Changes Over Time in Risk Factors for Cardiovascular Disease and Use of Lipid-Lowering Drugs in HIV-Infected Individuals and Impact on Myocardial Infarction

Data Collection on Adverse Events of Anti-HIV Drugs Study Group[a]

Background. Because of the known relationship between exposure to combination antiretroviral therapy and cardiovascular disease (CVD), it has become increasingly important to intervene against risk of CVD in human immunodeficiency virus (HIV)–infected patients. We evaluated changes in risk factors for CVD and the use of lipid-lowering therapy in HIV-infected individuals and assessed the impact of any changes on the incidence of myocardial infarction.

Methods. The Data Collection on Adverse Events of Anti-HIV Drugs Study is a collaboration of 11 cohorts of HIV-infected patients that included follow-up for 33,389 HIV-infected patients from December 1999 through February 2006.

Results. The proportion of patients at high risk of CVD increased from 35.3% during 1999–2000 to 41.3% during 2005–2006. Of 28,985 patients, 2801 (9.7%) initiated lipid-lowering therapy; initiation of lipid-lowering therapy was more common for those with abnormal lipid values and those with traditional risk factors for CVD (male sex, older age, higher body mass index [calculated as the weight in kilograms divided by the square of the height in meters], family and personal history of CVD, and diabetes mellitus). After controlling for these, use of lipid-lowering drugs became relatively less common over time. The incidence of myocardial infarction (0.32 cases per 100 person-years [PY]; 95% confidence interval [CI], 0.29–0.35 cases per 100 PY) appeared to remain stable. However, after controlling for changes in risk factors for CVD, the rate decreased over time (relative rate in 2003 [compared with 1999–2000], 0.73 cases per 100 PY [95% CI, 0.50–1.05 cases per 100 PY]; in 2004, 0.64 cases per 100 PY [95% CI, 0.44–0.94 cases per 100 PY]; in 2005–2006, 0.36 cases per 100 PY [95% CI, 0.24–0.56 cases per 100 PY]). Further adjustment for lipid levels attenuated the relative rates towards unity (relative rate in 2003 [compared with 1999–2000], 1.06 cases per 100 PY [95% CI, 0.63–1.77 cases per 100 PY]; in 2004, 1.02 cases per 100 PY [95% CI, 0.61–1.71 cases per 100 PY]; in 2005–2006, 0.63 cases per 100 PY [95% CI, 0.36–1.09 cases per 100 PY]).

Conclusions. Although the CVD risk profile among patients in the Data Collection on Adverse Events of Anti-HIV Drugs Study has decreased since 1999, rates have remained relatively stable, possibly as a result of a more aggressive approach towards managing the risk of CVD.

A number of studies have reported a link between combination antiretroviral therapy (cART) and cardiovascular disease (CVD) in HIV-infected individuals [1–8]. The use of cART is, however, only 1 of many factors that contribute to the development of CVD in HIV-infected individuals. Traditional risk factors for CVD, including male sex, older age, and cigarette smoking, are prevalent in this group [8]. Because HIV-infected individuals are surviving longer, they may experience clinical events consistent with those experienced by an aging population [9, 10]. Thus, attempts to reduce the

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[a] Members of the study group are listed at the end of the text.

risk of CVD have taken on greater importance in recent years.

The Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study has the unique ability to monitor risk factors for CVD in a large and geographically diverse population of HIV-infected individuals over time. The aim of the present analysis was to describe changes in CVD risk factors and the use of lipid-lowering drugs from December 1999 through February 2006 in DAD participants and to assess the impact of any changes on the incidence of myocardial infarction (MI).

METHODS

The DAD study is a large, observational study formed by the collaboration of 11 cohorts of HIV-infected patients. The primary aim of the study is to establish whether the use of cART is associated with an increased risk of CVD. The 11 cohorts currently contribute data on 33,389 HIV-infected patients monitored at 212 clinics in Europe, the United States, and Australia [8, 11]. Patients were all receiving active follow-up at the time of enrollment and were observed prospectively, with data obtained during regular outpatient visits. The standardized data set includes information on sociodemographic characteristics; clinical AIDS events and deaths; known risk factors for CVD; CD4 cell count; HIV RNA level; total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels; antiretroviral treatment history; and information on the use of lipid-lowering therapy, platelet aggregation inhibitors, angiotensin converting enzyme inhibitors, and antihypertensive, antidiabetic, or anabolic steroid therapy. All data are transferred to the coordinating center as anonymous computerized files and are merged into a central dataset. Detailed information regarding study end points (CVD and death) is provided in real time; each end point is validated and coded centrally. The DAD study has appropriate ethical committee approval from each participating country.

Statistical Analyses

Changes in risk factors over time. We considered 6 calendar intervals: 1999–2000, 2001, 2002, 2003, 2004, and 2005–2006. Patients undergoing follow-up in the DAD study in each interval were classified according to their risk factor status at the end of the interval, and patient characteristics were compared using χ^2 tests and analysis of variance, considering patients undergoing follow-up in each interval as independent groups. The definition of a "high-risk" individual, based on the National Cholesterol Education Program guidelines [12], included individuals with a previous episode of CVD (MI, stroke, or an invasive cardiovascular procedure), diabetes mellitus, or $\geq$2 of the following risk factors: older age ($\geq$45 years for men and $\geq$55 years for women), current smoker, family history of CVD, the presence of hypertension (systolic blood pressure, >140 mm Hg; diastolic blood pressure, >90 mm Hg; or use of antihypertensive drugs and/or angiotensin converting enzyme inhibitors), or dyslipidaemia (total cholesterol level, $\geq$6.2 mmol/L; HDL cholesterol level, $\leq$0.9 mmol/L; total cholesterol:HDL cholesterol ratio, $\geq$6.5; or the use of lipid-lowering drugs). All lipid measurements were considered, regardless of fasting status.

Use of lipid-lowering drugs. Poisson regression (GENMOD procedure in SAS, version 9 [SAS Institute]) identified factors associated with the initiation of lipid-lowering drugs, with the period of follow-up considered to be from the time of entry in the DAD study to the date of initiation of lipid-lowering drugs, the date of death, the patient's last clinic visit, or 1 February 2006 (whichever occurred first). Each individual's follow-up time was split into a series of 1-month periods, and their demographic characteristics, risk factors for CVD, and lipid levels were evaluated at the start of each period. The factors included in this analysis were calendar period, sex, age, HIV risk group (men who have sex with men, injection drug users, heterosexual persons, or other), ethnicity (white, black African, other known, or missing), body mass index (calculated as the weight in kilograms divided by the square of the height in meters), smoking status (current smoker, ex-smoker, never smoker, or unknown), family history of CVD, diagnosis of diabetes mellitus, a previous cardiovascular event, cumulative exposure to cART, and the patient's most recent CD4 cell count, HIV RNA level, total cholesterol level, HDL cholesterol level, and triglyceride level. Although high-risk status was considered as a factor in univariable analyses, it was not included in the multivariable analyses because of the strong collinearity with other CVD risk factors. A total of 1348 patients who were already receiving lipid-lowering drugs at enrollment and 3056 patients from 1 cohort that did not provide this information were excluded. Because fibrates and statins may have different effects on lipid parameters, the multivariable analyses were repeated without adjusting for the latest values of each lipid parameter. All analyses were adjusted for study cohort. Missing data on risk factors were generally incorporated through the inclusion of "unknown" categories for each variable. When lipid measurements were missing at entry in the DAD study, patient follow-up for analyses that included time-updated lipid levels was left-truncated until the time of the patient's first available lipid measurement.

Changes in the incidence of MI. We investigated trends over time in the incidence of MI and whether these could be explained by changes in the CVD risk profiles of patients. The analysis was similar to previous analyses performed in the DAD study [8] and used Poisson regression, as described above. Only the first MI during prospective follow-up was included in the analyses; thus, patient follow-up was censored once an MI had occurred. We considered the relationship between the incidence of MI and calendar period, as well as the relationship between

Table 1. Demographic characteristics of and risk factors for cardiovascular disease (CVD) in patients undergoing follow-up in the Data Collection on Adverse Events of Anti-HIV Drugs Study in the 6 calendar periods.

	Calendar period					
Variable	1999–2000	2001	2002	2003	2004	2005–2006
No. of patients who underwent follow-up	21,483	23,705	26,613	28,400	28,495	25,613
Male sex	16,203 (75.4)	17,922 (75.6)	19,906 (74.8)	21,092 (74.3)	21,027 (73.8)	18,857 (73.6)
Age, median years (IQR)	39 (35–45)	40 (35–46)	40 (36–47)	41 (36–48)	42 (37–48)	43 (38–49)
Risk group						
Men who have sex with men	9487 (44.2)	10,638 (44.9)	11,841 (44.5)	12,554 (44.2)	12,472 (43.8)	11,244 (43.9)
Injection drug user	4526 (21.1)	4673 (19.7)	4765 (17.9)	4779 (16.8)	4656 (16.3)	4135 (16.1)
Heterosexual	5769 (26.9)	6277 (26.5)	7602 (28.6)	8450 (29.8)	8808 (30.9)	7903 (30.9)
Other or unknown	1701 (7.9)	2117 (8.9)	2405 (9.0)	2617 (9.2)	2559 (9.0)	2331 (9.1)
Ethnicity						
White	10,615 (49.4)	11,260 (47.5)	11,703 (44.0)	12,130 (42.7)	12,544 (44.0)	11,170 (43.6)
Black African	2027 (9.4)	2451 (10.3)	2632 (9.9)	2761 (9.7)	2794 (9.8)	2494 (9.7)
Other	610 (2.8)	751 (3.2)	766 (2.9)	790 (2.8)	847 (3.0)	770 (3.0)
Not known	8231 (38.3)	9243 (39.0)	11,512 (43.3)	12,719 (44.8)	12,310 (43.2)	11,179 (43.7)
Risk factor for CVD						
Older age[a]	5375 (25.0)	6515 (27.5)	7672 (28.8)	8817 (31.1)	9520 (33.4)	9529 (37.2)
Current smoker[b]	8508 (47.5)	9307 (47.7)	9419 (44.5)	8772 (39.5)	8800 (38.7)	7868 (38.4)
Previous CVD	418 (2.0)	543 (2.3)	648 (2.4)	749 (2.6)	825 (2.9)	814 (3.2)
Diabetes mellitus	807 (3.8)	1005 (4.2)	1180 (4.4)	1376 (4.9)	1406 (4.9)	1321 (5.2)
Family history of CVD	1525 (7.1)	1732 (7.3)	1983 (7.5)	2082 (7.3)	2225 (7.8)	2142 (8.4)
Hypertension	2237 (10.4)	2881 (12.2)	3479 (13.1)	4091 (14.4)	4853 (17.0)	4792 (18.7)
Received lipid-lowering therapy[c]	1235 (6.3)	1885 (8.9)	2399 (10.0)	2918 (11.3)	3395 (13.0)	3527 (15.1)
Dyslipidaemia	7363 (34.3)	8678 (36.6)	9344 (35.1)	10,006 (35.2)	10,353 (36.3)	9098 (35.5)
Underwent an invasive procedure for CVD[d]						
Prior to myocardial infarction or stroke	79 (0.4)	96 (0.4)	116 (0.4)	139 (0.5)	158 (0.6)	157 (0.6)
After myocardial infarction or stroke	85 (0.4)	128 (0.5)	163 (0.6)	208 (0.7)	249 (0.9)	256 (1.0)
High-risk individual[e]	7576 (35.3)	9045 (38.2)	9896 (37.2)	10,483 (36.9)	11,206 (39.3)	10,569 (41.3)

NOTE. Data are no. (%) of patients, unless otherwise indicated. All comparisons were statistically significant ($P < .001$).

[a] Men aged ⩾45 years and women aged ⩾55 years were considered to be of older age.

[b] Based on those individuals for whom this information was available (17,931 in 1999–2000, 19,529 in 2001, 21,180 in 2002, 22,224 in 2003, 22,766 in 2004, and 20,479 in 2005–2006).

[c] Based on information from 10 of the 11 cohorts.

[d] Invasive procedures (coronary artery bypass, carotic endarterectomy, or angioplasty/stenting) were considered to be prior to myocardial infarction or stroke if they occurred in individuals who did not experience a myocardial infarction or stroke or in those who experienced one of these events, if the procedure occurred at least 1 month prior to the event.

[e] High-risk individuals were those who had previous CVD, had received a diagnosis of diabetes mellitus, or had ⩾2 risk factors for CVD (see Methods).

the incidence of MI and cumulative exposure to protease inhibitor and nonnucleoside reverse-transcriptase inhibitor therapy. These analyses were adjusted for (1) each individual's risk factor status at entry into the DAD study (a fixed covariate analysis), (2) changes in known risk factors (except lipid levels) over the course of the study (age, body mass index, family history of CVD, smoking status, and previous CVD; a time-updated analysis), and (3) these changes in addition to further adjustment for the latest lipid measurements as time-dependent covariates. The rationale for separating out the adjustment for lipid levels from other CVD risk factors is that lipid levels are known to be influenced by antiretroviral therapy and lipid-lowering drugs. The use of lipid-lowering drugs was not specifically included as a covariate, because it was anticipated that any effect of these drugs would act primarily through changes in an individual's lipid values. All analyses were also adjusted for cohort, risk group, and ethnicity.

RESULTS

Changes in risk factors over time. Risk factor profiles generally worsened over time, with increases in the proportions of patients who were older, had a history of CVD, had received a diagnosis of diabetes mellitus, had a family history of CVD, had hypertension, or had undergone an invasive cardiovascular procedure following an MI or stroke (table 1). At the same time, there was an increase in the proportions of patients receiving lipid-lowering therapy and undergoing invasive cardiovascular procedures prior to an MI or stroke. There was a reduction in the prevalence of smoking from 2003 onwards. Changes in risk factors were generally more pronounced in men than in women, with the proportions of men and women at high risk of CVD increasing from 40.1% during 1999–2000 to 47.8% during 2005–2006 and from 20.4% to 22.9% during the same periods, respectively. In contrast, the proportion of

patients at high risk of CVD remained relatively stable among those who were both younger (from 22.4% to 22.7%) and older (from 73.8% to 72.6%).

Use of lipid-lowering drugs. A total of 28,985 patients from 10 of the 11 cohorts were not receiving lipid-lowering drugs at study entry; 2801 (9.7%) of these patients started receiving lipid-lowering drugs during the follow-up period. At the time of initiation of lipid-lowering therapy, 2418 patients (86.3%) had at least 1 abnormal lipid measurement (1656 [59.1%] had a total cholesterol level ⩾6.2 mmol/L, 689 [24.6%] had an HDL cholesterol level ⩽0.9 mmol/L, and 1907 [68.1%] had a triglyceride level ⩾2.3 mmol/L), and 237 (8.5%) had experienced a prior cardiovascular event.

As expected, the rate of initiation of lipid-lowering drugs was substantially higher among those with higher total cholesterol levels (ranging from 0.59 episodes per 100 person-years [PY] among those with a total cholesterol level <3.9 mmol/L to 10.91 episodes per 100 PY among those with a total cholesterol level ⩾6.4 mmol/L), among those with higher triglyceride levels (ranging from 0.49 episodes per 100 PY among those with a triglyceride level <0.9 mmol/L to 10.10 episodes per 100 PY among those with a triglyceride level ⩾3.6 mmol/L), and among those with lower HDL cholesterol levels (ranging from 1.86 episodes per 100 PY among those with an HDL cholesterol level ⩾1.52 mmol/L to 3.63 episodes per 100 PY among those with an HDL cholesterol level <0.8 mmol/L). High-risk individuals had a significantly higher rate of initiation of lipid-lowering drugs (4.94 episodes per 100 PY), compared with low-risk individuals (1.17 episodes per 100 PY; $P = .001$). Other factors associated with a more rapid initiation of lipid-lowering therapy in univariable analyses were male sex, older age, higher body mass index, men who have sex with men (risk for HIV infection), white race, family or personal history of CVD, diagnosis of diabetes mellitus, increased exposure to cART, and earlier calendar year, whereas the rate of initiation of lipid-lowering therapy was lower among smokers (either current or ex-smokers).

In multivariable analyses that included the latest measurement of lipid parameters (table 2), the rate of starting lipid-lowering therapy was higher among men, those with a higher body mass index, those with a family history of CVD, those with diabetes mellitus, those who experienced a previous cardiovascular event, and older individuals. Compared with men who have sex with men, injection drug users were less likely to start lipid-lowering therapy. The rate of starting lipid-lowering therapy increased by 52% per 1 mmol/L higher total cholesterol level and by 10% per 1 mmol/L higher triglyceride level and was reduced by 33% per 1 mmol/L higher HDL cholesterol level. The rate of starting lipid-lowering therapy increased by 8% per year of exposure to cART. After controlling for these factors, there was a reduced rate of starting lipid-lowering therapy from 2002 onwards. Although statistically significant in univariable analyses, smoking status did not remain associated with the use of lipid-lowering therapy and was not included in the final multivariable model. There was no evidence that the relationship between the lipid levels and initiation of lipid-lowering therapy changed over time. As shown in table 2, analyses that did not incorporate the lipid levels provided similar results, although the effect of each risk factor was generally stronger in these analyses.

Changes in the incidence of MI over time. By 1 February 2006, a total of 445 episodes of MI had been reported over 137,310 PY of follow-up (median follow-up time, 4.5 years; event rate, 0.32 episodes per 100 PY; 95% CI, 0.29–0.35). The event rates in the 6 calendar periods (1999–2000, 2001, 2002, 2003, 2004, and 2005–2006) were 0.32 episodes per 100 PY (95% CI, 0.23–0.41), 0.43 episodes per 100 PY (95% CI, 0.34–0.51), 0.31 episodes per 100 PY (95% CI, 0.24–0.38), 0.34 episodes per 100 PY (95% CI, 0.27–0.41), 0.33 episodes per 100 PY (95% CI, 0.26–0.40), and 0.22 episodes per 100 PY (95% CI, 0.16–0.28), respectively. After adjusting for the baseline demographic and CVD risk factor status of patients at enrollment in the DAD study, there was a small but generally non–statistically significant (except for in 2005–2006) decrease in the MI rate over time (table 3). Adjustment for changes in known risk factors for MI (excluding lipid values) over the study period resulted in a clearer decrease in the rate of MI over time (table 3). This suggests that, were it not for the detrimental changes in the risk factor profile (largely driven by age) of participating patients over time (which would be expected to cause an increase in the risk of MI in this group), a decrease in incidence would have been seen. Importantly, when the analyses were adjusted for changes in each patient's updated lipid levels, as well as their other CVD risk factors, the reduction in the rate of MI from 2003 onwards became non–statistically significant, with relative rates that were close to unity (table 3). These findings suggest that any changes in MI incidence in this cohort over time can largely be attributed to changes in the lipid levels in patients in the cohort.

CONCLUSIONS

Since 1999, there has been a general worsening of the CVD risk factor profile among HIV-infected individuals in the DAD study. Individuals have aged, and possibly as a result, some have developed diabetes mellitus, hypertension, and/or dyslipidaemia or have undergone invasive procedures for CVD. There has been an encouraging decrease in the proportion of smokers since 2002, and individuals (particularly those at high risk of CVD) are more likely to be receiving lipid-lowering drugs. This targeted use of interventions among those at high risk of CVD has undoubtedly had a positive impact on the overall incidence of MI, largely as a result of improved lipid

Table 2. Estimated relative rate of factors independently associated with initiation of lipid-lowering therapy.

	Model including lipid parameters		Model excluding lipid parameters	
Variable	Relative rate (95% CI)	*P*	Relative rate (95% CI)	*P*
Male sex	1.19 (1.04–1.37)	.01	1.43 (1.27–1.61)	<.001
Age (per 5 years older)	1.14 (1.12–1.17)	<.001	1.18 (1.15–1.20)	<.001
BMI				
<18.0	0.72 (0.53–0.97)	.01	0.70 (0.53–0.92)	<.001
⩾18.0–26.0	1		1	
⩾26.1–30.0	1.04 (0.92–1.18)		1.29 (1.16–1.44)	
⩾30.1	1.28 (1.05–1.57)		1.38 (1.14–1.66)	
Not known	0.93 (0.83–1.05)		1.00 (0.90–1.10)	
Risk group				
Men who have sex with men	1	<.001	1	<.001
Injection drug user	0.64 (0.55–0.75)		0.46 (0.40–0.53)	
Heterosexual	0.94 (0.85–1.06)		0.94 (0.85–1.04)	
Other/unknown	1.02 (0.86–1.20)		0.91 (0.79–1.06)	
Family history of CVD	1.20 (1.05–1.38)	.01	1.34 (1.18–1.51)	<.001
Diagnosis of diabetes mellitus	1.47 (1.28–1.70)	<.001	1.81 (1.59–2.07)	<.001
Previous cardiovascular event	3.47 (2.96–4.07)	<.001	3.64 (3.15–4.21)	<.001
Cumulative exposure to cART (per year)	1.08 (1.06–1.10)	<.001	1.16 (1.14–1.18)	<.001
Calendar period				
1999–2000	1	<.001	1	<.001
2001	1.03 (0.88–1.21)		0.98 (0.86–1.12)	
2002	0.98 (0.83–1.16)		0.76 (0.66–0.87)	
2003	0.91 (0.77–1.08)		0.68 (0.59–0.78)	
2004	0.80 (0.67–0.95)		0.52 (0.45–0.61)	
2005–2006	0.59 (0.49–0.71)		0.36 (0.31–0.43)	
Latest TC level (per mmol/L higher)[a]	1.52 (1.49–1.55)	<.001	NA	
Latest HDLC level (per mmol/L lower)[a]	0.67 (0.59–0.74)	<.001	NA	
Latest TG level (per mmol/L higher)[a]	1.10 (1.08–1.11)	<.001	NA	

NOTE. Analyses include data for 28,985 patients from 10 of the 11 cohorts. BMI, body mass index (calculated as the weight in kilograms divided by the square of the height in meters); cART, combination antiretroviral therapy; CVD, cardiovascular disease; HDLC, high-density lipoprotein cholesterol; NA, not applicable; TC, total cholesterol; TG, triglyceride.

[a] Patients without baseline lipid measurements were excluded from the risk set for these analyses until the date of their first available lipid measurement.

profiles among these individuals. However, any decreases in MI incidence attributable to improved patient treatment appear to have been offset by a gradual worsening of the CVD risk profile of the cohort as patients have aged. Thus, overall, we have not seen as great a reduction in the incidence of MI over time as might have been expected.

Although there are some guidelines for the use of lipid-lowering therapy for individuals with HIV infection [13], evidence to support their effectiveness in the prevention of CVD in this population is lacking. The overall conclusions regarding the use of lipid-lowering therapy have often been confusing [14–16]. Our results from this current analysis suggest that clinicians have become increasingly willing to initiate lipid-lowering therapy for patients with abnormal lipid levels, diabetes, and other risk factors for CVD, although other work from our group [17] suggests that the use of lipid-lowering therapy in those with existing CVD remains suboptimal. Interestingly, the peak of initiation of lipid-lowering therapy occurred in 2001, with a subsequent decrease thereafter, possibly reflecting an early rapid uptake of these drugs among those with the greatest need for cART after the initial reports of a relationship between cART and MI and/or possible underuse of these drugs in later years. Unfortunately, the study did not collect information regarding the class of lipid-lowering drugs used (e.g., fibrates or statins). Because these different drug classes may have different effects on lipid levels, models that include these variables may be difficult to interpret. However, exclusion of the lipid parameters from these models led to similar conclusions regarding the other parameters in the model. It should be noted that injection drug users were less likely to receive lipid-lowering therapy after controlling for other confounding factors. Although we are unable to comment on whether this

Table 3. Relationship between calendar period, exposure to protease inhibitor (PI) and nonnucleoside reverse-transcriptase inhibitor (NNRTI) therapy, and the incidence of myocardial infarction, before and after adjustment for changes in risk factors for cardiovascular disease.

	Adjustment					
	Baseline risk factors only		Changes in non-lipid risk factors		Changes in non-lipid risk factors and lipid levels	
Variable	Relative rate (95% CI)	*P*	Relative rate (95% CI)	*P*	Relative rate (95%) CI)	*P*
Relationship with combination antiretroviral therapy						
Cumulative exposure to PIs (per year)	1.16 (1.11–1.21)	<.001	1.15 (1.11–1.20)	<.001	1.10 (1.05–1.16)	<.001
Cumulative exposure to NNRTIs (per year)	1.05 (0.99–1.11)	.09	1.04 (0.98–1.10)	.19	1.03 (0.96–1.10)	.39
Relationship with calendar period						
1999–2000	1		1		1	
2001	1.20 (0.84–1.71)	.31	1.15 (0.81–1.64)	.45	1.60 (0.97–2.65)	.06
2002	0.84 (0.58–1.21)	.34	0.75 (0.51–1.08)	.12	1.11 (0.66–1.86)	.69
2003	0.90 (0.62–1.29)	.56	0.73 (0.50–1.05)	.09	1.06 (0.63–1.77)	.82
2004	0.83 (0.57–1.20)	.32	0.64 (0.44–0.94)	.02	1.02 (0.61–1.71)	.95
2005–2006	0.50 (0.33–0.76)	.001	0.36 (0.24–0.56)	<.001	0.63 (0.36–1.09)	.10

NOTE. Cumulative exposure to PIs and NNRTIs were both treated as time-updated covariates in all analyses. Fixed risk factors were male sex, HIV exposure group, ethnicity, and cohort. Time-updated non-lipid covariates were age, body mass index (calculated as the weight in kilograms divided by the square of the height in meters), family history of cardiovascular disease, smoking status, and a previous cardiovascular event. Time-updated lipid covariates were cholesterol, high-density lipoprotein cholesterol, and triglyceride levels.

was a result of failure on the part of treating physicians to offer these drugs in the first place or of refusal by the patient to accept the drugs when offered, this highlights the importance of assessing risk factors in all HIV-infected persons and ensuring patient access to potentially beneficial interventions. It should be noted that injection drug use (and other covariates in our models, including risk factor and ethnicity) may also act as a surrogate for socioeconomic status; this information is not captured directly in the DAD study.

The proportion of patients undergoing invasive cardiovascular procedures in the cohort increased over time, both among those who had experienced a previous cardiovascular event and among those who had not experienced such an event. However, the correct interpretation of these findings is not clear. Although the proportion of individuals who require invasive procedures will likely increase as the risk of CVD among the cohort increases, the use of these procedures as pre-emptive interventions prior to the development of clinical CVD could become more attractive, because expected survival of HIV-infected patients has improved.

We have not considered changes to antiretroviral therapy in this analysis. However, it is recognized that some antiretroviral drugs are associated with more-deleterious lipid profiles than others [18–21], and switching antiretroviral regimens to those perceived to be more "lipid friendly" has generally been associated with improvement in lipid parameters [22–24]. Preliminary results from the DAD study have suggested that clinicians are increasingly likely to make such changes [25]; further detailed analyses of these findings are ongoing.

The DAD study includes a large, geographically diverse, and representative population of individuals with HIV infection who are from clinics that encompass a wide variety of treatment practices. To minimize bias, a number of standardized definitions for data collection have been introduced, and data quality checks are regularly performed. All cardiovascular events and deaths are centrally validated to ensure that they meet the stringent protocol-defined criteria.

A number of limitations of our study should be acknowledged. First, in some cohorts, the date of starting lipid-lowering therapy was estimated using the information available regarding the use of these drugs at consecutive DAD study visits. Second, information on changes in risk factors such as smoking may have relied on a patient's self-reported behavior. Although this information has been collected since the start of the DAD study, the quality of the information may have improved, which may introduce bias. Similarly, because clinicians and patients have become more aware of the relationship between cART and CVD, information on some variables (e.g., family history of CVD) may have been more actively sought, leading to a potential apparent increase in such reports. Third, because investigators at sites participating in the DAD study are likely to be particularly interested in CVD risk, they may have more vigorously promoted risk reduction through behavioral and therapeutic interventions; thus, changes in risk factors in this

cohort may be greater than those elsewhere. Fourth, the DAD study does not collect information regarding other behavioral factors, such as diet and exercise, although any changes to these factors would, to some extent, be reflected in changes to lipid levels. Fifth, despite the rigorous procedures in the DAD study to ensure that all end points are captured in a timely manner, the possibility that our results regarding MI incidence may have been affected by ascertainment bias must be considered, particularly in the most recent calendar period. It might be anticipated that clinicians may be less likely to report MIs as the study duration increases, contributing to an apparent decrease in incidence over time; however, because all centers are visited yearly and a substantial proportion of patients receiving follow-up are monitored, we believe that the risk of this should be minimal. Finally, because the DAD study is a closed cohort and patient follow-up for the analysis of MI incidence is censored after an individual develops an MI, there may be an artificial reduction in the incidence of MI as those patients at highest risk of MI drop out of the risk set.

In conclusion, our findings suggest that, although the CVD risk profile among patients observed in the DAD study has deteriorated since 1999, MI incidence rates have remained relatively stable. This is possibly a result of a more aggressive targeted approach to managing the risk of CVD.

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