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Ageing with HIV: a multidisciplinary review

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32 **Ageing with HIV: a multidisciplinary review**

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69 **Key words:** ageing, HIV, co-morbidities, immune senescence, toxicity, frailty, pharmacokinetics.

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74 **Abstract:**

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

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

99

100

101 **1. HIV and Frailty**

102

103 The definitions of ageing vary so widely among geriatricians, researchers, and governmental
104 agencies that there is not even a consensus regarding the “cutoff point” for defining “old age.” For
105 the general population, individuals aged 60–75 years are considered candidates for
106 monitoring/intervention, but in the case of HIV-infected patients, this limit falls to 50 years old [1].

107 Late presentation, new infections in elder patients and improved survival due to Highly Active
108 Antiretroviral Treatment (HAART) efficacy are the main reasons of increased age in the HIV
109 population [2].

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

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

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

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

133 Recently the Veterans Aging Cohort Study (VACS) proposed a new measure of health status in
 134 people ageing with HIV: the VACS index. It is a prognostic tool made up of both traditional HIV-
 135 related factors (CD4 count, viral load, hepatitis C co-infection, liver fibrosis as FIB-4 positive
 136 measure) and clinical-laboratoristic measures (haemoglobin, estimated glomerular filtration rate -
 137 eGFR, race and age) designed to predict mortality rates (and to implement tailored interventions)
 138 [1112]; however it can be considered as a frailty index being a measure of multisystem deterioration
 139 and vulnerability (Table 1).

140

STUDY	SETTING	INCLUSION CRITERIA	DESCRIPTION & SCORING	DEFICITS INCLUDED IN FRAILTY SCALE
<i>Multicenter Aids Cohort Study (Macs) [2007 And Later] [16-17]</i>	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)				<p>had difficulty performing your work or other activities (for example, it took extra effort)?</p> <p>3. Low activity: “does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports?”</p> <p>4. Slowness: timed 4m walk</p> <p>5. Weakness: grip strength measured with dynamometer</p>
<i>Veterans Aging Cohort Study - Virtual Cohort [18-19]</i> (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: $186.3 \times (\text{serum creatinine})^{-1.154} \times (\text{age})^{-0.203} \times 1.21$ if black 6. Hepatitis c status

141

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

144

145

146 Similarly to what observed in HIV-negative subjects frailty is more frequently detected in HIV-
147 positive patients with shorter formal education [13-15], unemployed or with lower incomes [13,16],
148 presenting diabetes [15], kidney disease [15], depressive symptoms [13-15] and HCV co-infection
149 [17]. Frailty is positively associated with current and nadir CD4 cell count [18-20], and detectable
150 HIV RNA viral load [14,15].

151

152 Increased free radical levels, mitochondrial dysfunction, and cytokines might activate inflammatory
153 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.**

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

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

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

205

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 coinfecting 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].

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

260

261 **4e. Cancer**

262 In recent years, HIV-infected patients have been shown to be more likely to present non-AIDS-
263 defining cancers such as Hodgkin lymphoma, anal, vaginal, liver, lung, melanoma, oropharyngeal,
264 colorectal, and renal cancer; they typically occur at earlier ages, especially anal and lung cancer,
265 and with a higher incidence rate than in the general population [55-57]. From 1996 to 2002, in the
266 HIV/AIDS Cancer Match Study, non-AIDS-defining cancer counted for the majority of cancers
267 (58% from 1996 to 2002 compared with 31.4% from 1991 to 1995); a higher overall risk of cancer
268 was reported in HIV-1-infected people than in the general population—with a standardized
269 incidence ratio (SIR) of 1.9 [58]. Interestingly, for anal and lung cancers, the SIRs were
270 significantly higher in the younger age groups, whereas for Hodgkin lymphoma, elevated risk
271 significantly increased with age. For liver, prostate, breast, and colon cancer there were no
272 significant trends toward increased risk at earlier ages [59].

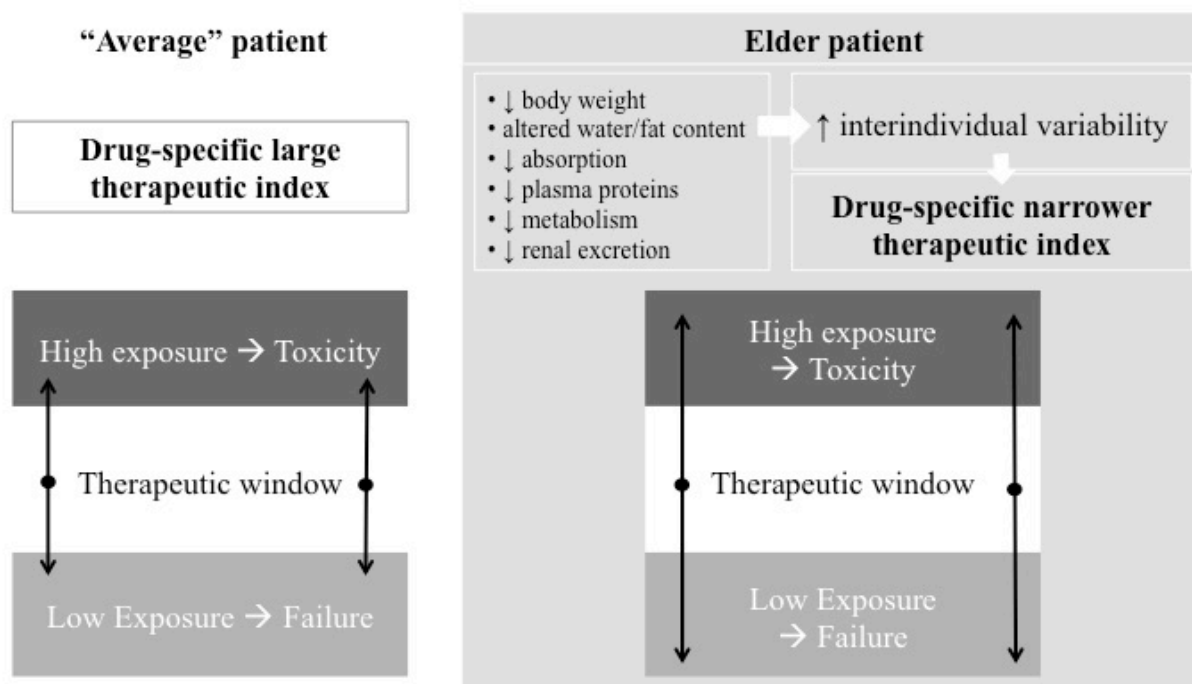
273 These results support use of the same cancer screening tests used in the general population for HIV-
274 1-infected persons, though probably at younger ages and particular attention should be reserved to
275 preventable or treatable viral coinfections (e.g., human papillomavirus, hepatitis B and C) and
276 preventable lifestyle factors traditionally associated with cancer (e.g., tobacco smoking, alcohol use,
277 obesity) that all may contribute to patients' risk of non-AIDS-defining malignancies [60].

278

279 **4. Pharmacokinetic changes in elder patients:**

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

282 this may have significant effects; drugs with a narrow therapeutic index are specifically involved
 283 [61]. Several data confirm that older patients have higher risk of laboratory abnormalities and side
 284 effects [62]. Beside this, elder patients usually present several comorbidities (increasing the risk of
 285 toxicities) and are treated with several drugs (increasing the risk of drug to drug interactions). In
 286 HIV-positive ageing patients these effects may be enhanced given the high rate of comorbidities,
 287 polypharmacy and hospital admission: drug to drug interactions are relatively common both in rich
 288 and in limited resource countries [63]. Marzolini and coll. reported the prevalence of co-
 289 medications in the Swiss HIV cohort: besides being far more frequent in patients aged above 50
 290 years several drug classes were identified at higher chance of causing significant drug to drug
 291 interactions (mainly drugs used in cardiovascular medicine such as antilipidemics,
 292 antiplatelets/anticoagulants, ace-inhibitors and diurectics) [64].



293
 294 **Figure 2. Schematic representation of pharmacokinetic modifications in elder patients and the**
 295 **potential associated consequences.** Rounds and arrows represent ideal average and range
 296 concentrations: in elder patients a higher variability increase the chance of supra- or sub-therapeutic
 297 exposures.
 298

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

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

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

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

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

345

346 **5. ART in elder patients:**

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

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

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

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

372 Lopinavir/ritonavir, indinavir and abacavir (ABC) exposure have been associated with increased
373 cardiovascular risk in the large prospective European D:A:D cohort study (RR: 1.9, 95%CI: 1.47-
374 2.45, p=0.0001) [82]. Conflicting information on abacavir have been published: an increased risk
375 of heart attack (myocardial infarction or MI) has been seen in several observational studies [79-81]
376 but not in other RCTs, cohorts, or in a FDA meta-analysis [82-90]. Regarding the potential
377 mechanism of action several inflammation (high sensitivity-C reactive protein, interleukin-6,

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

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

398 399 **6. Treating Frailty**

400 Persistent inflammation is a hallmark of HIV infection even in the presence of successful
401 antiretroviral therapy. The mechanism behind the inflammatory response in HIV are numerous and
402 diverse but it appears clear that such inflammation is responsible of premature ageing of HIV
403 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

430 misgiving is that the control animals, fed ad libitum become overweight and prone to early onset of
431 diseases and death, and thus may not be the ideal control animals for studies concerned with
432 comparisons of longevity [122,123]. However, calculations based on mortality data predict that if
433 cancer was eliminated as a cause of death, average human life span would increase only 3%–4%,
434 data are similar regarding cardiovascular disease. On the contrary caloric restriction, which retards
435 broad basic ageing processes, extends life span in animal models, by much larger increments. A
436 recent paper demonstrated that caloric restriction-derived high levels of beta-hydroxybutyrate
437 display anti-inflammatory properties by inhibition of the NLRP3 inflammasome. [124] It is
438 interesting to note that also high intensity exercise increases beta-hydroxybutyrate levels.
439 It appears evident that the simplest and safest interventions to reduce inflammation and grant a
440 healthy ageing appear to be moderate exercise and low caloric intake, but these approaches require
441 a higher motivation and effort from the patients and are certainly more time consuming and
442 demanding than ingurgitating a pill.

443

444 **7. Conclusions**

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

453

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466
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469

470

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