Demographics of HIV and aging

Dominique Costagliola[a,b]

Purpose of review
To describe and understand why the HIV-infected population is aging in high-income countries, the rate and causes of death in comparison with the general population, and to illustrate the impact of combined antiretroviral therapy (cART) on life expectancy and to discuss needs for further researches.

Recent findings
The HIV-infected population is aging in high-income countries because of increasing age at HIV infection, higher risk of late diagnosis in older individuals and decrease in the AIDS-defining and non-AIDS-defining death rates. Compared with the general population, the risk of death is no longer elevated in many non-IDU-infected individuals successfully treated with cART.

Summary
Further researches are needed to reconcile the absence of increased mortality risk in HIV-infected individuals with controlled viral load and restored immunity with the observed higher risk of comorbidities, such as cardiovascular diseases and non-AIDS-defining cancers, and the accelerated aging hypothesis, in particular, to help stratify HIV individuals who are at risk; to define the optimal management of multimorbidity and polypharmacy, even in the absence of a higher comorbidity risk; and to better account for increased life expectancy and multimorbidity burden to plan the future needs in care for HIV-infected individuals.

Keywords
aging, comorbidities, HIV infection, life expectancy, mortality

INTRODUCTION

Soon after combined antiretroviral therapy (cART) has become available in high-income countries, a rapid decrease in mortality among HIV-infected individuals was observed [1,2], which has been sustained over time [3]. As a consequence, there was a shift in the causes of death in people living with HIV [4,5] and rising concerns on chronic morbidities typically associated with age, such as non-AIDS-defining cancers, cardiovascular, renal, liver and bone, and possibly neurological diseases [6]. In this study, I review the main phenomena driving the aging of the population living with HIV in high-income countries, the consequences of age on access to care and response to treatment, risk of death, in particular, relative to the general population and changes in the cause of death. I also cover life expectancy and insurability for people living with HIV. I end by questioning the consequences of this aging and whether the burden of comorbidities will weight on all HIV-infected individuals.

AGE IN PEOPLE LIVING WITH HIV IN HIGH-INCOME COUNTRIES

In the USA, the estimated percentage of persons living with HIV who are 55 years of age or more increased from 13.2% in 2006 to 17.1% in 2009 [7], and it has been extrapolated that, by 2015, half of those living with HIV infection will be 50 years of age or older [6,8]. The French Hospital Database on HIV (FHDH ANRS CO4 [Agence nationale de recherches sur le SIDA et les hépatites virales, cohorte 4]) includes data on more than 120 000 HIV-infected individuals from 70 French general or university hospitals and has been shown to be representative of HIV-infected individuals under care in France [9]. As shown in Fig. 1a, the percentage of HIV-infected men 50 years of age or older increased from 8.5% in 1993 to 42.0% in 2012, including 13.8% who were 60 years of age or older. The corresponding figures for women were 6.0% in 1993 and 26.9% in 2012, including 8.2% who were

[a]Sorbonne Universités, UPMC Univ Paris 06 and [b]INSERM, UMRS 1136, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France

Correspondence to Dominique Costagliola, Institut Pierre Louis d'Epidémiologie et de Santé Publique, UMRS 1136, INSERM et Sorbonne Universités, UPMC Univ Paris 06, 56 Bd V Auriol, CS 81393, 75646 Paris Cedex 13, France. E-mail: dominique.costagliola@upmc.fr

Curr Opin HIV AIDS 2014, 9:294–301
DOI:10.1097/COH.0000000000000076

KEY POINTS

- In high-incomes countries, the HIV-infected population is aging because of an increase in age at infection, a higher risk of being diagnosed late and improved survival.
- Both the risk of AIDS-defining and non-AIDS-defining death rates have decreased over the cART era and it appears that mortality rates in many non-IDU HIV-infected individuals with restored CD4 cell count on cART are similar to those of the general population.
- Will the comorbidity risk of a nonsmoking individual diagnosed with HIV infection after 2000 with a CD4 level above 350/μl and quickly initiating a successful cART be elevated?
- Even in the absence of excess comorbidity burden, designing the optimal management of multimorbidity and polypharmacy will be critical for an aging HIV-infected population.
- Aging indicators better accounting for the increase in life expectancy as well as the extra burden of chronic diseases, if any, instead of simply using the proportion above 50 years of age, are urgently needed to plan the future needs in care for HIV-infected individuals.

60 years of age or older in 2012. In a supplement of the 2013 annual UNAIDS (Joint United Nations programme on HIV/AIDS) report [10], worldwide estimates were provided showing that for the first time since the start of the HIV epidemic, 10% of the adult population living with HIV in low- and middle-income countries is aged 50 or older, and in high-income countries, approximately 30% of all adults living with HIV are aged 50 years and over. The proportion of adults living with HIV aged 50 years and older has increased in all regions of the world, at varying rates, since 2007 (Fig. 1b). What can explain this dramatic change?

AGE AT HIV INFECTION AND ITS IMPACT ON DISEASE PROGRESSION

CASCADE (Concerted Action on SeroConversion to AIDS and Death in Europe) is a collaboration of 29 cohorts from 14 European countries, Australia, Canada and Africa, of persons with well documented dates of HIV seroconversion that is funded by the European Union (EU) EuroCoord network. First, as shown in Fig. 2 (Kholoud Porter, personal communication), in CASCADE, the median age at HIV infection increased from 26.2 years of age [interquartile range (IQR) 21.5–32.7] in those infected before 1986 to 33.2 years of age (IQR 27.3–40.3) in those infected between 2006 and 2010, showing an increasing age at infection over the course of the epidemic. Being infected at an older age impacts the course of the disease. Many studies before the cART era showed that natural history of HIV infection was inversely associated with age at infection [11], with a shorter time to AIDS or to death in older individuals.

AGE AT PRESENTATION INTO CARE AND ITS IMPACT ON DEATH AND RESPONSE TO TREATMENT

Second, age at diagnosis has increased over time. For instance, in France [12], individuals 50 years of age or older represent 17% of newly diagnosed individuals in 2011 and this proportion increased from 12% in 2003. As shown in Fig. 3, age at access to care increased over time in the FHDH, with the percentage of newly enrolled individuals 50 years of age or older increasing from 8.5 to 19.1% between 1993 and 2012 in men, and from 6.6 to 19.5% in women. The North American AIDS Cohort Collaboration on Research and Design (NA-ACCORD) is a National Institutes of Health (NIH)-funded (IeDEA [International Epidemiologic Database to Evaluate AIDS]) collaboration of 25 cohorts in the USA and Canada. In NA-ACCORD, from 1997 to 2007, the proportion of individuals presenting for HIV care who were at least 50 years old increased from 17 to 27% [13]. This is partly due to older age at infection, as explained above, and also to a higher risk of late access to care in individuals over 50 years of age [13–15]. In FHDH [14], the odds ratio (OR) of late presentation to care was estimated as 2.8 [95% confidence interval (CI) 2.4–3.4] for individuals 60 years of age or older and 2.2 (95% CI 2.0–2.5) for those 50–60 years of age, relative to individuals younger than 30 years of age. Similarly, in Cohere, a EU-funded (EUROCOORD) collaboration of 23 cohorts in 35 European countries [15], older age was associated with a higher risk of late presentation (adjusted OR 1.41/10 year older, 95% CI 1.39–1.43). In NA-ACCORD also [13], individuals 50 years of age or older were more likely to present with AIDS compared to younger patients (13 versus 10%) and had consistently lower CD4 cell counts at presentation over time.

Presenting late is critical. In FHDH, a dramatically higher risk of death within several years after presentation was observed for those presenting with AIDS (with hazard ratio ranging from 48.3 during the first 6 months of follow-up to 4.8 during months 12–48), or with a CD4 cell count below 200/μl (8.1 and 2.3, respectively), and even in those with a CD4 cell count between 200 and 350/μl (hazard ratio 3.0 and 1.8 for months 6–12 and 12–48, respectively), relative to those presenting with a CD4 cell count

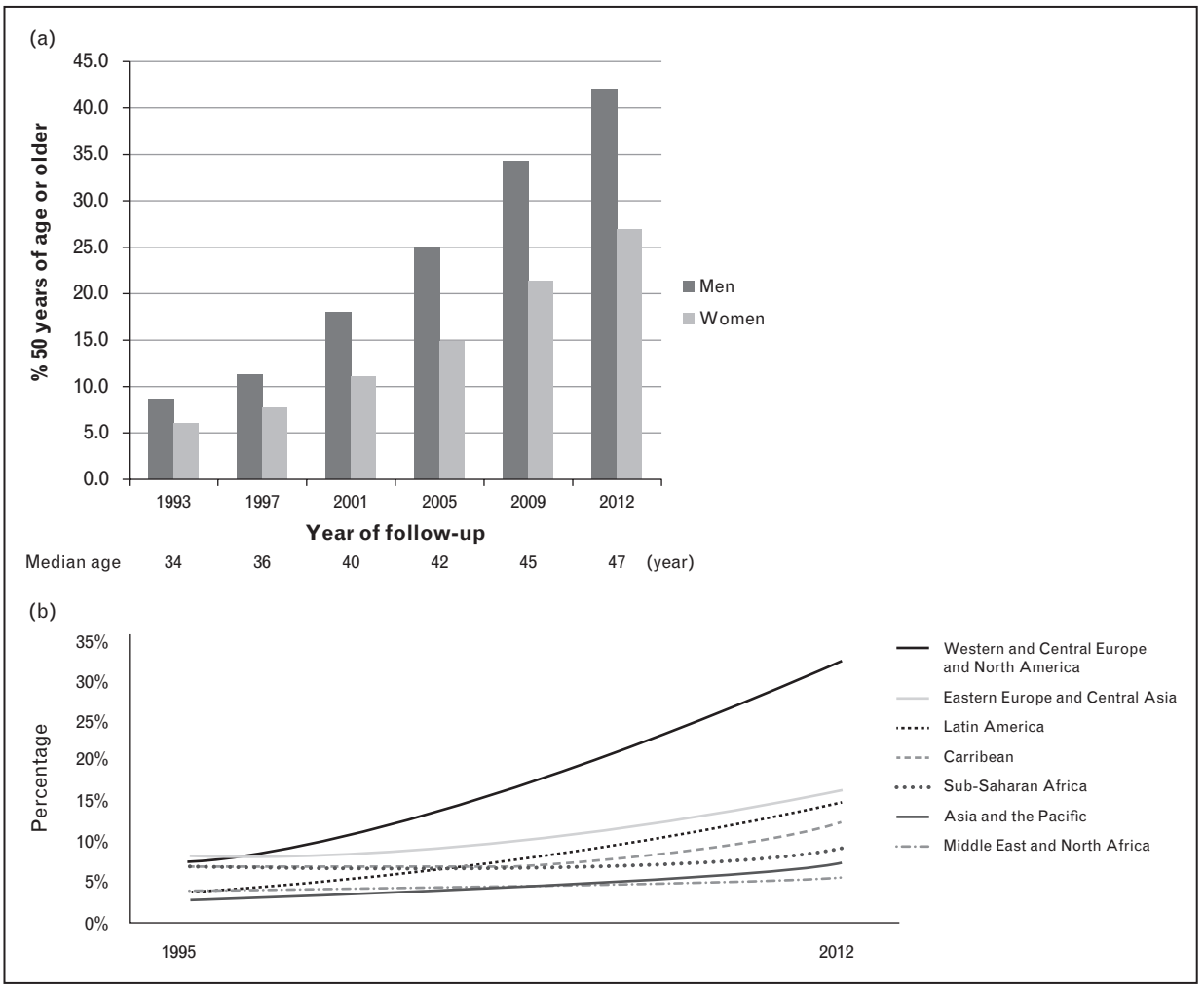

FIGURE 1. (a) Proportion of patients 50 years of age or older in the French Hospital database on HIV (FHDH ANRS CO4) by year of follow-up. (b) People aged 50 years or older, as a percentage of all adults 15 years or older living with HIV by region, 1995–2012 (UNAIDS 2012).

above 350/μl, even though cART was rapidly initiated in those presenting late [14]. In addition, several studies have shown that whereas the virological response tended to be better in older patients, the immunologic response after cART initiation is decreased in individuals 50 years of age or older, even after accounting for difference in CD4 cell count prior to cART initiation [16–18]. Therefore, both in Europe and North America, older patients present with lower CD4 cell count and remained longer with low CD4 cell count after treatment initiation, which put them at risk for progression and death as compared with younger patients.

RISK OF DEATH RELATIVE TO THE GENERAL POPULATION

A third reason for increasing age of persons living with HIV, as explained in the Introduction section, is the dramatic decrease in the death rate observed soon after cART became available both in the USA and in Europe [1,2], which remained sustained over time [3]. When comparing the risk of death in HIV-infected individuals who initiated cART as early as 1997–1999 to that in the general population of the same age and sex in France, Lewden *et al.* [19] evidenced an overall standardized mortality ratio (SMR) of 7.0 (95% CI 6.2–7.8). In individuals with a restored CD4 cell count (CD4 >500 cells/μl), the mortality reached the level of the general population 6 years after cART initiation (SMR 0.5, 95% CI 0.1–1.6). More recently, in the Antiretroviral Cohort Collaboration (ART-CC), a Medical Research Council (MRC)-funded collaboration of European and North American cohorts, in patients who initiated cART as naïve up to 2006 [20], the SMR for men who have sex with men (MSM) who started cART free of AIDS reached a CD4 cell count of at least 350 cells/μl, and suppressed viral replication to

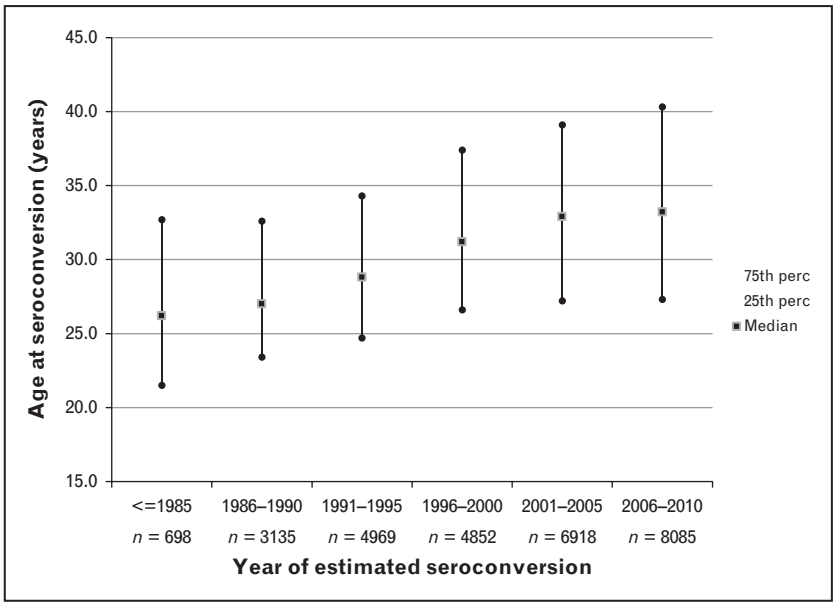

FIGURE 2. Median (25th–75th percentiles) age at seroconversion in CASCADE collaboration in EUROCOORD by seroconversion period.

500 copies/ml or less by the sixth month was the lowest, estimated as 1.05 (95% CI 0.82–1.35), no longer elevated as compared to the general population. In Cohere, when considering individuals initiating cART as naive between 1998 and 2008 [21▪▪], the overall mortality rate was 1.2/100 person-years (1.3 for men and 0.9 for women), 4.2 times as high as that in the general population (3.8 for men and 7.4 for women). Among those reaching a CD4 cell count at least 500/μl, the mortality rate was estimated as 0.37 per 100 person-years; mortality rates were similar to those of the general population in non-IDU men (SMR 0.9, 95% CI 0.7–1.3) and, after 3 years, in women (SMR 1.1, 95% CI 0.7–1.7). The trends were the same in all age groups (18–39, 40–59, 60 and over). However, a prior AIDS diagnosis was associated with higher mortality and mortality rates remained elevated in IDUs. Similar results were also observed in the continuous antiviral therapy arms of SMART (Strategies for Management of Antiretroviral Therapies) and ESPRIT (Evaluation of Subcutaneous Proleukinin a

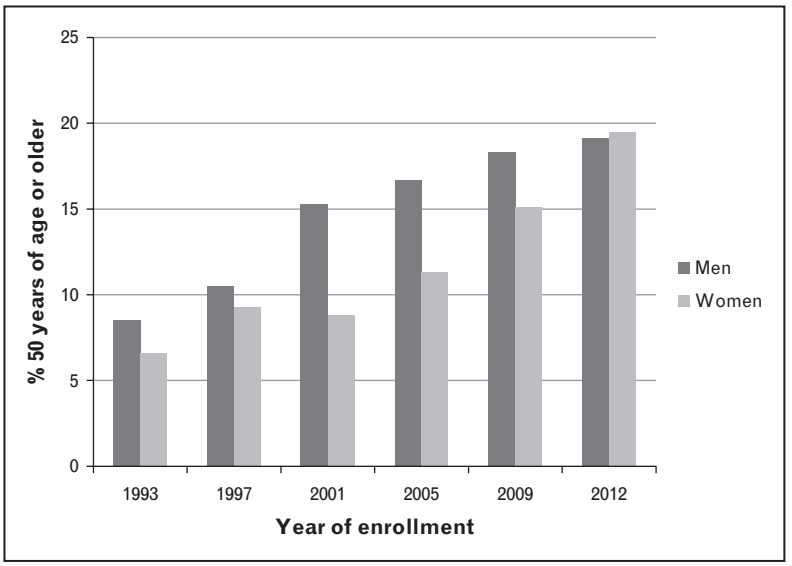

FIGURE 3. Proportion of newly enrolled patients 50 years of age or older in the French Hospital database on HIV (FHDH ANRS CO4) by year of enrollment.

Randomized International Trial) [22▪], in HIV-infected individuals on cART, with a recent undetectable viral load, who maintained or had recovery of CD4 cell counts to at least 500 cells/μl. Overall, it appears that mortality rates in many non-IDU HIV-infected individuals with restored CD4 cell count on cART are similar to those of the general population, even though the risk of many comorbidities, such as cardiovascular diseases, non-AIDS-defining infectious and noninfectious cancers, osteoporosis, liver disease, renal disease, and possibly neurocognitive decline, are higher in HIV-infected patients compared to the general population. Of note, in FHDH, 60% of those under cART for at least 6 months have a CD4 cell count above or equal to 500/μl, illustrating that not all individuals reached this goal in 2012.

CAUSES OF DEATH

People often stated that the non-AIDS-defining mortality has increased in HIV-infected individuals in the cART era; however, this is not true. In fact, both the AIDS-defining and non-AIDS-defining mortality rates have declined in the cART era, as nicely shown in the Swiss HIV cohort [23▪▪]. In this cohort, the AIDS-defining, non-AIDS-defining and unknown-cause mortality rates all decreased over time, reaching 0.21, 0.86 and 0.26 per 100 person-years in 2010, respectively. However, the relative proportion of AIDS-defining and non-AIDS-defining causes of death has changed dramatically, although comparison between studies are difficult due to different coding of causes and differences in underlying population such as sex, age group, socioeconomic status, access to care, health insurance and hepatitis C virus (HCV) infection [23▪▪]. Nonetheless, non-AIDS-defining causes of death are increasingly becoming the major causes of death [23▪▪,24,25]. For instance, in France [24], the underlying cause of death was AIDS-defining in 25% of deaths in 2010 versus 36% in 2005 and 47% in 2000, whereas, non-AIDS nonviral hepatitis-related malignancy represented 22% of deaths in 2010, (versus 17% in 2005 and 11% in 2000), liver-related deaths represented 11% of death in 2010 (versus 15 and 13% in previous studies), cardiovascular diseases 10% (versus 8 and 7%) and non-AIDS-related infections 9% (versus 4 and 7%).

LIFE EXPECTANCY AND INSURABILITY

The decrease in the risk of death has been associated with increased life expectancy in persons living with HIV infection. For instance, in ART-CC [26], life expectancy [standard error (SE)] at age 20 years increased from 36.1 (SE 0.6) years to 49.4 (SE 0.5) years for individuals initiating cART as naive between 1996 and 1999 versus 2003 and 2005, and life expectancy at age 35 years increased from 25.0 (SE 0.4) years to 31.7 (SE 0.2) years. Life expectancy was strongly associated with CD4 cell count at cART initiation, with life expectancy at age 35 years being 27.0 (SE 0.4) in those initiating with a CD4 less than 100 cells/μl versus 37.2 (SE 0.3) years in those initiating with a CD4 at least 200 cells/μl. Similar results were obtained in UK [27], both for increase in life expectancy over time and for the effect of CD4 at cART initiation. In addition, they showed that although life expectancy in people treated for HIV infection has increased by over 15 years during 1996–2008, it was still about 13 years less than that of the UK population. Results were also similar in North America [28]. Recently, the UK Collaborative HIV Cohort (UK-CHIC) investigators [29▪▪] showed that successfully treated HIV-positive individuals have a normal life expectancy, whereas patients who started ART with a low CD4 cell count significantly improve their life expectancy if they have a good CD4 cell count response and undetectable viral load: after 5 years on ART, expected age at death of 35-year-old men varied from 54 (48–61) (CD4 cell count <200 cells/μl and no viral suppression) to 80 (76–83) years (CD4 cell count ≥350 cells/μl and viral suppression), compared to 78 years for men in the general UK population.

In line with those results, it was shown in ART-CC [30▪], using data from France, Italy, UK, Spain and Switzerland, that life insurance with sufficiently long duration to cover a mortgage is feasible for above 50% HIV-positive people successfully treated with ART for more than 6 months.

FUTURE RESEARCH DIRECTIONS

The hypothesis of premature aging associated with HIV infection was raised because age-related comorbidities, including non-AIDS-defining cancers, occurred at a much younger age (10–20 years younger) in patients infected with HIV compared to uninfected individuals [31]. However, as first highlighted by Shiels *et al.* [32] and as shown in Fig. 4, for France, age distributions of the HIV-infected and the general population are quite different with a much higher proportion of old people in the general population. After adjusting for the difference in age distribution between patients with AIDS and the general population, Shiels *et al.* [32] showed that the differences in median age at diagnosis of non-AIDS cancers were modest and most of them were not significant. Similar results have been found by

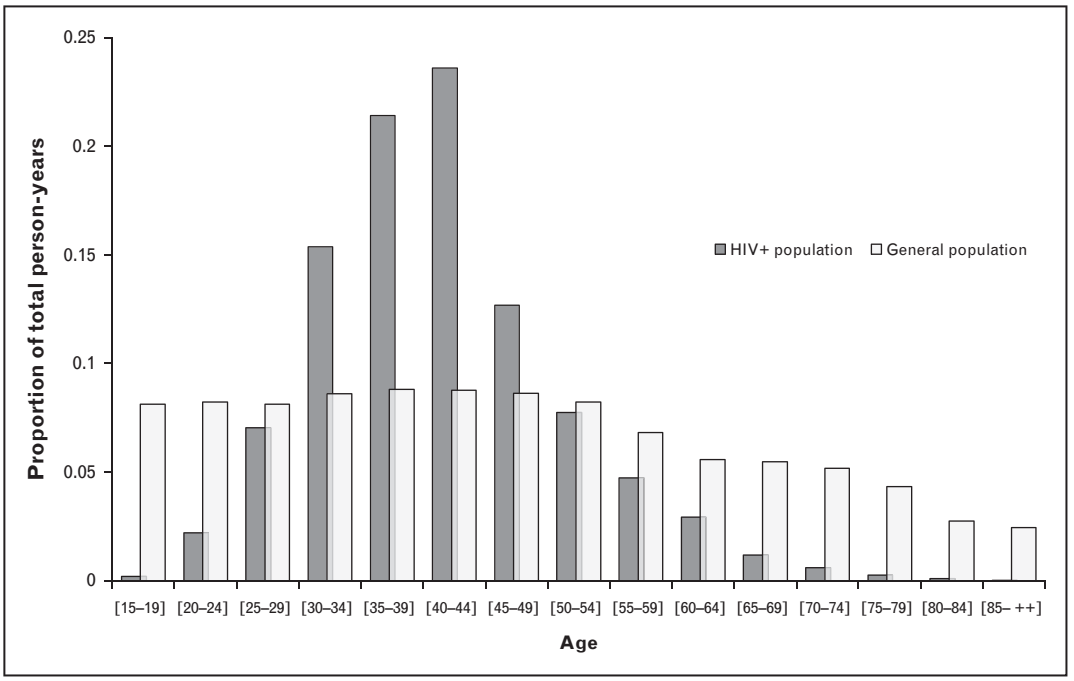

FIGURE 4. Age distributions of the HIV-infected (FHDH-ANRS CO4) and general (FRANCE) populations.

others, including for AIDS-defining cancers [33,34]. However, more data are needed for other comorbidities as the effect of HIV infection may be morbidity-dependent [35▪], and as it has been associated accelerated immune senescence [36].

As explained above, it appears that there is only a limited impact of HIV infection at the population level on the mortality risk, at least for successfully treated individuals, that is, those in which the CD4 cell count is equal to or above 500/μl; however, a higher risk of comorbidities has been widely described [37]. How can we reconcile these discrepant results? A first explanation may be the choice of the comparison population. As the general population may differ from the HIV-infected population by many factors such as sex, age group, geographic origin, race, socioeconomic status, access to care, health insurance and hepatitis coinfection, the best strategy for choosing a reference group is not straightforward as thoroughly discussed by Wong *et al.* [38]. Another likely explanation is that not all people living with HIV today are at increased risk of comorbidities and, it is therefore important to define those at risk. An important work in this area is the development of the VACS index [39]. The VACS index was developed within the Veterans Aging Cohort Study to predict the risk of death. It is based on age and HIV biomarkers (CD4 cell count and HIV-RNA) and non-HIV biomarkers (hemoglobin, a marker of anemia; fibrosis 4 score (FIB-4), a marker of liver fibrosis; estimated glomerular filtration rate (eGFR), a marker of renal function; and hepatitis C infection). It was later validated in several settings in Europe and North America [40▪,41] and shown to be sensitive to cART treatment initiation [42]. Apart from age, the most important predictor of the risk of death, this index accounts for cART success (with CD4 and HIV-RNA) as well as organ damages, which likely explain its predictive ability. We recently noticed in the FHDH that individuals diagnosed early in the epidemic, prior to 1996 when cART became available and who survived till now (32% of patients under care in France in 2012), have many traditional and HIV-associated risk factors which have been associated with a higher risk of chronic diseases. As a matter of fact, individuals who were naive of antiretroviral drugs at enrollment in FHDH and were diagnosed before 1996 are older (50 years of age or older: 44 versus 29%), more often smokers (55 versus 36%), HCV co-infected (31 versus 8%), with lower CD4 cell nadir (CD4 nadir $<200/\mu l$: 51 versus 45%), more likely to have initiated with mono or dual therapy (35 versus 7%), exposed to antiretroviral therapy for longer periods (12.3 versus 4.5 years), more likely to have received first-generation nucleoside reverse transcriptase inhibitors (ever exposed to zidovudine or stavudine or didanosine or zalcitabine 87 versus 50%) or first-generation protease inhibitors (73 versus 53%) than those who were diagnosed since 1996. In preliminary analyses, we also found that individuals with a diagnosis prior to 1996 carry a

higher risk of myocardial infarction or non-AIDS-defining cancers. Further work is needed to better characterize those at risk of the various comorbidities, and to better stratify HIV-infected individuals for whom interventions other than cART are warranted. Another important issue, even in the absence of an elevated risk of comorbidities compared with the general population, given the increasing age observed in the HIV-infected population, will be the optimal management of multimorbidity and multidrug exposures [43].

Finally, as recently illustrated in the general population [44,45▪], one may question the use of the proportion of individuals older than a given age (50 years of age in most of the published HIV literature!) to characterize aging in the HIV-infected population. Aging indicators better accounting for the increase in life expectancy as well as the extra burden of chronic diseases, if any, are urgently needed to plan the future needs in care for HIV infected individuals.

CONCLUSION

In high-incomes countries, the HIV infected population is aging because of an increase in age at infection, a higher risk of being diagnosed late and improved survival. In fact, both the risk of AIDS-defining and non-AIDS-defining death rates have decreased over the cART era. Although the risk of many chronic diseases, such as cardiovascular diseases, non-AIDS-defining infectious and noninfectious cancers, osteoporosis, liver disease, renal disease, and possibly neurocognitive decline, are higher in HIV-infected patients compared to the general population, it appears that the risk of death is no longer elevated relative to the risk in the general population for many non-IDU HIV-infected individuals with restored CD4 cell count on cART. It is therefore critical to define those HIV-infected individuals whose risk is elevated. Even in the absence of an elevated risk, aging of the HIV-infected population implies an increasing burden of multimorbidity and polypharmacy over time, whose management and resources in healthcare services need to be optimized.

Acknowledgements

None.

Conflicts of interest

Dominique Costagliola has received travel grants, consultancy fees, honoraria and study grants from various pharmaceutical companies including Bristol-Myers-Squibb, Gilead Sciences, Janssen-Cilag, Merck-Sharp & Dohme-Chibret, and ViiV Healthcare.

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