

Presence of the Metabolic Syndrome Is Not a Better Predictor of Cardiovascular Disease Than the Sum of Its Components in HIV-Infected Individuals

Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study*

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OBJECTIVE — It is much debated whether the metabolic syndrome contributes additional information over and above that provided by the individual components of the syndrome alone. Among HIV-infected individuals, we investigated whether any particular combinations of the components included in the definition of the metabolic syndrome are associated with a higher risk of cardiovascular disease (CVD).

RESEARCH DESIGN AND METHODS — We followed 33,347 HIV-infected individuals in a prospective observational study. The effect of combinations of components of the metabolic syndrome (low HDL cholesterol, high triglycerides, high BMI, hypertension, and diabetes) on the risk of CVD was assessed by Poisson regression incorporating interactions between each component pair and adjusting for age, sex, family history of CVD, smoking status, calendar year, and exposure to antiretroviral therapy. We reduced the risk of type 1 errors by randomly splitting the data set for training (70% of sample) and validation (remaining 30%).

RESULTS — In the training data set, 671 patients experienced a CVD event over 110,652 person-years. Unadjusted, the presence of metabolic syndrome at study enrollment (≥ 3 of the factors) was associated with a 2.89 higher risk of CVD (95% CI 2.34–3.59; $P = 0.0001$) compared with individuals without the metabolic syndrome. After adjustment for the individual components, the metabolic syndrome as an entity no longer predicted the risk of CVD (adjusted relative risk 0.85; 95% CI 0.61–1.17; $P = 0.32$). No significant positive interactions were found among the components of the metabolic syndrome.

CONCLUSIONS — The presence of the metabolic syndrome in HIV-infected individuals did not appear to increase the CVD risk over and above that conferred by the components of the syndrome separately.

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*A full list of members of the Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study is available in an online appendix.

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HI V-1 infection is treated with combination antiretroviral therapy (cART). Although treatment is usually highly effective, the success of treatment is frequently complicated by lipodystrophy (peripheral fat loss and accumulation of central adiposity), dyslipidemia, insulin resistance, and overt diabetes (1,2). The clustering of these abnormalities has striking similarities to the metabolic syndrome, a term used to describe a clustering of risk factors for cardiovascular disease (CVD), including high triglycerides, low HDL cholesterol, hypertension, hyperglycemia/insulin resistance, and abdominal obesity. Prior studies have reported that the relative frequency of the components of the metabolic syndrome differ between HIV-infected individuals and the general population, with hypertriglyceridemia and low HDL cholesterol being predominant features in "HIV metabolic syndrome" (3,4). However, most of the studies that have explored the metabolic syndrome in HIV-infected individuals have been cross-sectional and have not considered its relationship with clinical end points as such as CVD (3,5,6). Several reports from HIV-infected patients receiving cART suggested increased incidence of CVD and related mortality (7). Because many components of the metabolic syndrome may be induced by cART, it is important to investigate the predictive ability of the metabolic syndrome for CVD in this population.

The metabolic syndrome is recognized as a "CVD risk enhancer" by the U.S. National Cholesterol Educational Program (NCEP) (8), and the presence of metabolic syndrome is associated with an increased risk of CVD (9,10). However, whether the syndrome has any independent prognostic value over and above its components is controversial (11). The aim of this study was to investigate whether the presence of the metabolic syndrome in an HIV-infected individual

constitutes an additional risk for CVD over and above that which would be expected for the individual given his or her known risk factors for CVD. In particular, we wished to investigate whether any particular combinations of the components included in the definition of metabolic syndrome are associated with a higher risk of CVD than would be expected from combining the risk attributable to each component separately.

RESEARCH DESIGN AND METHODS

METHODS—The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D) study is a prospective, observational study formed by the collaboration of 11 cohorts following 33,347 HIV-infected subjects at 212 clinics in Europe, Australia, and the U.S. The primary objective of the study is to investigate the possible association between ART and the onset of myocardial infarction. The D:A:D study methodology has been described in detail elsewhere (12).

Data collection

Patients are followed prospectively during visits to outpatient clinics as a part of regular medical care. At enrollment and at least every 8 months thereafter, standardized data collection forms are completed at the sites, providing information from physical examination, patient interview concerning family history of coronary heart disease, prior history of CVD and diabetes, cigarette smoking, blood pressure, lipid-lowering and antihypertensive therapy, and the presence of physician-defined lipodystrophy and serum lipid levels (total cholesterol, HDL cholesterol, and triglycerides and information on fasting conditions), as well as HIV-related information (antiviral therapy, CD4 cell counts, HIV viral loads, and dates of diagnoses of all AIDS-defining diseases).

We considered a modified NCEP definition of the metabolic syndrome (13), which incorporated five criteria: triglycerides $\geq 1.7 \text{ mmol/l}$; HDL cholesterol $\leq 1.0 \text{ mmol/l}$ in men or $\leq 1.3 \text{ mmol/l}$ in women; high blood pressure indicated by systolic blood pressure $\geq 130 \text{ mmHg}$ or diastolic blood pressure $\geq 85 \text{ mmHg}$; BMI $> 30 \text{ kg/m}^2$ as a surrogate of waist circumference; and a diagnosis of diabetes as a surrogate of fasting glucose. A patient was defined as having the metabolic syndrome on the first date that at least three of the five components were present. When information was missing for an individual for any component of

the definition, that component was assumed to be absent. Furthermore, for our main analyses, the various components of the metabolic syndrome were assumed to be irreversible; thus, once an individual had met one of the criteria, it was assumed that he or she would always meet that criterion.

Ascertainment of outcomes

All incident cases of myocardial infarction, all 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 earlier reports from the study (14).

The incidence of a composite CVD end point of myocardial infarction, stroke, invasive coronary procedure (ICP), or death from other cardiovascular cause was calculated by dividing the number of such events by the total person-years of follow-up in the cohort. Patient follow-up was counted from the time of enrollment in D:A:D until the date of the first CVD event, 1 February 2007, or 6 months after the patient's last clinic visit. Only the first new CVD event during prospective follow-up was considered in the analyses.

Diabetes has been collected as a secondary D:A:D end point since the start of the study. New-onset diabetes was considered as a definite diagnosis if fasting plasma glucose $\geq 7.0 \text{ mmol/l}$ (126 mg/dl) was measured on two consecutive occasions or as a possible diagnosis if the patient had a physician-reported date of diabetes onset and was known to have initiated antidiabetes therapy.

Statistical analysis

Because of the potential for a high type I error rate due to multiple testing, we investigated the possible presence of interactions between the various components of the metabolic syndrome in a random sample of 70% of the cohort (training sample: $n = 23,202$). Initially, for exploratory purposes, patients were grouped on the basis of their status at entry in D:A:D into the four strata that resulted from the combination of each component pair, and the incidence of the CVD end point was calculated for each strata. We then explored whether the components of the definition acted synergistically on the end point by the incorporation of each component into a multivariable Poisson regression analysis along with each pairwise interaction term. Any statistically significant

interaction ($P < 0.05$) with a rate ratio (RR) > 1 would suggest a positive synergistic effect between the metabolic syndrome components. These analyses were adjusted for other potential confounders for CVD (sex, age, family history of CVD, smoking status, calendar year, cohort, HIV risk group, ethnic group, and exposure to the protease inhibitor, nucleoside reverse transcriptase inhibitor [NRTI], and non-nucleoside reverse transcriptase inhibitor [NNRTI] classes of drugs). Finally, we examined whether the presence of the metabolic syndrome as an entity was associated with the risk of CVD, both before and after controlling for each of the five individual components of the definition and other possible confounders as listed above. These analyses were then repeated using information on changes over follow-up (a time-updated analysis) to assess whether the results were robust to any such changes. To rule out the possibility that any significant interactions may have reflected chance findings, the analysis was then repeated using the remaining 30% of the study cohort (validation sample: $n = 10,145$).

A series of sensitivity analyses were performed for the time-updated analyses on the training set. First, we allowed the lipid and hypertension components of the metabolic syndrome to be reversible. Thus, if a patient experienced a drop in triglycerides or blood pressure below the threshold or an increase in HDL cholesterol above the threshold, irrespective of the cause (including the use of lipid-lowering or antihypertensive drugs), he or she no longer met that criterion. Secondly, we reran the analyses after excluding follow-up (and events) that occurred while a patient had incomplete information for any metabolic syndrome component. Finally, the metabolic syndrome definition was further adapted to ensure that measurements (triglycerides, HDL cholesterol, or blood pressure) had been obtained in the previous year; if a patient did not have a measurement within any 1-year period, he or she was temporarily excluded from the risk set until a new measurement became available.

To ensure that our results were not overly influenced by patients having diabetes and CVD at baseline, the analyses were repeated after 1) adjustment for baseline myocardial infarction status (fixed analyses) and 2) excluding those with a myocardial infarction and/or diabetes at entry in the D:A:D study (time-updated analyses). The results from these

Table 1—Characteristics at enrollment in D:A:D of the 23,202 patients included in the training sample

	All patients in training sample	Metabolic syndrome at enrollment	
		Yes	No
n	23,202	1,025	22,177
Male sex	17,168 (74.0)	853 (83.2)	16,315 (73.6)
Age (years)	38 (33–45)	43 (37–52)	38 (33–44)
CD4 count (cells/mm ³)	410 (249–600)	449 (274–660)	408 (248–598)
HIV RNA (\log_{10} cp/ml)	2.7 (1.7–4.2)	1.9 (1.7–3.5)	2.7 (1.7–4.3)
Current smoker	7,823 (33.7)	410 (40.0)	7,413 (33.4)
Lipodystrophy	4,309 (18.6)	401 (39.1)	3,908 (17.6)
Prior myocardial infarction	172 (0.7)	18 (1.8)	154 (0.7)
Exposure to antiretroviral therapy			
Any NRTI	16,928 (73.0)	884 (86.2)	16,044 (72.4)
Total exposure (years)	3.1 (1.6–4.8)	3.6 (2.2–5.3)	3.0 (1.5–4.7)
Any protease inhibitor	13,505 (58.2)	794 (77.5)	12,711 (57.3)
Total exposure (years)	2.3 (1.2–3.2)	2.7 (1.7–3.6)	2.3 (1.2–3.2)
Any NNRTI	7,652 (33.0)	366 (35.7)	7,286 (32.9)
Total exposure (years)	0.9 (0.4–1.6)	1.0 (0.5–1.7)	0.9 (0.4–1.6)
MS components present at enrollment in D:A:D*			
High TRIG	8,923 (38.5)	979 (95.5)	7,944 (35.8)
Low HDL	4,934 (21.3)	872 (85.1)	4,062 (18.3)
High BP	3,278 (14.1)	838 (81.8)	2,440 (11.0)
High BMI	1,019 (4.4)	301 (29.4)	718 (3.2)
Diabetes	651 (2.8)	238 (23.2)	413 (1.9)

Data are n (%) or median (interquartile range). *High triglycerides (TRIG): ≥ 1.7 mmol/l; low HDL cholesterol: ≤ 1.0 mmol/l (men) or ≤ 1.3 mmol/l (women); high blood pressure (BP): systolic BP > 130 mmHg or diastolic BP > 85 mmHg; high BMI: > 30 kg/m²; diabetes: an established diagnosis of diabetes.

analyses showed conclusions similar to those of the primary analyses (data not shown).

Analyses were performed using the GENMOD procedure in SAS version 9.1. P < 0.05 was considered to be statistically significant.

RESULTS— Of the 23,202 patients in the training set, 1,025 (4.4%) had the metabolic syndrome at enrollment (Table 1). The most common components of the metabolic syndrome at study entry were elevated triglycerides (95.5% of those with the metabolic syndrome), low HDL cholesterol (85.1%), and high blood pressure (81.8%). As expected, compared with those without the metabolic syndrome at study enrollment, those with the metabolic syndrome at enrollment were significantly more likely to be male, to be older, to be current smokers, to have lipodystrophy, and to have previously experienced a myocardial infarction (all P < 0.001). Furthermore, those with the metabolic syndrome at enrollment were more likely to have received the NRTI and protease inhibitor classes of drugs and had

higher CD4 counts and lower HIV RNA levels at enrollment than those without the metabolic syndrome (all P < 0.001).

Individuals included in the training set were followed for a median (range) of 5.1 (3.2–6.5) person-years (total follow-up 110,652 person-years), with no significant difference in follow-up time between those with and without the metabolic syndrome at enrollment (P = 0.93, Mann-Whitney U test). Over this time, 671 (2.0%) patients experienced a CVD event, with the first event being a myocardial infarction in 51.9%, a stroke in 27.9%, an ICP in 18.0% (angioplasty 12.8%, coronary bypass 4.3%, and endarterectomy 0.9%), and cardiovascular death in 2.2%. There were no major differences in the distribution of first events among those with and without the metabolic syndrome at study enrollment (data not shown).

Incidence of CVD according to components of the metabolic syndrome at study enrollment

When patients were categorized according to the presence of the metabolic syndrome components at enrollment in the

D:A:D study, event rates ranged from 3.7 (95% CI 3.2–4.2) per 1,000 person-years among patients with a normal triglyceride level and no hypertension to 43.3 (25.2–69.3) per 1,000 person-years among patients with diabetes and a BMI > 30 kg/m² (Table 2). In multivariable analysis adjusting for other potential confounders, there was no evidence of any synergistic associations between the metabolic syndrome component pairs. Whereas weak negative interactions were noted between high triglycerides and hypertension and between low HDL cholesterol and hypertension, these were of borderline significance. For example, individuals with low HDL cholesterol and high blood pressure appeared to have a lower risk of CVD than would be expected based on the effects of these factors alone.

The CVD event rate increased as the number of metabolic syndrome components present at study enrollment increased, from 3.2 (95% CI 2.7–3.8) per 1,000 person-years in those with no components present to 33.9 (41.0–122.5) in those with five components present. In unadjusted analyses, the rate of CVD increased by 65% (RR 1.65, 95% CI 1.54–1.77; P = 0.0001) for each additional component that was present at study enrollment; after adjusting for potential confounders, the effect of an increasing number of metabolic syndrome components remained significant (adjusted RR [ARR] 1.33, 95% CI 1.23–1.44; P = 0.0001). Individuals with the metabolic syndrome at study enrollment (≥ 3 of the factors) were almost three times as likely (RR 2.89, 95% CI 2.34–3.59; P = 0.0001) to develop CVD as those without the metabolic syndrome at study enrollment. However, after adjustment for the components of the metabolic syndrome themselves and for other potential confounders, the metabolic syndrome as an entity no longer predicted the risk of CVD (ARR 0.85, 95% CI 0.61–1.17; P = 0.32).

Incidence of CVD according to components of the metabolic syndrome over follow-up

When patients were categorized according to the presence of the metabolic syndrome components over prospective follow-up, event rates were lowest in those with a normal triglyceride level and normal HDL cholesterol (ARR 1.2, 95% CI 0.8–1.6 per 1,000 person-years) and highest in those with diabetes and a BMI > 30 kg/m² (28.7, 17.7–39.8 per 1,000 person-years) (Table 2).

Table 2—CVD incidence rates stratified by each metabolic syndrome component “pair”

Criterion 1*	Criterion 2*	At baseline (fixed)		Over follow-up (time-updated)	
		Rate/1,000 person-years (95% CI)	Interaction P value†	Rate/1,000 person-years (95% CI)	Interaction P value†
Low TRIG	High HDL	4.0 (3.4–4.5)		2.8 (2.2–3.5)	
Low TRIG	Low HDL	5.9 (4.5–7.2)		1.2 (0.8–1.6)	
High TRIG	High HDL	7.5 (6.5–8.6)		5.1 (4.3–6.0)	
High TRIG	Low HDL	10.1 (8.7–11.6)	0.78	8.6 (7.8–9.4)	0.30
Low TRIG	No high BP	3.7 (3.2–4.2)		2.4 (1.8–2.9)	
Low TRIG	High BP	9.1 (6.9–11.3)		5.5 (3.8–7.1)	
High TRIG	No high BP	8.1 (7.2–9.0)		5.9 (5.2–6.6)	
High TRIG	High BP	11.1 (8.8–13.4)	0.06‡	9.3 (8.3–10.4)	0.07
Low TRIG	No diabetes	4.0 (3.5–4.5)		2.9 (2.3–3.4)	
Low TRIG	Diabetes	19.2 (11.7–27.7)		11.0 (4.8–22.2)	
High TRIG	No diabetes	7.5 (6.7–8.3)		6.4 (5.9–7.0)	
High TRIG	Diabetes	39.2 (29.5–48.8)	0.19	25.9 (20.8–31.1)	0.23
Low TRIG	Low BMI	4.3 (3.8–4.8)		2.9 (2.3–3.5)	
Low TRIG	High BMI	4.8 (2.6–8.2)		5.2 (2.7–9.0)	
High TRIG	Low BMI	8.3 (7.5–9.2)		7.2 (6.5–7.8)	
High TRIG	High BMI	15.1 (9.7–20.5)	0.38	10.1 (7.5–12.8)	0.14
High HDL	No high BP	4.5 (4.0–5.0)		3.2 (2.7–3.8)	
High HDL	High BP	10.1 (8.0–12.1)		6.7 (5.2–8.2)	
Low HDL	No high BP	8.0 (6.9–9.1)		6.3 (5.4–7.2)	
Low HDL	High BP	10.3 (7.9–12.8)	0.04‡	9.4 (8.3–10.6)	0.05‡
High HDL	No diabetes	4.7 (4.2–5.1)		3.7 (3.1–4.2)	
High HDL	Diabetes	24.7 (17.5–31.9)		17.8 (10.9–24.6)	
Low HDL	No diabetes	7.3 (6.4–8.3)		6.8 (6.2–7.5)	
Low HDL	Diabetes	39.4 (27.6–51.2)	0.80	26.3 (20.5–32.1)	0.53
High HDL	Low BMI	5.0 (4.5–5.5)		4.0 (3.4–4.5)	
High HDL	High BMI	7.3 (4.5–10.2)		5.0 (2.8–7.1)	
Low HDL	Low BMI	8.2 (7.2–9.2)		7.5 (6.8–8.2)	
Low HDL	High BMI	14.8 (8.6–23.6)	0.52	12.6 (9.0–16.2)	0.32
No high BP	No diabetes	4.9 (4.4–5.3)		4.1 (3.6–4.6)	
No high BP	Diabetes	27.9 (20.8–35.0)		20.7 (14.2–27.2)	
High BP	No diabetes	8.8 (7.3–10.3)		7.5 (6.6–8.4)	
High BP	Diabetes	36.3 (23.1–49.6)	0.55	25.5 (19.4–31.7)	0.21
No high BP	Low BMI	5.3 (4.8–5.8)		4.6 (4.0–5.1)	
No high BP	High BMI	8.3 (5.2–11.4)		4.8 (2.9–7.6)	
High BP	Low BMI	10.1 (8.4–11.7)		8.2 (7.3–9.2)	
High BP	High BMI	11.4 (5.6–17.1)	0.23	12.1 (8.8–15.5)	0.43
No diabetes	Low BMI	5.4 (4.9–5.8)		5.3 (4.8–5.7)	
No diabetes	High BMI	6.0 (3.7–8.4)		6.1 (4.2–7.9)	
Diabetes	Low BMI	28.2 (21.6–34.7)		22.2 (17.3–27.1)	
Diabetes	High BMI	43.3 (25.2–69.3)	0.12	28.7 (17.7–39.8)	0.44

Data are CVD incidence rates per 1,000 person years (95% CI). *High triglycerides (TRIG): $\geq 1.7 \text{ mmol/l}$; low HDL cholesterol: $\leq 1.0 \text{ mmol/l}$ (men) or $\leq 1.3 \text{ mmol/l}$ (women); high blood pressure (BP): systolic BP $> 130 \text{ mmHg}$ or diastolic BP $> 85 \text{ mmHg}$; diabetes: an established diagnosis of diabetes. †P values for the interaction between each component pair were obtained from a multivariable Poisson regression model that included all main effects and all pairwise interactions, as well as adjustment for other potential confounders (see RESEARCH DESIGN AND METHODS). ‡ARRs were all <1 , suggesting an antagonistic rather than synergistic effect of each combination of components.

The CVD event rate again increased as the number of metabolic syndrome components present over prospective follow-up increased with rates of 2.3 (95% CI 1.6–3.0), 3.5 (2.8–4.1), 6.4 (5.6–7.3), 9.6 (8.3–10.8), 14.4 (10.6–18.2), and 39.8 (23.6–62.8) per 1,000 person-years in those with zero, one, two, three, four, and five components present, respectively. In unadjusted analyses, the

rate of CVD increased by 64% (RR 1.64, 95% CI 1.53–1.76; $P = 0.0001$) for each additional component present; after adjustment for potential confounders, the rate of CVD increased by 46% (ARR 1.46, 95% CI 1.34–1.58; $P = 0.0001$) for each additional component. Before adjustment, individuals with the metabolic syndrome over follow-up were 2.4 times as likely (RR 2.40, 95% CI 2.06–2.79; $P =$

0.0001) to develop CVD than those without the metabolic syndrome (Table 3). However, as before, after adjustment for the components of the metabolic syndrome themselves and for other potential confounders, the metabolic syndrome as an entity no longer predicted the risk of CVD (ARR 0.94, 95% CI 0.69–1.27; $P = 0.67$). The results were confirmed in the validation data set (303 events over

Metabolic syndrome and risk of CVD

Table 3—Association between the metabolic syndrome (time-updated analyses), its components, and CVD from main and sensitivity analyses

Factor*	Main analysis: training set (671 events, 110,652 person-years)	Main analysis: validation set (303 events, 48,741 person-years)	Metabolic syndrome components reversible (671 events, 110,652 person-years)	No missing data on metabolic syndrome components (377 events, 57,536 person-years)
Unadjusted				
MS	2.40 (2.06–2.79); 0.0001	2.71 (2.16–3.40); 0.0001	3.02 (2.54–3.59); 0.0001	3.34 (2.36–4.74); 0.0001
Adjusted†				
MS	0.94 (0.69–1.27); 0.67	1.00 (0.64–1.57); 0.99	1.03 (0.77–1.39); 0.83	0.88 (0.52–1.49); 0.63
High TRIG	1.50 (1.18–1.91); 0.001	1.26 (0.88–1.79); 0.20	1.47 (1.23–1.76); 0.0001	1.39 (1.10–1.76); 0.006
Low HDL	1.41 (1.12–1.76); 0.003	1.61 (1.12–2.30); 0.009	1.25 (1.03–1.51); 0.02	1.44 (1.12–1.86); 0.005
High BP	1.26 (0.98–1.62); 0.07	1.40 (0.95–2.05); 0.09	1.14 (0.92–1.41); 0.23	1.23 (0.98–1.53); 0.07
Diabetes	2.31 (1.83–2.92); 0.0001	1.96 (1.39–2.77); 0.0001	2.27 (1.77–2.92); 0.0001	2.07 (1.43–2.99); 0.0001
High BMI	1.33 (1.01–1.74); 0.04	1.38 (0.94–2.03); 0.10	1.13 (0.79–1.60); 0.51	1.09 (0.67–1.79); 0.72

Data are ARR (95% CI); P values. *High triglycerides (TRIG): $\geq 1.7 \text{ mmol/l}$; low HDL cholesterol: $\leq 1.0 \text{ mmol/l}$ (men) or $\leq 1.3 \text{ mmol/l}$ (women); high blood pressure (BP): systolic BP $> 130 \text{ mmHg}$ or diastolic BP $> 85 \text{ mmHg}$; diabetes: an established diagnosis of diabetes; high BMI: $> 30 \text{ kg/m}^2$. †Adjusted estimates obtained from a multivariable Poisson regression model that also includes adjustment for other potential confounders as sex, age, family history of CVD, smoking status, calendar year, cohort, HIV risk group, ethnic group, and exposure to the protease inhibitor, NRTI, and NNRTI classes of drugs.

48,741 person-years), and all sensitivity analyses reached similar conclusions (Table 3).

In the main analyses, of the metabolic syndrome components diabetes was the strongest independent predictor of CVD with an ARR of 2.31 (95% CI 1.83–2.92; $P = 0.0001$) followed by high triglycerides (1.50, 1.18–1.91; $P = 0.001$) and low HDL cholesterol (1.41, 1.12–1.76; $P = 0.003$). A high BMI was more weakly associated with CVD (1.33, 1.01–1.74; $P = 0.04$), whereas high blood pressure was not independently associated with the risk of CVD (1.26, 0.98–1.62; $P = 0.07$). Similar results were obtained in the validation data set (Table 3).

CONCLUSIONS — There is a strong association between the presence of an increasing number of the components of the metabolic syndrome in HIV-infected patients and an increased CVD risk in the D:A:D study. In particular, the CVD rate was 2.4–2.8 times higher in those with the metabolic syndrome than in those without the metabolic syndrome. However, there was no evidence from our study that the metabolic syndrome as a specific entity was associated with a higher CVD risk than would be anticipated based on the presence of the individual components alone. In particular, there was no evidence that any of the components of the metabolic syndrome acted synergistically on an individual's risk of CVD, and the presence of the metabolic syndrome did not increase CVD risk over and above that conferred by the components of the syndrome. The results from our sensitivity analyses, which ex-

plored the robustness of the findings to missing data and to changes in lipid and blood pressure measurements, were all consistent with our main analyses.

The components included in the definition of the metabolic syndrome are all established independent risk factors for CVD in populations not infected with HIV. If the metabolic syndrome provides additional information on the CVD risk over and above that provided by these components separately, we would expect to see some synergy between the components. So far, only a few studies exploring the predictive ability of metabolic syndrome on a CVD outcome have specifically addressed this question by adjusting for the components of the syndrome. These studies either showed lower hazard ratios for the metabolic syndrome compared with the individual risk factors or showed that metabolic syndrome by itself does not contribute any additional information (15–17).

To date, although several studies of HIV-infected individuals have assessed the impact of the various components of the metabolic syndrome on the risk of CVD, no study has been able to consider the impact of the metabolic syndrome itself on clinical end points. However, data from a post hoc analysis of the naive sub-study of the INITIO trial (based on 21 CVD events) suggested that incident metabolic syndrome was associated with CVD with a hazard ratio of 2.56 (95% CI 0.86–7.60) (18). This result did not reach statistical significance and, as noted by the authors, should be interpreted with caution. With the aging of the HIV-infected population, brought about by an

increased life expectancy after the widespread use of cART, it is likely that the long-term metabolic complications among HIV-infected individuals will place this group at risk of CVD in the future. An increasing number of HIV-infected patients are starting to develop diabetes (19). The results from the present analysis confirm our previous finding that diabetes is an important risk factor for myocardial infarction and CVD among HIV-infected individuals (12). Although dyslipidemia remains an important predictor of CVD, this condition appears to be decreasing in frequency, largely due to increased use of lipid-lowering drugs (19).

We have recently reported an increased risk of myocardial infarction associated with the use of the protease inhibitor drug class (12), which was partly explained by dyslipidemia. From the NRTI drug class, abacavir was recently reported to be associated with myocardial infarction and CVD (20,21), which might be due to changes in inflammation, i.e., interleukin-6 and high-sensitivity C-reactive protein (21). Both biomarkers are independently associated with CVD (15,22). Increased inflammation is reported to be associated with the metabolic syndrome among HIV-infected (6) and uninfected (15) individuals. However, neither C-reactive protein nor other biomarkers are included in the definition of the metabolic syndrome, although the inclusion of such biomarkers may provide useful information. Unfortunately, the D:A:D study does not collect information on these biomarkers, so it is unclear whether their inclusion would have

changed our conclusion. Future research will provide further insight into HIV-induced as well as antiretroviral therapy-induced inflammation.

The debate about the existence of the metabolic syndrome as an entity and its prognostic value is ongoing (11,23,24). Some of the critique has focused on the independent predictive ability of the metabolic syndrome for CVD. We aimed in this study to investigate whether the presence of the metabolic syndrome in an HIV-infected individual constitutes an additional risk for CVD, over and above that which would be expected in the individual given his or her known risk factors for CVD. A priori, we believed that certain combinations of risk factors would be more frequent than others. If these combinations were of any independent prognostic information, we would then expect to find positive interactions between these risk factor combinations (i.e., the presence of both factors would be associated with a greater than expected increase in the risk of CVD). However, this was not the case. Even by including "overt diabetes" in the syndrome definition instead of fasting glucose, we still did not find the metabolic syndrome as an independent predictor of CVD. We do not believe that the inclusion of fasting glucose would have resulted in major differences.

Limitations

Our study population is largely male (70%), and so our results should be extrapolated to women with some caution. As the D:A:D study does not collect waist circumference, we used increased BMI to reflect this component of the metabolic syndrome, as in other studies (17). The use of BMI may have resulted in lower estimated effects compared with waist circumference, because BMI includes total fat mass. However, it has been suggested that waist circumference more closely reflects visceral fat mass that is directly related to insulin resistance (6). Furthermore, the lipodystrophic changes with central fat accumulation and loss of peripheral subcutaneous fat may underestimate the prevalence of the metabolic syndrome, as these patients may have a normal BMI and might not have been sufficiently captured by our modified NCEP definition. Furthermore, many of the metabolic changes in HIV are induced by antiretroviral therapy, and their impact on CVD risk may differ from that in the general population. Of note, measure-

ments of hypertension and lipids were generally obtained through routine clinical care and, as such, are not always based on the standardized protocols that may be used in a trial setting. As a result, we may have overestimated the frequency of these conditions in this study.

In summary, we did not find that the metabolic syndrome was an independent predictor of CVD in HIV-infected individuals once we had considered the risk conferred by the components of the syndrome. However, we found a strong association between an increasing number of the components of the metabolic syndrome and CVD risk, emphasizing the importance of the identification and management of all CVD factors in this population, including those not included in the metabolic syndrome definition (e.g., smoking); the identification of one CVD risk factor should immediately lead the physician to search for other CVD risk factors. Patients should also be evaluated for CVD risk at least annually (25).

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