D:A:D

9th International Congress on Drug Therapy in HIV Infection Glasgow 2008

Predicting the short term risk of diabetes in HIV infected patients
The D:A:D study group

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BACKGROUND

- Diabetes mellitus (DM) is a major risk factor for cardiovascular disease (CVD) among the general population, and a strong risk factor for CVD in HIV infected patients
- Prediction models for DM exist in the general population, but have not yet been assessed in the HIV infected population. In the Framingham Offspring Study, a simple prediction algorithm was developed to determine the 8 year risk for Type 2 DM. Included in this algorithm were: parental diabetes, BMI, blood pressure, HDL, triglycerides, and fasting glucose level
- We developed a DM risk equation for HIV infected patients

METHODS

- The D:A:D study is a prospective, multi-national observational study formed by the collaboration of 11 cohorts of HIV-infected patients. The primary objective of the study is to establish whether the use of combination antiretroviral therapy is associated with an increased risk of cardiovascular disease
- 33,389 HIV infected individuals are followed in 212 clinics in Europe, the US and Australia
- New onset DM endpoint was defined as either definite, if there was documented fasting plasma glucose of higher than or equal to 7.0 mmol/L measured on two or more consecutive occasions, or; possible if the patient was recorded as being diabetic with a reported date of onset,and was known to have initiated anti-diabetic therapy
- The analyses include all patients recruited to D:A:D with follow-up data and a complete DM risk factor profile, without prior DM or MI or other CVD events. Risk factors included: plasma glucose (fasting or non-fasting), gender, family history of MI (as a proxy for family history of DM), systolic and diastolic blood pressure, triglycerides (fasting or non-fasting), HDL, HCV status, BMI, smoking status, age, mode of HIV infection, prior AIDS, CD4 count, HIV viral load, lipodystrophy and cumulative HAART
- Baseline was defined as the first time point at or after inclusion to the D:A:D study when all DM risk factors were present
- Data were randomly split, stratified by cohort, into a training ($2/3^{rds}$) and validation ($1/3^{rd}$) data set
- A D:A:D predictive model for the short-term risk of DM was determined in the training dataset using Poisson regression methods
- Traditional DM risk factors assessed were established a priori and included: age, sex, ethnicity, glucose, blood pressure, HDL, LDL, BMI, triglycerides, smoking status (ever, never), family history of coronary heart disease (as a surrogate for DM)
- The following HIV related covariates were also considered for inclusion: HIV exposure category, duration since HIV positive test, prior AIDS, CD4, HIV viral load, lipodystrophy, duration ART exposure, and ART class exposure; as well as HCV and HBV status (ever/never positive)
- To avoid overfitting, individual ARV drugs were not included as covariates. Smoking appeared protective, and also was excluded. Race was not available for many patients, and so was excluded to maximise generalisability to other populations.
- Expected 8-year probabilities of DM events were determined based on the Framingham algorithm, using data on parental CVD, BMI, blood pressure, HDL, triglycerides, and fasting glucose level (a non-fasting glucose ›7.8 mmol/L was considered equivalent to a fasting value ›5.6 mmol/L). The predicted 8-year risk of DM was then converted to a prediction over the shorter D:A:D follow-up using a linear model, and was then recalibrated in the training dataset
- The D:A:D model and the recalibrated Framingham model were then assessed in the validation dataset. Area under the ROC (AROC), discrimination of low to high risk, and predicted number of events versus observed were determined for the D:A:D and recalibrated Framingham models

RESULTS

- 13,609 patients had a complete risk factor profile, 251 cases of new onset DM occurred during 50,296 person-years. Median follow-up was 3.50 years (IQR: 1.36 – 6.16)
- Training dataset: 8,990 patients with 170 cases of new onset DM. Median follow-up 3.51 years (IQR: 1.36 – 6.16)
- Validation dataset: 4,619 patients with a median follow-up: 3.47 years (IQR: 1.36 – 6.12), and 81 new onset DM

Training dataset

- Factors predictive of DM in the D:A:D study included glucose, BMI, age, HDL, triglycerides, sex and mode of HIV exposure (**Table 1**)
- The Framingham algorithm predicted 72.5 DM events in the training dataset, and the score was subsequently recalibrated to give the total 170 observed DM events in the training dataset
- Overall area under the ROC (AROC) for the D:A:D and Framingham equations in the training dataset are shown in **Figures 1 and 2**

Validation dataset: Performance of the D:A:D and Framingham equations

- The D:A:D risk equation estimates determined in the training dataset were used to predict the number of events in the validation dataset. The model yielded an AROC curve of 0.81 (95% CI: 0.76, 0.85). See **Figure 3**
- The Framingham algorithm yielded an AROC curve of 0.77 (95% CI: 0.71, 0.83). See **Figure 4**
- Figure 5 illustrates the incidence rates of new onset DM by levels of risk for both the D:A:D and the Framingham equations. The D:A:D equation discriminated better than the recalibrated Framingham equation for the lower risk groups, and also identified better for patients at high risk of new onset DM.
- Figure 6 illustrates the observed and predicted (D:A:D and Framingham models) DM events. The D:A:D model fared better than the Framingham model for sex, age, and BMI group, among others

CONCLUSIONS

- The D:A:D risk equation, developed on HIV positive patients incorporated a subset of the conventional risk factors that applies in the general population
- The D:A:D risk equation accurately predicted DM in the validation data set, and performed better than the Framingham in terms of discriminating high from low risk
- The D:A:D model also fared better than the Framingham in specific key subgroups

Table 1

The D:A:D DM Predictive model

Model	IRR	95 % CI	p-value
Gluocose: › 5.6 (f)/7.8 (nf) mmol/L	12.22	9.0–16.59	‹ 0.001
BMI			
› = 25 to ‹ 30	2.19	1.56-3.07	‹ 0.001
› =30	3.60	2.28-5.69	‹ 0.001
Male	1.66	1.05-2.61	0.029
Age (per 5 years older)	1.23	1.14-1.33	‹ 0.001
IDU	2.2	1.42-3.39	‹ 0.001
Heterosexual	1.52	1.02-2.26	0.038
Other	2.52	1.47-4.32	‹ 0.001
HDL: › =1.034 mmol/L	0.57	0.42-0.78	‹ 0.001
Trig: › =1.693 mmol/L	1.19	1.10-1.28	‹ 0.001

Discrimination of the risk equations as assessed by AROC

Figure 1:D:A:D training dataset

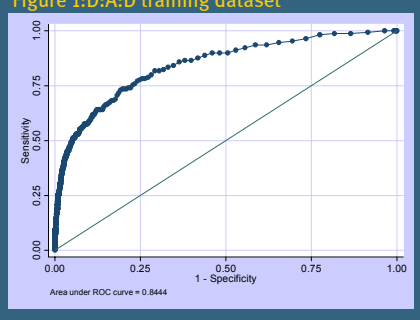


Figure 2: Framingham training dataset

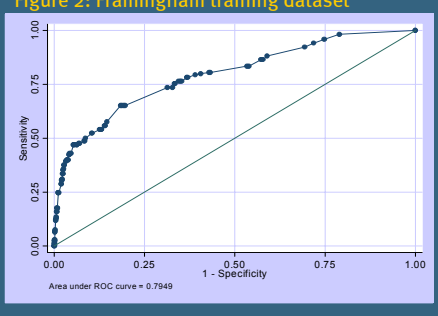


Figure 3:D:A:D training dataset

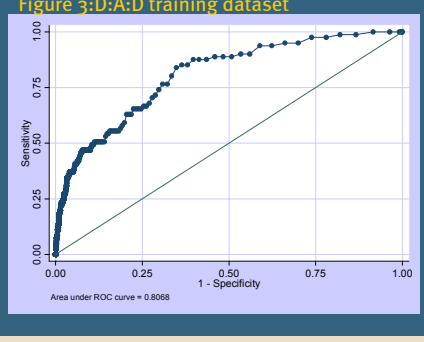


Figure 4: Framingham training dataset

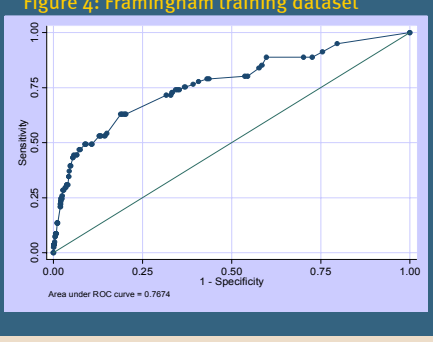


Figure 5

Rate of new onset DM by risk category

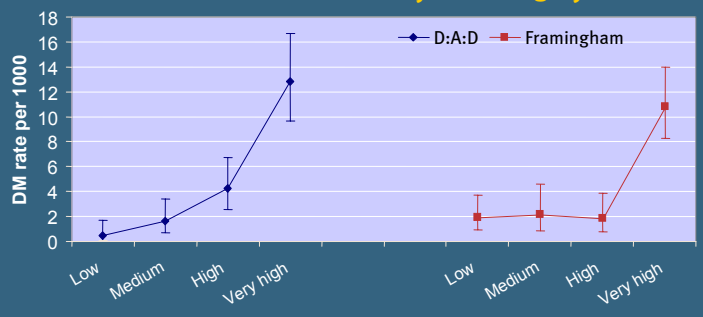
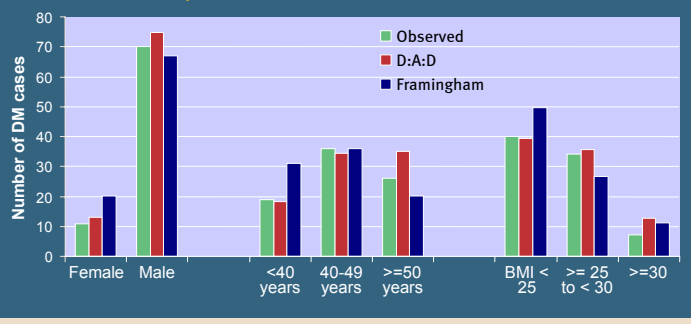


Figure 6

Observed versus predicted new onset DM – validation dataset



Acknowledgements:
Cohort PI's: W E-Sadr * (CPCRA), G Calvo * (BASS), F Dabis * (Aquitaine), O Kirk * (EuroSida), M Law * (AHOD), A d'Arminio Monforte * (ICONA), L Morfeldt * (HivBIVUS), C Pradier * (Nice), P Reiss * (ATHENA), R Weber * (SHCS), S De Wit * (Brussels)
Cohort coordinators and datamanagers: S Zaheri, L Gras (ATHENA), R Thiébaut, E Balestre (Aquitaine), K Petoumenos, S Marashi Pour (AHOD), S Mateu, F Torres (BASS), B Poll (Brussels), G Bartsch, G Thompsen (CPCRA), J Kjær (EuroSIDA), P Pezzotti (ICONA), E Fontas, C Caissotti (Nice), A Sundström, G Thulin (HivBIVUS), M Rickenbach, O Keiser (SHCS)
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Steering Committee: Members indicated w/*; ¢ chair;
Additional members: S Storfer *, F Rousseau *, I Weller *
Funding: 'Oversight Committee for The Evaluation of Metabolic Complications of HAART' with representatives from academia, patient community, FDA, EMEA and a consortium of "Abbott, Agouron, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck, Pfizer, and Hoffman-La Roche"

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