2013 American College of Cardiology/American Heart Association and 2004 Adult Treatment Panel III cholesterol guidelines applied to HIV-infected patients with/without subclinical high-risk coronary plaque

Markella V. Zanni[a], Kathleen V. Fitch[a], Meghan Feldpausch[a], Allison Han[a], Hang Lee[b], Michael T. Lu[c], Suhny Abbara[c], Heather Ribaudo[e], Pamela S. Douglas[f], Udo Hoffmann[c,d], Janet Lo[a] and Steven K. Grinspoon[a]

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Background: The 2013 American College of Cardiology/American Heart Association (ACC/AHA) cholesterol guidelines are being applied to HIV-infected patients but have not been validated in this at-risk population, which is known to have a high prevalence of subclinical high-risk morphology (HRM) coronary atherosclerotic plaque.

Objective: To compare recommendations for statins among HIV-infected subjects with/without HRM coronary plaque according to 2013 ACC/AHA versus 2004 Adult Treatment Panel III guidelines.

Methods/design: Data from 108 HIV-infected subjects without known cardiovascular disease (CVD) or lipid-lowering treatment who underwent contrast-enhanced computed tomography angiography were analyzed. Recommendations for statin therapy according to 2013 versus 2004 guidelines were assessed among those with/without HRM coronary plaque.

Results: Among all subjects, 10-year atherosclerotic cardiovascular disease (ASCVD) risk score was 3.3% (1.6, 6.6), yet 36% of subjects had HRM coronary plaque. Among those with HRM coronary plaque, statins would be recommended for 26% by 2013 guidelines versus 10% by 2004 guidelines ($P = 0.04$). Conversely, among those without HRM coronary plaque, statins would be recommended for 19% by 2013 guidelines versus 7% by 2004 guidelines ($P = 0.005$). In multivariate modeling, while 10-year ASCVD risk score related to HRM coronary plaque burden ($P = 0.02$), so too did other factors not incorporated into 2013 guidelines.

Conclusion: The 2013 ACC/AHA cholesterol guidelines recommend statin therapy for a higher percentage of subjects with and without HRM coronary plaque relative to 2004 guidelines. However, even by 2013 guidelines, statin therapy would not be recommended for the majority (74%) of HIV-infected subjects with subclinical HRM coronary plaque. Outcome studies are needed to determine the utility of new statin recommendations and the contribution of HRM coronary plaque to CVD events among HIV-infected subjects.

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[a]Program in Nutritional Metabolism, [b]Biostatistics Center, [c]Department of Radiology, Cardiovascular Imaging Section, [d]Division of Cardiology, Massachusetts General Hospital and Harvard Medical School, [e]Harvard School of Public Health, Boston, Massachusetts, and [f]Division of Cardiology, Duke University School of Medicine, Durham, North Carolina, USA.

Correspondence to Markella V. Zanni, MD, Program in Nutritional Metabolism, Massachusetts General Hospital, 55 Fruit Street, LON 207, Boston, MA 02114, USA.

Tel: +1 617 724 6926; fax: +1 617 724 8998; e-mail: mzanni@mgh.harvard.edu
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Background

In November 2013, the American College of Cardiology/American Heart Association (ACC/AHA) released a Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [1]. This guideline replaced the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III – or ATP III – guideline), last updated in 2004 [2]. Cholesterol treatment guidelines such as these, designed for the general population, are typically extrapolated to HIV-infected patients. However, among HIV-infected patients, unique factors relating to infection, treatment, and the body's immune response may contribute to cardiovascular disease (CVD) risk [3–5]. In addition, studies show that HIV-infected patients have more high-risk coronary plaque [6,7] that may potentially increase risk for CVD events. Nontraditional CVD risk factors and noninvasive cardiac imaging data are not included in traditional CVD risk assessment algorithms. Thus, a critical question arises as to how well current guidelines identify HIV-infected patients at highest CVD risk who would benefit most from statin therapy.

Relative to 2004 guidelines, 2013 ACC/AHA guidelines introduce major changes for identifying those for whom statins would be recommended, and the implications for HIV-infected patients remain unclear. The 2004 guidelines relied on low-density lipoprotein (LDL) cholesterol level thresholds tied to an individual's CVD risk categorization. Categorizations were, in turn, based on number of coronary heart disease (CHD) risk factors/risk equivalents and 10-year Framingham risk score (FRS) for hard CHD – that is percentage risk of myocardial infarction (MI) or coronary death in the next 10 years. The 2004 guidelines further defined non-high-density lipoprotein (non-HDL) cholesterol thresholds for drug therapy upon achievement of LDL goals [2]. In contrast, the 2013 ACC/AHA guidelines abandoned LDL and non-HDL thresholds and goals and instead identified four groups likely to benefit from statin therapy. Benefit groups included individuals: age 21 or older with clinical atherosclerotic cardiovascular disease (ASCVD); age 21 or older with LDL 190 mg/dl or higher; age 40–75 with diabetes and LDL 70–189 mg/dl; and age 40–75 with a 10-year ASCVD risk score – that is, percentage risk of nonfatal MI, coronary death, nonfatal/fatal stroke within the next 10 years – 7.5% or higher by the Pooled Cohort Equations calculator [1]. Analysis of data from 3773 participants in the National Health and Nutrition Examination Surveys (NHANES) database has suggested that application of 2013 ACC/AHA guidelines (versus 2004 guidelines) would markedly increase the percentage of individuals for whom statins would be recommended [8], but specific data in the HIV population have not been obtained.

Since the release of the 2013 ACC/AHA guidelines, use of the 10-year ASCVD risk score to determine recommendations for statin therapy has come under scrutiny. When applied to selected primary prevention cohorts, the calculator appears to overestimate observed CVD events by 75–150% [9]. However, the 2013 ASCVD risk calculator may underestimate risk among groups of patients – including HIV-infected patients – in whom atherosclerosis is driven, in part, by nontraditional CVD risk factors. Authors of the guidelines suggest that for individuals outside designated statin benefit groups who are nevertheless considered to be at high risk for CVD, noninvasive cardiac imaging studies may provide useful additional data to consider [1].

Our research group and others have employed noninvasive contrast-enhanced coronary computed-tomography angiography (CCTA) to characterize prevalence and morphology of subclinical coronary atherosclerosis among HIV-infected patients without clinical CVD. We and others have previously published that HIV-infected patients have more noncalcified coronary plaque [6,10–12] and high-risk morphology (HRM) coronary plaque [7] than matched non-HIV controls. HRM coronary plaque may be marked by low attenuation (low density compatible with a necrotic lipid core) and/or positive remodeling (dilation of vessel at plaque site), and these features suggest vulnerability to rupture [13]. Importantly, noncalcified and HRM coronary plaque predict CVD events in the general population [14,15]. Detailed information on coronary plaque morphology may be more useful than coronary artery calcium score for predicting plaque rupture and ensuing MI – particularly if accrued calcification stabilizes individual high-risk coronary plaques, as suggested by recent studies [16,17].

In the present study, we consider how 2013 ACC/AHA guidelines would apply to a cohort of well phenotyped HIV-infected patients without known CVD who have undergone CCTA. Specifically, employing 2013 ACC/AHA versus 2004 ATP III guidelines, we compare recommendations for statin therapy among HIV-infected patients with and without subclinical HRM coronary plaque. Further, we characterize differences among HIV-infected patients for whom statins would/would not be recommended and among HIV-infected patients with and without HRM coronary plaque. Finally, we determine the relationship between 2013 10-year ASCVD risk score and HRM coronary plaque burden. We hypothesize that 2013 ACC/AHA guidelines would not recommend statins for a

sizeable proportion of those HIV-infected patients with subclinical high-risk coronary plaque, despite that these patients may potentially benefit from statin therapy.

Methods

Study participants

A total of 150 patients (101 men, 49 women) ages 18–60 years and HIV-infected for at least 5 years with no recent antiretroviral therapy (ART) changes were recruited into a study of cardiovascular health and successfully underwent CCTA. By design, patients with previously diagnosed coronary artery disease, cerebrovascular disease, or peripheral vascular disease were excluded. Other key exclusion criteria and recruitment/consenting methods are as per published reports [6,7,10,11]. From this cohort of 150 patients, 42 patients were excluded from this comparative analysis of guideline-driven recommendations for statins: 21 for statin use, 15 for use of nonstatin lipid-lowering medications, and six for insufficient CVD risk factor data. In total, data from 108 patients (68 men, 40 women) were analyzed. Previous publications have reported on subclinical atherosclerosis [6,10] and HRM coronary plaque [7] among men, and on subclinical atherosclerosis among women [11]. Analyses comparing application of 2013 and 2004 cholesterol treatment guidelines among this cohort have never before been reported.

Assessment of historical data, body composition, and metabolic and immunologic parameters

Methods for collecting historical/body composition data and for determining levels of metabolic and immune parameters are as per published reports [6,7,10,11].

Determination of recommendations for statins by 2013 American College of Cardiology/American Heart Association Guidelines

Patients with known clinical CHD were excluded from the analyses, which focused on primary prevention recommendations for statin therapy. Patients for whom statins would be recommended according to the 2013 guidelines included those: ages 21 years or older with LDL 190 mg/dl or higher, ages 40–75 years with diabetes and LDL 70–189 mg/dl, and/or ages 40–75 years with 10-year ASCVD risk score 7.5% or higher. Parameters factoring into ASCVD risk score include age, sex, race, total cholesterol, HDL, SBP, antihypertensive medication use, diabetes, and smoking [1]. In our analyses, for patients ages 21 years or older and younger than 40 years ($n = 24$), ASCVD score was not calculated; determination of whether statins would be recommended for these patients was based on LDL level ($\geq$190 mg/dl or not). For patients aged 40 or older, we interpreted that statins would be recommended based on LDL level 190 mg/dl or higher, presence of diabetes, and/or ASCVD risk score 7.5% or higher. With respect to select other ASCVD risk score parameters: total cholesterol was entered as 130 mg/dl for patients whose levels were $<$ 130 mg/dl ($n = 11$). HDL was entered as 100 mg/dl for patients whose levels were higher than 100 mg/dl ($n = 3$).

Determination of recommendations for statins by 2004 Adult Treatment Panel III guidelines

Based on exclusion criteria, no patient had CHD. Diabetes was counted as a CHD risk equivalent. Number of CHD risk factors and 10-year FRS were calculated. Patients for whom statins would be recommended according to the 2004 guidelines included those categorized as: high-risk (CHD risk equivalent, 10-year FRS $>$20%) with LDL 100 mg/dl or higher, moderately high-risk (2+ CHD risk factors, 10-year FRS 10–20%) with LDL 130 mg/dl or higher, moderate-risk (2+ CHD risk factors, 10-year FRS $<$10%) with LDL 160 mg/dl or higher, and lower-risk (0–1 CHD risk factors) with LDL 190 mg/dl or higher [2].

Multidetector row contrast-enhanced coronary computed-tomography angiography

A 64-slice computed tomography (CT) scanner (Sensation 64; Siemens Medical Solutions, Forchheim, Germany) was used to obtain contrast-enhanced coronary CT angiograms for research purposes, as per published reports [6,7,10,11].

Assessment of subclinical high-risk morphology coronary atherosclerotic plaque by coronary computed-tomography angiography

Coronary arterial segments previously identified as having plaque were re-evaluated by trained experts (M.T.L, B.W., S.A.). Low-attenuation plaque was defined as plaque with a mean minimal attenuation less than 40 Hounsfield Units [18]. Positive remodeling was defined as plaque segment diameter/normal reference segment diameter more than 1.05 [18]. Methods for assessing HRM features are as per published reports [7].

Statistical analysis

For the whole group, data on demographic and clinical parameters are presented – mean $\pm$ standard deviation (SD) for normally distributed data and median (interquartile range, IQR) for nonnormally distributed data. McNemar's tests were used to compare the percentages of patients for whom statins would be recommended according to 2013 versus 2004 guidelines among the whole group and among subgroups with/without coronary plaque and with/without HRM coronary plaque. Between-group comparisons of demographic and clinical parameters were made for those for whom statins would/would not be recommended according to 2013 guidelines and for those with and without HRM coronary plaque (at least one plaque with at least one HRM feature). Normally distributed data were compared by Student's t test, nonnormally distributed data by

Wilcoxon test, and dichotomous data by χ^2 test. Spearman's rho was used to evaluate the relationship between 2013 10-year ASCVD risk score and burden of subclinical HRM coronary atherosclerotic plaque (defined as number of high-risk features in the highest-risk coronary plaque). Multivariate linear regression modeling for HRM coronary plaque burden as the dependent variable was performed. Independent variables entered into the model were 10-year ASCVD risk score as well as other parameters, which tended to be different between patients with/without HRM coronary plaque (P value threshold <0.15) and which were not represented in the 10-year ASCVD risk score.

Results

Baseline demographics

Baseline demographic and clinical characteristics of the whole group are presented in Table 1. Among the entire group, 45% (49/108) had coronary atherosclerotic plaque and 36% (39/108) had HRM coronary plaque.

Recommendations for statins (2013 versus 2004 guidelines)

Among the entire group, statins would be recommended for 21% (23/108) by 2013 guidelines versus 8% (9/108) by 2004 guidelines ($P=0.0005$). Among those with any coronary atherosclerotic plaque, statins would be recommended for 29% (14/49) by 2013 guidelines versus 12% (6/49) by 2004 guidelines ($P=0.01$). Conversely, among those without coronary plaque, statins would be recommended for 15% (9/59) by 2013 guidelines versus 5% (3/59) by 2004 guidelines ($P=0.01$) (Fig. 1a). Among those with HRM coronary atherosclerotic plaque, statins would be recommended for 26% (10/39) by 2013 guidelines versus 10% (4/39) by 2004 guidelines ($P=0.04$). Conversely, among those without HRM coronary plaque, statins would be recommended for 19% (13/69) by 2013 guidelines versus 7% (5/69) by 2004 guidelines ($P=0.005$) (Fig. 1b) (Supplemental Table 1, http://links.lww.com/QAD/A539).

Comparison of demographic and clinical characteristics of patients for whom statins would/would not be recommended according to 2013 American College of Cardiology/American Heart Association guidelines

By 2013 guidelines, those for whom statins would be recommended (versus those for whom statins would not be recommended) tended to be older with higher 10-year Framingham and ASCVD risk scores. Those for whom statins would be recommended also had a longer duration of time since HIV diagnosis, a higher CD4 count, and higher levels of the circulating monocyte activation marker soluble CD163. Among those for whom statins would be recommended, there was also a greater prevalence of diabetes and antihypertensive medication use. There was no statistically significant between-group difference in presence of HRM coronary atherosclerotic plaque (Table 2).

Comparison of demographic and clinical characteristics of patients with and without subclinical high-risk morphology coronary atherosclerotic plaque

Patients with HRM coronary plaque (versus those without) tended to be older, with higher blood pressure, triglyceride levels, and 10-year Framingham and ASCVD risk scores. The group with HRM coronary plaque (versus the group without) featured a higher percentage of males and individuals of non-Hispanic ethnicity. The percentage of patients in the HRM coronary plaque group with a family history of premature CHD tended to be higher, although the difference was not statistically significant. Additionally, patients in the HRM coronary plaque group tended to have a longer duration of ART use and higher viral load, although these differences were not statistically significant (Table 3).

Relationship between 2013 10-year atherosclerotic cardiovascular disease risk score and high-risk morphology coronary plaque burden

Ten-year ASCVD risk score was related to HRM coronary plaque burden on univariate analysis (rho $=0.36$, $P=0.0007$). In multivariate linear regression modeling for HRM coronary plaque burden, 10-year ASCVD risk score remained significant ($P=0.02$) when controlling for ethnicity, family history of premature CHD, duration of ART use, and viral load. Ethnicity, family history, and duration of ART use also remained significant in modeling for HRM coronary plaque burden (Table 4).

Discussion

In this study, we compare for the first time statin recommendations according to 2004 versus 2013 cholesterol treatment guidelines among a cohort of HIV-infected patients without clinical CVD for whom CCTA data on presence or absence of HRM coronary atherosclerotic plaque are available. We find that by 2013 ACC/AHA guidelines (versus 2004 guidelines), statins would be recommended for more patients with and without HRM coronary plaque. And yet, statins would not be recommended for the majority of patients with HRM coronary plaque. Traditional CVD risk factors encompassed in the 2013 10-year ASCVD risk score relate to HRM coronary plaque burden, but so too do other factors, both traditional (e.g., family history) and HIV-specific (duration of ART use) not encompassed in the guidelines.

Table 1. Baseline demographic and clinical characteristics of all patients.

	$N = 108$
Demographics and cardiovascular risk parameters	
Age (years)	46 (40, 52)
Age ≥40 (%)	78 (84/108)
Sex, % male	63 (68/108)
Race (%)	
White	50 (54/108)
Black	42 (45/108)
Other	8 (9/108)
Ethnicity, % Hispanic	11 (12/108)
Family history premature CHD (NCEP) (%)	21 (22/106)
Current smoking (%)	50 (54/108)
Current diabetes (%)	9 (10/108)
HbA1c (%)	5.5 (5.2, 5.7)
BMI (kg/m^2)	26.4 ± 5.2
Current use of antihypertensives (%)	20 (22/108)
SBP (mmHg)	117 ± 12
DBP (mmHg)	75 ± 9
Total cholesterol (mg/dl)	175 ± 36
LDL cholesterol (mg/dl)	98 ± 31
HDL cholesterol (mg/dl)	49 (40, 62)
Triglycerides (mg/dl)	90 (74, 143)
Number of Framingham risk factors	1 (0, 2)
10-year Framingham risk score (%)	3 (1, 5)
10-year ASCVD risk score (%)	3.3 (1.6, 6.6)
HIV disease-specific parameters	
Years since HIV diagnosis	14 ± 6
CD4$^+$ T-cell count (cells/μl)	528 (369, 748)
Viral load (copies/ml)	49 (47, 49)
Undetectable viral load (%)	78 (72/92)
[a]Nadir CD4$^+$ T-cell count (cells/μl)	192 (61, 298)
[b]Duration of ART use (years)	8 (2, 11)
Current ART use (%)	94 (102/108)
NRTI (%)	91 (98/108)
NNRTI (%)	32 (35/108)
Protease inhibitor (%)	50 (54/108)
Hepatitis C co-infection (%)	31 (34/108)
Inflammatory and immune markers	
CRP (mg/dl)	0.13 (0.05, 0.34)
hs IL-6 (pg/ml)	1.06 (0.75, 1.86)
sCD163 (ng/ml)	1218 (777, 1744)
sCD14 (ng/ml)	431 (210, 1874)
Plaque parameters	
Percentage of patients with any coronary plaque	45 (49/108)
Total number of coronary plaque segments per subject	0 (0, 2)
	1.6 ± 2.5[c]
Percentage of patients with any noncalcified or mixed coronary plaque	45 (49/108)
Percentage of patients with any calcified coronary plaque	11 (12/107)
Percentage of patients with any HRM coronary plaque	36 (39/108)
HRM features in most high-risk coronary plaque (0–2)	0 (0, 1)
	0.5 ± 0.7[c]
CAC score (0–800)	0 (0, 5.9)
Statin recommendations	
Percentage of patients for whom statins would be recommended according to 2004 ATP III guidelines	8 (9/108)
Percentage of patients for whom statins would be recommended according to 2013 ACC/AHA guidelines	21 (23/108)

ACC/AHA, American College of Cardiology/American Heart Association; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; ATP, adult treatment panel; CAC, coronary artery calcium; CHD, coronary heart disease; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HRM, high-risk morphology; hs IL-6, high-sensitivity interleukin-6; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Panel; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; sCD14, soluble CD14; sCD163, soluble CD163.
[a]Self-reported, missing data from 20 subjects.
[b]Missing data from 24 patients.
[c]Provided for descriptive purposes.

The 2013 ACC/AHA cholesterol treatment guidelines aim to accurately identify individuals for whom statin therapy would meaningfully reduce the risk of incurring a CVD event. HIV-infected patients, when compared with uninfected controls, face a 1.5 to 2-fold heightened MI risk [19–21] and 1.5-fold heightened stroke risk [22]. 2013 guidelines suggest that for populations with perceived high CVD risk for whom statins are not recommended, additional clinical information, where available, should be considered.

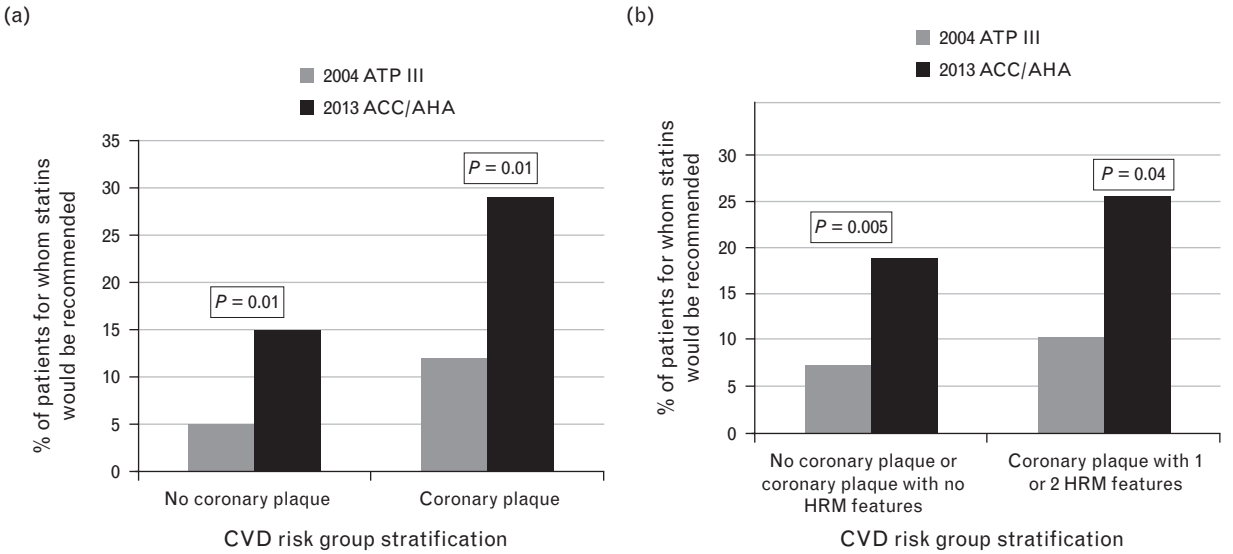

Fig. 1. Statin recommendations among HIV-infected patients stratified by coronary plaque parameters. (a) Percentage of patients with and without subclinical coronary atherosclerotic plaque for whom statins would be recommended according to 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines versus 2004 Adult Treatment Panel (ATP) III guidelines. (b) Percentage of patients with and without subclinical high-risk morphology coronary atherosclerotic plaque for whom statins would be recommended according to 2013 ACC/AHA guidelines versus 2004 ATP III guidelines.

Leveraging a cohort of HIV-infected patients without known CVD who have undergone CCTA, we analyzed recommendations for statin therapy according to 2013 ACC/AHA guidelines in relation to the presence or absence of any plaque and of HRM coronary atherosclerotic plaque. In the general population, the presence of HRM coronary plaque predicts a markedly increased risk of incident CVD. Motoyama *et al.* showed that among 1059 patients evaluated for 27 ± 10 months, those with no coronary atherosclerotic plaque and those with plaque absent HRM features incurred ACS at rates of 0% and 0.5%, respectively. In contrast, those with coronary plaque characterized by one or two HRM features incurred ACS at rates of 3.7 and 22.2%, respectively [15]. HIV-infected patients, relative to non-HIV controls, have a higher prevalence and burden of HRM coronary plaque [7], but whether this observation underlies increased CVD risk in HIV is unknown. Of note, in the general population, statin therapy has been shown to stabilize HRM plaque features [23,24]. Such stabilization, which may be mediated through LDL-lowering effects and/or through pleiotropic immune-modulatory effects, is presumed to reduce plaque vulnerability to rupture. Whether HIV-infected patients with subclinical HRM coronary atherosclerotic plaque face an unacceptably high risk of incurring a CVD event – specifically MI – and would potentially benefit from statin therapy is unknown.

When applied to our cohort, 2013 ACC/AHA guidelines (versus 2004 guidelines) increased by roughly 2.5-fold the number of patients for whom statins would be recommended, but the percentage of patients for whom statins would be recommended remained low even under the new guidelines. Increased percentages of patients for whom statins would be recommended were noted in both the subgroups with and without subclinical HRM coronary atherosclerotic plaque. Importantly, in our cohort, although 2013 ACC/AHA guidelines generally increased the number of patients for whom statins would be recommended, statin therapy would not be recommended for the majority (74%) of HIV-infected patients with HRM coronary plaque.

Our analyses provide insights as to why, according to the current guidelines, statin therapy might not be recommended for HIV-infected patients with subclinical HRM coronary atherosclerotic plaque. In our cohort, patients with HRM coronary plaque tended to be young (15% under age 40), with low LDL levels (100 ± 30 mg/dl). Thus, in this subgroup, even though the prevalence of selected traditional CVD risk factors like smoking (54%) was high, cumulative traditional CVD risk as estimated by the 2013 10-year ASCVD risk score (5.5%) was low. That relatively young HIV-infected patients with low LDL levels may still face heightened MI risk is supported by Freiberg's analysis of data from 82 459 patients in the Veterans Aging Cohort Study. In this large cohort, although 46.4% of HIV-infected patients had LDL cholesterol levels less than 100 mg/dl, HIV-infected patients (versus non-HIV controls) had higher relative incidence rates of acute MI across all age groups, and particularly in the 30 to 39-year-old group [21].

Our data suggest that the 2013 10-year ASCVD risk score encompasses some but not all potential risk factors for the development of HRM coronary atherosclerotic plaque

Table 2. Demographic and clinical characteristics of patients for whom statins would/would not be recommended according to 2013 ACC/AHA guidelines.

	Statins not recommended, $N=85$	Statins recommended, $N=23$	P value
Demographics and cardiovascular risk parameters			
Age (years)	45 (39, 49)	52 (47, 55)	<0.0001*
Sex, % male	64 (54/85)	61 (14/23)	0.82
Race (%)			0.009*
White	57 (48/85)	26 (6/23)	
Black	34 (29/85)	70 (16/23)	
Other	9 (8/85)	4 (1/23)	
Ethnicity, % Hispanic	12 (10/85)	9 (2/23)	0.67
Family history premature CHD (%)	20 (17/83)	22 (5/23)	0.90
Current smoking (%)	52 (44/85)	43 (10/23)	0.48
Current diabetes (%)	0 (0/85)	43 (10/23)	<0.0001*
HbA1C (%)	5.4 (5.1, 5.6)	5.7 (5.3, 6.1)	0.003*
BMI (kg/m^2)	26.1 ± 5.0	27.7 ± 5.5	0.21
Current use of antihypertensives (%)	13 (11/85)	48 (11/23)	0.0006*
SBP (mmHg)	115 ± 11	125 ± 13	0.003*
DBP (mmHg)	74 ± 9	80 ± 8	0.001*
Total cholesterol (mg/dl)	172 ± 33	183 ± 44	0.27
LDL cholesterol (mg/dl)	95 ± 27	111 ± 40	0.09
HDL cholesterol (mg/dl)	50 (41, 64)	47 (39, 59)	0.30
Triglycerides (mg/dl)	85 (73, 143)	97 (82, 167)	0.27
Number of Framingham risk factors	1 (0, 2)	2 (1, 3)	0.002*
10-year Framingham risk score (%)	2 (1, 5)	4 (1, 12)	0.03*
10-year ASCVD risk score (%)	2.6 (1.4, 4.8)	8.7 (6.5, 11.0)	<0.0001*
HIV disease-specific parameters			
Years since HIV diagnosis	13 ± 6	17 ± 7	0.01*
CD4$^+$ T-cell count (cells/μl)	474 (351, 717)	655 (482, 857)	0.05*
Viral load (copies/ml)	49 (47, 49)	47 (47, 52)	0.37
Undetectable viral load (%)	78 (58/74)	78 (14/18)	0.96
[a]Nadir CD4$^+$ T-cell count (cells/μl)	165 (47, 293)	244 (119, 313)	0.17
[b]Duration of ART use (years)	8 (2,11)	10 (4, 13)	0.24
Current ART use (%)	95 (81/85)	91 (21/23)	0.48
NRTI (%)	92 (78/85)	87 (20/23)	0.50
NNRTI (%)	33 (28/85)	30 (7/23)	0.82
Protease inhibitor (%)	53 (45/85)	39 (9/23)	0.24
Hepatitis C co-infection (%)	28 (24/85)	43 (10/23)	0.17
Inflammatory and immune markers			
CRP (mg/dl)	0.13 (0.05, 0.36)	0.10 (0.03, 0.22)	0.20
hs IL-6 (pg/ml)	1.05 (0.74, 1.93)	1.20 (0.82, 1.51)	0.94
sCD163 (ng/ml)	1167 (699, 1663)	1495 (921, 2112)	0.05*
sCD14 (ng/ml)	431 (205, 1830)	701 (241, 2002)	0.37
Plaque parameters			
Percentage of patients with any coronary plaque	41 (35/85)	61 (14/23)	0.09
Total number of coronary plaque segments per subject	0 (0, 2) 1.4 ± 2.3[c]	1 (0, 4) 2.4 ± 3.1[c]	0.10
Percentage of patients with any noncalcified or mixed coronary plaque	41 (35/85)	61 (14/23)	0.09
Percentage of patients with any calcified coronary plaque	8 (7/84)	22 (5/23)	0.09
Percentage of patients with any HRM coronary plaque	34 (29/85)	43 (10/23)	0.41
HRM features in most high-risk coronary plaque (0–2 features)	0 (0, 1) 0.5 ± 0.7[c]	0 (0, 1) 0.7 ± 0.8[c]	0.34
CAC score (0–800)	0 (0, 5)	0 (0, 8)	0.62

ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; CAC, coronary artery calcium; CHD, coronary heart disease; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HRM, high-risk morphology; hs IL-6, high-sensitivity interleukin-6; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; sCD14, soluble CD14; sCD163, soluble CD163.
*Statistically significant *P*-value.
[a]Self-reported, missing data from 20 subjects.
[b]Missing data from 24 patients.
[c]Provided for descriptive purposes.

among HIV-infected patients. On univariate analysis, 10-year ASCVD risk score indeed relates to HRM coronary plaque burden. This relationship remains significant when controlling for factors, which appear to differ in HIV-infected patients with and without HRM coronary plaque but which are not already encompassed in the ASCVD risk score: family history of premature CHD, ethnicity, duration of ART use, and viral load. However, in the model for HRM plaque burden, family history, ethnicity, and duration of ART use also remain significant. The model, although highly significant, does not fully explain the variance in HRM coronary plaque burden, suggesting that other factors are contributing. Based on current understandings of

Table 3. Demographic and clinical characteristics of patients with and without subclinical HRM coronary atherosclerotic plaque.

	No HRM coronary plaque, $N=69$	HRM coronary plaque, $N=39$	P value
Demographics and cardiovascular risk parameters			
Age (years)	45 (39, 51)	48 (45, 52)	0.04*
Age ≥40 (%)	74 (51/69)	85 (33/39)	0.19
Sex, % male	54 (37/69)	79 (31/39)	0.006*
Race (%)			0.04*
White	42 (29/69)	64 (25/39)	
Black	46 (32/69)	33 (13/39)	
Other	12 (8/69)	3 (1/39)	
Ethnicity, % Hispanic	16 (11/69)	3 (1/39)	0.02*
Family history premature CHD (%)	16 (11/67)	28 (11/39)	0.15
Current smoking (%)	48 (33/69)	54 (21/39)	0.55
Current diabetes (%)	12 (8/69)	5 (2/39)	0.25
BMI (kg/m^2)	26.7 ± 5.4	26.0 ± 4.7	0.47
Current use of antihypertensives (%)	14 (10/69)	31 (12/39)	0.05*
SBP (mmHg)	115 ± 13	120 ± 11	0.03*
DBP (mmHg)	73 ± 8	79 ± 10	0.002*
Total cholesterol (mg/dl)	172 ± 37	178 ± 33	0.39
LDL cholesterol (mg/dl)	97 ± 32	100 ± 30	0.59
HDL cholesterol (mg/dl)	49 (41, 65)	46 (38, 60)	0.32
Triglycerides (mg/dl)	84 (73, 118)	105 (75, 180)	0.05*
Number of Framingham risk factors	1 (0, 2)	2 (1, 2)	0.001*
10-year Framingham risk score (%)	2 (1, 5)	4 (2, 8)	0.0008*
10-year ASCVD risk score (%)	2.3 (1.4, 5.1)	5.5 (3, 7.5)	0.002*
HIV disease-specific parameters			
Years since HIV diagnosis	13 ± 6	15 ± 6	0.24
CD4$^+$ T-cell count (cells/μl)	521 (388, 714)	541 (273, 818)	0.99
Viral load (copies/ml)	49 (47, 49)	49 (47, 54)	0.14
Undetectable viral load (%)	79 (50/63)	76 (22/29)	0.71
[a]Nadir CD4$^+$ T-cell count (cells/μl)	200 (53, 324)	163 (65, 259)	0.64
[b]Duration of ART use (years)	7 (2, 10)	10 (5, 12)	0.06
Current ART use (%)	94 (65/69)	95 (37/39)	0.88
NRTI (%)	90 (62/69)	92 (36/39)	0.67
NNRTI (%)	29 (20/69)	38 (15/39)	0.31
Protease inhibitor (%)	52 (36/69)	46 (18/39)	0.55
Hepatitis C co-infection (%)	28 (19/69)	38 (15/39)	0.24
Inflammatory and immune markers			
CRP (mg/dl)	0.13 (0.04, 0.38)	0.12 (0.05, 0.26)	0.61
hs IL-6 (pg/ml)	1.18 (0.79, 1.85)	1.02 (0.73, 1.95)	0.55
sCD163 (ng/ml)	1202 (697, 1709)	1268 (877, 1881)	0.32
sCD14 (ng/ml)	464 (213, 2025)	384 (205, 1220)	0.42
Statin recommendations			
Percentage of patients for whom statins would be recommended according to 2004 ATP III guidelines	7 (5/69)	10 (4/39)	0.59
Percentage of patients for whom statins would be recommended according to 2013 ACC/AHA guidelines	19 (13/69)	26 (10/39)	0.41

ACC/AHA, American College of Cardiology/American Heart Association; ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; ATP, adult treatment panel; CHD, coronary heart disease; CRP, C-reactive protein; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; HRM, high-risk morphology; hs IL-6, high-sensitivity interleukin-6; LDL, low-density lipoprotein; NNRTI, nonnucleoside reverse transcriptase inhibitor; NRTI, nucleoside reverse transcriptase inhibitor; sCD14, soluble CD14; sCD163, soluble CD163.
*Statistically significant P-value.
[a]Self-reported, missing data from 20 patients.
[b]Missing data from 24 patients.

immune-mediated atherosclerosis in HIV [3,4,5], these factors may include yet-untested markers of immune activation/inflammation.

Applying 2013 versus 2004 cholesterol treatment guidelines among HIV-infected patients with and without HRM coronary plaque, we find that according to 2013 guidelines, statins would be recommended for more patients in both groups. Nevertheless, even with the application of 2013 guidelines, statin therapy would not be recommended for the majority (74%) of patients with HRM coronary plaque. In modeling for HRM coronary plaque burden, the 2013 10-year ASCVD risk score accounts for only part of the variance, and other factors (including family history, ethnicity, and duration of ART use) also contribute. Study limitations include the relatively small sample size and the uncertainty of using presence of subclinical HRM coronary atherosclerotic plaque as a gold standard for defining high CVD risk and statin benefit. Moreover, in our modeling, the dependent variable (HRM plaque burden) is not normally distributed such that the magnitude of the beta estimates for independent variables is less relevant, but the directionality and significance of the estimates are robust.

Table 4. Multivariate linear regression model for subclinical HRM coronary atherosclerotic plaque burden.

	ß Estimate	Standard error	*P* value
10-year ASCVD risk score (%)	0.05	0.02	0.02
Hispanic ethnicity	−0.38	0.17	0.03
Family history of premature CHD	0.38	0.11	0.001
Duration of ART use (years)	0.04	0.02	0.02
Viral load (copies/ml)	0.0001	0.00008	0.12

HRM plaque burden represents number of HRM features in the highest risk plaque (0 = no plaque or plaque with no HRM features; 1 = plaque with 1 HRM feature; 2 = plaque with 2 HRM features). R^2 for overall model = 0.35, $P = 0.0006$. ART, antiretroviral therapy; ASCVD, atherosclerotic cardiovascular disease; CHD, coronary heart disease; HRM, high-risk morphology.

Nevertheless, our study takes into consideration new knowledge about the pathophysiology of atherosclerosis among HIV-infected patients and furnishes novel insights on the potential for even 2013 ACC/AHA guidelines to underestimate CVD risk in HIV. An event-driven randomized controlled trial of statin therapy in HIV would definitively determine baseline factors predictive of CVD in this population and identify subgroups of HIV-infected individuals most likely to substantially benefit from statin therapy.

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Conflicts of interest

There are no conflicts of interest.

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