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Treatment with pravastatin and fenofibrate improves atherogenic lipid profiles but not inflammatory markers in ACTG 5087

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Abstract

Objectives—Statins and fibrates alter lipids, apolipoproteins and inflammatory markers in persons without HIV. The objective of this study was to evaluate changes in lipoproteins, apolipoproteins and other markers of inflammation with the use of pravastatin and fenofibrate.

Design—Evaluation of participants in ACTG A5087, a randomized trial of pravastatin 40 mg/day or fenofibrate 200 mg/day for the treatment of dyslipidemia. Participants that failed single-agent therapy at week 12 were given the combination.

Methods—Participants with available specimens were tested for apolipoproteins A1 and B, adiponectin, plasminogen-activator inhibitor type 1 (PAI-1), P-selectin, and high-sensitivity C-reactive protein (hs-CRP).

Results—74 participants (37 per randomized arm) received either pravastatin or fenofibrate for 12 weeks with 60 receiving combination treatment from weeks 12–48. There were no significant changes in hs-CRP, PAI-1, and P-selectin. From baseline to week 12, the median Apo B levels (−8 mg/dL, $P=0.01$ for fenofibrate and −27 mg/dL, $P<0.01$ for pravastatin) and ApoB/A1 ratios (−0.16, $P<0.01$ for both arms) significantly decreased. From baseline to week 48, median adiponectin (−1 ng/dL, $P<0.01$), Apo B (−22 mg/dL, $P<0.01$) and Apo B/A1 ratios (−0.2, $P<0.01$) all decreased in those who went on combination therapy, whereas Apo A1 (9.5 mg/dL, $P=0.01$) levels increased.

Conclusion—Treatment with pravastatin or fenofibrate improves the atherogenic lipid profile within the first 12 weeks and is sustained through 48 weeks with combination therapy. Adiponectin levels decrease with lipid-lowering therapy. However, markers of inflammation and platelet

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activation were not appreciably changed suggesting that the biologic properties of these agents differ in persons with HIV infection.

Keywords

Dyslipidemia; Inflammation; Lipoproteins; Apolipoproteins; HIV; Antiretroviral therapy; Pravastatin; Fenofibrate

Introduction

Atherosclerosis is a complex inflammatory disorder that progresses over many decades. [1] Coronary atherosclerosis has emerged as a major co-morbid condition associated with both untreated HIV infection and the use of certain antiretroviral agents.[2–4] As the population with HIV infection lives longer, co-morbid health problems like coronary heart disease (CHD) will become more prevalent with advancing age and are likely to become increasingly important in the overall management of this population.

In the general population, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors also known as “statins” and fibrates have been shown to reduce the morbidity and mortality from CHD.[5–6] Much of this treatment benefit is associated with a reduction in low-density lipoprotein cholesterol (LDL-C). However, some of the benefit cannot be explained by reductions in LDL-C and has been attributed to improvements in a myriad of other abnormalities associated with CHD.[7] For example, treatment with statins has been shown to alter markers of inflammation, endothelial function, lower apolipoprotein B (ApoB) levels and improve atherogenic lipid profiles in persons without known HIV infection.[8–13] Fibrates have also been associated with improvements in atherogenic lipid profiles and a reduction CHD events in some but not all studies [14–17]. There are limited data on the clinical effectiveness of lipid-lowering therapy in persons with HIV infection. There are no randomized trials demonstrating a reduction in morbidity or mortality from CHD with the use of statins in persons with HIV infection. Furthermore, because of the complexity and cost of clinical endpoint trials of CHD, it is unlikely there will be a study in the HIV-infected population in the near future. Thus, it would be useful to determine if lipid-lowering therapy has similar biologic effects on markers of inflammation and endothelial function in persons with HIV infection as those published in persons without known HIV infection.

We hypothesized that pravastatin and fenofibrate are likely to have similar benefits in the reduction of atherogenic lipid profiles in HIV infected patients as those previously reported in the general population. However, because HIV is a chronic infection that results in widespread inflammation, we hypothesized the effects on markers of endothelial function and inflammation would not significantly change with the use of these lipid-lowering agents. The objective of this study was to evaluate the short-term effects of fenofibrate, pravastatin and the combination of the two on the following parameters: High-sensitivity C-reactive protein (hs-CRP); Plasminogen-activator inhibitor Type-1 (PAI-1); P-Selectin; Adiponectin; Apolipoproteins A1 (Apo A1) and B. These markers were selected based upon their association with CHD risk and reductions observed with the use of statins and fibrates.

Methods

ACTG A5087 was a randomized, multi-center, 48 week open-label non-inferiority study of two lipid-lowering agents in HIV-infected persons with combined hyperlipidemia.[18] All participants were on stable antiretroviral therapy prior to enrollment. Participants were randomized to micronized fenofibrate 200 mg or pravastatin 40 mg daily for 12 weeks followed by dual agent therapy for 36 weeks for persons that did not meet National Cholesterol Education

Project (NCEP) goals for LDL-C or study-defined desirable goals for HDL-C and triglyceride levels. Entry criteria required participants to have an LDL-C ≥ 130 mg/dL and triglyceride (TG) value ≥ 200 mg/dL. Participants used combined therapy if any one of the following three values were not achieved by 12 weeks: LDL-C ≤ 100 mg/dL (2 or more cardiovascular risk factors) or LDL-C < 130 mg/dL (0–1 cardiovascular risk factors); TG < 200 mg/dL (if entry TG was between 200–800 mg/dL) or TG < 400 mg/dL (if entry TG was more than 800 mg/dL); and HDL-C ≤ 35 mg/dL. There were 174 participants randomized to the main study, 88 to fenofibrate and 86 to pravastatin (Figure 1). A total of 136 participants subsequently received combination lipid-lowering therapy.

Study participants had plasma and serum samples obtained at baseline study entry, week 12 and week 48 after an overnight fast for at least 8 hours. Samples were underwent refrigerated centrifugation within 1 hour of collection and were subsequently aliquotted in 1 mL tubes and stored at -70°C at each site. Participants were excluded from this analysis for the following reasons: missing samples at one or more time points; insufficient quantity of samples at one or more time points; failure to complete 48 weeks of the study; or discontinuation of treatment. One-hundred and two study participants had sufficient samples available for further analysis including 53 participants initially randomized to fenofibrate (Arm A) and 49 participants randomized to pravastatin (Arm B). Funding was available to test 74 participants. Participants were placed in a master list by unique identification number. Every other subject was excluded until we eliminated 16 from Arm A and 12 from Arm B to derive the sample size of 37 participants from each arm. The study team recognizes that this was not a truly random sampling of the study population because only those with complete samples were considered for participation and, therefore, may represent a bias on generalizing results to the entire study.

Laboratory evaluations at baseline, Week 12 and Week 48 were done centrally at Quest Diagnostics and Nichols Institute. Total cholesterol, HDL-C and TG were measured using standard CDC-certified methods. LDL-C was measured by ultracentrifugation (Nichols Institute). Apolipoproteins B/A1 were measured by nephelometry (Dade Behring BN II System).[19] The Apo A1 dynamic range (2.5th – 97.5th percentile) was from 1.10–2.15 g/L. The Apo B dynamic range (2.5th – 97.5th percentile) was from 0.55–1.40 g/L. Plasminogen-activator inhibitor Type-1 was measured by Enzyme Immunoassay (American Diagnostica). The lower limit of detection was 1 ng/mL.[20] P-selectin was measured by Enzyme Immunoassay (R&D Systems). The lower limit of detection was 0.5 ng/mL. Adiponectin was measured by Enzyme Immunoassay (B-Bridge International). The linear range of the assay was from 0.375–12 ng/mL. High-sensitivity CRP (hs-CRP) was measured by enhanced immunonephelometry using BN systems (Dade Behring). The dynamic range was from 0.175 to 1100 mg/L. CD4 counts and HIV-1 RNA levels were done at local site labs using standard flow cytometry and RT-PCR methodologies.

Participants were stratified at randomization to the main trial by the presence or absence of 0–1 or 2 or more cardiovascular risk factors (e.g., hypertension, smoking status, low HDL-C, family history). The first objective of this study was to compare the change in the above parameters at week 12 in participants randomized to either fenofibrate or pravastatin single-agent therapy within each arm. The second objective was to compare the change in above parameters from week 12 to 48 in participants randomized to either fenofibrate or pravastatin who added the other agent within each arm. The third objective was to estimate the changes from baseline to week 48 in participants that took combination lipid-lowering therapy. For continuous variables, within-arm evaluations were accomplished using the Wilcoxon Signed-Rank tests or Sign tests if the distributions of the variables were not symmetric. Between-arm comparisons are performed using regression, where the markers of interest are used as outcome measures, and treatment arm, CD4 counts, baseline HIV-RNA viral load, and baseline markers of interest are used as covariates. For analyses estimating changes from baseline to week 48,

we combined all participants who used combination therapy using the above statistical methods. Significance testing was performed at the 0.05 level, and all reported *p* values are two-sided with no adjustment for multiple comparisons.

Results

Seventy-four participants were included in this analysis. The baseline characteristics are shown in table 1. There were 5 participants in the fenofibrate arm and 9 participants in the pravastatin arm that continued on monotherapy for the entire 48 weeks. There were no significant differences in baseline study characteristics, median CD4 counts or percentage of participants with an undetectable HIV viral load. Baseline glucose levels were similar in the pravastatin and fenofibrate groups (median values 87 vs. 91 mg/dL, respectively) and did not change significantly at weeks 12 or 48 (data not shown). The use of a protease inhibitor-based regimen was similar in both groups with 37 subjects taking 12 different specific regimens. Ritonavir was used in 17 of these subjects. Most of the remaining subjects were using a non-nucleoside reverse transcriptase inhibitor based regimen. The baseline characteristics of these 74 participants did not differ significantly from the overall cohort (174 participants, data not shown).

The short-term effects of pravastatin and fenofibrate alone after 12 weeks of administration are shown in table 2. Of note, hs-CRP levels were significantly higher at baseline in the pravastatin group (median 3.5 vs. 2.4, $P=0.023$). There were no significant changes in PAI-1, P-selectin or hs-CRP from baseline to week 12. From baseline to week 12, there were significant declines in Apo B levels and the Apo B/A1 ratio in both arms of the study. Apolipoprotein A1 levels significantly increased in the fenofibrate arm from baseline to week 12. Adiponectin levels declined in the pravastatin arm from baseline to week 12. These results did not change when analyses were restricted to subjects with an undetectable plasma HIV-1 RNA level (data not shown).

Pravastatin or fenofibrate were added in participants who did not respond to their initial randomized monotherapy after 12 weeks. There were 32 participants that initially received fenofibrate who added pravastatin and 28 participants randomized to pravastatin that added fenofibrate after week 12. Analysis of changes in markers of interest from week 12 through 48 overall demonstrated little change (Table 3). Only Apo B and Apo B/A1 ratio significantly changed in the group that initially received fenofibrate and added pravastatin.

In the analysis of 60 participants who initially received either fenofibrate or pravastatin and then went on dual therapy after week 12, there were no significant changes in hs-CRP or P-selectin levels from baseline to week 48 (Table 4). As expected, Apo B levels decreased with improvements in the Apo B/A1 ratio and an increase in Apo A1 levels. There was a significant decline in adiponectin levels from baseline to week 48. PAI-1 levels increased though this was of borderline statistical significance. We further restricted analyses to subjects with undetectable plasma HIV-1 RNA levels during the course of the study ($n=48$) and there were no significant changes in the overall results with any of the above markers (data not shown).

We analyzed whether changes in markers of interest correlated with changes in lipoprotein and apolipoprotein values at weeks 12 or 48. There were no significant correlations between changes in total cholesterol, TG or LDL-C and P-selectin, Adiponectin, PAI-1 and hs-CRP (data not shown). There was a positive correlation between Apo A1 levels, total cholesterol ($R=0.45$, 95% CI, 0.25, 0.62; $P<0.001$) and LDL-C ($R=0.42$, 95% CI, 0.21, 0.60; $P<0.01$) at week 12. The correlation persisted somewhat at week 48 for LDL-C ($R=0.24$, 95% CI, -0.002 , 0.45; $P=0.05$) but not for total cholesterol ($R=0.10$, 95% CI, -0.14 , 0.32, $P=0.43$). The TG levels negatively correlated with Apo A1 at week 48 ($R=-0.24$, 95% CI, -0.45 , -0.007 ;

$P=0.04$) but not week 12 ($R=-0.14$, 95% CI, $-0.36, 0.10$, $P=0.24$). The most significant correlations occurred between Apo B and total cholesterol and LDL-C levels at weeks 12 and 48. Changes in Apo B positively correlated with changes in total cholesterol at weeks 12 ($R=0.67$, 95% CI, $0.52, 0.78$; $P<0.001$) and 48 ($R=0.58$, 95% CI, $0.39, 0.71$; $P<0.001$). Similarly, changes in Apo B positively correlated highly with changes in LDL-C at weeks 12 ($R=0.54$, 95% CI, $0.35, 0.69$; $P<0.001$) and 48 ($R=0.39$, 95% CI, $0.16, 0.57$; $P<0.01$). There was no correlation between Apo B and TG at week 12 ($R=0.11$, 95% CI, $-0.13, 0.33$, $P=0.36$) but there was one at week 48 ($R=0.24$, 95% CI, $0.004, 0.45$; $P=0.04$). Significant positive correlations were also observed with the Apo B/A1 ratio at weeks 12 and 48 for total cholesterol and TG but not for LDL-C (data not shown). In the combined group analysis, BMI did not change during the study measured at weeks 12 or 48 ($P=0.56$ and $P=0.61$, respectively).

Discussion

The main finding in this study is that the use of pravastatin, fenofibrate or the combination was generally associated with favorable changes in atherogenic lipoproteins and apolipoproteins. Pravastatin and fenofibrate were both associated with significant declines in Apo B and the Apo B/A1 ratio after 12 weeks. Fenofibrate was also associated with increases in Apo A1 at week 12. As expected, fenofibrate use was associated with LDL-C particle generation at week 12 but there were differences at week 48 depending upon whether you added fenofibrate or pravastatin. The addition of pravastatin after 12 weeks resulted in significant declines in LDL-C whereas the addition of fenofibrate was associated with an increase in LDL-C at 48 weeks. However, after 48 weeks of lipid-lowering therapy there were sustained decreases in Apo B, increases in Apo A1 and a decrease in the Apo B/A1 ratio. These changes complement the main findings in ACTG A5087 demonstrating improvements in combined dyslipidemia at weeks 12 and 48.[18] In ACTG A5087 there were improvements in lipid levels in both arms at week 12 with median declines in total cholesterol of 16%, LDL-C of 20% and TG of 13% in the pravastatin arm and median declines in total cholesterol of 5% and TG of 35% in the fenofibrate arm. After 48 weeks, overall there were median declines in total cholesterol of 14%, LDL-C of 8% and TG of 35% while HDL-C increased by 11%. Thus, the increase in Apo A1, the major apolipoprotein associated with HDL-C metabolism, and the decline in Apo B, the major apolipoprotein associated with LDL-C metabolism are consistent with a biologic improvement with the use of pravastatin and fenofibrate.

Markers of glucose homeostasis, thrombogenesis, endothelial function and inflammation did not change as much with the use of pravastatin and fenofibrate. Pravastatin was associated with a slight decline in adiponectin after 12 weeks. Adiponectin levels also declined after the use of combination therapy. No changes were observed in glucose levels and insulin levels were not measured in this study. Plasminogen-activator inhibitor type 1 levels increased after 48 weeks, though this was of borderline statistical significance. There were no significant changes in hs-CRP and P-selectin.

The lipid-lowering treatment effects on lipoproteins and apolipoproteins observed in this study are consistent with those found in other studies of the general population. In the LIPID trial, pravastatin resulted in decreases in Apo B levels by 24% and increases in Apo A1 by 3% at 12 months.[11]. Similarly, Steinmetz reported a decline in Apo B of 20–23% and an increase of Apo A1 of 2–10% with the use of fenofibrate for 12 weeks. [21] Combination therapy with atorvastatin and fenofibrate has also been reported to result in decreases in Apo B and increases in Apo A1.[22] Importantly, these changes have been associated with improvements in the progression of atherosclerosis and endothelial function. For example, the LIPID trial demonstrated a reduction in the progression of atherosclerosis associated with declines in Apo B and increases in Apo A1 levels.[23] Furthermore, Koh and colleagues demonstrated improvements in flow-mediated dilatation associated with significant changes in

apolipoproteins B and A1 with the combined use of fenofibrate and atorvastatin.[22] Thus, the changes in lipoproteins and apolipoproteins observed in our study are similar to those conducted in prior studies of the population without known HIV infection and have correlated with improved CHD markers of outcome like atherosclerosis progression and endothelial function.

The absence of changes in markers of inflammation, endothelial function and glucose homeostasis differs with most studies reported in the general population. For example, adiponectin is an adipose tissue derived protein with anti-inflammatory properties. Higher levels are associated with lower risk of CHD.[24] Pravastatin has been shown to increase adiponectin levels in persons with impaired glucose tolerance and CHD.[25] Similarly, fenofibrate has been associated with increases in adiponectin levels in persons with primary hypertriglyceridemia.[26] It was disappointing that adiponectin levels declined in our study. In addition, numerous studies of statins and fibrates have demonstrated improvements in hs-CRP, P-selectin and PAI-1 levels. [8–12] For example, hs-CRP levels declined by 16.9% with the use of pravastatin 40 mg daily after 24 weeks in the PRINCE study.[27] The absence of improvements in these markers suggests that the pleiotropic effects observed with pravastatin and fenofibrate in other populations may not translate to those with HIV infection. However, whether statins or fibrates are associated with improvements in CHD outcomes in HIV infected persons may be unrelated to effects observed on markers of inflammation or endothelial dysfunction.

There are published studies reporting the effects of lipid-lowering therapy on lipoproteins, apolipoproteins, inflammation, endothelial function, and markers of cardiovascular risk in the same population with HIV infection. Our findings of changes in lipoproteins and apolipoproteins appear consistent with prior reports. In HIV-infected patients, a randomized-placebo controlled study of 12 participants taking pravastatin resulted in a significant median decrease in Apo B by 34 mg/dL but no significant change in Apo A1 levels after 12 weeks of treatment.[28] The lack of changes in PAI-I and hs-CRP levels in our study were similar to those observed by Mallon in 34 participants randomized to pravastatin or placebo for 12 weeks. [29] Badiou also studied 36 HIV infected subjects randomized to vitamin E 500 mg/day or fenofibrate 200 mg/day for 3 months and then the combination for an additional 3 months. [30] They observed declines in total cholesterol (13%), TG (40%), LDL-C (16%), ApoB (13%) and ApoCIII (26%) with increases in HDL-C (14%), ApoA1 (12%) and LDL particle size with the use of fenofibrate. Similar to our study, they observed no change in CRP levels.[30] Finally, Stein reported no significant change in flow-mediated dilatation with the use of 8 weeks of pravastatin in a placebo-controlled cross-over design study of 20 HIV-infected participants. [31] Thus, prior studies confirm our findings of changes in lipoproteins and apolipoproteins. The consistency of prior reports and our study confirming the absence of changes in markers of inflammation and endothelial function suggest that HIV infection or possibly other co-morbid infections may mitigate the ability to measure changes in these effects associated with lipid-lowering agents. Alternatively, the effectiveness of specific lipid-lowering agents may be ameliorated by drug-drug interactions with antiretroviral agents. Indeed, pravastatin levels and efficacy has been observed to be diminished in persons using some protease inhibitors. [32] However, it is unclear what role these pleiotropic effects of lipid-lowering agents may have, if any, on CHD outcomes in persons with HIV infection.

There are some limitations to the findings observed in this study. Antiretroviral therapy regimens were not provided by the study. All subjects were on stable antiretroviral treatment for at least 6 months. However, there may be differences in lipoprotein, apolipoprotein and inflammatory marker responses to lipid-lowering agents based upon concurrent use of specific antiretroviral agents. We did not study more potent statins that have been associated with greater reductions in lipoproteins, apolipoproteins and improvements in rates of atherosclerosis

progression.[33] However, there are clinical endpoint trials demonstrating a survival benefit with the use of pravastatin in the general population with CHD.[34] Our sample size may limit some of the conclusions. For example, based upon a sample size of 37 subjects we would have an 83.7% power to detect a mean change of 3.0 mg/L in hs-CRP within arms from baseline to week 12. We could have missed a smaller change in some of the parameters. However, there was no obvious directional signal suggesting improvements in these markers. Thus, although our sample size may not be sufficient to exclude a statistically important effect we think it is less likely that we missed an important biologic effect. While we cannot infer a correlation between outcome data and changes in circulating lipids it is encouraging that there were biologically important declines in total cholesterol, LDL-c, and Apo B. We recognize that biologic improvements in lipoproteins and apolipoproteins do not always translate to a benefit in clinical outcomes, a finding illustrated by a large raloxifene study [35]. We also did not test for the presence of other co-morbid chronic infections like hepatitis B or C that might affect the anti-inflammatory benefits of statins or fibrates. Our analyses were limited to participants with complete samples available and may not be representative of the entire study population. We did not find any significant differences in baseline characteristics of those studied and those omitted from analysis (data not shown). As with any study where multiple statistical comparisons are performed there is a chance for false positive results. Finally, we did not incorporate measures of endothelial function or atherosclerosis progression to determine whether beneficial effects may occur despite the absence of changes in surrogate markers of CHD.

Overall, we confirmed some of the beneficial effects of statins and fibrates in improving lipoprotein and apolipoprotein levels associated with the risk of CHD. The lack of changes in hs-CRP and other markers of endothelial function and inflammation are disappointing but not surprising given that HIV infection is a chronic inflammatory process and there are complex drug-drug interactions between statins and antiretroviral therapy. The importance of these findings require further investigation to determine if lipid-lowering therapy currently recommended for persons with HIV infection extends the same benefits as those observed in persons without HIV infection.

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List of Abbreviations

ACTG	AIDS Clinical Trials Group
Apo B	Apolipoprotein B
Apo A1	Apolipoprotein A1
CDC	Centers for Disease Control and Prevention
CD4 count	CD4+ lymphocyte count
CHD	Coronary heart disease
CV	Coefficient of variation
HDL-C	High density lipoprotein cholesterol
hs-CRP	High sensitivity C-Reactive Protein
HIV	Human immunodeficiency virus-1
HMG-CoA	3-hydroxy 3-methylglutaryl coenzyme A
LDL-C	Low density lipoprotein cholesterol
PAI-1	Plasminogen-activator inhibitor, type 1
RT-PCR	Reverse transcriptase polymerase chain reaction
TG	Triglycerides
TC	Total cholesterol

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Table 1

Baseline Characteristics at Time of Randomization

	Overall	Arm A Fenofibrate (n=37)	Arm A F→PF* (n=32)	Arm B Pravastatin (n=37)	Arm B P→FP* (n=28)	Dual: FP or PF (n=60)
Gender						
Male	71 (96%)	37 (100%)	32 (100%)	34 (92%)	25 (89%)	57 (95%)
Female	3 (4%)			3 (8%)	3 (11%)	3 (5%)
Race/Ethnicity						
White	54 (73%)	28 (76%)	24 (75%)	26 (70%)	24 (86%)	47 (78%)
Black	6 (8%)	2 (5%)	2 (6%)	4 (11%)	4 (14%)	2 (3%)
Hispanic	12 (16%)	5 (14%)	4 (13%)	7 (19%)		9 (15%)
Other	2 (2%)	2 (5%)	2 (6%)			2 (4%)
Median Age (years) (range)	44 (28–62)	46 (28–62)	45 (28–53)	42 (31–57)	42.5 (31–57)	44 (28–57)
IDU (Current/Previous)	4 (5%)	1 (3%)	-	3 (8%)	2 (7%)	3 (5%)
Stratification						
< 2 CV risks	39 (53%)	17 (46%)	16 (50%)	22 (59%)	13 (46%)	29 (48%)
≥ 2 CV risks	35 (47%)	20 (54%)	16 (50%)	15 (41%)	15 (54%)	31 (52%)
Median Body mass index (25 th – 75 th percentiles)	26 (22.7–29.0) (n=69)	25.4 (22.2–27.1)	25.4 (22.2–27.1)	26.4 (24.0–30.9)	26.0 (23.0–30.4)	25.9 (22.6–28.3)
Median CD4 count (cells/mm ³) (25 th – 75 th percentiles)	418 (289–681)	358 (276–573)	349 (269–612)	462 (312–690)	483 (318–730)	415 (283–695)
HIV-1 RNA levels						
≤50 copies/mL	58 (78%)	29 (78%)	26 (81%)	29 (78%)	22 (79%)	48 (80%)
>50 copies/mL	16 (22%)	8 (22%)	6 (19%)	8 (22%)	6 (21%)	12 (20%)

* P→Pravastatin; F→Fenofibrate; F→PF (Randomized to fenofibrate and added pravastatin); P→FP (Randomized to pravastatin and added fenofibrate)

Table 2

Median (25th to 75th percentile interquartile ranges) Values for Coronary Heart Disease Markers at Baseline and Week 12

	Fenofibrate (n=37)		Change 0–12 weeks		Pravastatin (n=37)		Change 0–12 weeks [†]
	Baseline	Week 12			Baseline	Week 12	
Hs-CRP (mg/L)	2.4 (1.2, 3.9)	3.7 (1.2, 6.9)	0.2 (−0.60, 2.25) (P=0.18)		3.5 (2.1, 6.0)	3.35 (1.95, 5.95)	−0.2 (−1.0, 1.1) (P=0.76)
P-Selectin (ng/mL)	56 (49, 75)	55 (50, 73)	−1 (−10, 6) (P=0.77)		58 (48, 77)	57 (48, 66)	−1 (−12, 7) (P=0.37)
PAI-1 (ng/mL)	79 (61, 112)	84 (57, 95)	11 (−46, 40) (P=1.00)		76 (44, 95)	77 (55, 97)	7.5 (−14.5, 33.5) (P=0.14)
Adiponectin (ng/mL)	4 (3, 6)	4 (3, 6)	0 (−1, 0) (P=0.36 [*])		4.5 (3, 7)	4 (3, 7)	0 (−1, 0) (P=0.04)
Apo A1 (mg/dL)	142.5 (130.6, 157.0)	153 (135, 177)	10 (2, 25) (P=0.01)		146 (132.0, 164.5)	141 (123, 160)	−5 (−18, 5) (P=0.10)
Apo B (mg/dL)	159.5 (140.5, 177.0)	148 (126, 166)	−8 (−31.5, 3.5) (P=0.01)		151.0 (134.5, 174)	121 (103, 149)	−27 (−42.5, −10.5) (P<0.01)
Apo B/A1 ratio	1.13 (0.99, 1.25)	0.99 (0.76, 1.08)	−0.16 (−0.28, −0.06) (P<0.01)		1.01 (0.87, 1.29)	0.88 (0.68, 1.06)	−0.16 (−0.33, −0.01) (P<0.01)
Cholesterol (mg/dL)	281 (252, 325)	274 (228, 299)	−16 (−54, 4) (P=0.01)		260 (249, 289)	226 (202, 270)	−40 (−62, −19) (P<0.01)
LDL (mg/dL)	148 (132, 176)	169 (135, 198)	15 (−1, 51) (P=0.01)		160 (145, 179)	120 (109, 153)	−33 (−58, −21) (P<0.01)
HDL (mg/dL)	34 (30, 39)	38 (30, 43)	2 (−1, 7) (P=0.01)		35 (32, 41)	34 (30, 39)	−2 (−5, 3) (P=0.2)
Triglycerides (mg/dL)	375 (262, 457)	211 (166, 360)	−119 (−161, −35) (P<0.01)		307 (225, 399)	289 (209, 399)	18 (−110, 109) (P=0.98)

^{*} sign test p-value

[†] Median of the changes

Table 3

Median Values (25th to 75th percentile interquartile ranges) of Coronary Heart Disease Markers from weeks 12 to 48.

	Week 12		Week 48		Change from Week 12-48 [†]	
	Fenofibrate Arm A (n=32)	Pravastatin Arm B (n=28)	F→PF* Arm A (n=32)	P→PF* Arm B (n=28)	Arm A F→FP* (n=32)	Arm B P→PF* (n=28)
Hs-CRP (mg/L)	3.90 (1.20, 6.40)	2.80 (1.70, 5.90) (n=27)	2.25 (1.15, 5.85)	4.45 (1.35, 8.35)	0.05 (-1.45, 0.90) (P=0.73)	0.10 (-1.4, 2.6) (P=0.58)
P-Selectin (ng/mL)	55.5 (50.0, 73.5)	56 (47.5, 68.0)	59.5 (49.0, 74.5)	58.0 (51.5, 78.0)	-1 (-6, 12) (P=0.92)	9 (-6, 19) (P=0.07)
PAI-1 (ng/mL)	85 (67, 96)	80 (57, 108) (n=27)	89.5 (59.5, 126.0)	84 (66.5, 128.0)	2.0 (-14.5, 47.0) (P=0.37)	14.0 (-16, 65) (P=0.35)
Adiponectin (ng/mL)	4 (3, 6)	4 (3, 6) (n=27)	3 (2, 5)	4 (3, 7)	0 (-1, 0) (P=0.40)	0 (-1, 0) (P=0.67)
Apo A1 (mg/dL)	153 (134, 176)	139 (122, 159) (n=27)	161 (141, 168)	148.5 (141, 164)	-3.5 (-10.5, 10) (P=0.67)	10 (-7, 21) (P=0.07)
Apo B (mg/dL)	149.5 (128.5, 167.5)	133 (112, 159) (n=27)	136 (102.0, 151.5)	136 (120.5, 158.0)	-17.5 (-37, -3) (P<0.01)	7.00 (-8, 22) (P=0.13)
Apo B/A1 ratio	0.99 (0.76, 1.16)	0.93 (0.81, 1.18) (n=27)	0.85 (0.66, 1.01)	0.86 (0.77, 1.06)	-0.10 (-0.24, 0.03) (P=0.01)	-0.02 (-0.14, 0.16) (P=0.93)
Cholesterol (mg/dL)	275.5 (232.5, 307)	242.5 (203.5, 279)	244 (188, 265) (n=31)	248 (213, 288) (n=27)	-32 (-58, -10) (P<0.01)	6 (-5, 34) (P=0.08)
LDL (mg/dL)	171.5 (132.5, 198.5)	119.5 (105, 157.5)	150 (108, 172)	148 (135, 172) (n=26)	-24 (-44, 1) (P<0.01)	32 (1, 51) (P<0.01)
HDL (mg/dL)	37.5 (30.5, 41)	32 (28, 38)	36 (32, 45) (n=31)	35 (31, 41) (n=27)	1 (-4, 4) (P=0.65)	2 (-2, 6) (P=0.1)
Triglycerides (mg/dL)	231.5 (167, 365)	339.5 (240.5, 462.5)	188 (130, 289) (n=31)	228 (187, 367) (n=27)	-20 (-105, 18) (P=0.08)	-51 (-125, -7) (P=0.01)

* P=Pravastatin; F=Fenofibrate; F→PF (Randomized to fenofibrate and added pravastatin); P→FP (Randomized to pravastatin and added fenofibrate).

[†] Median of the changes

Table 4

Evaluation of Coronary Heart Disease Markers Using Combination Lipid-lowering Therapy after Week 12.

	Baseline Median Values	Week 48 Median Values	Median Change Baseline-Week 48 [†]	P value
Hs-CRP (mg/L) (25 th –75 th percentiles)	2.7 (1.5, 4.5) (n=58)	3.2 (1.25, 7.10) (n=58)	−0.05 (−0.80, 2.70)	P=0.56
P-Selectin (ng/mL) (25 th –75 th percentiles)	58 (48.5, 75.5) (n=60)	58.5 (50, 75) (n=60)	1.5 (−8.5, 16)	P=0.46
PAI-1 (ng/mL) (25 th –75 th percentiles)	79.5 (60.5, 114) (n=60)	86.5 (61, 128) (n=60)	14 (−26, 49)	P=0.05
Adiponectin (ng/mL) (25 th –75 th percentiles)	4 (3, 6) (n=58)	3.5 (2, 6) (n=58)	−1 (−1, 0)	P<0.01
Apo A1 (mg/dL) (25 th –75 th percentiles)	145 (130, 157) (n=58)	154 (141, 168) (n=58)	9.5 (−6, 20)	P=0.01
Apo B (mg/dL) (25 th –75 th percentiles)	154 (137, 178) (n=58)	136 (115, 153) (n=58)	−22 (−44, −2)	P<0.01
Apo B/A1 ratio (25 th –75 th percentiles)	1.10 (0.95, 1.24) (n=58)	0.85 (0.75, 1.04) (n=58)	−0.2 (−0.33, −0.02)	P<0.01
Cholesterol (mg/dL) (25 th –75 th percentiles)	269 (248.5, 316) (n=60)	245 (208, 275) (n=58)	−40 (−73, −7)	P<0.01
LDL (mg/dL) (25 th –75 th percentiles)	156.5 (139, 179) (n=60)	148 (122, 172) (n=57)	−10 (−38, 25)	P=0.08
HDL (mg/dL) (25 th –75 th percentiles)	35 (30, 39) (n=60)	36 (31, 42) (n=58)	2 (−2, 8)	P=0.04
Triglycerides (mg/dL) (25 th –75 th percentiles)	355 (252.5, 468.5) (n=60)	206 (164, 338) (n=58)	−86.5 (−248, −6)	P<0.01

[†] Median of the changes