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)

Worm, S W; De Wit, S; Weber, R; Sabin, C A; Reiss, P; El-Sadr, W; Monforte, A D; Kirk, O; Fontas, E; Dabis, F; Law, M G; Lundgren, J D; Friis-Møller, N (2009). 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, 119(6):805-811.

Postprint available at: http://www.zora.uzh.ch

Posted at the Zurich Open Repository and Archive, University of Zurich.
http://www.zora.uzh.ch

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)

Abstract

BACKGROUND: Although guidelines in individuals not infected with the human immunodeficiency virus (HIV) consider diabetes mellitus (DM) to be a coronary heart disease (CHD) equivalent, there is little information on its association with CHD in those infected with HIV. We investigated the impact of DM and preexisting CHD on the development of a new CHD episode among 33,347 HIV-infected individuals in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study). METHODS AND RESULTS: Over 159,971 person-years, 698 CHD events occurred. After adjustment for gender, age, cohort, HIV transmission, ethnicity, family history of CHD, smoking, and calendar year, the rate of a CHD episode was 7.52 times higher (Poisson regression, 95% CI 6.02 to 9.39, P=0.0001) in those with preexisting CHD than in those without preexisting CHD, but it was only 2.41 times higher (95% CI 1.91 to 3.05, P=0.0001) in those with preexisting DM compared with those without DM. No statistical interactions were apparent between either diagnosis and sex; although older people with DM had an increased CHD rate compared with younger people, older people with preexisting CHD had a lower event rate. A statistically significant interaction between preexisting DM and CHD (P=0.003) suggested that the CHD rate in those with preexisting CHD and DM is lower than expected on the basis of the main effects alone. CONCLUSIONS: DM and preexisting CHD are both important risk factors for CHD events in HIV-infected individuals. There is a need for targeted interventions to reduce the risk of CHD in both high-risk groups of HIV-infected individuals.
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)

Signe W. Worm, Stephane De Wit, Rainer Weber, Caroline A. Sabin, Peter Reiss, Wafaa El-Sadr, Antonella D’Arminio Monforte, Ole Kirk, Eric Fontas, Francois Dabis, Matthew G. Law, Jens D. Lundgren and Nina Friis-Møller

Circulation 2009;119;805-811; originally published online Feb 2, 2009;
DOI: 10.1161/CIRCULATIONAHA.108.790857

Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2009 American Heart Association. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/cgi/content/full/119/6/805

Data Supplement (unedited) at:
http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.108.790857/DC1

Subscriptions: Information about subscribing to Circulation is online at http://circ.ahajournals.org/subscriptions/

Permissions: Permissions & Rights Desk, Lippincott Williams & Wilkins, a division of Wolters Kluwer Health, 351 West Camden Street, Baltimore, MD 21202-2436. Phone: 410-528-4050. Fax: 410-528-8550. E-mail: journalpermissions@lww.com

Reprints: Information about reprints can be found online at http://www.lww.com/reprints
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)

Signe W. Worm, MD; Stephane De Wit, PhD; Rainer Weber, MD; Caroline A. Sabin, PhD; Peter Reiss, PhD; Wafaa El-Sadr, PhD; Antonella D’Arminio Monforte, DMSc; Ole Kirk, DMSc; Eric Fontas, MD; Francois Dabis, PhD; Matthew G. Law, PhD; Jens D. Lundgren, DMSc; Nina Friis-Møller, PhD

Background—Although guidelines in individuals not infected with the human immunodeficiency virus (HIV) consider diabetes mellitus (DM) to be a coronary heart disease (CHD) equivalent, there is little information on its association with CHD in those infected with HIV. We investigated the impact of DM and preexisting CHD on the development of a new CHD episode among 33,347 HIV-infected individuals in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D Study).

Methods and Results—Over 159,971 person-years, 698 CHD events occurred. After adjustment for gender, age, cohort, HIV transmission, ethnicity, family history of CHD, smoking, and calendar year, the rate of a CHD episode was 7.52 times higher (Poisson regression, 95% CI 6.02 to 9.39, \( P = 0.0001 \)) in those with preexisting CHD than in those without preexisting CHD, but it was only 2.41 times higher (95% CI 1.91 to 3.05, \( P = 0.0001 \)) in those with preexisting DM compared with those without DM. No statistical interactions were apparent between either diagnosis and sex; although older people with DM had an increased CHD rate compared with younger people, older people with preexisting CHD had a lower event rate. A statistically significant interaction between preexisting DM and CHD (\( P = 0.003 \)) suggested that the CHD rate in those with preexisting CHD and DM is lower than expected on the basis of the main effects alone.

Conclusions—DM and preexisting CHD are both important risk factors for CHD events in HIV-infected individuals. There is a need for targeted interventions to reduce the risk of CHD in both high-risk groups of HIV-infected individuals.

(Circulation. 2009;119:805-811.)

Key Words: coronary disease ■ diabetes mellitus ■ risk factors ■ human immunodeficiency virus ■ epidemiology

Diabetes mellitus (DM) is an important risk factor for coronary heart disease (CHD). In the National Cholesterol Education Program guidelines,1 DM is considered to be a “CHD risk equivalent,” which means that it is believed that a diagnosis of DM places a patient at similar risk of a future episode of CHD as a prior CHD episode. Several sources of evidence support this paradigm,2–5 although others do not.6–9

D

Editorial p 770
Clinical Perspective p 811

In those infected with human immunodeficiency virus (HIV), the underlying cause and origin of DM may differ from that of the general population. For example, DM is a known complication of several antiretroviral therapies, being associated with both short-term10,11 and longer-term12,13 exposure to some of these drugs. Lipodystrophy is associated with insulin resistance and, in some cases, overt DM.14–16 The reported prevalence of DM in HIV-infected populations ranges from 2% to 14%, with differences in prevalence explained by differences in demographic characteristics, lifestyle, and antiretroviral exposure.17–20

Among those infected with HIV, the risk of myocardial infarction (MI) is more than doubled in those with DM.21,22 With the aging of the HIV-infected population, brought about...
by an increased life expectancy after the use of combination antiretroviral therapy, the prevalence of DM is likely to increase. A more thorough understanding of the impact of DM on CHD risk in those infected with HIV and how this risk compares with that associated with preexisting CHD may have major public health implications. Thus, the purpose of the present study is to describe the predictive value of preexisting DM and CHD for subsequent CHD events among HIV-infected patients in the Data Collection on Adverse Events of Anti-HIV Drugs (the D:A:D study).

Methods

 Study Population
The D:A:D study is a prospective, observational study formed by the collaboration of 11 cohorts following up 33,347 HIV-infected subjects at 212 clinics in Europe, Australia, and the United States. The primary objective of the study is to investigate the possible association between combination antiretroviral therapy and the risk of MI. The D:A:D study methodology has been described in detail elsewhere.22,23

 Data Collection
Patients are followed up prospectively during visits to outpatient clinics as a part of regular medical care. At enrollment and at least every 8 months, standardized data collection forms are completed at the sites that provide information relating to physical status; family history of CHD; prior history of cardiovascular disease and DM; cigarette smoking; blood pressure; the use of lipid-lowering, antihypertensive, and antiplatelet therapy; the presence of clinical signs of lipodystrophy as defined by the physician; and serum lipid levels (total cholesterol, HDL cholesterol, and triglycerides, including information on whether values were obtained under fasting conditions), as well as HIV-related information (antiretroviral therapy, CD4 cell counts, HIV viral loads, and dates of diagnoses of all AIDS-defining diseases).

Ascertainment of Outcomes
All incident cases of MI, invasive procedures involving the coronary arteries (angioplasty or bypass), and all deaths (irrespective of cause) are reported to the coordinating office for validation and coding, as described in previous reports from the study.17,24 DM has been described in previous reports from the study.17,24 DM has been diagnosed in 1 of 2 ways: A definite diagnosis of DM if a fasting plasma glucose ≥7.0 mmol/L (126 mg/dL) was measured on 2 consecutive occasions, or a possible diagnosis if the patient had a physician-reported date of DM onset and was known to have initiated antidiabetes therapy. For the purposes of the present analyses, definite and possible diagnoses were combined.

Statistical Methods
We considered the incidence of a new/recurrent CHD event in patients with or without preexisting CHD at study entry and in patients with or without DM at study entry. For these analyses, a CHD event was deemed to have occurred on the date of the earliest of an MI, an invasive coronary procedure, or death due to CHD. Patients who had already experienced an MI (266 patients) or coronary revascularization (bypass: 52 patients; angioplasty: 131 patients) before study entry were defined as having preexisting CHD. These events were not validated centrally. Follow-up time was counted from the date of study entry to the date of a CHD episode; death due to non-CHD causes; February 1, 2007; or 6 months after the patient’s last clinic visit, whichever occurred first. Only the first CHD event during prospective follow-up was considered in the analyses.

In exploratory analyses, the rate of CHD was compared in the 4 groups defined by preexisting CHD and DM at study entry (ie, no CHD or DM; DM but no CHD; CHD but no DM; and both CHD and DM) with multivariable Poisson regression. The subgroup with no preexisting CHD or DM was treated as the reference group for these analyses, which were also adjusted for gender, age, cohort, HIV transmission mode, ethnicity, family history of CHD, smoking, and calendar year. These methods assume that within each calendar period, the risk of a CHD event is constant over time. We then fitted a Poisson regression model that included the main effects of each diagnosis, as well as other potential confounding factors. We explored whether any associations between preexisting DM or CHD and the development of CHD differed by sex and age by incorporating interaction terms with preexisting DM/CHD and female sex and older age (defined as >45 years in men and >55 years in women). We then assessed whether the prognostic value of either diagnosis differed according to the presence or absence of the other diagnosis by incorporating an interaction term between the diagnoses.

Sensitivity analyses were performed to assess whether any reported associations were modified by further adjustment for the use of treatments to reduce the risk of CHD (ie, lipid-lowering, antihypertensive, and antiplatelet medication) or by adjustment for the latest HDL cholesterol (log-transformed) and triglyceride measurements, both as continuous time-updated covariates. A further sensitivity analysis assessed the associations between preexisting DM, CHD, and fatal cardiovascular disease, in which this end point was deemed to have occurred if a patient died within 28 days of an MI, stroke, or coronary revascularization. Finally, sensitivity analysis considered a narrower CHD outcome that was based on the development of MI or CHD-related death only (ie, coronary revascularization events were excluded from the outcome).

As a further analysis, we then assessed whether the association between DM and the development of CHD differed according to the length of time that an individual had been diagnosed with DM. For these analyses, we included all preexisting diagnoses of DM at study entry and new diagnoses of DM that occurred over prospective follow-up. Patient follow-up time and the occurrence of events were classified into 4 groups according to the time since DM diagnosis: (1) No diagnosis of DM; (2) a diagnosis of DM after study entry but in the last 2 years; (3) a diagnosis of DM after study entry but >2 years previously; and (4) a diagnosis of DM before study entry. This variable was incorporated into a Poisson regression model as a time-updated covariate to allow patients to move between categories as the time from their DM diagnosis lengthened, and it was adjusted for all variables listed previously, including CHD at baseline.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
Of the 33,347 patients included in the study, 352 (1.1%) had preexisting CHD at study entry and 952 (2.9%) had preexisting DM. When split into the 4 groups defined on the basis of the presence or absence of each of these diagnoses at study entry, 296 (0.9%) patients had CHD but no DM, 896 (2.7%) had DM but no CHD, and 56 (0.2%) had both diagnoses at study entry. The characteristics of patients at entry into D:A:D, stratified by their CHD and DM status, are shown in Table 1.

Patients with either DM or CHD at entry into D:A:D were more likely to be male and were older than their counterparts without these events at study entry. Patients with DM or CHD also had higher levels of total cholesterol and triglycerides and lower HDL cholesterol levels than those without these events, and those with CHD in particular had received more medical interventions with lipid-lowering, antiplatelet and...
antihypertensive drugs. Greater proportions of patients with DM or CHD had lipodystrophy. Patients with preexisting CHD were more likely to have a family history of cardiovascular disease than those without preexisting CHD. Although exposure to antiretroviral therapy was generally greater in those with preexisting CHD or DM, the differences in duration of exposure were relatively small.

Incidence of CHD
Overall, 698 patients experienced an episode of CHD over 159,971 person-years of follow-up (rate 4.4 per 1000 person-years, 95% CI 4.0 to 4.7). The distribution of events, stratified by the 4 baseline groups, is shown in Table 2.

Among patients with preexisting CHD, the rates of a recurrent CHD episode were 101.9 (95% CI 58.3 to 145.5) and 76.4 (95% CI 60.8 to 92.0) per 1000 person-years, respectively, in those with and without DM at study entry. Conversely, in patients without preexisting CHD, the rates of a new CHD episode were 16.4 (95% CI 12.5 to 20.3) and 3.4 (95% CI 3.1 to 3.6) per 1000 person-years, respectively, in those with and without DM at study entry. Compared with patients with no preexisting CHD or DM (the reference group), patients with preexisting CHD were at substantially higher risk of experiencing a recurrent episode of CHD regardless of whether they did (adjusted relative risk [RR] 11.66, 95% CI 7.42 to 18.32, \(P \leq 0.0001\)) or did not (adjusted RR 9.04, 95% CI 7.10 to 11.49, \(P \leq 0.0001\)) have DM at study entry (Figure). In contrast, the increased risk of an event in those who had preexisting DM but no CHD at study entry, although statistically significant, was smaller (adjusted RR 3.03, 95% CI 2.34 to 3.93, \(P \leq 0.001\)). In a regression model that included the main effects of each covariate (and adjustment for other confounders), the adjusted relative risk of a recurrent CHD episode associated with preexisting CHD was 7.52 (95% CI 6.02 to 9.39, \(P \leq 0.0001\)) whereas that associated with preexisting DM was 2.41 (95% CI 1.91 to 3.05, \(P \leq 0.0001\)). In these models, there was no evidence that the association between DM and the risk of CHD differed according to sex (\(P\) value for interaction with female sex 0.85), although the association between DM and CHD appeared to be stronger in older people than in younger people (RR in older people 2.48, 95% CI 1.93 to 3.18; RR in younger people 1.88, 95% CI 0.97 to 3.66; \(P\) for interaction=0.004). In contrast, although there was no evidence that the association between preexisting CHD and the risk of a subsequent CHD event differed according to sex (\(P\) for interaction=0.85).

### Table 1. Characteristics of Patients at Entry in D:A:D According to CHD and DM Status at Study Entry

<table>
<thead>
<tr>
<th></th>
<th>No DM or CHD (n=32,099)</th>
<th>CHD but No DM (n=296)</th>
<th>DM but No CHD (n=896)</th>
<th>DM and CHD (n=56)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td>38 (33–44)</td>
<td>51 (44–58)</td>
<td>48 (40–55)</td>
<td>57 (47–64)</td>
</tr>
<tr>
<td><strong>Male sex</strong></td>
<td>23651 (73.7)</td>
<td>273 (22.2)</td>
<td>722 (80.6)</td>
<td>46 (82.1)</td>
</tr>
<tr>
<td><strong>CD4, cells/mm³</strong></td>
<td>410 (250–600)</td>
<td>426 (264–585)</td>
<td>364 (203–575)</td>
<td>481 (318–614)</td>
</tr>
<tr>
<td><strong>HIV RNA, log₁₀ copies/mL</strong></td>
<td>2.7 (1.7–4.2)</td>
<td>2.1 (1.7–3.5)</td>
<td>2.6 (1.7–4.1)</td>
<td>1.9 (1.7–4.0)</td>
</tr>
<tr>
<td><strong>Transmission</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Homosexual</td>
<td>13789 (43.0)</td>
<td>176 (59.5)</td>
<td>387 (43.2)</td>
<td>24 (42.9)</td>
</tr>
<tr>
<td>Heterosexual</td>
<td>9682 (30.2)</td>
<td>65 (22.0)</td>
<td>282 (31.5)</td>
<td>18 (32.1)</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>5824 (18.1)</td>
<td>21 (7.1)</td>
<td>102 (11.4)</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>10996 (34.3)</td>
<td>108 (36.5)</td>
<td>196 (21.9)</td>
<td>16 (28.6)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>5334 (16.6)</td>
<td>96 (32.4)</td>
<td>175 (19.5)</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>Family history of CVD</td>
<td>2114 (6.6)</td>
<td>66 (22.3)</td>
<td>63 (7.0)</td>
<td>7 (12.5)</td>
</tr>
<tr>
<td>Exposed to each drug class; median (IQR) years of exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PIs</td>
<td>18441 (57.5)</td>
<td>216 (73.0)</td>
<td>629 (70.2)</td>
<td>46 (82.1)</td>
</tr>
<tr>
<td>Median (IQR) years of exposure</td>
<td>2.3 (1.2–3.2)</td>
<td>2.6 (1.6–3.4)</td>
<td>2.5 (1.6–3.4)</td>
<td>2.7 (1.9–3.2)</td>
</tr>
<tr>
<td>NRTIs</td>
<td>22351 (72.4)</td>
<td>257 (86.8)</td>
<td>742 (82.8)</td>
<td>49 (87.5)</td>
</tr>
<tr>
<td>Median (IQR) years of exposure</td>
<td>3.0 (1.6–4.7)</td>
<td>4.0 (2.3–5.7)</td>
<td>3.9 (2.3–5.8)</td>
<td>4.2 (3.4–5.5)</td>
</tr>
<tr>
<td>NNRTIs</td>
<td>10501 (32.7)</td>
<td>138 (46.6)</td>
<td>396 (44.2)</td>
<td>28 (50.0)</td>
</tr>
<tr>
<td>Median (IQR) years of exposure</td>
<td>0.9 (0.4–1.6)</td>
<td>1.0 (0.4–1.7)</td>
<td>1.0 (0.4–1.7)</td>
<td>1.2 (0.8–1.8)</td>
</tr>
<tr>
<td>Lipodystrophy</td>
<td>5817 (18.1)</td>
<td>92 (31.1)</td>
<td>303 (33.8)</td>
<td>24 (42.9)</td>
</tr>
<tr>
<td>TC, mmol/L</td>
<td>4.9 (4.1–5.8)</td>
<td>5.5 (4.7–6.4)</td>
<td>5.4 (4.6–6.3)</td>
<td>5.6 (4.9–6.3)</td>
</tr>
<tr>
<td>TG, mmol/L</td>
<td>1.6 (1.0–2.6)</td>
<td>2.2 (1.4–3.5)</td>
<td>2.4 (1.4–4.0)</td>
<td>3.0 (1.8–4.4)</td>
</tr>
<tr>
<td>HDL, mmol/L</td>
<td>1.1 (0.9–1.4)</td>
<td>1.0 (0.8–1.2)</td>
<td>1.0 (0.8–1.3)</td>
<td>0.9 (0.8–1.5)</td>
</tr>
<tr>
<td><strong>Antihypertensive drugs</strong></td>
<td>1062 (3.3)</td>
<td>152 (51.4)</td>
<td>164 (18.3)</td>
<td>27 (48.2)</td>
</tr>
<tr>
<td>Antiplatelet drugs</td>
<td>289 (0.9)</td>
<td>149 (50.3)</td>
<td>41 (46)</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>Lipid-lowering drugs</td>
<td>1091 (3.4)</td>
<td>118 (39.9)</td>
<td>123 (13.7)</td>
<td>19 (33.9)</td>
</tr>
</tbody>
</table>

CVD indicates cardiovascular disease; IQR, interquartile range; PI, protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside transcriptase inhibitor; TC, total cholesterol; and TG, triglycerides.

Table entries are n (%) or median (IQR) as appropriate.
tion=0.42), the association between preexisting CHD and a recurrent CHD event was weaker in older than in younger people (RR in older people 6.06, 95% CI 4.72 to 7.78; RR in younger people 26.07, 95% CI 16.70 to 40.69; P for interaction=0.0001). Both interactions with older age remained unchanged after adjustment for the use of interventions (lipid-lowering, antiplatelet, and antihypertensive medication).

To more formally investigate whether the effect of each diagnosis on a subsequent event differed according to the presence or absence of the other diagnosis, we included a statistical interaction term between the 2 diagnoses. The statistical interaction between the 2 was significant (interaction RR 0.43, 95% CI 0.25 to 0.75, P=0.003), which suggests that the rate of CHD in those with CHD and DM at study entry was lower than would be expected on the basis of the main effects alone. Further analyses then explored the effect of incorporating the use of medical interventions (lipid-lowering therapy, antihypertensive, and antiplatelet medication) and, in a separate model, the impact of adjustment for the latest triglyceride and HDL cholesterol levels; neither adjustment altered our main conclusions (data not shown).

When we considered associations with fatal cardiovascular disease (242 events), we again found a greater impact of preexisting CHD compared with that of DM, although differences were smaller than in the main analysis (Table 3). Compared with patients without preexisting DM or CHD, those with preexisting CHD were at 4.61 times (95% CI 2.82 to 7.53, P=0.0001) the risk of a new event if they did not have preexisting DM and at 11.12 (95% CI 5.75 to 21.50, P=0.0001) times the risk if they did. Patients without preexisting CHD but with DM were at 2.82 (95% CI 1.84 to 4.32, P=0.0001) times the risk of a new event compared with those with neither diagnosis at baseline.

Additional sensitivity analyses in which coronary revascularizations were excluded as a component of the composite end point (Table 3) again reached similar conclusions: Patients with preexisting CHD were at a much higher risk of a recurrent episode of CHD regardless of whether they did (10.62, 95% CI 6.04 to 18.67, P=0.0001) or did not (4.73, 95% CI 3.32 to 6.75, P=0.0001) have DM at study entry. In contrast, those with preexisting DM but not CHD at study entry were at 2.95 (95% CI 2.23 to 3.91, P=0.0001) times the risk of those with neither diagnosis at study entry.

**Impact on Development of CHD of New Diagnoses of DM**

When all diagnoses of DM (including those that occurred during follow-up) were incorporated, the CHD rate was 3.8 (95% CI 3.5 to 4.1) per 1000 person-years among patients who were not diagnosed with DM. The CHD rate was higher among patients diagnosed with DM, and this rate appeared to increase with longer duration of DM; specifically, the rate was 8.2 (95% CI 4.5 to 13.8) per 1000 person-years among patients followed up within the first 2 years after DM diagnosis, 11.6 (95% CI 6.2 to 19.9) per 1000 person-years among those followed up for ≥2 years after DM (but in whom the diagnosis was made after entry in D:A:D), and 20.5 (95% CI 16.2 to 24.8) per 1000 person-years among patients with DM before entry in D:A:D. In multivariable analysis, the adjusted RR of a CHD event associated with recent (ie, in the last 2 years) DM diagnosis was 1.35 (95% CI 0.79 to 2.31,
HIV infection, and the relative prognostic importance of important risk factor for both DM and CHD in those with or 40s). As in the HIV-uninfected population, age is an included in the D:A:D study are younger (usually in their 30s who were often in their 50s, the HIV-infected patients general population studies that have considered this issue, taken into consideration. First, unlike the participants in the CHD and subsequent CHD events, several points should be increased with longer duration of DM emphasizes the impor- tance of targeted interven- tion, both diagnoses were associated with a substantial increase in risk. Thus, there is a need for targeted interven- tions to reduce the risk of CHD events in these 2 high-risk groups. In particular, the present finding that the risk of CHD increased with longer duration of DM emphasizes the impor- tance of regular screening for this potentially modifiable condition. Although the present findings appeared to show a weaker association between DM and CHD than between preexisting CHD and subsequent CHD events, several points should be taken into consideration. First, unlike the participants in the general population studies that have considered this issue, who were often in their 50s, the HIV-infected patients included in the D:A:D study are younger (usually in their 30s or 40s). As in the HIV-uninfected population, age is an important risk factor for both DM and CHD in those with HIV infection, and the relative prognostic importance of these 2 diagnoses may change as the population ages. Second, DM in HIV-infected individuals is not only caused by the mechanisms seen in the general population (eg, obesity, physical inactivity, and genetic predisposition) but may also result from the use of antiretroviral therapy. Drugs from both the protease inhibitor and nucleoside reverse transcriptase inhibitor classes may each contribute to insulin resistance and DM through different mechanisms. The mitochondrial dysfunction caused by the thymidine analogues within the nucleoside reverse transcriptase inhibitor drug class results in insulin resistance both in healthy volunteers and in HIV-infected patients even in the absence of overt lipodystrophy. In addition, the HIV-infected population has a different risk profile for both DM and CHD than the general population, with a greater prevalence of smoking and coinfection with hepatitis C virus but a lower prevalence of obesity. Third, in the present study, the risk of CHD increased with longer duration of DM. The relatively recent onset of DM (an average time since diagnosis of 5 years) may be insufficient to cause macrovascular damage, which would result in a weaker association between DM and CHD than that seen in the general population. Indeed, studies of recently diagnosed diabetic patients tend to report weaker associations with CHD. If the CHD outcomes are restricted to fatal events, then it is likely that any apparent impact of DM will be greater, as we have also reported here in a sensitivity analysis. Compared with patients without preexisting CHD, patients with a history of CHD had received more “prophylactic” interventions, including invasive cardiovascular disease procedures, lipid-lowering drugs, and antihypertensive medication; however, the use of these interventions remained suboptimal in these high-risk individuals, particularly in those with DM. Adjustment for the use of these interventions did not modify our conclusions. Furthermore, a sensitivity analysis in which we excluded coronary revascularizations from the composite end point reached similar conclusions. We found that although the association between DM and CHD was stronger in older people than in younger people, the opposite was true for the association between preexisting and recurrent CHD. Although it is possible that this association may simply reflect a chance finding, older people with preexisting CHD may survive for a shorter time after their initial CHD event than younger individuals, leaving them at risk of a new event for less time. Alternatively, the use of secondary interventions may be more common in older people, leading to a reduction in risk.

### Discussion

The D:A:D study currently contains information on >33,000 HIV-infected patients followed up for almost 160,000 person-years. Although the increased risk of a CHD event associated with preexisting CHD was substantially greater than that associated with DM, which appears not to support the paradigm that DM is a CHD risk equivalent in this population.34–36 Indeed, studies of preexisting CHD may survive for a shorter time after their initial CHD event than younger individuals, leaving them at risk of a new event for less time. Alternatively, the use of secondary interventions may be more common in older people, leading to a reduction in risk.

### Study Limitations

The present study definition of definite DM is conservative compared with the definition recommended in the American Diabetes Association guidelines, which could have led to an underestimation of the number of DM events in the present study. Unfortunately, the D:A:D study does not collect detailed data on insulin resistance or anthropometrics, which means that we were unable to investigate whether some
patients not having DM actually had pre-DM, which may also increase the risk of CHD.\textsuperscript{37}

In conclusion, both DM and preexisting CHD are important risk factors for subsequent CHD events in the HIV-infected population. There is evidence to suggest that DM is becoming an increasing problem among those infected with HIV, and we have recently reported an increase of DM among patients under follow-up from 3.8% in 1999/2000 to 5.2% in 2005/2006.\textsuperscript{43} Furthermore, we recently reported that only one fifth of patients with DM in the D:A:D study who were not taking lipid-lowering drugs initiated such primary prevention.\textsuperscript{40} Thus, we suggest that targets for interventions among HIV-infected individuals should consider an individual’s entire risk factor profile, including their history of CHD and DM.

Sources of Funding
The D:A:D study is funded by the Highly Active Antiretroviral Therapy (HAART) Oversight Committee, a European Medicines Evaluation Agency (EMEA) initiative supported by Abbott Laboratories, the AIDS Treatment Activists Coalition (ATAC), Boehringer-Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb, European AIDS Treatment Group (EATG), US Food and Drug Administration (FDA), F. Hoffmann-La Roche Ltd, Gilead Sciences Inc, GlaxoSmithKline, Merck & Co Inc, and Pfizer Inc.

Disclosures
Dr Weber has received honoraria or travel grants from Abbott Laboratories, Boehringer-Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb, Gilead Sciences Inc, GlaxoSmithKline, Merck Sharp & Dohme, Roche, and Tibotec. Dr Lundgren has received honoraria from Abbott Laboratories, Boehringer-Ingelheim Pharmaceuticals Inc, Bristol-Myers Squibb, Gilead Sciences Inc, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer Inc, and Roche. Dr Weber has received honoraria or travel grants from Abbott Laboratories, European AIDS Treatment Group (EATG), US Food and Drug Administration (FDA), F. Hoffmann-La Roche Ltd, Gilead Sciences Inc, GlaxoSmithKline, Merck Sharp & Dohme, Roche, and Tibotec. The remaining authors report no conflicts.

References


**CLINICAL PERSPECTIVE**

With the aging of the human immunodeficiency virus (HIV)–infected population, brought about by an increased life expectancy after the widespread use of combination antiretroviral therapy, it is likely that the prevalence of diabetes mellitus (DM) will increase. DM is an important risk factor for coronary heart disease (CHD) in HIV-infected populations. Among those infected with HIV, the risk of myocardial infarction is more than doubled in those with DM; however, it is currently unknown whether the CHD risk attributable to DM in patients with HIV infection is similar to that observed in the general HIV-uninfected population. In the present large, international HIV observational study with >33,000 patients, it was demonstrated that the risk for CHD over 5 years was 7.52 times as high in those with preexisting CHD and 2.41 times as high in those with preexisting DM as in those patients without preexisting diseases. Our study acknowledges the importance of DM; in particular, our finding that the risk of CHD increased with longer duration of DM emphasizes the importance of regular screening for this potentially modifiable condition. Guidelines on the prevention of CHD should be based on data from randomized, controlled trials, but our data emphasize the need for targeted interventions to reduce the risk of CHD in HIV-infected individuals with DM. Thus, we suggest that targets for interventions among HIV-infected individuals should consider an individual’s entire risk factor profile, including their history of CHD and DM.
SUPPLEMENTAL MATERIAL

APPENDIX

D:A:D Steering Committee: Persons with * below (#: chair) and S.Collins, S Storpher, F Rousseau, I. Weller;
D:A:D Central Coordination: N. Friis-Møller, S.W. Worm, C.A. Sabin, A Sjøl (verification of primary endpoint), J.D. Lundgren;

The members of the 11 Cohorts are as follows:

ATHENA (AIDS Therapy Evaluation Project Netherlands):

Central coordination: F. de Wolf, S. Zaheri, L. Gras;
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:** R. Salamon (chair), J. Beylot, M. Dupon, M. Le Bras, J.L. Pellegrin, J.M. Ragnaud;


**AHOD (Australian HIV Observational Database, Australia):**

**Central coordination: M. Law**, K. Glenday and K. Petoumenos (Sydney, New South Wales);


**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).

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):
Coordinating Centre Staff: J Lundgren (project leader), O Kirk, A Mocroft, N Friis-Møller, A Cozzi-Lepri, W Bannister, M Ellefson, A Borch, D Podlekareva, J Kjær, L Peters, J Reekie

Argentina: (M Losso), A Duran, Hospital JM Ramos Mejia, Buenos Aires.

Austria: (N Vetter) Pulmologisches Zentrum der Stadt Wien, Vienna.

Belarus: (I Karpov), A Vassilenko, Belarus State Medical University, Minsk, VM Mitsura, Gomel State Medical University, Gomel; O Suetnov, Regional AIDS Centre, Svetlogorsk.

Belgium: (N Clumeck) S De Wit, B Poll, Saint-Pierre Hospital, Brussels; R Colebunders, Institute of Tropical Medicine, Antwerp

Bulgaria: K Kostov, Infectious Diseases Hospital, Sofia.

Croatia: J Begovac, University Hospital of Infectious Diseases, Zagreb.

Czech Republic: (L Machala) H Rozsypal, Faculty Hospital Bulovka, Prague; D Sedlacek, Charles University Hospital, Plzen.

Denmark: (J Nielsen) J Lundgren, T Benfield, O Kirk, Hvidovre Hospital, Copenhagen; J Gerstoft, T Katzenstein, A-B E Hansen, P Skinhøj, Rigshospitalet, Copenhagen; C Pedersen, Odense University Hospital, Odense, L Oestergaard, Skejby Hospital, Aarhus.
Estonia: (K Zilmer) West-Tallinn Central Hospital, Tallinn, Jelena Smidt, Nakkusosakond Siseklinik, Kohtla-Järve.

Finland: (M Ristola), Helsinki University Central Hospital, Helsinki.

France: (C Katlama) Hôpital de la Pitié-Salpêtrière, Paris; J-P Viard, Hôpital Necker-Enfants Malades, Paris; P-M Girard, Hospital Saint-Antoine, Paris; JM Livrozet, Hôpital Edouard Herriot, Lyon; P Vanhems, University Claude Bernard, Lyon; C Pradier, Hôpital de l’Archet, Nice; F Dabis, Unité INSERM, Bordeaux.

Germany: (J Rockstroh) Universitäts Klinik Bonn; R Schmidt, Medizinische Hochschule Hannover; J van Lunzen, O Degen, University Medical Center Hamburg-Eppendorf, Infectious Diseases Unit, Hamburg; HJ Stellbrink, IPM Study Center, Hamburg; S Staszewski, JW Goethe University Hospital, Frankfurt; J Bogner, Medizinische Poliklinik, München; G. Fätkenheuer, Universität Köln, Cologne.

Greece: (J Kosmidis) P Gargalianos, G Xylomenos, J Perdios, Athens General Hospital; G Panos, A Filandras, E Karabatsaki, 1st IKA Hospital; H Sambattakou, Ippokration General Hospital, Athens.

Hungary: (D Banhegyi) Szent Lásló Hospital, Budapest.

Ireland: (F Mulcahy) St. James's Hospital, Dublin.

Israel: (I Yust) D Turner, M Burke, Ichilov Hospital, Tel Aviv; S Pollack, G Hassoun, Rambam Medical Center, Haifa; S Maayan, Hadassah University Hospital, Jerusalem.

Italy: (A Chiesi) Istituto Superiore di Sanità, Rome; R Esposito, I Mazeu, C Mussini, Università Modena, Modena; C Arici, Ospedale Riuniti, Bergamo; R Pristera, Ospedale Generale Regionale, Bolzano; F Mazzotta, A Gabbuti, Ospedale S Maria Annunziata, Firenze; V Vullo, M Lichtner, University di Roma la Sapienza, Rome; A Chirianni, E Montesarchio, M Gargiulo, Presidio Ospedaliero AD Cotugno, Monaldi Hospital, Napoli; G Antonucci, F Iacomi, P Narciso, C Vlassi, M Zaccarelli, Istituto Nazionale Malattie Infettive Lazzaro Spallanzani, Rome; A Lazzarin, R Finazzi, Ospedale San Raffaele, Milan; M Galli, A Ridolfo, Osp. L. Sacco, Milan; A d’Arminio Monforte, Istituto Di Clinica Malattie Infettive e Tropicale, Milan.

Latvia: (B Rozentale) P Aldins, Infectology Centre of Latvia, Riga.

Lithuania: (S Chaplinskas) Lithuanian AIDS Centre, Vilnius.

Luxembourg: (R Hemmer), T Staub, Centre Hospitalier, Luxembourg.

Netherlands: (P Reiss) Academisch Medisch Centrum bij de Universiteit van Amsterdam, Amsterdam.

Norway: (J Bruun) A Maeland, V Ormaasen, Ullevål Hospital, Oslo.
Poland: (B Knysz) J Gasiorowski, Medical University, Wroclaw; A Horban, Centrum Diagnostyki i Terapii AIDS, Warsaw; D Prokopowicz, A Wiercinska-Drapalo, Medical University, Bialystok; A Boron-Kaczmarska, M Pynka, Medical Univesity, Szczecin; M Beniowski, E Mularska, Osrodek Diagnostyki i Terapii AIDS, Chorzow; H Trocha, Medical University, Gdansk.

Portugal: (F Antunes) E Valadas, Hospital Santa Maria, Lisbon; K Mansinho, Hospital de Egas Moniz, Lisbon; F Maltez, Hospital Curry Cabral, Lisbon.

Romania: (D Duiculescu) Spitalul de Boli Infectioase si Tropicale: Dr. Victor Babes, Bucuresti.

Russia: (A Rakhmanova), Medical Academy Botkin Hospital, St Petersburg; E Vinogradova, St Petersburg AIDS Centre, St Peterburg; S Buzunova, Novgorod Centre for AIDS, Novgorod.

Serbia: (D Jevtovic), The Institute for Infectious and Tropical Diseases, Belgrade.

Slovakia: (M Mokrāš) D Staneková, Dérer Hospital, Bratislava.

Spain: (J González-Lahoz) V Soriano, L Martin-Carbonero, P Labarga, Hospital Carlos III, Madrid; B Clotet, A Jou, J Conejero, C Tural, Hospital Germans Trias i Pujol, Badalona; JM Gatell, JM Miró, Hospital Clinic i Provincial, Barcelona; P Domingo, M Gutierrez, G Mateo, MA Sambeat, Hospital Sant Pau, Barcelona.

Sweden: (A Karlsson), Karolinska University Hospital, Stockholm; PO Persson, Karolinska University Hospital, Huddinge; L Flamholc, Malmö University Hospital, Malmö.

Switzerland: (B Ledergerber) R Weber, University Hospital, Zürich; P Francioli, M Cavassini, Centre Hospitalier Universitaire Vaudois, Lausanne; B Hirschi, E Boffi, Hospital Cantonal Universitaire de Geneve, Geneve; H Furrer, Inselspital Bern, Bern; M Battegay, L Elzi, University Hospital Basel.

Ukraine: (E Kravchenko) N Chentsova, Kiev Centre for AIDS, Kiev.

United Kingdom: (S Barton) St. Stephen's Clinic, Chelsea and Westminster Hospital, London; AM Johnson, D Mercey, Royal Free and University College London Medical School, London (University College Campus); A Phillips, MA Johnson, A Mocroft, Royal Free and University College Medical School, London (Royal Free Campus); M Murphy, Medical College of Saint Bartholomew's Hospital, London; J Weber, G Scullard, Imperial College School of Medicine at St. Mary's, London; M Fisher, Royal Sussex County Hospital, Brighton; R Brettle, Western General Hospital, Edinburgh.
HivBivus (Sweden):

**Central coordination:** L. Morfeldt*, G. Thulin, A. Sundström;

**participating physicians(city):** B. Åkerlund (Huddinge); K. Koppel, A. Karlsson (Stockholm); L. Flamholc, C. Häkangård (Malmö).

ICONA (Italy):

**Central coordination:** A. d’Arminio Monforte*, P. Pezzotti;

**PARTICIPATING PHYSICIANS AND CENTERS**

**Italy** M. Montroni, G. Scalise, A Costantini, A. Riva (Ancona); U. Tirelli, F. Martelotta (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 (Chiari); G Carnevale, A Zoncada (Cremona); F. Ghinelli, L. Sighinolfi (Ferrara); F. Leocinii, F. Mazzotta, M. Pozzi, S. Lo Caputo (Firenze); B. Grisorio, S. Ferrara (Foggia); G. Pagano, G. Cassola, A. Alessandri, 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. Chiriani, CM Izzo, M. De Marco, R. Viglietti, E Manzillo (Napoli); C. Ferrari, A. Piazzaferri (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. Vull, 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;
