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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

<b>STUDY</b>	<b>SETTING</b>	<b>INCLUSION CRITERIA</b>	<b>DESCRIPTION &amp; SCORING</b>	<b>DEFICITS INCLUDED IN FRAILTY SCALE</b>
<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].

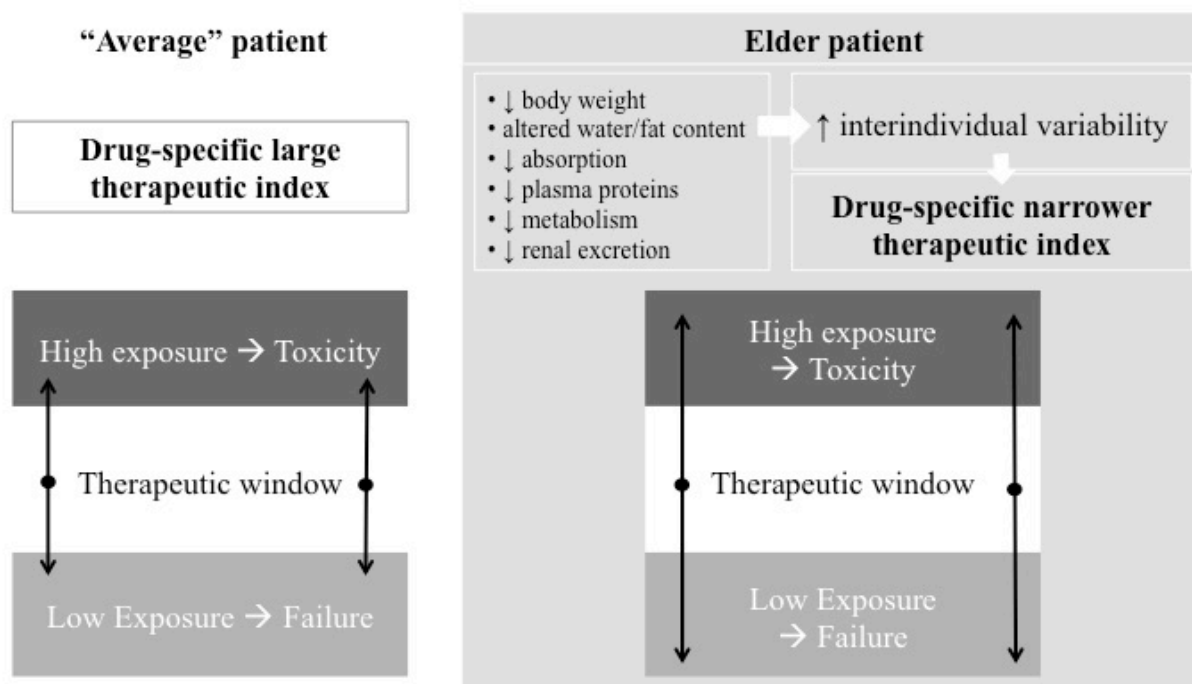
273 These results support use of the same cancer screening tests used in the general population for HIV-  
274 1-infected persons, though probably at younger ages and particular attention should be reserved to  
275 preventable or treatable viral coinfections (e.g., human papillomavirus, hepatitis B 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<sup>+</sup> 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

## 471 References

- 472 1. Centers for Disease Control – CDC (USA). *AIDS among persons aged > or = 50 years – United States, 1991–1996. MMWR Morb Mortal*  
473 *Wkly Rep.* 1998;47:21–7.)
- 474 2. Brothers T. D. and Rockwood K. *Biologic aging, frailty, and age-related disease in chronic HIV infection. Curr Opin HIV AIDS* 2014, 9:412–  
475 418
- 476 3. Pathai S, Bajjlan H, Landay AL, High KP. *Is HIV a model of accelerated or accentuated aging? J Gerontol A Biol Sci Med Sci* 2014; 69:  
477 833–842
- 478 4. Thomas DR. *Loss of skeletal muscle mass in aging: Examining the relationship of starvation, sarcopenia and cachexia. Clin Nutr* 2007; 26:  
479 389–399
- 480 5. McComsey GA, Tebas P, Shane E, Yin MT, Overton ET, Huang JS, Aldrovandi GM, Cardoso SW, Santana JL, Brown TT. *Bone disease in*  
481 *hiv infection: a practical review and recommendations for hiv care providers. Clin Infect Dis* 2010; 51: 937-946.
- 482 6. Michaud M, Balardy L, Moulis G, et al. *Proinflammatory cytokines, aging, and age-related diseases. J Am Med Dir Assoc* 2013;14:877-82.
- 483 7. Young B, Dao CN, Buchacz K, et al. *Increased rates of bone fracture among HIV-infected persons in the HIV Outpatient Study (HOPS)*  
484 *compared with the US general population, 2000-2006. Clin Infect Dis* 2011;52:1061-8
- 485 8. Costagliola D. *Demographics of HIV and aging. Curr Opin HIV AIDS* 2014, 9:294-301
- 486 9. Desquilbet L, Jacobson LP, Fried LP, Phair JP, Jamieson BD, Holloway M, Margolick JB; *Multicenter AIDS Cohort Study. HIV-1 infection is*  
487 *associated with an earlier occurrence of a phenotype related to frailty. J Gerontol A Biol Sci Med Sci* 2007;62:1279-86R.
- 488 10. Detels R, Jacobson L, Margolick J, Martinez-Maza O, Muñoz A, Phair J, Rinaldo C, Wolinsky S. *The multicenter AIDS Cohort Study, 1983*  
489 *to ... Public Health.* 2012 March ; 126(3): 196–198
- 490 11. Justice AC, Dombrowski E, Conigliaro J, Fultz SL, Gibson D, Madenwald T, Goulet J, Simberkoff M, Butt AA, Rimland D, Rodriguez-  
491 Barradas MC, Gibert CL, Oursler KA, Brown S, Leaf DA, Goetz MB, Bryant K. *Veterans Aging Cohort Study (VACS): Overview and*  
492 *description. Med Care.* 2006 Aug;44(8 Suppl 2):S13-24.
- 493 12. Womack JA, Goulet JL, Gibert C, Brandt CA, Skanderson M, Gulanski B, Rimland D, Rodriguez-Barradas MC, Tate J, Yin MT, Justice AC;  
494 *Veterans Aging Cohort Study Project Team. Physiologic frailty and fragility fracture in HIV infected male veterans. Clin Infect Dis*  
495 *2013;56(10):1498-504.*
- 496 13. Onen NF, Agbebi A, Shacham E, Stamm KE, Onen AR, Overton ET. *Frailty among HIV-infected persons in an urban outpatient care*  
497 *setting. J Infect* 2009; 59:346–352.
- 498 14. Piggott DA, Muzaale AD, Mehta SH, Brown TT, Patel KV, Leng SX, Kirk GD. *Frailty, HIV infection, and mortality in an aging cohort of*  
499 *injection drug users. PLoS One* 2013; 8:e54910.
- 500 15. Althoff KN, Jacobson LP, Cranston RD, Detels R, Phair JP, Li X, Margolick JB, *Multicenter ACS: Age, comorbidities, and AIDS predict a*  
501 *frailty phenotype in men who have sex with men. J Gerontol A Biol Sci Med Sci* 2014, 69:189-198.
- 502 16. Erlandson KM, Allshouse AA, Jankowski CM, Duong S, Mawhinney S, Kohrt WM, Campbell TB. *Comparison of functional status*  
503 *instruments in HIV-infected adults on effective antiretroviral therapy. HIV Clin Trials* 2012; 13:324–334.
- 504 17. Ianas V, Berg E, Mohler MJ, Wendel C, Klotz SA. *Antiretroviral therapy protects against frailty in HIV-1 infection. J Int Assoc Provid AIDS*  
505 *Care* 2013; Jan-Feb;12(1):62-6. doi: 10.1177/1545109712457241.
- 506 18. Terzian AS, Holman S, Nathwani N, Robison E, Weber K, Young M, Greenblatt RM, Gange SJ; *Women's Interagency HIV Study. Factors*  
507 *associated with preclinical disability and frailty among HIV-infected and HIV-uninfected women in the era of ART. J Womens Health*  
508 *(Larchmt)* 2009; 18:1965–1974.
- 509 19. Pathai S, Gilbert C, Weiss HA, Cook C, Wood R, Bekker LG, Lawn SD. *Frailty in HIV-infected adults in South Africa. J Acquir Immune*  
510 *Defic Syndr* 2013; 62:43–51.
- 511 20. Adeyemi O, Livak B. *Higher Veterans Aging Cohort Study (VACS) index scores in HIV-positive adults with CD4 counts < 200 cells/mm3*  
512 *despite viral suppression. J Acquir Immune Defic Syndr* 2013; 63:e78–e81.

- 513 21. Onen NF, Overton ET. A review of premature frailty in HIV-infected persons; another manifestation of HIV-related accelerated aging. *Curr*  
514 *Aging Sci.* 2011;4:33-41.
- 515 22. Erlandson KM, Allshouse AA, Jankowski CM, Lee EJ, Rufner KM, Palmer BE, Wilson CC, MaWhinney S, Kohrt WM, Campbell TB.  
516 Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral  
517 therapy *JID* 2013;208:249-59
- 518 23. Rickbaugh TM, Kilpatrick RD, Hultin LE, Hultin PM, Hausner MA, Sugar CA, Althoff KN, Margolick JB, Rinaldo CR, Detels R, Phair J,  
519 Effros RB, Jamienson BD. The dual impact of HIV-1 infection and aging on naïve CD4+ T-cells: additive and distinct patterns of  
520 impairment *PLoS ONE* 2011; Vol 6 e16459
- 521 24. Viard JP, Macroft A, Chiesi A, Kirk O, Røge B, Panos G, Vetter N, Bruun JN, Johnson M, Lundgren JD; EuroSIDA Study Group. Influence  
522 of age on CD4 cell recovery in human immunodeficiency virus-infected patients receiving highly active antiretroviral therapy: evidence from  
523 the EuroSIDA study. *J. Infect Dis* 2001; 183:1290-1294
- 524 25. Teixeira L, Valdez H, McCune JM, Koup RA, Badley AD, Hellerstein MK, Napolitano LA, Douek DC, Mbisa G, Deeks S, Harris JM, Barbour  
525 JD, Gross BH, Francis IR, Halvorsen R, Asaad R, Lederman MM. Poor CD4 cell restoration after suppression of HIV-1 replication may  
526 reflect lower thymic function *AIDS* 2001; 15: 1749-1756
- 527 26. Alcaide ML, Parmigiani A, Pallikkuth S, Roach M, Freguja R, Della Negra M, Bolivar H, Fischi MA, Pahwa S. Immune activation in HIV-  
528 infected aging women on antiretrovirals-Implication for age-associated comorbidities: A cross-sectional pilot study *PLoS ONE*  
529 2013;8(5):e63804
- 530 27. Hasse B, Ledergerber B, Furrer H, Battegay M, Hirschel B, Cavassini M, Bertisch B, Bernasconi E, Weber R. Swiss HIV Cohort  
531 Study.Morbidity and aging in HIV-infected persons: the Swiss HIV cohort study. *Clin Infect Dis.* 2011 Dec;53(11):1130-9
- 532 28. Guaraldi G, Orlando G, Zona S, Menozzi M, Carli F, Garlassi E, Berti A, Rossi E, Roverato A, Palella F. Premature age-related  
533 comorbidities among HIV-infected persons compared with the general population. *Clin Infect Dis* 2011;53: 1120-1126
- 534 29. Kendall CE, Wong J, Taljaard M, Glazier RH, Hogg W, Younger J, Manuel DG. A cross-sectional, population-based study measuring  
535 comorbidity among people living with HIV in Ontario. *BMC Public Health.* 2014 Feb 13;14:161. doi: 10.1186/1471-2458-14-161
- 536 30. De Socio GV, Ricci E, Parruti G, Maggi P, Madeddu G, Quirino T, Bonfanti P. Chronological and biological age in HIV infection. *J Infect*  
537 2010; 61:428-430
- 538 31. De Socio GV, Ricci E, Maggi P, Parruti G, Pucci G, Di Biagio A, Calza L, Orofino G, Carezzi L, Cecchini E, Madeddu G, Quirino T,  
539 Schillaci G; CISA Study Group. Prevalence, awareness, treatment, and control rate of hypertension in HIV-infected patients: the HIV-HY  
540 study. *Am J Hypertens.* 2014 Feb;27(2):222-8
- 541 32. Satlin MJ, Hoover DR, Glesby MJ. Glycemic control in HIV-infected patients with diabetes mellitus and rates of meeting American Diabetes  
542 Association management guidelines. *AIDS Patient Care STDS.* 2011 Jan;25(1):5-12
- 543 33. Madeddu G, Fois AG, Calia GM, Babudieri S, Soddu V, Becciu F, Fiori ML, Spada V, Lovigu C, Mannazzu M, Caddeo A,  
544 Piras B, Pirina P, Mura MS. Chronic obstructive pulmonary disease: an emerging comorbidity in HIV-infected patients in the  
545 HAART era? *Infection.* 2013;41(2):347-53.
- 546 34. Freiberg MS, Chang CC, Kuller LH, Skanderson M, Lowy E, Kraemer KL, Butt AA, Bidwell Goetz M, Leaf D, Oursler KA, Rimland D,  
547 Rodriguez Barradas M, Brown S, Gibert C, McGinnis K, Crothers K, Sico J, Crane H, Warner A, Gottlieb S, Gottdiener J, Tracy RP, Budoff  
548 M, Watson C, Armah KA, Doebler D, Bryant K, Justice AC. HIV Infection and the Risk of Acute Myocardial Infarction. *JAMA Intern Med.*  
549 2013;173(8):614-622
- 550 35. Zanni MV, Fitch KV, Feldpausch M, Han A, Lee H, Lu MT, Abbara S, Ribaldo H, Douglas PS, Hoffmann U, Lo J, Grinspoon SK. 2013  
551 American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-  
552 infected patients with/without subclinical high-risk coronary plaque. *AIDS.* 2014 Sep 10;28(14):2061-70
- 553 36. Nadkarni GN, Konstantinidis I, Wyatt CM. HIV and the aging kidney. *Curr Opin HIV AIDS.* 2014 Jul;9(4):340-5
- 554 37. Bonjoch A, Figueras M, Estany C, Perez-Alvarez N, Rosales J, del Rio L, di Gregorio S, Puig J, Gómez G, Clotet B, Negredo E;  
555 Osteoporosis Study Group. High prevalence of and progression to low bone mineral density in HIV-infected patients: a longitudinal cohort  
556 study. *AIDS* 2010; 24: 2827-2833
- 557 38. Onen NF, Overton ET, Seyfried W, Stumm ER, Snell M, Mondy K, Tebas P. Aging and HIV infection: a comparison between older HIV-  
558 infected persons and the general population. *HIV Clin Trials* 2010; 11: 100-109
- 559 39. Castronuovo D, Cacopardo B, M Pinzone MR. Bone disease in the setting of HIV infection:update and review of the literature. *Eur Rev*  
560 *Med Pharmacol Sci* 2013; 17: 2413-2419
- 561 40. Shiau ST, Broun EC, Arpadi SM, Yin MT. Incident fractures in HIV-infected individuals. *AIDS.* 2013;27(12):1949-1957
- 562 41. Lam J, Takeshita S, Barker JE, Kanagawa O, Ross FP, Teitelbaum SL. TNF-alpha induces osteoclastogenesis by direct stimulation of  
563 macrophages exposed to permissive levels of RANK ligand. *J Clin Invest* 2000;106:1481-8
- 564 42. Stellbrink HJ, Orkin C, Arribas JR, Compston J, Gerstoft J, Van Wijngaerden E, Lazzarin A, Rizzardini G, Sprenger HG, Lambert J, Sture  
565 G, Leather D, Hughes S, Zucchi P, Pearce H; ASSERT Study Group. Comparison of changes in bone density and turnover with abacavir-  
566 lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. *Clin Infect Dis* 2010;51:963-72
- 567 43. Sax PE, Zolopa A, Brar I, Elion R, Ortiz R, Post F, Wang H, Callebaut C, Martin H, Fordyce MW, McCallister S. Tenofovir alafenamide vs.  
568 tenofovir disoproxil fumarate in single tablet regimens for initial HIV-1 therapy: a randomized phase 2 study. *J Acquir Immune Defic Syndr*  
569 2014 Sep 1;67(1):52-8
- 570 44. Kearney F, Moore AR, Donegan CF, Lambert J. The ageing of HIV: implications for geriatric medicine. *Age Ageing* 2010;39:536-41
- 571 45. Weber R, Sabin CA, Friis-Møller N, Reiss P, El-Sadr WM, Kirk O, Dabis F, Law MG, Pradier C, De Wit S, Akerlund B, Calvo G, Monforte  
572 Ad, Rickenbach M, Ledergerber B, Phillips AN, Lundgren JD. Liver-related deaths in persons infected with the human immunodeficiency  
573 virus: the D:A:D study. *Arch Intern Med.* 2006 Aug 14-28;166(15):1632-41
- 574 46. Warriner AH, Burkholder GA, Overton ET. HIV-Related Metabolic Comorbidities in the Current ART Era. *Infect Dis Clin N Am* 2014; 28:  
575 457-476
- 576 47. McArthur J Steiner J, Sacktor N, Nath A. *Ann Neurol.* 2010 Jun;67(6):699-714. *Ann Neurol* 2010;67:699-714; 2
- 577 48. Valcour VG. HIV, Aging, and Cognition: Emerging Issues *Top Antivir Med.* 2013;21(3):119-123
- 578 49. Ciccarelli N, Fabbiani M, Grima P, Falasca K, Tana M, Baldonero E, Colafigli M, Silveri MC, Vecchiet J, Cauda R, Di  
579 Giambenedetto S. Comparison of cognitive performance in HIV or HCV mono-infected and HIV-HCV co-infected patients.  
580 *Infection.* 2013 Dec;41(6):1103-9.

- 581 50. Heaton RK, Franklin DR, Ellis RJ, McCutchan JA, Letendre SL, Leblanc S, Corkran SH, Duarte NA, Clifford DB, Woods SP, Collier AC,  
582 Marra CM, Morgello S, Mindt MR, Taylor MJ, Marcotte TD, Atkinson JH, Wolfson T, Gelman BB, McArthur JC, Simpson DM, Abramson I,  
583 Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I; CHARTER Group; HNRC Group. HIV-associated neurocognitive disorders  
584 before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol* 2011;17:3-16.
- 585 51. Calcagno A, Alberione MC, Romito A, Imperiale D, Ghisetti V, Audagnotto S, Lipani F, Raviolo S, Di Perri G, Bonora S. Prevalence and  
586 predictors of blood-brain barrier damage in the HAART era. *J Neurovirol*. 2014 Oct;20(5):521-5. doi: 10.1007/s13365-014-0266-2. Epub  
587 2014 Jun 28.
- 588 52. Letendre S. Central Nervous System Complications in HIV Disease: HIV-Associated Neurocognitive Disorder. *Neurocognitive Disorders in  
589 HIV Volume 19 Issue 4 November 2011*
- 590 53. Marquine MJ, Umlauf A, Rooney AS, Fazeli PL, Gouaux BD, Paul Woods S, Letendre SL, Ellis RJ, Grant I, Moore DJ; HIV  
591 Neurobehavioral Research Program (HNRP) Group. The Veterans Aging Cohort Study Index is Associated With Concurrent Risk for  
592 Neurocognitive Impairment. *J Acquir Immune Defic Syndr* 2014;65:190-197
- 593 54. Sherr L, Clucas C, Harding R, Sibley E, Catalan J. HIV and depression—a systematic review of interventions. *Psychol Health Med*. 2011  
594 Oct;16(5):493-527.
- 595 55. Albini L, Calabresi A, Gotti D, Ferraresi A, Festa A, Donato F, Magoni M, Castelli F, Quiros-Roldan E. Burden of non-AIDS-defining and  
596 non-virus-related cancers among HIV-infected patients in the combined antiretroviral therapy era. *AIDS Res Hum Retroviruses* 2013; 29:  
597 1097-1104
- 598 56. Helleberg M, Kronborg G, Larsen CS, Pedersen G, Pedersen C, Gerstoft J, Obel N. Causes of death among Danish HIV  
599 patients compared with population controls in the period 1995-2008. *Infection*. 2012;40(6):627-34.
- 600 57. Ehren K, Hertenstein C, Kümmerle T, Vehreschild JJ, Fischer J, Gillor D, Wyen C, Lehmann C, Cornely OA, Jung N,  
601 Gravemann S, Platten M, Wasmuth JC, Rockstroh JK, Boesecke C, Schwarze-Zander C, Fätkenheuer G. Causes of death in  
602 HIV-infected patients from the Cologne-Bonn cohort. *Infection*. 2014;42(1):135-40.
- 603 58. Engels EA, Biggar RJ, Hall HI, Cross H, Crutchfield A, Finch JL, Grigg R, Hylton T, Pawlish KS, McNeel TS, Goedert JJ. Cancer risk in  
604 people infected with human immunodeficiency virus in the United States. *Int J Cancer*. 2008 Jul 1;123(1):187-94.
- 605 59. Shiels MS, Pfeiffer RM, Engels EA. Age at cancer diagnosis among persons with AIDS in the United States. *Ann Intern Med*. 2010 Oct  
606 5;153(7):452-6
- 607 60. Brooks JT, Buchacz K, Gebo KA, Mermin J. HIV Infection and Older Americans. *Am J Public Health*. 2012;102(8):1516-1526
- 608 61. Reeve E, Wiese MD, Mangoni AA. Alterations in drug disposition in older adults. *Expert Opin Drug Metab Toxicol*. 2015 Jan 19:1-18.  
609 [Epub ahead of print] PubMed PMID: 25600059.
- 610 62. Alhawassi TM, Krass I, Bajorek BV, Pont LG. A systematic review of the prevalence and risk factors for adverse drug reactions in the  
611 elderly in the acute care setting. *Clin Interv Aging*. 2014 Dec 1;9:2079-86.
- 612 63. Holtzman C, Armon C, Tedaldi E, Chmiel JS, Buchacz K, Wood K, Brooks JT; , and the HOPS Investigators. Polypharmacy and risk of  
613 antiretroviral drug interactions among the aging HIV-infected population. *J Gen Intern Med*. 2013 Oct;28(10):1302-10.
- 614 64. Marzolini C, Back D, Weber R, Furrer H, Cavassini M, Calmy A, Vernazza P, Bernasconi E, Khoo S, Battegay M, Elzi L; Swiss HIV Cohort  
615 Study Members. Ageing with HIV: medication use and risk for potential drug-drug interactions. *J Antimicrob Chemother*. 2011  
616 Sep;66(9):2107-11.
- 617 65. Klotz U. Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev*. 2009;41(2):67-76.
- 618 66. McLachlan AJ, Pont LG. Drug metabolism in older people—a key consideration in achieving optimal outcomes with medicines. *J Gerontol A  
619 Biol Sci Med Sci*. 2012 Feb;67(2):175-80.
- 620 67. Turret J, Deray G, Isnard-Bagnis C. Tenofovir effect on the kidneys of HIV-infected patients: a double-edged sword? *J Am Soc Nephrol*.  
621 2013;24(10):1519-27.
- 622 68. Poizat-Martin I, Solas C, Allemand J, Obry-Roguet V, Pradel V, Bregigeton S, Faucher O, Lacarelle B. Renal impairment in patients  
623 receiving a tenofovir-ART regimen: impact of tenofovir trough concentration. *J Acquir Immune Defic Syndr*. 2013;62(4):375-80.
- 624 69. Calcagno A, Gonzalez de Requena D, Simiele M, D'Avolio A, Tettoni MC, Salassa B, Orofino G, Bramato C, Libanore V, Motta I, Bigliano  
625 P, Orsucci E, Di Perri G, Bonora S. Tenofovir plasma concentrations according to companion drugs: a cross-sectional study of HIV-  
626 positive patients with normal renal function. *Antimicrob Agents Chemother*. 2013;57(4):1840-3.
- 627 70. Kakuda TN, Wade JR, Snoeck E, Vis P, Schöller-Gyüre M, Peeters MP, Corbett C, Nijs S, Vingerhoets J, Leopold L, De Smedt G,  
628 Woodfall BJ, Hoetelmans RM. Pharmacokinetics and pharmacodynamics of the non-nucleoside reverse-transcriptase inhibitor etravirine in  
629 treatment-experienced HIV-1-infected patients. *Clin Pharmacol Ther*. 2010 Nov;88(5):695-703.
- 630 71. Crawford KW, Spritzler J, Kalayjian RC, Parsons T, Landay A, Pollard R, Stocker V, Lederman MM, Flexner C; AIDS Clinical Trials  
631 Protocol 5015 Team. Age-related changes in plasma concentrations of the HIV protease inhibitor lopinavir. *AIDS Res Hum Retroviruses*.  
632 2010 Jun;26(6):635-43.
- 633 72. Winston A, Jose S, Gibbons S, Back D, Stohr W, Post F, Fisher M, Gazzard B, Nelson M, Gilson R, Orkin C, Johnson M, Palfreeman A,  
634 Chadwick D, Leen C, Schwenk A, Anderson J, Gompels M, Dunn D, Khoo S, Sabin C; UK Collaborative HIV Cohort Study. Effects of age  
635 on antiretroviral plasma drug concentration in HIV-infected subjects undergoing routine therapeutic drug monitoring. *J Antimicrob  
636 Chemother*. 2013 Jun;68(6):1354-9.
- 637 73. Cattaneo D, Baldelli S, Cerea M, Landonio S, Meraviglia P, Simioni E, Cozzi V, Fucile S, Gazzaniga A, Clementi E, Galli M, Rizzardini G,  
638 Gervasoni C. Comparison of the in vivo pharmacokinetics and in vitro dissolution of raltegravir in HIV patients receiving the drug by  
639 swallowing or by chewing. *Antimicrob Agents Chemother*. 2012 Dec;56(12):6132-6.
- 640 74. Croteau D, Letendre S, Best B, Clifford D, Gelman B, Marra C, McArthur J, McCutchan JA, Simpson D, Grant I. Older age is associated  
641 with higher ARV concentrations in CSF in HIV+ individuals. 19th Conference on Retroviruses and Opportunistic Infections. March 5-8,  
642 2012. Seattle. Abstract 592.
- 643 75. Gervasoni C, Meraviglia P, Landonio S, Riva A, Galli M, Rizzardini G, Cattaneo D. Tenofovir plasma concentrations in post-menopausal  
644 versus pre-menopausal HIV-infected women. *J Antimicrob Chemother*. 2013 May;68(5):1206-7
- 645 76. Dumond JB, Nicol MR, Kendrick RN, Garonzik SM, Patterson KB, Cohen MS, Forrest A, Kashuba AD. Pharmacokinetic modelling of  
646 efavirenz, atazanavir, lamivudine and tenofovir in the female genital tract of HIV-infected pre-menopausal women. *Clin Pharmacokinet*.  
647 2012;51(12):809-22..

- 648 77. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil  
649 fumarate in HIV-infected patients. *Clin Infect Dis*. 2010 Sep 1;51(5):496-505. doi: 10.1086/655681.
- 650 78. Nishijima T, Komatsu H, Gatanaga H, Aoki T, Watanabe K, Kinai E, Honda H, Tanuma J, Yazaki H, Tsukada K, Honda M, Teruya K,  
651 Kikuchi Y, Oka S. Impact of small body weight on tenofovir-associated renal dysfunction in HIV-infected patients: a retrospective cohort  
652 study of Japanese patients. *PLoS One*. 2011;6(7):e22661.
- 653 79. Gallant JE, Moore RD (2009) Renal function with use of a tenofovir-containing initial antiretroviral regimen. *AIDS* 23: 1971-1975.
- 654 80. El-Sadr WM, Lundgren J, Neaton JD, Gordin F, Abrams D, Arduino RC, Babiker A, Burman W, Clumeck N, Cohen CJ, Cohn D, Cooper D,  
655 Darbyshire J, Emery S, Fätkenheuer G, Gazzard B, Grund B, Hoy J, Klingman K, Losso M, Markowitz N, Neuhaus J, Phillips A, Rappoport  
656 C. Strategies for Management of Antiretroviral Therapy (SMART) Study Group. CD4+ count-guided interruption of antiretroviral  
657 treatment. *N Engl J Med*. 2006;355:2283-2296
- 658 81. Tripathi A, Liese AD, Winniford MD, Jerrell JM, Albrecht H, Rizvi AA, Zhang J, Duffus WA. Impact of clinical and therapeutic factors on  
659 incident cardiovascular and cerebrovascular events in a population-based cohort of HIV-infected and non-HIV-infected adults. *Clin Cardiol*.  
660 2014 Sep;37(9):517-22.
- 661 82. Sabin C, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, D'Arminio Monforte A, Friis-Møller N, Kirk O, Pradier C,  
662 Weller I, Phillips AN, Lundgren JD. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected  
663 patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008;371:1417-1426.
- 664 83. Obel N, Farkas DK, Kronborg G, Larsen CS, Pedersen G, Riis A, Pedersen C, Gerstoft J, Sørensen HT. Abacavir and risk of myocardial  
665 infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Medicine*  
666 2010;11:130-6.
- 667 84. Strategies for Management of Anti-Retroviral Therapy/INSIGHT; DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors  
668 and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008;22:F17-F24.
- 669 85. Bavinger C, Bendavid E, Niehaus K, Olshen RA, Olkin I, Sundaram V, Wein N, Holodniy M, Hou N, Owens DK, Desai M. Risk of  
670 cardiovascular disease from antiretroviral therapy for HIV: a systematic review. *PLoS One*. 2013;8:e59551
- 671 86. Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, Boccara F, Costagliola D; Clinical Epidemiology Group of the French  
672 Hospital Database on HIV. Impact of individual antiretroviral drugs on the risk of myocardial infarction in human immunodeficiency virus-  
673 infected patients: a case-control study nested within the French Hospital Database on HIV ANRS cohort CO4. *Arch Intern Med*  
674 2010;170(14):1228-1238.
- 675 87. Bedimo R, Westfall AO, Drechsler H, Vidiella G, Tebas P. Abacavir use and risk of acute myocardial infarction and cerebrovascular events  
676 in the highly active antiretroviral therapy era. *Clin Infect Dis* 2011;53(1):84-91.
- 677 88. Brothers C, Hernandez J, Cutrell A, Curtis L, Ait-Khaled M, Bowlin SJ, Hughes SH, Yeo JM, Lapierre DH. Risk of myocardial infarction and  
678 abacavir therapy: no increased risk across 52 GlaxoSmithKline-sponsored clinical trials in adult subjects. *J Acquir Immune Defic Syndr*  
679 2009;51:20-28.
- 680 89. Cruciani M, Zanichelli V, Serpelloni G, Bosco O, Malena M, Mazzi R, Mengoli C, Parisi SG, Moyle G. Abacavir use and cardiovascular  
681 disease events: a meta-analysis of published and unpublished data. *AIDS* 2011;25:1993-2004.
- 682 90. Ding X, Andraca-Carrera E, Cooper C, Miele P, Komegay C, Soukup M, Marcus KA. No association of abacavir use with myocardial  
683 infarction: findings of an FDA meta-analysis. *J Acquir Immune Defic Syndr* 2012;61(4):441-7.
- 684 91. Martin A, Amin J, Cooper DA, Carr A, Kelleher AD, Bloch M, Baker D, Woolley I, Emery S; STEAL study group. Abacavir does not affect  
685 circulating levels of inflammatory or coagulopathic biomarkers in suppressed HIV: a randomized clinical trial. *AIDS* 2010; 24:2657-2663.
- 686 92. Martinez E, Larrousse M, Podzamczar D, Perez I, Gutierrez F, Lonca M, Barragan P, Deulofeu R, Casamitjana R, Mallolas J, Pich J,  
687 Gatell JM; BICOMBO Study Team. Abacavir-based therapy does not affect biological mechanisms associated with cardiovascular  
688 dysfunction. *AIDS* 2010; 24:F1-F9.
- 689 93. Jong E, Meijers JC, van Gorp EC, Spek CA, Mulder JW. Markers of inflammation and coagulation indicate a prothrombotic state in HIV-  
690 infected patients with long-term use of antiretroviral therapy with or without abacavir. *AIDS Res Ther* 2010;16:7-9.
- 691 94. Baum PD, Sullam PM, Stoddart CA, McCune JM. Abacavir increases platelet reactivity via competitive inhibition of soluble guanylyl  
692 cyclase. *AIDS*. 2011;25:2243-8.
- 693 95. Wohl DA, Arnoczky G, Fichtenbaum CJ, Campbell T, Taiwo B, Hicks C, McComsey GA, Koletar S, Sax P, Tebas P, Ha B, Massengale K,  
694 Walsh K, Stein JH.. Comparison of cardiovascular disease risk markers in HIV-infected patients receiving abacavir and tenofovir: the  
695 nucleoside inflammation, coagulation and endothelial function (NICE) study. *Antivir Ther*. 2014;19:141-7.
- 696 96. US Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and  
697 adolescents. Available from: <http://www.aidsinfo.nih.gov/ezp-prod1.hul.harvard.edu/ContentFiles/> accessed October 2014
- 698 97. Marcotullio S, Andreoni M, Antinori A, d'Arminio Monforte A, Di Perri G, Galli M, Ippolito G, Perno CF, Rizzardini G, Lazzarin A; Rapporteur  
699 Committee, Cinque P, Fares G, Foglia E, Gervasoni C, Murri R, Nozza S, Rusconi S. The Less Drugs Regimens (LDRs) therapy approach  
700 in HIV-1: an Italian expert panel perspective for the long-term management of HIV-1 infection. *New Microbiol*. 2012; 35(3):259-77.
- 701 98. Reynes J, Trinh R, Pulido F, Soto-Malave R, Gathe J, Qaqish R, Tian M, Fredrick L, Podsadecki T, Norton M, Nilius A. Lopinavir/ritonavir  
702 combined with raltegravir or tenofovir/emtricitabine in antiretroviral-naive subjects: 96-week results of the PROGRESS study. *AIDS Res*  
703 *Hum Retroviruses*. 2013; 29(2):256-65.
- 704 99. Nozza S, Galli L, Antinori A, Chiappetta S, Mazzotta F, Zaccarelli M, Ottou S, De Battista D, Pogliaghi M, Di Pietro M, Malnati M, Ripa M,  
705 Bonora S, Lazzarin A; VEMAN Study Group. Maraviroc 150 mg daily plus lopinavir/ritonavir, a nucleoside/nucleotide reverse transcriptase  
706 inhibitor-sparing regimen for HIV-infected naive patients: 48-week final results of VEMAN study. *Clin Microbiol Infect*. 2014 Dec 11. pii:  
707 S1198-743X(14)00142-6. doi: 10.1016/j.cmi.2014.12.006.
- 708 100. Calcagno A, Nozza S, Gonzalez de Requena D, Galli A, D'Avolio A, Simiele M, Chiappetta S, Di Perri G, Lazzarin A, Bonora S.  
709 Pharmacokinetics of maraviroc administered at 150 mg once daily in association with lopinavir/ritonavir in HIV-positive treatment-naive  
710 patients. *J Antimicrob Chemother*. 2013; 68(7):1686-8.
- 711 101. Boyd MA, Kumarasamy N, Moore CL, Nwizu C, Losso MH, Mohapi L, Martin A, Kerr S, Sohn AH, Teppler H, Van de Steen O, Molina JM,  
712 Emery S, Cooper DA. Ritonavir-boosted lopinavir plus nucleoside or nucleotide reverse transcriptase inhibitors versus ritonavir-boosted  
713 lopinavir plus raltegravir for treatment of HIV-1 infection in adults with virological failure of a standard first-line ART regimen (SECOND-  
714 LINE): a randomised, open-label, non-inferiority study. *Lancet*. 2013; 381(9883):2091-9.
- 715 102. Raffi F, Babiker AG, Richert L, Molina JM, George EC, Antinori A, Arribas JR, on behalf NEAT001/ANRS143 Study Group. Ritonavir-  
716 boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results

- 717 from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014 Nov 29;384(9958):1942-51. doi: 10.1016/S0140-  
718 6736(14)61170-3
- 719 103. Grarup J, Hudson F, Schwimmer C, Saillard J, Wallet C, Jansson PO, Allavena C, Van Leeuwen R, Delfraissy JF, Vella S, Chêne G,  
720 Pozniak A; NEAT001/ANRS143 Study Group. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in  
721 antiretroviral-naïve adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. *Lancet*. 2014  
722 Nov 29;384(9958):1942-51.
- 723 104. Kozal MJ, Lupo S, DeJesus E, Molina JM, McDonald C, Raffi F, Benetucci J, Mancini M, Yang R, Wirtz V, Percival L, Zhang J, Zhu L,  
724 Arikan D, Farajallah A, Nguyen BY, Leavitt R, McGrath D, Lataillade M, The Spartan Study Team. A nucleoside- and ritonavir-sparing  
725 regimen containing atazanavir plus raltegravir in antiretroviral treatment-naïve HIV-infected patients: SPARTAN study results. *HIV Clin  
726 Trials*. 2012;13(3):119-30.
- 727 105. Nishijima T, Gatanaga H, Shimbo T, Komatsu H, Endo T, Horiba M, Koga M, Naito T, Itoda I, Tei M, Fujii T, Takada K, Yamamoto M,  
728 Miyakawa T, Tanabe Y, Mitsuya H, Oka S; SPARE study team. Switching tenofovir/emtricitabine plus lopinavir/r to raltegravir plus  
729 Darunavir/r in patients with suppressed viral load did not result in improvement of renal function but could sustain viral suppression: a  
730 randomized multicenter trial. *PLoS One*. 2013; 8(8):e73639
- 731 106. Di Giambenedetto S, Fabbiani M, Colafigli M, Ciccarelli N, Farina S, Sidella L, D'Avino A, Mondì A, Cingolani A, Tamburrini E, Murri R,  
732 Navarra P, Cauda R, De Luca A. Safety and feasibility of treatment simplification to atazanavir/ritonavir + lamivudine in HIV-infected  
733 patients on stable treatment with two nucleos(t)ide reverse transcriptase inhibitors + atazanavir/ritonavir with virological suppression  
734 (Atazanavir and Lamivudine for treatment Simplification, AtLaS pilot study). *J Antimicrob Chemother*. 2013;68(6):1364-72.
- 735 107. Reliquet V, Chirouze C, Allavena C, Muret P, Peytavin G, André-Garnier E, Bettinger D, Ferré V, Hoen B, Raffi F. Nevirapine-raltegravir  
736 combination, an NRTI and PI/r sparing regimen, as maintenance antiretroviral therapy in virologically suppressed HIV-1-infected patients.  
737 *Antivir Ther*. 2014;19(1):117-23.
- 738 108. Rockstroh JK, Lennox JL, DeJesus E, Saag MS, Lazzarin A, Wan H, Walker ML, Xu X, Zhao J, Tepler H, Dinubile MJ, Rodgers AJ,  
739 Nguyen BY, Leavitt R, Sklar P; STARTMRK Investigators. Long-term treatment with raltegravir or efavirenz combined with  
740 tenofovir/emtricitabine for treatment-naïve human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. *Clin  
741 Infect Dis*. 2011 Oct;53(8):807-16.
- 742 109. Landovitz RJ, Ribaldo HJ, Ofotokun I, Wang H, Baugh BP, Leavitt RY, Rooney JF, Seekins D, Currier JS, and Lennox JL for the A5257  
743 Study Team. Efficacy and tolerability of atazanavir, raltegravir, or darunavir with FTC/Tenofovir: ACTG 5257. 21st Conference on  
744 Retroviruses and Opportunistic Infections 2014, Abstract #85
- 745 110. Raffi F, Rachlis A, Stellbrink HJ, Hardy WD, Torti C, Orkin C, Bloch M, Podzamczar D, Pokrovsky V, Pulido F, Almond S, Margolis D,  
746 Brennan C, Min S; SPRING-2 Study Group. Once-daily dolutegravir versus raltegravir in antiretroviral-naïve adults with HIV-1 infection: 48  
747 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013;381:735-743.
- 748 111. Walmsley SL, Antela A, Clumeck N, Duiculescu D, Eberhard A, Gutiérrez F, Hocqueloux L, Maggiolo F, Sandkovsky U, Granier C, Pappa  
749 K, Wynne B, Min S, Nichols G; SINGLE Investigators. Dolutegravir plus abacavir-lamivudine for the treatment of HIV-1 infection. *N Engl J  
750 Med*. 2013;369:1807-1818.
- 751 112. Clotet B, Feinberg J, van Lunzen J, Khuong-Josses MA, Antinori A, Dumitru I, Pokrovskiy V, Fehr J, Ortiz R, Saag M, Harris J, Brennan C,  
752 Fujiwara T, Min S; ING114915 Study Team. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naïve adults with HIV-1  
753 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. *Lancet*. 2014;383:2222-223
- 754 113. Curtis G, Nichols C, Stainsby J, Lim, Aylott A, Wynne B, Clark A, Bloch M, Maechler G, Martin-Carpenter L, Raffi F, Min S. Dolutegravir:  
755 Clinical and Laboratory Safety in Integrase Inhibitor-Naïve Patients. *HIV Clin Trials* 2014;15(5):199-208
- 756 114. Quercia R, Roberts J, Martin-Carpenter L, Zala C, Comparative Changes of Lipid Levels in Treatment-Naïve, HIV-1-Infected Adults  
757 Treated with Dolutegravir vs. Efavirenz, Raltegravir, and Ritonavir-Boosted Darunavir-Based Regimens Over 48 Weeks, *Clin Drug Investig*  
758 2015, DOI 10.1007/s40261-014-0266-2
- 759 115. Theou O, Stathokostas L, Roland KP, Jakobi JM, Patterson C, Vandervoort AA, Jones GR. The effectiveness of exercise interventions for  
760 the management of frailty: a systematic review. *J Aging Res*. 2011;2011:569194.
- 761 116. Gill TM, Baker DI, Gottschalk M, Peduzzi PN, Allore H, Byers A. A program to prevent functional decline in physically frail, elderly persons  
762 who live at home. *N Engl J Med*. 2002;347:1068-1074
- 763 117. Fiatarone MA, O'Neill EF, Ryan ND, Clements KM, Solares GR, Nelson ME, Roberts SB, Kehayias JJ, Lipsitz LA, Evans WJ. Exercise  
764 training and nutritional supplementation for physical frailty in very elderly people. *N Engl J Med*. 1994;330:1769-1775.
- 765 118. Forster A, Lambley R, Hardy J, Young J, Smith J, Green J, Burns E. Rehabilitation for older people in long-term care. *Cochrane Database  
766 Syst Rev*. 2009;(1):CD004294.
- 767 119. Longo V, Bonato M, Bossolasco S, Laura Galli, Andrea Caumo, Gaspare Pavei, Adriano Lazzarin, Giampiero Merati, Antonio LaTorre,  
768 Paola Cinque. Brisk Walking Improves Inflammatory Markers in ART-Treated Patients. CROI 2104, Abstract 763.
- 769 120. Lin AL, Coman D, Jiang L, Rothman DL, Hyder F. Caloric restriction impedes age-related decline of mitochondrial function and neuronal  
770 activity. *J Cereb Blood Flow Metab*. 2014 Sep;34(9):1440-3.
- 771 121. Farazi M, Nguyen J, Goldufsky J, Linnane S, Lukaesko L, Weinberg AD, Ruby CE. Caloric restriction maintains OX40 agonist-mediated  
772 tumor immunity and CD4 T cell priming during aging. *Cancer Immunol Immunother*. 2014 Jun;63(6):615-26.
- 773 122. Soare A, Weiss EP, Pozzilli P. Benefits of caloric restriction for cardiometabolic health, including type 2 diabetes mellitus risk. *Diabetes  
774 Metab Res Rev*. 2014 Mar;30 Suppl 1:41-7.
- 775 123. Rizza W, Veronese N, Fontana L. What are the roles of calorie restriction and diet quality in promoting healthy longevity? *Ageing Res Rev*.  
776 2014 Jan;13:38-45
- 777 124. Fontana L.; Partridge L.; Longo V.D. Extending healthy lifespan—from yeast to humans. *Science* 328:321–326; 2010.
- 778 125. Lorenzini A. How Much Should We Weigh for a Long and Healthy Life Span? The Need to Reconcile Caloric Restriction versus Longevity  
779 with Body Mass Index versus Mortality Data. *Front Endocrinol (Lausanne)*. 2014 Jul 30;5:121.
- 780 126. Sohal RS, Forster MJ. Caloric restriction and the aging process: a critique. *Free Radic Biol Med*. 2014 Aug;73:366-82.
- 781 127. Youm YH, Nguyen KY, Grant RW, Goldberg EL, Bodogai M, Kim D, D'Agostino D, Planavsky N, Lupfer C, Kanneganti TD, Kang S,  
782 Horvath TL, Fahmy TM, Crawford PA, Biragyn A, Alnemri E, Dixit VD. The ketone metabolite -hydroxybutyrate blocks NLRP3  
783 inflammasome-mediated inflammatory disease. *Nat Med*. 2015. [Epub ahead of print]
- 784 128. Brothers TD, Kirkland S, Guaraldi G, Falutz J, Theou O, Johnston BL, Rockwood K. Frailty in people aging with human immunodeficiency  
785 virus (HIV) infection. *J Infect Dis*. 2014 Oct 15;210(8):1170-9. doi: 10.1093/infdis/jiu258.



- 786 129. Leenders M, van Loon LJ (2011) Leucine as a pharmaconutrient to prevent and treat sarcopenia and type 2 diabetes. *Nutr Rev* 69:675-  
787 689
- 788 130. Qin LQ, Xun P, Bujnowski D, Daviglius ML, Van HL, Stamler J, He K (2011) Higher branched-chain amino acid intake is associated with a  
789 lower prevalence of being overweight or obese in middle aged East Asian and western adults. *J Nutr* 141:249-254
- 790 131. Cavuoto P, Fenech MF (2012) A review of methionine dependency and the role of methionine restriction in cancer growth control and life-  
791 span extension. *Cancer Treat Rev* 38:726-736
- 792 132. McPherson RA, Hardy G (2011) Clinical and nutritional benefits of cysteine-enriched protein supplements. *Curr Opin Clin Nutr Metab Care*  
793 14:562-568
- 794 133. Ripps H, Shen W (2012) Review taurine: a "very essential" amino acid. *Mol Vis* 18:2673-2686
- 795 134. Gualano B, Roschel H, Lancha-Jr AH, Brightbill CE, Rawson ES (2012) In sickness and in health: the widespread application of creatine  
796 supplementation. *Amino Acids* 43:519-529
- 797 135. Bollhalder L, Pfeil AM, Tomonaga Y, Schwenglen M (2013) A systematic literature review and meta-analysis of randomized clinical trials  
798 of parenteral glutamine supplementation. *Clin Nutr* 32(2):213-223.
- 799 136. Kitamura A, Tsurugizawa T, Uematsu A, Torii K, Uneyama H (2012) New therapeutic strategy for amino acid medicine: effects of dietary  
800 glutamate on gut and brain function. *J Pharmacol Sci* 118:138-144
- 801 137. Jonker R, Engelen MP, Deutz NE (2012) Role of specific dietary amino acids in clinical conditions. *Br J Nutr* 108(Suppl 2):S139-S148
- 802 138. Smith RL, de Boer R, Brul S, Budovskaya Y, van Spek H Premature and accelerated aging: HIV or HAART?. *Front Genet.* 2013 Jan  
803 28;3:328
- 804 139. Biagi E, Candela M, Turroni S, Garagnani P, Franceschi C., Brigidi P. Ageing and gut microbes: Perspectives for health maintenance and  
805 longevity *Pharmacological Research* 69 (2013) 11- 20
- 806 140. Klatt NR, Canary LA, Sun X, et al. Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected  
807 macaques. *J Clin Invest* 2013; 123:903-907.
- 808 141. Ortiz AM, Klase ZA, Carmack KM, et al. Probiotic and IL-21 Treatment Promotes Th17 Cell Recovery in ARV-Treatment of Pigtail  
809 Macaques. CROI 2014 Abstract 83.
- 810 142. Gori A, Rizzardini G, Van 't Land B, et al. Specific probiotics modulate gut microbiota and immune activation in HAART-naive HIV-infected  
811 adults. Results of the 'COPA' pilot randomized trial. *Mucosal Immunol* 2011; 4:554-563.
- 812 143. Wilson NL, Moneyham LD, Alexandrov AW. A systematic review of probiotics as a potential intervention to restore gut health in HIV  
813 infection. *J Assoc Nurses AIDS Care* 2013; 24:98-111.
- 814 144. Gonzalez-Hernandez LA, Jave-Suarez LF, Fafutis-Morris M, et al. Synbiotic therapy decreases microbial translocation and inflammation  
815 and improves immunological status in HIV-infected patients: a double-blind randomized controlled pilot trial. *Nutr J* 2012; 11:90.
- 816 145. Stiksrud B, Nowak P, Kvale D, et al. Decreased Levels of D-Dimer After Probiotic Supplementation in Patients Receiving ART. CROI 2014  
817 Abstract 342.
- 818 146. Overton E., Kitch D., Benson C. A, Hunt P. W., Stein J. H, Smurzynski M., Ribaud H. J., Tebas P. Effect of Statin Therapy in Reducing  
819 the Risk of Serious Non-AIDS-Defining Events and Nonaccidental Death *Clinical Infectious Diseases* 2013;56(10):1471-9
- 820 147. Rasmussen LD, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, et al. (2013) Statin Therapy and Mortality in HIV-Infected Individuals; A  
821 Danish Nationwide Population-Based Cohort Study. *PLoS ONE* 8(3): e52828
- 822 148. Funderburg N, Jiang Y, Debanne S., Storer N, Labbato D, Clagett B, Robinson J, Lederman M., and McComsey G. Rosuvastatin  
823 Treatment Reduces Markers of Monocyte Activation in HIV-Infected Subjects on Antiretroviral Therapy *Clinical Infectious Diseases*  
824 2014;58(4):588-95
- 825 149. Eckard AR, Jiang Y, Debanne S, Funderburg N, McComsey G. Effect of 24 Weeks of Statin Therapy on Systemic and Vascular  
826 Inflammation in HIV-Infected Subjects Receiving Antiretroviral Therapy *The Journal of Infectious Diseases* 2014;209:1156-64
- 827 150. Longenecker CT, Hileman Co Storer NJ, et al. Rosuvastatin Lowers Cystatin C in HIV-Infected Subjects On Antiretroviral Therapy:  
828 SATURN-HIV. Abstract 743.
- 829 151. Skaaby T, Husemoen LL, Pisinger C, Jorgensen T, Thuesen BH, Fenger M, et al. Vitamin D status and cause-specific mortality: a general  
830 population study. *PLoS ONE.* 2012;7(12):e52423.
- 831 152. Schottker B, Ball D, Gellert C, Brenner H. Serum 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis  
832 of prospective cohort studies. *Ageing Res Rev.* 2013;12(2):708-18
- 833 153. Shardell M, Hicks GE, Miller RR, Kritchevsky S, Andersen D, Bandinelli S, Cherubini A, Ferrucci L. Association of low vitamin D levels with  
834 the frailty syndrome in men and women. *J Gerontol A Biol Sci Med Sci.* 2009 Jan;64(1):69-75.
- 835 154. Escota GV, Cross S, Powderly WG. Vitamin D and calcium abnormalities in the HIV-infected population. *Endocrinol Metab Clin North Am.*  
836 2014 Sep;43(3):743-67.
- 837 155. Eckard AR, McComsey GA. Vitamin D deficiency and altered bone mineral metabolism in HIV-infected individuals. *Curr HIV/AIDS Rep.*  
838 2014 Sep;11(3):263-70.
- 839 156. Havers F, Smeaton L, Gupte N, Detrick B, Bollinger RC, Hakim J, Kumarasamy N, Andrade A, Christian P, Lama JR, Campbell TB, Gupta  
840 A; ACTG PEARLS; NWCS 319 Study Teams. 25-Hydroxyvitamin D insufficiency and deficiency is associated with HIV disease  
841 progression and virological failure post-antiretroviral therapy initiation in diverse multinational settings. *J Infect Dis.* 2014 Jul 15;210(2):244-  
842 53.
- 843 157. Shepherd L, Souberbielle JC, Bastard JP, Fellahi S, Capeau J, Reekie J, Reiss P, Blaxhult A, Bickel M, Leen C, Kirk O, Lundgren JD,  
844 Mocroft A, Viard JP; EuroSIDA in EuroCOORD. Prognostic value of vitamin D level for all-cause mortality, and association with  
845 inflammatory markers, in HIV-infected persons. *J Infect Dis.* 2014 Jul 15;210(2):234-43.
- 846 158. Piconi S, Parisotto S, Rizzardini G, Passerini P, Terzi R, Argentero B, Meraviglia P, Capetti A, Biasin M, Trabattoni D and M Clerici  
847 Hydroxychloroquine drastically reduces immune activation in HIV-infected, antiretroviral therapy-treated immunologic nonresponders 2011  
848 118: 3263-3272
- 849 159. Pettersen FO, Torheim EA, Dahm AE, Aaberge IS, Lind A, Holm M, Aandahl EM, Sandset PM, Taskén K, Kvale D. An exploratory trial of  
850 cyclooxygenase type 2 inhibitor in HIV-1 infection: downregulated immune activation and improved T cell-dependent vaccine responses. *J*  
851 *Viro.* 2011 Jul;85(13):6557-66.
- 852 160. Carcelain G, Autran B. Immune interventions in HIV infection. *Immunol Rev.* 2013 Jul;254(1):355-71

- 853 161. Sereti I, Estes JD, Thompson WL, Morcock DR, Fischl MA, Croughs T, Beq S, Lafaye de Micheaux S, Yao MD, Ober A, Wilson EM,  
854 Natarajan V, Imamichi H, Boulassel MR, Lederman MM, Routy JP. Decreases in colonic and systemic inflammation in chronic HIV  
855 infection after IL-7 administration. *PLoS Pathog.* 2014 Jan 30;10(1):e1003890
- 856 162. Cimbri R, Vassena L, Arthos J, Cicala C, Kehrl JH, Park C, Sereti I, Lederman MM, Fauci AS, Lusso P. IL-7 induces expression and  
857 activation of integrin  $\alpha 4\beta 7$  promoting naive T-cell homing to the intestinal mucosa. *Blood.* 2012 Sep 27;120(13):2610-9.
- 858 163. Schuetz A, Phuang-Ngern Y, Rerknimitr R, et al. Early ART Initiation Prevents Disruption of the Mucosal Barrier and Subsequent T-Cell  
859 Activation. *CROI 2014 Abstract 77.*
- 860 164. Massanella M, Libre JM, Marfil S, et al. Effect of Raltegravir Intensification in the Cytokine Profile of Treated HIV+ Individuals. *CROI 2014*  
861 *Abstract 300.*
- 862 165. Cipriani S, Francisci D, Mencarelli A, Renga B, Schiaroli E, D'Amore C, Baldelli F, Fiorucci S. Efficacy of the CCR5 Antagonist Maraviroc in  
863 Reducing Early, Ritonavir-Induced Atherogenesis and Advanced Plaque Progression in Mice *Circulation.* 2013;127:2114-2124
- 864 166. Hunt PW, Martin JN, Sinclair E, Epling L, Teague J, Jacobson MA, Tracy RP, Corey L, Deeks SG. Valganciclovir reduces T cell activation  
865 in HIV-infected individuals with incomplete CD4+ T cell recovery on antiretroviral therapy *J Infect Dis.* 2011 May 15;203(10):1474-83.
- 866 167. Cahn P, Ruxrungtham K, Gazzard B, Diaz RS, Gori A, Kotler DP, Vriesema A, Georgiou NA, Garssen J, Clerici M, Lange JM; (BTE)  
867 Blinded Nutritional Study for Immunity and Tolerance Evaluation Study Team. The immunomodulatory nutritional intervention NR100157  
868 reduced CD4+ T-cell decline and immune activation: a 1-year multicenter randomized controlled double-blind trial in HIV-infected persons  
869 not receiving antiretroviral therapy (The BITE Study). *Clin Infect Dis.* 2013 Jul;57(1):139-46
- 870 168. Sperber K, Quraishi H, Kalb TH, Panja A, Stecher V, Mayer L. Selective regulation of cytokine by hydroxychloroquine: inhibition of  
871 interleukin-1 alpha (IL-1 alpha) and IL-6 in human monocytes and T cells. *J Rheumatol* 1993;20(5):803-808
- 872 169. Routy JP, Angel J, Patel M, Kanagaratham C, Radzioch D, Kema I, Gilmore N, Ancuta P, Singer J, Jenabian MA. Assessment of  
873 chloroquine as a modulator of immune activation to improve CD4 recovery in immune nonresponding HIV-infected patients receiving  
874 antiretroviral therapy. *HIV Med.* 2015 Jan;16(1):48-56
- 875 170. Shan L, Siliciano RF. Unraveling the relationship between microbial translocation and systemic immune activation in HIV infection. *J Clin*  
876 *Invest.* 2014 Jun 2;124(6):2368-71.
- 877 171. Kristoff J, Haret-Richter G, Ma D, Ribeiro RM, Xu C, Cornell E, Stock JL, He T, Mobley AD, Ross S, Trichel A, Wilson C, Tracy R, Landay  
878 A, Apetrei C, Pandrea I. Early microbial translocation blockade reduces SIV-mediated inflammation and viral replication. *J Clin Invest.*  
879 2014 Jun 2;124(6):2802-6.
- 880 172. Sandler NG, Zhang X, Bosch RJ, Funderburg NT, Choi AI, Robinson JK, Fine DM, Coombs RW, Jacobson JM, Landay AL, Douek DC,  
881 Tressler R, Read SW, Wilson CC, Deeks SG, Lederman MM, Gandhi RT; AIDS Clinical Trials Group A5296 Team. Sevelamer does not  
882 decrease lipopolysaccharide or soluble CD14 levels but decreases soluble tissue factor, low-density lipoprotein (LDL) cholesterol, and  
883 oxidized LDL cholesterol levels in individuals with untreated HIV infection. *J Infect Dis.* 2014 Nov 15;210(10):1549-54.
- 884 173. Hunt PW, Shulman NS, Hayes TL, Dahl V, Somsouk M, Funderburg NT, McLaughlin B, Landay AL, Adeyemi O, Gilman LE, Clagett B,  
885 Rodriguez B, Martin JN, Schacker TW, Shacklett BL, Palmer S, Lederman MM, Deeks SG. The immunologic effects of maraviroc  
886 intensification in treated HIV-infected individuals with incomplete CD4+ T-cell recovery: a randomized trial. *Blood.* 2013 Jun  
887 6;121(23):4635-46
- 888 174. Fowler BJ, Gelfand BD, Kim Y, Kerur N, Tarallo V, Hirano Y, Amarnath S, Fowler DH, Radwan M, Young MT, Pittman K, Kubes P, Agarwal  
889 HK, Parang K, Hinton DR, Bastos-Carvalho A, Li S, Yasuma T, Mizutani T, Yasuma R, Wright C, Ambati J. Nucleoside reverse  
890 transcriptase inhibitors possess intrinsic anti-inflammatory activity. *Science.* 2014 Nov 21;346(6212):1000-3