

Ecological Study of the Predictors of Successful Management of Dyslipidemia in HIV-Infected Patients on ART: the Swiss HIV Cohort Study

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Purpose: Antiretroviral therapy (ART) may induce metabolic changes and increase the risk of coronary heart disease (CHD). Based on a health care system approach, we investigated predictors for normalization of dyslipidemia in HIV-infected individuals receiving ART. **Method:** Individuals included in the study were registered in the Swiss HIV Cohort Study (SHCS), had dyslipidemia but were not on lipid-lowering medication, were on potent ART for ≥ 3 months, and had ≥ 2 follow-up visits. Dyslipidemia was defined as two consecutive total cholesterol (TC) values above recommended levels. Predictors of achieving treatment goals for TC were assessed using Cox models. **Results:** Analysis included 958 individuals with median follow-up of 2.3 years (IQR 1.2–4.0). 454 patients (47.4%) achieved TC treatment goals. In adjusted analyses, variables significantly associated with a lower hazard of reaching TC treatment goals were as follows: older age (compared to 18–37 year olds: hazard ratio [HR] 0.62 for 45–52 year olds, 95% CI 0.47–0.82; HR 0.40 for 53–85, 95% CI 0.29–0.54), diabetes (HR 0.39, 95% CI 0.26–0.59), history of coronary heart disease (HR 0.27, 95% CI 0.10–0.71), higher baseline TC (HR 0.78, 95% CI 0.71–0.85), baseline triple nucleoside regimen (HR 0.12 compared to PI-only regimen, 95% CI 0.07–0.21), longer time on PI-only regimen (HR 0.39, 95% CI 0.33–0.46), longer time on NNRTI only regimen (HR 0.35, 95% CI 0.29–0.43), and longer time on PI/NNRTI regimen (HR 0.34, 95% CI 0.26–0.43). Switching ART regimen when viral load was undetectable was associated with a higher hazard of reaching TC treatment goals (HR 1.48, 95% CI 1.14–1.91). **Conclusion:** In SHCS participants on ART, several ART-related and not ART-related epidemiological factors were associated with insufficient control of dyslipidemia. Control of dyslipidemia in ART recipients must be further improved. **Key words:** adverse effects, antiretroviral therapy, dyslipidemia, lipid-lowering drugs

In HIV-infected individuals, important metabolic changes, such as hyperlipidemia, insulin resistance, impaired glucose tolerance, type II diabetes, and visceral and body fat deposition, have been increasingly noted following the introduction of antiretroviral therapy (ART).^{1–4} Results from the prospective multinational cohort study of Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) indicate that exposure to ART increases the relative risk of myocardial infarction (MI). For every year an individual was exposed to ART, the

risk of MI rose by 26% (95% CI 12%–41%).⁵ These findings were confirmed in an additional prospective cohort study.⁶ More recent evidence from the

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D:A:D study indicated that the relative risk of MI has decreased over calendar time to 1.16 (95% CI 1.09–1.23), an effect explained by recent lipid levels.⁷ This same study found that increased exposure to protease inhibitors (PIs) is associated with increased risk of MI (relative risk [RR] 1.10, 95% CI 1.03–1.17) after adjusting for lipid levels (RR for total cholesterol 1.24/mmol/L, 95% CI 1.14–1.34).⁷ Although the absolute increase in risk of MI is small in these relatively young individuals, the management of risk factors for coronary heart disease (CHD) is becoming increasingly important due to the prolonged survival and aging of HIV-infected ART recipients.

There exists very little surveillance data on interventions to reduce the risk of CHD in HIV populations receiving ART.⁸ In the Swiss HIV Cohort Study (SHCS), many individuals are at elevated risk of CHD; of males aged ≥ 40 years, 33.5% and 7.3% have a 10%–20% and $>20\%$ risk, respectively, of CHD in 10 years according to the Framingham risk profile. The corresponding figures for females aged ≥ 40 years are 4.3% and 0.5%.^{9,10}

The goal of this study is to identify predictors for control of dyslipidemia in HIV-infected ART recipients with hypercholesterolemia requiring antilipidemic drug treatment based on Swiss guidelines for the management of dyslipidemia.¹¹

METHOD

Study Population and Definitions

The SHCS is a prospective cohort study with continuing enrollment of HIV-infected individuals aged 16 years or older. Visits take place every 6 months at seven outpatient clinics from participating HIV centers, associated hospitals, or specialized private practices. On April 1, 2000, a cardiovascular risk factor (CVRF) questionnaire was introduced into the SHCS with questions about risk factors and diagnosis of cardiovascular events. The study population consists of all individuals registered before February 1, 2006, who were classified as having dyslipidemia.

Patients were identified as having dyslipidemia if they had two consecutive measurements of total cholesterol (TC) above the thresholds set by Swiss guidelines for drug treatment with antilipidemic drugs. The date of the second elevated TC was then defined as the baseline visit. Swiss guidelines

define cutoffs for drug treatment of dyslipidemia in the context of an individual's overall 10-year risk for CHD as well as additional risk factors for CHD (Table 1). The Swiss guidelines are based on the Framingham risk score but are adapted to the Swiss epidemiological situation that consists of higher population mean value of total cholesterol but a lower incidence of CHD in comparison to the Caucasian US population. For evaluation of the endpoint, the risk category for an individual was determined at the baseline visit and considered to be fixed during follow-up. This was done to protect against changes in risk factors that would have a large impact on the endpoint evaluation but not on total cholesterol itself. For example, if a patient quit smoking, this could lower their risk category and correspondingly lower the treatment goals for TC. They would then have a higher chance of reaching treatment goals without actually having lowered their cholesterol, which is the primary interest of the study.

Individuals classified as having dyslipidemia were further selected for the analysis based on the following criteria: (a) on potent ART for a minimum of 3 months at baseline, (b) not receiving lipid-lowering medication at baseline, and (c) had at least two additional cohort visits after baseline.

Explanatory Variables

A comprehensive list of available explanatory variables thought to influence an individual's ability to reach treatment goals for TC was selected a priori for inclusion in the analysis. Laboratory data were measured within 30 days of the cohort visit. Explanatory variables that were measured at the baseline visit and treated as fixed covariates were as follows: age, gender, obesity (body mass index [BMI] > 30 kg/m²), current or past intravenous (IV) drug use, education (<9 years, ≥ 9 years), CD4 cell count (<200 , 200–349, 350–499, ≥ 500 per 10⁹/L), experience of physician (years of experience working with the SHCS at the time of the patient's baseline visit), baseline TC, diabetes, history of CHD, current ART regimen (PI only, non-nucleoside reverse transcriptase inhibitor [NNRTI] only, PI/NNRTI, triple nucleoside), and cumulative exposure to ART regimens (PI only, NNRTI only, PI/NNRTI). Variables measuring cumulative exposure to ART were categorized according to their sample distributions. Whether an individual switched their ART

Table 1. Total cholesterol and LDL-cholesterol goals and levels at which to initiate therapy

Risk category	Swiss guidelines ^{11a}	Total cholesterol mmol/L (mg/dL)	NCEP ATP III guidelines ^{12b}	
	Risk category definition		Risk category definition	LDL-cholesterol mmol/L (mg/dL)
High	CHD OR CHD risk equivalents or diabetes	>5.0 (>193)	CHD OR CHD risk equivalents (10-yr risk >20%)	≥3.36 (≥130)
Moderate	≥1 risk factor ^a (men or women after menopause)	>6.5 (>251)	≥2 risk factors ^a , and 10-year risk 10%–20%	≥3.36 (≥130)
	OR ≥2 risk factor (women before menopause)		≥2 risk factors ^a , and 10-year risk <10%	≥4.14 (≥160)
Low	0 risk factor ^a (men or women after menopause) OR 0–1 risk factor (women before menopause)	>8.0 (>309)	0–1 risk factor ^a	≥4.91 (≥190)

Note: LDL = low-density lipoprotein; NCEP ATP III = Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults; CHD = coronary heart disease.

^aRisk factors according to Swiss guidelines are smoking, hypertension (≥140/90 mm Hg or ≥135/85 in diabetics), family history of CHD (first-degree relative, male <55 years, female <65 years), age (males >50, females >60 years), obesity (BMI >30 kg/m²), and fasting triglycerides >2.0 mmol/L.

^bRisk factors according to NCEP ATP III guidelines are smoking, hypertension (≥140/90 mm Hg), family history of CHD (first-degree relative, male <55 years, female <65 years), age (males ≥45, females ≥55 years), and HDL-cholesterol <1.03 mmol/L (40 mg/dL).

regimen while viral load was undetectable (HIV-1 RNA <50 copies/mL), time on ART regimens since baseline (PI only, NNRTI only, and PI/NNRTI regimens), and time on lipid-lowering medication since baseline were treated as time-dependent covariates and were evaluated at each follow-up visit.

Statistical Analyses

A time-to-event analysis was performed using a Cox proportional hazards model to study the effects of explanatory variables on the event incidence. Events were defined as reaching treatment goals for TC. Treatment goals for TC were defined according to Swiss guidelines published during the time period of the study (Table 1). Events required confirmation by a second consecutive measurement meeting treatment goals. The event date was the first date treatment goals were achieved. For individuals who did not experience an event, follow-up was considered censored at February 1, 2006, or

date of loss to follow-up or death. The association between explanatory variables and achieving treatment goal for TC was assessed by using hazard ratios and 95% confidence intervals; hazard ratios above 1 indicate a covariate is positively associated with the event probability. All analyses were done with SAS 9.1 (SAS Institute, Cary, North Carolina, USA) and S-plus 6.0 (Insightful Corporation, Seattle, Washington, USA).

Sensitivity Analysis

As opposed to the Swiss guidelines that consider TC, the Third Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) bases its recommendations for cutpoints at which to consider lipid-lowering medication on LDL-cholesterol.¹² Because the SHCS does not require blood to be drawn in the fasting state, very few patients have evaluable LDL

values, as calculated by Friedewald's equation.¹³ However, it was of interest to consider the consistency of our findings across guidelines and lipid measurements. Therefore, as a sensitivity analysis, we repeated our primary analysis using treatment goals for LDL-cholesterol based on NCEP ATP III guidelines (Table 1).

RESULTS

In total, 8,033 patients were registered in the SHCS, completed at least one CVRF questionnaire, and had corresponding lab data between April 1, 2000, and February 1, 2006. During the study period, 1,504 (18.7%) individuals were classified as having dyslipidemia. Of these, 1,201 were currently on ART for a minimum of 3 months and had at least two additional follow-up visits. Of these, 243 were excluded because they were pretreated ($n = 35$) with or were currently on lipid-lowering medication at baseline. A total of 958 patients over 4,167 visits were included in the analysis. The total prospective follow-up until the event date or until the censoring date for those without an event was 2,465 person-years, with a median individual follow-up time of 2.3 years (interquartile range [IQR], 1.2–4.0). The median number of follow-up visits after baseline was 8 (range, 3–12).

Baseline characteristics of all registered patients, those with dyslipidemia and those included in the analysis, are summarized in Table 2. Twenty-eight percent of patients started lipid-lowering medication after the baseline visit. A total of 454 patients (47.4%) achieved treatment goals for TC.

Swiss guidelines categorize individuals into risk categories (low, moderate, and high) for CHD and determine cutoffs for antilipidemic drug treatment based on the overall risk (Table 1). An individual's risk category was evaluated at baseline and was considered fixed during the follow-up period. Over the course of the follow-up period, 138 individuals (14.4%) had changes in their baseline risk category; 53.9% of these changes were from moderate to high, 42.6% from moderate to low, and 3.6% from low to moderate.

Forty-nine percent of patients changed their ART regimen after the first elevated average TC. Of the 987 regimen changes made, 7.2% were a change from a PI-based regimen to an NNRTI-based regimen, 2.0% from a PI-based regimen to a triple nucleoside regimen, 12.1% to a regimen with abacavir

(2.5% of these were a switch from a regimen with stavudine), and 3.7% from lopinavir to atazanavir. Although we lack information for the exact reason for switching ART, 64.0% of regimen changes were made without evidence of treatment failure (HIV-1 RNA viral load <50 copies/mL). Ninety patients (9.4%) stopped at least one drug during the follow-up period due to elevated cardiovascular risk. After July 2003 when more specific reasons for stopping drugs were made available, 92.3% of drugs were stopped specifically for dyslipidemia, 3.9% for cardiovascular disease, and 3.9% for diabetes.

In unadjusted analyses, older age, male sex, baseline CD4 cell count ≥ 500 cells per 10^9 /L (compared to <200 cells per 10^9 /L), higher baseline TC, diabetes, longer time on NNRTI-only regimen, longer time on PI/NNRTI regimen, and longer time on lipid-lowering medication were associated with a lower hazard, whereas being cared for by a physician with more years of experience and switching ART while viral load was undetectable were associated with a higher hazard of reaching TC treatment goals (Table 3). Basic education, IV drug use, obesity, baseline ART regimen, baseline cumulative exposure to ART regimens (PI only, NNRTI only, PI/NNRTI), and time on PI regimen were not significantly associated with reaching TC treatment goals.

In adjusted analyses, variables significantly associated with a lower hazard of reaching TC treatment goals were as follows: older age (compared to 18–37 year olds: HR 0.62 for 45–52 year olds, 95% CI 0.47–0.82; HR 0.40 for 53–85, 95% CI 0.29–0.54), diabetes (HR 0.39, 95% CI 0.26–0.59), history of CHD (HR 0.27, 95% CI 0.10–0.71), higher baseline TC (HR 0.78, 95% CI 0.71–0.85), baseline triple nucleoside regimen (HR 0.12 compared to PI-only regimen, 95% CI 0.07–0.21), longer time on PI-only regimen (HR 0.39, 95% CI 0.33–0.46), longer time on NNRTI-only regimen (HR 0.35, 95% CI 0.29–0.43), and longer time on PI/NNRTI regimen (HR 0.34, 95% CI 0.26–0.43) (Table 3). Although increasing exposure since baseline to all three types of ART regimens (PI only, NNRTI only, and PI/NNRTI) was significantly associated with less occurrence of a TC event (reaching treatment goals for TC), baseline cumulative exposure to these regimens was not significantly associated with a TC event. Switching ART regimen while viral load was undetectable was associated with a higher hazard of reaching TC treatment goals (HR 1.48, 95% CI 1.14–1.91).

Table 2. Baseline characteristics of individuals included in the analysis

Characteristics	All registered patients	Individuals with dyslipidemia	Eligible patients
Total, <i>n</i> (%)	8,033	1,504	958
Median age, years (IQR)	38 (33–44)	45 (38–53)	44.5 (38–53)
Male gender, %	69.1	83.8	84.5
Basic education, ^a %	28.3	17.6	17.4
Ethnic, ^b %	16.3	7.9	7.2
HIV transmission category, %			
Homosexual	34.1	48.3	48.5
Heterosexual	37.6	36.5	36.2
IV drug	24.6	11.0	11.2
Other or unknown	3.8	4.3	4.1
Past or present IV drug use, %	26.7	11.7	11.7
Previous AIDS diagnosis, %	21.7	29.3	32.3
CD4 count, cells per 10 ⁹ /L			
Median (IQR)	391 (233.5–583)	406 (242–595)	465 (302–670)
<200	20.1%	19.0%	10.4%
200–349	23.3%	21.3%	21.7%
350–499	21.9%	23.4%	22.7%
≥500	34.7%	36.3%	45.2%
Median log plasma HIV RNA, copies/mL (IQR)	2.5 (0–4.3)	1.6 (0–3.4)	0 (0–1.8)
Current regimen, %			
PI only (no NNRTI)	35.9	50.0	51.9
NNRTI only (no PI)	14.0	14.8	23.4
PI/NNRTI	4.9	11.6	19.1
Triple nucleoside	45.3	23.7	5.6
Median cumulative exposure, years			
PI only (IQR)	2.3 (1.0–3.3)	2.7 (1.5–3.5)	3.0 (1.7–4.2)
NNRTI only (IQR)	0.6 (0.3–1.2)	0.7 (0.4–1.2)	1.2 (0.6–2.0)
PI/NNRTI (IQR)	0.8 (0.3–1.4)	0.8 (0.3–1.4)	1.1 (0.6–2.0)
Median BMI, kg/m ² (IQR)	22.5 (20.6–24.9)	23.4 (21.5–25.8)	23.7 (21.7–26.3)
High blood pressure, ^c %	25.7	39.4	42.2
Smokers, %	57.0	54.4	49.5
Diabetes mellitus, %	3.7	11.2	9.7
Prior history of CHD, %	0.7	2.6	1.2
Median total cholesterol, mmol/L (IQR)	4.8 (4.0–5.8)	6.4 (5.5–7.3)	7.0 (6.6–7.8)
Median triglycerides, mmol/L (IQR)	1.6 (1.1–2.5)	2.7 (1.7–4.1)	3.1 (2.1–4.9)
Median HDL, mmol/L (IQR)	1.2 (0.9–1.4)	1.1 (0.9–1.4)	1.2 (1.0–1.4)
Median LDL, mmol/L (IQR)	2.7 (2.1–3.5)	3.7 (3.0–4.5)	3.8 (3.0–4.5)
Framingham 10-year risk of CHD ^d			
Low (<10%)	82.3	49.7	39.0
Moderate (10%–20%)	14.8	37.9	45.3
High (>20%)	2.9	12.5	15.8
Risk category for treatment of dyslipidemia (Swiss guidelines)			
Low	29.0	5.9	1.0
Moderate	63.6	68.4	57.8
High	7.5	25.7	41.1
Years experience of physician in the SHCS, median (IQR)	1.8 (0.5–8.6)	1.9 (0.5–8.7)	1.9 (0.5–9.0)

Note: BMI = body mass index; CHD = coronary heart disease; PI = protease inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitor; IQR = interquartile range; SHCS = Swiss HIV Cohort Study.

^aNine years of mandatory schooling or less.

^bOf any origin that is not Caucasian.

^cHigh blood pressure is defined as ≥140/90 mm Hg or ≥135/85 in diabetics.

^dCalculated using the Framingham Point Scores as outlined in the NCEP ATP III guidelines.¹²

Table 3. Association of baseline characteristics and time-dependent covariates with the rate of occurrence of normalization of total cholesterol using a Cox proportional hazards model^{a*}

	Patients <i>n</i>	Events <i>n</i> (%)	Unadjusted model		Adjusted model	
			Relative hazard (95% CI)	<i>p</i>	Relative hazard (95% CI)	<i>p</i>
Age in years						
18–37	215	122 (57)	Reference		Reference	
38–44	264	146 (55)	0.94 (0.74–1.20)	.61	1.06 (0.82–1.38)	.66
45–52	239	99 (41)	0.62 (0.48–0.81)	<.001	0.62 (0.47–0.82)	<.001
53–85	240	87 (36)	0.48 (0.37–0.64)	<.001	0.40 (0.29–0.54)	<.001
Gender						
Female	149	79 (53)	Reference		Reference	
Male	809	375 (46)	0.76 (0.60–0.97)	.03	0.81 (0.62–1.06)	.13
Basic education ^b	160	63 (39)	0.84 (0.64–1.10)	.20	0.79 (0.60–1.05)	.11
IV drug use (current or past)	112	53 (47)	1.02 (0.77–1.36)	.88	0.80 (0.58–1.10)	.17
BMI >30 kg/m ²	75	31 (41)	0.85 (0.59–1.22)	.38	1.06 (0.73–1.53)	.76
CD4 cell count, cells per 10 ⁶ /L						
<200	99	34 (34)	Reference		Reference	
200–349	207	94 (45)	1.14 (0.79–1.64)	0.48	1.03 (0.71–1.50)	.88
350–499	217	101 (47)	1.29 (0.90–1.84)	0.17	1.08 (0.74–1.56)	.69
≥500	432	224 (52)	1.35 (0.97–1.88)	0.07	1.09 (0.77–1.54)	.62
Baseline total cholesterol (mmol/L)			0.89 (0.83–0.96)	0.003	0.78 (0.71–0.86)	<.001
Diabetes	93	27 (29.0)	0.41 (0.28–0.61)	<0.001	0.39 (0.26–0.59)	<.001
Prior history of CHD	11	5 (45.5)	0.75 (0.31–1.81)	0.52	0.27 (0.10–0.71)	.008
Years experience of physician (on log scale)			1.38 (1.05–1.81)	0.02	1.13 (0.83–1.52)	.344
Baseline ART regimen						
PI only	497	249 (50)	Reference		Reference	
NNRTI only	224	100 (45)	0.86 (0.68–1.09)	0.21	1.15 (0.67–1.97)	.62
PI/NNRTI	183	85 (46)	0.87 (0.68–1.12)	0.28	1.14 (0.64–2.02)	.66
Triple nucleoside	54	20 (37)	0.81 (0.52–1.28)	0.37	0.12 (0.07–0.21)	<.001
Switched ART when viral load was undetectable ^c			1.35 (1.05–1.72)	0.02	1.48 (1.14–1.91)	.003
Baseline cumulative exposure to PI						
None	108	48 (44)	Reference		Reference	
≤3 years	425	194 (46)	1.04 (0.76–1.42)	0.83	1.00 (0.71–1.42)	.99
>3 years	425	212 (50)	1.11 (0.81–1.52)	0.50	1.13 (0.77–1.65)	.53
Baseline cumulative exposure to NNRTI						
None	664	327 (49)	Reference		Reference	
≤1.2 years	150	61 (41)	0.78 (0.61–1.05)	0.10	0.88 (0.59–1.29)	.50
>1.2 years	144	66 (46)	0.95 (0.73–1.24)	0.72	0.93 (0.57–1.53)	.79
Baseline cumulative exposure to PI and NNRTI						
None	723	348 (48)	Reference		Reference	
None	119	49 (41)	0.81 (0.60–1.09)	0.16	1.12 (0.72–1.74)	.61
≤1.1 years	116	57 (49)	0.99 (0.75–1.31)	0.93	1.22 (0.72–2.06)	.46
>1.1 years						
Time on PI only since baseline (years)			0.95 (0.86–1.06)	0.33	0.39 (0.33–0.46)	<.001
Time on NNRTI only since baseline (years)			0.79 (0.69–0.89)	<0.001	0.35 (0.29–0.43)	<.001
Time on PI/ NNRTI since baseline (years)			0.83 (0.72–0.96)	0.01	0.34 (0.26–0.43)	<.001
Time on lipid-lowering medication since baseline (years)			0.81 (0.67–0.98)	0.03	1.11 (0.90–1.38)	.32

Note: BMI = body mass index; IV = intravenous; CHD = coronary heart disease; ART = antiretroviral therapy; PI = protease inhibitors; NNRTI = non-nucleoside reverse transcriptase inhibitor.

^aNormalization of total cholesterol is defined as having two consecutive visits below thresholds recommended by Swiss guidelines (Table 1).

^bNine years of mandatory schooling or less.

^cUndetectable viral load = HIV-1 RNA < 50 copies/mL.

In the sensitivity analysis, only 175 of the 958 patients (18.3%) had calculated LDL values in the fasting state, met all entry criteria, and were included in the analysis. A total of 71 patients (40.6%) achieved treatment goals for LDL-cholesterol based on NCEP ATP III guidelines (Table 1). The adjusted Cox model yielded almost identical results to the primary analysis with TC events as the endpoint (data not shown). In this analysis, male sex and baseline LDL values were not significantly associated with achieving LDL treatment goals. Baseline exposure to PI/NNRTI regimens of 1.1 years or less was associated with a lower hazard for reaching LDL treatment goals (HR 0.05 compared to no baseline exposure, 95% CI 0.01–0.52).

DISCUSSION

In this ecological study, we explored factors influencing the management of hypercholesterolemia in ART recipients meeting Swiss guidelines for the treatment of dyslipidemia. Overall roughly 50% of individuals achieved TC treatment goals. We identified several important predictors that were associated with a lower achievement of TC goals: older age, diabetes, history of CHD, baseline TC, triple nucleoside regimen at baseline, and time on ART (PI only, NNRTI only, and PI/NNRTI) since baseline. Older individuals, diabetics, and persons with a history of CHD are at higher risk for CHD, and the lower probability of these individuals to regulate TC most likely reflects an unfavorable constellation. Persons on a triple nucleoside regimen at baseline were already on ART with an unfavorable lipid profile and therefore might have had a more difficult time lowering their TC than individuals on a PI-only regimen. It was not the length of pretreatment with ART (measured by cumulative exposure to ART at baseline) but length of treatment with ART after being classified as having dyslipidemia that made it more difficult to achieve TC treatment goals. Individuals who changed their ART regimen despite having an undetectable viral load were 1.5 times more likely to achieve treatment goals. There was some suggestion that more experienced physicians were better able to control dyslipidemia in their patients, but this was not an independent predictor of treatment success.

Remarkably, we found no association between the time on lipid-lowering medication and the probability to achieve TC treatment goals. In the

SHCS, specific data are not collected that might help explain this finding, such as the type and dose of lipid-lowering drugs used by treating physicians or a patient's adherence to antilipidemic medication. Suboptimal dosing of lipid-lowering drugs due to potential drug interactions could be a reason for our findings. Only 28% of patients were taking lipid-lowering medication but 49% made changes to their ART regimen over the study period, at least 25% to regimens with a better cardiovascular profile. As a majority of these changes to ART were made without evidence of virologic failure and those making changes were more likely to achieve TC treatment goals, these findings may indicate that physicians are initially attempting to control dyslipidemia through regimen changes.

To our knowledge, this is the first large cohort study to address the issue of treatment of dyslipidemia in HIV-infected individuals on ART and at moderate-to-high risk of CHD. This study follows a large number of individuals for 6 years with a median number of eight evaluations per individual, allowing us to explore management of dyslipidemia over time and ART regimens by class. Lack of fasting lab values resulted in a small sample of patients who could be evaluated for dyslipidemia using LDL-cholesterol values. However, results of the sensitivity analysis were very similar to the primary analysis, suggesting our results are robust to type of lipid measurement and guidelines utilized to evaluate the management of dyslipidemia.

However, this study has several limitations. First, as this is not an intervention study, we only have access to data regularly collected by the SHCS as part of the D:A:D study protocol. The SHCS does not collect information as to nonpharmacological interventions, if any, physicians recommend for CVRF management, such as diet or regular exercise. In addition, the SHCS does not collect data on the type and dose of cholesterol-lowering drugs that are taken, which makes it difficult to interpret some of our findings. We also have limited information on whether ART regimens were changed specifically in response to dyslipidemia. So although persons changing regimens with an undetectable viral load were more likely to normalize their TC, it is difficult to attribute success or failure of therapy to any particular strategy. Second, the study population included in this analysis is a very specific selection of SHCS patients. They were more likely to be at moderate-to-high risk for CHD and therefore were

more often older, male, smokers, hypertensive, and diabetics. They were more often on PIs or NNRTIs, longer on ART, had good control of HIV-plasma viral load, and sufficient control visits (Table 2). This population is not representative of all HIV-infected individuals in the SHCS or elsewhere, however it does represent those ART recipients who should be targeted for CHD risk factor management. Our findings should be repeated in larger more diverse populations.

Only 28% of individuals with TC values above thresholds recommended for treatment began taking lipid-lowering therapy; less than 50% were able to reach therapeutic goals. These numbers are similar to those found in the non-HIV population.¹⁴ At the present stage, we have to speculate about the reasons for the insufficient control of dyslipidemia despite effective medications being available. There is a large body of evidence indicating that statins lower clinical endpoints in non-HIV-infected populations¹⁵ and clinically relevant cardiovascular surrogate endpoints in HIV-infected persons.¹⁶ However, there is some evidence of drug-drug interactions between statins and ART. One study of HIV-negative volunteers treated with boosted saquinavir found that the area under the curve (AUC) was increased by 3059% for simvastatin, increased by 79% for atorvastatin, and decreased by 50% for pravastatin.¹⁷ Thus, physicians may be hesitant to use statins despite evidence from a recent small four-arm trial that suggests that using pravastatin and bezafibrate in patients receiving PIs is more effective in lowering TC than switching to NNRTIs.¹⁸ There may be other plausible reasons for not treating dyslipidemia in ART recipients, such as limited life expectancy from HIV infection, liver toxicity from antilipidemic drugs, especially in those coinfecting with HCV, or fear to increase pill burden and endanger adherence to ART.

In conclusion, management and control of dyslipidemia in HIV-infected individuals in the SHCS is insufficient. The low percentage of lab values collected in the fasting state is indicative of the lack of emphasis placed on the cardiovascular health of these patients. More aggressive treatment of risk factors of CHD is indicated and enhanced counseling of HIV-infected patients is needed.¹⁹ For example, over 50% of patients in the SHCS are smokers. If half of them would quit smoking, the expected risk of 10-year CHD events would drop by 25% and reduce the risk of smoking-related cancer. Interdis-

ciplinary approaches are needed for HIV-infected patients receiving ART and at high risk for a CHD event with support from preventive cardiologists, internists, and nurse specialists with broad skills for counseling and management of risk factors for CHD. Such approaches should be evaluated by clinical trials focusing on multifactorial interventions and optimized ART regimens with favorable metabolic profiles. Cohort studies should expand the collection of specific data, such as types of lipid-lowering and antihypertensive drugs and more precise information on reasons for stopping and changing ART regimens.

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