CE: Satish ED: Sushma Op: nvs HJR: LWW_HJR_200632

Wolters Kluwer Health | Lippincott Williams & Wilkins

EUROPEAN SOCIETY OF CARDIOLOGY®

Original Scientific Papers

Predicting the risk of cardiovascular disease in HIV-infected patients: the Data collection on Adverse Effects of Anti-HIV Drugs Study

Nina Friis-Møller[a], Rodolphe Thiébaut[b], Peter Reiss[d], Rainer Weber[e], Antonella D'Arminio Monforte[f], Stephane De Wit[g], Wafaa El-Sadr[h], Eric Fontas[c], Signe Worm[a], Ole Kirk[a], Andrew Phillips[i], Caroline A. Sabin[i], Jens D. Lundgren[a] and Matthew G. Law[j]; for the DAD study group

[a]Copenhagen HIV Programme (CHIP), University of Copenhagen/Faculty of Health Science, Copenhagen, Denmark, [b]Aquitaine, INSERM, ISPED, Université Victor Segalen Bordeaux, Bordeaux, [c]Nice Cohort, CHU Nice Hopital de l'Archet, Nice, France, [d]ATHENA, HIV Monitoring Foundation, Academic Medical Center, Amsterdam, The Netherlands, [e]SHCS, Division of Infectious Diseases and Hospital Epidemiolog, Department of Internal Medicine, University Hospital Zurich, Zurich, Switzerland, [f]ICONA, Hospital San Paolo, University of Milan, Italy, [g]Saint-Pierre Cohort, CHU Saint-Pierre Hospital, Brussels, Belgium, [h]CPCRA, Columbia University/Harlem Hospital, New York, USA, [i]Royal Free Centre for HIV Medicine and Department of Primary Care and Population Sciences, Royal Free and University College, London, UK and [j]AHOD, National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia

Received 7 September 2009 **Accepted** 9 November 2009

Aims **HIV-infected patients receiving combination antiretroviral therapy may experience metabolic complications, potentially increasing their risk of cardiovascular diseases (CVDs). Furthermore, exposures to some antiretroviral drugs seem to be independently associated with increased CVD risk. We aimed to develop cardiovascular risk-assessment models tailored to HIV-infected patients.**

Methods and results **Prospective multinational cohort study. The data set included 22 625 HIV-infected patients 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 Study. Using cross-validation methods, separate models were developed to predict the risk of myocardial infarction, coronary heart disease, and a composite CVD endpoint. Model performance was compared with the Framingham score. The models included age, sex, systolic blood pressure, smoking status, family history of CVD, diabetes, total cholesterol, HDL cholesterol and indinavir, lopinavir/r and abacavir exposure. The models performed well with area under the receiver operator curve statistics of 0.783 (range 0.642–0.820) for myocardial infarction, 0.776 (0.670–0.818) for coronary heart disease and 0.769 (0.695–0.824) for CVD. The models estimated more accurately the outcomes in the subgroups than the Framingham score.**

Conclusion **Risk equations developed from a population of HIV-infected patients, incorporating routinely collected cardiovascular risk parameters and exposure to individual antiretroviral therapy drugs, might be more useful in estimating CVD risks in HIV-infected persons than conventional risk prediction models. *Eur J Cardiovasc Prev Rehabil* 00:000–000**

European Journal of Cardiovascular Prevention and Rehabilitation 2010, **00**:000–000

Keywords: antiretroviral drugs, cardiovascular risk, HIV, prediction model

Correspondence to Nina Friis-Møller, MD, PhD, Copenhagen HIV Programme (CHIP), University of Copenhagen/Faculty of Health Science, Building 21.1./Blegdamsvej 3B, Copenhagen N DK-2200, Denmark
Tel: +45 3545 5757; fax: +45 3545 5758;
e-mail: nfm@cphiv.dk

Introduction

Evidence from the Data collection on Adverse Effects of Anti-HIV Drugs Study(DAD) and other studies has established that exposure to certain antiretroviral drugs

1741-8267 © 2010 The European Society of Cardiology DOI: 10.1097/HJR.0b013e328336a150

is associated with an increase in the rate of cardiovascular disease (CVD) events [1–7]. Of particular use in individual patient management would be a risk equation that could be used to identify HIV-positive patients at high risk of CVD events. Earlier analyses have suggested that drug-induced lipid changes and other conventional CVD risk factors drive the risk of myocardial infarction (MI) [8]. However, the use of conventional cardiovascular risk equations is of uncertain accuracy because of the established association with antiretroviral drugs, apparent increased risk immediately after starting treatment with some of these drugs, and differences in patient populations. In particular, the average age of HIV-infected persons is lower than the age distribution in the populations for whom conventional CVD risk prediction models were developed. And further, there may be an association between HIV infection itself and CVD risk [9], which would not be captured in risk equations developed in the HIV-uninfected population. The purpose of the present analyses was to develop prediction equations for the risk of CVD endpoints specifically for patients with HIV. As exposures and CVD risk profiles are dynamic, the prediction models have been created to identify patients at risk of CVD endpoints over the shorter term. However, our risk estimates can be extrapolated to provide 5-year CVD risk predictions (in which the estimates will reflect the risk assuming that the risk profile remains unchanged).

Methods

The DAD study is a prospective, observational study formed by the collaboration of 11 cohorts of HIV-infected patients currently contributing data on 33 308 patients from 212 clinics in Europe, Argentina, Australia and the US. The DAD study methodology has been described in detail elsewhere [10]. The standardized data set includes information on sociodemographic characteristics, AIDS events and deaths, known risk factors for CVD, laboratory markers [CD4 cell counts, HIV RNA, total cholesterol, HDL cholesterol (HDL) and triglyceride (TG) levels], antiretroviral treatment (ART) history and information on treatments influencing the CVD risk (including lipid-lowering therapy, treatment with antiplatelets, insulin or oral antidiabetes treatment and antihypertensive therapy). Blood pressure was measured in the cohorts according to clinical practice. The study endpoints include all incident cases of MI, stroke, invasive cardiovascular procedures and deaths, which were reported to the study coordinating office for central validation and coding as detailed earlier [10,11].

Statistical analyses

Developing the Data collection on Adverse Effects of Anti-HIV Drugs Study risk equation(s)

Analyses were based on all patients recruited to the DAD Study with follow-up data, excluding those who had an earlier CVD, and patients without a complete risk factor profile. The baseline for this analysis was defined as the first time point at or after inclusion in the DAD Study when information on all CVD risk factors was present. Three endpoints were analyzed: MI (including nonfatal and fatal cases), a composite coronary heart disease endpoint (CHD) of MI, invasive coronary artery procedure (including coronary artery bypass or angioplasty) or death from other CHD (end-stage ischemic heart disease), a composite CVD endpoint (CVD) of all of the above, carotid artery endarterectomy, or stroke. Characteristics of the study population and endpoints definitions applied are outlined in Tables 1 and 2.

Predictive risk equations were developed based on Poisson regression models. The underlying time scale was the prospective follow-up from baseline, and till the time of the event, the time of death, time of last follow-up visit in the study or 1 February 2008, whichever occurred first. Predictive models were fitted using time-

Table 1 Description of characteristics and outcome variables used in the model development datasets from the DAD and Framingham cohorts

Cohort	Setting	Study population	Year of baseline examination and follow-up	Definition of myocardial infarction[a]	Definition of coronary heart disease[b]	Definition of cardiovascular disease
DAD Study	Cohort collaboration; 188 clinics in Europe and Australia	HIV-infected persons; 16 765 men and 5860 women, aged 16–85 years (median 40 years) at baseline	Baseline: 2000, median follow-up 4.8 years	Fatal and nonfatal MI, including sudden death	Invasive coronary artery procedure (PTCA with stenting or coronary artery by-pass operation), MI, death from other CHD	Stroke, endarterectomy of carotid artery, CHD
Framingham Heart Study	Town of Framingham, Massachusetts, USA	2590 men and 2983 women from original and offspring cohorts, aged 30–74 years at baseline	Baseline: 1968–1971 (original cohort), 1971–1975 (offspring cohort); mean follow-up (both cohorts) approximately 12 years	Fatal and nonfatal MI, including silent MI	Angina pectoris, unstable angina, MI	Stroke, transient ischemic attack (TCI), peripheral vascular disease, CHD, death from other CVD

CHD, coronary heart disease; CVD, coronary vascular disease; DAD, Data collection on Adverse Effects of Anti-HIV Drugs Study; MI, myocardial infarction. [a]The diagnosis of MI was based on an established algorithm adapted from standardized criteria that included cardiac pain, cardiac enzyme or troponin levels, electrocardiographic readings, and in cases of death, autopsy results if available. All events had to satisfy the criteria for a definite, possible, or unclassifiable myocardial infarction and were categorized as nonfatal (when the patient survived to 28 days after onset) or fatal. The definition was similar to that applied in the WHO MONICA study [12,13]. [b]Proportion MI of CHD endpoint, 68% in DAD versus 50% in Framingham.

Table 2 Follow-up information and characteristics of the population included in the DAD equation at the time of their first complete cardiovascular risk profile

Number of participants	22 625
Number of CVD/CHD/MI events	663/554/387
Median follow-up years (IQR)	4.80 (3.04–7.00)
Time at risk (person-years)	106 821
Median baseline date (IQR)	July 2000 (May 2000–Aug 2001)
Median (IQR)	
Age (years)	40 (35–47)
cART exposure (years)	2.5 (0.5–3.9)
PI exposure (years)	1.7 (0.0–3.3)
CD4 count	447 (290–641)
Systolic blood pressure (mmHg)	120 (110–130)
Diastolic blood pressure (mmHg)	80 (70–81)
Total cholesterol (mmol/l)	5.0 (4.2–6.0)
HDL cholesterol (mmol/l)	1.1 (0.9–1.4)
Ratio total:HDL cholesterol	4.4 (3.4–5.7)
Triglyceride (mmol/l)	1.6 (1.1–2.7)
BMI (kg/m^2)	23.0 (21.0–25.3)
%	
Female	25.9
HIV-RNA $<$50 cps/ml	50.9
Family history of CVD	9.2
Diabetes	3.0
Current cigarette smoker	53.3
Ex-smoker	15.8
Transmission group	
Heterosexual	32.6
Homosexual	42.4
Intravenous drug use	19.3
Ethnicity	
White	60.6
Non-white	9.2
Unknown	30.2

BMI, body mass index; cART, combination antiretroviral therapy; CHD, coronary heart disease; CVD, coronary vascular disease; DAD, Data collection on Adverse Effects of Anti-HIV Drugs Study; HDL, high-density lipoprotein; IQR, interquartile range; MI, myocardial infarction; PI, protease inhibitor.

updated covariates for most key laboratory parameters. This different approach from that generally used in creating prognostic risk equations was taken for several reasons. First, models based on time-updated data may more accurately capture and predict the current risk, in particular as several of the risk factors are reversible. Second, HIV-infected patients receiving ARTs are seen by clinicians on a very regular basis, usually 3 or 4 times a year. Hence, the need is for relatively short-term risk predictions. Third, in recent years there has been a rapidly evolving improvement in CVD risk management in HIV-infected patients, something that a model with time-updated covariates would be better placed to accommodate. Poisson models were used to aid direct comparison with other DAD analyses, and also because the relatively short time periods used in a time-updated analysis can be fitted adequately using piece-wise constant hazards.

An a priori choice of conventional CVD risk factors, known to also predict in the HIV-1 infected patient population [4], included age, sex, serum total and HDL, blood pressure, smoking (current, former, never) and diabetes mellitus (defined as two consecutive measurements of fasting plasma glucose above 7 mmol/l or treatment with antidiabetic drugs). In addition, the following covariates were considered for inclusion: duration of the protease inhibitors (PIs) lopinavir/r and indinavir, current exposure to the nucleoside reverse transcriptase inhibitor (NRTI) abacavir, family history of CVD, TGs, CD4 count, HIV RNA, body mass index, reported lipodystrophy and HIV exposure category. Among the latter, covariates were selected using backward selection and were included in the model if the association with the outcome was significant ($P < 0.05$). All covariates were fitted as time updated. To avoid overfitting of ART data in the subset of the DAD data analyzed here, ARTs considered in the modeling were restricted to those drugs currently well established to be associated with cardiovascular outcomes [5–7,14–16]. Other ARTs were not considered to avoid generating probably spurious associations in this subset of data. Most laboratory covariates were included, a priori, as continuous variables rather than as risk thresholds because of the expanding literature that now suggests there are no safe cut-offs for risk factors and that increases and decreases in covariates at any level are associated with increased or decreased cardiovascular risk [17–20] Furthermore, modern computing facilities and web-based tools reduce the need for simple computational algorithms or scoring systems [21].

Separate models were considered with and without HDL, and replacing systolic with diastolic blood pressure. Patients were included in the analyses only if, and from when, full covariate data were available. One cohort was excluded from the analyses because of incomplete covariate data (CPCRA).

Interactions between sex and other significant factors were evaluated while no other interactions between covariates were assessed to avoid overfitting.

Comparison with standard cardiovascular risk equations

The derived DAD risk equations were compared with the Framingham equation derived by Anderson *et al.* [22], a risk equation based on non-HIV-infected American individuals. The Framingham equation was chosen for comparison, as it is probably the most widely used and quoted conventional cardiovascular risk equation. There are also data to suggest that other conventional risk equations, whereas they may be better calibrated to certain populations, tend to order patient risk estimates similarly (in non-HIV-infected populations) [23,24]. The formulation of the Framingham equation derived by Anderson *et al.* [22] was chosen as this allowed most direct comparison with the endpoints collected in the DAD Study, and also allowed reasonably straightforward computations. For comparative purposes, the Framingham equation was also fitted to the DAD Study data in a

time-updated fashion, estimating for each patient the probability of not having an event in each updated time period, and then multiplying these probabilities up to give for each patient an overall probability of not having an event during study follow-up. Key study features, and endpoint definitions, for the DAD and Framingham studies are summarized in Table 1.

Assessing the performance of the risk equation(s)

The performance of the prognostic models were assessed using an internal–external cross-validation [25,26]. Briefly, the prognostic models were fitted in (n-1) subcohorts and then validated in the remaining subcohort, thus mimicking the notion of independent training and validation data sets. This process was repeated n times, to give n separate validations. Average performance was summarized across these n validations in two ways. First, the discrimination of the risk equations was compared with the Framingham equation using the 'area under the receiver operating characteristic curve' (AROC) analyses. Second, the calibration of the risk equations was compared with the Framingham equation by comparing the ratio of predicted-to-observed events in each validation cohort. Data were summarized using a mean weighted by the inverse of the variance, or the observed number of events for the AROC and predicted-to-observed event ratio respectively.

The accuracy of the DAD and Framingham equations was further assessed across the whole data set by comparing the observed versus the predicted numbers of events in the subgroups defined by age and sex, smoking status and diabetes. In these analyses, the predicted number of events from the Framingham equation was recalibrated such that the predictions summed to the observed total numbers of events across the entire cohort. This was done to allow a better sense of whether the Framingham equation managed to order risk of patients within the subgroups. Goodness-of-fit was also assessed by dividing patients into quartiles of predicted risk for each equation, and then comparing observed versus predicted events using the Hosmer–Lemeshow statistic.

Applying the risk equation to obtain absolute risk estimates

The final risk equation for CHD was further used to estimate the proportions that were at low (< 1%), moderate (1–5%), high (5–10%) and very high (> 10%) risk of CHD over a 5-year period.

The data set for the analyses was processed and prepared using SAS (version 9.1, SAS Institute Inc., Cary, North Carolina, USA). Model development and comparisons were conducted with Stata (version 10.0, StataCorp LP., College Station, Texas, USA).

Results

Study population

A total of 22 625 individuals were free of earlier CVD and had complete data on all the risk factors included in the model. The characteristics of these individuals are shown in Table 2. The average follow-up time was 4.8 years (interquartile range 3.0–7.0), for a total of 106.821 person-years. The characteristics and risk factor profiles were largely similar to those of the entire DAD Study population [5].

Endpoints

The following endpoints were available in this subset: 375 cases of MI, 138 stroke, 136 invasive procedures (96 coronary artery angioplasty, 31 coronary bypass and nine carotid endarterectomies) and 52 deaths from other CHD. The composite CHD endpoint (n = 554) consisted of 375 MI, 127 invasive CVD procedures and 52 cases of death from other CHD. The composite CVD endpoint (n = 663) consisted of 366 MI, 138 Stroke, 134 invasive CVD procedures and 25 cases of death from other CHD. Approximately 14% of MIs were sudden deaths.

The models

The models include the conventional risk factors of age, sex, family history of CVD (CHD and CVD models), systolic blood pressure and smoking status, total and HDL cholesterol, diabetes and, in addition, exposure to the individual ART drugs lopinavir/r, indinavir (MI and CVD) and abacavir. Relative rates from the DAD Poisson regression models are illustrated in Table 3.

Thus the following parameters were assessed and excluded based on nonsignificance: body mass index, lipodystrophy, TGs, CD4 count and HIV-RNA. Models that incorporated diastolic blood pressure predicted marginally less well than models with systolic blood pressure. TGs were not found to be predictive of our endpoints after adjustment for other parameters, principally other lipids (cholesterol and HDL). Blood pressure was retained in the models for all three outcomes despite its marginal statistical significance (for MI and CHD; Table 3) because of its well-known association with CVD.

There were no significant interactions between sex and other predictors included in the models.

Internal–external cross validation

The performance of the DAD equations in individual cohorts, and a comparison with the Framingham equations, was assessed using internal–external cross validation. In this process, four of the 10 DAD subcohorts with fewer than 20 MI events were combined into a single cohort, thus giving a total of seven validations.

The DAD models performed reasonably well in terms of discriminating risks, with mean AROC of 0.783, 0.776 and

Table 3 Estimates (RR) based on Poisson regression models[a]

Endpoint	CVD		CHD		MI	
Predictor	HR	95% CI	HR	95% CI	HR	95% CI
Indinavir (per additional year)	1.04	1.00–1.08	–		1.07	1.02–1.12
Lopinavir/r (per additional year)	1.08	1.02–1.14	1.08	1.01–1.15	1.12	1.04–1.20
Abacavir (current exposure)	1.63	1.38–1.92	1.73	1.45–2.06	2.04	1.66–2.51
Male sex	1.70	1.32–2.18	1.76	1.33–2.32	1.93	1.36–2.74
Age (per 5 years older)	1.42	1.37–1.47	1.41	1.35–1.46	1.34	1.27–1.40
Family history of CVD	1.43	1.16–1.77	1.55	1.24–1.94	–	
Current cigarette smoking	2.35	1.92–2.87	2.78	2.21–3.51	4.02	2.96–5.46
Ex-smoking	1.27	1.00–1.61	1.62	1.23–2.12	2.01	1.41–2.86
Diabetes	1.92	1.55–2.38	1.93	1.52–2.44	2.28	1.73–3.01
Total cholesterol (per mmol/l higher)	1.21	1.16–1.27	1.24	1.19–1.30	1.28	1.22–1.34
HDL cholesterol (per mmol/l higher)	0.67	0.55–0.82	0.60	0.48–0.74	0.66	0.51–0.86
Systolic blood-pressure (per 10 mmHG higher)	1.05	1.03–1.08	1.04	1.00–1.07	1.04	1.00–1.08

CHD, coronary heart disease; CI, confidence interval; CVD, coronary vascular disease; HDL, high-density lipoprotein; HR, hazard ratio; RR, relative risk. [a]Variables not significantly associated with the outcome were excluded (indinavir from the CHD model, Family history of CVD from the MI model).

Table 4 Internal–external cross validation

	CVD		CHD		MI	
	DAD	Framingham	DAD	Framingham	DAD	Framingham
Area under the receiver operator characteristic curves						
Mean[a] (SD)	0.783 (0.040)	0.775 (0.040)	0.776 (0.044)	0.775 (0.032)	0.769 (0.032)	0.769 (0.031)
Range	0.642–0.820	0.648–0.807	0.670–0.818	0.661–0.809	0.695–0.824	0.686–0.817
Ratio of predicted to observed events						
Mean[a] (SD)	0.97 (0.25)	1.14 (0.30)	0.96 (0.25)	1.35 (0.35)	0.95 (0.24)	1.51 (0.37)
Range	0.71–1.45	0.78–1.71	0.67–1.44	0.91–2.00	0.76–1.42	1.13–2.26

CHD, coronary heart disease; CVD, coronary vascular disease; DAD, Data collection on Adverse Effects of Anti-HIV Drugs Study; MI, myocardial infarction. [a]Weighted mean and standard deviation (SD) across n cohorts of the DAD equation derived in (n-1) cohorts and applied to 1 cohort. Mean weighted by 1/variance. See text for further details.

0.769 for MI, CHD and CVD endpoints, respectively (Table 4). However, the Framingham equation appeared to give almost identical AROCs of 0.775, 0.775 and 0.769, respectively, indicating that this equation performed well in terms of the overall ordering of patients' cardiovascular risk.

The DAD equations, however, were found to be appreciably better calibrated. The mean ratio of the predicted-to-observed number of events was 0.97, 0.96 and 0.95 for the MI, CHD and CVD endpoints, respectively, compared with 1.14, 1.35 and 1.51, respectively, for the uncalibrated Framingham equation (Table 4). This indicates that while the Framingham equation orders patient risk well, it tended to overpredict the patient risk on a systematic basis. The DAD equation, on average across the independent validation subcohorts, seemed to calibrate well, although it is worth noting that the calibration in individual subcohorts with the DAD equation was still somewhat variable, ranging from ratios of around 0.7–1.4.

Accuracy and comparison with the Framingham model

Predicted and observed numbers of events for key prognostic subgroups are compared in Table 5 for the DAD risk equation and the Framingham equation (uncalibrated and recalibrated), respectively. This confirms that the uncalibrated Framingham equation tends to overpredict the risk of events, particularly for CHD and CVD endpoints. However, even the recalibrated Framingham equation, which has been forced to sum to the total observed number of events in the DAD cohort, does not predict well in certain subgroups. In particular, the Framingham tended to underpredict risk compared with the DAD equations in women (for MI and CHD outcomes), in former smokers and in diabetic patients, but over-predicted in never smokers. There was some borderline statistical evidence of lack of goodness-of-fit for the DAD equation ($P = 0.044$, 0.020 and 0.353 for CVD, CHD and MI, respectively). This compared with very highly statistically significant lack of fit using the recalibrated Framingham equation ($P < 0.001$ for all three endpoints).

Absolute risk

The absolute 5-year risk of CHD was calculated by applying the DAD CHD equation to each individual from the start of their follow-up. Overall, 8.7% of the study population was estimated to be at a high risk, and 3.1% at a very high risk, of developing CHD over a 5-year follow-up period (Table 6). These proportions were lowest in women (1.5 and 0.5% vs. 11.2 and 4.1% in men), younger

Table 5 Predicted versus observed number of endpoints over the observation period in 22 625 participants with complete CVD profile

	CVD observed	CVD predicted DAD equation	CVD predicted uncalibrated Framingham	CVD predicted recalibrated Framingham	CHD observed	CHD predicted DAD CHD equation	CHD predicted uncalibrated Framingham	CHD predicted recalibrated Framingham	MI observed	MI predicted DAD MI equation	MI predicted uncalibrated Framingham	MI predicted recalibrated Framingham
Total	663 (100)	631.1 (100)	1003.1 (100)	663 (100)	554 (100)	531.4 (100)	747.1 (100)	554.0 (100)	387 (100)	375.1 (100)	439.5 (100)	387.0 (100)
Men total	590 (89)	560.2 (89)	879.2 (88)	581.1 (88)	495 (89)	474.1 (89)	675.9 (90)	501.2 (90)	350 (90)	338.9 (90)	407.4 (93)	358.7 (93)
men ≤ 45	147 (22)	159.3 (25)	284.3 (28)	187.9 (28)	126 (23)	138.0 (26)	235.4 (32)	174.6 (32)	96 (25)	106.8 (28)	137.9 (31)	121.4 (31)
men > 45	443 (67)	400.9 (64)	594.9 (59)	393.2 (59)	369 (67)	336.1 (63)	440.5 (59)	326.6 (59)	254 (66)	232.1 (62)	269.5 (61)	237.3 (61)
Women total	73 (11)	70.9 (11)	123.9 (12)	81.9 (12)	59 (11)	57.3 (11)	71.2 (10)	52.8 (10)	37 (10)	35.2 (9)	32.2 (7)	28.3 (7)
women ≤ 55	48 (7)	48.6 (8)	92.1 (9)	60.9 (9)	41 (7)	39.9 (8)	51.5 (7)	38.2 (7)	26 (7)	27.0 (7)	23.3 (5)	20.5 (5)
women > 55	25 (4)	22.3 (4)	31.8 (3)	21.0 (3)	18 (3)	17.4 (3)	19.7 (3)	14.6 (3)	11 (3)	9.2 (2)	8.9 (2)	7.8 (2)
Smokers current	394 (59)	374.3 (59)	589.0 (59)	389.3 (59)	337 (61)	322.4 (61)	424.7 (57)	315.0 (57)	258 (67)	249.1 (67)	288.7 (66)	254.2 (66)
Former	132 (20)	125.5 (20)	178.6 (18)	118.0 (18)	119 (21)	114.0 (21)	139.6 (19)	103.5 (19)	78 (20)	75.7 (20)	66.2 (15)	58.3 (15)
Never	137 (21)	131.3 (21)	235.5 (23)	155.7 (23)	98 (18)	95.1 (18)	182.8 (25)	135.5 (24)	51 (13)	50.2 (13)	84.6 (19)	74.5 (19)
Diabetes No	557 (84)	536.0 (85)	884.8 (88)	584.8 (88)	467 (84)	451.8 (85)	666.6 (89)	494.3 (89)	321 (83)	313.4 (84)	383.3 (87)	337.5 (87)
Yes	106 (16)	95.1 (15)	118.3 (12)	78.2 (12)	87 (16)	79.6 (15)	80.5 (11)	59.7 (11)	66 (17)	61.6 (16)	56.7 (13)	49.5 (13)

Columns may not sum exactly due to rounding errors. CHD, coronary heart disease; CVD, coronary vascular disease; DAD, Data collection on Adverse Effects of Anti-HIV Drugs Study; MI, myocardial infarction.

Table 6 CHD 5-year risk stratification

	Low	Moderate	High	Very high
	< 1% 5-year risk	1–5%	5–10%	>10%
% population	34.7	53.5	8.7	3.1
% of men	21.6	63.1	11.2	4.1
% of women	71.9	26.1	1.5	0.5
% of nonsmokers	57.4	36.8	4.4	1.4
% of current smokers	23.2	62.9	10.2	3.7
% of younger individuals <40	57.3	42.0	0.7	0.04
% of older individuals 40 +	11.7	65.3	16.8	6.3
% of nondiabetics	35.8	54.0	7.9	2.3
% of diabetics	6.7	40.2	28.8	24.3

CHD, coronary heart disease.

individuals (0.7 and 0.04% vs. 16.8 and 6.3% in older) and nonsmokers (4.4 and 1.4% vs. 10.2 and 3.7% in current smokers).

Discussion

In a cohort of HIV-infected individuals, we created prediction equations for the risk of CVD endpoints, the performance of which seem superior to the Framingham prediction models in this population. The models include exposure to individual ART drugs (indinavir, lopinavir/r, abacavir) in addition to conventional CVD risk factors, and more accurately estimated the risk of CVD outcomes in the cohort overall and in subgroups. Cross validation suggests that the models are robust. However, validation of the models on independent data sets is warranted to determine whether the equations can be generalized among HIV-infected individuals.

Although earlier studies suggest higher rates of CVD in HIV-infected individuals compared with the background population [27,28], we found that the Framingham equation overpredicted all the assessed outcomes in our population. It should be noted that the applied Framingham equation is known to overpredict in European populations [23,29,30].

When comparing our risk estimates with those obtained from the Framingham equation, particular attention should be paid to the differences in the study demographics and outcome definition used in the studies (Table 1). First, the Framingham risk score was developed for a non-HIV-infected and non-ART-exposed American population, aged 30–74 years, followed for up to 12 years from a baseline between 1968 and 1975. The HIV-infected population in the DAD Study is slightly younger, with diverse geographical distribution (although predominantly European), and the majority is ART exposed. Follow-up in the DAD Study is also substantially shorter, limiting the time periods over which predictions can reliably be made.

The endpoint that is most similar between the studies is the narrowest MI, although some differences also apply for this endpoint. For example, unclassifiable MIs (sudden death) were included in the DAD endpoint but not in the original Framingham risk function [22]. However, silent MIs were included in the Framingham risk function but not in the DAD Study.

Broader definitions of the composite CHD and CVD endpoints were applied in the Framingham Study than what was available and applied in the DAD Study (Table 1).

At its conception, the DAD Study decided to collect data on 'hard CVD outcomes' according to definitions applied in the WHO MONICA Study [12], and information on angina pectoris has not been obtained.

Recalibration of the Framingham score to some extent facilitates comparison of predictions, which is further aided by comparing the proportional distribution of predicted risk in subgroups (Table 5).

To this effect, the DAD equation predicted higher relative proportions of all three endpoints in the subgroup of smokers (current or former).

A dose–effect relationship of smoking and CVD risk is well described [17], and very high smoking prevalence and individual cigarette consumption have been reported in populations of HIV-infected persons [31–33]. This would imply that the net effect of smoking fitted in the Framingham equation as a qualitative parameter is likely to be less than the effect in an HIV-infected population, which could explain the differential impact of smoking.

Age is an important predictor of CVD. It has been proposed that chronic infections, and in particular, the faulty immunological processes seen in HIV infection, may be associated with an accelerated aging process [34]. However, at present, our findings do not suggest a larger-than-expected effect of aging with respect to CVD risk. Notably, the risk of CVD in younger HIV-infected individuals does not exceed predictions from the Framingham score.

In our study, the Framingham equation tended to underestimate the risk of CHD outcomes in patients with diabetes. This suggests that the presence of diabetes in HIV-infected persons, although not a CHD risk equivalent [35], is not a lesser risk factor for CHD than would be the case for a diagnosis of diabetes in the background population, but rather the opposite.

The presence of diabetes was associated with similar relative risks of all assessed CVD endpoints in women compared with men, but no amplified effect as reported by some studies of non-HIV-infected populations [36–38].

Equally, all other predictors were associated with similar relative risks in both sexes (i.e. there were no significant interactions), although the absolute risk of all CVD endpoints was considerably lower in women.

However, as the number of endpoints in women is limited, chance variation may influence these findings, which should be interpreted cautiously. At present the DAD Study has too limited data in women to develop separate sex-specific prediction models.

Earlier studies, which have used prediction models to estimate CHD risk in HIV-infected patients and included the potential impact of ART drugs on CHD risk, have done this by incorporating the observed risk factor profiles and have not taken into account the potential independent effect of individual ART drugs over and above their metabolic effects [8,39,40]. Through the present models, we wanted to incorporate all established important and independent risk factors for CVD in HIV-infected patients. At present, there is evidence to suggest that the PIs, lopinavir/r and indinavir and the nucleoside analogue, abacavir, have independent effects on CHD risk over and above their potential metabolic effects [5–7,14,15,41]. As the pattern of the MI risk association described earlier for these drugs differs, with a cumulative effect described for the PIs but an on/off effect of more acute onset for abacavir, the drugs were fitted accordingly in our models. Indeed, we found very similar associations as reported earlier. It should be noted that the present models can be considered as 'fully adjusted'. For the PIs, the association of these drugs with the risk of CHD is in part explained through their effect on lipid levels. Hence, the full effect of these drugs on the risk of CHD includes their lipid effect and the independent drug effect.

With regard to the overall ordering of patients' cardiovascular risk, the DAD equations performed marginally better than the Framingham equation, as assessed by the AROC analyses. However, the DAD equations proved superior with regard to accuracy and prediction in subgroups. This finding was in accordance with earlier analyses based on baseline rather than time-updated data [42].

Nevertheless, the Framingham also performed well, suggesting that the conventional CVD risk factors may be largely interpreted, at least qualitatively, similarly in HIV-infected populations as uninfected populations – with the above-mentioned caveats.

It should be noted that the calibration varied between DAD subcohorts, likely, in part, reflecting the regional differences in underlying the CVD rates [12].

Application of models

Calculating an individual's predicted risks is described in the Appendix. Although pending external validation, our

models are intended for clinical usage to inform doctor–patient discussions on CVD risks and interventions, and for research purposes of estimations of predicted risk/benefit ratios associated with ART therapy. With regard to the latter, several equations have been developed and validated, which predict the risk of HIV disease progression for patients receiving combination ART [43,44]. 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. In addition, if the prognosis regarding the risk of CVD determined by these models is poor for an individual patient, more targeted interventions to reduce this risk may be recommended, including life-style changes and medicinal interventions [45].

Acknowledgements

DAD Steering Committee: Persons with * below (#: chair) and S. Collins, D. Pizzuti, S. Storfer, I. Weller; DAD Central Coordination: S.W. Worm, C.A. Sabin, N. Friis-Mller, J. Tverland, A. Sjl (verification of primary endpoint), J.D. Lundgren; DAD data managers: A. Sawitz (coordinator), M. Rickenbach, L. Fanti, E. Krum, L. Gras, S. Geffard, A. Sundström, M. Delforge, E. Fontas, F. Torres, K. Petoumenos, J. Kjær. ATHENA (AIDS Therapy Evaluation Project Netherlands): Central coordination: F. de Wolf, S. Zaheri, L. Gras; Participating physicians (city): W. Bronsveld, M.E. Hillebrand-Haverkort (Alkmaar), J.M. Prins, J.C. Bos, J.K.M. Eeftinck Schattenkerk, S.E. Geerlings, M.H. Godfried, J.M.A. Lange, F.C. van Leth, S.H. Lowe, J.T.M. van der Meer, F.J.B. Nellen, K. Pogány, T. van der Poll, P. Reiss*, Th.A. Ruys, Sankatsing, R. Steingrover, G. van Twillert, M. van der Valk, M.G.A. van Vonderen, S.M.E. Vrouenraets, M. van Vugt, F.W.M.N. Wit, A. van Eeden, J.H. ten Veen, P.S. van Dam, J.C. Roos, K. Brinkman, P.H.J. Frissen, H.M. Weigel, J.W. Mulder, E.C.M. van Gorp, P.L. Meenhorst, A.T.A. Mairuhu, J. Veenstra, S.A. Danner, M.A. Van Agtmael, F.A.P. Claessen, R.M. Perenboom, A. Rijkeboer, M. van Vonderen (Amsterdam); C. Richter, J. van der Berg, R. van Leusen (Arnhem); R. Vriesendorp, F.J.F. Jeurissen, R.H. Kauffmann, E.L.W. Koger, HAGA (Den Haag); B. Bravenboer (Eindhoven); C.H.H. ten Napel, G.J. Kootstra (Enschede); H.G. Sprenger, W.M.A.J. Miesen, R. Doedens, E.H. Scholvinck (Groningen); R.W. ten Kate (Haarlem); D.P.F. van Houte, M. Polee (Leeuwarden); F.P. Kroon, van den Broek, J.T. van Dissel, E.F. Schippers (Leiden); G. Schreij, S. van de Geest, A. Verbon (Maastricht); P.P. Koopmans, M. Keuter, F. Post, A.J.A.M. van der Ven (Nijmegen); M.E. van der Ende, I.C. Gyssens, M. van der Feltz, J.G. den Hollander, S. de Marie, J.L. Nouwen, B.J.A. Rijnders, T.E.M.S. de Vries (Rotterdam); J.R. Juttmann, C. van de Heul, M.E.E. van Kasteren, St Elisabeth (Tilburg); M.M.E. Schneider, M.J.M. Bonten, J.C.C. Borleffs, P.M. Ellerbroek, I.M. Hoepelman, C.A.J.J. Jaspers, I. Schouten, C.A.M. Schurink (Utrecht); W.L. Blok, A.A. Tanis (Vlissingen); P.H.P. Groeneveld (Zwolle). Aquitaine (France): Scientific committee: M. Dupon, M. Longy-Boursier, P. Morlat, J.L. Pellegrin, J.M. Ragnaud and F. Dabis; Central coordination: F. Dabis*, G. Chêne, R. Thiébaut, S. Lawson-Ayayi, M. Bruyand, M.J. Blaizeau, M. Decoin, S. Delveaux, C. Hannapier, C. d'Ivernois, O. Leleux, B. Uwamaliya-Nziyumvira, S. Geffard, G. Palmer, D. Touchard. Participating physicians (city): F. Bonnal, S. Farbos (Bayonne); M. Bonarek, F. Bonnet, N. Bernard, O. Caubet, C. Cazanave, F.A. Dauchy, C. De La Taille, M. Dupon, P. Duffau, H. Dutronc, C. Greib, D. Lacoste, S. Lafarie, E. Lazaro, D. Malvy, P. Mercié, P. Morlat, D. Neau, A. Ochoa, J.L. Pellegrin, M. Pillot-Debelleix, T. Pistone, J.M. Ragnaud, M.C. Receveur, M.A. Vandenhende, J.F. Viallard, P. Blanco, J.F. Moreau, H. Fleury, M.E. Lafon, B. Masquelier, I. Pellegrin, D. Breilh, G. Miremont-Salamé (Bordeaux); L. Caunègre, Y. Gerard, P. Loste (Dax); J. Ceccaldi, S. Tchamgoué (Libourne); S. De Witte (Mont de Marsan). AHOD (Australian HIV Observational Database, Australia): Central coordination: M. Law*, K. Petoumenos (Sydney, New South Wales); Participating physicians(city, state): J. Anderson, P. Cortossis, J. Hoy, K. Watson, N. Roth, J. Nicholson (Melbourne, Victoria); M. Bloch, T. Franic, D. Baker, R. McFarlane, A. Carr, D. Cooper (Sydney, New South Wales); J. Chuah, W. Fankhauser (Gold Coast, Queensland), S. Mallal, C. Forsdyke (Perth, Western Australia). BASS (Spain): Central coordination: G. Calvo*, F. Torres, S. Mateu (Barcelona); Participating physicians (city): P. Domingo, M.A. Sambeat, J. Gatell, E. Del Cacho, J. Cadafalch, M. Fuster (Barcelona); C. Codina, G. Sirera, A. Vaqué (Badalona). The Brussels St Pierre Cohort (Belgium): N. Clumeck, S. De Wit*, M. Gerard, K. Kabeya, D. Konopnicki, A. Libois, M.C. Payen, B. Poll, Y. Van Laethem. CPCRA (USA): Central coordination: J. Neaton, G. Bartsch, W.M. El-Sadr*, E. Krum, G. Thompson, D. Wentworth; Participating physicians (city, state): R. Luskin-Hawk (Chicago, Illinois); E. Telzak (Bronx, New York); W.M. El-Sadr (Harlem, New York); D.I. Abrams (San Francisco, California); D. Cohn (Denver, Colorado); N. Markowitz (Detroit, Michigan); R. Arduino (Houston, Texas); D. Mushatt (New Orleans, Louisiana); G. Friedland (New Haven, Connecticut); G. Perez (Newark, New Jersey); E. Tedaldi (Philadelphia, Pennsylvania); E. Fisher (Richmond, Virginia); F. Gordin (Washington, DC); L.R. Crane (Detroit, Michigan); J. Sampson (Portland, Oregon); J. Baxter (Camden, New Jersey). EuroSIDA (multinational): Central coordination: O. Kirk*, A. Mocroft, M. Ellefson, A.N. Phillips*, J.D. Lundgren*,#; Participating countries and physicians: Argentina: M. Losso, C. Elias, Austria: N. Vetter) R. Zangerle, Belarus: I. Karpov, A. Vassilenko, V.M. Mitsura, O. Suetnov, Belgium: N. Clumeck, S. De Wit, B. Poll, R. Colebunders, L. Vandekerckhove, Bosnia: V. Hadziosmanovic, Bulgaria:

K. Kostov, Croatia: I. Begovac, Czech Republic: L. Machala, H. Rozsypal, D. Sedlacek, Denmark: J. Nielsen, G. Kronborg, T. Benfield, M. Larsen, J. Gerstoft, T. Katzenstein, A.-B.E. Hansen, P. Skinhj, C. Pedersen, L. Oestergaard, Estonia: K. Zilmer, Jelena Smidt, Finland: M. Ristola,. France: C. Katlama, J.-P. Viard, P.-M. Girard, J.M. Livrozet, P. Vanhems, C. Pradier, F. Dabis, D. Neau, Germany: J. Rockstroh, R. Schmidt, J. van Lunzen, O. Degen, H.J. Stellbrink, S. Staszewski, J. Bogner, G. Fätkenheuer, Greece: J. Kosmidis, P. Gargalianos, G. Xylomenos, J. Perdios, G. Panos, A. Filandras, E. Karabatsaki, H. Sambatakou, Hungary: D. Banhegyi, Ireland: F. Mulcahy, Israel: I. Yust, D. Turner, M. Burke, S. Pollack, G. Hassoun, S. Maayan, Italy: A. Chiesi, R. Esposito, I. Mazeu, C. Mussini, C. Arici, Ospedale Riuniti, Bergamo, R. Pristera, F. Mazzotta, A. Gabbuti, V. Vullo, M. Lichtner, A. Chirianni, E. Montesarchio, M. Gargiulo, G. Antonucci, F. Iacomi, P. Narciso, C. Vlassi, M. Zaccarelli, A. Lazzarin, R. Finazzi, M. Galli, A. Ridolfo, A. d'Arminio Monforte, Latvia: B. Rozentale P. Aldins, Lithuania: S. Chaplinskas, Luxembourg: R. Hemmer, T. Staub, Netherlands: P. Reiss, Norway: J. Bruun, A. Maeland, V. Ormaasen, Poland: B. Knysz, J. Gasiorowski, A. Horban, E. Bakowska, D. Prokopowicz, R. Flisiak, A. Boron-Kaczmarska, M. Pynka, M. Beniowski, E. Mularska, Chorzow; H. Trocha, (E. Jablonowska) E. Malolepsza, K. Wojcik, Portugal: F. Antunes, E. Valadas, K. Mansinho, F. Maltez, Romania: D. Duiculescu,. Russia: A. Rakhmanova, E. Vinogradova, S. Buzunova, Serbia: D. Jevtovic, Slovakia: M. Mokráš, D. Staneková, Slovenia: J. Tomazic, Spain: J. González-Lahoz, V. Soriano, L. Martin-Carbonero, P. Labarga, (S. Moreno), B. Clotet, A. Jou, R. Paredes, C. Tural, J. Puig, I. Bravo, J.M. Gatell, J.M. Miró, P. Domingo, M. Gutierrez, G. Mateo, M.A. Sambeat, Sweden: A. Karlsson, P.O. Persson, L. Flamholc, Switzerland: B. Ledergerber, R. Weber, Francioli, M. Cavassini, B. Hirschel, E. Boffi, H. Furrer, M. Battegay, L. Elzi, Ukraine: E. Kravchenko, N. Chentsova, (G. Kutsyna), (S. Servitskiy), (S. Antoniak), (M. Krasnov), United Kingdom: S. Barton, A.M. Johnson, D. Mercey, A. Phillips, M.A. Johnson, A. Mocroft, M. Murphy, J. Weber, G. Scullard, M. Fisher, C. Leen. HivBivus (Sweden): Central coordination: L. Morfeldt*, G. Thulin, A. Sundström; Participating physicians (city): B. Akerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholc, C. Håkangård (Malmö). The ICONA Foundation (Italy): Central coordination: A. d'Arminio Monforte*, P. Pezzotti; Participating physicians (city): M. Montroni, G. Scalise, A. Costantini, A. Riva (Ancona); U. Tirelli, F. Martellotta (Aviano-PN); G. Pastore, N. Ladisa, (Bari); F. Suter, F. Maggiolo (Bergamo); F. Chiodo, V. Colangeli, C. Fiorini, (Bologna); G. Carosi, G. Cristini, C. Torti, C. Minardi, D. Bertelli (Brescia); T. Quirino, (Busto Arsizio); P.E. Manconi, P. Piano (Cagliari); E. Pizzigallo, M. D'Alessandro (Chieti); G. Carnevale, A. Zoncada (Cremona); F. Ghinelli, L. Sighinolfi (Ferrara); F. Leoncini, F. Mazzotta, M. Pozzi, S. Lo Caputo (Firenze); B. Grisorio, S. Ferrara (Foggia); G. Pagano, G. Cassola, A. Alessandrini, R. Piscopo (Genova); F. Soscia, L. Tacconi (Latina); A. Orani, P. Perini (Lecco); D. Tommasi, P. Congedo (Lecce); F. Chiodera, P. Castelli (Macerata); M. Moroni, A. Lazzarin, G. Rizzardini, L. Caggese, A. d'Arminio Monforte, A. Galli, S. Merli, C. Pastecchia, M.C. Moioli (Milano); R. Esposito, C. Mussini (Modena); A. Gori, S. Cagni (Monza), N. Abrescia, A. Chirianni, C.M. Izzo, M. De Marco, R. Viglietti, E. Manzillo (Napoli); C. Ferrari, P. Pizzaferri (Parma); G. Filice, R. Bruno, (Pavia); G. Magnani, M.A. Ursitti (Reggio Emilia); M. Arlotti, P. Ortolani (Rimini); R. Cauda, M. Andreoni, A. Antinori, G. Antonucci, P. Narciso, V. Tozzi, V. Vullo, A. De Luca, M. Zaccarelli, R. Acinapura, P. De Longis, M.P. Trotta, M. Lichtner, F. Carletti, (Roma); M.S. Mura, M. Mannazzu (Sassari); P. Caramello, G. Di Perri, G.C. Orofino, M. Sciandra (Torino); E. Raise, F. Ebo (Venezia); G. Pellizzer, D. Buonfrate (Vicenza). The Nice Cohort (France): Central coordination: C. Pradier*, E. Fontas, C. Caissotti; Participating physicians: P. Dellamonica, L. Bentz, E. Bernard, F. De Salvador-Guillouet, J. Durant, V. Mondain-Miton, I. Perbost, B. Prouvost-Keller, P. Pugliese, V. Rahelinirina, P.M. Roger, F. Vandenbos. S.H.C.S. (Swiss HIV Cohort Study, Switzerland): M. Battegay, E. Bernasconi, J. Böni, H. Bucher, Ph. Bürgisser, S. Cattacin, M. Cavassini, R. Dubs, M. Egger, L. Elzi, P. Erb, M. Fischer, M. Flepp, A. Fontana, P. Francioli (President of the SHCS), H.J. Furrer, M. Gorgievski, H. Günthard, B. Hirschel, L. Kaiser, C. Kind, Th. Klimkait, U. Lauper, B. Ledergerber, M. Opravil, F. Paccaud, G. Pantaleo, L. Perrin, J.-C. Piffaretti, M. Rickenbach, C. Rudin, P. Schmid, J. Schüpbach, R. Speck, A. Telenti, A. Trkola, P. Vernazza, R. Weber*, S. Yerly. The study was supported by the Oversight Committee for The Evaluation of Metabolic Complications of HAART, a collaborative committee with representation from academic institutions, the European Agency for the valuation of Medicinal Products, the Food and Drug Administration, the patient community, and all pharmaceutical companies with licensed anti-HIV drugs in the US market: Abbott, Boehringer Ingelheim, Bristol–Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Hoffman–LaRoche. Supported by a grant (CURE/97-46486) from the Health Insurance Fund Council, Amstelveen, The Netherlands, to the AIDS Therapy Evaluation Project Netherlands (ATHENA); by a grant from the Agence Nationale de Recherches sur le SIDA (Action Coordonnée no.7, Cohortes), to the Aquitaine Cohort; AHOD is funded by the Australian Government Department of Health and Ageing and is supported in part by grants from the U.S. National Institutes of Health's National Institute of Allergey and Infectious Diseases (NIAID) grant no U01-AI069907, and the Foundation for AIDS Research; by grants from the Fondo de Investigación Sanitaria (FIS 99/0887) and Fundación para la Investigación y la Prevención del SIDA en Espanã (FIPSE 3171/00), to the Barcelona Antiretroviral Surveillance Study

(BASS); by the National Institute of Allergy and Infectious Diseases, National Institutes of Health (grants 5U01AI042170–10 and 5U01AI046362–03), to the Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA); by grants from the BIOMED 1 (CT94–1637) and BIOMED 2 (CT97–2713) programs and the fifth framework program (QLK2-2000–00773)of the European Commission and grants from Bristol-Myers Squibb, GlaxoSmithKline, Boehringer Ingelheim, and Roche, to the EuroSIDA study; by unrestricted educational grants of Abbott, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, GSK, Pfizer, Janssen-Cilag to the Italian Cohort Naive to Antiretrovirals (The ICONA Foundation); and by a grant from the Swiss National Science Foundation, to the Swiss HIV Cohort Study (SHCS). Disclosures: M.G. Law has received research grants, consultancy and/or travel grants from Abbott; Boehringer Ingelheim; Bristol–Myers Squibb; Gilead; GlaxoSmithKline; Janssen-Cilag; Johnson & Johnson; Merck Sharp & Dohme; Pfizer; Roche; CSL Ltd.

References

1 Mary-Krause M, Cotte L, Simon A, Partisani M, Costagliola D. Increased risk of myocardial infarction with duration of protease inhibitor therapy in HIV-infected men. *AIDS* 2003; **17**:2479–2486.
2 Holmberg SD, Moorman AC, Williamson JM, Tong TC, Ward DJ, Wood KC, *et al.* Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* 2002; **360**:1747–1748.
3 Iloeje U, Yuan Y, L'Italien G, Mauskopf J, Holmberg S, Moorman A, *et al.* Protease inhibitor exposure and increased risk of cardiovascular disease in HIV-infected patients. *HIV Med* 2005; **6**:37–44.
4 The D:A:D Study group. Risk of myocardial infarction in association with different classes of antiretroviral drugs. *N Engl J Med* 2007; **356**:1723–1735.
5 Sabin CA, Worm SW, Weber R, Reiss P, El-Sadr W, Dabis F, *et al.* Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* 2008; **371**:1417–1426.
6 Strategies for Management of Anti-Retroviral Therapy/INSIGHT and DAD Study Groups. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients. *AIDS* 2008; **22**:F17–F24.
7 Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, *et al.* Risk of myocardial infarction in HIV patients exposed to specific antiretroviral drugs from the three major drug classes: the D:A:D study. *J Infect Dis* 2009; **201**:318–330.
8 Law MG, Friis-Moller N, El-Sadr WM, Weber R, Reiss P, d'Arminio MA, *et al.* The use of the Framingham equation to predict myocardial infarctions in HIV-infected patients: comparison with observed events in the D:A:D Study. *HIV Med* 2006; **7**:218–230.
9 El-Sadr WM, Lundgren JD, Neaton JD, Gordin F, Abrams D, Arduino RC, *et al.* CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* 2006; **355**:2283–2296.
10 The D:A:D Study group. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; **349**:1993–2003.
11 D'Arminio A, Sabin CA, Phillips AN, Reiss P, Weber R, Kirk O, *et al.* Cardio- and cerebrovascular events in HIV-infected persons. *AIDS* 2004; **18**:1811–1817.
12 Tunstall-Pedoe H, Kuulasmaa K, Amouyel P, Arveiler D, Rajakangas AM, Pajak A. Myocardial infarction and coronary deaths in the World Health Organization MONICA Project. Registration procedures, event rates, and case-fatality rates in 38 populations from 21 countries in four continents. *Circulation* 1994; **90**:583–612.
13 WHO MONICA Project. MONICA Manual, part IV, Event Registration. [Accessed 28 October 2009], at (*http:/www.ktl.fi/publications/monica/manual/part4/iv-1.htm*). 1999.
14 Lang S, Mary-Krause M, Cotte L, Gilquin J, Partisani M, Simon A, et al. (abstract #43LB) Impact of specific NRTI and PI exposure on the risk of myocardial infarction: a case-control study nested within FHDH ANRS CO4. Montreal, Canada: 16th Conference on Retroviruses and Opportunistic Infections; 2009.
15 Hsue PY, Hunt PW, Wu Y, Schnell A, Ho JE, Hatano H, *et al.* Association of abacavir and impaired endothelial function in treated and suppressed HIV-infected patients. *AIDS* 2009; **23**:2021–2027.
16 Martin A, Bloch M, Amin J, Baker D, Cooper DA, Emery S, Carr A. Simplification of antiretroviral therapy with tenofovir-emtricitabine or abacavir-lamivudine: a randomized, 96-week trial. *Clin Infect Dis* 2009; **49**:1591–1601.
17 Teo KK, Ounpuu S, Hawken S, Pandey MR, Valentin V, Hunt D, *et al.* Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006; **368**:647–658.
18 Lewington S, Whitlock G, Clarke R, Sherliker P, Emberson J, Halsey J, *et al.* Blood cholesterol and vascular mortality by age, sex, and blood pressure: a meta-analysis of individual data from 61 prospective studies with 55 000 vascular deaths. *Lancet* 2007; **370**:1829–1839.
19 Lewington S, Clarke R, Qizilbash N, Peto R, Collins R. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet* 2002; **360**:1903–1913.
20 Chirovsky DR, Fedirko V, Cui Y, Sazonov V, Barter P. Prospective studies on the relationship between high-density lipoprotein cholesterol and cardiovascular risk: a systematic review. *Eur J Cardiovasc Prev Rehabil* 2009; **16**:404–423.
21 Thomsen T. HeartScore: a new web-based approach to European cardiovascular disease risk management. *Eur J Cardiovasc Prev Rehabil* 2005; **12**:424–426.
22 Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. *Am Heart J* 1991; **121**(1 Pt 2):293–298.
23 De Visser CL, Bilo HJ, Thomsen TF, Groenier KH, Meyboom-de Jong B. Prediction of coronary heart disease: a comparison between the Copenhagen risk score and the Framingham risk score applied to a Dutch population. *J Intern Med* 2003; **253**:553–562.
24 D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001; **286**:180–187.
25 Royston P, Parmar MK, Sylvester R. Construction and validation of a prognostic model across several studies, with an application in superficial bladder cancer. *Stat Med* 2004; **23**:907–926.
26 May M, Royston P, Egger M, Justice AC, Sterne JA. Development and validation of a prognostic model for survival time data: application to prognosis of HIV positive patients treated with antiretroviral therapy. *Stat Med* 2004; **23**:2375–2398.
27 Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007; **92**:2506–2512.
28 Obel N, Thomsen HF, Kronborg G, Larsen CS, Hildebrandt PR, Sorensen HT, Gerstoft J. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis* 2007; **44**:1625–1631.
29 Cooper JA, Miller GJ, Humphries SE. A comparison of the PROCAM and Framingham point-scoring systems for estimation of individual risk of coronary heart disease in the Second Northwick Park Heart Study. *Atherosclerosis* 2005; **181**:93–100.
30 Thomsen TF, McGee D, Davidsen M, Jorgensen T. A cross-validation of risk-scores for coronary heart disease mortality based on data from the Glostrup Population Studies and Framingham Heart Study. *Int J Epidemiol* 2002; **31**:817–822.
31 Friis-Moller N, Weber R, Reiss P, Thiebaut R, Kirk O, d'Arminio MA, *et al.* Cardiovascular disease risk factors in HIV patients–association with antiretroviral therapy. Results from the DAD study. *AIDS* 2003; **17**:1179–1193.
32 Benard A, Tessier JF, Rambeloarisoa J, Bonnet F, Fossoux H, Neau D, *et al.* HIV infection and tobacco smoking behaviour: prospects for prevention? ANRS CO3 Aquitaine Cohort, 2002. *Int J Tuberc Lung Dis* 2006; **10**:378–383.
33 Patel N, Talwar A, Reichert VC, Brady T, Jain M, Kaplan MH. Tobacco and HIV. *Clin Occup Environ Med* 2006; **5**:193–207, xi.
34 Effros RB. From Hayflick to Walford: the role of T cell replicative senescence in human aging. *Exp Gerontol* 2004; **39**:885–890.
35 Worm SW, De WS, Weber R, Sabin CA, Reiss P, El-Sadr W, *et al.* Diabetes mellitus, preexisting coronary heart disease, and the risk of subsequent coronary heart disease events in patients infected with human

immunodeficiency virus: the data collection on adverse events of Anti-HIV Drugs (D:A:D Study). *Circulation* 2009; **119**:805–811.
36 Barrett-Connor EL, Cohn BA, Wingard DL, Edelstein SL. Why is diabetes mellitus a stronger risk factor for fatal ischemic heart disease in women than in men? The Rancho Bernardo Study. *JAMA* 1991; **265**:627–631.
37 Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, *et al.* Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet* 2004; **364**:937–952.
38 Lee WL, Cheung AM, Cape D, Zinman B. Impact of diabetes on coronary artery disease in women and men: a meta-analysis of prospective studies. *Diabetes Care* 2000; **23**:962–968.
39 Kaplan RC, Kingsley LA, Sharrett AR, Li X, Lazar J, Tien PC, *et al.* Ten-year predicted coronary heart disease risk in HIV-infected men and women. *Clin Infect Dis* 2007; **45**:1074–1081.
40 May M, Sterne JA, Shipley M, Brunner E, d'Agostino R, Whincup P, *et al.* A coronary heart disease risk model for predicting the effect of potent antiretroviral therapy in HIV-1 infected men. *Int J Epidemiol* 2007; **36**:1309–1318.
41 Kristoffersen US, Kofoed K, Kronborg G, Benfield T, Kjaer A, Lebech AM. Changes in biomarkers of cardiovascular risk after a switch to abacavir in HIV-1-infected individuals receiving combination antiretroviral therapy. *HIV Med* 2009; **10**:627–633.
42 Friis-Moller N, Thiebaut R, Reiss P, El-Sadr W, Worm S, Kirk O, et al. (abstract 808) Predicting the Risk of Coronary Heart Disease in HIV-infected Patients: The D:A:D Risk Equation. Los Angeles: 14th Conference on Retroviruses and Opportunistic Infections; 2007.
43 Lundgren JD, Mocroft A, Gatell JM, Ledergerber B, d'Arminio MA, Hermans P, *et al.* A clinically prognostic scoring system for patients receiving highly active antiretroviral therapy: results from the EuroSIDA study. *J Infect Dis* 2002; **185**:178–187.
44 May MT, Sterne JA, Costagliola D, Sabin CA, Phillips AN, Justice AC, *et al.* HIV treatment response and prognosis in Europe and North America in the first decade of highly active antiretroviral therapy: a collaborative analysis. *Lancet* 2006; **368**:451–458.
45 Lundgren JD, Battegay M, Behrens G, De WS, Guaraldi G, Katlama C, *et al.* European AIDS Clinical Society (EACS) guidelines on the prevention and management of metabolic diseases in HIV. *HIV Med* 2008; **9**:72–81.

Appendix

The risk of CVD, CHD or MI are estimated as:

$1 - \exp^{(-H*t)}$; where

$$H = \exp^{\beta_0+\beta_1x_1+\beta_2x_2+\beta_3x_3+\beta_4x_4+\beta_5x_5+\beta_6x_6 +\beta_7x_7+\beta_8x_8+\beta_9x_9+\beta_{10}x_{10}+\beta_{11}x_{11}+\beta_{12}x_{12}}$$

The values for beta and x for the three endpoints are summarised below:

	CVD	CHD	MI	Covariate, x
β_0	−10.970	−11.014	−11.695	
β_1	0.041	0	0.069	Multiply by duration of indinavir in years
β_2	0.077	0.074	0.111	Multiply by duration of lopinavir in years
β_3	0.489	0.547	0.715	β value if receiving abacavir, 0 otherwise
β_4	0.530	0.563	0.660	β value if male, 0 if female
β_5	0.348	0.342	0.291	β value times age/5
β_6	0.361	0.439	0	β value if family CVD history,0 otherwise
β_7	0.854	1.024	1.390	β value if current smoker, 0 otherwise
β_8	0.238	0.481	0.697	β value if ex-smoker, 0 otherwise
β_9	0.652	0.654	0.826	β value if diabetes, 0 otherwise
β_{10}	0.195	0.219	0.246	multiply by cholesterol (mmol/l)
β_{11}	−0.402	−0.518	−0.415	multiply by HDL (mmol/l)
β_{12}	0.054	0.035	0.039	multiply by systolic blood pressuer/10

CHD, coronary heart disease; CVD, coronary vascular disease; HDL, high-density lipoprotein; MI, myocardial infarction.

Data in the DAD study are set up in monthly time units (0.085 years); the above equation therefore produces a monthly probability of developing CVD, CHD or MI. A reasonably good approximation for calculating the estimated probability over longer time periods, t, is to multiply 'H' by t years, and use indinavir + t/2 (if continuing on indinavir), lopinavir + t/2 (if continuing lopinavir) and age + t/2 in the equation. More exact computation will be available through a calculator on the DAD website (*http://www.cphiv.dk/*).

Worked example

Consider an individual who is male, 48.7 years of age, received 1 year indinavir in the past, currently receiving lopinavir for 1.5 years, not receiving abacavir, no family history of CVD, current smoker, no diabetes, and with cholesterol = 6 mmol/l, HDL = 1.0 mmol/l and systolic BP = 130 mmHg.

To calculate a 12 month estimated risk of CVD we first calculate:

$$\beta_1 x_1 = 0.041 * 1, \beta_2 x_2 = 0.154\,[\text{calculated as } 0.077^* (1.5 + 1/2)], \beta_3 x_3 = 0, \beta_4 x_4 = 0.530$$

$$\beta_5 x_5 = 3.424\,\{\text{calculated as } 0.348 * [(48.7 + 1/2)/5]\}, \beta_6 x_6 = 0, \beta_7 x_7 = 0.854, \beta_8 x_8 = 0$$

$$\beta_9 x_9 = 0, \beta_{10} x_{10} = 0.195 * 6.0 = 1.170, \beta_{11} x_{11} = -0.402 * 1, \text{and } \beta_{12} x_{12} = 0.054 * (130/10) = 0.702$$

$$\text{Then } H * t = 1 * (-10.970 + 0.041 + 0.154 + 0.530 + 3.424 + 0 + 0.854 + 0 + 0 + 1.170 - 0.402 + 0.702) = -4.497$$

The converted 12 month predicted risk of CVD is

$$\text{then } 1 - \exp[-\exp(-4.497)] = 1.1\%$$

Recalibrated Framingham equation

Calculation of the uncalibrated Framingham predicted risk of CVD, CHD and MI used in our study is described in the paper by Andersen *et al.* [22]. An algorithm for calculating the uncalibrated Framingham risk is also available on the CHIP website (*www.cphiv.dk*) under TOOLS. The calibrated predicted risk used in our study is calculated by multiplying the uncalibrated predicted risks for CVD, CHD and MI by 0.66, 0.74 and 0.88, respectively.

AUTHOR QUERY FORM

LIPPINCOTT
WILLIAMS AND WILKINS

JOURNAL NAME: HJR
ARTICLE NO: 200632
QUERIES AND / OR REMARKS

QUERY NO.	Details Required	Author's Response
	No queries	