

N-125 Changes in Markers of Atherogenic Dyslipidemia, Inflammation, and Platelet Activation with Treatment with Pravastatin, Fenofibrate, or the Combination: Results from ACTG A5087

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Abstract

Background: Atherosclerosis is a complex inflammatory process. Treatment of dyslipidemia with statins or fibrates alters lipids and markers of inflammation however there are few published studies in persons with HIV. The objective of this study was to evaluate changes in apolipoproteins and markers of platelet activation (PAI-1) and inflammation (high-sensitivity C-reactive protein, P-selectin) with use of statins and/or fibrates.

Methods: Evaluation of 174 subjects enrolled in ACTG A5087, a randomized trial of pravastatin (P) or fenofibrate (F) for the treatment of combined hyperlipidemia in persons with HIV. Subjects that failed single-agent therapy at week 12 were given combination (PF) therapy. Subjects with available specimens were tested for apolipoproteins A1 and B, lipoprotein(a) (Lp(a)), adiponectin, PAI-1, P-selectin, HS-CRP at baseline, week 12 and week 48.

Results: Of the 174 subjects randomized, 102 had available specimens. 74 subjects (37 per randomized arm) were selected randomly for testing and received the following treatment for 48 weeks (based on week 12 response): F alone (n=37), P alone (n=37), F + 12 weeks adding P through week 48 (n=32); and P + 12 weeks adding F through week 48 (n=32). 77 subjects were male; 54 were white and 26 (34%) had 25 risk factors for coronary heart disease. The subjects were well matched by baseline CD4+, HIV viral load, and demographics. There were no significant changes in hs-CRP, PAI-1, and P-selectin from baseline to week 12 or week 12-48. From baseline to week 12, adiponectin, apoB and ApoB/A1 ratios all significantly decreased in the P and F arms. Lp(a) and Apo A1 increased significantly in the F arm only (P<0.01 for both). From weeks 12-48, only Apo B levels (and ApoB/A1 ratio) declined significantly in those treated initially with F and added P (P<0.01 and P<0.01, respectively). From baseline to week 48, adiponectin levels significantly decreased in the combination treatment groups (P<0.02 and P<0.01, respectively for those starting with F or P). Apo B decreased significantly in all groups except those treated with F alone.

Conclusions: Treatment with Pravastatin or Fenofibrate improves the atherogenic lipid profile within the first 12 weeks of treatment and it is sustained through 48 weeks with combination therapy. Adiponectin levels also decrease with lipid-lowering therapy. General markers of inflammation and platelet activation were not appreciably changed despite improvement in lipids.

Introduction

• Atherosclerosis is a complex inflammatory disorder that occurs over many decades.

• Treatment with statins and/or fibrates has been shown to alter markers of inflammation, endothelial function and atherogenic lipid profiles in persons without HIV infection.

• There is limited data on the clinical endpoint effectiveness of lipid-lowering therapy in persons with HIV infection.

• It would be useful to determine if lipid-lowering therapy has similar effects on these various markers in persons with HIV infection as those published in persons without HIV infection.

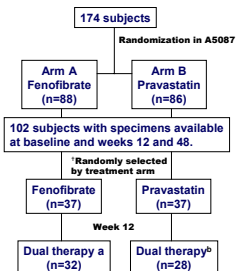
• The objective of this study was to evaluate the short-term effects of fenofibrate, pravastatin or the combination of the two on the following parameters:

- Hs-CRP (High-sensitivity C-reactive protein)
- Lp(a) (Lipoprotein(a)-atherogenic particle)
- PAI-1 (Plasminogen activator inhibitor-1)
- P-Selectin (Cell adhesion molecule)
- Adiponectin (Hormone regulating glucose/lipids)
- Apolipoproteins A1/B (Associated with CHD Risk)

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Methods



*5 subjects in the fenofibrate arm remained on monotherapy after week 12.
*9 subjects in the pravastatin arm remained on monotherapy after week 12.

ACTG A5087 was a randomized trial of HIV-infected persons with combined hyperlipidemia. Subjects were randomized to fenofibrate or pravastatin monotherapy for 12 weeks followed by dual agent therapy for persons that did not meet NCEP goals for LDL, HDL and triglyceride levels.

*102 subjects had sufficient samples available (48 in Arm A & 53 in Arm B). We chose every other subject till we eliminated 12 in Arm A and 16 in Arm B to derive the sample size of 74 total subjects based upon available resources.

Evaluations at Entry, Week 12 and Week 48 were done centrally at Quest Diagnostics and Nichols Institute:

- Fasting (> 8 h) triglycerides, total cholesterol, HDL and LDL cholesterol
- LDL cholesterol – Ultracentrifugation
- Lp(a) – Immunoturbidimetric (PolyMED)
- Hs-CRP – Nephelometry (Dade Behring BN II System)
- PAI-1 – Enzyme Immunoassay (American Diagnostica)
- Apolipoproteins A1/B – Nephelometry (Dade Behring BN I System)
- P-selectin – Enzyme Immunoassay (R&D Systems)
- Adiponectin – Enzyme Immunoassay (B-Bridge International)

• CD4 counts and HIV-1 RNA levels were done at local site labs.

Statistical Methods:

Subjects were stratified at randomization to the main trial by Cardiovascular risk factors (e.g. hypertension, smoking status, low HDL, family history, age).

The first objective of this study was to compare the change in the above parameters at week 12 in subjects randomized to either fenofibrate (F) or pravastatin (P) single-agent therapy within each arm.

The second objective was to compare the change in above parameters from week 12 to 48 in subjects randomized to either F or P who added the other agent within each arm.

The third objective was to compare the changes from baseline to week 48 in subjects that took combination therapy (P – PF or F – FP).

Within-arm evaluations used the Wilcoxon Signed-Rank tests. Significance testing was performed at the 0.05 level with no adjustment for multiple comparisons.

Table 1 - Baseline Demographics at Time of Randomization

	Total	Arm A F –PF* (n=32)	Arm A F (n=5)	Arm B P –FP* (n=28)	Arm B P (n=9)
Gender					
Male	71 (96%)	32 (100%)	5 (100%)	25 (89%)	9 (100%)
Female	3 (4%)			3 (11%)	
Race/Ethnicity					
White	54 (73%)	24 (75%)	4 (80%)	23 (82%)	3 (33%)
Black	6 (8%)	2 (6%)		2 (8%)	4 (44%)
Hispanic	12 (16%)	4 (13%)	1 (20%)	5 (18%)	2 (22%)
Other	2 (2%)	2 (6%)			
Age					
25-34 years	8 (11%)	2 (6%)	1 (20%)	4 (14%)	1 (11%)
35-44 years	34 (46%)	14 (44%)	1 (20%)	14 (50%)	5 (56%)
45-54 years	30 (41%)	10 (31%)	2 (40%)	9 (32%)	3 (33%)
> 55 years	2 (3%)	1 (3%)	1 (20%)	1 (4%)	
IDU (Current/Previous)	4 (5%)	1 (3%)	0	2 (7%)	1 (11%)
Stratification					
< 2 CV risks	39 (53%)	16 (50%)	1 (20%)	13 (46%)	9 (100%)
≥ 2 CV risks	35 (47%)	16 (50%)	4 (80%)	15 (54%)	
Median CD4 count (interquartile range)	418 (289-681)	349 (269-612)	422 (314-546)	483 (318-730)	453 (309-635)
HIV-1 RNA levels					
≤50 copies/mL	58 (78%)	26 (81%)	3 (60%)	22 (79%)	7 (78%)
>50 copies/mL	16 (22%)	6 (19%)	2 (40%)	6 (21%)	2 (22%)

*Changed to combination therapy after week 12.

Table 2 • Median (25% to 75% Interquartile ranges) Values for Selected Parameters at Baseline and Week 12

	Fenofibrate (n=37)		Change 0-12 wk	Pravastatin (n=37)		Change 0-12 wk
	Baseline	Week 12		Baseline	Week 12	
Hs-CRP (mg/L)	2.4* (1.2, 3.9)	3.7 (1.2, 6.9)	0.2* (P=0.18)	3.5* (2.1, 6.0)	3.35* (1.95, 5.95)	-0.2* (P=0.76)
P-Selectin (ng/mL)	56 (48, 75)	55 (50, 73)	-1 (P=0.77)	58 (48, 77)	57 (48, 66)	-1 (P=0.37)
PAI-1 (ng/mL)	79 (61, 112)	84 (57, 95)	11 (P=1.00)	76 (44, 95)	77* (55, 97)	7.5* (P=0.14)
Lp(a) (nmol/L)	24.5* (13, 86)	36.5* (13, 100)	1* (P=0.01)	35.5* (13, 191)	22.0 (13, 190)	0* (P=1.00)
Adiponectin (mcg/mL)	4.0* (3, 6)	4 (3, 6)	0* (P=0.03)	4.5* (3, 7)	4* (3, 7)	0* (P=0.04)
Apo A1 (mg/dL)	142.5* (130.6, 157.0)	153 (135, 177)	10* (P=0.01)	146.0* (132.0, 164.5)	141* (123, 160)	-5* (P=0.10)
Apo B (mg/dL)	159.5* (140.5, 177.0)	148 (126, 166)	-8* (P=0.01)	151.0* (134.5, 174)	121* (103, 149)	-27* (P<0.01)
Apo B/A1 ratio	1.13* (0.99, 1.25)	0.99 (0.76, 1.08)	-0.16* (P<0.01)	1.01* (0.87, 1.29)	0.88* (0.68, 1.06)	-0.16* (P<0.01)

*missing 1 subject for analysis; *missing 2 subjects for analysis; *missing 3 subjects for analysis.

Table 3 – Median values and changes in selected parameters from weeks 12 to 48 and weeks 0 to 48.

	Change from Week 12-48		Change from baseline to week 48		Combined analysis (n=90)	
	Arm A F –PF* (n=32)	Arm B P –FP* (n=28)	Arm A F –PF* (n=32)	Arm B P –FP* (n=28)	Value at Week 48 (25%-75% interquartile range)	Median change from 0-48 weeks
Hs-CRP (mg/L)	0.05 (P=0.73)	0.10* (P=0.58)	-0.05 (P=0.57)	0.10* (P=0.91)	3.20 (1.25, 7.10)	-0.05* (P=0.56)
P-Selectin (ng/mL)	-1 (P=0.92)	9 (P=0.07)	-1 (P=0.89)	2 (P=0.35)	58.5 (50, 75)	1.5 (P=0.46)
PAI-1 (ng/mL)	2.0 (P=0.37)	14.0* (P=0.35)	13.0 (P=0.51)	20.0 (P=0.03)	86.5 (61, 128)	14.0 (P=0.05)
Lp(a) (nmol/L)	0* (P=0.74)	0* (P=0.91)	0* (P=0.44)	0* (P=0.84)	31* (13, 154)	0* (P=0.66)
Adiponectin (mcg/mL)	0 (P=0.40)	0* (P=0.67)	-1* (P=0.02)	-1* (P<0.01)	3.5 (2, 6)	-1* (P=0.01)
Apo A1 (mg/dL)	-3.5 (P=0.67)	10* (P=0.07)	10* (P=0.01)	6* (P=0.25)	154 (141, 168)	9.5* (P=0.01)
Apo B (mg/dL)	-17.5 (P<0.01)	7.00* (P=0.13)	-32* (P<0.01)	-16* (P<0.01)	136 (115, 153)	-22* (P<0.01)
Apo B/A1 ratio	-0.10 (P=0.10)	-0.02* (P=0.93)	-0.29* (P<0.01)	-0.16* (P=0.01)	0.85 (0.75, 1.04)	-0.20* (P<0.01)

*missing 1 subject for analysis; *missing 2 subjects for analysis; *missing 3 subjects for analysis.

Summary and Conclusions

• From baseline to week 12 fenofibrate was associated with:
 • ↓ Adiponectin, ↓ Apo B; ↓ Apo B/A1 ratio
 • ↓ Lp(a); ↓ Apo A.

• From baseline to week 12 pravastatin was associated with:
 • ↓ Adiponectin; ↓ Apo B; and ↓ Apo B/A1 ratio.

• These changes were largely sustained when one compared baseline values to those at 48 weeks analyzing subjects who received either fenofibrate or pravastatin and added the other drug after week 12.

• At week 48, Apo B levels and the Apo B/A1 ratio declined when pravastatin was added to fenofibrate after week 12.

• These changes are consistent with other published studies in non-HIV infected persons that have demonstrated an improvement in the atherogenic profile of lipids associated with the use of statins and fibrates.

• The absence of changes in markers of inflammation and endothelial function suggest that HIV infection or other co-morbid infections may mitigate the ability to measure anti-inflammatory effects associated with lipid-lowering agents.