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An updated prediction model of the global risk of cardiovascular disease in HIV-positive persons: The Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study

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Abstract

Background: With the aging of the population living with HIV, the absolute risk of cardiovascular disease (CVD) is increasing. There is a need to further facilitate the identification of persons at elevated risk in routine practice.

Methods and results: Prospective information was collected on 32,663 HIV-positive persons from 20 countries in Europe and Australia, who were free of CVD at entry into the Data-collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study. Cox regression models (full and reduced) were developed that predict the risk of a global CVD endpoint. The predictive performance of the D:A:D models were compared with a recent CVD prediction model from the Framingham study, which was assessed recalibrated to the D:A:D dataset. A total of 1010 CVD events occurred during 186,364.5 person-years. The full D:A:D CVD prediction model included age, gender, systolic blood pressure, smoking status, family history of CVD, diabetes, total cholesterol, high-density lipoprotein, CD4 lymphocyte count, cumulative exposure to protease- and nucleoside reverse transcriptase-inhibitors, and current use of abacavir. A reduced model omitted antiretroviral therapies. The D:A:D models statistically significantly predicted risk more accurately than the recalibrated Framingham model (Harrell's c-statistic of 0.791, 0.783 and 0.766 for the D:A:D full, D:A:D reduced, and Framingham models respectively; $p < 0.001$). The D:A:D models also more accurately predicted five-year CVD-risk for key prognostic subgroups.

Conclusions: An updated, easily recalibrated, global CVD-risk equation tailored to HIV-positive persons was developed using routinely collected CVD risk parameters and incorporating markers on immune function (CD4 lymphocyte count), and exposure to antiretroviral therapies. The estimated CVD risk can be used to quantify risk and to guide preventive care.

Keywords

HIV, AIDS, CVD risk prediction, epidemiology

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Introduction

Successful antiretroviral therapy results in life expectancies for persons with HIV infection that now approach those of HIV-negative people.[1] At the same time, however, a number of conditions associated with aging have become more prevalent in HIV-positive populations, including hypertension, diabetes, dyslipidaemia and renal impairment[2,3] As patients are living longer, chronic health complications such as cardiovascular disease (CVD) represent an increasingly important health issue, attributed to both HIV-related and traditional risk factors.[4,5] While the incidence and prevalence of opportunistic diseases have dramatically decreased, the care of HIV-positive persons at present includes prevention and management of co-morbidities, and in particular the vigorous monitoring of and interventions for risk factors for CVD.[6]

We have previously published prediction models that could be used to identify HIV-positive persons at increased risk of CVD outcomes.[7] However, these models have reportedly proven somewhat complicated to use in the clinical setting, in part due to the inclusion of time-updated measures and the multiplicity of estimated outcomes.

Recently, a simplified model for a global CVD outcome has been developed for the general population based on the Framingham Study.[8] This was developed in order to enable physicians to identify high-risk candidates for any and all initial atherosclerotic CVD events using measurements readily available at the clinic.

The purpose of the present analyses was to develop similar simplified prediction equations for the risk of a composite CVD endpoint specifically for patients with HIV, facilitating application in clinical practice.

Methods

The D:A:D study is a prospective, observational study formed by the collaboration of 11 cohorts of HIV-positive persons. The primary objective of the study is to establish whether the use of combination antiretroviral therapy is associated with an increased risk of CVD. The 11 cohorts currently contribute data on 49,734 patients at 212 clinics in Europe, Argentina, Australia and the USA. The D:A:D study methodology has been described in detail elsewhere.[9] The standardized dataset includes information on socio-demographic characteristics, AIDS events and deaths, known risk factors for CVD, body composition (body mass index (BMI) and lipodystrophy), laboratory markers (CD4 lymphocyte counts, HIV RNA, total cholesterol (TC), high-density lipoprotein (HDL)-cholesterol and triglyceride levels), antiretroviral treatment history and information on treatments influencing the CVD risk (including lipid lowering therapy, treatment with anti-platelets, insulin or oral anti-diabetes treatment, and anti-hypertensive therapy).

The study endpoints include all incident cases of MI, stroke, invasive cardiovascular procedures and deaths which were reported to the study co-ordinating office for central validation and coding as detailed previously.[9,10] We used the MI definition applied in the World Health Organization MONICA Project.[11] Non-fatal MIs not associated with clinical symptoms (silent MIs) were not included.

Confirmed (haemorrhagic or ischaemic) strokes are events in which symptoms persisted for more than 24 h, there was a sudden symptom onset, there were specific neurological symptoms indicative of stroke and no evidence of any non-atherosclerotic central nervous system (CNS) events. Only confirmed strokes were included.

Death from other CHD includes deaths from end-stage ischaemic heart disease as the underlying cause of death.

All CVD outcomes reported in D:A:D are adjudicated following independent review by a cardiologist, a review which is blinded to information on the patient's clinical status. All reported deaths are adjudicated according to the CODE methodology.[12]

Statistical analyses

Developing the D:A:D CVD risk equation. Analyses were based on all patients recruited to the D:A:D study with follow-up data, excluding those who had a prior CVD and patients without a complete CVD risk factor profile. Baseline for the present analysis was defined as the first time point at or after inclusion in the D:A:D study when information on all CVD risk factors was present. A composite CVD endpoint was analysed that included MI, invasive coronary artery procedure (including coronary artery by-pass or angioplasty), stroke, carotid artery endarterectomy or death from CHD. Follow-up in these analyses commenced at the time of complete risk factor data, and ended at the first of: CVD event, loss to follow-up, date last attended for care plus six months, or 1 February 2011.

An a priori choice of HIV related factors and conventional CVD risk factors that are known to also predict in the HIV-1 positive patient population[7] were included: age, sex, exposure category, ethnicity, diabetes, the presence of lipodystrophy, reported family history of CVD, current and former smoking, BMI, systolic and diastolic blood pressure, and serum measurements of total cholesterol, HDL, triglycerides, glucose, CD4 lymphocyte count and detectable HIV viral load. To improve fit and reduce the influence of extreme values, the natural logarithm was taken of all

continuous covariates (log2 of CD4 lymphocyte count to be consistent with previous analyses). To avoid overfitting, antiretroviral treatment (ART) was considered only for those drugs that have been previously found to be associated with an increased risk of CVD or MI in previous D:A:D analyses and elsewhere:[13–15] cumulative combination antiretroviral treatment (cART), protease inhibitor, nucleoside reverse transcriptase inhibitor (NRTI), lopinavir and indinavir exposure and current abacavir exposure. Of note, in this model ART exposure was fitted at D:A:D baseline, but the ART drugs (and thus CVD risk associated with exposure) may be changed during subsequent follow-up. Because of this complexity, and in acknowledgement of the controversy regarding ART as a predictor of CVD, a second reduced model was developed which excluded ART covariates.

Fixed covariate values at the start of follow-up were used as risk factors. Time varying analyses, which allowed covariate values to change over time, were also conducted and gave similar results, and in particular did not appreciably improve model predictions (not presented).

Cox regression models were used to identify covariates associated with CVD. Backward stepwise approaches to model building were used, with entry and exit determined using $p < 0.05$. Because the vast majority of events in D:A:D are in men, a single model including sex as a covariate was created. Tests for interaction between covariates and sex were not significant and so interactions were not included. Absolute risk of CVD was modelled based on the Cox survival estimate at five years, using the mean values of the predictors in the final models. Five years is less than the median follow-up in the D:A:D study, so predictions out this far are quite robust.

One advantage of using a Cox model in this way is that it creates a risk equation that can be easily recalibrated to other cohorts. A second cohort could recalibrate our risk equation by replacing the D:A:D mean values of predictors in the equations with their own mean values, and also replacing the D:A:D absolute five-year risk estimate with an estimate from follow-up of their own cohort (see online Appendix 1).

Comparison with standard cardiovascular risk equations. The derived D:A:D risk equations were compared with the recently developed simplified Framingham CVD risk equation derived by d'Agostino et al.,[8] a risk equation based on non-HIV-positive American individuals. The Framingham equation was chosen for comparison as it is probably the most widely used and quoted conventional cardiovascular risk equation, and as the approach used for developing our simplified CVD model tailored to HIV patients mimics the approach used by d'Agostino and colleagues for the single CVD risk function. For comparative purposes, we put our model predictions side by side with those of a Framingham equation recalibrated to the D:A:D five-year CVD risk estimates.[8]

Assessing the performance of the risk equation(s). The discrimination performance of the prognostic models were assessed using Harrell's c-statistic to assess model discrimination.[16] We evaluated the calibration of our risk prediction model, a measure of agreement between observed and predicted events within five years, using a modified Hosmer–Lemeshow χ^2 statistic. For this purpose, we used the Kaplan–Meier estimator to obtain the observed incidence of CVD events, which was then compared with the CVD risk predicted by the model and classified into deciles.[8]

The ideal method of validating our models, using an independent validation cohort, is not possible because a cohort with similar CVD endpoints and CVD covariate data is not available for HIV-positive persons. Hence, we additionally validated model performance using internal–external cross-validation.[17] Briefly, the prognostic models were fitted in four sub-cohorts and then validated in the remaining sub-cohort, thus mimicking the notion of independent training and validation datasets. This process was repeated five times to give five separate validations. Average performance was summarized across these five validations using Harrell's c-statistic. In the absence of an independent cohort for validation, we believe this internal–external cross-validation is the best compromise of ensuring power of the analyses by using all data, and assessing any overfitting within a single dataset.

Further, we looked at the accuracy of predicted CVD risk in key subgroups, defined by age, sex, smoking status and diabetes. The clinical relevance of any differences in prediction with the D:A:D models was assessed using the net reclassification index (NRI).[18,19] The NRI gives a measure of the new prediction model to correctly re-classify patients into a higher (or lower) risk category than the category they would have been classified into based on the original model. The NRI can be interpreted as the sum of improvements in classification of risk for cases and controls.

The dataset for the analyses was processed and prepared in SAS (version 9.1). Model development and comparisons were conducted in STATA (version 12).

Results

Study population

A total of 32,663 individuals, who were free of prior CVD and had complete data on all risk factors, were

Table 1. Follow-up information and baseline characteristics.

	No event $N = 31,653$	Events[a] $N = 1010$
Median (IQR)		
Follow-up, years	5.38 (2.93, 8.84)	3.39 (1.61, 5.77)
Age, years	39 (33, 46)	47 (41, 57)
cART exposure, years	1.75 (0, 3.75)	3.19 (1.44, 4.34)
PI exposure, years	0.68 (0, 2.93)	2.58 (0.53, 3.85)
NRTI exposure, years	2.42 (0.20, 5.10)	4.29 (2.37, 6.77)
CD4 lymphocyte count, cells/μl	440 (290, 630)	402 (260, 611)
Systolic blood pressure, mmHg	120 (110, 130)	130 (120, 140)
Diastolic blood pressure, mmHg	80 (70, 80)	80 (72, 90)
Total cholesterol, mmol/l	4.8 (4.1, 5.7)	5.6 (4.8, 6.5)
HDL cholesterol, mmol/l	1.14 (0.91, 1.42)	1.06 (0.85, 1.34)
Triglycerides, mmol/l	1.53 (1.01, 2.45)	2.20 (1.39, 3.53)
BMI, kg/m^2	23.1 (21.0, 25.4)	23.3 (21.3, 25.6)
n (column per cent)		
Receiving abacavir at baseline	4225 (13.4)	232 (23.0)
Female	8230 (26.0)	126 (12.5)
HIV-RNA <50 copies/ml	17,022 (53.8)	481 (47.6)
Reported family history of CVD	2609 (8.2)	136 (13.5)
Diabetes	900 (2.8)	105 (10.4)
Smoker		
Current	16,420 (51.9)	621 (61.5)
Former	5279 (16.7)	176 (17.4)
Mode of HIV acquisition		
Heterosexual	10,776 (34.0)	259 (25.6)
MSM	14,034 (44.3)	924 (51.9)
Injecting drug use	5047 (15.9)	157 (15.5)
Ethnicity		
White	18,072 (57.1)	620 (61.4)
Non-White	3313 (10.5)	47 (4.7)
Unknown	10,268 (32.4)	343 (34.0)

[a]493 myocardial infarction, 295 stroke, 36 bypass, 129 angioplasty, 13 carotid endarterectomy, 44 other cardiovascular disease deaths. IQR: interquartile range; cART: combination antiretroviral treatment; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; HDL: high-density lipoprotein; BMI: body mass index; CVD: cardiovascular disease

included in the model. Characteristics of the study population and of patients experiencing a CVD event are outlined in Table 1. The median age at enrolment was 39 years (interquartile range (IQR), 33–46), and 26% of the patients were female. Among the 67.6% of patients for whom information on race or ethnic background (ascertained by different methods in different centres) was available, 84.4% were White. The median CD4+ lymphocyte count at enrolment was 440 cells per cubic millimetre (IQR, 290–630). At enrolment, 68.6% of participants were current or former smokers, 2.8% had diabetes, 14.4% had hypertension and 42.0% had dyslipidaemia. The median follow-up time was 5.7 (IQR, 2.9–8.8) years, for a total of 186,364.5 person-years. The characteristics and risk factor profiles were largely similar to that of the entire D:A:D study population.[20]

Endpoints

A total of 1010 CVD events were included (Table 1), consisting of: 493 cases of MI, 295 strokes, 178 invasive procedures (129 coronary artery angioplasty, 36 coronary by-pass and 13 carotid endarterectomy) and 44 deaths from other CHD. Eighty of the 493 MIs and 40 of the 295 strokes were fatal.

The overall rate of CVD among the included HIV-positive persons was 5.42 per 1000 person-years of follow-up (95% confidence interval (CI), 5.09–5.76).

Patients excluded

A total of 16,307 individuals were excluded from analyses because of lacking information on one or more CVD risk factors. The median age of these individuals was 37 years, 28% were women, 2.2% were diabetic, median systolic and diastolic blood pressures were 120 and 80 mmHg respectively. The majority had missing information on smoking (60%) and family history of CVD (65%). There were 435 CVD events in these patients, a rate per 1000 person-years of 4.88 (95% CI, 4.43–5.36).

The models

The models include the conventional risk factors of age, gender, family history of CVD, systolic blood pressure and smoking status, TC and HDL cholesterol, diabetes and, in addition, the following risk factors unique to HIV infected persons: CD4 lymphocyte count, cumulative protease inhibitor and NRTI exposure, and current abacavir use. Hazard ratios (HRs) from Cox regression models are presented in Table 2.

The HR estimates for the conventional CVD risk factors were slightly altered in the reduced model that omitted ART exposure (Table 2). The HR estimate of 0.89 per doubling (Ln2) of CD4 lymphocyte count corresponds to a 11% reduction of risk and the HR of 1.47 for current abacavir use to a 47% increased five-year risk of CVD.

The following parameters were excluded based on non-significance: BMI, lipodystrophy, triglycerides

Table 2. Multivariable risk factor models.

	Full model				Reduced model			
Predictor	HR	(95% CI)	*p*	β	HR	(95% CI)	*p*	β
Ln age	22.0	(16.3, 29.6)	<0.001	3.090	24.0	(17.9, 32.1)	<0.001	3.178
Male *vs.* female	1.37	(1.13, 1.66)	0.001	0.314	1.41	(1.16, 1.71)	<0.001	0.344
Diabetes (yes *vs.* no)	1.96	(1.59, 2.42)	<0.001	0.675	2.08	(1.69, 2.56)	<0.001	0.731
Family history (yes *vs.* no)	1.37	(1.14, 1.64)	0.001	0.314	1.39	(1.16, 1.67)	<0.001	0.330
Smoke								
Current *vs.* never	2.25	(1.91, 2.63)	<0.001	0.809	2.26	(1.93, 2.65)	<0.001	0.816
Former *vs.* never	1.24	(1.01, 1.51)	0.038	0.213	1.27	(1.04, 1.55)	0.019	0.239
Ln cholesterol (mmol/l)	2.58	(2.04, 3.27)	<0.001	0.948	2.98	(2.35, 3.78)	<0.001	1.092
Ln HDL (mmol/l)	0.61	(0.51, 0.72)	<0.001	−0.501	0.59	(0.50, 0.71)	<0.001	−0.519
Ln systolic blood pressure (mmHg)	4.59	(2.84, 7.42)	<0.001	1.523	4.56	(2.82, 7.39)	<0.001	1.518
Ln2 CD4 count (cells/mm^3)	0.89	(0.84, 0.94)	<0.001	−0.119	0.89	(0.84, 0.94)	<0.001	−0.114
Receiving abacavir (yes *vs.* no)	1.47	(1.26, 1.71)	<0.001	0.384	–			
PI exposure (per year)	1.048	(1.009, 1.088)	0.015	0.0467	–			
NRTI exposure (per year)	1.028	(1.003, 1.054)	0.028	0.0278	–			
Framingham model (2008)								
	Women				Men			
Ln age (years)	10.3	(5.6, 18.6)	<0.001	2.329	21.4	(14.0, 32.5)	<0.001	3.061
Diabetes (yes *vs.* no)	2.00	(1.49, 2.67)	<0.001	0.692	1.78	(1.43, 2.20)	<0.001	0.574
Smoker current *vs.* no	1.70	(1.40, 2.06)	<0.001	0.529	1.92	(1.65, 2.24)	<0.001	0.655
Ln cholesterol	3.35	(2.00, 5.62)	<0.001	1.209	3.08	(2.05, 4.62)	<0.001	1.124
Ln HDL	0.49	(0.35, 0.69)	<0.001	−0.708	0.39	(0.30, 0.52)	<0.001	−0.933
Ln SBP if not treated	15.8	(7.9, 31.9)	<0.001	2.762	6.91	(3.91, 12.20)	<0.001	1.933
Ln SBP if treated	16.8	(8.5, 33.5)	<0.001	2.823	7.38	(4.22, 12.92)	<0.001	1.999

β corresponds to ln(HR). HR: hazard ratio; CI: confidence interval; Ln: log (base e); Ln2: log (base 2); HDL: high-density lipoprotein; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; SBP: systolic blood pressure

and HIV-RNA. Models that incorporated diastolic blood pressure predicted marginally less well than models with systolic blood pressure. Triglycerides were not found to be predictive of our endpoints after adjustment for other parameters, principally other lipids (TC and HDL cholesterol). Models that included cumulative exposure to all protease inhibitors predicted somewhat better than models that included the single drug exposures to lopinavir and indinavir.

Model performance

The D:A:D models performed well in terms of discriminating risks, with Harrell's c-statistics of 0.791 and 0.783 for the full and reduced CVD models respectively (Table 3). However, the Harrell's c-statistic for the Framingham equation was 0.766, indicating that this equation also performed well in terms of the overall ordering of patients' cardiovascular risk ($p < 0.001$ for the comparison of the three models). In the internal–external cross-validation six of the 10 D:A:D sub-cohorts with fewer than 50 CVD events were combined into a single cohort, thus giving a total of five sub-cohorts and five validations (Table 3). In this process, the D:A:D prediction models did show some modest shrinkage in prediction. Across the five validations, the mean c-statistics for the full D:A:D model reduced from 0.791 to 0.786 (a 0.6% reduction). Similarly across the validations the mean c-statistics for the reduced D:A:D model decreased from 0.783 to 0.778 (a 0.6% reduction). For the Framingham, as would be expected, the mean c-statistic across the five validations did not reduce, and actually increased from 0.766 to 0.770. However, the D:A:D prediction models still showed modestly improved model prediction compared with the Framingham, indicating that the better predictions of the D:A:D models are not due to overfitting.

The D:A:D prediction models, however, were found to be appreciably better calibrated when comparing estimated and observed five-year CVD risk for patients ordered according to deciles of predicted risk.

Table 3. Model discrimination.

	Harrell's c-statistic[a] 95% CI	Internal–external cross-validation[b]	
		Mean[c] (SD)	[range]
D:A:D full model	0.791 (0.777, 0.804)	0.786 (0.0346)	[0.713–0.831]
D:A:D reduced model	0.783 (0.768, 0.797)	0.778 (0.0342)	[0.710–0.822]
Framingham model	0.766 (0.751, 0.781)	0.770 (0.0418)	[0.669–0.818]

[a]$p < 0.001$ for the comparison of the three models. [b]Based on five cohorts, the six smaller cohorts with $n < 50$ events combined into one cohort. [c]Mean c-statistic weighted by 1/variance.

Table 4. Calibration by subgroups.

	Mean five-year predicted risk of CVD			
Subgroup	D:A:D full model	D:A:D reduced model	Framingham model	Kaplan–Meier estimate of five-year CVD risk[a] (95% CI)
Overall	2.49%	2.42%	2.22%	2.67% (2.47–2.87%)
Sex				
Female	1.22%	1.18%	1.74%	1.27% (1.03–1.58%)
Male	2.93%	2.85%	2.41%	3.14% (2.90–3.41%)
Smokes				
Never	1.65%	1.60%	1.79%	1.82% (1.55–2.14%)
Former	2.57%	2.49%	2.04%	2.86% (2.40–3.41%)
Current	2.97%	2.90%	2.57%	3.10% (2.82–3.42%)
Age, years				
<30	0.32%	0.34%	0.41%	0.24% (0.12–0.48%)
30–39	1.14%	1.14%	1.12%	1.15% (0.96–1.38%)
40–49	2.72%	2.59%	2.34%	2.97% (2.62–3.38%)
50+	6.71%	6.53%	5.87%	7.32% (6.57–8.14%)
Diabetes				
No	2.29%	2.22%	2.07%	2.42% (2.23–2.62%)
Yes	8.95%	8.67%	7.73%	10.45% (8.44–12.89%)

[a]The Kaplan–Meier estimate is for the entire D:A:D population in that stratum. CVD: cardiovascular disease; CI: confidence interval

The Hosmer–Lemeshow χ^2 values were 13.33 and 12.73 (on eight degrees of freedom), $p = 0.101$ and 0.121, respectively for the full and the reduced D:A:D CVD prediction models, indicating no evidence of lack of goodness of fit. In comparison, the Hosmer–Lemeshow χ^2 value for the recalibrated Framingham model was 37.81 (eight degrees of freedom), $p < 0.001$, indicating a statistically significant lack of fit.

Accuracy and comparison with the Framingham model

Predicted and observed five-year risk of CVD for key prognostic subgroups are compared in Table 4. Overall the D:A:D models more accurately predicted five-year risk of CVD in subgroups defined by age, sex, diabetes and smoking than the Framingham model.

We also compared the clinical relevance of the D:A:D model predictions with the Framingham equation using the NRI. For each model, we categorized each individual's five-year predicted CVD risk into one of the following categories: <1%, 1–5%, 5–10% and >10% five-year CVD predicted risk. Compared with Framingham, the D:A:D full model predicted a higher risk category for 23.5% of individuals who went on to have a CVD event and for 10.9% of individuals who did not, and a lower risk category for 6.1% of individuals who had a CVD event and for 8.0% of individuals who did not. This gave a NRI of 14.5% (= 23.5%–6.1% + 8.0%–10.9%). This represents the sum of improvements in prediction for the D:A:D model compared with Framingham, with more higher risk categories predicted for CVD events using D:A:D, and more lower risk categories for controls. For the D:A:D reduced model compared with the Framingham model the NRI was 8.1%, and for the D:A:D full model compared with the D:A:D reduced model it was 6.4%.

Discussion

In a cohort of HIV-positive persons, we created simplified prediction equations for the global five-year risk of CVD endpoints. The performance of the models was superior to that of a recalibrated Framingham CVD prediction model in this population. The full D:A:D CVD prediction model includes exposure to ART drugs (cumulative protease inhibitor and NRTI exposure, current abacavir use) and markers of immunodeficiency (CD4 lymphocyte count), in addition to conventional CVD risk factors, and more accurately estimated the risk of CVD outcomes in the cohort overall as well as in subgroups.

The present CVD risk prediction models are based on almost twice as much follow-up time and differ from our prior work in important ways: while the association

of ART with CVD risk in earlier work is analysed in exploratory Poisson regression models, with ART fitted in a time-updated manner, the present models are more pragmatic. Rather than pinpointing risks associated with individual ART drugs, the purpose of the prediction models is to estimate an individual's overall CVD risk in a simple manner. Here the ART exposure has been fitted at baseline (cumulative for the NRTI and protease inhibitor drug classes, current exposure at baseline for abacavir). Because changes to ART are common during follow-up, and as the association between ART use and CVD risk is somewhat controversial, we also developed a reduced D:A:D model omitting ART covariates. Of note, the full model risk estimates for the association of ART exposure and CVD risk are slightly lower than previously reported.[14] This is in part explained by the inclusion of ART baseline exposure only; for example, for abacavir, where the association with CVD risk appears to be primarily linked with current or recent exposure, a five-year risk extrapolation from baseline ignores that patients may have started or stopped abacavir over follow-up. Further, the full D:A:D prediction model can be considered 'fully adjusted' at baseline as it includes the lipid measurements. For the protease inhibitors, the association of these drugs with the risk of CVD is in part explained through their effect on lipid levels. Hence, the full effect of these drugs on the risk of CVD includes their lipid effect and the independent drug effect.

The evidence for a potential role of immune depression (CD4 lymphocyte depletion) in the development of CVD among individuals with HIV infection is conflicting.[21–25] Prior detailed analyses from the D:A:D study have analysed various measures of immune depression, including nadir and latest CD4 lymphocyte count, and duration of immune depression, with the risk of CVD outcomes. These analyses did not find strong evidence of increased risk of coronary heart disease in HIV patients with lower CD4 lymphocyte count; the strongest association of immune depression was found for stroke and fatal CVD outcomes.[23] In the present models a lower CD4 lymphocyte count at baseline remains a modest albeit independent predictor of the global CVD risk, with an estimated incremental risk of 11% per halving of the CD4 lymphocyte counts. The finding is consistent with the notion that immunodeficiency in HIV is associated not only with the risk of AIDS but also with increased risk of non-AIDS morbidity.[26]

The estimation of global CVD risk provided here facilitates the matching of risk factors with the estimated probability of disease, thereby facilitating targeted interventions and rendering treatment (lipid-lowering, anti-hypertensive) most cost-effective. In addition to reducing the number needed to treat to prevent a CVD event, multivariable risk assessment also avoids overlooking high risk CVD candidates with multiple marginal risk factors and avoids needlessly alarming persons at low global CVD risk, where attention might be better focused on other HIV- or treatment-related issues. For CVD risk to be classified as 'high', it is generally considered to correspond to the CVD risk in someone with diabetes mellitus (DM) or the equivalent estimated 10-year risk of CVD.[27–28] Similar guidance based on five-year global CVD risk estimates from the D:A:D models would therefore suggest a threshold for high CVD risk of around 10% (DM risk, Table 4).

We were not able to validate our models in a truly independent cohort of HIV-positive persons as we were unable to identify a cohort of sufficient size with all the required endpoints and covariates. However, internal external cross-validation suggests that the D:A:D models are an improvement compared with a recalibrated Framingham model, and do not simply appear to be an improvement due to overfitting within a cohort. However, as always, generalizability of the prediction models requires external independent validation. A key advantage of our methodology is that the risk equation is easily recalibrated to other cohorts and populations. Another advantage is that our models enable us to take into account the effects of drugs which, while perhaps controversial, are probably real causal effects.

Prediction models are limited by restrictions in the available data and follow-up time available for model development. The strengths of our model are that it has been developed from a high quality dataset of substantial size, a reasonable amount of follow-up, with carefully collected information on all known conventional CVD risks, HIV specific risks and ascertained clinical CVD outcomes. A limitation is the lack of additional parameters of interest, such as markers of inflammation. Another limitation is the discrepancies in definitions of composite CVD outcomes, restricting direct comparisons with some conventional prediction tools. Of note, the composite CVD outcome assessed in the Framingham study[8] is somewhat more inclusive than our outcome: a composite of coronary CHD (coronary death, MI, coronary insufficiency and angina), cerebrovascular events (including ischaemic stroke, haemorrhagic stroke and transient ischaemic attack), peripheral artery disease (intermittent claudication) and heart failure. Studies comparing different risk scores in HIV-positive populations must take this into account; that is, there are differences in CVD outcome definitions and differences in the populations from which the risk scores were developed. It is beyond the scope of this paper to examine whether the risks attributable to individual risk factors included in the model differ from their impact in other prediction scores

(non-HIV). Further, as the Framingham score was recalibrated to our dataset, the present analysis does not address a possible independent effect of HIV on CVD risk.

In our analyses we omitted patients with missing data on any of the required risk factors. For the majority of these excluded patients, smoking and family history of CVD were the missing data. These patients appeared similar on compared covariates that were available, and the overall CVD event rate was not dissimilar to the patients included in the analyses. The covariates included in our risk models were also similar to those identified in previous D:A:D analyses that included all patients.[9,10,13,14,20] Hence, we believe that the risk of substantial bias in the developed risk models due to exclusion of patients with missing data in unlikely to be substantial.

There are further limitations on our models. First, the number of endpoints in women in our study is limited, and so chance variation may in particular influence predictions in women. Second the proportion of non-White patients in our study was relatively small (10.5%). The extent to which our models can be directly applied in largely non-White populations remains to be explored. However, the design of the model allows for easy recalibration to other populations. Third, the risk associated with ART drugs should not be extrapolated beyond duration of exposures available in the development dataset, and predictions may not be valid beyond the actual available follow-up time.

Application of models

Calculation of an individual's predicted risk is described in online Appendix 1. Our models may be both used in the clinical context to inform doctor–patient discussions on CVD risks and interventions and for research purposes of estimations of predicted risk at population levels. Although the risk of CVD endpoints is only in part attributable to therapy, this incremental risk associated with ART drugs may be estimated, and in individuals at high risk of CVD other treatment choices may be more attractive. However, if treatment data are not readily available, a useful CVD risk estimate that does not include treatment specific data can be calculated from the reduced model. If the prognosis regarding CVD risk determined by these models is poor for an individual patient, more targeted interventions to reduce this risk may be recommended, including lifestyle changes and medicinal interventions.[6]

Perspectives

This paper presents simplified prediction tools of global CVD risk tailored to the HIV-positive population. Validation of these tools in independent cohorts of HIV-positive persons is warranted, and to our knowledge several such studies are ongoing.

There is emerging data from a number of studies contributing to the understanding of the complexity of CVD risk in HIV-positive persons, and future studies may show whether bio-markers of inflammation or thrombosis can contribute with additional predictive value in HIV-positive persons.[29]

With the aging of the population living with HIV, the absolute risk of CVD is expected to increase, with a greater proportion of the population requiring interventions against CVD. With continued follow-up of the D:A:D study and other large HIV cohorts, increasing knowledge about CVD risk in subgroups of HIV patients may be obtained (e.g. in women), and it will be possible to better explore and quantify potential risks associated with some of the more current ART drugs. By early identification of adverse drug effects a timely consideration of the risk/benefit ratio can be performed, and often individuals more susceptible to the adverse effect can be identified for discontinuation of the drug or targeted pre-emptive measures.

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Conflict of interest

The authors declare that there is no conflict of interest.

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