Small Dense Lipoproteins, Apolipoprotein B, and Risk of Coronary Events in HIV-Infected Patients on Antiretroviral Therapy: The Swiss HIV Cohort Study

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Objectives: HIV infection and exposure to certain antiretroviral drugs is associated with dyslipidemia and increased risk for coronary events. Whether this risk is mediated by highly atherogenic lipoproteins is unclear. We investigated the association of highly atherogenic small dense low-density lipoproteins (LDLs) and apolipoprotein B and coronary events in HIV-infected individuals receiving antiretroviral therapy.

Methods: We conducted a case–control study nested into the Swiss HIV Cohort Study to investigate the association of small dense LDL and apolipoprotein B and coronary events in 98 antiretroviral drug–treated patients with a first coronary event (19 fatal and 79 nonfatal coronary events with 53 definite and 15 possible myocardial infarctions, 11 angioplasties or bypasses) and 393 treated controls matched for age, gender, and smoking status. Lipids were measured by ultracentrifugation.

Results: In models including cholesterol, triglycerides, high-density lipoprotein cholesterol, blood pressure, central obesity, diabetes, and family history, there was an independent association between small dense LDL and coronary events [odds ratio (OR) for 1 mg/dL increase: 1.06, 95% confidence interval (CI): 1.00 to 1.11] and apolipoprotein B (OR for 10 mg/dL increase: 1.16, 95% CI: 1.02 to 1.32). When adding HIV and antiretroviral therapy–related variables, ORs were 1.04 (95% CI: 0.99 to 1.10) for small dense LDL and 1.13 (95% CI: 0.99 to 1.30) for apolipoprotein B. In both models, blood pressure and HIV viral load was independently associated with the odds for coronary events.

Conclusions: HIV-infected patients receiving antiretroviral therapy with elevate small dense LDL and apolipoprotein B are at increased risk for coronary events as are patients without sustained HIV suppression.

Key Words: antiretroviral therapy, apolipoprotein B, coronary heart disease, HIV infection, LDL cholesterol, small dense LDL

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INTRODUCTION

Dyslipidemia is a frequent risk factor for coronary heart disease (CHD) in individuals with HIV infection.[1] It may be induced by HIV infection itself and antiretroviral drugs, in particular ritonavir-boosted protease inhibitors that raise total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides.[2,3] Exposure to the nucleoside reverse transcriptase inhibitors didanosine and abacavir and the protease inhibitors lopinavir and indinavir are associated with an increased risk of myocardial infarction.[1,4] These associations, however, can only partially be attributed to changes in total cholesterol and triglycerides induced by these drugs and raise questions about additional involved factors. Epidemiological studies in non–HIV-infected individuals indicate an increased risk and improved risk prediction for carotid atherosclerosis

and CHD with increases in highly small dense LDL particles and apolipoprotein B,[5,6] but these findings were not confirmed in other studies.[7,8]

In vitro studies show that certain boosted protease inhibitors may decrease the proteosomal degradation of apolipoprotein B, and thus increase the assembly and secretion of very LDLs and small dense LDL, which lead to increased risk of CHD.[3] Patients treated with boosted protease inhibitors or with triple nucleoside reverse transcriptase inhibitor combinations experience important shifts to highly atherogenic small dense LDL compared with HIV-negative controls with similar levels of LDL cholesterol.[9,10] Protease inhibitors like lopinavir may also increase apolipoprotein B, a parameter that best reflects the total burden of atherogenic LDL particles, but these alterations are less frequently seen with atazanavir, a newer protease inhibitor.[9,11]

No study so far has investigated the association of CHD events and small dense LDL particles and apolipoprotein B in antiretroviral drug–treated HIV-infected individuals, which is the purpose of this case–control study that is nested into the Swiss HIV Cohort Study (SHCS).

METHODS

We conducted a case–control study that was nested within the SHCS, an open national cohort of HIV-infected individuals in Switzerland, aged 16 or older who are followed bi-annually in 7 centers. Details of the study are reported elsewhere.[12]

Selection of Cases and Controls

We included all SHCS participants with a first acute coronary event between April 1, 2000, and July 31, 2008. Eligible cases had to have a plasma sample in the 12 months preceding the event and to be on antiretroviral therapy at the time of the plasma sample. Coronary events were defined as definitive myocardial infarction, possible myocardial infarction or unstable angina, coronary artery bypass grafting, coronary angioplasty or stenting, or fatal coronary event based on the protocol definition of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study.[13] Fatal myocardial infarction included, sudden cardiac death, death from chronic ischemic heart disease, and death due to heart failure other than hypertensive or nonrheumatic valve disorders.

Controls were selected for each case at random without replacement because this method has slightly higher statistical efficiency.[14] To avoid biased estimates, controls were selected such that a future case could be selected as a control in the time period before the event.[15] Four controls were randomly selected from the risk set of each case. The risk set was defined as individuals with no documented coronary event (at least) until the date of the coronary event of the corresponding case, with a plasma sample within ±30 days of the plasma sample date of the respective case and treated with antiretroviral therapy at the time of the plasma sample. Controls in addition were matched to the case with respect to age (year of birth), gender, and smoking status at the time of the plasma sample of the corresponding case. Matching factors were kept at an absolute minimum to avoid overmatching and loss of power.[16] Antiretroviral therapy was defined as any combination therapy that included either a protease inhibitor or a nonnucleoside reverse transcriptase inhibitor with at least 2 other drugs or a triple nucleoside reverse transcriptase inhibitor therapy. Patients without plasma samples, taking lipid-lowering drugs, or missing information on smoking, blood pressure, body mass index, and waist–hip circumference in the 12 months preceding the event date for cases and the matching date of controls were excluded.

Variables and Measurement

All clinical parameters from cases and controls were extracted from the SHCS database: age, gender, risk group of HIV transmission, CD4 cells, and viral load at start of first antiretroviral therapy, current CD4 cell count and viral load, previous AIDS event, start date of first antiretroviral therapy, current antiretroviral therapy (protease inhibitor vs. nonnucleoside reverse transcriptase inhibitor, abacavir vs. no abacavir), hepatitis C antibodies, family history of CHD, systolic blood pressure, body mass index, waist–hip ratio, diabetes mellitus (defined as blood glucose >11.1 mmol/L at any time, >5.6 mmol/L in fasting state, or taking glucose-lowering drugs), metabolic syndrome (defined according to International Diabetes Federation),[17] smoking status, and clinically documented central adipositas and lipoatrophy.

Blood samples were drawn and centrifuged within 6 hours of collection to obtain citrate plasma. Plasma was deep frozen at $-70°C$ until analysis. VLDL were separated by ultracentrifugation (Airfuge, Beckman Coulter, Krefeld, Germany) at a density of 1.006 g/mL (4 hours, 20°C, 95,000 rpm) using an A-95 rotor with 8×20 mm Ultraclear tubes. LDL cholesterol was determined after removal of VLDL in the resulting infranatant by subtracting high-density lipoprotein (HDL) cholesterol from total cholesterol concentration. Total cholesterol, HDL cholesterol, and triglycerides in plasma and lipoprotein fractions were determined with commercially available enzymatic assays (Synchron CX5, Beckman Coulter, Krefeld, Germany), apolipoprotein B, apolipoprotein A-I, and lipoprotein (a) by nephelometry (Immage, Beckman Coulter, Krefeld, Germany). Small dense LDL apolipoprotein B was determined after ultracentrifugation of plasma at a density 1.044 g/mL in the resulting infranatant. All procedures and methods were checked for their compatibility with citrate plasma. The obtained values were corrected according to the dilution of blood with sodium citrate. High-sensitive C-reactive protein was measured by nephelometry (Image) and D-dimer by turbidimetry (Quantex D-Dimer, Instrumentation Laboratory, Kirchheim, Germany, CX5). All determinations were performed at the laboratory of the Institute for Lipid Metabolism, Munich, Germany. CD4 T lymphocytes were quantified by flow cytometry at the center laboratories of the SHCS. The plasma HIV-1 RNA level was measured by a polymerase chain reaction assay (Amplicor HIV monitor; Roche Diagnostic System, Rotkreuz Switzerland; limit of detection <50 copies/mL).

Statistical Analysis

Conditional logistic regression stratified by case–control stratum was used to investigate the relationship between an outcome—coronary event for cases or a nonevent

for controls—and a set of prognostic factors. As we sample controls from the risk set at the occurrence of the respective coronary event, the odds ratio (OR) is a direct estimate of the rate ratio without any rare-disease assumption.[18] We concentrated specifically on the effect of small dense LDL and apolipoprotein B on the occurrence of coronary events and proceeded in 3 steps. In the first step, unadjusted ORs and 95% confidence intervals (CIs) were calculated for the 2 markers separately. We tested for nonlinear or threshold effects by using transformations or including the biomarkers as spline functions. Second, the 2 markers were tested separately in models adjusted for the classical cardiovascular risk factors as follows: total cholesterol, triglycerides, HDL cholesterol, systolic blood pressure, central obesity, diabetes, and family history of CHD. In a third step, we added HIV-specific covariates to the model as follows: (past or current) intravenous drug use, years on protease inhibitor–based antiretroviral therapy, years on abacavir, HIV viral load, and nadir CD4 cell count. We additionally adjusted for time between the plasma sample date and the event date.

In a sensitivity analysis, the analyses described above was repeated after adding an indicator variable for patients who interrupted treatment after the plasma sample and before the coronary event and excluding case–control pairs where the case switched the antiretroviral therapy regimen between the time of the plasma sample and the coronary event, but these analyses did not change the results (data not shown).

Power Calculation

Power calculations were only performed for univariate associations between a lipid parameter and coronary events as assessed by conditional logistic regression and assuming that 98 matched case–control strata were available. Further, it was assumed that within strata, the lipid parameter for the case and control came from distributions with the same variance σ^2 but an expected value which differed by a shift delta.[19] We estimated the true standardized mean difference Δ/σ for 4 matched controls per case needed to be at least 0.32 or 0.37 for a power of 80% or 90%. In our sample, the standardized mean difference was 0.40 and 0.34 for small-dense LDL (sd-LDL) and apolipoprotein B, respectively, indicating we had sufficient power to detect differences in these lipid parameters and coronary events.

Analyses were performed with the statistical software SAS 9.2 (SAS Institute Inc., Cary, NC) and Stata 10.0 (StataCorp., College Station, TX).

RESULTS

Of 7471 HIV-infected individuals actively enrolled in the SHCS in September 2008, there were 264 individuals with a first CHD event, with 102 events occurring before the introduction of cardiovascular risk factor assessments. Of these 162 individuals had a first risk assessment before their event, 2 individuals did not have a plasma sample 1 year preceding the event, 23 individuals were not on antiretroviral therapy at the time of plasma sample, 37 individuals were on lipid-lowering drugs in the year before event, and 2 individuals had missing information on smoking, blood pressure, and weight information in the year preceding the event. We identified 98 cases with a CHD event [19 with fatal myocardial infarctions (of those 9 were sudden deaths), 79 with nonfatal coronary events (53 definite myocardial infarctions, 15 possible myocardial infarctions, and 11 coronary angioplasties or bypasses)] and these were matched with 392 controls. In 15 of 98 cases and 80 of 392 controls, blood specimens were taken in fasting state, for 28 measurements (8 cases and 20 controls), the information was unknown. The median duration from the dates of sampling to the event or the respective control date was 4 months (interquartile range: 2–6).

Of all cases and controls, 78.6% were males, 61.2% were current, and 6.5% past smokers. Compared with controls, cases were more often injecting drug users (27.6% vs. 23.9%), less likely to be virologically suppressed (HIV-1 plasma RNA >400 copies per milliliter; 20.4% vs. 8.7%), more often on abacavir-containing regimens (21.4% vs. 9.9%), and somewhat less often on boosted protease inhibitors (31.6% vs. 37.2%) (Table 1). Cases had a higher percentage of risk factors for CHD (metabolic syndrome, family history, central obesity, diabetes, and hypertension) and more unfavorable lipid parameters (higher total cholesterol, triglycerides, LDL cholesterol, small dense LDL and apolipoprotein B, and lower HDL cholesterol) when compared with controls.

In univariable conditional logistic regression analysis of lipid and inflammation parameters, small dense LDL, apolipoprotein B, non–HDL cholesterol, LDL apolipoprotein B, very LDL and VLDL cholesterol, VLDL apolipoprotein B, and intermediate dense lipoproteins cholesterol were significantly associated with a coronary event (Table 2). High-sensitive C-reactive protein and D-dimer were not associated with coronary events.

In a multivariable model including established risk factors for CHD, increases in small dense LDL remained significantly associated with increased odds of a coronary event (OR for 1 mg/dL increase: 1.06, 95% CI: 1.00 to 1.11) (Table 3). Small dense LDL was significantly associated with increased odds for a coronary event when adjusting for intravenous drug use, HIV-specific variables, and type of antiretroviral therapy treatment (for 1 mg/dL increase: OR: 1.07, 95% CI: 1.03 to 1.12). Adding both risk factors for CHD and HIV-specific variables weakened the association of small dense LDL with coronary events (OR: 1.04, 95% CI: 0.99 to 1.10). However, small dense LDL was highly correlated with total cholesterol ($\rho = 0.50$), and when total cholesterol was removed from the model, the effect of small dense LDL was significant and very similar to that of the univariable model (OR: 1.07, 95% CI: 1.01 to 1.12).

Similar results were found in models with apolipoprotein B (Table 4). Apolipoprotein B was significantly associated with the odds for a coronary event in the both the multivariable model with established risk factors for CHD (for 10 mg/dL increase: OR: 1.16, 95% CI: 1.02 to 1.32), and in the model including intravenous drug use, HIV-related variables and antiretroviral therapy (OR per 10 mg/dL increase: 1.12, 95% CI: 1.04 to 1.20). The association between apolipoprotein B and coronary events was of

TABLE 1. Baseline Characteristics of Study Population as of the Plasma Sample Date

Variable	Cases	Controls
n	98	392
General characteristics		
White, %	94.9	92.9
Past or current injecting drug users, %	27.6	23.9
Body mass index (kg/m^2)—mean (SD)	24.1 (3.8)	23.0 (3.8)
Cardiovascular disease characteristics		
Family history of premature CHD*, %	19.4	11.0
Waist-hip ratio—mean (SD)	0.95 (0.07)	0.92 (0.08)
Metabolic syndrome†, %	41.1	22.0
Hypertriglyceridemia, %	43.9	43.1
Low HDL cholesterol, %	89.9	83.4
Hypertension, %	68.0	52.9
Diabetes‡, %	14.4	8.5
Abdominal obesity, %	44.2	29.1
Lipid measurements (mg/dL), median (IQR)		
Total cholesterol§	145.5 (112–177)	129.5 (106–168.5)
HDL cholesterol§	26 (20–35)	27.5 (21–37)
Triglycerides‖	137.5(88–246)	120 (81.5–190.5)
LDL cholesterol§	87 (68–107)	77.5 (59–105.5)
Small-dense LDL¶	8.2 (4.0–11.9)	5.4 (3.4–9.0)
Apolipoprotein A1¶	150 (116–193)	146 (112–192.5)
Apolipoprotein B¶	72 (54–104)	62 (46–87)
HIV infection characteristics		
AIDS, %	25.5	32.1
Hepatitis C, %	28.6	26.0
Fat loss, %	32.6	30.7
Fat accumulation, %	34.7	25.8
HIV-1 RNA (copies/mL)		
Log RNA, median (IQR)	0 (0–2.3)	0 (0–1.3)
<50	65.3	80.1
50–399	14.3	11.2
>400	20.4	8.7
CD4 (cells/mm^3)		
Median (IQR)	474 (350–663)	440.5 (289.5–617)
<200	3.1	10.0
201–349	22.5	25.3
350–500	31.6	25.0
≥500	42.9	39.8
CD4 nadir (cells/mm^3), median (IQR)	159.5 (71–260)	130.5 (42–222.5)
Regimen type, %		
Nonnucleoside reverse transcriptase inhibitors	24.5	30.4
Nonboosted protease inhibitors	22.5	22.5
Boosted protease inhibitors	31.6	37.2
Triple nucleoside reverse transcriptase inhibitor	21.4	9.9
Abacavir exposure, %		
In the last 6 months	38.8	26.0
More than 6 months ago	12.2	10.5
Never	49.0	63.5
Time on abacavir (yrs), median (IQR)	0.02 (0–2.8)	0 (0–1.2)
Time on protease inhibitors (yrs), median (IQR)	3.6 (1.8–5.9)	3.8 (1.3–6.1)

*Patients were considered to have a family history of CHD if any first degree relative had a myocardial infarction or stroke before the age of 50.
†According to the definition of the International Diabetes Federation (*Lancet.* September 24, 2005;366:1059–1062).
‡Diabetes mellitus was defined as a definitive diagnosis, fasting plasma glucose ≥5.6 mmol/L, plasma glucose >11 mmol/L, or use of antidiabetic drugs.
§To convert to mmol/L, divide by 38.66.
‖To convert to mmol/L, divide by 87.50.
¶To convert to μmol/L, multiply by 0.0182.
IQR, interquartile range.

TABLE 2. Univariable Stratified Conditional Logistic Regression Models for Lipid Parameters and the Odds for Coronary Event

Variable	Univariable, OR (95% CI)	*P*
Small dense LDL (per 1 mg/dL)*		
In all patients	1.07 (1.03 to 1.11)	0.001
In those with triglycerides ≤500 mg/dL	1.08 (1.03 to 1.12)	<0.001
Apolipoprotein A1 (per 10 mg/dL)*	0.99 (0.96 to 1.04)	0.80
Apolipoprotein B (per 10 mg/dL)*	1.11 (1.04 to 1.19)	0.003
Total cholesterol (per 10 mg/dL)†	1.03 (0.99 to 1.07)	0.11
HDL cholesterol (per 10 mg/dL)†	0.98 (0.96 to 1.00)	0.10
Non-HDL cholesterol (per 10 mg/dL)†	1.05 (1.00 to 1.10)	0.04
Triglycerides (per 10 mg/dL)	1.01 (0.99 to 1.03)	0.08
LDL cholesterol (per 10 mg/dL)†	1.05 (0.99 to 1.11)	0.09
LDL apolipoprotein B (per 10 mg/dL)*	1.11 (1.03 to 1.20)	0.008
VLDL cholesterol (per 10 mg/dL)†‡	1.12 (1.00 to 1.24)	0.05
VLDL triglycerides (per 10 mg/dL)‡	1.01 (0.99 to 1.03)	0.12
VLDL apolipoprotein B (per 10 mg/dL)*	1.05 (1.02 to 1.09)	0.002
VLDL triglycerides /apolipoprotein‡	1.00 (0.99 to 1.02)	0.87
IDL cholesterol (per 10 mg/dL)†	1.04 (1.00 to 1.07)	0.05
IDL triglycerides (per 10 mg/dL)	1.00 (0.99 to 1.02)	0.65
IDL apolipoprotein B (per 10 mg/dL)*	1.16 (0.66 to 2.04)	0.60
IDL triglycerides /apolipoprotein B	1.03 (0.95 to 1.13)	0.46
High-sensitive C-reactive protein (per 1.0 mg/L)	1.03 (0.83 to 1.28)	0.78
D-Dimer (per 10 mg/dL)	1.00 (0.99 to 1.01)	0.90

*To convert to μmol/L, multiply by 0.0182.
†To convert to mmol/L divide by 38.66.
‡To convert to mmol/L divide by 87.50.
IDL, intermediate density lipoprotein.

borderline significance when both risk factors for CHD and HIV-specific variables were added to the model (OR per 10 mg/dL increase: 1.13, 95% CI: 0.99 to 1.30). However, apolipoprotein B was highly correlated with total cholesterol ($\rho = 0.73$), and when removing total cholesterol from the model, increases in apolipoprotein B were associated with a significantly increased risk of a coronary event (OR per 10 mg/dL increase: 1.17, 95% CI: 1.06 to 1.28).

Small dense LDL and apolipoprotein B were also highly correlated ($\rho = 0.58$), and if both small dense LDL and apolipoprotein B were included in the multivariable model without total cholesterol, apolipoprotein B remained significantly associated with CHD events (OR: 1.14, 95% CI: 1.02 to 1.27) but small dense LDL did not (OR: 1.03, 95% CI: 0.97 to 1.09). Models with replacement of small dense LDL by the small dense LDL to apolipoprotein A1 ratio and models with replacement of apolipoprotein B by the apolipoprotein B to apolipoprotein A1 ratio gave similar estimates for CHD event associations (data not shown).

In final multivariable models for apolipoprotein B, systolic blood pressure (OR: 1.23, 95% CI: 1.03 to 1.48), abdominal obesity (OR: 2.06, 95% CI: 1.09 to 3.88), family history of CHD (OR: 2.29, 95% CI: 1.12 to 4.65), past or current intravenous drug use (OR: 2.37, 95% CI: 1.12 to 5.01), years on abacavir (OR: 1.19, 95% CI: 1.03 to 1.36), log HIV-1 plasma RNA (OR: 1.55, 95% CI: 1.27 to 1.90), and CD4 cell nadir (OR: 1.35, 95% CI: 1.13 to 1.62) were significantly associated with an increased odds for a coronary event. Replacing viral load at the time of sampling with cumulative exposure of unsuppressed viral load gave similar estimates of increased risk for coronary events (data not shown). Time on boosted or unboosted protease inhibitors, however, was not associated with increased odds for a coronary event in any models.

COMMENT

This study found an association between highly atherogenic lipid subfractions and coronary events in HIV-infected patients treated with antiretroviral therapy. Small dense LDL and apolipoprotein B were both associated with a coronary event in models that included total cholesterol, HDL cholesterol, triglycerides, and other established risk factors for CHD. Associations were only slightly weakened when additional parameters were added to our models; this was likely due to the reduced power.

Small dense LDL particles may be more accurate than total cholesterol to measure atherogenic risk because they are more easily oxidized, have high affinity for extracellular matrix, and are retained in the arterial wall.[20,21] Furthermore, smaller LDL particles exhibit reduced binding to LDL receptors and persist in the circulation and hence are subject to a greater degree of structural modification, which again may increase the atherogenic potential.[22–24] Small dense lipoprotein often coexist with high triglycerides, low HDL, diabetes, insulin resistance, central obesity, and the metabolic syndrome.[25] These findings support the hypothesis that small dense LDL levels can be used to improve risk prediction and to evaluate the response to lipid therapy.[26] Measurement of small dense LDL, however, has not entered clinical routine because the measurement is labor intense and expensive, although fully automated assays are underway.[27] For this study, we used ultracentrifugation, the gold standard for the measurement of small dense LDLs and the method that ultimately defines the LDL subclasses. Evidence from epidemiological studies in HIV-negative populations is conflicting as to whether small dense LDL is an independent predictor for CHD.[5,6,8]

Apolipoprotein B is found in chylomicrons, VLD lipoprotein, LDL-cholesterol, and lipoprotein A particles. Each of theses particles contain 1 single apolipoprotein B molecule, therefore, measurement of apolipoprotein B represents the total burden of particles considered to be most atherogenic.[28] Apolipoprotein B can be directly measured with no need for calculation via other lipid parameters and does not require fasting samples. Several epidemiological studies indicate that apolipoprotein B is an excellent predictor for CHD and may act as a substitute for LDL cholesterol.[29,30] In this study, apolipoprotein B was a strong and better predictor for coronary events than total cholesterol. There is little data on apolipoprotein B in HIV-infected individuals. Exposure to boosted lopinavir and indinavir was found to be associated with increases in apolipoprotein B in several small studies.[9,11,31,32] In one case–control study, no difference in apolipoprotein B in HIV-infected individuals treated with

TABLE 3. Stratified Conditional Logistic Regression Models for Small Dense LDL and the Odds for a Coronary Event

Variable	Univariable, OR (95% CI)	Multivariable With CHD Risk Variables Only, OR (95% CI)	Multivariable With HIV Infection Variables Only, OR (95% CI)	Multivariable, All Variables OR (95% CI)	Multivariable, All Variables Except Cholesterol OR (95% CI)
Small dense LDL (per 1 mg/dL)*	1.07 (1.03 to 1.11)	1.06 (1.00 to 1.11)	1.07 (1.03 to 1.12)	1.04 (0.99 to 1.10)	1.07 (1.01 to 1.12)
Total cholesterol (per 10 mg/dL)†	1.03 (0.99 to 1.07)	1.05 (0.98 to 1.13)	—	1.08 (1.00 to 1.17)	
Triglycerides (per 10 mg/dL)‡	1.01 (0.99 to 1.03)	0.99 (0.97 to 1.01)	—	0.99 (0.97 to 1.01)	1.00 (0.98 to 1.02)
HDL cholesterol (per 10 mg/dL)†	0.98 (0.96 to 1.00)	0.97 (0.94 to 0.99)	—	0.96 (0.93 to 0.99)	0.98 (0.96 to 1.00)
Systolic blood pressure (per 10 mm Hg)	1.25 (1.07 to 1.45)	1.23 (1.04 to 1.46)	—	1.23 (1.03 to 1.48)	1.20 (1.01 to 1.44)
Abdominal obesity§	2.14 (1.29 to 3.55)	1.64 (0.95 to 2.85)	—	1.86 (1.00 to 3.46)	1.90 (1.04 to 3.50)
Diabetes‖	1.83 (0.92 to 3.65)	1.64 (0.77 to 3.51)	—	1.84 (0.82 to 4.14)	1.75 (0.78 to 3.94)
Family history of premature CHD¶	1.88 (1.06 to 3.34)	1.68 (0.88 to 3.20)	—	2.06 (1.01 to 4.19)	2.02 (1.00 to 4.05)
Past or current IDU	1.28 (0.72 to 2.28)	—	1.95 (1.00 to 3.78)	2.35 (1.10 to 5.01)	2.08 (0.99 to 4.38)
Years on abacavir (per year)	1.19 (1.06 to 1.34)	—	1.19 (1.05 to 1.35)	1.20 (1.04 to 1.37)	1.18 (1.03 to 1.36)
Years on PI (boosted/unboosted, per year)	0.98 (0.91 to 1.06)	—	0.99 (0.91 to 1.08)	0.98 (0.89 to 1.08)	0.99 (0.90 to 1.08)
Log RNA (copies/ml)	1.28 (1.10 to 1.50)	—	1.44 (1.20 to 1.72)	1.55 (1.27 to 1.89)	1.53 (1.26 to 1.85)
CD4 nadir (per 100 cells/mm^3)	1.24 (1.08 to 1.44)	—	1.29 (1.09 to 1.53)	1.33 (1.11 to 1.59)	1.31 (1.10 to 1.57)
Weeks between plasma sample and event	0.96 (0.92 to 0.99)	—	0.96 (0.92 to 1.00)	0.96 (0.92 to 1.00)	0.96 (0.91 to 1.00)

*To convert to μmol/L multiply by 0.0182, patients were considered to have a family history of CHD if any first-degree relative had a myocardial infarction or stroke before the age of 50.

†To convert to mmol/L, divide by 38.66.

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§According to the definition of the International Diabetes Federation (*Lancet.* September 24, 2005;366:1059–1062).

‖Diabetes mellitus was defined as a definitive diagnosis, fasting plasma glucose ≥5.6 mmol/L, plasma glucose >11 mmol/L, or use of antidiabetic drugs.

¶Patients were considered to have a family history of CHD if any first degree relative had a myocardial infarction or stroke before the age of 50.

IDU, injecting drug use; PI, protease inhibitor.

antiretroviral therapy was found, but metabolic syndrome and hypertension were more prevalent in controls.[33] In a substudy from the French Aquitaine Cohort Study, apolipoprotein B was associated with metabolic syndrome and a better predictor for atherosclerosis and carotid intima-media thickness than LDL cholesterol.[34]

A large body of evidence indicates that lowering LDL cholesterol with statins reduces cardiovascular morbidity and mortality in non–HIV-infected individuals, but only half of all premature CHD deaths are prevented by statin therapy.[35–38] Findings from this study may indicate that specifically targeting the reduction of small dense LDL in addition to LDL cholesterol could be beneficial in patients with a highly atherogenic lipid phenotype receiving antiretroviral therapy. Small pilot studies and clinical trials in HIV-infected individuals indicate that ezetimibe and fenofibrate alone or in combination with statins may reduce small dense LDL and apolipoprotein B, but more trials are needed.[39,40]

Our study has several limitations. A case–control design is potentially prone to confounding if there is differential ascertainment of risk factors between cases and controls. The use of nested study design with standard data collection as applied in SHCS and the use of clinical data and samples before the event, and the selection of a random control sample should minimize this bias. In addition, variation of exposure due to putative risk factors over time may introduce bias. We tried to correct for this particular bias by defining strict exclusion criteria, for example, the use of lipid-modifying drugs before the event. We tried to minimize bias for the selection of controls by not excluding future cases from the control set before the coronary event. Our findings could be biased due to unmeasured confounding or imprecise measurement of other important risk factors such as hypertension. When defining the risk set we matched for calendar time (by using a narrow time window for the selection of samples before the event of interest), age, gender and smoking. Because smoking is highly prevalent in this cohort, we matched for this important risk factor and can therefore not be evaluated in the analysis. Thus, findings from this study may not relate to a similar extent to nonsmoking HIV-infected individuals. Over-matching can also reduce the ability to detect a relevant difference in variables of interest. However, given the difference in gender and age distribution of patients with coronary events in the SHCS, and the remaining population we considered this matching to be critical. Because of sample shortage, we were unable to measure all markers (in particular IL-6) as initially determined in the protocol.

This study has several strengths. This case–control study was nested into the SHCS, a large cohort study with excellent follow-up data that is representative for the level of care provided to HIV-infected individuals in Switzerland. We included all individuals within the SHCS taking combination antiretroviral therapy (cART) with a documented new coronary event and were able to include a large set of confounding risk factors into our analysis, which further strengthens our findings.

A large body of evidence indicates that atherosclerosis is an inflammatory disease.[41] High-sensitive C-reactive protein, a marker of inflammation is elevated in individuals with unstable angina and a risk factor for CHD in healthy individuals.[42] In this study, we found no association between either high-sensitive C-reactive protein or D-dimer and

TABLE 4. Stratified Conditional Logistic Regression Models for Apolipoprotein B and the Odds for a Coronary Event

Variable	Multivariable With CHD Risk Variables Only, OR (95% CI)	Multivariable With HIV Infection Variables Only, OR (95% CI)	Multivariable, All Variables OR (95% CI)	Multivariable, All Variables Except Cholesterol, OR (95% CI)
Apolipoprotein B (per 10 mg/dL)*	1.16 (1.02 to 1.32)	1.12 (1.04 to 1.20)	1.13 (0.99 to 1.30)	1.17 (1.06 to 1.28)
Total cholesterol (per 10 mg/dL)†	1.00 (0.91 to 1.10)	—	1.03 (0.93 to 1.15)	
Triglycerides (per 10 mg/dL)‡	1.00 (0.98 to 1.02)	—	1.00 (0.98 to 1.02)	1.00 (0.99 to 1.02)
HDL cholesterol (per 10 mg/dL)†	0.97 (0.94 to 1.00)	—	0.97 (0.94 to 1.00)	0.97 (0.95 to 1.00)
Systolic blood pressure (per 10 mm Hg)	1.23 (1.04 to 1.46)	—	1.24 (1.03 to 1.48)	1.23 (1.03 to 1.48)
Abdominal obesity§	1.73 (0.99 to 3.03)	—	2.01 (1.06 to 3.81)	2.06 (1.09 to 3.88)
Diabetes‖	1.53 (0.71 to 3.28)	—	1.73 (0.75 to 3.98)	1.69 (0.74 to 3.88)
Family history of premature CHD¶	1.83 (0.96 to 3.49)	—	2.27 (1.11 to 4.62)	2.29 (1.12 to 4.65)
Past or current IDU	—	2.00 (1.04 to 3.84)	2.42 (1.14 to 5.13)	2.37 (1.12 to 5.01)
Years on abacavir (per year)	—	1.19 (1.05 to 1.35)	1.19 (1.04 to 1.37)	1.19 (1.03 to 1.36)
Years on PI (boosted/unboosted, per year)	—	0.99 (0.91 to 1.08)	0.98 (0.89 to 1.08)	0.98 (0.90 to 1.08)
Log RNA (copies/mL)	—	1.42 (1.19 to 1.70)	1.56 (1.27 to 1.90)	1.55 (1.27 to 1.90)
CD4 nadir (per 100 cells/mm^3)	—	1.31 (1.11 to 1.55)	1.35 (1.13 to 1.62)	1.35 (1.13 to 1.62)
Weeks between plasma sample and event	—	0.96 (0.92 to 1.00)	0.96 (0.92 to 1.00)	0.96 (0.91 to 1.00)

*To convert to μmol/L, multiply by 0.0182.
†To convert to mmol/L, divide by 38.66.
‡To convert to mmol/L, divide by 87.50.
§According to the definition of the International Diabetes Federation (*Lancet.* September 24, 2005;366:1059–1062).
‖Diabetes mellitus was defined as a definitive diagnosis, fasting plasma glucose ≥5.6 mmol/L, plasma glucose >11 mmol/L, or use of antidiabetic drugs.
¶Patients were considered to have a family history of CHD if any first-degree relative had a myocardial infarction or stroke before the age of 50.
IDU, injecting drug use; PI, protease inhibitor.

coronary events. Van Vonderen et al[43] have shown that initiation of antiretroviral therapy reduces inflammatory markers and markers of hypercoagulability. Our study had an explicit focus on the association of highly atherogenic lipids in cART-treated patients, which could explain our negative findings. However, we found in all models a consistent association between unsuppressed HIV viral load and risk of a coronary event. This finding is remarkable given that we included only cART-treated patients into our study and indicates that HIV may promote endothelial inflammatory activation even in antiretroviral therapy–treated patients with suboptimal viral control. This is a strong argument for sustained suppression of HIV to reduce the risk of coronary events.[44]

Finally, we confirmed an association of coronary events with cumulative exposure to abacavir as previously found in the DAD. study.[4,13] Evidence on the risk of myocardial infarction and abacavir from additional cohort studies is conflicting, mainly due to different study design and control of bias.[45] Evidence from a meta-analysis of randomized controlled trials comparing abacavir-containing regimens versus control is also inconclusive due to much lower number of events and observation compared with the DAD study.[46]

In an additional analysis requested by the reviewers, we also confirmed an association of current exposure to abacavir and coronary events [full multivariate models for small dense lipoprotein OR: 2.09 (95% CI: 1.18 to 3.69) and for apolipoprotein B OR: 2.05 (95% CI: 1.16 to 3.62)]. The findings of an association of current and cumulative use of abacavir and coronary events from this study strengthen the existing evidence for such an association as only confirmed cases with coronary events were included. We were able to adjust for relevant confounders including intravenous drug use and highly atherogenic lipoproteins that were shown to be increased with abacavir exposure in the Bicombo backbone switch trial.[47]

In conclusion, this study indicates that small dense LDL cholesterol and apolipoprotein B are associated with increased risk of coronary events in HIV-infected patients treated with antiretroviral therapy. Further studies are needed to better explore these associations and whether particular antiretroviral drugs promote the generation of highly atherogenic lipoproteins. In all models, we found a consistent association of an increased risk for coronary events in intravenous drug users, patients without complete virological suppression, and use of abacavir. Exposure to abacavir should be avoided in patients at risk of CHD. Our study provides further arguments that maintaining sustained virological control in addition to aggressive management of cardiovascular risk factors is an important goal to help reduce potential cardiovascular events in HIV-infected patients.

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REFERENCES

1. Friis-Moller N, Weber R, Reiss P, et al. Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. *AIDS*. 2003;17:1179–1193.
2. Riddler SA, Smit E, Cole SR, et al. Impact of HIV infection and HAART on serum lipids in men. *JAMA*. 2003;289:2978–2982.
3. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med*. 2005;352:48–62.
4. Worm SW, Sabin C, Weber R, et al. Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D: A:D) study. *J Infect Dis*. 2010;201:318–330.
5. Mora S, Szklo M, Otvos JD, et al. LDL particle subclasses, LDL particle size, and carotid atherosclerosis in the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis*. 2007;192:211–217.
6. St-Pierre AC, Cantin B, Dagenais GR, et al. Low-density lipoprotein subfractions and the long-term risk of ischemic heart disease in men: 13-year follow-up data from the Quebec Cardiovascular Study. *Arterioscler Thromb Vasc Biol*. 2005;25:553–559.
7. Arsenault BJ, Lemieux I, Despres JP, et al. Cholesterol levels in small LDL particles predict the risk of coronary heart disease in the EPIC-Norfolk prospective population study. *Eur Heart J*. 2007;28:2770–2777.
8. Sacks FM, Campos H. Clinical review 163: cardiovascular endocrinology: low-density lipoprotein size and cardiovascular disease: a reappraisal. *J Clin Endocrinol Metab*. 2003;88:4525–4532.
9. Badiou S, Merle De BC, Dupuy AM, et al. Decrease in LDL size in HIV-positive adults before and after lopinavir/ritonavir-containing regimen: an index of atherogenicity? *Atherosclerosis*. 2003;168:107–113.
10. Riddler SA, Li X, Otvos J, et al. Antiretroviral therapy is associated with an atherogenic lipoprotein phenotype among HIV-1-infected men in the Multicenter AIDS Cohort Study. *J Acquir Immune Defic Syndr*. 2008;48:281–288.
11. Schmitz M, Michl GM, Walli R, et al. Alterations of apolipoprotein B metabolism in HIV-infected patients with antiretroviral combination therapy. *J Acquir Immune Defic Syndr*. 2001;26:225–235.
12. Schoeni-Affolter F, Ledergerber B, Rickenbach M, et al. Cohort profile: the Swiss HIV cohort study. *Int J Epidemiol*. 2009;39:1179–1189.
13. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med*. 2003;349:1993–2003.
14. Lubin JH. Extensions of analytic methods for nested and population-based incident case-control studies. *J Chronic Dis*. 1986;39:379–388.
15. Robins JM, Gail MH, Lubin JH. More on "biased selection of controls for case-control analyses of cohort studies". *Biometrics*. 1986;42:293–299.
16. Wacholder S, Silverman DT, McLaughlin JK, et al. Selection of controls in case-control studies. III. Design options. *Am J Epidemiol*. 1992;135:1042–1050.
17. Alberti KG, Zimmet P, Shaw J. The metabolic syndrome—a new worldwide definition. *Lancet*. 2005;366:1059–1062.
18. Essebag V, Genest J Jr, Suissa S, et al. The nested case-control study in cardiology. *Am Heart J*. 2003;146:581–590.
19. Lachin JM. Sample size evaluation for a multiply matched case-control study using the score test from a conditional logistic (discrete Cox PH) regression model. *Stat Med*. 2008;27:2509–2523.
20. Packard CJ, Shepherd J. Lipoprotein heterogeneity and apolipoprotein B metabolism. *Arterioscler Thromb Vasc Biol*. 1997;17:3542–3556.
21. Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. *J Lipid Res*. 2002;43:1363–1379.
22. Campos H, Walsh BW, Judge H, et al. Effect of estrogen on very low density lipoprotein and low density lipoprotein subclass metabolism in postmenopausal women. *J Clin Endocrinol Metab*. 1997;82:3955–3963.
23. Packard CJ, Demant T, Stewart JP, et al. Apolipoprotein B metabolism and the distribution of VLDL and LDL subfractions. *J Lipid Res*. 2000;41:305–318.
24. Chapman MJ, Guerin M, Bruckert E. Atherogenic, dense low-density lipoproteins. Pathophysiology and new therapeutic approaches. *Eur Heart J*. 1998;19(suppl A):A24–A30.
25. Kim DS, Kim YK, Kim DS, et al. Low-density lipoprotein particle size in hepatic steatosis and metabolic syndrome. *Diabetol Metab Syndr*. 2010;2:18.
26. Brunzell JD, Davidson M, Furberg CD, et al. Lipoprotein management in patients with cardiometabolic risk: consensus conference report from the American Diabetes Association and the American College of Cardiology Foundation. *J Am Coll Cardiol*. 2008;51:1512–1524.
27. Albers JJ, Kennedy H, Marcovina SM. Evaluation of a new homogenous method for detection of small dense LDL cholesterol: Comparison with the LDL cholesterol profile obtained by density gradient ultracentrifugation. *Clin Chim Acta*. 2010;412:1181–1187.
28. Brunzell JD. Clinical practice. Hypertriglyceridemia. *N Engl J Med*. 2007;357:1009–1017.
29. Yusuf S, Hawken S, Ounpuu S, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952.
30. Walldius G, Jungner I, Holme I, et al. High apolipoprotein B, low apolipoprotein A-I, and improvement in the prediction of fatal myocardial infarction (AMORIS study): a prospective study. *Lancet*. 2001;358:2026–2033.
31. Magenta L, Dell-Kuster S, Richter WO, et al. Lipid and lipoprotein profile in HIV-infected patients treated with lopinavir/ritonavir as a component of the first combination antiretroviral therapy. *AIDS Res Hum Retroviruses*. 2010;27:525–533.
32. Umpleby AM, Das S, Stolinski M, et al. Low density lipoprotein apolipoprotein B metabolism in treatment-naive HIV patients and patients on antiretroviral therapy. *Antivir Ther*. 2005;10:663–670.
33. Catzin-Kuhlmann A, Castillo-Martinez L, Colin-Ramirez E, et al. No evidence of increased risk for certain highly atherogenic lipoprotein phenotypes in HIV-infected patients. *Arch Med Res*. 2008;39:84–91.
34. Badiou S, Thiebaut R, Aurillac-Lavignolle V, et al. Association of non-HDL cholesterol with subclinical atherosclerosis in HIV-positive patients. *J Infect*. 2008;57:47–54.
35. Briel M, Studer M, Glass TR, et al. Effects of statins on stroke prevention in patients with and without coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2004;117:596–606.
36. Briel M, Ferreira-Gonzalez I, You JJ, et al. Association between change in high density lipoprotein cholesterol and cardiovascular disease morbidity and mortality: systematic review and meta-regression analysis. *BMJ*. 2009;338:B92.
37. Studer M, Briel M, Leimenstoll B, et al. Effect of different antilipidemic agents and diets on mortality: a systematic review. *Arch Intern Med*. 2005;165:725–730.
38. Brunzell JD. Increased ApoB in small dense LDL particles predicts premature coronary artery disease. *Arterioscler Thromb Vasc Biol*. 2005;25:474–475.
39. Badiou S, Merle De BC, Dupuy AM, et al. Fenofibrate improves the atherogenic lipid profile and enhances LDL resistance to oxidation in HIV-positive adults. *Atherosclerosis*. 2004;172:273–279.
40. Bennett MT, Johns KW, Bondy GP. Ezetimibe is effective when added to maximally tolerated lipid lowering therapy in patients with HIV. *Lipids Health Dis*. 2007;6:15.
41. Ross R. Atherosclerosis—an inflammatory disease. *N Engl J Med*. 1999;340:115–126.
42. Ridker PM, Hennekens CH, Buring JE, et al. C-reactive protein and other markers of inflammation in the prediction of cardiovascular disease in women. *N Engl J Med*. 2000;342:836–843.
43. van Vonderen MG, Hassink EA, van Agtmael MA, et al. Increase in carotid artery intima-media thickness and arterial stiffness but improvement in several markers of endothelial function after initiation of antiretroviral therapy. *J Infect Dis*. 2009;199:1186–1194.
44. Behrens GM, Reiss P. Abacavir and cardiovascular risk. *Curr Opin Infect Dis*. 2010;23:9–14.
45. Costagliola D, Lang S, Mary-Krause M, et al. Abacavir and cardiovascular risk: reviewing the evidence. *Curr HIV/AIDS Rep*. 2010;7:127–133.
46. Cruciani M, Zanichelli V, Serpelloni G, et al. Abacavir use and cardiovascular disease events: a meta-analysis of published and unpublished data. *AIDS*. 2011;25:1993–2004.
47. Saumoy M, Ordonez-Llanos J, Martinez E, et al. Low-density lipoprotein size and lipoprotein-associated phospholipase A2 in HIV-infected patients switching to abacavir or tenofovir. *Antivir Ther*. 2011;16:459–468.