blocks mTOR, leading to a reduction in T-cell activation and proliferation) were also suggested as possible therapeutic approaches to reduce immune activation in HIV patients, but currently no significant results on immune activation were demonstrated, regardless of some reports of clinical benefit in HIV-infected patients.

Other possible immune-based therapeutic approaches include the blockade of molecules involved in immune checkpoints such as programmed death (PD)-1. PD-1 has a central role in virus-specific CD8 T-cell exhaustion, it is upregulated in most CD8 T-cell populations during HIV infection and correlates with the level of CD8 T-cell exhaustion and with disease progression. Several studies on animal models showed how PD-1 blockade was able to enhance proliferation of CD4 and CD8

Figure 2. Role of interleukin7 (IL-7). IL-7 is a stromal cell-derived cytokine that provides continuous signals in all levels of lymphocytes maturation. Ag: antigen.
T-cells, especially HIV-specific clones; moreover, an increased proliferation of resting memory B-cells and a reduction in microbial translocation were also demonstrated in animals treated with anti-PD-1 antibodies. Other potential immune checkpoints target for immune intervention may be CTLA-4, Lag-3, Tim-3 and TIGIT and several investigators are exploring therapeutic options directed at these molecules.

Conclusions

Life expectancy of people living with HIV increased thanks to the efficacy of antiretroviral therapy and to improved care of HIV-related conditions. Thus, the management of older patients with HIV infection represents an increasingly prevalent issue. Furthermore, HIV itself is able to accelerate this process contributing to premature aging, further impairing an already damaged immunological system and contributing to the emergence of comorbidities.

The clinician must be able to adapt to this new scenario by selecting an appropriate treatment taking into consideration all the players involved in an aging HIV-infected patients, being able not only to adequately manage infection-related issues but also to identify and care for age-associated conditions.

Abbreviations

3TC lamivudine  
ABC abacavir  
D comedication decrease concentration of ART  
DTG dolutegravir  
E comedication increases concentration of ART  
EVG/COBI elvitegravir/cobicistat  
FTC emtricitabine  
RAL raltegravir  
RPV rilpivirine  
RV/r darunavir/ritonavir  
TAF tenofovir alafenamide  
TDF Tenofovir Disoproxil Fumarate  
↑ ART increases concentration of the comedication  
↓ ART decreases concentration of the comedication  
= no significant interactions

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Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.
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