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Intensive Lifestyle Modification Reduces Lp-PLA$_2$ in Dyslipidemic HIV/HAART Patients

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Abstract

Patients with dyslipidemia associated with HIV-1 infection and highly active antiretroviral therapy (HAART) have elevated levels of Lp-PLA$_2$ and CCL5/RANTES, which may increase risk of cardiovascular disease.

Purpose—This study aimed to determine whether an intensive diet and exercise (D/E) program, independently or combined with fenofibrate or niacin, could reduce Lp-PLA$_2$ or RANTES.

Methods—Hypertriglyceridemic HIV patients on stable HAART (n=107) were randomized to one of five interventions: 1) Usual Care (UC); 2) D/E with placebos; 3) D/E with fenofibrate and placebo; 4) D/E with niacin and placebo; or 5) D/E with fenofibrate and niacin for 24 weeks. Lp-PLA$_2$ and RANTES concentrations were measured in fasting plasma samples at baseline and post-intervention. General linear models were used to compare Lp-PLA$_2$ and RANTES levels between the five groups post-intervention, controlling for baseline levels, age, BMI, CD4$^+$ T-cell count, viral load, duration of infection, and HAART.

Results—At baseline, fasting plasma Lp-PLA$_2$ (388.5 ± 127.5 ng/mL) and RANTES (43.8 ± 25.5 ng/mL) levels were elevated when compared to healthy controls. Post-treatment Lp-PLA$_2$ mass was lower in patients who received D/E only (323.0 ± 27.2 ng/mL), D/E plus fenofibrate (327.2 ± 25.9 ng/mL) and D/E plus niacin (311.1 ± 27.8 ng/mL) when compared to patients receiving UC (402.2 ± 25.3 ng/mL). RANTES concentrations were not significantly affected by any intervention.

Conclusions—Elevated plasma Lp-PLA$_2$ mass can be reduced by an intensive diet and exercise program in patients with HIV/HAART-associated dyslipidemia. RANTES is elevated but is not reduced by lifestyle modification, fenofibrate or niacin.

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Keywords

platelet-activating factor acetylhydrolase; fenofibrate; niacin; dyslipidemia; RANTES

INTRODUCTION

Patients with HIV infection receiving highly active antiretroviral therapy (HAART) frequently develop a unique and complex metabolic syndrome characterized by dyslipidemia, lipodystrophy, central visceral obesity and insulin resistance (10, 13, 27). These features are established, independent risk factors for cardiovascular disease, and place patients with HIV/HAART-associated dyslipidemia or lipodystrophy at increased risk of atherosclerosis (4, 7, 18). Dyslipidemia in HIV patients is frequently accompanied by abnormal plasma levels of a number of emerging and "non-traditional" cardiovascular risk factors, including plasma lipoprotein associated factors such as lipoprotein-associated phospholipase A_2 (Lp-PLA_2) and inflammatory chemokines such as CCL5 or RANTES (regulated on activation, normal T-cell expressed and secreted) (19, 21, 25). The presence of these factors could accelerate atherosclerosis in HIV patients due to their coexisting highly inflammatory state.

Lp-PLA_2, also known as platelet-activating factor acetylhydrolase (PAF-AH), is a calcium-independent phospholipase that is secreted by macrophages and other inflammatory cells in the vessel wall (6, 34, 39). Circulating Lp-PLA_2 is bound to apolipoprotein B-containing proteins and to a lesser extent by high-density lipoproteins (6, 12, 34, 39). Lp-PLA_2 hydrolyzes the sn-2-acyl bond of phospholipids in cell membranes and lipoproteins, yielding nonesterified fatty acids and lysophospholipids that are precursors of several proinflammatory mediators (17). In the Lp-PLA_2 Studies Collaboration (36), Lp-PLA_2 activity and mass were associated with risk for coronary heart disease that was similar in magnitude to that of non-HDL cholesterol (non-HDL-C) or systolic blood pressure. According to the Heart Protection Study (14), the associations of Lp-PLA_2 mass and activity with vascular outcomes and events depend partly on plasma lipid levels. Furthermore, Lp-PLA_2 activity is thought to be a significant mediator in the pathogenesis of several neurological, cardiovascular, and metabolic manifestations associated with HIV-1 infection and the acquired immunodeficiency syndrome (AIDS) (21, 30). This is supported by the elevated Lp-PLA_2 activity observed in the plasma of patients with AIDS compared to controls (21).

Chemokines and their G-protein coupled receptors contribute significantly to the pathogenesis of both atherosclerosis and HIV infection (19). RANTES is a CC chemokine that is stored in the alpha granules of platelets. Following platelet activation, it is released and deposited on inflamed or atherosclerotic endothelium mediating monocyte transmigration. The receptor for RANTES is CCR5, well-known for its role as a co-receptor for HIV-1 infection (19). RANTES is elevated in patients with HIV infection or AIDS (25, 31, 41) compared to healthy controls, and appears to be variably elevated in populations of patients with coronary artery disease (8, 15).

Hypertriglyceridemia and low HDL cholesterol are characteristic lipid defects in HIV patients on HAART. Adverse drug interactions between HAART drugs and cytochrome P450 3A4-metabolized statins (6, 12), and a high prevalence of hepatitis renders standard lipid-lowering approaches inadequate in achieving recommended treatment goals in HIV patients. Previous work by our group and others (summarized in Ref 3) indicated that the key underlying defects are excessive lipolysis and inadequate oxidation of the released fatty

acids. This prompted the choice of niacin (an anti-lipolytic drug) and fenofibrate (which promotes fatty acid oxidation) as the lipid-lowering agents in the Heart Positive trial.

Diets high in saturated fat and physical inactivity are associated with elevated levels of Lp-PLA_2 and RANTES (1, 40). There have been limited studies focused on the effects of dietary factors and physical activity or exercise on Lp-PLA_2 and RANTES. The general consensus is that dietary and lifestyle factors that reduce LDL-cholesterol likely result in Lp-PLA_2 reduction (40). In contrast, it remains unclear if similar diet and physical activity modifications would reduce RANTES levels; however, Garcia et al., (11) showed that single session of moderate intensity exercise (70% VO_2max) for one hour can decrease RANTES levels in sedentary women.

The aim of this study was to assess if an intensive diet and exercise program, independently or combined with fenofibrate or niacin, could reduce elevated plasma levels of Lp-PLA_2 mass and RANTES in a subset of patients enrolled in the Heart Positive Study, a randomized, double-blind, placebo-controlled trial to compare the effects of usual care to diet, exercise, fenofibrate or niacin on lipid profiles of patients with HIV/HAART-associated dyslipidemia (3).

METHODS

Subjects and Design

Details of the Heart Positive Study's research design have been reported previously (3). All experimental protocols were approved by the Institutional Review Board of Baylor College of Medicine, Legacy Community Health Center and the Harris County Hospital District. Written informed consent was obtained from all participants (N=107) prior to enrollment into the study.

Inclusion criteria were: age 21–65 years, fasting triglycerides >150 mg/dL (1.70 mmol/L), body mass index (BMI) 18.5–35 kg/m^2, and stable HAART for six months with $CD4^+$ T cell count >100/mm^3 and viral load (VL) <5000 copies /cm^3. Exclusion criteria were fasting triglycerides >1000 mg/dL (11.3 mmol/L), history of coronary artery disease or diabetes, untreated hypogonadism or thyroid dysfunction, pregnancy, renal insufficiency, alcoholism, ALT or AST >2 times upper limit of normal, or use of nutritional supplements or lipid-lowering drugs for 6 weeks prior to entry. Participants were randomized (Figure 1) to five study groups: 1) Usual Care with two placebos; 2) Intensive diet and exercise (D/E) with two placebos; 3) D/E with active fenofibrate and niacin placebo; 4) D/E with active niacin and fenofibrate placebo; 5) D/E with active fenofibrate and active niacin. Details of randomization, stratification by classes of HAART, and interventions were as described previously (3). Briefly, participants in the Usual Care group received general advice on a heart-healthy diet and maintaining physical fitness. Participants in the other four groups (Groups 2–5) were taught a weight-maintaining diet with 50% calories from carbohydrates, 30% calories from fat (<7% saturated, 15% monounsaturated, 8% polyunsaturated, minimal trans), cholesterol <200 mg/day and fiber 20–30 g/day. For the first two weeks, all meals were packaged by the Baylor General Clinical Research Center kitchen and delivered to the subjects. During this stabilization period, subjects were instructed on food selection and preparation. Three days of food records were verified by a dietitian at 0, 8, 16 and 24 weeks. Participants in Groups 2–5 also participated in an exercise program at a study gymnasium. The sessions were supervised by certified trainers, three times weekly for 75–90 minutes, with aerobic and resistance exercise components. For subjects who could not attend the study gymnasium, membership was provided at a commercial fitness center. Study trainers provided exercise plans to subjects in this alternative program and reviewed their progress bi-weekly. Importantly, to avoid the confounding factor of weight loss in assessing the effect

of the diet composition and exercise interventions on the outcome measures, caloric intake was adjusted by study dietitians to maintain a stable body weight throughout the study (3).

Participants in Groups 4 and 5 took sustained-release niacin (Niaspan, Abbott Laboratories, Abbott Park, IL), starting with one 500 mg tablet plus three placebo pills at bedtime for two weeks, increasing by one active tablet bi-weekly (with corresponding decrease in placebo) to four tablets from the seventh week. To minimize unblinding due to flushing, one placebo pill contained 50 mg niacin (3). Participants in Groups 3 and 5 took 145 mg of fenofibrate (Tricor, Abbott Laboratories, Abbott Park, IL) at bedtime, while the other participants took placebos. Medication compliance was reviewed during monthly refills.

Baseline characteristics, lipid levels and levels of $LpPLA_2$ and RANTES were also compared to those of a cohort of 22 healthy adult control subjects (without chronic illnesses, medications or HIV risk factors), matched to the HIV/HAART subjects for age and BMI.

Analytical Methods

Fasting (10 hr) plasma samples were collected at baseline and following the 24-week intervention, and stored at −80°C until analysis. Every effort was made to collect plasma samples between 0700 and 1000 h. $CD4^+$ T cell counts were measured by LabCorp (Burlington, NC) using flow cytometry. HIV-1 viral load was measured by LabCorp or Quest Diagnostics (Madison, NJ) using either of two quantitative real-time PCR assays (routine, with a lower limit of 400 copies/cc, or ultrasensitive, with a lower limit of 50 copies/cc). Viral load values measured as <400 copies/cc by the first assay were assigned a value of 200 copies/cc and all the viral load values were log-transformed prior to analysis.

Fasting plasma lipid levels were measured in the Atherosclerosis Clinical Laboratory of Baylor College of Medicine using an Olympus AU400e automated chemistry analyzer in which total cholesterol is measured using cholesterol dehydrogenase combined with the esterase and oxidase into a single enzymatic reagent. Triglycerides are measured by a procedure based on a series of coupled enzymatic reactions after hydrolysis by microbial lipases to release glycerol and fatty acids - glycerol is phosphorylated by glycerol kinase GK to produce glycerol-3-phosphate, which is oxidized by glycerol phosphate oxidase to produce H_2O_2 and dihydroxyacetone phosphate. The H_2O_2 oxidatively couples p-chlorophenol and 4-aminoantipyrine with catalysis by peroxidase to produce a red dye with an absorbance maximum at 500 nm; the increase in absorbance at 520/600 nm is proportional to the triglyceride content of the sample. HDL cholesterol is measured in two steps - first, free cholesterol in non-HDL-lipoproteins is solubilized and consumed by cholesterol oxidase, peroxidase, and DSBmT to generate a colorless end product, and second, a detergent selectively solubilizes HDL-lipoproteins. The HDL cholesterol is released for reaction with cholesterol esterase, cholesterol oxidase and a chromogen system to yield a blue color complex which can be measured bichromatically at 600/700nm. The resulting increase in absorbance is directly proportional to the HDL-C concentration. Plasma LDL-cholesterol concentrations were calculated according to the Friedewald equation.

Levels of $Lp\text{-}PLA_2$ mass (diaDexus Inc., San Francisco, CA) and RANTES (R&D Systems, Minneapolis, MN) were measured using commercially available enzyme-linked immunosorbent assay kits. The sensitivity of the $Lp\text{-}PLA_2$ and RANTES assays were 15.6 pg/mL and 0.34 ng/mL. The coefficient of variation was <5% for both $Lp\text{-}PLA_2$ and RANTES assays.

Statistical Analysis

Based on the assumption that the D/E program compared to Usual Care, and fenofibrate plus niacin with D/E compared to D/E alone, would reduce $Lp\text{-}PLA_2$ mass by at least 10%,

assuming alpha = 0.05, power = 0.80 and a two-tailed test, the necessary sample size was calculated to be 90 total subjects. Hence, 107 subjects were selected at random from a total of 127 who completed the 24-week intervention in the Heart Positive study. All descriptive data are presented as mean ± SEM. Independent sample t-tests were used to compare baseline age and BMI, as well as levels of lipids and lipoproteins, Lp-PLA_2 and RANTES. Separate general linear models (SPSS 18.0) were used to compare the five randomized groups with respect to Lp-PLA_2, RANTES and lipid and lipoprotein concentrations, while controlling for age, baseline BMI, baseline $CD4^+$ T-cell count, baseline viral load, duration of HIV, and duration of HAART, as well as baseline outcome measures. When differences between groups were detected at $P<0.05$, Groups 2–5 were each compared with Group 1 (simple contrast) using the sequential Sidak multiple comparison procedure. The mean of Groups 2–5 (all receiving D/E) was also compared with Group 1 (Usual Care) while controlling for the same covariates as above. Simple Pearson product correlations were conducted to identify significant relationships between general descriptive characteristics (age, BMI, baseline $CD4^+$ T-cell count, baseline viral load, duration of HIV and HAART), Lp-PLA_2, RANTES and lipid and lipoprotein concentrations. $P<0.05$ was considered significant.

RESULTS

As previously reported (3), the weight-maintaining lifestyle intervention resulted in no significant changes or group differences in weight or BMI. (Study dieticians advised subjects at monthly visits to reduce or increase calories as needed to maintain baseline weight. As in all exercise programs, there were minor fluctuations of weight despite the attempts at dietary correction - on average, weight change was approximately ±1.5 kg. Compliance with medications, diet and gym visits have been reported (3), and were not different between the groups. A similar number of patients in each group participated in the alternative exercise program (9 in Group 2, 8 in Group 3, 11 in Group 4, 9 in Group 5).

Demographic characteristics and baseline levels of HIV/HAART–related parameters and fasting plasma lipid, Lp-PLA_2 and RANTES levels of the subjects are shown in Table 1. At baseline there were no significant differences in these parameters between Groups 1–5. When compared to healthy controls (Table 2) matched for age and BMI, the HIV group displayed significantly higher plasma concentrations of triglycerides (+169%), non-HDL-C (+22%), TC:HDL ratio (+66%), Lp-PLA_2 (+38%) and RANTES (+95%), and significantly lower HDL-C concentration (−39%). Despite normal total plasma cholesterol concentrations, the HIV group had markedly elevated plasma Lp-PLA_2 and RANTES levels.

Post-intervention responses of D/E, fenofibrate and niacin on concentrations of lipids, lipoproteins, Lp-PLA_2 and RANTES are compared to Usual Care in Table 3. Following the 24-week intervention, Lp-PLA_2 concentration was significantly lower in Group 2 patients who participated in D/E only (323.0 ± 27.2 ng/mL), Group 3 patients who received D/E plus fenofibrate (327.2 ± 25.9 ng/mL), and Group 4 patients who received D/E plus niacin (311.1 ± 27.8 ng/mL), than among Group 1 patients who received Usual Care (402.2 ± 25.3 ng/mL). There was no significant difference in Lp-PLA_2 between patients who received D/E only, D/E plus fenofibrate or D/E plus niacin. No significant differences were observed between groups for RANTES concentrations following the 24-week intervention. Interestingly, Group 5, who received D/E and both fenofibrate and niacin, did not have significant reductions in Lp-PLA_2 and RANTES, although this was the only group to demonstrate significantly lower plasma concentrations of triglycerides (−47%), non-HDL-C (−19%) and TC:HDL ratio (−29%), and increase in HDL-C concentration (+30%) compared to Usual Care.

When all treatment groups (2–5) were combined and compared to the group receiving Usual Care (Group 1), all patients in the intensive exercise and dietary program had significantly lower triglycerides (−33%), non-HDL-C (−12%), TC:HDL ratio (−16%) and Lp-PLA_2 (−19%), and higher HDL-C (+16%) following the 24-week intervention. Baseline Lp-PLA_2 levels correlated with total cholesterol (r = 0.192), non-HDL-C (r = 0.205) and percent change in Lp-PLA_2 (r = −0.416). These correlations are similar to those previously reported (for Lp-PLA_2 with total cholesterol, r = 0.28 (CI: 0.25–0.31); for Lp-PLA_2 with non-HDL-C, r = 0.30 (CI: 0.27–0.34)) [15]. Baseline levels of Lp-PLA_2 and RANTES showed no significant correlation (r = 0.021, P=0.83). No significant correlations were observed between RANTES and the patients' demographic characteristics or lipid / lipoprotein levels.

DISCUSSION

The present data demonstrate that plasma Lp-PLA_2 mass is markedly elevated in patients with HIV/HAART-associated dyslipidemia, and that it can be significantly reduced by 24 weeks of intensive diet and exercise. Addition of niacin (2 g/day) or fenofibrate (160 mg/day) to the lifestyle modification does not confer significant additional benefit in regard to Lp-PLA_2 mass reduction. Plasma levels of RANTES are highly variable but generally markedly elevated in these patients compared to those observed in many studies of populations with CAD, but none of the interventions utilized in this study resulted in significant reductions of this cytokine.

The Lp-PLA_2 responses to fenofibrate (combined with diet and exercise) contrast with those observed in other dyslipidemic populations receiving fenofibrate without intensive lifestyle modification. Rosenson (32) showed that treatment with fenofibrate (160 mg/day) for three months reduced concentrations of Lp-PLA_2 by 13.2% in hypertriglyceridemic patients with metabolic syndrome, and that this was associated with reductions in LDL cholesterol, total LDL particles, and small LDL particles. Treatments that lower plasma LDL-cholesterol such as fibrates and statins might be expected to lower Lp-PLA_2 mass and activity as well (26). An effect of fenofibrate on Lp-PLA_2 was not observed in the present study, but fenofibrate alone was not tested and it is possible that the effect of the intensive lifestyle modification obscured a small direct effect of fenofibrate.

A few studies have examined the effects of niacin on Lp-PLA_2 mass and activity. Kuvin et al. (22) reported 20% reduction in Lp-PLA_2 mass following three months of niacin treatment (1 g/day) in patients with CAD, together with 7.5% increase in HDL-C and 15% reduction in triglycerides. In the present study, the HIV/HAART patients who received both the diet and exercise program and niacin (2 g/day) experienced the largest mean reduction (−23%) in Lp-PLA_2 mass, but this effect was not significantly greater than that of diet and exercise with placebo. Paradoxically, the patients who received diet and exercise with both niacin and fenofibrate did not achieve a significant reduction in Lp-PLA_2 mass, but consistent with the overall results of the Heart Positive study (3) they were the only group with significant improvements in triglyceride, total cholesterol, HDL-C and non-HDL-C levels. In aggregate, these data suggest discordance between Lp-PLA_2 mass and lipid and lipoprotein metabolism in HIV/HAART-associated dyslipidemia. Khovidhunkit et al. (21) also observed that the higher Lp-PLA_2 activity in AIDS patients could not be explained by a relationship with plasma lipids, since the AIDS patients had lower total cholesterol and LDL-C concentrations than healthy control subjects. Furthermore, there was no relationship between plasma Lp-PLA_2 activity and plasma cholesterol, LDL-C or apo B-100 concentrations. Factors such as macrophage activation, generation of platelet activating factor and oxidized phospholipids, and elevated cytokines observed during HIV infection may stimulate Lp-PLA_2 activity or synthesis (21). Alterations of specific HAART regimens have also been reported to reduce Lp-PLA_2 activities in a dose-dependent manner (37), but

this would not have affected the results of the present study because the subjects were on stable HAART regimens throughout and were stratified on three combinations of classes of HAART at randomization.

Dietary modifications with or without exercise training have demonstrated varied outcomes in lipid and lipoprotein-cholesterol concentrations among HIV patients. In a group of HIV/HAART patients with dyslipidemia and lipodystrophy, Terry et al. (35) reported no significant changes in plasma triglycerides, total cholesterol, or HDL-C following 12-weeks of aerobic exercise training combined with a low-fat diet despite 25% increase in VO_2max. Interestingly, the low-fat diet only group did not show improvements in blood lipids and lipoproteins, even with reductions in both body-fat and waist-to-hip ratio. In contrast, a small group of lipodystrophic HIV/HAART patients who completed a 10-week aerobic and resistance exercise program experienced reductions in total cholesterol and triglyceride concentrations (20). The changes in blood lipids were matched by an increase in body mass and a reduction in body fat, indicating a positive adaptation in body composition. Interestingly, Lazzaretti et al. (24) showed that patients assigned a low-fat diet prior to initiating HAART maintained total cholesterol and LDL-C levels and reduced triglyceride concentrations by ~25% at 12 months, when compared to HAART-treated patients without the dietary intervention. During longer-term follow-up, 21% who received the low-fat diet displayed a dyslipidemic profile compared to 68% of the controls. Hence, diet alone could have a salutary effect on the lipid profile in HIV/HAART patients. The design of our study does not permit us to distinguish the separate effects of diet and exercise, but collectively, these data suggest that lifestyle changes (with attention to factors such as the type of exercise training, the amount and type of fat in the diet, and timing of lifestyle modifications at the inception of HAART) should be considered part of an optimal treatment approach to dyslipidemia in HIV patients.

The Lp-PLA_2 Studies Collaboration, a meta-analysis of 32 prospective studies, reported that Lp-PLA_2 mass and activity were associated with each other ($r = 0.51$, 95% CI: 0.47–0.56), with proatherogenic lipids, and with risk for coronary heart disease and vascular death (36). With reference to epidemiologic data in which the 50^{th} percentile Lp-PLA_2 mass cut-point of 235 ng/ml is used to identify patients at increased CVD risk (23), the HIV/HAART patients in the present study were clearly at elevated risk. Their baseline Lp-PLA_2 mass was 388.5 ± 12.3 ng/ml (mean ± SEM), and fewer than 7% had an Lp-PLA_2 mass <235 ng/ml. These data underscore the clinical relevance of the ability of lifestyle modification to reduce Lp-PLA_2 mass in HIV/HAART patients with dyslipidemia.

The relevance of circulating RANTES levels to atherosclerosis and cardiovascular risk remains uncertain, in part because of wide ranges in its population levels, variability depending on whether the plasma samples are depleted of platelets, and ethnicity. Nomura et al. (28) found elevated levels of RANTES in patients with acute coronary syndromes, whereas Cavusoglu et al. (8) found that low levels of RANTES predicted adverse outcomes in patients with chronic CAD, and a recent large cross-sectional study of stored samples noted no association between CAD and RANTES levels (15). There may be a closer association between circulating RANTES levels and plaque characteristics – Virani et al. noted positive associations between RANTES and carotid wall thickness and lipid-core volume, suggesting that higher RANTES levels may be associated with extensive carotid atherosclerosis and plaques at high risk of rupturing (38). As in the present study, RANTES levels have been noted previously to be elevated in HIV-infected patients; however, we found no relationship between RANTES levels and lipid / lipoprotein measures, and the treatments utilized in the present study did not reduce RANTES levels.

A limitation of the present study is that we measured only Lp-PLA_2 mass but not Lp-PLA_2 activity. However, Lp-PLA_2 mass and activity are known to be strongly correlated with each other (r = 0.51; CI: 0.47–0.56) (36). In addition, we did not use platelet-free plasma for analyses of RANTES, which may pose a limitation in the comparison of RANTES levels with those in other studies. Given that we did not observe significant differences between study groups before or following treatment, this would not affect the outcomes of the study. It is also possible that the study was not adequately powered to observe an effect of the interventions on RANTES levels; the variance in mean RANTES level was wide in this cohort, and a larger sample size might be required to observe such an effect. Despite these limitations, the results of this randomized, controlled trial in well-characterized HIV patients with dyslipidemia provide strong evidence for the effectiveness of intensive lifestyle modification in reducing the levels of Lp-PLA_2.

The metabolic abnormalities in HIV patients on HAART are complex and heterogeneous, characterized by varying degrees of centripetal fat distribution, dyslipidemia, insulin resistance and increased risk for CVD (2, 29). The complexity of the condition is reflected in the discordant lipid-lowering effects of the combination of fenofibrate and niacin (with diet and exercise), which did not decrease Lp-PLA_2 mass while it achieved significant decrease in triglycerides (−47%), non-HDL-C (−19%) and TC:HDL ratio (−29%), and increase in HDL-C concentration (+30%) when compared to the Usual Care group. There is no simple explanation for these discordant effects, which may be due in part to interactions between the lipid lowering drugs and HAART (5, 9) and multiple pathogenic mechanisms acting in concert that are responsible for the marked and sustained post-prandial hyperlipidemia observed in this population (33).

In summary, this randomized, controlled study is the first to demonstrate that when compared to standard medical care, an intensive diet and exercise program in patients with HIV/HAART-associated dyslipidemia can reduce plasma Lp-PLA_2 mass. Further research is warranted to understand the discordance between Lp-PLA_2 mass and lipid and lipoprotein metabolism in this condition.

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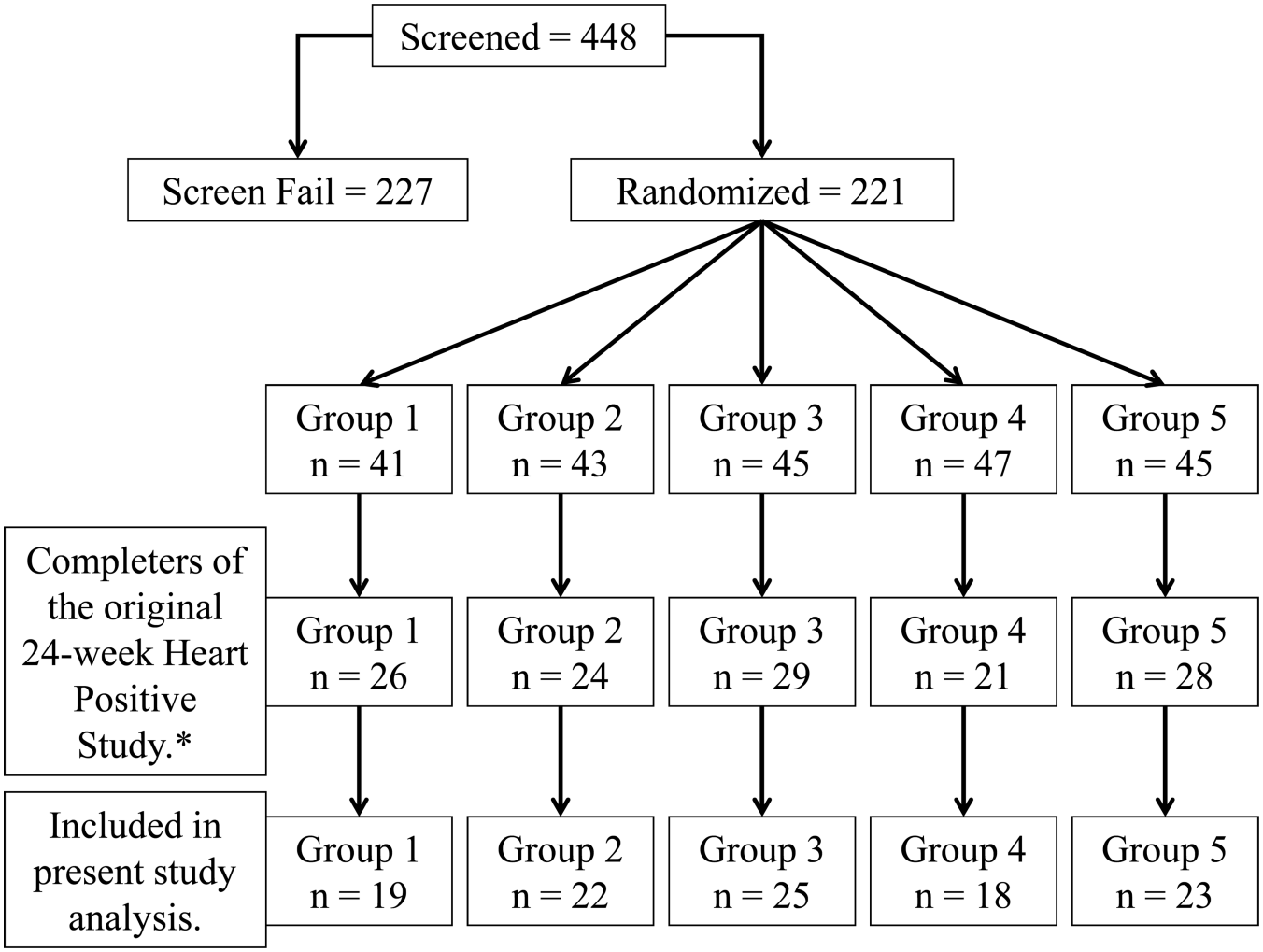

Figure 1.
Flow diagram of subject screening, recruitment, and randomization. [The original consort diagram was previously published in Balasubramanyam et al. (3).]

Table 1

Demographic and HIV/HAART characteristics, and lipid, Lp-PLA_2 and RANTES levels of patients at baseline.

		Group						
Variable	**All**	**1**	**2**	**3**	**4**	**5**	**2–5**	***P***
N	107	19	22	25	18	23	88	
Age (years)	44.8 ± 0.9	49.0 ± 2.0	44.0 ± 1.3	43.0 ± 1.8	43.6 ± 2.1	45.0 ± 2.3	43.9 ± 0.9	0.22
Baseline BMI (kg/m^2)	26.6 ± 0.3	26.4 ± 0.6	26.7 ± 0.8	26.6 ± 0.9	26.5 ± 0.7	26.6 ± 0.8	26.6 ± 0.4	0.99
Baseline $CD4^+$ count	504.3 ± 29.2	523.1 ± 52.2	565.5 ± 61.0	425.8 ± 45.7	530.6 ± 103.8	495.1 ± 65.9	500.3 ± 33.7	0.60
Baseline Viral Load (copies/ml) *	202.8 ± 487.8	266.7 ± 2603.2	202.8 ± 18.7	206.4 ± 509.8	183.1 ± 15.8	200.0 ± 50.0	201.24 ± 147.3	0.06
Duration of HIV (y)	9.9 ± 0.6	11.4 ± 1.4	10.9 ± 1.5	10.0 ± 1.3	11.1 ± 1.4	6.4 ± 1.2	9.5 ± 0.7	0.07
Duration of HAART (y)	5.9 ± 0.5	6.0 ± 1.0	6.4 ± 1.0	5.8 ± 1.0	7.2 ± 1.3	4.5 ± 0.8	5.9 ± 0.5	0.46
Gender								
Male	98	16	21	22	17	22	82	
Race								
African-American	18	3	3	2	3	7	15	
Hispanic	48	9	8	15	6	10	39	
Asian	1	1	0	0	0	0	0	
White	40	6	11	8	9	6	34	
Total cholesterol (mg/dL)	204.9 ± 4.8	213.6 ± 12.4	199.3 ± 9.5	206.5 ± 11.3	200.5 ± 9.6	204.4 ±10.5	202.9 ± 5.1	0.91
Triglycerides (mg/dL)	305.3 ± 16.5	361.9 ± 50.1	285.3 ± 42.3	301.3 ± 25.7	298.2 ± 34.8	287.6 ± 33.4	293.1 ± 16.8	0.62
HDL cholesterol (mg/dL)	39.3 ± 0.9	41.9 ± 2.8	40.9 ± 2.4	39.5 ± 1.6	36.6 ± 1.8	37.3 ± 1.4	38.7 ± 0.9	0.33
Non-HDL cholesterol (mg/dL)	165.6 ± 4.3	171.7 ± 10.9	158.4 ± 8.7	167.1 ± 10.4	163.9 ± 8.6	167.1 ± 9.4	164.3 ± 4.7	0.52
TC:HDL-C	5.3 ± 0.1	5.3 ± 0.3	5.0 ± 0.2	5.3 ± 0.2	5.5 ± 0.2	5.5 ± 0.2	5.3 ± 0.1	0.91
Lp-PLA_2 (ng/mL)	388.5 ± 12.3	415.1 ± 31.7	387.2 ± 17.9	403.3 ± 31.7	373.0 ± 22.9	363.7 ± 29.1	382.7 ± 13.3	0.69
RANTES (ng/mL)	43.8 ± 2.4	42.4 ± 5.9	40.0 ± 3.2	44.3 ± 4.7	52.6 ± 9.2	41.3 ± 4.6	44.1 ± 2.7	0.58

Data are unadjusted means ± SEM.

*Baseline viral load is displayed as median copies/ml. Group 1 = Usual Care + 2 placebos; Group 2 = intensive diet/exercise (D/E) + 2 placebos; Group 3 = D/E + fenofibrate; Group 4 = D/E + niacin; Group 5 = D/E + fenofibrate + niacin.

Table 2

Baseline characteristcs of HIV/HAART patients compared to healthy controls.

Variable	HIV	Controls	*P*
N	107	22	-
Age (years)	44.8 ± 0.9	48.9 ± 0.7	NS
Baseline BMI (kg/m^2)	26.6 ± 0.3	25.6 ± 0.2	NS
Gender			
Male	98	14	-
Race			
African-American	18	1	-
Hispanic	48	9	-
Asian	1	2	-
White	40	10	-
Total cholesterol (mg/dL)	204.9 ± 4.8	199.9 ± 2.1	NS
Triglycerides (mg/dL)	305.3 ± 16.5	113.6 ± 2.5	<0.001
HDL cholesterol (mg/dL)	39.3 ± 0.9	64.6 ± 0.9	<0.001
Non-HDL cholesterol (mg/dL)	165.6 ± 4.3	135.4 ± 1.9	0.004
TC:HDL-C	5.3 ± 0.1	3.2 ± 0.1	<0.001
Lp-PLA$_2$ (ng/mL)	388.5 ± 12.3	281.3 ± 4.3	<0.001
RANTES (ng/mL)	43.8 ± 2.4	22.5 ± 1.0	<0.001

Data are unadjusted means ± SEM. NS = not significant.

Table 3

Comparison of post-intervention concentrations of lipids, lipoproteins, Lp-PLA_2, and RANTES.

Group	N	Total cholesterol (mg/dL)	Triglycerides (mg/dL)	HDL-C (mg/dL)	Non-HDL-C (mg/dL)	TC:HDL-C	Lp-PLA_2 (ng/mL)	RANTES (ng/mL)
1	18	209.8 ± 11.6	397.3 ± 57.6	38.2 ± 3.3	167.1 ± 11.4	5.6 ± 0.4	402.2 ± 25.3	50.9 ± 10.4
2	22	203.5 ± 12.5	336.1 ± 62.4	41.6 ± 3.5	158.3 ± 12.3	5.2 ± 0.4	323.0 ± 27.2 *	55.0± 11.3
3	25	191.6 ± 11.9	259.6 ± 59.3	42.4 ± 3.3	147.1 ± 11.7	4.8 ± 0.4	327.2 ± 25.9 *	61.5 ± 10.8
4	18	190.0 ± 12.7	268.3 ± 63.6	43.6 ± 3.5	145.4 ± 12.6	4.7 ± 0.4	311.1 ± 27.8 †	47.7 ± 11.7
5	23	186.6 ± 12.5	209.8 ± 62.7 †	49.5 ± 3.5 †‡	135.5 ± 12.4 *	4.0 ± 0.4 †‡	347.9 ± 27.4	42.0 ± 11.4
2–5	88	192.7 ± 10.9	266.2 ± 55.0 †	44.2 ± 3.1 *	146.5 ± 10.8 *	4.7 ± 0.4 †	327.6 ± 23.6 †	52.8 ± 10.0

Data (mean ± SE) are adjusted for age, baseline BMI, baseline $CD4^+$ T-cell count, baseline viral load, duration of HIV, duration of HAART and baseline concentrations of the analytes. Group 1 = Usual Care + 2 placebos; Group 2 = D/E + 2 placebos; Group 3 = D/E + fenofibrate; Group 4 = D/E + niacin; Group 5 = D/E + fenofibrate + niacin.

* $P<0.05$,

† $P<0.01$, compared to Group 1.

‡ $P<0.05$ compared to Group 2.