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Increased risk of cardiovascular disease (CVD) with age in HIV-positive men: a comparison of the D:A:D CVD risk equation and general population CVD risk equations*

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Objectives

The aim of the study was to statistically model the relative increased risk of cardiovascular disease (CVD) per year older in Data collection on Adverse events of anti-HIV Drugs (D:A:D) and to compare this with the relative increased risk of CVD per year older in general population risk equations.

Methods

We analysed three endpoints: myocardial infarction (MI), coronary heart disease (CHD: MI or invasive coronary procedure) and CVD (CHD or stroke). We fitted a number of parametric age effects, adjusting for known risk factors and antiretroviral therapy (ART) use. The best-fitting age effect was determined using the Akaike information criterion. We compared the ageing effect from D:A:D with that from the general population risk equations: the Framingham Heart Study, CUORE and ASSIGN risk scores.

Results

A total of 24 323 men were included in analyses. Crude MI, CHD and CVD event rates per 1000 person-years increased from 2.29, 3.11 and 3.65 in those aged 40–45 years to 6.53, 11.91 and 15.89 in those aged 60–65 years, respectively. The best-fitting models included inverse age for MI and age + age² for CHD and CVD. In D:A:D there was a slowly accelerating increased risk of CHD and CVD per year older, which appeared to be only modest yet was consistently raised compared with the risk in the general population. The relative risk of MI with age was not different between D:A:D and the general population.

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[†]See Appendix S1.

Conclusions

We found only limited evidence of accelerating increased risk of CVD with age in D:A:D compared with the general population. The absolute risk of CVD associated with HIV infection remains uncertain.

Keywords: ageing, cardiovascular disease, HIV.

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Introduction

Successfully treated HIV-positive people remain at increased risk of a number of age-related non-AIDS morbidities, such as cardiovascular disease (CVD), cancer, and liver and kidney diseases [1]. A number of studies suggest that these complications occur at a higher rate among HIV-positive patients compared with general populations [2,3]. HIV-positive persons have also been reported to experience greater multimorbidity than general populations [4]. Careful interpretation of these studies is required as the comparisons are often with unmatched HIV-negative populations, or population based, or retrospective in nature, probably resulting in unmeasured confounding.

CVD events in HIV-positive patients have been reported to occur at higher rates compared with HIV-negative or general populations of similar age [4–7]. Triant *et al.* demonstrated not only a consistently higher rate of myocardial infarction (MI) for all age groups in HIV-positive compared with HIV-negative persons, but that the difference in rates between HIV-positive and HIV-negative persons also increased with age [5]. Currier *et al.* demonstrated increased rates of CVD in HIV-positive compared with HIV-negative persons in the younger age groups of 18–34 years in men and up to 44 years in women. Yet, by age ≥ 65 years, rates were higher in HIV-negative people, probably as a result of HIV-positive individuals dying earlier [8]. Rates of MI, for instance, have been reported in various studies to range from 1.11 to 3.5 per 1000 person-years among HIV-positive patients [5,7,9,10]. However, the risk of CVD in HIV-positive people is influenced not only by the traditional cardiovascular risk factors, which are highly prevalent in this now ageing population, genetics and family history, but also by the effect of antiretroviral therapy (ART), and the effect of HIV itself. It is well known that the risk of CVD increases with age, yet it remains unclear whether this age-related increase is more rapid in HIV-positive people than in the general HIV-negative population. Results to date have primarily relied on comparisons with general populations. Some comparisons matched for age and sex, but not many for the remaining risks factors, in particular smoking.

We hypothesized that, if the risk of CVD increases faster with age in HIV-positive people, then we would expect the relative increased risk of CVD events per year older to be higher in Data collection on Adverse events of anti-HIV drugs (D:A:D) than in the general population. The objective of this study therefore was to statistically model in detail the relative increased risk of CVD per year older in D:A:D and to compare this with the relative increased risk of CVD per year older in the general population risk equations.

Methods

The D:A:D cohort has been described in detail previously [9]. In brief, the D:A:D study is a prospective, multi-cohort observational collaborative study, including 11 previously established cohorts of 49 734 HIV-positive patients followed at 212 clinics in Europe, Argentina, Australia and the USA. The primary objective of the study was to investigate the possible association between combination antiretroviral therapy (cART) and the risk of MI. Patients were under active follow-up in the individual cohorts, and were included in D:A:D irrespective of whether or for how long they had been receiving ART. Data were collected as part of routine clinical care and included demographic and other prospectively collected data, such as age, sex, body mass index (BMI), hepatitis B and C status, history of CVD, diabetes mellitus (DM), family history of CVD, cigarette smoking, DM therapy, lipid-lowering and antihypertensive therapy, and serum lipid levels. HIV-related core clinical data collected include mode of HIV transmission, ART received, CD4 count, viral load and all clinical AIDS diagnoses.

Inclusion criteria

In this analysis we included men without prior CVD and with conventional CVD risk factors available [covariates identified in the D:A:D CVD risk equation: age, gender, family history of CVD, smoking, cumulative (per year) lopinavir and indinavir use, recent (within 6 months) abacavir use, diabetes, cholesterol, high-density lipoprotein (HDL) cholesterol and systolic blood pressure]. Similar inclusion criteria were used to develop the D:A:D CVD risk equation [11].

Analyses were limited to men because the vast majority of CVD endpoints in D:A:D are in men (> 90%), meaning that we were able to estimate the ageing effect in men most accurately. We would have limited power to accurately estimate a different ageing effect in women.

We analysed three endpoints: MI, coronary heart disease (CHD: MI or invasive coronary procedure or CVD death) and CVD (CHD or stroke). These events also included death from these causes. Baseline was the time at which all risk factors were first present. Follow-up ended at a CVD event, the date of loss to follow-up (defined as the date on which the patient last attended for care plus 6 months for patients whose last clinic visit was at least 1 year prior to data close-out) or 1 February 2011, whichever occurred first.

Statistical methods

Determination of the best-fitting age effect

We refitted a number of parametric age effects to the risk of CVD, adjusting for the known risk factors and ART use in the D:A:D CVD prediction equation [8]. The age effects considered were: linear age (as originally fitted in the D:A:D CVD risk equation), age^2 , age^3 , $\text{age}^{0.5}$, $\text{age} + \text{age}^2$, inverse age, square-root of age, natural logarithm of age ($\log \text{age}$), $(\log \text{age})^2$, $(\log \text{age})^3$, $(\log \text{age})^{0.5}$, and $\log \text{age} + (\log \text{age})^2$. Poisson regression analyses were used to fit each of the age effects, and the best-fitting age effect was determined using the Akaike information criterion (AIC). The AIC is a measure of the quality of the model selection; the lower the AIC the better the model fit.

Sensitivity analyses

We conducted several sensitivity analyses to assess the consistency of the best-fitting age effect for each of the three endpoints: (1) adjusting for calendar year; (2) adjusting for participating cohort; (3) adjusting for time since entry into D:A:D; (4) restricting the analysis to age < 65 years, and (5) including men with missing risk factors.

Comparison with general risk equations

We compared the best-fitting D:A:D age effects with general population CVD risk equations that included broadly similar endpoints, gave age parametric forms for men, followed patients prospectively, and had active ascertainment for these endpoints. These were the Framingham Heart Study risk scores by Anderson *et al.* (FHS_A) [12], Wilson *et al.* (FHS_W) [13] and D'Agostino *et al.* (FHS_D) [14], including more than 5500 men aged between 30 and 74 years; the CUORE risk score [15], derived from a study including a combination of 11 Italian cohorts with more than 6800 men aged between 35 and 69 years; and the ASSIGN risk score

[16], derived from the Scottish Heart Health Extended cohort study, which includes several cohorts with more than 6000 men aged between 30 and 74 years. Other general equations initially considered but subsequently excluded were the Prospective Cardiovascular Munster study (PROCAM) [17] and QRISK (derived from the QResearch database) [18]. The decision to exclude these equations was predominately because of their follow-up procedures. In PROCAM [17], follow-up was passive, occurring every 2 years via questionnaire. If there was evidence of mortality or morbidity then hospital and attending physician records were obtained. In QRISK1 [18], follow-up was through record linkage to hospital admissions and death records.

Relative risk

As the absolute risk of CVD is known to differ between populations [19], and the absolute effect of HIV infection on CVD risk is uncertain, we compared the relative increased risk of CVD per year older in the D:A:D data with general risk equations. The D:A:D and general population models were compared by graphing relative risk increase from age 40 years to age 65 years. The general population risk equations used parametric (FHS_A) or Cox regression models (FHS_W, FHS_D, CUORE and ASSIGN) to determine the relative hazards for age. Each of the equations fitted different age effects [$\log \text{age}$ (FHS_A and FHS_D) or linear (FHS_W, CUORE and ASSIGN)]. As we did not have access to the raw data from these general population risk equations, formal statistical comparisons were not possible. However, 95% confidence intervals (CIs) for the D:A:D models were included to illustrate variability. It was not possible to obtain CIs for the general population models because the standard errors for the respective age coefficients were not reported for these equations.

Risk modification

Finally, to assess how the increasing risk of CVD with ageing in D:A:D might be reduced with changes in other modifiable risk factors, we also plotted the relative risk increases with age, by investigating individually the impact of stopping smoking, reducing cholesterol by 1 mmol/mL, or reducing systolic blood pressure by 10 mmHg, at the age of 50 years. All the remaining CVD risk factors were assumed to be equal for all ages up to age 50 years, at which time risk was modified. This approach assumes an instantaneous change in risk, although, in reality, the change in risk would be more gradual.

Results

A total of 24 323 men were included in the analyses. Table 1 presents baseline characteristics for this population.

Table 1 Patient characteristics at baseline

Number of participants	24 323
Number of MI/CHD/CVD events	474/683/884
Time at risk (person-years)	139115
Age (years) [median (IQR)]	40.68 (35.21–47.74)
cART exposure (years) [median (IQR)]	1.94 (0.01–3.87)
NRTI exposure (years) [median (IQR)]	2.58 (0.21–5.27)
NNRTI exposure (years) [median (IQR)]	0.00 (0–1.10)
PI exposure (years) [median (IQR)]	0.86 (0–3.13)
CD4 count (cells/ μ L) [median (IQR)]	440 (288–630)
Systolic blood pressure (mmHg) [median (IQR)]	120 (115–133)
Diastolic blood pressure (mmHg) [median (IQR)]	80 (70–85)
Total cholesterol (mmol/l) [median (IQR)]	4.90 (4.06–5.80)
HDL cholesterol (mmol/l) [median (IQR)]	1.09 (0.88–1.32)
Total:HDL cholesterol ratio [median (IQR)]	4.49 (3.51–5.71)
Triglycerides (mmol/l) [median (IQR)]	1.69 (1.10–2.70)
BMI (kg/m ²) [median (IQR)]	23.25 (21.37–25.39)
HIV RNA < 50 copies/mL [<i>n</i> (%)]	11 144 (46.23)
Family history of CVD [<i>n</i> (%)]	2083 (8.56)
Diabetes mellitus [<i>n</i> (%)]	815 (3.35)
Current cigarette smoker [<i>n</i> (%)]	13 134 (55.24)
Ex-smoker [<i>n</i> (%)]	4032 (17.69)
Transmission group [<i>n</i> (%)]	
Heterosexual	4996 (20.54)
Homosexual	14 525 (59.72)
Injecting drug user	3529 (14.51)
Other/unknown	1273 (5.23)
Ethnicity [<i>n</i> (%)]	
White	14 469 (59.49)
Non-white	1372 (5.65)
Unknown	8482 (34.87)

BMI, body mass index; cART, combination antiretroviral therapy; CHD, coronary heart disease; CVD, cardiovascular disease; HDL, high-density lipoprotein; IQR, interquartile range; MI, myocardial infarction; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

Median age at enrolment was 41 [interquartile range (IQR) 35–48] years, and main modes of HIV acquisition were: homosexual sex (60%), heterosexual sex (20%), and injecting drug use (15%). Among some of the general CVD risk factors, median baseline HDL cholesterol was 1.09 (IQR 0.88–1.32) mmol/L, median baseline total cholesterol was 4.90 (IQR 4.06–5.80) mmol/L, and 55% were current smokers and 18% ex-smokers. The median cART exposure was 1.94 (IQR 0–3.87) years.

Total follow-up was 139 115 person-years, including 474 MI, 683 CHD and 884 CVD incident events. Crude MI, CHD and CVD event rates per 1000 person-years increased from 2.29 (95% CI 1.80–2.88), 3.11 (95% CI 2.53–3.79) and 3.65 (95% CI 3.02–4.38) in those aged 40–45 years to 6.53 (95% CI 4.73–8.78), 11.91 (95% CI 9.41–14.86) and 15.89 (95% CI 12.95–19.26) in those aged 60–65 years, respectively.

Determining best-fitting D:A:D age effects

Table S1 reports the various age effects as fitted to the D:A:D data for each of the endpoints. The top five best-

fitting age effects were similar for all endpoints. These were inverse age (best-fitting age effect for MI), age + age² (best-fitting for CHD and CVD), log age + (log age)², (log age)^{0.5} and log age. The increase in the relative risk of events from age 40 to 65 years using the best-fitting age effects are plotted in Figure 1. This figure illustrates that the differing age effects fitted all gave similar increasing risks of events.

Figure S1 shows the relative risk increases with age for each of the five sensitivity analyses. The broad increasing risk of events with age remained consistent and similar across the sensitivity analyses, demonstrating the overall robustness of the fitted age effects. The greatest deviations seemed to be when we adjusted for calendar year, or time since cohort entry. In these analyses, the increasing relative risk with age appeared to be slightly higher.

Comparison with general population risk equations

Figure 2 compares the D:A:D relative risk increase with age with those from the general population equations. In D:A:D there was an increasing risk of CHD and CVD per year older, which was modestly raised compared with the general population-based equations for CHD and CVD. For CHD, at age 65 years, an HIV-positive person was at 5.75-fold increased risk (95% CI 4.65, 7.12) compared with age 40 years, while for the general population these relative risks were 3.34 (FHS_W), 3.79 (FHS_A) and 4.85 (CUORE). For CVD, at age 65 years the relative risk for an HIV-positive person compared with age 40 years was 5.84 (95% CI 4.85, 7.02), while in the general population the relative risks were 4.16 (ASSIGN), 4.42 (FHS_D) and 4.73 (FHS_A). Equally, the risk of MI at age 65 years relative to age 40 years was 4.00 for HIV-positive individuals in D:A:D and 4.40 for the general population (FHS_A).

Risk modification

Stopping smoking, reducing cholesterol, or reducing systolic blood pressure at age 50 years all reduced the risk of CVD (Fig. 3). If smoking is ceased at age 50 years, the risk of CVD at age 65 years relative to age 40 years can be reduced from 5.84 to 3.04. Similarly, reducing cholesterol by 1 mmol/mL from the age of 50 years reduced the relative risk at age 65 years to 4.78, and reducing systolic blood pressure by 10 mmHg reduced the relative risk to 5.20. This modelling of risk modification assumes an instantaneous change in relative risk; however, in reality we would expect the change in risk to occur more slowly. For example, the effect of smoking cessation would probably occur within 1 to 2 years.

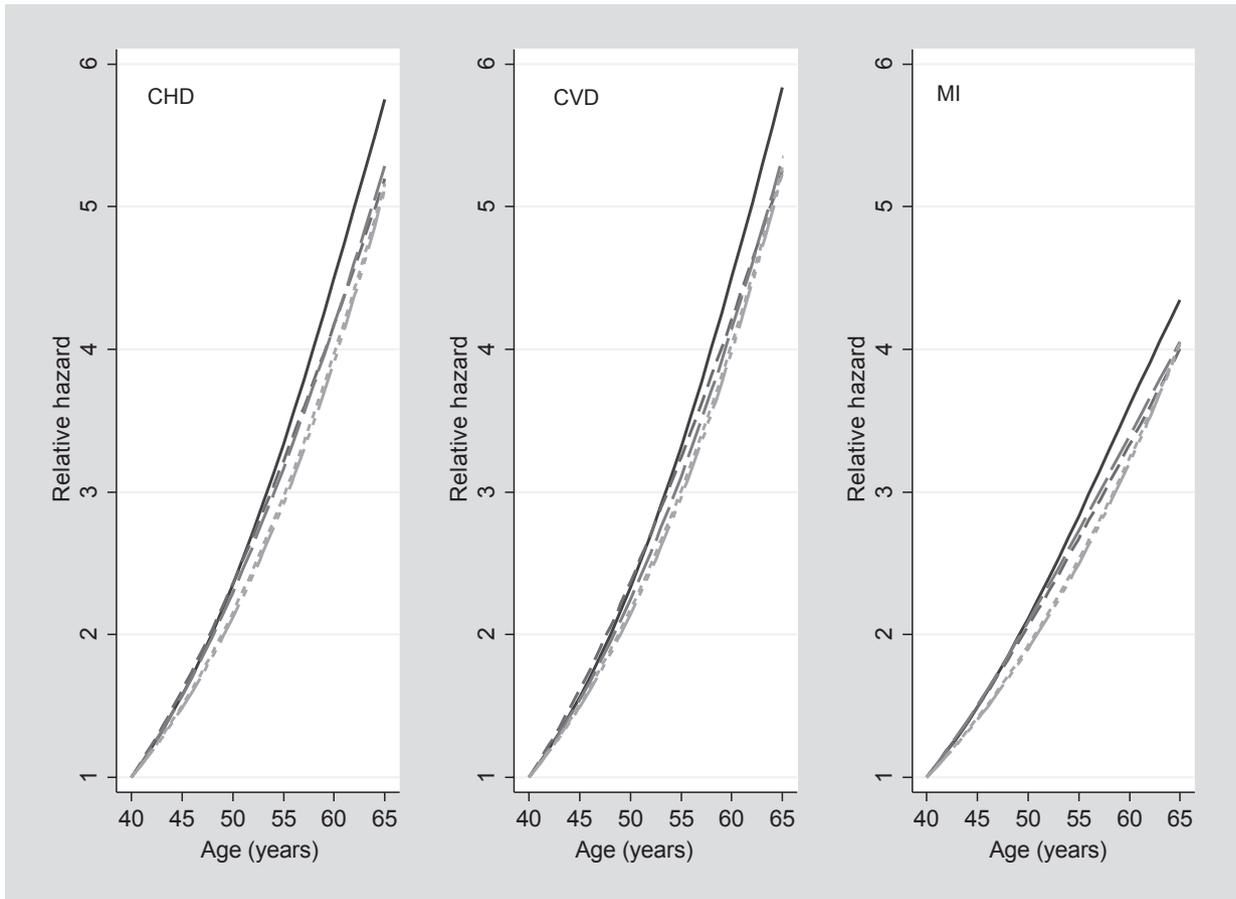


Fig. 1 Comparison of the top five best-fitting modelled age effects for coronary heart disease (CHD), cardiovascular disease (CVD) and myocardial infarction (MI). Age effects: age + (age)², continuous line; inverse age, dashed line; log(age), long-dashed–short-dashed line; log(age) + [log(age)]², long-dashed line; [log(age)]^{0.5}, short-dashed line.

Discussion

In this study, we modelled in detail the relative increased risk of MI, CHD and CVD per year older in D:A:D and compared it with the relative increased risk of these events per year older obtained using general population CVD risk equations. In our study, the risk of CVD events increased consistently with age. We observed only limited evidence of a greater increased risk with ageing in D:A:D compared with the corresponding increased risk with ageing based on general population equations of similar design for most of the general population equations for CHD and CVD, and we found no such evidence for MI. Thus, it remains difficult to conclude with any certainty that the relative risk of ageing was appreciably raised in D:A:D.

Our study compared the relative risk increase with ageing, as it is not possible to account for an absolute risk difference between HIV-positive and HIV-negative popu-

lations. A few studies have attempted to determine the impact (or contribution) that HIV infection itself has on increased risk [5,6,20]. Triant *et al.* [5], in a health care system-based cohort, found an increased relative risk of 1.75 in acute MI rates among HIV-positive people compared with HIV-negative people after adjustment for traditional risk factors. This group also found diverging rates of MI between HIV-positive and HIV-negative people with increasing age [5]. To understand how our results compare with the Triant *et al.* findings, we fitted the D:A:D MI relative risks to the estimates reported in Triant *et al.* for men, using the youngest age group as the reference category [5]. We also then applied the relative risk of MI in HIV-positive men compared with HIV-negative men reported in Triant *et al.* to the D:A:D ageing effect to illustrate how the HIV-negative population also compared. Our results show quite a good fit for both HIV-positive and HIV-negative trends (Fig. 4), suggesting that the effect

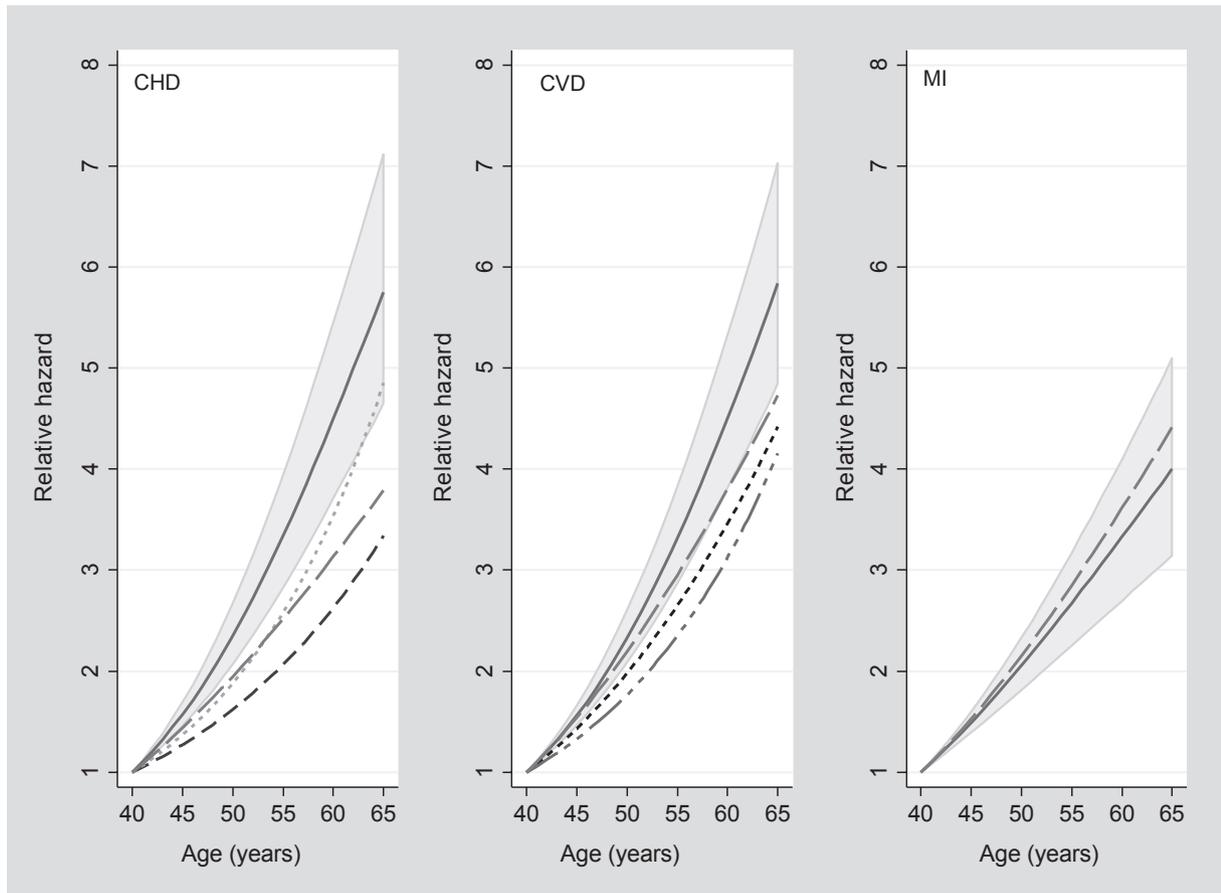


Fig. 2 Relative risk of coronary heart disease (CHD), cardiovascular disease (CVD) and myocardial infarction (MI) from age 40 years for D:A:D and respective general population equations: FHS_A (Framingham Heart Study, Anderson *et al.* [12]), FHS_W (Framingham Heart Study, Wilson *et al.* [13]), FHS_D (Framingham Heart Study, D'Agostino *et al.* [14]), CUORE and ASSIGN. Risk equations: D:A:D equation in all three panels, continuous line (95% confidence limits, blue shaded area); FHS_A, long-dashed line (all three endpoints); FHS_W, dashed line (CHD endpoint); FHS_D, short-dashed line (CVD endpoint); CUORE, very short-dashed line (CHD endpoint); ASSIGN, long-dashed–short-dashed line (CVD endpoint).

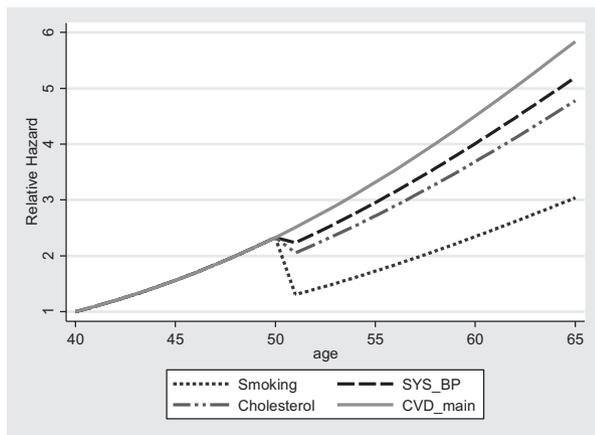


Fig. 3 Relative risk of cardiovascular disease (CVD) from age 40 years including stopping smoking, reducing cholesterol (by 1 mmol/L) or reducing systolic blood pressure (SYS_BP) (by 10 mmHg) at age 50 years.

of HIV infection on the risk of CVD is not unlike that of other risk factors, such as the effect of smoking, where the absolute CVD risk increases with age more in smokers than in nonsmokers.

One modifiable CVD risk factor for HIV-positive patients is ART. We have previously demonstrated in the D:A:D study risk equation [11] that the per year additional risk of CVD, CHD and MI among patients receiving lopinavir ranged from 8 to 12% per year, with almost a doubling in risk over 10 years. Current use of abacavir increased the risk of CVD, CHD and MI by 1.63, 1.73 and 2.03 times, respectively. We estimated the ageing effect on the risk for CVD, CHD and MI to be about a 2-fold increased risk per decade older (see Fig. 1). Hence our results suggest that reducing exposure to lopinavir by 10 years or stopping abacavir roughly corresponds to being a decade younger in terms of CVD risk.

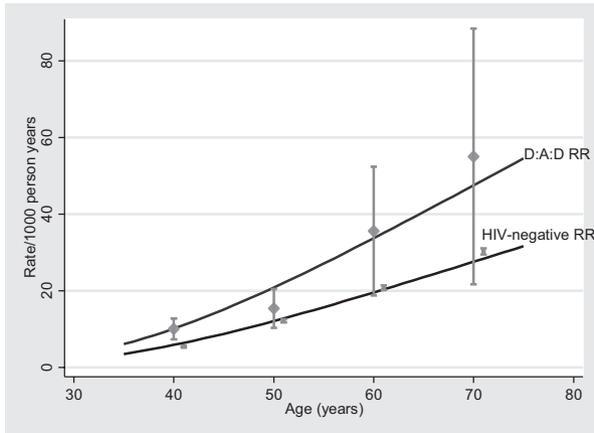


Fig. 4 Application of D:A:D relative risk of myocardial infarction (MI) to Triant *et al.* estimates of MI in HIV-positive relative to HIV-negative men. Estimates with 95% confidence bounds are MI rates reported in Triant *et al.* [5] for HIV-positive (diamond shaped point estimates) and HIV-negative men. The D:A:D MI relative risks were fitted to the estimates reported in Triant *et al.* for men, using the youngest age group as the reference category (the upper fitted line; D:A:D RR). The relative risk of MI in HIV positive men compared with HIV-negative men reported in Triant *et al.* was applied to the D:A:D ageing effect (the lower fitted line; HIV negative RR).

The AGEHIV cohort study reported that the overall prevalence of age-associated noncommunicable comorbidity (AANCC) was significantly greater in HIV-positive people compared with well-matched HIV-negative people (75% *vs.* 62%, respectively) based on self-report. After adjustment for age, gender and smoking, longer documented duration of HIV-seropositivity was associated with a significantly higher risk of an increasing number of AANCCs [odds ratio (OR) 1.7; 95% CI 1.07–1.27]. A similar burden of AANCC appeared to occur 5 years earlier in HIV-positive people compared with HIV-negative people [21]. In a cross-sectional study comparing rates of MI in HIV-positive people and the general French population, a relative risk of 1.5 was reported [20], while some others have reported similar relative rates for various CVD endpoints for HIV-positive people compared with HIV-negative populations of around 1.6–1.7 [6,7]. Taken together, these studies suggest that HIV infection increases the absolute risk of CVD by about 1.2- to 2-fold.

While the literature to date suggests that HIV infection does appear to increase the risk of CVD, most of these studies relied on insufficiently matched controls, and were mostly cross-sectional in nature. It is well known that HIV-positive people have a greater prevalence of several of the traditional CVD risk factors, in particular smoking

[22–24]. Until data from appropriately designed cohort studies are reported, the absolute risk of CVD for an HIV-positive person relative to an HIV-negative person and the impact of HIV infection itself will remain uncertain.

It is somewhat encouraging that the risk of CVD does not appear to rapidly increase with age in HIV-positive people. First, there are a number of modifiable risk factors, such as smoking, cholesterol and blood pressure, that, when treated, can quite markedly reduce an individual's CVD risk. Smoking is of particular importance in HIV-positive populations with prevalence rates consistently between 40% and 70% [22,25–27], and conferring a 2-fold or greater increased risk of CVD in HIV-positive patients [9,28]. We have also previously shown in D:A:D a decreasing risk of CVD for every additional year of having stopped smoking, similar to that seen in the general population [29]. In our current analyses where we illustrated the effect of stopping smoking and reducing cholesterol and systolic blood pressure, we showed not only a reduction in the absolute risk of CVD but also a slowing of the increase in risk with age (Fig. 4). Secondly, HIV-positive patients receiving ART are seen regularly as part of their HIV care. This provides opportunities for counselling, monitoring and intervention regarding modifiable CVD risk factors in a more complete manner than may be possible in the general population. Treatment guidelines for CVD interventions have also more recently been developed for HIV-positive patients.

Limitations

We were not able to perform formal statistical comparisons of the age effects with the general population, and have had to rely on more qualitative comparison. We were, however, able to include CIs on the D:A:D estimates, giving some idea of variability. Analysing a number of endpoints, and comparing with the available general population risk equations, also provided insight into the consistency of results.

Furthermore, lack of statistical power meant that we were unable to accurately estimate the relative risk for women. In D:A:D we have shown that the relative risk of CVD in women is approximately 0.7 to that of men [11]. This is not inconsistent with general population studies, where similar risks have been shown [14,16]. In the Framingham study [14], the age effect in women was approximately half that in men, although it was modelled separately to that in men. However, in the few studies to date that have compared HIV-positive women with HIV-negative women, not only were HIV-positive women at higher risk for CVD compared with HIV-negative women, but the relative risk was greater than that observed for HIV-positive men compared with HIV-negative men [5,20].

Finally, our models extrapolate over a 25-year period (age 40 to 65 years) and beyond based on a median follow-up of 6 years. Hence our models essentially assume that the effect of ageing is independent of the duration of infection and treatment. We have previously shown a 26% increased risk of MI per year of exposure for up to 6 years [9]. Given that effective combination therapy for HIV has only been available for some 15 years, this is an unverifiable assumption. A small proportion (5%) of patients in D:A:D have a total duration of infection of over 20 years at the end of follow-up.

In conclusion, we found only limited evidence of the risk of CVD with age in D:A:D increasing more rapidly than in the general population. HIV-positive patients in clinical care are routinely assessed, which may allow clinicians to intervene early. Interventions can reduce these CVD risks, and guidelines specific for the reduction of CVD risk have been developed for HIV-positive patients.

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Supporting information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Fig. S1 Sensitivity analyses for coronary heart disease (CHD), cardiovascular disease (CVD) and myocardial infarction (MI) endpoints. Sensitivity analyses: dark blue continuous line, final age effect in all three panels (age + age² for CHD and CVD and inverse age for MI). The remaining lines are the final age effects adjusted for calendar year (green long-dashed line), participating cohort (red dashed line), time since entry into D:A:D (orange short dashed line), age < 65 years (black long-dashed–short-dashed line), and men regardless of missing CVD risk factors (purple short-dashed–dotted line).

Table S1 Age effects for myocardial infarction (MI), coronary heart disease (CHD) and cardiovascular disease (CVD) and respective Akaike information criterion (AIC).

Appendix S1 D:A:D participating cohorts.