Low-Density Lipoprotein Cholesterol Levels and Statin Treatment by HIV Status Among Multicenter AIDS Cohort Study Men

Anne K. Monroe,¹ Wei Fu,² Michelle N. Zikusoka,³ Lisa P. Jacobson,² Mallory D. Witt,⁴
Frank J. Palella,⁵ Lawrence A. Kingsley,⁶ Wendy S. Post,^{2,3} and Todd T. Brown⁷

Abstract

Treating cardiovascular disease (CVD) risk factors, including dyslipidemia, is important in HIV care. Low-density lipoprotein cholesterol (LDL-c) target achievement is a readily available benchmark for dyslipidemia control, although use of this target is not uniformly endorsed by professional societies. We examined whether HIV serostatus is associated with not achieving LDL-c target. Among Multicenter AIDS Cohort Study (MACS) participants completing visit 56 (10/1/2011–3/31/2012), we categorized each man as on or off statin therapy and used NCEP ATP III guidelines to determine if each man was at LDL-c target or not at target. We compared proportions of men not at target and determined predictors using multivariate logistic regression. Sixty of 543 (11.1%) HIV-infected men and 87 of 585 (14.9%) HIV-uninfected men not receiving statin therapy were not at target ($p=0.07$), while 31 of 230 (13.5%) HIV-infected and 29 of 204 (14.2%) HIV-uninfected men receiving statin therapy were not at target ($p=0.82$). Factors associated with not being at target (among men not receiving statin therapy) included current smoking (OR=2.31, 95% CI 1.31, 4.06) and a diagnosis of hypertension (OR=4.69, 95% CI 2.68, 8.21). Factors associated with not being at target (among men receiving statin therapy) included current smoking (OR=2.72, 95% CI 1.30, 5.67) and diabetes (OR=5.31, 95% CI 2.47, 11.42). HIV-infected and HIV-uninfected men receiving statin therapy demonstrated similar nonachievement of LDL-c targets. Comorbidities (e.g., diabetes) lowered targets and may explain why goals were less likely to be met.

Introduction

SINCE THE INTRODUCTION of antiretroviral therapy (ART), HIV-infected individuals have experienced a dramatic decline in AIDS-related mortality, but increasing morbidity and mortality from other non-AIDS conditions such as cardiovascular disease (CVD).^{1–4} Increased CVD events have been observed among HIV-infected patients,^{5–8} and several large cohorts have revealed CVD-related mortality as a major cause of death among HIV-infected patients.^{9,10} Many factors might contribute to CVD in HIV-infected patients including effects of HIV infection (inflammation, hypercoagulability, endothelial dysfunction, immune activation),

effects of ART, lifestyle risk factors including higher smoking rates, and other chronic medical comorbidities such as hypertension (HTN), diabetes (DM), and dyslipidemia, which are common in HIV-infected patients.^{11–13} Furthermore, DM, HTN, and dyslipidemia are frequently not well controlled in HIV-infected patients.¹⁴ Although suboptimal cardiovascular risk factor control is also observed in HIV-uninfected populations, the implications of these findings may be more serious in HIV-infected patients given their overall increased CVD risk.

The hallmark of CVD prevention in the general population as well as HIV-infected patients has been the identification and control of risk factors including DM, HTN, and dyslipidemia,

¹Division of General Internal Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland.

²Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland.

³Division of Cardiology, Johns Hopkins University School of Medicine, Baltimore, Maryland.

⁴Division of HIV Medicine, Harbor UCLA Medical Center, Torrance, California.

⁵Division of Infectious Diseases, Feinberg School of Medicine of Northwestern University, Chicago, Illinois.

⁶Department of Infectious Diseases and Microbiology, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania.

⁷Division of Endocrinology, Diabetes & Metabolism, Johns Hopkins University School of Medicine, Baltimore, Maryland.

as well as the encouragement of tobacco use cessation. Interventions include lifestyle modification and pharmacological therapy. Until recently, clinicians frequently followed the recommendations of the National Cholesterol Education Program Adult Treatment Plan III (NCEP ATP III),¹⁵ updated in 2004.¹⁶ These guidelines assess the appropriate timing of interventions, including lifestyle modification and the initiation of pharmacological therapies, based on a patient lipid profile and 10-year risk for coronary heart disease (CHD) events using Framingham risk score calculation.¹⁷

The mainstay of pharmacological lipid control is used of statin drug therapy, with a focus on low-density lipoprotein cholesterol (LDL-c). The implementation of statin therapy has greatly reduced CVD-associated mortality.¹⁸ Despite the presence of data supportive of the benefits of statin therapy, observational studies have noted the undertreatment of persons with elevated LDL-c.^{19,20} Recently, the American College of Cardiology/American Heart Association (ACC/AHA) released new cholesterol treatment guidelines aimed at reducing CVD risk that removed LDL-c targets and recommended moderate- or high-intensity statin treatment for patients with elevated CVD risk [patients with CVD or diabetes, LDL-c ≥ 190 mg/dl (4.91 mmol/liter), or estimated 10-year CVD risk $\geq 7.5\%$].²¹ However, other groups, such the American Association of Clinical Endocrinologists, continue to endorse LDL-c target attainment^{22,23} and clinicians may still believe that these targets are relevant, particularly in their high-risk patients.

Our primary objective in the current analysis was to determine whether HIV-infected men were less likely than HIV-uninfected men to receive treatment with lipid-lowering therapy according to national guidelines recommendations (which were NCEP ATP III guidelines at the time the analysis was conducted). Prior work has shown that HIV-infected men may be undertreated for their CVD risk factors.^{24,25} With multiple competing comorbidities and polypharmacy among HIV-infected men, potentially affecting prescribing patterns and/or medication adherence, we hypothesized that HIV-infected men would be less aggressively treated, and would be less likely to take indicated treatment or meet targets for dyslipidemia compared with HIV-uninfected men.

Materials and Methods

We used cross-sectional data from participants in the Multicenter AIDS Cohort Study (MACS) to determine the proportion of men in the MACS not achieving their LDL-c target, comparing HIV-infected with HIV-uninfected men.

Study population

The MACS was initiated in 1984 as a study of men who have sex with men conducted at four study sites in Baltimore/Washington, DC, Chicago, Los Angeles, and Pittsburgh. A total of 6,973 men were enrolled during four time periods: 1,813 HIV-infected and 3,141 HIV-uninfected men in 1984–1985, 425 HIV-infected and 243 HIV-uninfected men in 1987–1990, 705 HIV-infected and 646 HIV-uninfected men, primarily minorities, in 2001–2003, and 21 HIV-infected and 29 HIV-uninfected men in 2010 (enrollment ongoing). Participants undergo semiannual study visits consisting of a detailed interview, physical examination, and collection of biological specimens. Details of the study design and methods have been published.²⁶ The protocol was approved by In-

stitutional Review Boards at each site and each study participant signed an informed consent.

Men who completed Visit 56 (10/1/2011–3/31/2012) were eligible for inclusion. Men receiving statin therapy at Visit 56 were excluded if they had been receiving statin therapy at the time of MACS enrollment. Men were excluded if more than 2 years lapsed between the visit prior to statin therapy initiation and the statin therapy initiation visit because in these situations we were unable to determine an accurate treatment goal (clinical data were outdated). At the time of Visit 56, 22% of the HIV-infected and 21% of the HIV-uninfected men from the 1984 cohort, 21% of the HIV-infected and 13% of the HIV-uninfected men from the 1987 cohort, and 64% of the HIV-infected and 47% of the HIV-uninfected men from the 2001 cohort participated.

Outcomes

The main outcome measure was whether each participant attained his LDL-c target. Total cholesterol and high-density lipoprotein cholesterol (HDL-c) were measured from all fasting and nonfasting blood draw samples. LDL-c was calculated from fasting blood draw samples with triglycerides < 400 mg/dl using the Friedewald equation.²⁷ LDL-c was directly measured on fasting blood draw samples with triglycerides ≥ 400 mg/dl and on all nonfasting blood draw samples. Lipid testing was performed at the Heinz Nutrition Laboratory at the University of Pittsburgh.^{28–30}

We started by categorizing each man as either receiving or not receiving statin therapy. This was determined by participant self-report at Visit 56.

For men not receiving statin therapy at Visit 56, we next utilized the NCEP ATP III guidelines to establish an LDL-c level for appropriate initiation of lipid-lowering intervention as well as appropriate LDL-c target for each participant (Appendix A). We categorized each man as (1) not on statin therapy, not at LDL-c target or (2) not on statin therapy, at LDL-c target. We compared percentages of men not receiving statin therapy and not at LDL-c target by HIV serostatus using chi-square testing.

For men receiving statin therapy at Visit 56, a similar process was undertaken (Appendix B). We categorized each man as (1) on statin therapy, not at LDL-c target or (2) on statin therapy, at LDL-c target. Additionally, we examined whether men who had initiated therapy met the criteria for statin therapy based on ATP III guidelines: we examined their risk factors and LDL-c level at the visit prior to starting statin therapy and determined whether therapy would have been indicated using ATP III.

Measures of interest

Covariates included in the analysis included race, body mass index (BMI), smoking (self-reported), medical insurance coverage and insurance coverage for medications (self-reported), statin potency (for men receiving statin therapy), hepatitis C coinfection (laboratory values consistent with chronic hepatitis C) at Visits 54–56, and elevated aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels. Insurance coverage was defined as “not having insurance” by a negative response to either or both of the following questions at the Visit 56 interview: “Since your last visit, have you had any medical coverage, such as HMO

coverage, Blue Cross, or Medicare?" and "Since your last visit, have you received assistance from ADAP or Ryan White?" Insurance coverage for medications was defined as "not having coverage" by a negative response to the question, "Since your last visit, did you have insurance coverage that pays for any of your medications?" Statin potency was defined as "high potency" for participants on atorvastatin, rosuvastatin, or simvastatin at Visit 56. Elevated AST or ALT levels was defined as having an AST or ALT > 80 IU/liter at a visit up to 1 year prior to Visit 56 [more than two times the upper limit of normal (ULN)].

Statistical analysis

We compared demographic and clinical characteristics of HIV-infected and HIV-uninfected participants, using chi-

square tests to compare counts and prevalence measurements. To compare continuous variables, we used the two sample *t*-test or Wilcoxon rank sum test depending on the distribution of the variables.

We constructed four separate multiple logistic regression models as follows: (1) for all men not receiving statin therapy, (2) for HIV-infected men not receiving statin therapy, (3) for all men receiving statin therapy, and (4) for HIV-infected men receiving statin therapy. Models including all men were adjusted for HIV serostatus. All models were adjusted for age, race, and BMI. Models including only HIV-infected men also included as predictor variables CD4⁺ T lymphocyte cell count (CD4, greater or less than 200 cells/mm³) and plasma HIV RNA levels (greater or less than 50 copies/ml). Models for men receiving statins were adjusted for statin potency. Finally, all multivariate models included covariates that had

TABLE 1. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MEN NOT RECEIVING STATIN THERAPY (N=1,128)

	N included	HIV ⁺ (N=543) N (%) or median (IQR)	HIV ⁻ (N=585) N (%) or median (IQR)	p value
Age (years)	1,128	51 (45, 57)	56 (49, 62)	<0.0001
Body mass index (kg/m ²)				
<25	1,128	218 (40.1)	207(35.4)	0.16
25–30		154 (28.4)	193 (33.0)	
>30		171 (31.5)	185 (31.6)	
Race				
White	1,128	238 (43.8)	403 (68.9)	<0.0001
Black		204 (37.6)	120 (20.5)	
Hispanic/other		101 (18.6)	62 (10.6)	
Smoking at index visit				
Never	1,126	129 (23.8)	154 (26.4)	0.0003
Former		230 (42.4)	296 (50.7)	
Current		183 (33.8)	134 (22.9)	
HDL cholesterol (mg/dl)	1,115	46 (38, 55)	50 (42, 59)	<0.0001
LDL cholesterol current (mg/dl)	1,128	105 (83,127)	116 (96, 138)	<0.0001
CD4 ⁺ T cell count (cells/ μ l)	542	564 (416, 750)	—	—
Median (IQR) HIV RNA (men with detectable virus)	133	1160 (211, 32,700)	—	—
Chronic HCV	1,106	64 (12.0)	31 (5.4)	<0.0001
AST and/or ALT > 80 U/liter	1,128	34 (6.3)	11 (1.9)	0.0002
No medical insurance	1,128	23 (4.2)	97 (16.6)	<0.0001
No insurance coverage for medications	1,128	82 (15.1)	97 (16.6)	0.50
Diabetes	850	51 (13.1)	38 (8.3)	0.02
Hypertension	1,113	235 (43.7)	232 (40.3)	0.26
Family history of premature CHD	1,128	0 (0)	0 (0)	
Framingham risk score, Visit 56				
Low (<10%)	983	290 (62.1)	294 (57)	0.26
Medium (10–20%)		160 (34.3)	202 (39.1)	
High (>20%)		17 (3.6)	20 (3.9)	
Current PI use	543	232 (42.7)	—	—
Current EFV use	543	43 (7.9)	—	—
Current PI + EFV use	543	9 (1.7)	—	—
No current PI or EFV use	543	277 (51.0)	—	—
On BAS	1,128	1 (0.2)	3 (0.5)	
On niacin	1,128	6 (1.1)	9 (1.5)	
On fibrate	1,128	25 (4.6)	8 (1.3)	
On ezetimibe	1,128	3 (0.6)	4 (0.7)	
On omega 3	1,128	2 (0.4)	1 (0.5)	

HDL, high-density lipoprotein; LDL, low-density lipoprotein; IQR, interquartile range; HCV, hepatitis C virus; AST, aspartate aminotransferase; ALT, alanine aminotransferase; CHD, coronary heart disease; PI, protease inhibitor; EFV, efavirenz; BAS, bile acid sequestrant.

demonstrated an association with the outcome of interest with a p -value less than 0.10 in the univariate models. Multivariate models included all participants with complete data.

Analyses were conducted using SAS Version 9.2 (Cary, NC), and a p -value < 0.05 was considered statistically significant.

Results

A total of 1,926 men completed Visit 56 and 564 men (29.3%) reported statin therapy use at that visit. Twenty-nine men receiving statin therapy at Visit 56 were excluded because

they had been receiving statin therapy when they joined the MACS, so their target LDL-c could not be calculated. Fifty-six men were excluded because more than 2 years had elapsed between the visit prior to statin therapy initiation and the statin therapy initiation visit. One hundred and thirteen men did not respond to the medication use questions, and therefore were excluded from the analysis. Therefore, 479 men receiving statin therapy and 1,249 men not receiving statin therapy were considered for analysis. Among men not on statins, 1,128 had lipid data from Visit 54–56 to determine whether they had achieved their LDL-c target. For 434 men receiving statins, we were able

TABLE 2. DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF MEN RECEIVING STATIN THERAPY (N=434)

	N included	HIV ⁺ (N=230) N (%) or median (IQR)	HIV ⁻ (N=204) N (%) or median (IQR)	p value
Age (years)	434	51 (46, 55)	55 (48, 62)	<0.0001
Body mass index (kg/m ²)				
<25	434	96 (41.7)	54 (26.5)	0.0003
25–30		86 (37.4)	77 (37.7)	
>30		48 (20.9)	73 (35.8)	
Race				
White	434	176 (76.5)	176 (86.3)	0.007
Black		31 (13.5)	22 (10.8)	
Hispanic/other		23 (10.0)	6 (2.9)	
Smoking at index visit				
Never	434	60 (26.1)	58 (28.4)	0.51
Former		118 (51.3)	109 (53.4)	
Current		52 (22.6)	37 (18.1)	
HDL cholesterol current (mg/dl)	419	48 (40, 55)	50 (43, 59)	0.06
LDL cholesterol current (mg/dl)	434	94 (75, 115)	92 (75, 111)	0.39
LDL cholesterol prior to statin initiation (mg/dl)	434	132 (103, 156)	140 (118, 162)	0.004
CD4 ⁺ T cell count (cells/ μ l)	230	621 (465, 824)	—	—
Median (IQR) HIV RNA (men with detectable virus)	31	182 (94, 17,981)	—	—
Chronic HCV	427	7 (3.1)	2 (1.0)	0.13
AST and/or ALT > 80 U/liter	434	8 (3.5)	1 (0.5)	0.03
No medical insurance	434	8 (3.5)	5 (2.5)	0.53
No insurance coverage for medications	434	17 (7.4)	12 (5.9)	0.53
Diabetes	336	27 (15.6)	22 (13.5)	0.58
Hypertension	426	111 (49.6)	104 (51.5)	0.69
Family history of premature CHD	434	50 (24.5)	53 (23)	0.72
Framingham risk score, visit prior to starting statin therapy				
Low (<10%)	374	96 (49.5)	82 (45.6)	0.73
Medium (10–20%)		86 (44.3)	87 (48.3)	
High (>20%)		12 (6.2)	11 (6.1)	
On high-potency statin ^a	434	167 (72.6)	183 (89.7)	<0.0001
Current PI use	230	111 (48.3)		
Current EFV use	230	27 (11.7)		
Current PI+EFV use	230	9 (3.9)		
No current PI or EFV use	230	101 (43.9)		
PI use at visit prior to starting statin therapy	225	123 (54.7)		
EFV use at visit prior to starting statin therapy	225	58 (25.8)		
PI+EFV use at visit prior to starting statin therapy	225	22 (9.8)		
No PI or EFV use at visit prior to starting statin therapy	225	66 (29.3)		
On BAS	434	2 (0.9)	3 (1.5)	
On niacin	434	17 (7.4)	6 (2.9)	
On fibrate	434	39 (17.0)	14 (6.9)	
On ezetemibe	434	13 (5.7)	2 (1.0)	
On omega 3	434	11 (4.8)	1 (0.5)	

^aAtorvastatin, rosuvastatin, simvastatin.

to determine their LDL-c target from historical data and had current lipid data available to determine if they achieved LDL-c target at Visit 56. This comprised our final sample size.

Demographics

Table 1 presents the distribution of relevant demographic and clinical characteristics according to HIV serostatus for men not receiving statin therapy. The HIV-infected men ($n=543$) were younger, more likely to be black and to have a normal or underweight BMI, to be a current smoker, and to have hepatitis C. HIV-infected men had lower current HDL-c and LDL-c. Table 2 presents demographic and clinical characteristics for men receiving statin therapy. HIV-infected men were younger, more likely to have lower BMI, more likely to be black, and more likely to be current smokers. LDL-c was lower among HIV-infected men compared with HIV-uninfected men prior to statin therapy initiation (132 mg/dl vs. 140 mg/dl, $p=0.004$). HIV-uninfected men had higher current HDL-c compared with HIV-uninfected men. Similar proportions of HIV-infected men (28.2%) and HIV-uninfected men (27.3%) ($p=0.73$) were receiving statin therapy at Visit 56. More HIV-uninfected men than HIV-infected men on a statin (72.6% vs. 89.7%, $p<0.0001$) were on a high-potency statin. Statin therapy was not indicated according to ATP III guidelines at the visit prior to statin initiation in 31.2% of HIV-infected men and 39.1% of HIV-uninfected men ($p=0.09$).

Predictors of not achieving LDL-c target, all men

Among all men, there was a similar prevalence of not achieving LDL-c target among HIV-infected (11.8%) and

HIV-uninfected men (14.7%) (age- and race-adjusted prevalence ratio 1.01, 95% CI 0.97, 1.05, $p=0.53$).

Predictors of not achieving LDL-c target for men not receiving statin therapy

Eleven percent of HIV-infected and 15% of HIV-uninfected men not receiving statin therapy were not at their LDL-c target ($p=0.07$). In univariate analyses (Table 3), the following factors (based on Visit 56 assessments) were associated with not achieving LDL-c target among men not receiving statin therapy ($p<0.10$): older age, Hispanic race, obesity, diabetes, smoking, hypertension, chronic hepatitis C virus infection, not having medical insurance, and not having insurance coverage for medications. In multivariate analysis, factors associated with not achieving LDL-c target among men not receiving statin therapy included current smoking (OR=2.31, 95% CI 1.31, 4.06), hypertension (OR=4.69, 95% CI 2.68, 8.21), chronic hepatitis C virus infection (OR=0.19, 95% CI 0.04, 0.85), and not having insurance coverage for medications (OR=0.11, 95% CI 0.02, 0.56).

Predictors of not achieving LDL target for men not receiving statin therapy, HIV-infected men only

In univariate analysis among HIV-infected men (Table 4), the following factors were associated ($p<0.10$) with not

TABLE 3. MULTIVARIABLE LOGISTIC REGRESSION EXAMINING PREDICTORS OF NOT BEING AT LOW-DENSITY LIPOPROTEIN CHOLESTEROL TARGET FOR MEN NOT RECEIVING STATIN THERAPY (HIV⁺/HIV⁻)

	Univariate	Multivariate (N=838)
HIV (infected vs. uninfected)	0.71 (0.47, 1.07)	0.71 (0.43, 1.19)
Age	1.05 (1.03, 1.08)	1.02 (0.99, 1.05)
Race		
Black (reference)	1	1
Hispanic/other	0.40 (0.16, 1.00)	1.05 (0.35, 3.15)
White	1.34 (0.85, 2.12)	1.56 (0.80, 3.04)
Body mass index category		
<25 mg/kg ² (reference)	1	1
25–30	1.53 (0.92, 2.56)	1.46 (0.80, 2.66)
>30	1.83 (1.11, 3.00)	1.73 (0.94, 3.17)
Diabetes	2.00 (1.09, 3.67)	1.22 (0.62, 2.38)
Current smoking	1.55 (1.02, 2.36)	2.31 (1.31, 4.06)
Hypertension	5.77 (3.57, 9.32)	4.69 (2.68, 8.21)
No medical insurance	0.45 (0.18, 1.12)	2.69 (0.63, 11.52)
No insurance coverage for medications	0.19 (0.07, 0.52)	0.11 (0.02, 0.56)
Chronic HCV	0.29 (0.09, 0.93)	0.19 (0.04, 0.85)
AST and/or ALT >80 U/liter	0.68 (0.21, 2.23)	*

*NS ($p>0.10$) in univariate.

Note: no one in this group reported a family history of premature CHD.

TABLE 4. MULTIVARIABLE LOGISTIC REGRESSION EXAMINING PREDICTORS OF NOT BEING AT LOW-DENSITY LIPOPROTEIN CHOLESTEROL TARGET FOR MEN NOT RECEIVING STATIN THERAPY (HIV⁺ MEN ONLY)

	Univariate	Multivariate (N=524)
Age	1.08 (1.04, 1.12)	1.04 (1.00, 1.09)
Race		
Black (reference)	1	1
Hispanic/other race	0.27 (0.06, 1.23)	0.57 (0.12, 2.70)
White	1.74 (0.89, 3.41)	1.56 (0.73, 3.35)
Body mass index category		
<25 mg/kg ² (reference)	1	1
25–30	0.91 (0.41, 2.00)	0.85 (0.37, 1.95)
>30	1.14 (0.55, 2.35)	1.12 (0.51, 2.46)
Diabetes	2.00 (0.82, 4.89)	*
Current smoking	1.31 (0.69, 2.49)	*
Hypertension	7.40 (3.22, 16.99)	6.13 (2.60, 14.48)
No medical insurance	1.11 (0.25, 4.91)	*
No insurance coverage for medications	**	**
Chronic HCV	**	**
AST and/or ALT >80 U/liter	0.71 (0.17, 3.08)	*
HIV RNA >50 copies/ml	0.38 (0.15, 1.00)	0.52 (0.19, 1.44)
CD4 <200 cells/ μ l	**	**
Current PI use	0.70 (0.36, 1.34)	*
Current EFV use	2.03 (0.80, 5.12)	*
Current PI+EFV use	1.46 (0.18, 11.99)	*
No current PI or EFV use	1.11 (0.60, 2.08)	*

*NS ($p>0.10$) in univariate.

**Excluded due to poor model fit.

Note: no one in this group had a family history of premature CHD.

being at LDL-c target: older age, hypertension, and HIV RNA >50 copies/ml. Factors associated with not being at LDL target among HIV-infected men not receiving statin therapy in multivariate analysis included age (OR=1.04, 95% CI=1.00, 1.09) and hypertension (OR=6.13, 95% CI 2.60, 14.48). There was no association between current antiretroviral therapy and not being at LDL-c target.

Predictors of not achieving LDL-c target for men receiving statin therapy

Thirty-one of 230 (13.5%) HIV-infected and 29 of 204 (14.2%) HIV-uninfected men on statin therapy were not at their LDL-c target ($p=0.82$ for comparison by HIV serostatus). In univariate analysis (Table 5), the following factors were associated ($p<0.10$) with not achieving LDL-c target: white race, diabetes, current smoking, hypertension, no medical insurance, and no insurance coverage for medications. Factors associated with not achieving LDL-c target in multivariate analysis among men receiving statins included current smoking (OR=2.72, 95% CI 1.30, 5.67) and diabetes (OR=5.31, 95% CI 2.47, 11.42). Ninety-four high-risk men receiving statins were evaluated for the optional goal of LDL-c <70 mg/dl. Of those men, 10/45 (22%) of HIV-uninfected and 14/49 (28.6%) of HIV-infected men achieved LDL-c <70 mg/dl ($p=0.5$). One hundred and forty-three moderately high-risk men receiving statins were evaluated for the optional goal of

achieving LDL-c <100 mg/dl. Of those, 40/67 (60%) of HIV-uninfected and 43/76 (57%) of HIV-infected men achieved LDL-c <100 mg/dl ($p=0.8$). Fibrate use did not influence not being at LDL-c target.

Predictors of not achieving LDL target for men receiving statin therapy, HIV-infected men only

In univariate analysis among HIV-infected men (Table 6), the following factors were associated ($p<0.10$) with not achieving LDL-c target: white race, diabetes, current smoking, and AST or ALT >80 U/liter. Factors associated with not achieving LDL target among HIV-infected men receiving statins in multivariable analysis included diabetes (OR=9.48, 95% CI 3.00, 29.95) and AST or ALT >80 (OR=8.78, 95% CI 1.14, 67.77). There was no association between historical and/or current ART and not being at LDL-c target. Again, fibrate use did not influence not being at LDL-c target.

Finally, we examined whether our results differed when considering whether or not men receiving statins achieved their LDL-c target based on their clinical and laboratory data from Visit 56, rather than based on historical data; the number of men receiving statins included in this analysis increased from 434 to 502. Thirty-seven of 256 HIV-infected men (14.3%) and 28 of 244 HIV-uninfected men (11.5%) were not at their target LDL-c in this assessment ($p=0.41$). The predictors of not achieving target LDL were a diagnosis of diabetes (OR=2.33, 95% CI 1.24, 4.36) or hypertension (OR=3.38, 95% CI 1.62, 7.06) for all men and diabetes (OR=3.58, 95% CI 1.50, 8.58) among HIV-infected men only.

Discussion

In this cross-sectional analysis, we found that the likelihood of not receiving indicated drug treatment for dyslipidemia did not vary by HIV serostatus. There were similar proportions of HIV-infected and HIV-uninfected men (11.1% and 14.9%, respectively) not receiving statin therapy for whom such therapy was clinically indicated. Factors associated with nonachievement of target LDL-c for men not receiving lipid-lowering therapy included smoking, hypertension, and white race. Furthermore, we found that HIV-infected men receiving statin treatment were as likely not to have achieved target LDL-c level as HIV-uninfected men (13.5% and 14.2%, respectively). Among men receiving statin therapy, factors associated with nonachievement of LDL-c target included smoking and diabetes. These findings were contrary to our initial hypothesis that HIV-infected men would be less likely to receive indicated lipid-lowering therapy and that when treated, they would be less likely to achieve target LDL-c values.

Our hypothesis was based on HIV-infected patients frequently having multiple comorbid illnesses that require separate pharmacological treatments, resulting in competing health priorities compared to their HIV-negative counterparts. However, an opposing perspective that may explain our findings is that HIV-infected persons receive more health monitoring, more diagnoses, and more treatment than HIV-uninfected persons of a similar age.³¹

Compared with findings from other studies, the proportion of men in our sample who achieved their LDL-c target was

TABLE 5. MULTIVARIABLE LOGISTIC REGRESSION EXAMINING PREDICTORS OF FAILURE TO ACHIEVE LOW-DENSITY LIPOPROTEIN CHOLESTEROL TARGET FOR MEN RECEIVING STATIN THERAPY (HIV⁺/HIV⁻ MEN)

	Univariate	Multivariate (N=333)
HIV (infected vs. uninfected)	0.94 (0.55, 1.62)	0.78 (0.38, 1.62)
Age	0.97 (0.94, 1.01)	0.97 (0.93, 1.02)
Race		
Black (reference)	1	1
Hispanic/other race	1.09 (0.37, 3.16)	1.05 (0.28, 4.03)
White	0.45 (0.22, 0.93)	0.72 (0.29, 1.74)
Body mass index category		
<25 mg/kg ² (reference)	1	1
25–30	0.91 (0.46, 1.79)	0.87 (0.38, 1.95)
>30	1.53 (0.78, 2.96)	0.93 (0.39, 2.25)
Diabetes	5.70 (2.88, 11.25)	5.31 (2.47, 11.42)
Current smoking	2.65 (1.47, 4.78)	2.72 (1.30, 5.67)
Hypertension	1.79 (1.01, 3.15)	1.85 (0.91, 3.76)
No medical insurance	2.90 (0.86, 9.72)	1.12 (0.17, 7.41)
No insurance coverage for medications	3.12 (1.35, 7.23)	2.63 (0.86, 8.04)
Statin potency (high vs. low)	0.68 (0.36, 1.29)	0.60 (0.28, 1.31)
Family history of premature CHD	1.32 (0.72, 2.44)	**
Chronic HCV	0.78 (0.10, 6.32)	**
AST or ALT >80 U/liter	3.23 (0.79, 13.27)	*
Current fibrate use	1.32 (0.61, 2.87)	*

*NS ($p>0.10$) in univariate.

**Excluded due to poor model fit.

TABLE 6. MULTIVARIABLE LOGISTIC REGRESSION EXAMINING PREDICTORS OF FAILURE TO ACHIEVE LOW-DENSITY LIPOPROTEIN CHOLESTEROL TARGET FOR MEN RECEIVING STATIN THERAPY (HIV⁺ MEN ONLY)

	Univariate	Multivariate (N = 170)
Age	0.99 (0.94, 1.05)	1.03 (0.95, 1.11)
Race		
Black (reference)	1	1
Hispanic/other race	1.47 (0.41, 5.33)	2.06 (0.31, 13.52)
White	0.50 (0.18, 1.39)	0.56 (0.14, 2.18)
Body mass index category		
< 25 mg/kg ² (reference)	1	1
25–30	1.25 (0.54, 2.90)	1.08 (0.36, 3.21)
> 30	1.00 (0.35, 2.85)	0.37 (0.07, 2.04)
Diabetes	6.99 (2.76, 17.68)	9.48 (3.00, 29.95)
Current smoking	2.12 (0.94, 4.77)	2.32 (0.74, 7.25)
Hypertension	1.02 (0.47, 2.20)	*
No medical insurance	4.16 (0.94, 18.36)	6.36 (0.74, 54.83)
No insurance coverage for medications	3.00 (0.97, 9.20)	1.49 (0.31, 7.14)
Family history of premature CHD	1.73 (0.76, 3.94)	*
Statin potency (high vs. low)	0.70 (0.29, 1.68)	0.67 (0.21, 2.17)
Chronic HCV	**	**
AST or ALT > 80 U/liter	4.16 (0.94, 18.36)	8.78 (1.14, 67.77)
HIV RNA > 50 copies/ml	0.96 (0.31, 2.98)	0.53 (0.11, 2.57)
CD4 < 200 cells/ μ l	0.37 (0.07, 1.99)	0.39 (0.05, 3.39)
Current PI use	0.87 (0.41, 1.85)	*
Current EFV use	0.48 (0.11, 2.14)	*
Current PI+EFV use	1.89 (0.38, 9.55)	*
No current PI or EFV use	1.66 (0.78, 3.56)	*
PI use at visit prior to starting statin therapy	0.64 (0.30, 1.38)	*
EFV use at visit prior to starting statin therapy	0.66 (0.25, 1.69)	*
PI+EFV use at visit prior to starting statin therapy	**	**
No PI or EFV use at visit prior to starting statin therapy	1.39 (0.63, 3.09)	*
Current fibrate use	1.89 (0.77, 4.60)	*

*NS ($p > 0.10$) in univariate.

**Excluded due to poor model fit.

higher than previously demonstrated. A report from the HIV Outpatient Study (HOPS) data showed that 81–87% of patients with elevated LDL-c or non-HDL-c received the indicated therapy.³² Slightly over half of the HOPS patients, 52.8%, achieved their LDL-c treatment goal. Similar to our findings, HOPS patients at higher cardiovascular risk based on ATP III guidelines were less likely to achieve their target. When the presence of CVD risk factors (e.g., diabetes and smoking) resulted in lower LDL-c targets that require more aggressive lipid-lowering therapy, those targets were less

likely to be met. This has also been demonstrated in the general population, with only 56% of diabetic patients meeting their LDL-c goal³³ and evidence suggesting that smokers are less likely to meet LDL-c targets.³⁴

What is less clear, and what could be explored with future research, is whether nonadherence, undertreatment, or underlying biological mechanism results in these patients make them less likely to reach their target. The HIV-HEART study showed that among HIV-infected patients with moderate to high CHD risk there were more than 50% moderate risk and more than 30% high CHD risk patients who did not receive drug treatment for elevated LDL-c.²⁴ One potential explanation for the novelty of our findings in comparison to previous reports from other cohorts is that MACS participants (both HIV-infected and HIV-uninfected participants) differ from the clinic-based sample in the HOPS and the cohort recruited for the HIV-HEART study; they have been in long-term follow-up and may represent a group that is generally more adherent to medical intervention. Furthermore, MACS participants undergo regular lipid screening as a result of their participation in the study, which is not the case in other observational cohorts. Also, there are relatively fewer MACS participants with intravenous drug use as their primary HIV transmission risk factor and relatively fewer participants of low socioeconomic status.

Another possible factor that may have influenced our findings is the timing of the assessments. Our data were from late 2011 to early 2012, whereas data from other studies reflect earlier time periods (observation began in 2002 in HOPS and in 2004 in the HIV-HEART Study). Although increases in atherogenic serum lipids with antiretroviral therapy have been noted since early in the epidemic,³⁵ in recent years there has been an increased emphasis placed on the atherogenic effect of HIV-related inflammation^{36,37} and on the importance of optimizing the management of chronic comorbidities among HIV-infected patients. Finally, our patients may have demonstrated high rates of target attainment due to enhanced adherence around the time of MACS assessments, a previously described phenomenon.³⁸

We found that among HIV-infected men receiving statin therapy, having an AST or ALT greater than two times the ULN was associated with nonachievement of the LDL-c target. A common clinical question is whether prescribed statin doses should be increased in order to meet LDL-c targets among patients with abnormal liver transaminases. Several large randomized controlled trials have found no difference in persistently elevated transaminase levels among such patients when comparing statins to placebo.^{39–41} Additionally, recent (2012) labeling of statins by the U.S. Food and Drug Administration does not recommend routine monitoring of liver function tests among patients receiving statins, noting that serious liver injury attributable to statin use is “rare and unpredictable.”⁴² However, labeling for atorvastatin and rosuvastatin, commonly prescribed statins in HIV infection, lists active liver disease, including unexplained persistent transaminase elevations, as a contraindication to therapy.

Caution is suggested when considering statin therapy for individuals who consume large volumes of alcohol and/or have a history of liver disease.^{43,44} Several small studies have examined the safety of statin therapy among patients with chronic HCV^{45–47} and HCV/HIV coinfection^{48,49}; these

studies have not demonstrated increased statin-associated hepatotoxicity. A post hoc analysis of data from a statin treatment trial revealed that individuals with baseline transaminase elevations two to three times ULN did not experience increased statin-associated hepatotoxicity compared to participants with normal baseline liver function tests.⁵⁰ Nevertheless, providers may still be reluctant to aggressively prescribe statin for their HIV-infected patients with abnormal transaminases, particularly among patients receiving protease inhibitors that may impact the drug levels and toxicities associated with statin use.

ACC/AHA cholesterol treatment guidelines released in late 2013 removed LDL-c targets, citing insufficient evidence from randomized controlled trials that customizing statin therapy to achieve a specific target decreased CVD event risk.²¹ However, other professional societies continue to endorse LDL-c target use both for monitoring the response to statin therapy and for assessing the degree of CVD risk reduction attained.²³ Furthermore, even if providers are not as attuned to LDL-c targets in the future, it is reassuring that our data demonstrate that HIV-infected patients are not less likely (and perhaps more likely) to receive statin therapy than HIV-uninfected persons, a possible reflection of the increased emphasis placed upon CVD risk management by providers for their HIV-infected patients. The extent to which recent guideline modifications in lipid management regarding CVD risk reduction are appropriate for HIV-infected persons remains unclear. Likewise, consensus has not yet been achieved regarding the extent to which HIV infection itself should routinely be considered a CHD risk equivalent and how best to quantify that risk when undertaking CHD risk stratification.

Strengths of our study include the inclusion of an HIV-uninfected person, compared to prior studies that examined lipid treatment among HIV-infected persons only. We studied a large sample number of patients with extensive longitudinal clinical and laboratory data allowing us to use pretreatment data to determine the LDL-c goal. The applicability of our data is somewhat limited because the MACS does not include women and represents a group of patients that is generally adherent to medical intervention. We are still intrigued as to why not having insurance coverage for medications was inversely associated with not being at target among men not on statins, but suspect that unmeasured confounders may be a factor—that the men without insurance coverage for medications are perhaps less engaged in care, possibly reflecting that they are sicker in some way that makes them more likely to have a lower LDL-c that we did not capture with the current covariates.

Control of CVD risk factors among HIV-infected patients is an important component of HIV care, particularly as HIV-infected persons age. We found that the likelihood of nonachievement of LDL targets did not differ by HIV serostatus. Several potential factors [frequency of primary care visits and lipid monitoring in a “real world” (nonstudy-prompted) clinical care setting, and type of practitioner from whom care was provided] merit further study. Future work should also evaluate whether current lipid-lowering guidelines in the general population are adequate for HIV-infected individuals, given the potential for increased HIV-associated CVD risk. Furthermore, other HIV-infected populations in care should undergo evaluation to ascertain whether our findings are generalizable.

Acknowledgments

The MACS is funded by the National Institute of Allergy and Infectious Diseases, with additional supplemental funding from the National Cancer Institute and the National Heart, Lung and Blood Institute: UO1-AI-35042, UL1-RR025005, UO1-AI-35043, UO1-AI-35039, UO1-AI-35040, UO1-AI-35041, R03-DA-026038, M01 RR00425 (GCRC), UL1TR000124, R01 HL095129.

These data were previously presented at the 20th Conference on Retroviruses and Opportunistic Infections (CROI 2013), March 3–6, Atlanta, GA.

Author Disclosure Statement

F.J.P. has received honoraria from Gilead Sciences, Tibotec Pharmaceuticals, and Bristol Myers Squibb. T.T.B. has received honoraria from Bristol Myers Squibb, Gilead Sciences, Tibotec Pharmaceuticals, ViiV, and Merck, and serves as a consultant to EMD-Serono and Theratechnologies.

References

1. Palella FJ Jr, Baker RK, Moorman AC, *et al.*: Mortality in the highly active antiretroviral therapy era: Changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 2006;43(1):27–34.
2. Sterne JAC, Hernán MA, Ledergerber B, *et al.*: Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: A prospective cohort study. *Lancet* 2005; 366 (9483):378–384.
3. Barbaro G: Highly active antiretroviral therapy-associated metabolic syndrome: Pathogenesis and cardiovascular risk. *Am J Ther* 2006;13(3):248–260.
4. Wada N, Jacobson LP, Cohen M, *et al.*: Cause-specific life expectancies after 35 years of age for human immunodeficiency syndrome-infected and human immunodeficiency syndrome-negative individuals followed simultaneously in long-term cohort studies, 1984–2008. *Am J Epidemiol* 2013; 177(2):116–125.
5. Saves M, Chêne G, Ducimetiere P, *et al.*: Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis* 2003;37:292–298.
6. Triant V, Lee H, Hadigan C, and Grinspoon S: Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. *J Clin Endocrinol Metab* 2007;92(7):2506–2512.
7. Currier J, Taylor A, Boyd F, *et al.*: Coronary heart disease in HIV-infected individuals. *J Acquir Immune Defic Syndr* 2003;33(4):506–512.
8. Freiberg MS, Chang CCH, Skanderson M, *et al.*: The risk of incident coronary heart disease among veterans with and without HIV and hepatitis C. *Circulation* 2011;4(4):425–432.
9. Palella FJ Jr, Baker RK, Buchacz K, *et al.*: Increased mortality among publicly insured participants in the HIV Outpatient Study despite HAART treatment. *AIDS* 2011; 25(15):1865–1876.
10. Sackoff JE, Hanna DB, Pfeiffer MR, and Torian LV: Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. *Ann Intern Med* 2006;145(6):397–406.
11. Brown TT, Cole SR, Li X, *et al.*: Antiretroviral therapy and the prevalence and incidence of diabetes mellitus in the

- multicenter AIDS cohort study. *Arch Intern Med* 2005; 165(10):1179–1184.
12. De Wit S, Sabin CA, Weber R, *et al.*: Incidence and risk factors for new-onset diabetes in HIV-infected patients. *Diabetes Care* 2008;31(6):1224–1229.
 13. Baekken M, Os I, Sandvik L, and Oektedalen O: Hypertension in an urban HIV-positive population compared with the general population: Influence of combination antiretroviral therapy. *J Hypertens* 2008;26(11):2126–2133.
 14. Satlin MJ, Hoover DR, and Glesby MJ: Glycemic control in HIV-infected patients with diabetes mellitus and rates of meeting American Diabetes Association management guidelines. *AIDS Patient Care STDS* 2011;25(1):5–12.
 15. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III): Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. *Circulation* 2002;106(25):3143–3421.
 16. Grundy SM, Cleeman JI, Merz CNB, *et al.*: Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *J Am Coll Cardiol* 2004;44(3):720–732.
 17. Anderson KM, Wilson P, Odell PM, and Kannel WB: An updated coronary risk profile. A statement for health professionals. *Circulation* 1991;83(1):356–362.
 18. Baigent C, Keech A, Kearney Pa, *et al.*: Cholesterol Treatment Trialists' (CTT) Collaborators. Efficacy and safety of cholesterol-lowering treatment: Prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366(9493):1267–1278.
 19. Zafir B and Cohen S: Primary prevention in high-risk dyslipidemic patients without an established cardiovascular disease: Undertreatment and rationale for lipid-lowering therapy. *Eur J Int Med* 2006;17(7):495–499.
 20. Pearson TA: The undertreatment of LDL-cholesterol: Addressing the challenge. *Int J Cardiol* 2000;74:S23–S28.
 21. Stone NJ, Robinson J, Lichtenstein AH, *et al.*: 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;63(25 Pt B):2889–2934.
 22. Jellinger PS, Smith DA, Mehta AE, *et al.*: American association of clinical endocrinologists' guidelines for management of dyslipidemia and prevention of atherosclerosis. *Endocrine Practice* 2012;18:1–78.
 23. American Association of Clinical Endocrinologists (AACE): Press statement. <http://media.aace.com/press-release/press-statement>. Accessed March 27, 2014.
 24. Reinsch N, Neuhaus K, Esser S, *et al.*: Are HIV patients undertreated? Cardiovascular risk factors in HIV:R of the HIV-HEART study. *Eur J Prev Card* 2012;19(2):267–274.
 25. Nüesch R, Wang Q, Elzi L, *et al.*: Risk of cardiovascular events and blood pressure control in hypertensive HIV-infected patients: Swiss HIV Cohort Study (SHCS). *JAIDS J Acquir Immune Defic Syndr* 2013;62(4):396–404.
 26. Kaslow RA, Ostrow DG, Detels R, *et al.*: The Multicenter AIDS Cohort Study: Rationale, organization, and selected characteristics of the participants. *Am J Epidemiol* 1987;126(2):310–318.
 27. Friedewald WT, Levy RI, and Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18(6):499–502.
 28. Allain CC, Poon LS, Chan CS, *et al.*: Enzymatic determination of total serum cholesterol. *Clin Chem* 1974;20(4):470–475.
 29. Warnick GR and Albers J: A comprehensive evaluation of the heparin-manganese precipitation procedure for estimating high density lipoprotein cholesterol. *J Lipid Res* 1978;19(1):65–76.
 30. Bucolo G, Yabut J, and Chang TY: Mechanized enzymatic determination of triglycerides in serum. *Clin Chem* 1975; 21(3):420–424.
 31. Schouten J, Wit FW, Stolte IG, *et al.*: Comorbidity and ageing in HIV-1 infection: The AGEHIV Cohort Study. XIX International AIDS Conference. July 22–27, 2012. Washington, DC. Abstract THAB0205.
 32. Lichtenstein KA, Armon C, Buchacz K, *et al.*: Provider compliance with guidelines for management of cardiovascular risk in HIV-infected patients. *Prev Chron Dis* 2013;10:E10.
 33. Casagrande SS, Fradkin JE, Saydah SH, *et al.*: The prevalence of meeting A1C, blood pressure, and LDL goals among people with diabetes, 1988–2010. *Diabetes Care* 2013;36(8):2271–2279.
 34. Banta MR, Ma F, Bravata DM, *et al.*: Incidence of and factors associated with achieving target lipid levels in patients with peripheral arterial disease. *J Gen Intern Med* 2006;21(7):711–714.
 35. Riddler S, Li X, Chu H, *et al.*: Longitudinal changes in serum lipids among HIV-infected men on highly active antiretroviral therapy. *HIV Med* 2007;8(5):280–287.
 36. Subramanian S, Tawakol A, Burdo TH, *et al.*: Arterial inflammation in patients with HIV. *JAMA* 2012;308(4):379–386.
 37. Zanni MV, Abbara S, Lo J, *et al.*: Increased coronary atherosclerotic plaque vulnerability by coronary computed tomography angiography in HIV-infected men. *AIDS* 2013;27(8):1263–1272.
 38. Cramer JA, Scheyer RD, and Mattson RH: Compliance declines between clinic visits. *Arch Intern Med* 1990;150(7): 1509–1510.
 39. Downs JR, Clearfield M, Weis S, *et al.*: Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: Results of AFCAPS/TexCAPS. *JAMA* 1998;279(20):1615–1622.
 40. Heart Protection Study Collaborative Group: MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20536 high-risk individuals: A randomised placebo-controlled trial. *Lancet* 2002;360(9326):7–22.
 41. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: The Scandinavian Simvastatin Survival Study (4S). *The Lancet* 1994;344(8934):1383–1389.
 42. United States Food and Drug Administration: FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Accessed March 27, 2014.
 43. Atorvastatin prescribing information: <http://labeling.pfizer.com/ShowLabeling.aspx?id=587>. Accessed March 27, 2014.
 44. Rosuvastatin prescribing information: <http://1.astrazeneca-us.com/pi/crestor.pdf>. Accessed March 27, 2014.
 45. Gibson K and Rindone JP: Experience with statin use in patients with chronic hepatitis C infection. *Am J Cardiol* 2005;96(9):1278–1279.

46. Khorashadi S, Hasson NK, and Cheung RC: Incidence of statin hepatotoxicity in patients with hepatitis C. *Clin Gastroenterol Hepatol* 2006;4(7):902–907.
47. Chalasani N, Aljadhey H, Kesterson J, *et al.*: Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology* 2004;126(5):1287–1292.
48. Stroup JS and Harris B: Is statin therapy safe in patients with HIV/hepatitis C coinfection? *Proc (Bayl Univ Med Cent)* 2010;23(2):111–113.
49. Milazzo L, Menzaghi B, Corvasce S, *et al.*: Safety of statin therapy in HIV/hepatitis C virus-coinfected patients. *J Acquir Immune Defic Syndr* 2007;46(2):258–260.
50. Athyros VG, Tziomalos K, Gossios TD, *et al.*: Safety and efficacy of long-term statin treatment for cardiovascular events in patients with coronary heart disease and abnormal liver tests in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) Study: A post-hoc analysis. *Lancet* 2010;376(9756):1916–1922.

Address correspondence to:

Anne K. Monroe

Division of General Internal Medicine

Johns Hopkins University School of Medicine

1830 East Monument Street, Room 8060

Baltimore, Maryland 21287

E-mail: amonroe4@jhmi.edu