Epidemiology of ageing with HIV: what can we learn from cohorts?

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Abstract

The last decade has seen a dramatic change in the demographic structure of the population of people living with HIV (PLWH). The majority of PLWH who start treatment with combination antiretroviral therapy now have good virological and immunological responses and this has resulted in improvements in life expectancy. In addition, there have also been continued new HIV diagnoses (and new HIV infections) in those aged >50 years. The average age of those attending HIV clinics has therefore increased, with this trend expected to continue into the future. As the cohort of PLWH has aged, so the spectrum and burden of age-associated non-communicable comorbidities (AANCCs) in the cohort has increased. PLWH are likely, therefore, to have increased healthcare needs for the foreseeable future. Whilst it appears that the average age at diagnosis of several AANCC is lower in PLWH, current evidence remains insufficient to demonstrate that HIV infection leads to either accelerated or accentuated aging. The results from several well-designed longitudinal cohorts, with appropriately matched control groups, will provide more robust evidence to confirm a potential impact of HIV on the incidence of these AANCC. However, regardless of the impact of HIV itself, the role of other, non-HIV factors, is becoming increasingly important, with coinfection with other viral infections and lifestyle factors playing an increasing role in the development of many AANCC. It is likely that attempts to reduce smoking prevalence and obesity may be associated with important reductions in the incidence of some of these events in the future.

Introduction

The last decade has seen a dramatic change in the demographic structure of the population of people living with HIV (PLWH) with most HIV clinics now caring for an increasing number of people aged ≥50 years. These people are likely to have increased healthcare needs in the coming years [1]. In this article, we review some of the literature about the changing epidemiology of ageing with HIV, with a particular focus on the information that has been provided by cohort studies.

What is a cohort study?

Cohort studies follow groups of individuals over time, generally with the aim of describing the incidence of some event and/or identifying prognostic markers for this event. Whilst the observational nature of the study design means that it is impossible to eliminate the potential for confounding to introduce bias, the longitudinal and prospective follow-up of study participants in a cohort study does allow the time sequence of events leading up to the outcome to be assessed, and thus investigators are often able to make strong inferences about the potential causal nature of any associations that are seen. Cohort studies provide an ideal infrastructure for the study of ageing in PLWH and it is not surprising, therefore, the many cohort investigators have looked to their cohorts for data that might support an assessment of the future healthcare needs of PLWH.

Why is the age structure of PLWH increasing?

It is now accepted that the majority of PLWH who start treatment with combination antiretroviral therapy (cART) will have a rapid virological response and a good immunological recovery on treatment. This has resulted in dramatic improvements in life expectancy in PLWH in many settings. Using data from the UK Collaborative HIV Cohort (UK CHIC) Study, May and colleagues reported that life expectancy of PLWH at age 20 had increased from 30.0 to 45.8 years from 1996-9 to 2006-8 [2]. However, despite this increase, overall life expectancy was only 39.5 for men and 50.2 years for women compared with 57.8 and 61.6 years for men and women in the general population (1996-2006). Thus, at the time of the study, life expectancy remained about 13 years less than that of the general UK population. Using data from the Danish HIV Cohort Study, Legarth reported that median survival time from age 50 years among PLWH had increased from 11.8 years during 1996-1999 to 22.8 years from 2006-2014 [3]. However, when compared to an individually-matched cohort from the background population, mortality rates remained substantially higher (from 3.8 times higher in those aged 50-55 years to 1.6 times higher in those aged 75-80 years). Among a subset of the cohort of 517 well-treated PLWH without AIDS or existing comorbidities, median survival time from age 50 years was 25.6 years compared to 34.2 years in the matched general population sample. In a second study from the Danish HIV Cohort, Rasmussen [4] reported that the proportion of PLWH aged >50 years increased from 13% in 1995 to 43% in 2014. With the exception of non-virus/smoking associated cancers, PLWH had a higher excess and relative risk of all age-related diseases than did the controls. Similar trends have been reported from the United States and Canada [5], where life expectancy at age 20 increased from 36.1 to 51.4 years from 2000-2002 to 2006-2007. Worldwide, whilst estimated life expectancy has improved in recent years, PLWH continue to have an estimated life expectancy at age 20 years that is 10.9-39.7% lower than that of the general population, depending on the geographic setting [6].

In an updated analysis from the UK CHIC study [7], life expectancy among PLWH receiving cART was found to depend heavily on the attained CD4 count and viral load; after 5 years on ART, the expected age at death of a 35-year-old man varied from 54 years (if the man's CD4 cell count was <200 cells/mm^3 and he had no viral suppression) to 80 years (if his CD4 cell count was ≥350 cells/mm^3 and he had viral suppression). Importantly, life expectancy in men and women with good CD4 and viral load responses appeared to be at least as good as, if not better than, that in the general population. The possibility of improved life expectancy in some subgroups had previously been reported by the COHERE collaboration [8], a large European collaboration of cohort studies. In this study, mortality rates among those on cART with a CD4 count ≥500 cells/mm^3 were similar to those of the general population in non-injection drug using men (standardised mortality ratio when compared to the general population 0.9 [95% confidence interval 0.7-1.3]) and, after 3 years of cART, in women (1.1 [0.7-1.7]).

In addition to the increased life expectancy of PLWH, there have also been continued new HIV diagnoses (and new HIV infections) in those aged >50 years. Data from Public Health England show that the proportion of people newly diagnosed with HIV who were over the age of 50 had increased from 9.2% in 2005 to 18.6% in 2014 [9]. Among the 733 adults known to be newly infected in 2014 (as determined by the Recent Infection Testing Algorithm), 9.7% were aged 50 or older [10]. The impact of these changes in life expectancy and patterns of new diagnoses has been dramatic. Within Europe, the proportion of new HIV diagnoses among individuals aged 50 or over has increased from 7.4% in 2005 to 12.0% in 2014 [11]. Anecdotally, many HIV clinics have reported that the average age of those attending their clinics has increased, with the proportion of attendees over the age of 50 increasing dramatically (see, for example, Figure 1, which shows the changing age distribution of participants in the Dutch national ATHENA study over time [12]). Globally, the estimated number of PLWH who are thought to be aged over 50 years has increased from 650,000 in 1990 to 5,800,800 in 2015 [13]. But these increases in age are also expected to continue into the future: using information from the ATHENA study, Smit [14] constructed an individual-based model of the ageing HIV-positive population which predicted that the median age of patients receiving treatment for HIV will increase in the Netherlands from 43.9 years in 2010 to 56.6 years in 2030, with the proportion of patients aged >50 years predicted to increase from 28% to 73% over the same period.

What are the major consequences of an ageing clinic population?

As the cohort of PLWH has aged, and the incidence of AIDS-related conditions has reduced with effective cART, so the spectrum and burden of comorbidities in the cohort has increased. This has been most noticeable when considering patterns of mortality. When deaths do occur, these now tend to be in older people and the causes of death are different to those previously reported. In the Swiss HIV Cohort study [15], AIDS-related mortality peaked in 1992 and decreased to a low level in 2006. Compared to deceased persons in 2005, those who died only 4 years later in 2009 tended to be older (49 vs. 45 years at death), with a higher CD4 count (321 vs. 257 cells/mm^3), less likely to be antiretroviral therapy naïve (5% vs. 13%) and less likely to have died of AIDS-related causes (9% vs. 23%); 84% of all deaths occurring between 2005-2009 were due to non-AIDS-related causes. In France [16], Morlat reported a drop in the proportion of deaths among PLWH that were due to AIDS-related causes, with an increase in the proportion of deaths from non-AIDS-defining malignancies and cardiovascular disease (CVD) compared to earlier years. Similar findings were reported from the

large, multinational Data Collection on Adverse Effects of anti-HIV Drugs (D:A:D) study [17], with a reduction over time in the proportion of deaths due to AIDS-related causes being mirrored by an increase in the proportion of deaths that were due to cancers. The lack of increase in the proportion of deaths that were due to CVD in this study was likely due to improvements in interventions to prevent or treat CVD, particularly in those who had a primary myocardial infarction (MI) in whom survival had improved [18].

There has also been an increase in the number of PLWH who are also living with co-morbidities. Among participants in the Dutch AGEhIV Cohort study, HIV-positive participants had a mean of 1.3 age-associated non-communicable comorbidities (AANCC) in comparison to only 1 in demographically matched HIV-negative controls [19]. Hypertension, myocardial infarction (MI), peripheral arterial disease, and impaired renal function were all significantly more prevalent among the HIV-positive participants in the study. Notably, the co-morbidity profile of HIV-positive participants in this cohort, more closely matched that of an HIV-negative control that was 5-10 years older. Similar associations have been reported from other European settings [20]. With the continued increase in the age distribution of PLWH, the prevalence of co-morbidities is expected to increase, with Smit [14] predicting that by 2030, 84% of PLWH will have at least one AANCC (an increase from 28% in 2010), with 28% of PLWH expected to have three or more such AANCC. As a consequence, it is estimated that 54% of PLWH will be prescribed co-medications in 2030 compared with 13% in 2010, with 20% taking three or more co-medications. The implications of this for clinic costs have been studied in one cohort in Canada [21]; in this cohort, the proportion of older patients increased from 9.6% to 25.4% from 1999 to 2010. Over this time, older patients incurred higher costs for all aspects of HIV care such that by 2010, the proportion of clinic costs incurred by older patients had increased from 25% to 31%. More expensive ART as a consequence of more complex regimens, more comorbid interactions and greater adherence accounted for most of the cost difference.

Of the AANCC that have been described, CVD and cancers are arguably the most commonly studied. CVD is of particular concern in PLWH given the documented associations with some antiretroviral drugs as well as the high, and increasing, prevalence of known risk factors for CVD in the HIV-positive population [22]. The prevalence of dyslipidaemia and hypertension are increasing in most cohort populations, largely as a result of the ageing population although ART-associated effects on lipids and blood pressure and immunosuppression/exposure to HIV viraemia may also contribute [23-25]. The jury is still out on whether these key risk factors for CVD have the same impact on subsequent MI rates as in the general population. In the Veterans Aging Cohort Study Virtual Cohort [26], hazard ratios associated with various degrees of hypertension (compared to those with normal blood pressure levels) appeared to be greater in those with HIV than in HIV-uninfected controls, suggesting that the combination of HIV and hypertension may confer a greater risk of MI than that conferred by hypertension alone. Among participants in the Swiss HIV Cohort Study [27], insufficient control of hypertension was associated with increased risk of cardiovascular events, indicating the need for improved management of hypertension in PLWH.

The literature around the cancer field remains somewhat inconsistent. In primarily black-African clinic cohorts in Maryland, there was a rapid increase in the incidence of new cancers, which was driven largely by an increase in the incidence of non-AIDS-defining cancers, with the incidence of AIDS-defining cancers remaining relatively stable [28]. In contrast, an early meta-analysis conducted

by Shiels [29] showed that, compared to the general population, there had been an increased rate of many non-AIDS defining cancers, notably anal cancer, Hodgkin's lymphoma, liver, stomach and lung cancers, in both the cART and non-cART eras. Interestingly there was a reduced risk of both prostate and breast cancers in those with HIV, possibly reflecting more close monitoring in those with HIV. In a more recent analysis from the French Hospital's Database on HIV in which the authors restricted the population to those who had been on cART with a good CD4 count response, there didn't appear to be any increased risk of lung cancer compared to expected rates from the general population, but rates of both Hodgkin's lymphoma and liver cancer remained elevated [30]. An updated analysis of the Veterans Aging Cohort Study reported that whilst the overall all-cancer crude incidence rate had increased between 1997-2000 and 2009-2012, once rates were standardized for age changes, there were significant declines in PLWH in the rates of all cancer, AIDS-defining cancers, non-AIDS-defining cancers, and non-virus-related non-AIDS-defining cancers [31].

Can cohorts help to differentiate between models of accelerated and accentuated ageing

The observation that many AANCC and deaths from non-AIDS causes tend to occur at an earlier age in PLWH than in the general population, has led some to propose that HIV infection is able to lead to either accelerated or accentuated ageing. *Accelerated ageing* refers to a situation where, at the time of HIV infection, the risk of AANCC associated with each additional year of age increases at a faster rate relative to the age-related changes that would be expected in the general population (Figure 2b). In contrast, *accentuated ageing* refers to the situation where there is a one-off increase in the risk of AANCC at the time of HIV infection, but where subsequent year-on-year increases in the risk of the AANCC are the same as those seen in the general population (Figure 2c). A combination of accelerated and accentuated ageing would also be possible (Figure 2d). Any of these situations would lead to an earlier average age at diagnosis of the AANCC in PLWH. Whilst cross-sectional studies can suggest the possibility of accelerated or accentuated ageing, only cohort studies which follow people over time as they age are truly able to differentiate between the two.

However, a younger age at diagnosis of an AANCC is not sufficient evidence that HIV infection is leading to either accelerated or accentuated aging in a cohort, as age at diagnosis will also reflect the underlying age distribution of the cohort as a whole. Analyses of age at the time of an event, such as an AANCC, are conditional on the fact that an individual has experienced the event. In a cohort that has a young average age (as is typical in most HIV cohorts), those who experience AANCCs will, by the very demographic nature of the cohort, be younger (as there will be very few older individuals in the cohort who can experience an AANCC). Thus, the average age at the time of the AANCC will reflect the age make-up of the cohort. In contrast, the general population is likely to include many older individuals who may also experience the AANCC, leading to a much older average age at the time of the event. Figure 3a shows a hypothetical general population cohort in which the average at diagnosis of an AANCC is 67.5 years. In Figure 3b, the cohort is restricted so that the underlying age distribution of participants is more typical of an HIV cohort – in this restricted cohort, the median age at diagnosis of an AANCC is 10 years younger (57.5 years) simply because there are fewer older individuals in the cohort. Thus, the finding that there is a younger age at the time of the event in an HIV cohort does not provide any evidence that HIV has, in any way, hastened the onset of that event. This is an extreme form of confounding, where the characteristics of the HIV cohort are different to those of the general population. To address this bias, it would be necessary to consider

either the absolute *risk* of the AANCC at a given age, or to restrict the general population cohort in some way such that it has the same age distribution.

But age is only one factor that may confound comparisons of the risk of AANCC between cohorts of PLWH and the general population. Populations may also differ with respect to gender and ethnic origin, both factors that may be associated with the incidence of comorbidities and mortality. Furthermore, PLWH are known to have an increased risk of several behavioural, lifestyle and viral factors (e.g. smoking, recreational drug use, sexually transmitted infections, and viral coinfections), all of which place the group at higher risk of many AANCC. Without adequate control of these confounders, comparisons between outcomes in PLWH and the general population may be seriously biased. Unfortunately, population-based surveillance datasets (which are often used for such comparisons) rarely collect information on these factors.

Several studies have, however, started to address this through the recruitment of appropriately matched control subjects and/or restriction of the comparison group to those with similar characteristics. The Co-morbidity in relation to AIDS (COBRA) study has recruited a cohort of 134 PLWH over the age of 45 who were receiving cART and had viral suppression, along with an appropriately matched HIV-negative control group. Using data from a sub-set of this cohort, Kootstra [32] demonstrated that whereas many markers of T-cell activation, exhaustion and senescence exhibited large differences when compared to a group of age-matched blood-bank donors (a 'typical' control group for this type of study), differences in the markers between the PLWH and the matched controls, were much reduced.

The Veterans Aging Cohort Study Virtual Cohort makes use of the fact that the HIV-negative Veterans are not only well-matched for age, ethnicity and clinical site, but are also drawn from the same underlying population. In analyses from the study [33], mean age at diagnosis of MI and non-AIDS-defining cancer did not differ by HIV status, whereas HIV-positive participants were diagnosed with end-stage renal disease at an average age that was 5.5 months younger than uninfected adults.

To investigate the potential role of ageing on the risk of MI in the D:A:D study, Petoumenos compared the association that was seen in the study between age and the risk of MI to that reported by several published CVD risk scores (Framingham, CUORE and ASSIGN) from the general population [34]. After recalibration of the scores to reflect the higher risk of CVD in PLWH, the shape of the association with age did not appear to be appreciably different in the D:A:D risk equation, more consistent with accentuated rather than accelerated ageing.

What is the role of other, non-HIV, factors?

As the cohort of PLWH ages, the role of other, non-HIV factors, is becoming increasingly important. Of the deaths that occurred in the Danish HIV cohort, only 55% could be attributable to HIV, with 31.5% of deaths being attributable to hepatitis C virus (HCV) or other comorbidities, and 13.6% being attributable to other causes [35]. Although it is likely that the increased use of direct acting antivirals will reduce the impact of HCV infection in the coming years, little is being done to reduce the impact of smoking. Using data from the ART Cohort Collaboration, Helleberg reported that smoking claimed more life-years than HIV-related factors [36] with Rasmussen estimating that smoking cessation could potentially prevent more than 40% of MIs among PLWH [37]. Whilst there is some evidence to support a greater impact of smoking on both CVD [34] and cancer risk [38] than in

the general population, evidence from the Age$_h$IV study does not support a differential effect of smoking in PLWH on markers of inflammation, immune activation or coagulation [39]. Nevertheless, using the D:A:D risk equation, Petoumenos suggested that smoking cessation would be associated with a greater reduction in CVD risk than could be achieved by reductions in either total cholesterol or systolic blood pressure [40].

Obesity has traditionally not been a major concern in PLWH, but now that people are living for longer with HIV, obesity rates are increasing. There are complex associations with BMI [41] with non-linear associations between BMI at ART initiation and the risk of subsequent serious non-AIDS conditions, including cardiovascular disease, hepatic disease, cancer, renal disease and death, with the risk of most of these events being highest in those whose pre-ART BMI puts them in the underweight to normal categories. In addition to pre-ART BMI, changes in BMI once individuals start cART are also important (with the implications of these changes being dependent on what the individuals pre-ART BMI was) [42].

In addition to smoking and obesity, several other lifestyle and socio-economic factors are also likely to contribute to the development of AANCC and to reductions in life expectancy in PLWH. For example, the large multinational COHERE study demonstrated increased mortality rates among migrant women from the Caribbean and migrant heterosexual men from Latin America when compared to native populations in western European cohorts [43] and also reported delayed HIV diagnosis and initiation of ART in those with lower educational level [44]. The potential impact of excessive alcohol use and illicit drug use on survival has been summarised in a recent review by Petoumenos [45]. These studies support the need for improvements in the collection of data on socio-economic factors in many cohort studies, as well as for consideration of these factors when identifying appropriate HIV-negative control groups for comparative studies.

Conclusions/summary

Most PLWH will now experience a good virological and immunological response to cART and, as such, they are far less likely to develop AIDS or die from AIDS-related causes. But other co-morbidities are common and the risk of some of these may be increased by HIV and/or its treatment. It is likely that attempts to reduce smoking prevalence and obesity may be associated with important reductions in the incidence of some of these events in the future. Whilst it is tempting to speculate that current recommendations for earlier cART initiation may also lead to a reduction in the incidence of many of these AANCC, the lack of robust evidence demonstrating causal associations between these co-morbidities and HIV infection means that the impact of earlier cART on these events is difficult to predict and may only become apparent in the years to come.

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Figure headings

Figure 1: Increasing age of the HIV-positive participants in the Dutch ATHENA observational HIV cohort study over calendar time ([10], reprinted with permission).

Figure 2: Schematic showing possible associations between increased age and the prevalence of an AANCC in the situations where there is a) no impact of HIV on aging, b) accelerated aging by HIV, b) accentuated aging by HIV, and d) accelerated and accentuated aging by HIV.

Figure 3: Median age at diagnosis of AANCC calculated in a) a typical general population cohort with an unrestricted age range from 20 to 80 years, and b) a typical HIV cohort with a younger age distribution. Red figures indicate individuals in the cohort who have the AANCC at their age of diagnosis. Blue figures indicate individuals in the cohort who remain free of the AANCC.

Figure 1

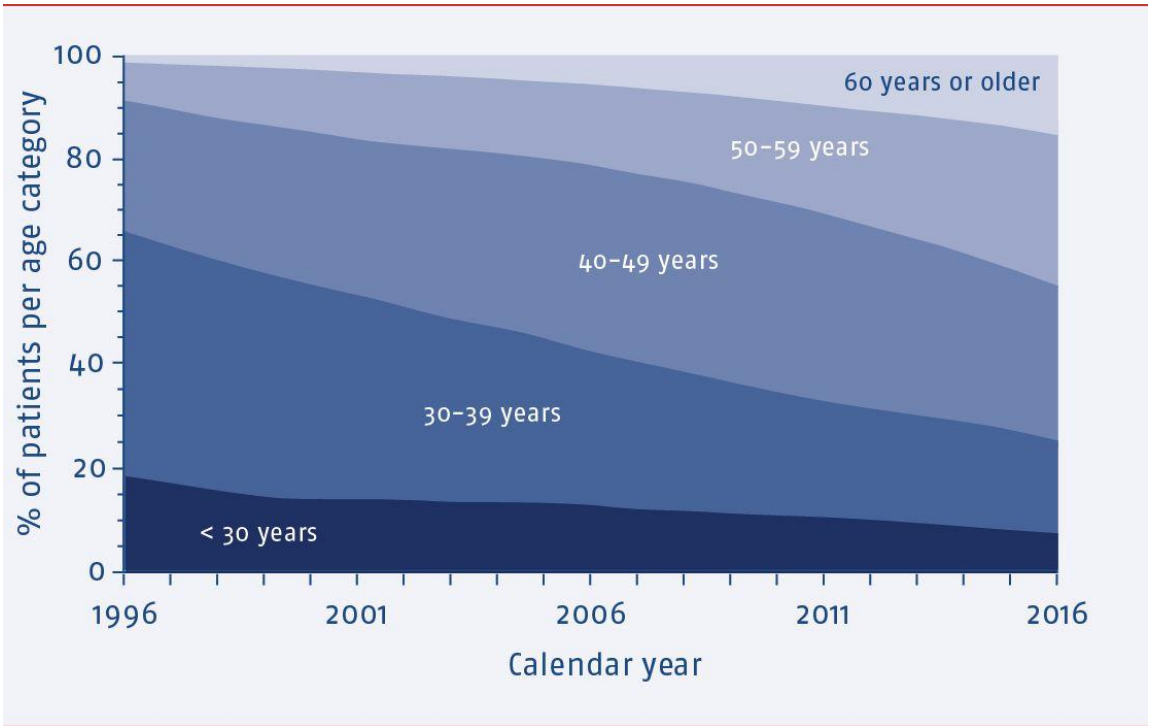

100
80
60
40
20
0
% of patients per age category
60 years or older
50-59 years
40-49 years
30-39 years
< 30 years
1996
2001
2006
2011
2016
Calendar year

Figure 2

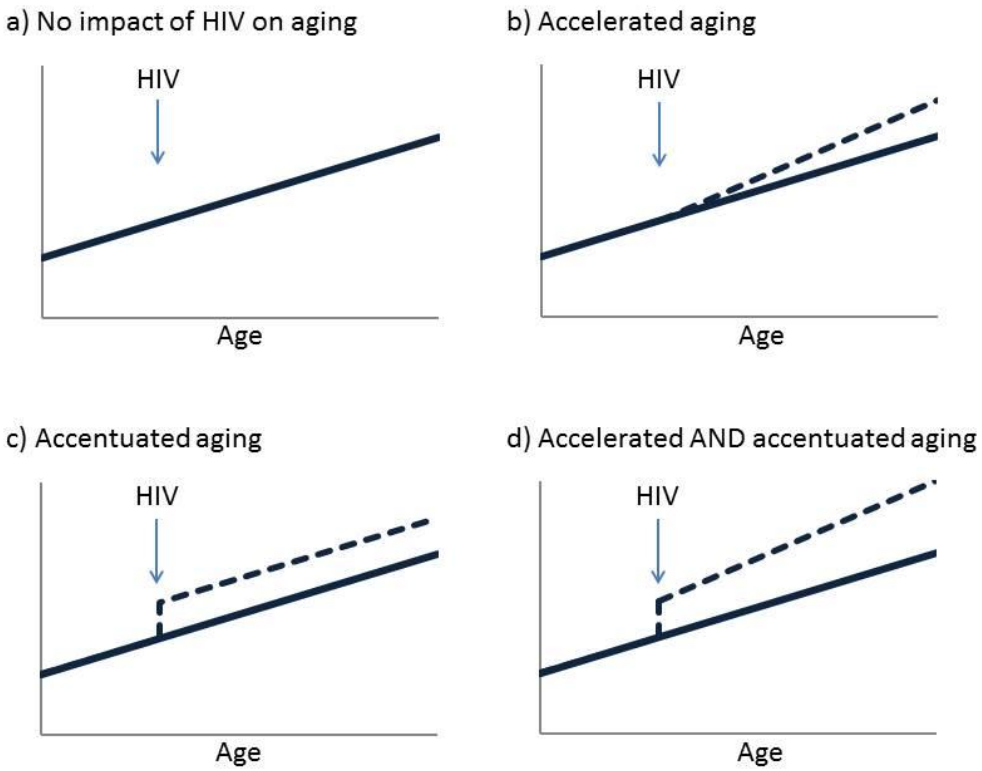
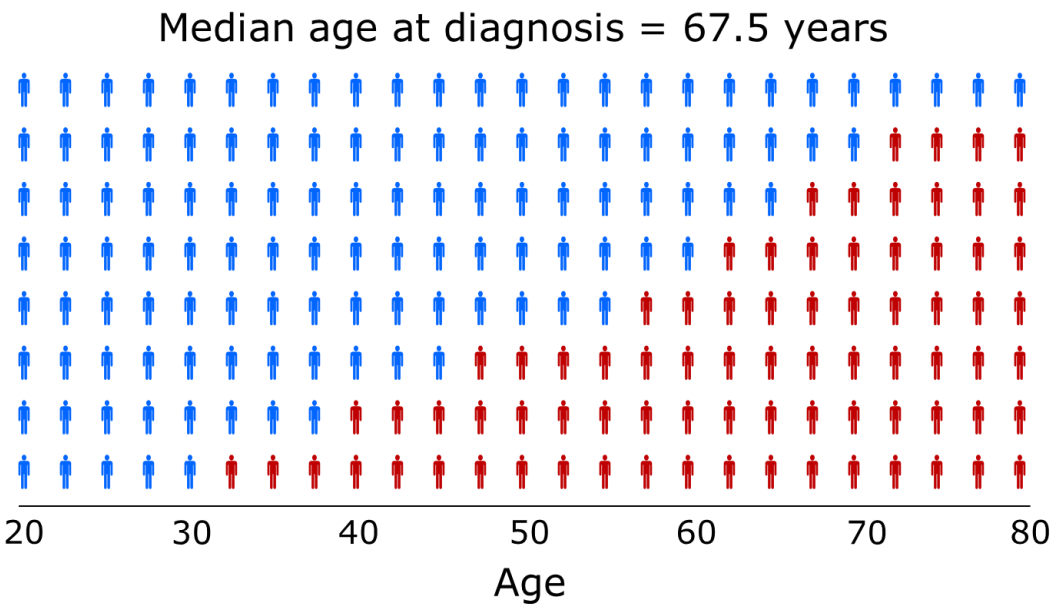

a) No impact of HIV on aging
HIV
Age
b) Accelerated aging
HIV
Age
c) Accentuated aging
HIV
Age
d) Accelerated AND accentuated aging
HIV
Age

Figure 3

a) Typical general population cohort with unrestricted age range from 20 to 80 years



b) Typical HIV cohort with younger age distribution