Ageing with HIV: a multidisciplinary review

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[1]Calcagno A, [2]Nozza S, [3]Mussi C, [4]Celesia BM, [5]Carli F, [6]Piconi S, [7]De Socio GV, [8]Cattelan AM, [9]Orofino G, [10]Ripamonti D, [11]Riva A and [1]Di Perri G.

1 Unit of Infectious Diseases, Department of Medical Sciences, University of Torino, Torino; 2 Department of Infectious Diseases, San Raffaele Scientific Institute, Milano; 3 Centro di Valutazione e Ricerca Gerontologica, University of Modena and Reggio Emilia, University of Modena and Reggio Emilia, Modena; 4 Department of Clinical and Molecular Biomedicine, Division of Infectious Diseases, University of Catania, ARNAS Garibaldi, Catania; 5 University of Modena and Reggio Emilia, Department of Mother, Child and Adult Medicine and Surgical Science, Infectious Diseases Clinic, Modena; 6 1st Division of Infectious Diseases Unit, University of Milano, Ospedale L. Sacco, Milano; 7 Department of Infectious Diseases, Azienda Ospedaliero-Universitaria di Perugia, Perugia; 8 Unit of Infectious Diseases, Department of Internal Medicine, Azienda Ospedaliera-Universitaria di Padova, Padova; 9 Unit of Infectious Diseases, "Divisione A", Ospedale Amedeo di Savoia, ASLTO2, Torino; 10 Infectious Diseases Unit, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo; [11]3rd Division of Infectious Diseases, University of Milano, Ospedale L. Sacco, Milano, Italy.

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Corresponding Author:
Andrea Calcagno,
Unit of Infectious Diseases, Department of Medical Sciences
University of Torino
c/o Ospedale Amedeo di Savoia,
C.so Svizzera 164
10159, Torino, Italy
+390114393884, fax +390114393818
andrea.calcagno@unito.it

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Abstract:

After the introduction of highly active antiretroviral treatment the course of HIV-infection turned into a chronic disease and most of HIV-positive patients will be soon over 50 years old. This paper reviews the multiple aspects that physicians have to face while taking care of HIV-positive ageing patients including the definitions of frailty and the prevalence and risk factors of concomitant diseases. From a therapeutic point of view pharmacokinetic changes and antiretroviral-specific toxicities associated with ageing are discussed; finally therapeutic approaches to frailty are reviewed both in HIV-positive and negative patients. We conclude by suggesting that the combined use of drugs with the least toxicity potential and the promotion of healthy behaviours (including appropriate nutrition and exercise) might be the best practice for ageing HIV-positive subjects.

Since HIV infection was first described almost 30 years ago, its epidemiology has undergone continuous changes: one of the main feature is the increasing number of older person affected, a phenomenon called the "graying" of the epidemic. This paper reviews the multiple aspects that physicians have to face while taking care of HIV-positive ageing patients.

1. HIV and Frailty

The definitions of ageing vary so widely among geriatricians, researchers, and governmental agencies that there is not even a consensus regarding the "cutoff point" for defining "old age." For the general population, individuals aged 60–75 years are considered candidates for monitoring/intervention, but in the case of HIV-infected patients, this limit falls to 50 years old [1]. Late presentation, new infections in elder patients and improved survival due to Highly Active Antiretroviral Treatment (HAART) efficacy are the main reasons of increased age in the HIV population [2].

In recent years a recurrent research question has been formulated: does HIV accelerate or accentuate ageing? The answer is probably organ and disease/condition specific. For many processes, there appears to be a pattern of accelerated ageing. This is most clear in the immune system, but clinically, it is also clear that the development of specific geriatric syndromes such as multimorbidity, frailty, and polypharmacy are hastened in those with HIV. In specific end-organ diseases, it is less clear, but many illnesses appear to be accentuated rather than accelerated. Cardiovascular disease, diabetes, and several other conditions are more prevalent at all ages in those with HIV, suggesting there is an extra "hit" by HIV and/or antiretroviral therapy (ART)—that is, accentuated ageing while other organs, like the liver, are not particularly affected by ageing, but significantly contribute to morbidity and mortality in HIV patients [3].

While renal function decay and neurodegenerative diseases are relatively well-known in the setting of ageing HIV-positive, muscle abnormalities and sarcopenia are mostly relegated to geriatric medicine. The loss of bone (osteopenia, osteoporosis) and muscle mass and strength (sarcopenia) are common both in normal and HIV ageing patients [4]; though not universally accepted several data highlighted that these features may exist despite prolonged control of viral replication and normalization of commonly used immunological parameters [5-8].

All published studies of frailty in HIV-positive patients use frailty scales including a limited number of specific health measures, following the phenotype model; no published studies of frailty in people with HIV have used the cumulative deficit/frailty index approach, or scales based on clinical judgment. It is important to notice that frailty models created in the general population are well characterized in geriatric patients (aged more than 65 years).

In the Multicenter AIDS Cohort Study (MACS) a frailty scale based on 4 self-reported deficits was used: weight loss, exhaustion, impaired physical activity, and difficulty walking [9-10].

Recently the Veterans Aging Cohort Study (VACS) proposed a new measure of health status in people ageing with HIV: the VACS index. It is a prognostic tool made up of both traditional HIV-related factors (CD4 count, viral load, hepatitis C co-infection, liver fibrosis as FIB-4 positive measure) and clinical-laboratoristic measures (haemoglobin, estimated glomerular filtration rate - eGFR, race and age) designed to predict mortality rates (and to implement tailored interventions) [1112]; however it can be considered as a frailty index being a measure of multisystem deterioration and vulnerability (Table 1).

STUDY	**SETTING**	**INCLUSION CRITERIA**	**DESCRIPTION& SCORING**	**DEFICITS INCLUDED IN FRAILTY SCALE**
Multicenter Aids Cohort Study (Macs) [2007 And Later] [16-17]	Urban, community based Cohort of MSM	Age 18+; either HIV-, or HIV+ Receiving art	Considered frail if 3 or more deficits present	1. Weight loss: "since your last visit have you had unintended weight loss of at least 10 pounds?" 2. Exhaustion: "during the past 4 weeks, as a result of your physical health, have you

(USA)				had difficulty performing your work or other activities (for example, it took extra effort)? 3. Low activity: "does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?" 4. Slowness: timed 4m walk 5. Weakness: grip strength measured with dynamometer
Veterans Aging *Cohort Study -* *Virtual Cohort [18-19]* *(USA)*	All HIV-positive US military male veterans Receiving care in the veterans health administration System, enrolled between 1997 and 2009	Male gender	Items are summed for a continuous score	1. Age 2. Cd4 count 3. Hemoglobin 4. Fib-4 (a measure of liver fibrosis): (years of age x ast)/platelets in 100/l x square root of alt) 5. Estimated glomerular filtration rate: 186.3 x (serum creatinine)-1.154 x (age)-0.203 x 1.21 if black 6. Hepatitis c status

Table 1. Comparison of deficits included in MACS and VACS frailty scales applied to people living with HIV.

Similarly to what observed in HIV-negative subjects frailty is more frequently detected in HIV-positive patients with shorter formal education [13-15], unemployed or with lower incomes [13,16], presenting diabetes [15], kidney disease [15], depressive symptoms [13-15] and HCV co-infection [17]. Frailty is positively associated with current and nadir CD4 cell count [18-20], and detectable HIV RNA viral load [14,15].

Increased free radical levels, mitochondrial dysfunction, and cytokines might activate inflammatory pathways, leading to this condition. The levels of C-reactive protein, d-dimer, fibrinogen, and IL-6

154 are increased in older individuals with the frailty phenotype. Similarly, HIV infection and ART
155 toxicity activate the inflammatory mechanisms associated with frailty. HIV infection seems to
156 accelerate the development of frailty, even when the patient exhibits viral suppression under
157 HAART [21].
158
159

160 **2. Ageing Immunology versus Immunesenescence**

161 Recent studies have shown a link between physical function and frailty to immune activation and
162 inflammation in HIV infected people [22]. The pathogenic correlation of frailty with markers of
163 immune senescence and activation in HIV-positive individuals has not been established.
164 The reduced CD4-Tcells reserves, naïve T-cell and telomere shortening are only three of the main
165 immunological reasons for the more rapid progression of AIDS in older people and for decreased
166 response to antiretroviral therapy [23-25]. Moreover, a recent controlled study showed that ageing
167 HIV positive ART treated women have a higher state of immune activation, exhaustion and
168 senescence than uninfected age matched controls [26].
169

170 **3. HIV-associated Comorbidities in ageing patients**

171 Several chronic illnesses are linked with advancing age and appear to persist despite effective
172 antiretroviral treatment. It is clear that the vast majority of deaths in HIV-infected patients in
173 developed countries are currently caused by these non-AIDS-illnesses [27]. HIV-infected persons
174 have increased propensity to typical diseases of ageing and studies have provided evidence that
175 comorbidities are more common among HIV-infected elderly patients than HIV-uninfected controls
176 [28]. Additionally as expected, prevalence of multimorbidity among people with HIV increase with
177 age [59].
178

179 **4a. Cardiovascular and renal diseases.**

An important role in determining premature ageing and cardiovascular diseases has been attributed to lifestyle-related traditional risk factors (mainly smoking habits), as these are widely prevalent in HIV-infected people: the estimated vascular age was higher (approximately +9 years) than chronological age in HIV-people. The difference between chronological age and vascular age provides an idea of the increased ageing linked to traditional cardiovascular risk factors included in the Framingham model [30]. In addition considering traditional risk factors, the clinical management of hypertension [31], diabetes [32] and chronic obstructive pulmonary disease [33] were inadequate in many HIV patients. This significantly influences the damage in cardiovascular and renal diseases.

However conventional models for cardiovascular risk prediction may underestimate risk in HIV-infected patients, because atherosclerosis is driven in part by HIV/ART related risk factors. In fact epidemiological studies have reported greater risk of cardiovascular events among HIV-infected compared with the general population. Matthew S. Freiberg et al, from The Veterans Aging Cohort Study (VACS) showed that after adjusting for Framingham risk factors, comorbidities, and substance use, HIV-positive veterans had an increased risk of incident acute myocardial infarction compared with uninfected veterans (HR, 1.48; 95% CI, 1.27-1.72) [34]. A critical question raised by many investigations is how well current guidelines identify HIV-infected patients at highest cardiovascular risk who could benefit from preventive pharmacological therapy. Actually, primary prevention measure could be inadequate in HIV-positive subjects [35] .

Patients with HIV are at risk for both acute kidney injury and chronic kidney disease. Given the increased ageing of the HIV population and the loss of kidney function associated with increased age, kidney impairment is a major concern when treating with specific ART medications. The risks for renal dysfunction in patients with HIV are multifactorial (age, drugs, diabetes, hypertension, hepatitis, HIV itself) and the prevalence of chronic kidney disease is higher among HIV-infected adults than among HIV-negative adults [36].

206 **4b. Bone disease**

207 In several large cohort studies, the HIV-positive population experiences a reduced bone mineral
208 density with increased prevalence of osteopenia (up to 60%) and osteoporotic fractures (up to 15%)
209 compared with HIV-uninfected individuals [37-39]. Only very recently, a meta-analysis found that
210 HIV-infected individuals have a modestly increased risk for all fractures and fragility fractures
211 compared with the general population; however, the study was not able to perform adjusted
212 analyses including variables such as age, emphasizing an expected increased risk in the future
213 considering the ageing HIV population [40].

214 In addition to the established traditional risk factors for osteoporosis (such as smoking, alcohol use,
215 opiate use, physical inactivity, low body weight, hypogonadism and vitamin D deficiency), also
216 HCV infection seems to play a negative role on bone strength and increase fracture risk in the HIV-
217 HCV coinfected patients in which the increased risk of fracture is approximately 1.5–2 times
218 greater than HIV monoinfected individuals [40]. Furthermore, additional risk might be explained in
219 part by both direct HIV and inflammatory effects on bone reabsorption [41] and by antiretroviral
220 medications. The first period after antiretroviral regimen initiation has been associated with a
221 clinically significant loss of BMD (2%-6%), followed by stabilization and increase in BMD within
222 1-2 years. In some studies the exposure to either tenofovir or protease inhibitors was associated
223 with an increase in bone turnover markers (osteocalcin, bone specific alkaline phosphatase,
224 procollagen 1N-terminal propeptide and serum type 1 collagen cross-linked C telopeptide-CTx) and
225 with an increased incidence of osteoporotic fracture [42].

226 A captivating recently published study shows that treatment-naive patients treated with tenofovir
227 alafenamide as part of a STR compared to tenofovir disoproxil fumarate showed a significantly
228 smaller change in bone mineral density [43].

229

230 **4c. Liver disease**

231 Liver disease is the second cause of death in HIV-infected patients after AIDS-related
232 complications and the progression of chronic hepatitis C into cirrhosis is accelerated in HIV+
233 patients [44]. In the Swiss HIV Cohort Study a 4-fold increase in morbidity and mortality due to
234 liver diseases has been reported in older patients and among 446 deaths between 2005-2009, 45%
235 and 11% were in co-infected patients with HCV and HBV, respectively. In addition, when deaths
236 due to HCC were included among liver-related deaths (instead of non-AIDS defining cancers) liver
237 diseases became the first cause of death (17.9%) [45]. Accordingly the liver is the major target of
238 the ageing process that occurs in HIV infected people and hepatic injury is more common among
239 older individuals with HIV, especially among older individuals with a long exposure to some
240 antiretroviral therapies and with histories of heavy drug or alcohol abuse [46].
241
242 **4d. Neurocognitive impairment**
243 Neurocognitive impairment (NCI) continues to be highly prevalent in the era of ART, with
244 approximately half of HIV-infected persons experiencing some degree of NCI, especially in later
245 CDC HIV stages. Older age together with low CD4 count, plasma and CSF viral load, ARV
246 regimen, HCV co-infection and substance abuse represents an important risk factor for the
247 development of NCI [47-49]. While cART has been associated with a cognitive improvement,
248 studies of NCI in treated patients have documented high persisting rates of mild-to-moderate
249 neurocognitive impairment despite effective suppressing antiretroviral treatment, especially in
250 individuals with a history of low CD4 T cell nadir [50]. Blood brain barrier abnormalities are
251 common in elderly patients and altered permeability is common in HIV-positive ART treated
252 patients; all these factors may enhance neuronal damage and it has been linked to neurocognitive
253 disturbances [51,52]. Furthermore, across a large cohort study have been shown that higher VACS
254 Index scores are significantly associated with concurrent NCI, and older age is one of the most
255 important component strongly linked to NCI [53].

HIV-infected people also experience a higher frequency of psychiatric problems, including depression than age-matched HIV-negative controls, even after adjusting for contributory sociodemographic and behavioral risk factors. Both depressive symptoms and suicide are also most frequent among older persons, especially the elderly aged 65 years and older [54].

4e. Cancer

In recent years, HIV-infected patients have been shown to be more likely to present non-AIDS-defining cancers such as Hodgkin lymphoma, anal, vaginal, liver, lung, melanoma, oropharyngeal, colorectal, and renal cancer; they typically occur at earlier ages, especially anal and lung cancer, and with a higher incidence rate than in the general population [55-57]. From 1996 to 2002, in the HIV/AIDS Cancer Match Study, non-AIDS-defining cancer counted for the majority of cancers (58% from 1996 to 2002 compared with 31.4% from 1991 to 1995); a higher overall risk of cancer was reported in HIV-1–infected people than in the general population—with a standardized incidence ratio (SIR) of 1.9 [58]. Interestingly, for anal and lung cancers, the SIRs were significantly higher in the younger age groups, whereas for Hodgkin lymphoma, elevated risk significantly increased with age. For liver, prostate, breast, and colon cancer there were no significant trends toward increased risk at earlier ages [59].

These results support use of the same cancer screening tests used in the general population for HIV-1–infected persons, though probably at younger ages and particular attention should be reserved to preventable or treatable viral coinfections (e.g., human papillomavirus, hepatitis B and C) and preventable lifestyle factors traditionally associated with cancer (e.g., tobacco smoking, alcohol use, obesity) that all may contribute to patients' risk of non–AIDS-defining malignancies [60].

4. Pharmacokinetic changes in elder patients:

With the progression of age several physiological mechanisms are slowly impaired and they may impact drugs pharmacokinetics and pharmacodynamics. In patients with reduced functional reserve

this may have significant effects; drugs with a narrow therapeutic index are specifically involved [61]. Several data confirm that older patients have higher risk of laboratory abnormalities and side effects [62]. Beside this, elder patients usually present several comorbidities (increasing the risk of toxicities) and are treated with several drugs (increasing the risk of drug to drug interactions). In HIV-positive ageing patients these effects may be enhanced given the high rate of comorbidities, polypharmacy and hospital admission: drug to drug interactions are relatively common both in rich and in limited resource countries [63]. Marzolini and coll. reported the prevalence of co-medications in the Swiss HIV cohort: besides being far more frequent in patients aged above 50 years several drug classes were identified at higher chance of causing significant drug to drug interactions (mainly drugs used in cardiovascular medicine such as antilipidemics, antiplatelets/anticoagulants, ace-inhibitors and diurectics) [64].

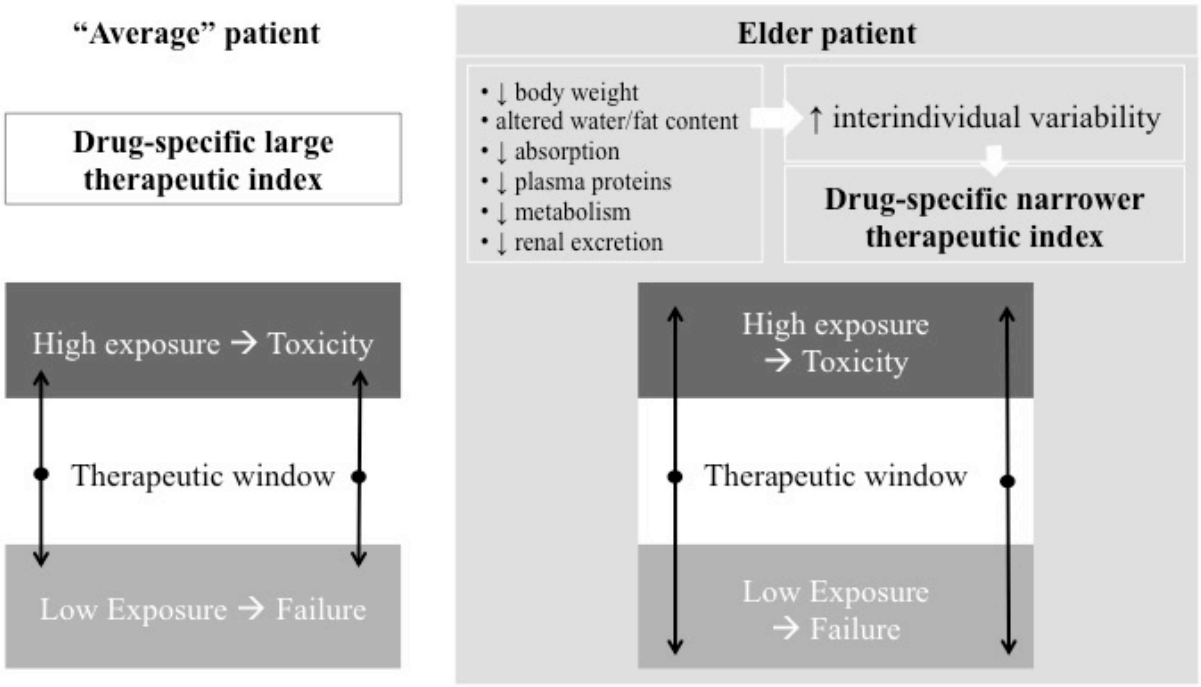

Figure 2. Schematic representation of pharmacokinetic modifications in elder patients and the potential associated consequences. Rounds and arrows represent ideal average and range concentrations: in elder patients a higher variability increase the chance of supra- or sub-therapeutic exposures.

Apart from specific ADME (Absorption, Distribution, Metabolism, Elimination) changes elder patients often present two characteristics: a reduced body weight (associated with higher doses per kilogram) and an altered fat/water distribution (with increased fat, reduced plasma volume, reduced water content that may impact the distribution and elimination of different compounds) [65]. Absorption is usually decreased due to increased gastric pH, slowed emptying and motility and a reduced absorption surface. Distribution may be affected in case of reduced albumin (and other proteins) levels and by the fat/water body composition. Metabolism can be significantly diminished as a consequence of reduced hepatic blood flow and mass and the reduced activity of some cytochrome iso-enzymes (such as CYP2C9 and CYP2D6). Renal elimination is usually affected given the high prevalence of chronic kidney disease and therefore of reduced filtration. Furthermore a gender effect is possible both for very low glomerular filtration rate and for hormonal changes (known to affect intracellular pathways of several drugs). The neat effect of these processes is hardly predictable a priori but a higher inter-patient variability is observed [66].

The effect of ageing on the pharmacokinetics of antiretroviral drugs has been studied although data are still limited given the relatively young age of most of HIV-positive patients and the exclusion of such patients from clinical trials. Nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) are small, hydrophilic, poorly protein-bound molecules that are mostly eliminated through the kidney: dose adjustments are suggested for very low filtration rates. Tenofovir, the most commonly used NRTI, has been associated with glomerular and tubular impairment and age has been recognized as one of the factors associated with renal damage (along with female gender, low body weight, co-medications such as protease inhibitors and genetic polymorphisms in renal transporters) [67]. Plasma tenofovir concentrations have been recognized to be higher in older patients with estimated glomerular filtration rate above 60 ml/min; since the drug has not been studied in patients above the age of 65, caution is usually advised in this subset of patients [68, 69]. Non-nucleoside reverse transcriptase inhibitors (NNRTIs), though more heterogeneous, are small, lipophilic, highly protein bound (with the exception of nevirapine) compounds; they are mostly metabolized through the liver.

No clear effect of age has been associated with efavirenz or nevirapine pharmacokinetics; etravirine exposure seems slightly affected with higher AUCs in older patients [70]. Protease inhibitors are large, lipophilic, highly protein-bound (with the exception of indinavir) compounds that are extensively metabolized through the liver. Several reports suggested slightly higher plasma concentrations in older patients: this was shown for lopinavir/ritonavir and partially for darunavir/ritonavir [71]. This was not confirmed by all reports and one paper, specifically, suggested that correcting for adherence (usually lower in younger patients) may increase the accuracy of this observation [72]. Raltegravir pharmacokinetics was not associated with age while much of its pharmacokinetics extreme variability can be explained by absorption (pH-dependant and increased by chewing the tablets) [73]. Very limited data are available on newer compounds such as maraviroc, rilpivirine, elvitegravir and dolutegravir.

Compartmental penetration may also be affected by age and associated modifications and following blood brain barrier alterations: efavirenz cerebrospinal fluid concentrations were reported to be highly increased above the age of 60 (compared to slightly increased plasma levels) [74]. The only other report of such effect was the observation of increased tenofovir plasma and genital concentrations in post-menopausal women (as compared to pre-menopausal subjects) [75, 76].

Given these relatively scarce data, antiretroviral treatment in older patients may warrant further caution and, at least in some cases of dose-dependant toxicities or multiple drug to drug interactions, therapeutic drug monitoring of plasma concentration may be suggested.

5. ART in elder patients:

The choice of antiretroviral therapy in elderly patients should be carefully evaluated for the presence of the aforementioned factors and the high prevalence of comorbidities for which a careful tailoring must be advised. The benefit of antiretroviral therapy in elderly patients is huge since HIV replication control has clear beneficial effects, however current guidelines recommend antiretroviral therapy without recommending any specific regimen.

As already mentioned several comorbidities have to be considered when introducing treatment in a ageing HIV-positive patient: age has been recognized a co-factor in most of HIV-associated non infectious diseases. Therefore the presence or the potential development of renal, bone, cardiovascular disease should guide the use or the avoidance of specific drugs.

A meta-analysis study has reported that the use of TDF is associated with a statistically significant though only modest renal dysfunction, and recommended no restriction of TDF use when regular monitoring of renal function and serum phosphate levels is not feasible [77]; higher risk is present in particular in subjects with body mass index lower than 59 kg [78]. However, the initial decline in eGFR following the commencement of TDF therapy stabilizes after the first 6 months, and the benefit of TDF treatment is considered to outweigh the risk of TDF-induced nephrotoxicity [79].

Since cardiovascular disease is a leading cause of death in elder patients and of growing relevance in HIV-positive subjects it influences the choice of antiretroviral drugs. However the benefits of HAART in reducing fatal and nonfatal events have recently been underscored by results from the Strategies for Management of AntiRetroviral Therapy (SMART) study, which showed that intermittent antiretroviral therapy (ART) based on $CD4^+$ cell count-guided drug withdrawal was associated with significantly greater disease progression and mortality risk (hepatic, renal, cardiovascular events) than continuous ART [80]. The role of different antiretroviral drug classes is still controversial; after adjusting for traditional risk factors and sociodemographic differences, there is higher risk of incident cardiovascular events among HIV-infected individuals exposed to combined antiretroviral medications compared to the general population [81].

Lopinavir/ritonavir, indinavir and abacavir (ABC) exposure have been associated with increased cardiovascular risk in the large prospective European D:A:D cohort study (RR: 1.9, 95%CI: 1.47-2.45, p=0.0001) [82]. Conflicting information on abacavir have been published: an increased risk of heart attack (myocardial infarction or MI) has been seen in several observational studies [79-81] but not in other RCTs, cohorts, or in a FDA meta-analysis [82-90]. Regarding the potential mechanism of action several inflammation (high sensitivity-C reactive protein, interleukin-6,

amyloid A, and amyloid P) and coagulation markers (D-dimer, prothrombin fragments, platelet hyperreactivity) have been explored but findings were controversial [91-95]. DHHS guidelines just reported that ABC use has been associated with cardiac events "in some, but not all observational studies" [96].

Given the aforementioned controversial results on tenofovir, abacavir and lopinavir/ritonavir toxicities several unconventional approaches have been tested: protease inhibitor monotherapy and dual therapies (protease inhibitor plus raltegravir, maraviroc or lamivudine and other less common approaches including unboosted atazanavir plus raltegravir and nevirapine plus raltegravir) have been studied [97-103]. Data on the benefits of such approaches (mostly on renal and bone alterations) have been published although no specific intervention was tested in elder HIV-positive patients. The uncertainty on the real benefits and the absence of indications in currently published guidelines may suggest to use alternative approaches when the expected benefit outweighs the potential risks (incomplete viral suppression and blunted immune recovery). However the long-term data from the STARTMRK trial [104] and from the randomized ACTG5257 [105] highlight the excellent tolerability of raltegravir-containing regimens: these observations suggest that raltegravir may be safe and effective in elder patients at increased risk of multiple comorbid conditions. Data on the recently approved integrase strand transfer inhibitor dolutegravir are very promising: it showed a comparable or superior efficacy (compared to efavirenz, darunavir/ritonavir and raltegravir), an excellent tolerability profile and very uncommon drug to drug interactions supporting its use in elder HIV-positive patients presenting several comorbidities. [106-110]

6. Treating Frailty

Persistent inflammation is a hallmark of HIV infection even in the presence of successful antiretroviral therapy. The mechanism behind the inflammatory response in HIV are numerous and diverse but it appears clear that such inflammation is responsible of premature ageing of HIV infected subjects eventually leading to several complications and frailty. Therefore the major aim of

404 therapeutic approaches to ageing and frailty in HIV infection is to reduce inflammation. In
405 gerontology several treatments have been pursued frequently leading to controversial or even
406 disappointing results. In Supplementary Table, we summarized several concepts that have been
407 explored in ageing and in HIV infection to reduce inflammation and improve health. In this paper
408 we particularly focus on two approaches that are simple albeit complicated to adopt, exercise and
409 caloric restriction. To date, exercise is the interventional modality that has most consistently shown
410 benefit in treating frailty and its key components [111-114]. In HIV infection, moderate intensity
411 exercise appeared beneficial in a study of 49 sedentary, ART-treated patients [115]. Participants
412 were enrolled in an exercise program that included one hour of brisk walking with or without 30
413 minutes of circuit training exercise 3 times weekly for 12 weeks. In a subset of 25 individuals who
414 completed the program and had inflammatory marker data available, d-dimer, IL-6, hsCRP, IL-18,
415 myostatin, and CD4 and CD8 activation markers (HLA-DR+, CD38+) all declined significantly,
416 while sCD14 did not. Additional benefits included significant declines in BMI, waist
417 circumference, total and LDL cholesterol. Although this intervention appeared to provide broad
418 reductions in inflammatory markers for those completing the program, 14/49 (29%) either dropped
419 out or had a low participation rate. The best-characterized external factor associated with healthy
420 ageing is moderate caloric restriction [116-119]. In nearly all species studied to date, experimental
421 restriction of caloric intake to levels below that when fed till but above that which causes starvation
422 is associated with increased longevity [120]. Caloric restriction may also enhance T cell function
423 and prevent immunosenescence in ageing nonhuman primates [121]. Whether this approach will
424 work in humans is not known because such diets are nearly impossible to maintain. However, in a
425 recent short-term prospective clinical trial, caloric restriction resulted in reduced energy
426 expenditure, increased mitochondrial content, and increased expression of many genes associated
427 with mitochondrial function and longevity. However, emerging evidence disputes some of the
428 primary tenets of this conception. One disparity is that the CR-related increase in longevity is not
429 universal and may not even be shared among different strains of the same species. A further

misgiving is that the control animals, fed ad libitum become overweight and prone to early onset of diseases and death, and thus may not be the ideal control animals for studies concerned with comparisons of longevity [122,123]. However, calculations based on mortality data predict that if cancer was eliminated as a cause of death, average human life span would increase only 3%–4%, data are similar regarding cardiovascular disease. On the contrary caloric restriction, which retards broad basic ageing processes, extends life span in animal models, by much larger increments. A recent paper demonstrated that caloric restriction-derived high levels of beta-hydroxybutyrate display anti-inflammatory properties by inhibition of the NLRP3 inflammasome. [124] It is interesting to note that also high intensity exercise increases beta-hydroxybutyrate levels.

It appears evident that the simplest and safest interventions to reduce inflammation and grant a healthy ageing appear to be moderate exercise and low caloric intake, but these approaches require a higher motivation and effort from the patients and are certainly more time consuming and demanding than ingurgitating a pill.

7. Conclusions

Luckily ageing with HIV will be common in the near future given the availability, efficacy and tolerability of antiretroviral drugs and the effectiveness of tailored programs for taking care of HIV-positive patients. HIV-positive patients may be frail and present reduced functional reserve as a consequence of an impaired and senescent immune system, of several co-morbid conditions and of many years of antiretroviral treatment: choosing the right combination is challenging given pharmacokinetic changes and several drug to drug interactions. However the combined use of drugs with the least toxicity potential and the promotion of healthy behaviours (including appropriate nutrition and exercise) might be the best practice for ageing HIV-positive subjects.

Disclosures

AC received grants, travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. SN received travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. CBM received grants, travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. DSGV received travel grants from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. AMC received grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. GO received travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. RD received travel grants and speaker's honoraria from Janssen-Cilag, Abbvie, BMS, Gilead, Viiv and MSD. RA grants, travel grants and speaker's honoraria from BMS, Gilead, Viiv, Janssen-Cilag, Novartis and MSD. GDP received grants, travel grants and speaker's honoraria from Abbvie, BMS, Gilead, Viiv, Janssen-Cilag and MSD. CM, CF, PS and OG reported no potential conflict of interest.

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