MAJOR ARTICLE

Lipid Profiles in HIV-Infected Patients Receiving Combination Antiretroviral Therapy: Are Different Antiretroviral Drugs Associated with Different Lipid Profiles?

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Levels of triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), and high-density lipoprotein cholesterol (HDL-c), as well as the TC:HDL-c ratio, were compared in patients receiving different antiretroviral therapy regimens. Patients receiving first-line regimens including protease inhibitors (PIs) had higher TC and TG levels and TC:HDL-c ratios than did antiretroviral-naive patients; patients receiving 2 PIs had higher levels of each lipid. Ritonavir-containing regimens were associated with higher TC and TG levels and TC:HDL-c ratios than were indinavir-containing regimens; however, receipt of nelfinavir was associated with reduced risk of lower HDL-c levels, and receipt of saquinavir was associated with lower TC:HDL-c ratios. Patients receiving non-nucleoside reverse-transcriptase inhibitors had higher levels of TC and LDL-c than did antiretroviral-naive patients, although the risk of having lower HDL-c levels was lower than that in patients receiving a single PI. Efavirenz was associated with higher levels of TC and TG than was nevirapine.

The etiology of coronary heart disease (CHD) is multifactorial [1, 2]. Among other factors, high levels of low-density lipoprotein cholesterol (LDL-c) [3, 4] and low levels of high-density lipoprotein cholesterol (HDL-

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c) [5–7] have been identified as risk factors for CHD in the general population.

HIV-infected patients generally experience a decrease in HDL-c and LDL-c levels, followed by an increase in plasma triglyceride (TG) levels, in the years before they develop AIDS [8, 9]. The treatment of HIV infection with protease inhibitors (PIs) and nonnucleoside reverse-transcriptase inhibitors (NNRTIs) is also associated with several metabolic disorders [10, 11], including dyslipidemia, which may result in an increased risk of CHD [12–17]. PI-containing combination antiretroviral therapy (CART), in particular, is associated with increased TG, total cholesterol (TC), and LDL-c levels [13, 15, 18–20]. There are data suggesting that the extent of these metabolic disturbances could differ according to different drugs within the PI class itself [11, 15, 19, 21–24]. Although regimens including an NNRTI may induce increases in TC and LDL-c levels, they may also induce a concurrent increase in HDL-c levels, in contrast to what is observed with PI-containing CART [25]. Less data are available on the comparison between different NNRTIs [26, 27], and the results of those studies are inconsistent. More recently, some studies have suggested that nucleoside reverse-transcriptase inhibitors (NRTIs) may also contribute to the development of dyslipidemia [28, 29].

The possible relationship between receipt of CART and the development of CHD has been investigated in studies of various designs, with conflicting results [30–32]. The Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study recently reported a 26% increase in the risk of myocardial infarction (MI) per year of exposure to CART [33]. In the present study, we use data collected as part of the baseline D:A:D data set to perform a cross-sectional comparison of lipid profiles in patients enrolled in the D:A:D study who were receiving different PIs and NNRTIs at enrollment. Furthermore, we also report the results of a comparison of lipid profiles in patients receiving specific drugs within each class. Although we have chosen not to focus on the NRTIs received, all analyses do control for the current and previous use of different NRTIs.

SUBJECTS, MATERIALS, AND METHODS

Study Population

The D:A:D study is a prospective observational study formed by the collaboration of 11 previously established cohorts of HIV-infected patients. The primary aim of the study is to establish whether an association exists between the use of CART (defined in the study as any combination antiretroviral drug regimen containing a PI and/or a NNRTI) and an increased risk of CHD. The 11 cohorts currently contribute data on >23,000 HIV-infected patients monitored at 188 clinics in the United States, Australia, and 19 countries in Europe. This article presents a cross-sectional analysis of information collected as part of the baseline D:A:D data set. Two of the 11 cohorts that are part of the D:A:D study (the CPCRA cohort from the United States and the St. Pierre Cohort from Belgium) did not submit data until a later stage and have not been included in this analysis. Thus, the total potential study population for the current analyses contains 17,852 patients from 9 of the 11 cohorts.

The D:A:D study methodology has been described in detail elsewhere [34]. In brief, patients eligible for inclusion in the D:A:D study were all being actively followed up at the time of initiation of the D:A:D protocol, irrespective of antiretroviral treatment status. Patients were followed prospectively, and data were obtained during visits to outpatient clinics scheduled as part of regular medical care. Patients were enrolled between 1 December 1999 and 1 April 2001. At enrollment, and at least every 8 months thereafter, standardized data collection forms were completed. Data collected include sociodemographic characteristics, clinical data (AIDS events and known risk factors for CHD), laboratory markers (CD4 cell counts, HIV RNA load, and TC, HDL-c, and TG levels, where available), and treatment variables (antiretroviral treatment and drugs that may modify lipid levels or risk of CHD). Lipid levels were not required to be obtained after an overnight fast, although, where possible, information was obtained on whether fasting or nonfasting samples had been analyzed. All collected data were transformed into a standardized format and transferred to the coordinating center (Copenhagen HIV Programme, Hvidovre Hospital, Denmark) as anonymized computerized files, where they are merged into a central data set.

Comparisons Performed

Two sets of analyses were performed: first, a between-class comparison of lipid profiles for patients receiving their first CART regimen including either a PI or an NNRTI at enrollment in the D:A:D study, and, second, a within-class comparison of lipid profiles for patients receiving specific drugs within each class.

Between-class comparison. For this analysis, we selected patients from the overall D:A:D cohort who, at the time of enrollment, were either antiretroviral naive or were receiving a first-line CART regimen that included either 1 PI (denoted as "single PI"), 2 PIs (denoted as "dual PI"), or 1 NNRTI. Although patients were receiving first-line CART regimens, they could have previously used NRTIs. Information with regard to the dose of ritonavir (RTV) received was not available; thus, it was not possible to distinguish between patients receiving dual-PI regimens in which RTV was used at a low dose for pharmacologic boosting of the other PI and patients receiving dual-PI regimens in which RTV was used at higher doses with intrinsic antiretroviral activity.

Within-class comparison. For this analysis, we selected all patients who were receiving either a PI-containing or an

NNRTI-containing regimen at enrollment in the D:A:D study. To maximize the power of the analyses and because some of the PIs and NNRTIs were predominantly used in antiretroviral-experienced patients, this comparison included all patients receiving these drugs, irrespective of treatment history.

For this within-class comparison, the effect on lipid profiles of various antiretroviral agents was evaluated via 2 sets of analyses. The first analysis considered patients receiving PI-containing regimens and compared lipid profiles in patients receiving combinations including indinavir (IDV), nelfinavir (NLF), saquinavir (SQV; soft-gel and hard-gel formulations were studied jointly), amprenavir (AMP), RTV, 2 PIs including RTV, and 2 PIs not including RTV. The group receiving IDV alone was designated as the reference group for this analysis. As before, information concerning the dose of RTV received was not available. The second analysis considered patients receiving efavirenz (EFV) and nevirapine (NVP). The NVP group was designated as the reference group. The number of patients receiving other PIs or NNRTIs was too small for comparison; therefore, these patients have been excluded.

Definitions of Dyslipidemia

The association between dyslipidemia at enrollment in D:A:D and the drugs received was explored by use of the following dependent variables: TC, HDL-c, and TG levels; TC:HDL-c ratio; and, for the between-class comparison only, LDL-c level (calculated by use of the Friedewald formula only when fasting values were available and when TG level was <4.52 mmol/L [35]; otherwise, LDL-c level was treated as missing). In each case, patients were classified as having dyslipidemia if their lipid level at enrollment was above (or, for HDL-c, below) a prespecified threshold level, as described elsewhere [34]. The threshold levels for TC ($\geqslant$6.2 mmol/L), HDL-c ($\leqslant$0.9 mmol/L), LDL-c ($\geqslant$4.1 mmol/L), and TG ($\geqslant$2.3 mmol/L) were based on cutoff values for high risk of CHD, as recommended in the US National Cholesterol Education Program (NCEP) guidelines [36]. A cutoff value for the TC:HDL-c ratio was not defined in the NCEP guidelines and was therefore chosen as $\geqslant$6.5, on the basis of other published studies, to define a group at high risk of CHD [2, 37].

Statistical Methods

The associations between the different treatment groups and variables of interest were studied in univariable analyses by use of the χ^2 test, for categorical variables, and by use of the Kruskal-Wallis test, for continuous variables. Unless otherwise stated, all P values reflect global comparisons across all treatment groups.

The relationships between the dependent variables (TC, HDL-c, LDL-c, and TG levels and TC:HDL-c ratio) and treatment group were studied by use of multiple logistic regression models. Associations were considered to be statistically significant if $P < .05$. All statistical analyses were performed by use of Statistical Analysis Software (version 6.12; SAS Institute).

The relationships between the dependent variables and treatment group were adjusted for demographic factors (i.e., age and sex), known risk factors for CHD (i.e., history of MI or stroke before age 50 years in first-degree relatives, personal history of MI or stroke, body mass index [BMI, classified similarly for both sexes as <18 kg/m^2, 18–26 kg/m^2, 26.1–30 kg/m^2, and >30 kg/m^2], smoking status [current, ex-smoker, unknown], presence of physician-reported lipodystrophy, hypertension [systolic blood pressure $\geqslant$150 mmHg and/or diastolic blood pressure $\geqslant$100 mmHg] or use of antihypertensive agents, diabetes or use of antidiabetic agents, and use of lipid-lowering or antiplatelet agents), and HIV-related variables (i.e., $\log_2$ CD4 T cell count and $\log_{10}$ HIV RNA load at entry to the D:A:D study, AIDS stage [defined according to 1993 CDC clinical classification] [38], and HIV risk group [homosexual or bisexual, heterosexual, injecting drug user, or other/unknown]). All regression analyses were also adjusted for cohort, which captures some differences in risk-factor profiles in different geographic regions. Because the EuroSIDA cohort includes patients from across Europe, with a wide gradient in both cardiovascular risk and risk-factor profiles, this cohort was further divided into 3 subcohorts for the purposes of adjustment: EuroSIDA North, EuroSIDA Central, and EuroSIDA South [39].

Adjustment for treatment history and the use of other concomitant NRTIs was performed differently for the 2 comparisons. For the between-class comparison, the analyses were adjusted to take into account the NRTIs received as part of the current treatment combination, the cumulative duration of exposure to NRTIs and to the current CART regimen at entry to the D:A:D study, and the duration of time receiving the current regimen (which were all set to zero for untreated patients). Because this comparison included an untreated group, it was not possible to adjust for the year of initiation of antiretroviral therapy. In contrast, patients included in the within-class comparison were all receiving CART at enrollment in the D:A:D study. Thus, for this comparison, analyses were adjusted for the NRTIs received as part of the current treatment combination, the year of antiretroviral therapy initiation, and whether the individual was antiretroviral naive at the time of initiating the PI or NNRTI. In addition, because patients in this group may have been heavily treatment experienced, the analyses also adjusted for previous exposure to treatment by adjusting for the number of and cumulative duration of exposure to NRTIs, PIs, and NNRTIs at entry to the D:A:D study.

Sensitivity Analyses

To confirm the robustness of the findings, several sensitivity analyses were performed, including analyses of lipid measure-

Table 1. Characteristics of patients at time of enrollment in the Data Collection on Adverse Events of Anti-HIV Drugs study cohort: between-class comparison.

Characteristic	Total (N = 7483)	Antiretroviral-naive (n = 2315)	Single PI (n = 3444)	Dual PI (n = 607)	NNRTI (n = 1117)	P[a]
Female, %	24.0	31.5	20.7	16.3	22.7	.001
Age, median (IQR), years	38 (34–44)	36 (32–41)	39 (35–46)	39 (35–46)	38 (33–44)	.0001
BMI, median (IQR)	23.1 (21.1–25.2)	22.9 (20.9–25.2)	23.2 (21.3–25.3)	22.9 (21.3–25.2)	22.9 (20.9–25.2)	.04
HIV RNA load <500 copies/mL, %	38.8	17.1	81.7	84.0	75.1	.0001
CD4 cell count, median (IQR), cells/mm^3	470 (309–667)	463 (305–658)	470 (308–670)	467 (302–657)	490 (320–686)	.07
Previous AIDS, %	19.9	7.8	27.6	33.9	16.4	.0001
HIV risk behavior, %						
Homosexual	39.7	30.0	41.5	54.2	45.8	
Heterosexual	30.6	35.2	28.7	27.2	28.0	
IDU	23.7	29.9	23.0	13.5	18.6	
Other/unknown	6.2	4.9	6.9	5.1	7.6	.001
Year of starting antiretroviral therapy, median (IQR)	…	…	1997 (1996–1998)	1996 (1995–1998)	1998 (1996–1999)	.0001
Antiretroviral naive at start of current regimen, %	…	…	56.6	50.1	55.0	.01
No. of NRTIs exposed to by entry in study, median (IQR)	…	…	2 (2–4)	3 (2–4)	2 (2–4)	.0001
Cumulative exposure to NRTIs, median (IQR), years	…	…	2.7 (1.8–3.9)	3.1 (1.7–4.2)	1.7 (0.8–3.3)	.0001
Cumulative exposure to current CART regimen, median (IQR), years	…	…	2.4 (1.5–3.1)	2.8 (1.7–3.4)	1.1 (0.6–1.5)	.0001
No. of NRTIs received as part of regimen						
Zidovudine	…	…	51.0	44.5	48.7	.009
Didanosine	…	…	14.0	10.1	24.2	.001
Zalcitabine	…	…	2.6	0.8	1.5	.004
Stavudine	…	…	47.2	51.2	45.5	.07
Lamivudine	…	…	83.4	74.6	74.8	.001
Abacavir	…	…	1.4	2.1	4.0	.001

NOTE. BMI, body mass index; CART, combination antiretroviral therapy; IDU, injecting drug user; IQR, interquartile range; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor.

[a] Comparisons of variables related to treatment exposure were performed across the 3 treatment groups, after excluding the group of patients who were antiretroviral naive at baseline.

ments known to be from fasting patients only, analyses that only included cohorts for whom lipid values were routinely measured in the majority of patients (cohorts were excluded from this analysis if >10% of data were missing for TC and TG levels and if >30% of data were missing for HDL-c and LDL-c levels and TC:HDL-c ratio), and, for the within-class comparison only, analyses based on the subpopulation of patients who were antiretroviral naive at the time of starting the current PI or NNRTI. Because of the smaller numbers of patients with fasting values available at enrollment, analyses of these measurements were not adjusted for current use of NRTIs at enrollment. Furthermore, because of the very small numbers of LDL-c level measurements included in the between-class comparison, these were not included in sensitivity analyses.

RESULTS

Between-Class Comparison

A total of 7483 patients from the D:A:D cohort were either antiretroviral naive (n = 2315 [31%]) or were receiving a CART regimen containing a single PI (n = 3444 [46%]), a dual PI (n = 607 [8%], 95% of whom used RTV), or an NNRTI (n = 1117 [15%]) for the first time at time of enrollment in the D:A:D study. These 7483 patients were included in the between-class comparison.

Patients receiving therapy were significantly older and more likely to be male than were antiretroviral-naive patients (table 1). Between 75% and 84% of patients in the different CART groups had an HIV RNA load <500 copies/mL, compared with

only 17% of patients who were antiretroviral naive. Patients receiving CART were more likely to have had an AIDS-defining illness, although 8% of antiretroviral-naive patients were also reported to have prior AIDS. Patients receiving a single PI–containing regimen had been receiving their current PI for a median of 2.4 years, whereas patients receiving dual PI–containing regimens had been receiving these PIs for a median of 2.8 years. Patients receiving an NNRTI-containing regimen had been exposed to their current regimen for a median of 1.1 years. Cumulative exposure time to NRTIs differed significantly between the groups: 2.7, 3.1, and 1.7 years, for single PI–containing, dual PI–containing, or NNRTI-containing CART, respectively. Patients receiving therapy were less likely to be current smokers but were more likely to have lipodystrophy, diabetes, and hypertension and to be using antiplatelet or lipid-lowering drugs than antiretroviral-naive patients (table 2).

Information on the number of patients with available lipid measurements, including measurements obtained after patients had fasted overnight, and the median concentrations of the lipids and lipoproteins at enrollment in the D:A:D study are shown, by therapy class, in table 3. Patients who were antiretroviral naive had the lowest TC and LDL-c levels, whereas levels in the 3 treated groups were higher, particularly in patients receiving dual PI–containing regimens. Similar patterns were seen for TG levels, with the lowest levels in patients who were antiretroviral naive and the highest levels in patients receiving PIs, although TG levels in patients receiving NNRTIs were similar to those in antiretroviral-naive patients. Median HDL-c levels did not differ greatly between patients who were antiretroviral naive and patients receiving PI-containing regimens, although levels were slightly higher in patients receiving NNRTIs-containing regimens. As a result, trends in the TC:HDL-c ratio generally mirrored those in TC levels, with the exception of the NNRTI group, in which the ratio was similar to that in antiretroviral-naive patients.

The prevalence of dyslipidemia in patients receiving each CART regimen is shown in figure 1. For TC levels, the prevalence of dyslipidemia was lowest in antiretroviral-naive patients and progressively increased in patients receiving an NNRTI-containing regimen, a single PI–containing regimen, and a dual PI–containing regimen, respectively. A similar trend was also seen in LDL-c and TG levels and TC:HDL-c ratio. In terms of a low HDL-c level, however, the prevalence of dyslipidemia was lower in patients receiving NNRTIs than in patients in all other groups.

Compared with antiretroviral-naive patients (reference group) and after adjustment for other potential confounding factors, patients receiving either a single PI– or a dual PI–containing regimen had a statistically significantly higher risk of dyslipidemia with respect to TG level and TC:HDL-c ratio (table 4). Although the risk estimates for these parameters for patients receiving an NNRTI-containing regimen were likewise increased, these differences were less marked. Patients receiving a dual PI–containing regimen had a statistically significantly increased risk of dyslipidemia with respect to TC level, whereas increased risks in patients receiving a single PI–containing regimen or an NNRTI-containing regimen did not reach statistical significance. There were no statistically significant differences between the CART regimens, in risk of dyslipidemia with respect to either LDL-c or HDL-c level.

We used a similar model to compare the risk of dyslipidemia directly between patients receiving a single PI–containing regimen (reference group) and patients receiving a dual PI–containing regimen or an NNRTI-containing regimen (table 4). Compared with patients receiving a single PI–containing regimen, patients receiving a dual PI–containing regimen were at an increased risk of dyslipidemia for each of the lipid parameters, except LDL-c and HDL-c levels. In contrast, patients receiving an NNRTI-containing regimen had a statistically significant lower risk of dyslipidemia with regard to LDL-c, HDL-c, and TG levels and TC:HDL-c ratio than did patients receiving a single PI–containing regimen.

Between-class sensitivity analyses. Analyses of fasting values yielded results similar to those of the models based on all patients; however, because of the smaller number of patients

Table 2. Percentage of patients with known risk factors for coronary heart disease (CHD) or increased lipid levels, at time of enrollment in the Data Collection on Adverse Events of Anti-HIV Drugs study cohort: between-class comparison.

Characteristic	Total (N = 7483)	Antiretroviral-naive (n = 2315)	Single PI (n = 3444)	Dual PI (n = 607)	NNRTI (n = 1117)	P
Current smoker	44.5	49.3	43.1	45.9	38.0	.001
Lipodystrophy	16.6	2.2	24.4	33.3	13.5	.001
Previous cardiovascular event	0.9	0.6	0.9	1.2	1.1	.30
Hypertension (or use of antihypertensive agents)	6.8	5.9	7.7	7.4	5.3	.007
Use of antiplatelet agents	0.8	0.3	1.0	0.9	1.0	.001
Use of lipid-lowering agents	2.3	0.2	3.6	5.6	0.6	.001
Diabetes mellitus (or use of antidiabetic agents)	1.7	1.2	2.4	1.2	1.3	.003
Family history of CHD	7.8	8.6	7.5	8.9	6.7	.19

NOTE. NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

Table 3. Lipid and lipoprotein values at entry to the Data Collection on Adverse Events of Anti-HIV Drugs study, overall and stratified by treatment group: between-class comparison

Characteristic	Total (N = 7483)	Antiretroviral-naive (n = 2315)	Single PI (n = 3444)	Dual PI (n = 607)	NNRTI (n = 1117)	P
TC level, median (IQR), mmol/L	5.0 (4.1–5.9)	4.4 (3.7–5.2)	5.3 (4.4–6.2)	5.7 (4.9–6.7)	5.1 (4.3–5.9)	.0001
No. (%) of patients with measurement available	6151 (82.2)	1887 (81.5)	2886 (83.8)	504 (83.0)	874 (78.2)	
No. (%) of patients with fasting measurement available	2486 (33.2)	1122 (48.5)	998 (29.0)	103 (17.0)	263 (23.5)	
HDL-c level, median (IQR), mmol/L	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.4)	1.3 (1.1–1.6)	.0001
No. (%) of patients with measurement available	3460 (46.2)	1112 (48.0)	1641 (47.6)	321 (52.9)	386 (34.9)	
No. (%) of patients with fasting measurement available	1411 (42.4)	578 (25.0)	614 (17.8)	82 (13.5)	137 (12.3)	
LDL-c level, median (IQR), mmol/L	3.2 (2.6–4.0)	2.9 (2.4–3.5)	3.6 (2.8–4.4)	3.8 (3.1–4.5)	3.2 (2.7–4.0)	.0001
No. (%) of patients with measurement available	1314 (17.6)	561 (47.6)	554 (47.2)	67 (52.4)	132 (33.9)	
No. (%) of patients with fasting measurement available[a]	1314 (17.6)	561 (47.6)	554 (47.2)	67 (52.4)	132 (33.9)	
TC:HDL-c ratio, median (IQR)	4.4 (3.4–5.7)	3.9 (3.1–4.9)	4.7 (3.6–6.1)	5.3 (4.1–6.9)	3.8 (2.9–5.0)	.0001
No. (%) of patients with measurement available	3424 (45.8)	1102 (47.6)	1625 (47.2)	318 (52.4)	379 (33.9)	
No. (%) of patients with fasting measurement available	1409 (18.8)	577 (24.9)	614 (42.8)	82 (13.5)	136 (12.2)	
TG level, median (IQR), mmol/L	1.5 (1.0–2.5)	1.3 (0.9–1.9)	1.8 (1.2–2.9)	2.5 (1.6–3.9)	1.3 (0.9–2.1)	.0001
No. (%) of patients with measurement available	6180 (82.6)	1912 (82.6)	2891 (83.9)	485 (79.9)	892 (79.9)	
No. (%) of patients with fasting measurement available	2599 (34.7)	1150 (49.7)	1059 (80.4)	120 (19.8)	270 (24.2)	

NOTE. HDL-c, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-c, low-density lipoprotein cholesteriol; NNRTI, nonnucleoside reverse-transcriptase inhibitor; PI, protease inhibitor; TC, total cholesterol; TG, triglycerides.

[a] LDL-c level was calculated using fasting values only.

included in the analyses (table 3), the results were, in some cases, less significant. Results of analyses of HDL-c levels based on fasting values, however, suggested stronger relationships. In particular, the odds ratios (ORs) for an HDL-c level ⩽0.9 mmol/L being associated with receipt of single PI– or dual PI–containing regimens were 1.66 (95% confidence interval [CI], 0.93–2.97; $P = .09$) and 2.25 (95% CI, 1.05–4.82; $P = .04$), respectively, suggesting an increased risk of a lower HDL-c level in patients receiving these treatment combinations. Results of analyses from those cohorts with the lowest amounts of missing data yielded results similar to those from the overall cohort.

Within-Class Comparison

Of the 17,852 patients included in the overall D:A:D cohort, 7729 (43.3%) were receiving ⩾1 PI at the time of enrollment (table 5), and 3476 (19.5%) were receiving an NNRTI (table 6). These 11,205 patients have been included in the within-class comparison.

Patients receiving PIs. Patients receiving IDV, NLF, SQV, and RTV were generally similar in terms of age, mode of infection, BMI, AIDS status, CD4 cell count, and HIV RNA load (table 5). The median CD4 cell count in these groups was >350 cells/mm^3, whereas the proportion of patients with an HIV RNA load <500 copies/mL was 64% in patients receiving SQV and 81% in patients receiving IDV. However, patients receiving AMP or the different PI combinations were markedly different, with lower CD4 cell counts and higher virus loads, which reflects the more-complex treatment histories of these patients. These patients had also been exposed to antiretroviral treatment for longer periods and had more-extensive exposure to PIs and NNRTIs at the time of starting the current regimen. The proportion of smokers was lowest in patients receiving RTV, as were the proportions of patients with lipodystrophy and personal and family history of cardiovascular events, but the use of lipid-lowering drugs was most prevalent in this group (table 7). Otherwise, the groups were broadly similar in terms of risk factors for CHD at entry in the D:A:D study.

TC levels were highest in patients receiving RTV, either alone or in combination with another PI, and were lowest in patients receiving SQV (table 8). Results relating to the prevalence of

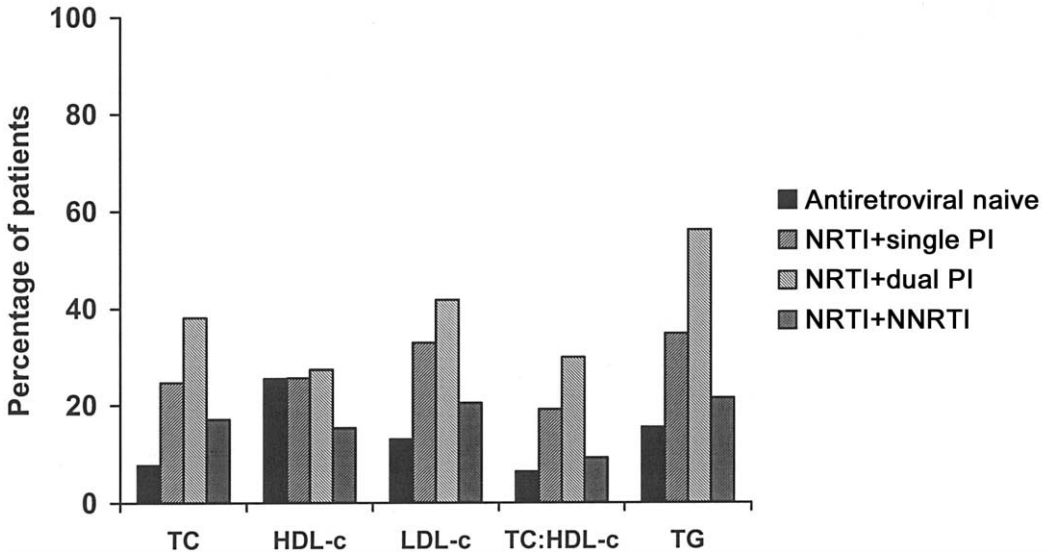

Figure 1. Prevalence of dyslipidemia in patients enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs study, by type of antiretroviral regimen received at initiation of the study. Dyslipidemia is defined as total cholesterol (TC) level ≥6.2 mmol/L, high-density lipoprotein cholesterol level (HDL-c) ≤0.9 mmol/L, low-density lipoprotein cholesterol level (LDL-c) ≥4.1 mmol/L, TC:HDL-c ratio ≥6.5, or triglyceride (TG) level ≥2.3 mmol. NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI, nucleoside reverse-transcriptase inhibitor; PI, protease inhibitor.

dyslipidemia confirmed these findings (figure 2); the proportion of patients with TC levels ≥6.2 mmol/L was significantly higher among patients receiving RTV and lower among patients receiving SQV. HDL-c levels were highest in patients receiving NLF, and, conversely, the proportion of patients with HDL-c levels ≤0.9 mmol/L was lower in this group. The proportion of patients whose TC:HDL-c ratio was ≥6.5 was highest in patients receiving RTV, either alone or in combination with another PI, and was lowest in patients receiving NLF and SQV. TG levels were generally higher in patients receiving RTV, either alone or in combination with another PI, and were lowest in patients receiving SQV.

In multivariable logistic regression analyses (table 9), the risk of a patient having a TC level ≥6.2 mmol/L remained significantly higher in patients receiving RTV, either alone or in combination, and, to a lesser extent, for patients treated with NLF. The risk of having an HDL-c level ≤0.9 mmol/L was significantly lower in patients receiving NLF than in patients receiving IDV. The other PIs were associated with comparable risks of a low HDL-c level. After adjustment for other potential confounding factors, the risk of having a TC:HDL-c ratio ≥6.5 was higher in patients receiving RTV, either alone or in combination with another PI, than in patients receiving IDV. The risk of having a TC:HDL-c ratio ≥6.5 was lower in patients receiving SQV. The trend observed in univariate analysis for a lower TC:HDL-c ratio in patients receiving NLF was maintained, although this relationship was not significant ($P = .08$). After adjustment for other potential confounding factors, only patients receiving RTV or a PI combination containing RTV had a significantly higher risk of having a TG level ≥2.3 mmol/L.

Patients receiving NNRTIs. Patients receiving NVP were more likely to be antiretroviral naive when starting the current treatment regimen than were patients receiving EFV (table 6). The cumulative duration of exposure to NNRTIs was 1.2 years in patients receiving NVP but only 0.7 years in patients receiving EFV, which reflects the more-recent licensing of the latter drug. The duration of exposure to PIs was 0.6 years in patients receiving NVP and 1.7 years in patients receiving EFV. Although patients receiving NNRTIs were less likely to be current smokers than were patients receiving PIs, there were few differences between the levels of risk factors for CHD between patients receiving NVP and those receiving EFV (table 10).

Although TC and TG levels were higher in patients receiving EFV at enrollment, levels of HDL-c and TC:HDL-c ratios were similar in the 2 treatment groups (figure 2 and table 11). After adjustment for other potential confounding factors (table 9), the risk of having a TG level ≥2.3 mmol/L was significantly higher in patients receiving EFV than in patients receiving NVP; the risk of having increased TC levels was similarly elevated. There were, however, no significant differences between either HDL-c level or the TC:HDL-c ratio between patients receiving EFV and those receiving NVP, either before or after adjustment for other factors.

Within-class sensitivity analyses. The analyses were repeated among patients whose lipid measurement had been obtained after they had fasted overnight (see tables 8 and 11 for

Table 4. Multivariable regression analyses showing relationship between class of drug received and odds of developing dyslipidemia, among patients enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs study: between-class comparison.

Reference category, antiretroviral regimen	TC level ≥6.2 mmol/L		HDL-c level ≤0.9 mmol/L		LDL-c level ≥4.1 mmol/L		TC:HDL-c ratio ≥6.5		TG level ≥2.3 mmol/L	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Antiretroviral-naive group										
Antiretroviral naive	1	…	1	…	1	…	1	…	1	…
Single PI	1.77 (0.91–3.42)	.09	1.20 (0.46–3.15)	.71	2.13 (0.30–15.26)	.45	4.77 (1.68–13.51)	.003	3.26 (1.82–5.87)	.0001
Dual PI	2.77 (1.44–5.35)	.002	1.26 (0.49–3.27)	.63	2.65 (0.36–19.68)	.34	7.46 (2.70–20.62)	.0001	5.87 (3.25–10.60)	.0001
NNRTI	1.40 (0.73–2.68)	.31	0.81 (0.31–2.14)	.67	1.08 (0.15–7.69)	.94	2.99 (1.04–8.60)	.04	1.90 (1.06–3.39)	.03
Single-PI group										
Single PI	1	…	1	…	1	…	1	…	1	…
Dual PI	1.55 (1.23–1.96)	.0003	1.04 (0.76–1.42)	.87	1.24 (0.69–2.22)	.48	1.58 (1.15–2.18)	.005	1.81 (1.44–2.28)	.0001
NNRTI	0.80 (0.62–1.02)	.08	0.68 (0.47–0.98)	.04	0.47 (0.26–0.85)	.01	0.61 (0.39–0.95)	.03	0.59 (0.47–0.74)	.0001

NOTE. All analyses are adjusted for all demographic factors, risk factors for coronary heart disease, HIV factors, and previous exposure to nucleoside reverse-transcriptase inhibitor and combination antiretroviral therapy, as described in Subjects, Materials, and Methods. CI, confidence interval; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; NNRTI, nonnucleoside reverse-transcriptase inhibitor; OR, odds ratio; PI, protease inhibitor; TC, total cholesterol; TG, triglycerides.

sample sizes) and also among cohorts with relatively small proportions of missing data. In both cases, both for the PI and NNRTI comparison, the results from the sensitivity analyses confirmed the findings in the main analysis. Finally, the analyses were repeated for the patients who were antiretroviral naive at the time of starting the current therapy. The results from the analysis of the groups receiving PIs generally confirmed the analysis of patients from the full population, in that RTV, whether administered alone or in combination with another PI, remained the PI associated with the highest risk of both hypercholesterolemia and hypertriglyceridemia. Analyses of previously antiretroviral-naive patients receiving NNRTIs yielded results broadly similar to those for the full population, although the relationship between EFV and an increased TG level did not remain in this analysis (OR, 0.80; $P = .57$).

DISCUSSION

HIV-infected patients enrolled in the D:A:D study and treated with different types of CART demonstrated clearly different plasma lipid profiles. In particular, patients receiving CART regimens which, for the first time, included either 1 or 2 PIs had higher TC and TG levels and TC:HDL-c ratios than did patients who were antiretroviral naive, with patients who received a dual PI–containing regimen having significantly higher levels of each lipid than patients who received a single PI–containing regimen. Although TC and LDL-c levels were still increased in patients receiving NNRTIs, compared with antiretroviral-naive patients, the risk of having a low HDL-c level was reduced in these patients, compared with patients receiving a single PI–containing regimen. HDL-c levels were slightly higher in patients receiving an NNRTI, which contributed to a lower TC:HDL-c ratio in this group.

Our results also suggest that the various PIs and NNRTIs within each class are associated with different risks of dyslipidemia. RTV-containing regimens were associated with the most pronounced elevations of TC and TG levels and TC:HDL-c ratios, NLF-containing regimens were associated with a lower risk of having a reduced HDL-c level, and SQV-containing regimens were associated with a lower risk of having an elevated TC:HDL-c ratio. Treatment regimens combining 2 PIs other than RTV did not appear to be associated with a higher risk of dyslipidemia, compared with single PI–containing regimens, with the exception of RTV. In comparison to treatment with NVP, the use of EFV was associated with higher TC and TG levels. HDL-c levels and TC:HDL-c ratios, however, were similar in patients receiving either EFV- or NVP-containing regimens.

Few other studies have reported differences in lipid profiles between patients receiving different classes of drugs, per se, although a number of clinical trials have reported comparisons of lipids in patients receiving specific treatment combinations involving different classes of drugs. In another study, [25] van der Valk et al. compared patients randomly assigned to a first-line regimen of stavudine and didanosine, together with either IDV, NVP, or lamivudine (3TC). After 24 weeks of treatment, patients receiving NVP had significantly higher increases in HDL-c levels, compared with other patients. Although the TC and LDL-c levels also increased, the TC:HDL-c ratio was significantly reduced and was lowest in patients receiving NVP. Virgili et al. [40] reported similar differential lipid changes in antiretroviral-naive patients receiving a combination of zidovudine plus 3TC, together with either NLF or NVP.

Table 5. Characteristics of patients receiving protease inhibitors (PIs) at time of enrollment in the Data Collection on Adverse Events of Anti-HIV Drugs study cohort: within-class comparison.

Characteristic	Total (N = 7729)	IDV (n = 2354)	NLF (n = 2574)	SQV (n = 576)	AMP (n = 72)	RTV (n = 515)	2 PIs incl. RTV (n = 1464)	2 PIs excl. RTV (n = 174)	P
Female, %	20.9	18.5	26.9	25.4	13.9	15.5	15.3	17.2	.001
Age, median (IQR), years	39 (35–46)	40 (35–47)	38 (34–45)	38 (34–45)	40 (33–47)	39 (35–45)	40 (35–46)	38 (34–46)	.0001
BMI, median (IQR)	23.0 (21.1–25.0)	23.3 (21.4–25.3)	22.8 (20.8–24.9)	23.1 (21.1–25.0)	23.6 (21.3–24.9)	22.9 (21.0–24.8)	22.7 (21.0–25.0)	22.2 (20.8–24.6)	.001
HIV RNA load <500 copies/mL, %	73.9	81.3	73.5	63.6	40.9	75.8	70.0	55.2	.0001
CD4 cell count, median (IQR), cells/mm^3	435 (277–630)	463 (307–664)	432 (273–616)	468 (294–686)	240 (130–478)	447 (290–639)	400 (248–590)	358 (206–567)	.0001
Previous AIDS, %	32.2	32.1	27.0	32.1	51.5	33.4	39.3	42.1	.001
HIV risk behavior, %									.001
Homosexual/bisexual	44.4	44.1	38.2	38.0	55.6	49.3	55.0	51.2	
Heterosexual	26.6	26.5	29.6	28.7	20.8	23.3	22.5	23.6	
IDU	22.6	23.3	25.1	28.0	16.7	20.6	16.3	20.7	
Other/unknown	6.4	6.2	7.0	5.4	6.9	6.8	6.2	4.6	.001
Year of starting antiretroviral therapy, median (IQR)	1996 (1994–1997)	1996 (1994–1997)	1997 (1995–1998)	1997 (1995–1997)	1995 (1993–1996)	1996 (1994–1997)	1996 (1994–1997)	1995 (1993–1996)	.0001
Antiretroviral-naive at start of PI, %	45.6	46.0	53.7	49.1	20.8	35.0	37.2	20.1	.001
No. of NRTIs exposed to, median (IQR)	4 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)	5 (4–7)	3 (2–4)	4 (3–5)	4 (3–5)	.0001
Cumulative exposure to NRTIs, median (IQR), years	3.2 (2.1–4.6)	3.3 (2.3–4.7)	2.7 (1.6–4.0)	3.0 (2.3–4.6)	4.4 (3.1–6.8)	3.6 (2.6–4.9)	3.6 (2.4–5.1)	3.8 (2.7–5.7)	.0001
No. of PIs exposed to, median (IQR)	1 (1–2)	1 (1–1)	2 (1–2)	1 (1–2)	3 (2–5)	1 (1–2)	2 (2–3)	3 (2–4)	.0001
Cumulative exposure to PIs, median (IQR), years	2.6 (1.8–3.3)	2.8 (2.1–3.4)	2.2 (1.4–3.0)	2.6 (2.0–3.3)	2.8 (1.9–3.6)	2.8 (1.9–3.5)	2.8 (2.0–3.5)	2.8 (2.3–3.5)	.0001
Previously exposed to NNRTIs, %	11.1	4.8	8.9	9.6	69.4	8.5	21.8	25.3	.001
NRTIs received as part of regimen, %									
Zidovudine	42.9	49.5	41.0	47.9	30.6	46.8	35.5	19.0	.001
Didanosine	17.1	11.5	18.9	17.9	43.1	17.3	20.3	27.6	.001
Zalcitabine	2.0	2.3	0.5	9.4	1.4	2.5	1.4	1.2	.001
Stavudine	52.4	48.4	56.8	47.2	43.1	47.2	53.8	65.5	.001
Lamivudine	78.3	86.2	80.2	69.8	62.5	80.0	68.4	53.5	.001
Abacavir	4.4	1.7	3.2	3.1	47.2	2.1	9.5	9.8	.001

NOTE. AMP, amprenavir; BMI, body mass index; EFV, efavirenz; excl., excluding; IDU, injecting drug user; IDV, indinavir; incl., including; IQR, interquartile range; NLF, nelfinavir; NRTI, nucleoside reverse-transcriptase inhibitor; RTV, ritonavir; SQV, saquinavir.

Table 6. Characteristics of patients receiving nonnucleoside reverse-transcriptase inhibitors (NNRTIs) at time of enrollment in the Data Collection on Adverse Events of Anti-HIV Drugs study cohort: within-class comparison.

Characteristic	Total (N = 3476)	NVP (n = 2040)	EFV (n = 1436)	P
Female, %	23.1	20.9	26.2	.001
Age, median (IQR), years	39 (35–47)	39 (35–47)	39 (34–46)	.14
BMI, median (IQR)	22.8 (20.9–25.0)	23.0 (21.0–25.2)	22.7 (20.7–24.8)	.001
HIV RNA load <500/copies/mL, %	75.8	73.6	78.8	.0006
CD4 cell count, cells/mm^3, median (IQR)	456 (289–648)	480 (308–663)	419 (265–613)	.0001
Previous AIDS, %	28.9	30.1	27.6	.14
HIV risk behavior, %				
Homosexual/bisexual	49.4	51.9	45.7	
Heterosexual	25.9	24.2	28.3	
IDU	17.0	16.4	17.8	
Other/unknown	7.3	7.6	8.2	.004
Year of starting antiretroviral therapy, median (IQR)	1997 (1995–1998)	1997 (1995–1998)	1996 (1994–1998)	.0005
Antiretroviral-naive at start of PI/NNRTI, no. (%)	19.5	21.4	16.9	.001
No. of NRTIs exposed to, median (IQR)	4 (2–5)	4 (2–4)	4 (2–5)	.0008
Cumulative exposure to NRTIs, median (IQR), years	3.0 (1.7–4.4)	2.9 (1.7–4.2)	3.1 (1.7–4.7)	.07
No. of PIs exposed to, median (IQR)	1 (0–2)	1 (0–1)	1 (0–2)	.0001
Cumulative exposure to PIs, median (IQR), years	1.1 (0–2.3)	0.6 (0–2.0)	1.7 (0–2.6)	.0001
No. of NNRTIs exposed to, median (IQR)	1 (1–1)	1 (1–1)	1 (1–1)	.0001
Cumulative exposure to NNRTIs, median (IQR), years	1.0 (0.5–1.5)	1.2 (0.7–1.7)	0.7 (0.4–1.2)	.0001
NRTIs received as part of regimen, %				
Zidovudine	41.7	42.4	40.7	.34
Didanosine	22.6	20.5	25.4	.001
Zalcitabine	1.1	1.0	1.1	.94
Stavudine	50.0	50.3	49.7	.76
Lamivudine	75.6	78.8	71.1	.001
Abacavir	12.3	8.0	18.3	.001

NOTE. BMI, body mass index; EFV, efavirenz; IDU, injecting drug user; IQR, interquartile range; NRTI, nucleoside reverse-transcriptase inhibitor; NVP, nevirapine; PI, protease inhibitor.

A number of studies have reported differences in lipid profiles among patients receiving drugs from the same class. For example, several studies have suggested that RTV, whether administered alone or in combination, may induce more-severe dyslipidemia than other PIs [15, 24, 41]. The results of the present study confirm these results with regard to both TC and TG levels. Furthermore, our finding that the TC:HDL-c ratio was highest in patients receiving RTV is also of interest, because the ratio may be a better indicator of ischemic coronary risk than either the LDL:HDL-c ratio or TC level [42]. It should be reiterated that we were not able to collect information on the dose of RTV given to patients receiving dual PI combinations, and, thus, we are unable to ascertain whether dyslipidemia is more common in patients receiving RTV at high dose in combination with another PI. It is of interest to note that combinations of 2 PIs that do not include RTV do not appear to induce a higher risk of dyslipidemia than these PIs alone, confirming the results published by Carr et al. [18].

In the present study, NLF-containing regimens were associated with a significantly lower risk of a low HDL-c level than were IDV-containing regimens, which, in turn, resulted in a lower TC:HDL-c ratio in these patients. In contrast, a study conducted in 1998 of 129 patients did not report any effect on HDL-c levels in patients receiving NLF [15]. It is unclear why NLF may induce a smaller reduction in HDL-c level than other PIs. This association is present even after adjusting for virus load and CD4 cell count and, thus, is not explained by a particular indirect effect of NLF on virus load [43]. The results of the present study also suggest that SQV, when used as a single PI, is associated with a significantly lower risk of a high TC:HDL-c ratio than is treatment with IDV. Because of its preferential use in combination with other PIs, especially RTV, very few studies have considered lipid changes in patients receiving SQV per se, and only one has focused on its link with hypercholesterolemia. Our results are consistent with those of a prior study [44], in which <10% of patients treated with soft-gel

Table 7. Percentage of patients receiving protease inhibitors (PIs) with known risk factors for coronary heart disease (CHD) or increased lipid levels, at time of enrollment in the Data Collection on Adverse Events of Anti-HIV Drugs study cohort: within-class comparison.

Characteristic	Total (N = 7729)	IDV (n = 2354)	NLF (n = 2574)	SQV (n = 576)	AMP (n = 72)	RTV (n = 515)	2 PIs incl. RTV (n = 1464)	2 PIs excl. RTV (n = 174)	P
Current smoker	44.4	41.5	47.4	45.1	43.7	36.8	45.6	45.7	.001
Lipodystrophy	29.4	28.8	27.1	25.9	37.5	21.9	36.6	42.5	.001
Previous cardiovascular event	1.3	1.6	1.2	1.1	…	0.4	1.8	0.6	.13
Hypertension (or use of antihypertensive agents)	8.2	9.0	8.8	5.0	11.1	5.2	7.9	8.1	.007
Use of antiplatelet agents	1.2	1.5	1.1	1.4	…	0.8	1.3	0.6	.64
Use of lipid-lowering agents	4.2	4.4	2.1	3.7	4.2	9.3	5.9	5.8	.001
Diabetes mellitus (or use of antidiabetic agents)	2.2	3.1	1.8	3.1	4.2	0.8	1.8	0.6	.001
Family history of CHD	7.8	7.1	7.8	7.7	13.0	5.9	9.7	7.1	.04

NOTE. AMP, amprenavir; excl., excluding; IDV, indinavir; incl., including; NLF, nelfinavir; RTV, ritonavir; SQV, saquinavir.

SQV had a TC level >6.5 mmol/L after a median exposure of 6.7 months. Similarly, in a clinical trial including >300 patients and comparing 2 boosted treatment strategies (IDV [800 mg]/RTV [100 mg] twice daily and SQV [1000 mg]/RTV [100 mg] twice daily) [45], Cahn et al. reported a larger increase of TG and TC levels in the IDV group than in the SQV group. Several hypotheses have been suggested to explain why SQV might induce fewer cholesterol abnormalities than other PIs, including lower bioavailability of the molecule in its capsule form [46] and its lower affinity for the p450 cytochrome isoenzyme [47].

To our knowledge, limited data are available concerning the comparison of the effects of EFV and NVP on the lipid profiles of HIV-infected patients. Studies of patients successfully treated with PI-containing CART, for whom their PI was replaced by either NVP or EFV, have also shown an increase in HDL-c levels [48–51]. Our findings suggest that, compared with PIs, NNRTIs are associated with a lower risk of dyslipidemia but that there are no significant differences between EFV and NVP with regard to either HDL-c levels or TC:HDL-c ratios. Statistically significant differences were demonstrated for TG and TC levels, although absolute differences were small. It is important to acknowledge that, at present, there is no conclusive evidence that drug-induced elevations of HDL-c levels will be associated with a lower risk of CHD [52]. Furthermore, if CART-induced dyslipidemia in the context of HIV infection translates into risk of CHD in a way similar to that of non-pharmaceutically induced dyslipidemia in the general population, a difference of 0.1 mmol/L in TC level (the difference observed in our study for EFV and NVP) would be associated with a difference of relative risk of CHD over 10 years of ~3% [53]. Results from the 2NN trial—a randomized comparison of once-daily NVP, twice-daily NVP, EFV, and NVP plus EFV in combination with 3TC and stavudine in antiretroviral-naive patients [27]—suggested larger differences in lipid profiles of the drugs and favored NVP. Further studies are required to determine the clinical impact of these differences.

It should be recognized that, although the present study and others have reported differences in lipid profiles between patients receiving different CART regimens, the relationship between antiretroviral-induced changes in plasma lipids and lipoproteins in HIV-infected patients and the risk of CHD remains unclear. In particular, it is not known whether increases (or decreases) in any of the lipid levels correlate with the same change in risk of CHD as is seen in HIV-negative patients. There is accumulating evidence that, among HIV-negative patients, abnormal serum lipid levels, especially increased levels of TC and TG, are correlated with increased thickening of the intima-media layer (IMT) of the arterial wall [54], which is closely correlated with increased risk of CHD [55]. A number of studies have found that thickening of IMT was more pronounced in patients receiving PI-containing regimens than in antiretroviral-naive patients and individuals without HIV infection [56, 57]; however, in 1 of these studies, this effect disappeared after adjusting for known CHD risk factors [57], and the relationship has not been reported in all studies [58]. Although preliminary analyses from the D:A:D study have begun to investigate the relationships between changes in plasma lipid levels and subsequent development of CHD [33], further follow-up is required before a definitive answer can be reached.

The present study has a number of limitations. First, the analysis is based on data obtained from a large number of observational cohorts. In this type of cohort, treatment allocation is rarely random, and, as a consequence, treatment groups differ substantially at entry to the D:A:D study. In particular, patients receiving PIs (either single or dual combinations) tended to have more-advanced disease than did patients receiving NNRTIs. Even among patients receiving PIs, patients receiving AMP or a combination of 2 PIs generally had more-

Table 8. Lipid and lipoprotein values in patients receiving protease inhibitors (PIs) at entry to Data Collection on Adverse Events of Anti-HIV Drugs study, overall and stratified by treatment group: within-class comparison.

Characteristic	Total (N = 7729)	IDV (n = 2354)	NLF (n = 2574)	SQV (n = 576)	AMP (n = 72)	RTV (n = 515)	2 PI incl. RTV (n = 1464)	2 PIs excl. RTV (n = 174)	P
TC level, median (IQR), mmol/L	5.3 (4.5–6.3)	5.3 (4.4–6.1)	5.2 (4.5–6.2)	4.8 (3.9–5.6)	5.1 (4.3–6.2)	5.7 (4.6–6.8)	5.6 (4.7–6.7)	5.4 (4.4–6.3)	.0001
No. (%) of patients with measurement available	6497 (84.1)	1972 (83.8)	2207 (85.7)	431 (74.8)	63 (87.5)	452 (87.8)	1226 (83.7)	146 (83.9)	
No. (%) of patients with fasting measurement available	1990 (25.7)	751 (30.5)	622 (24.2)	210 (53.4)	5 (5.9)	104 (20.2)	268 (18.3)	30 (17.2)	
HDL-c level, median (IQR), mmol/L	1.1 (0.9–1.4)	1.0 (0.9–1.3)	1.2 (1.0–1.4)	1.0 (0.9–1.3)	0.9 (0.7–1.4)	1.1 (0.9–1.4)	1.1 (0.9–1.3)	1.1 (0.9–1.4)	.0001
No. (%) of patients with measurement available	3785 (49.0)	1078 (45.8)	1431 (55.6)	175 (30.4)	31 (43.1)	223 (43.3)	782 (53.4)	65 (37.4)	
No. (%) of patients with fasting measurement available	1314 (17.0)	469 (19.9)	437 (17.0)	102 (17.7)	5 (6.9)	64 (12.4)	212 (14.5)	25 (14.4)	
TC:HDL-c ratio, median (IQR)	4.8 (3.7–6.3)	5.0 (3.9–6.4)	4.5 (3.5–5.9)	4.3 (3.3–5.4)	5.4 (3.8–6.7)	5.1 (4.0–6.9)	5.4 (4.0–6.9)	4.8 (3.4–6.3)	.0001
No. (%) of patients with measurement available	3749 (48.5)	1064 (45.2)	1423 (55.3)	172 (29.9)	31 (43.1)	220 (42.7)	776 (53.0)	63 (36.2)	
No. (%) of patients with fasting measurement available	1304 (16.9)	166 (7.1)	437 (17.0)	102 (17.7)	4 (5.6)	63 (12.2)	209 (14.3)	23 (13.2)	
TG level, median (IQR), mmol/L	1.9 (1.2–3.1)	1.8 (1.2–2.8)	1.7 (1.2–2.8)	1.6 (1.0–2.5)	2.4 (1.6–3.3)	2.8 (1.7–4.3)	2.5 (1.6–4.2)	2.2 (1.4–3.0)	.0001
No. (%) of patients with measurement available	6485 (83.9)	1996 (84.8)	2206 (85.7)	438 (76.0)	62 (86.1)	448 (87.0)	1190 (81.3)	145 (83.3)	
No. (%) of patients with fasting measurement available	2137 (27.6)	800 (34.0)	650 (25.3)	227 (39.4)	8 (11.1)	113 (21.9)	299 (20.4)	40 (23.0)	

NOTE. AMP, amprenavir; excl., excluding; HDL-c, high density lipoprotein cholesterol; IDV, indinavir; incl., including; IQR, interquartile range; NLF, nelfinavir; RTV, ritonavir; SQV, saquinavir; TC, total cholesterol; TG, triglycerides.

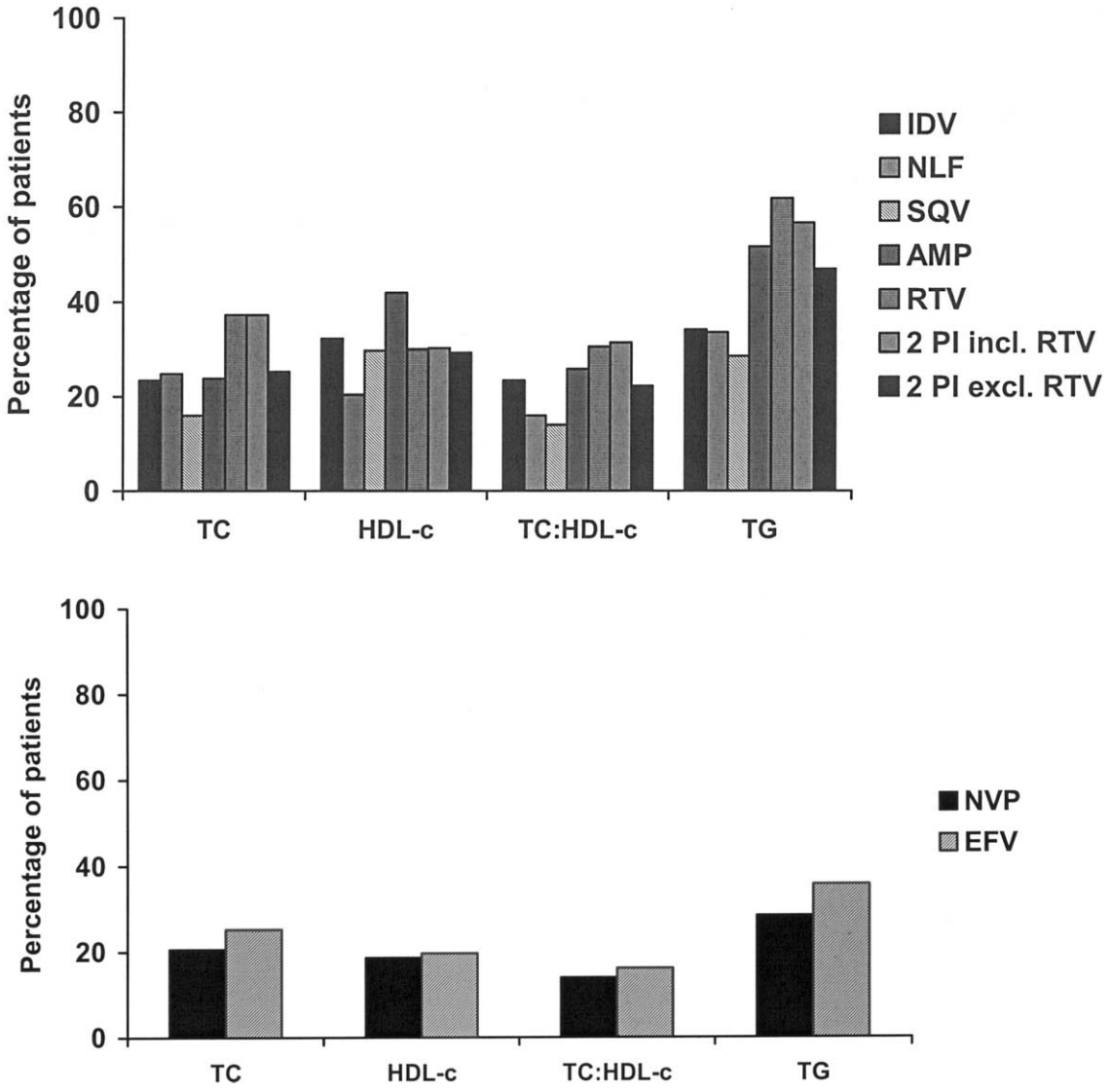

Figure 2. Prevalence of dyslipidemia in patients enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs study, by type of antiretroviral regimen received at initiation of the study. Dyslipidemia is defined as total cholesterol (TC) level ≥6.2 mmol/L, high density lipoprotein cholesterol (HDL-c) level ≤0.9 mmol/L, TC:HDL-c ratio ≥6.5, or triglyceride (TG) level ≥2.3 mmol. *Top,* Comparison of protease inhibitors (PIs). *Bottom,* Comparison of nonnucleoside reverse-transcriptase inhibitors. AMP, amprenavir; EFV, efavirenz; excl., excluding; IDV, indinavir; incl., including; NLF, nelfinavir; NVP, nevirapine; RTV, ritonavir; SQV, saquinavir.

advanced disease than did patients receiving other treatment regimens. Although our analyses were adjusted to take account of observed differences between treatment groups, it is possible that some unmeasured differences may remain. Furthermore, the complex treatment regimens received may complicate our ability to quantify treatment accurately. Thus, it is not possible to conclude that all potential bias has been eliminated.

Although we have reported relationships between specific treatment combinations and risk of dyslipidemia, the cross-sectional nature of the present study prevents us from establishing a causal relationship between the various drugs or classes and dyslipidemia. In particular, because information on pre-treatment lipid levels is unavailable for the majority of patients, we are unable to exclude the possibility that dyslipidemia occurred before exposure to CART. Because the routine monitoring of lipid measurements has only recently been recommended for patients receiving CART, it is not surprising that there are substantial amounts of data missing both at enrollment in the D:A:D study and at the start of CART. However, it is unlikely that these missing data will lead to a serious bias in the results. These data are missing primarily because, at that time, such information was not routinely collected by some of the cohorts, rather than because they had only been collected for patients thought to be at high risk of dyslipidemia. Fur-

Table 9. Multivariable regression analyses showing relationship between antiretroviral drugs and odds of developing dyslipidemia in patients enrolled in the Data Collection on Adverse Events of Anti-HIV Drugs study: within-class comparison.

	TC level ⩾6.2 mmol/L		HDL-c level ⩽0.9 mmol/L		TC:HDL-c ratio ⩾6.5		TG level ⩾2.3 mmol/L	
Patient group, drug	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Patients receiving PIs								
IDV	1	…	1	…	1	…	1	…
NLF	1.28 (1.07–1.54)	.007	0.61 (0.48–0.76)	.0001	0.80 (0.62–1.03)	.08	1.05 (0.89–1.24)	.54
SQV	0.75 (0.53–1.06)	.11	0.85 (0.56–1.31)	.47	0.52 (0.30–0.91)	.02	0.90 (0.68–1.20)	.48
AMP	1.16 (0.57–2.36)	.69	0.92 (0.39–2.17)	.84	0.81 (0.31–2.10)	.66	1.33 (0.73–2.43)	.36
RTV	1.99 (1.54–2.58)	.0001	0.98 (0.69–1.40)	.93	1.48 (1.02–2.14)	.04	3.22 (2.51–4.12)	.0001
2 PIs incl. RTV	2.13 (1.70–2.68)	.0001	0.79 (0.59–1.04)	.09	1.42 (1.06–1.91)	.02	1.95 (1.57–2.41)	.0001
2 PIs excl. RTV	1.19 (0.74–1.92)	.48	0.74 (0.40–1.39)	.35	0.81 (0.40–1.62)	.55	1.18 (0.78–1.79)	.44
Patients receiving NNRTIs								
NVP	1		1		1		1	
EFV	1.29 (1.00–1.66)	.05	1.38 (0.94–2.02)	.10	1.31 (0.86–1.98)	.21	1.46 (1.16–1.83)	.001

NOTE. All analyses are adjusted for demographic factors, risk factors for coronary heart disease and HIV factors, as described in Subjects, Materials, and Methods. AMP, amprenavir; CI, confidence interval; EFV, efavirenz; excl., excluding; IDV, indinavir; incl., including; NLF, nelfinavir; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NVP, nevirapine; OR, odds ratio; PI, protease inhibitor; RTV, ritonavir; SQV, saquinavir.

thermore, because knowledge about a possible relationship between CART and CHD risk is relatively recent, it is unlikely that this influenced the choice of initial CART regimen or that it could explain the differences in lipid profiles seen at baseline. Sensitivity analyses in which cohorts with substantial amounts of missing data were excluded reached conclusions similar to those of the main analyses.

Not all blood samples for lipid measurements were obtained after an overnight fast. The effect of fasting is of importance when analyzing TG levels [59] but should be minimal when analyzing TC or HDL-c levels [59–61]. We repeated the multivariable logistic regression analyses for each of the lipid parameters by use of only samples that were documented to have been obtained after an overnight fast. With the exception of the analyses for HDL-c levels for the between-class comparison, results of our sensitivity analyses were generally similar to those from the whole study population. For HDL-c levels, however, analyses excluding nonfasting values suggested a stronger relationship between PI-containing regimens and low HDL-c levels. However, because of the smaller number of patients in this analysis and because we could not adjust for current NRTI use in these sensitivity analyses, these results should be interpreted cautiously.

The study populations included in the analyses, particularly in the within-class comparison, were heterogeneous, both in terms of their treatment history and prior known risk factors for CHD. All analyses were adjusted for treatment history, and sensitivity analyses for the within-class comparison that considered only those patients who were naive for any treatment before their current regimen gave very similar results. It is possible that the NRTI backbone may have contributed to the differences in lipid profiles [28, 29], although, because adjustment was made for the current use of specific NRTIs, it is unlikely that differential use of NRTIs in the treatment groups can explain our findings. The proportion of patients who were already known to be receiving lipid-lowering agents ranged from 0.2% to 9.3% in the different treatment groups. Although we did not exclude these patients from our analyses, we did adjust for this factor in any multivariable analyses; therefore, it is unlikely that these factors could lead to bias in our results. Finally, because of the timing of recruitment for the D:A:D study, we were unable to consider the role of newer drugs and combinations on lipid profiles, such as lopinavir/RTV, which has been reported to have a greater impact on lipid profiles than NLF [62], or tenofovir or atazanavir, both of which have been reported

Table 10. Percentage of patients receiving nonnucleoside reverse-transcriptase inhibitors with known risk factors for coronary heart disease (CHD) or increased lipid levels, at time of enrollment in the Data Collection on Adverse Events of Anti-HIV Drugs study: within-class comparison.

Characteristic	Total (*N* = 3476)	NVP (*n* = 2040)	EFV (*n* = 1436)	*P*
Current smoker	38.5	38.5	38.4	.93
Lipodystrophy	30.8	30.0	32.1	.08
Previous cardiovascular event	1.7	1.9	1.6	.53
Hypertension (or use of antihypertensive agents)	8.7	9.4	7.7	.08
Use of antiplatelet agents	1.4	1.6	1.0	.24
Use of lipid-lowering agents	3.7	3.6	3.8	.85
Diabetes mellitus (or use of antidiabetic agents)	3.4	2.9	4.0	.12
Family history of CHD	8.6	7.8	9.7	.07

NOTE. EFV, efavirenz; NVP, nevirapine.

Table 11. Lipid and lipoprotein values in patients receiving nonnucleoside reverse-transcriptase inhibitors at entry to the Data Collection on Adverse Events of Anti-HIV Drugs study, overall and stratified by treatment group: within-class comparison.

Characteristic	Total (N = 3476)	NVP (n = 2040)	EFV (n = 1436)	P
TC level, median (IQR), mmol/L	5.3 (4.5–6.1)	5.2 (4.4–6.0)	5.3 (4.5–6.2)	.03
No. (%) of patients with measurement available	2709 (77.9)	1451 (71.1)	1258 (87.6)	
No. (%) of patients with fasting measurement available	785 (22.6)	448 (22.0)	337 (23.5)	
HDL-c level, median (IQR), mmol/L	1.2 (1.0–1.5)	1.2 (1.0–1.5)	1.2 (1.0–1.5)	.45
No. (%) of patients with measurement available	1299 (37.4)	558 (27.4)	741 (51.6)	
No. (%) of patients with fasting measurement available	498 (14.3)	249 (12.2)	249 (17.3)	
TC:HDL-c ratio, median (IQR)	4.3 (3.2–5.7)	4.2 (3.3–5.6)	4.4 (3.2–5.8)	.28
No. (%) of patients with measurement available	1280 (36.8)	547 (26.8)	733 (51.0)	
No. (%) of patients with fasting measurement available	493 (14.2)	246 (12.1)	247 (17.2)	
TG level, median (IQR), mmol/L	1.6 (1.0–2.7)	1.5 (1.0–2.5)	1.7 (1.1–2.9)	.0001
No. (%) of patients with measurement available	2750 (79.1)	1468 (72.0)	1282 (89.3)	
No. (%) of patients with fasting measurement available	822 (23.6)	468 (22.9)	354 (24.7)	

NOTE. EFV, efavirenz; HDL-c, high density lipoprotein cholesterol; IQR, interquartile range; NVP, nevirapine; TC, total cholesterol; TG, triglycerides.

to have smaller effects than earlier CART regimens [61, 63]. Further follow-up and a possible extension to the D:A:D study may enable us to consider these drugs in the future.

Studies such as D:A:D investigate whether antiretroviral therapy–associated metabolic disorders contribute to premature onset of CHD. Given the current need for lifelong therapy, considerations of longer-term toxicities, in addition to virological efficacy, are becoming increasingly important when choosing between different regimens that are anticipated to be similar virologically. Our results, particularly in terms of an increased risk of dyslipidemia in patients receiving RTV and a reduced risk of low HDL-c levels in patients receiving NNRTIs, particularly NVP, may be associated with differences in risk of CHD and, therefore, may give the NNRTI regimens an advantage over current PI-containing regimens, particularly in patients with preexisting known risk factors for CHD. However, we would like to underscore that, at this stage, this discussion remains speculative. With additional follow-up and clinical end points, the D:A:D study may, in due course, have data to assess the association between different types of antiretroviral regimens and risk of CHD.

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