Combination of Niacin and Fenofibrate with Lifestyle Changes Improves Dyslipidemia and Hypoadiponectinemia in HIV Patients on Antiretroviral Therapy: Results of "Heart Positive," a Randomized, Controlled Trial

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Context: HIV patients on antiretroviral therapy (ART) have a unique dyslipidemia [elevated triglycerides and non-high-density lipoprotein-cholesterol (HDL-C) , low HDL-C] with insulin resistance (characterized by hypoadiponectinemia).

Objective: The aim was to test a targeted, comprehensive, additive approach to treating the dyslipidemia.

Design and Setting: We conducted a randomized, double-blind, placebo-controlled, 24-wk trial of lifestyle modification, fenofibrate, and niacin in multiethnic HIV clinics at an academic center.

Participants: Hypertriglyceridemic adult patients were stratified on three combinations of ART classes. Subjects retained at the first measurement (2 wk) after entry were included in the analysis (n = 191).

Interventions: Subjects were randomized into five treatment groups: usual care (group 1); low-saturated-fat diet and exercise (D/E; group 2); D/E + fenofibrate (group 3); D/E + niacin (group 4); or D/E + fenofibrate + niacin (group 5).

Main Outcome Measures: We measured changes in fasting triglycerides, HDL-C, and non-HDL-C (primary), and in insulin sensitivity, glycemia, adiponectin, C-reactive protein, energy expenditure, and body composition (secondary). Data were analyzed as a factorial set of treatment combinations using a mixed repeated measures model, last observation carried forward, and complete case approaches (groups 2–5), and as an unstructured set of treatments (groups 1–5).

Results: Fenofibrate improved triglycerides ($P = 0.002$), total cholesterol ($P = 0.02$), and non-HDL-C ($P = 0.003$), whereas niacin improved HDL-C ($P = 0.03$), and both drugs decreased the total cholesterol-to-HDL-C ratio ($P = 0.005$–0.01). The combination of D/E, fenofibrate, and niacin provided maximal benefit, markedly reducing triglycerides (−52% compared to usual care; $P = 0.003$), increasing HDL-C (+12%; $P < 0.001$), and decreasing non-HDL-C (−18.5%; $P = 0.003$) and total cholesterol-to-HDL-C ratio (−24.5%; $P < 0.001$). Niacin doubled adiponectin levels.

Conclusions: A combination of fenofibrate and niacin with low-saturated-fat D/E is effective and safe in increasing HDL-C, decreasing non-HDL-C and hypertriglyceridemia, and ameliorating hypoadiponectinemia in patients with HIV/ART-associated dyslipidemia. (***J Clin Endocrinol Metab*** **96: 2236–2247, 2011)**

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Abbreviations: ALT, Alanine aminotransferase; ART, antiretroviral therapy; AST, aspartate aminotransferase; BMI, body mass index; BUN, blood urea nitrogen; CHD, coronary heart disease; CVD, cardiovascular disease; D/E, diet and exercise; FFA, free fatty acid; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HDL-C, HDL-cholesterol; HOMA-IR, homeostasis model assessment for insulin resistance; hsCRP, high-sensitivity C-reactive protein; LOCF, last observation carried forward; OGTT, oral glucose tolerance test; OGTT-AUC, area under the curve in the OGTT; VL, viral load.

Dyslipidemia and insulin resistance (1), associated with accelerated cardiovascular disease (CVD) risk (2–6), are prevalent among HIV-infected patients on antiretroviral therapy (ART). Key components of the dyslipidemia are hypertriglyceridemia, low high-density lipoprotein (HDL)-cholesterol (HDL-C), and increased non-HDL-C (7–9). Its unique pathogenic features include accelerated lipolysis (10, 11), inadequate fat oxidation (10), increased hepatic flux of free fatty acids (FFA) with accelerated very low-density lipoprotein synthesis (12), impaired dietary triglyceride clearance (13, 14), defects in HDL metabolism (8, 15), and hypoadiponectinemia (16, 17).

The distinctive pathophysiology, inimical interactions between ART drugs and CYP3A4-metabolized statins (18, 19), and a high prevalence of hepatitis render current lipid-lowering approaches inadequate in achieving recommended treatment goals. Treatment strategies are based on the National Cholesterol Education Program (NCEP) Adult Treatment Protocol III, which recommends niacin or fibrates for hypertriglyceridemia. Whereas lipid lowering and even CVD risk reduction can be achieved with these monotherapies among HIV-negative persons, there is sparse evidence from randomized, controlled trials demonstrating their effectiveness in patients with HIV/ART-associated dyslipidemia.

Heart Positive (www.ClinicalTrials.gov ID: NCT00246376) was a randomized, placebo-controlled, double-blind, 24-wk trial of a comprehensive, additive approach to measuring the effects of intensive lifestyle change (low-saturated-fat diet with exercise), niacin, and fenofibrate on triglyceride, HDL-C, and non-HDL-C levels among HIV patients on ART. Secondary outcomes included changes in glycemia, insulin sensitivity, adipokines, substrate oxidation, energy expenditure, and body composition. The interventions were selected to target the pathophysiology: low-saturated-fat diet to ameliorate lipemia, exercise and fenofibrate to enhance fat oxidation, and niacin to blunt lipolysis and diminish hepatic fatty acid flux. We hypothesized that each intervention would improve the lipid profile but that a combination would provide the greatest benefit. The results show that the combination of niacin and fenofibrate, together with diet and exercise (D/E), is more effective than lifestyle change alone or drug monotherapy with lifestyle change in substantially improving HIV/ART-associated dyslipidemia and hypoadiponectinemia.

Subjects and Methods

Subjects

Subjects were recruited mainly from the Legacy Community Health Center and Thomas Street Clinic of the Harris County Hospital District and from Houston Area Community Services and private clinics. The study was approved by the Institutional Review Boards of Baylor College of Medicine and Legacy, and informed consent was obtained.

Inclusion criteria were: age, 21–65 yr; fasting triglycerides, above 150 mg/dl (1.70 mmol/liter); body mass index (BMI), 18.5–35 kg/m^2; and stable ART for 6 months with CD4+ T cell count 100/mm^3 or greater and viral load (VL) no greater than 5000 copies/cm^3. (Rationale for the 150 mg/dl triglyceride cutoff was that HIV patients on ART do not have simple, isolated hypertriglyceridemia but have a cluster of CVD risk factors for which hypertriglyceridemia at any level is a marker.) Exclusion criteria were: fasting triglycerides above 1000 mg/dl (11.3 mmol/liter), history of coronary disease or diabetes, untreated hypogonadism or thyroid dysfunction, pregnancy, renal insufficiency, alcoholism, alanine aminotransferase (ALT) or aspartate aminotransferase (AST) more than two times the upper limit of normal, or use of nutritional supplements or lipid-lowering drugs for 6 wk before entry.

Subjects were randomized in blocks of 10 to five study groups: 1) usual care with two placebos; 2) intensive D/E with two placebos; 3) D/E with active fenofibrate and niacin placebo; 4) D/E with active niacin and fenofibrate placebo; and 5) D/E with active fenofibrate and active niacin. They were separately randomized for each of the following strata defined by three commonly used combinations of ART classes: 1) a protease inhibitor-containing regime; 2) a nonnucleoside reverse transcriptase inhibitor-containing regime; and 3) three nucleoside reverse transcriptase inhibitors. Study personnel were blinded to group allocations except for the person who performed the randomization and acted as liaison between the pharmacy and the clinical coordinator. Subjects received medical care from their primary HIV physicians.

Diet

Subjects in group 1 (usual care) received general advice on a heart-healthy diet, kept a 7-d food record, and received feedback on their caloric intake during a single baseline visit.

Subjects in groups 2–5 were taught a weight-maintaining diet (caloric requirements based on resting metabolic rate measured by indirect calorimetry) with 50% of calories from carbohydrates, 30% of calories from fat (≤7% saturated, 15% monounsaturated, 8% polyunsaturated, minimal trans), cholesterol no greater than 200 mg/d, and fiber 20–30 g/d. Details have been reported previously (20). For the first 2 wk, all meals were packaged by the Baylor General Clinical Research Center's kitchen and delivered to the subjects. During this stabilization period, subjects were instructed on food selection and preparation (20). Three days of food records (randomly selected from 7-d diaries) were verified by a dietitian at 0, 8, 16, and 24 wk.

Translational Metabolism Unit, Division of Diabetes, Endocrinology and Metabolism (A.B., I.C., P.P., D.I., R.V.S., P.C., E.C.-S., S.K.), Section of Cardiovascular Research (L.W.S., A.A.T., C.M.B., H.J.P.), Section of Infectious Diseases, Department of Medicine (T.P.G.), and Department of Pediatrics (E.O.S.), Baylor College of Medicine, Houston, Texas 77030; Endocrine Service (A.B., I.C., R.V.S.), Ben Taub General Hospital, Houston, Texas 77030; and Center for Cardiovascular Disease Prevention (C.M.B.), Methodist-DeBakey Heart Center, Houston, Texas 77030

Exercise

Group 1 subjects received a brochure with general fitness advice. Subjects in groups 2–5 participated in an exercise program at a study gymnasium, following guidelines of the American College of Sports Medicine. The sessions were supervised by certified trainers three times weekly for 75–90 min, with aerobic and resistance components (20). Fitness and body composition [total body cell mass and fat, using bioimpedance analysis (Quantum II; RJL Systems, Clinton Township, MI)] were measured at wk 0, 8, 16, and 24. 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 biweekly.

Drugs

Subjects 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 2 wk, increasing by one active tablet biweekly (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 (21). Subjects in groups 3 and 5 took 145 mg of fenofibrate (Tricor; Abbott Laboratories) at bedtime, whereas the other subjects took placebos. Medication compliance was reviewed during monthly refills.

Measurements

Fasting lipid levels were measured at baseline (twice) and at wk 2, 4, 8, 12, 16, and 24. Oral glucose tolerance tests (OGTT) and indirect calorimetry (Deltatrac, Sensormedics, Fullerton, CA; or MedGem, HealtheTech, Golden, CO) were performed at baseline and final study visits, with measurements of fasting plasma adiponectin, FFA, high-sensitivity C-reactive protein (hsCRP), and TSH. Blood counts and liver and kidney functions were measured at wk 2, 4, 8, 12, and 24.

Analysis

Fasting cholesterol, HDL-C, and triglycerides were measured in the Baylor Atherosclerosis Clinical Laboratory using an Olympus AU400e automated analyzer (22). Non-HDL-C was calculated as total cholesterol − HDL-C. Plasma glucose was measured by the glucose oxidase method and insulin by RIA. CD4 counts were measured by flow cytometry (LabCorp, Burlington, NC), and HIV-1 VL was measured at LabCorp or Quest Diagnostics (Madison, NJ) by quantitative PCR (lower limits of 400 or 50 copies/cc); levels less than 400/cc by the first assay were assigned a value of 200/cc, and all VL values were log-transformed for analysis. Adiponectin was measured by RIA (Linco, St. Louis, MO), and hsCRP by latex particle-enhanced immunoturbidimetric assay (Genzyme, Framingham, MA). FFA were measured by microtiter procedure (Wako Diagnostics, Richmond, VA). Collective interassay and intraassay coefficients of variation were 2–5 and 3–8%, respectively.

Statistics

Sample size was based on detecting differences between groups with respect to mean percentage and absolute change in triglyceride level in response to diet, exercise, niacin, and fenofibrate (20). Criteria for power calculations were: type I error = 0.05, and power = 0.80. Baseline characteristics were compared by ANOVA. Categorical variables were assessed for differences at baseline by χ^2 test. Primary outcomes analyses involved groups 2–5 for the four possible combinations of fenofibrate (yes/no) and niacin (yes/no), forming a two-factor design with all treatments on a background of D/E. Three approaches were used to analyze lipid variables at 24 wk: mixed repeated measures model with contrasts (primary model), last observation carried forward (LOCF), and complete cases. All methods assessed the main effects of fenofibrate and niacin as well as interactions between these two factors on outcomes at 24 wk while controlling for the baseline value of the outcome variable and these covariates: ART strata, sex, ethnicity, history of smoking, alcohol and drug use, and family history of diabetes.

For subjects who did not complete 24 wk, LOCF used the last value obtained as an estimate of the 24-wk value. For LOCF and complete cases, the general linear model was applied to 24-wk values for assessment of treatment main effects and interaction while accounting for covariates. The mixed repeated measures model approach used all available measurements at 2, 4, 8, 12, and 16 wk to model outcome as a function of fenofibrate (yes/no), niacin (yes/no), fenofibrate × niacin interaction, weeks in the study, and covariates to estimate 24-wk means for the treatment combinations. These estimated 24-wk means were subjected to contrasts, assessing treatment main effects and interactions at that time point. Both LOCF and mixed model methods included all subjects who attended the wk 2 visit, regardless of subsequent missing data. Although the mixed model is more efficient for treatment of missing values (23), LOCF was used to corroborate the results. Time (in weeks) was treated as categorical in the mixed model because the purpose was to estimate 24-wk means for comparison rather than estimation of slopes across time.

Secondary analyses compared outcomes of groups 2, 3, 4, or 5 with usual care (group 1) at 24 wk. This analysis also used mixed models and LOCF. Comparisons were not performed unless there was a significant *P* value in the overall test. Significant differences between group 2 (D/E only) and groups 3, 4, or 5 are also presented in tables, but only where the two-factorial analysis indicated a drug effect. For log-transformed data, final results are reported as geometric means.

Prespecified primary endpoints were changes in triglycerides, HDL-C, and non-HDL-C. Secondary endpoints were changes in glycemia, insulin sensitivity, adipokines, substrate oxidation, energy expenditure, and body composition. STATA 11.0 (StataCorp, College Station, TX) and SPSS 18.0 (SPSS Inc., Chicago, IL) software were used. $P < 0.05$ was considered significant.

Results

Of the 448 screened, 221 eligible subjects were randomized (Fig. 1). Thirty withdrew consent or dropped out before the first outcome measurements at wk 2. All 191 subjects who provided the first outcome measurement were included in the final analysis. There were no significant baseline differences between the 30 "early dropout" subjects and the 191 included in the final analysis.

The subjects were 87% male, 46% Hispanic, 36% White, and 17% African-American. At baseline, there

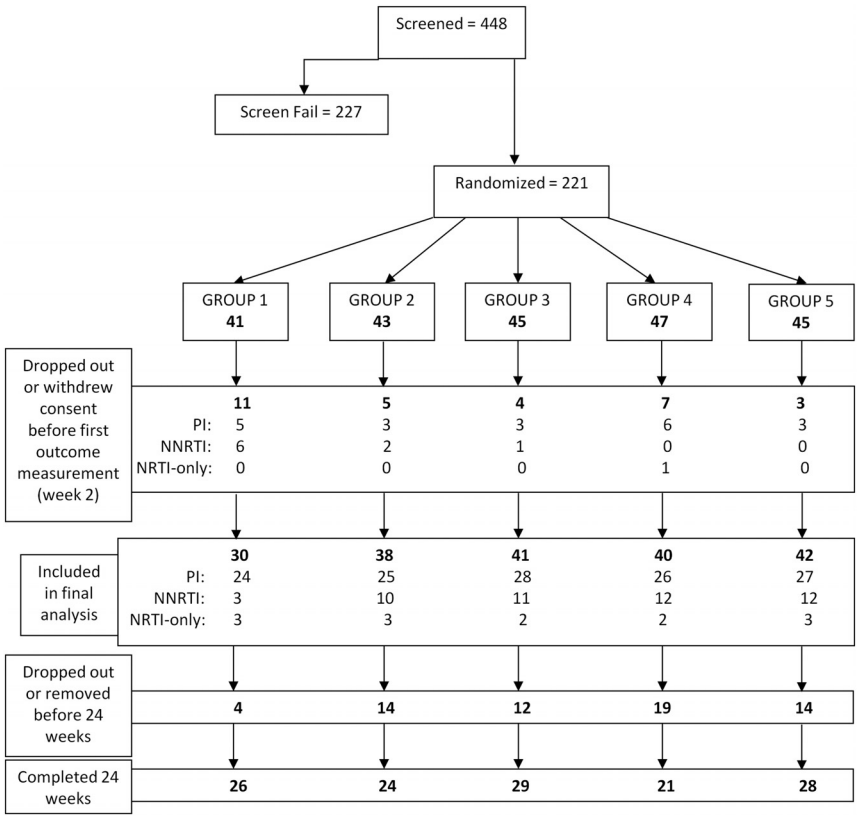

FIG. 1. Flow diagram of subject screening, recruitment, and randomization. At randomization, subjects were stratified by three combinations of ART classes: protease inhibitor-containing regime (PI), nonnucleoside reverse transcriptase inhibitor-containing regime (NNRTI), and regime with three nucleoside reverse transcriptase inhibitors without PI or NNRTI (NRTI-only).

were no significant group differences in age, sex, HIV duration, ART duration or strata, CD4 count, VL, BMI, race/ethnicity, or history of smoking, ethanol consumption, drug use, or viral hepatitis (Table 1). Family history of diabetes was less frequent in group 1. Baseline fasting lipid levels for the entire study cohort were (mean ± SE): total cholesterol, 211.3 ± 3.6 mg/dl (5.47 ± 0.09 mmol/liter); triglycerides, 306.4 ± 12.2 mg/dl (3.46 ± 0.14 mmol/liter); HDL-C, 39.7 ± 0.7 mg/dl (1.03 ± 0.02 mmol/liter); non-HDL-C, 171.7 ± 3.3 mg/dl (4.45 ± 0.09 mmol/liter); and total cholesterol-to-HDL-C ratio, 5.4 ± 0.1. There were no group differences in baseline lipid or glycemic levels, insulin, blood urea nitrogen (BUN), creatinine, ALT, AST, TSH, testosterone, FFA, leptin, adiponectin, hsCRP, or blood pressure (Table 2).

Table 3 displays results of two-factorial analysis of lipid outcomes among groups 2–5 at wk 24. Covariates were baseline values; ART strata; sex; race/ethnicity; history of smoking, alcohol or drug abuse; and family history of diabetes. There was no evidence of fenofibrate × niacin interaction for any parameters. By mixed model analysis of all 191 subjects, fenofibrate affected total cholesterol ($P = 0.02$), triglycerides ($P = 0.002$), and non-HDL-C ($P = 0.003$); niacin had an effect on HDL-C ($P = 0.03$); and both fenofibrate ($P = 0.005$) and niacin ($P = 0.01$) affected the ratio of total cholesterol to HDL-C. Analysis of the 127 subjects who completed the 24-wk intervention revealed the same effects, except for fenofibrate on total cholesterol. LOCF analysis corroborated the mixed model results in every respect.

Table 4 compares lipid outcomes between group 1 and groups 2–5 and displays differences between group 2 and groups 3–5. Total cholesterol ($P = 0.04$), triglycerides ($P = 0.003$), and non-HDL-C ($P = 0.003$) were lower in group 5 than in group 1; among the 24-wk completers, these levels were also lower in group 5 than in group 2. HDL-C was higher in groups 4 ($P = 0.04$) and 5 ($P < 0.001$) than in group 1; among the completers, HDL-C was also higher in group 5 than in group 2. Total cholesterol-to-HDL-C ratio was lower in groups 3, 4, and 5 compared with group 1 ($P = 0.01$, $P = 0.05$, and $P < 0.001$, respectively); among 24-wk completers, the ratio was also lower in group 5 than in group 2. Figure 2 displays individual lipid changes by group, together with their slopes and correlation coefficients.

Two-factorial analysis was performed on nonlipid outcomes in groups 2–5: FFA, glycosylated hemoglobin (HbA1c), fasting plasma glucose (FPG), area under the curve in the OGTT (OGTT-AUC) for glucose, fasting insulin, OGTT-AUC for insulin, fasting leptin, adiponectin, hsCRP, TSH, testosterone, homeostasis model assessment for insulin resistance (HOMA-IR), insulin sensitivity index, rate of elimination of CO_2, rate of oxygen consumption respiratory quotient, resting energy expenditure, CD4 count, log VL, weight, BMI, waist and hip circumferences, waist-hip ratio, body cell mass, fat mass, percentage body fat, blood pressure, ALT, AST, BUN, and creatinine. Covariates were the same as for the lipid analyses. There was no evidence of fenofibrate × niacin interaction for any parameters. There was an effect of niacin on FPG ($P = 0.002$), OGTT-AUC for glucose ($P = 0.02$), fasting insulin ($P = 0.03$), HOMA-IR ($P = 0.008$), insulin sensitivity index ($P = 0.007$), and adiponectin ($P < 0.0001$), and an effect of fenofibrate on creatinine ($P = 0.002$). Table 5 compares these outcomes between group 1 and groups 2–5 and displays differences between group 2 and groups 3–5. FPG levels were in-

TABLE 1. Baseline characteristics: demographic and virological parameters

Parameter	Group 1 (UC)	Group 2 (D/E)	Group 3 (D/E+F)	Group 4 (D/E+N)	Group 5 (D/E+F+N)	*P*
n	30	38	41	40	42	
Sex (n)						
Male	26	36	33	36	36	0.44
Female	4	2	8	4	6	
Age (yr)	44.5 ± 1.5	44.5 ± 1.5	43.6 ± 1.4	42.8 ± 1.4	43.2 ± 1.1	0.86
HIV duration (yr)	9.6 ± 1.1	10.5 ± 1.1	9.0 ± 0.9	9.0 ± 0.9	8.9 ± 0.9	0.76
ART duration (yr)	3.7 ± 0.4	5.8 ± 0.8	6.3 ± 0.8	5.8 ± 0.7	6.2 ± 0.8	0.12
CD4 (per ml)	445 ± 46	615 ± 52	544 ± 54	477 ± 46	466 ± 42	0.10
VL (copies/ml)	3334 ± 2051	301 ± 60	1251 ± 1017	796 ± 356	453 ± 145	0.17
Suppressed VL (n)	23 (77)	32 (84)	27 (66)	29 (73)	33 (79)	0.38
Weight (kg)	78.4 ± 1.9	81.6 ± 2.0	77.9 ± 2.1	80.2 ± 1.8	82.1 ± 2.3	0.52
BMI (kg/m^2)	26.31 ± 0.47	27.11 ± 0.53	26.56 ± 0.61	27.35 ± 0.58	27.20 ± 0.61	0.70
Ethnicity						
White	9 (30)	17 (45)	12 (29)	16 (40)	13 (31)	0.57
Hispanic	13 (44)	16 (42)	23 (56)	19 (48)	18 (43)	
African-American	7 (23)	5 (13)	5 (12)	5 (12)	11 (26)	
Other	1 (3)		1 (2)			
History of smoking	21 (68)	21 (58)	24 (59)	26 (65)	23 (54)	0.73
History of alcohol use	16 (52)	25 (58)	22 (54)	21 (53)	16 (37)	0.08
History of drug use	8 (26)	14 (39)	9 (22)	13 (33)	8 (19)	0.26
Family history of diabetes	7 (23)	17 (47)	121 (29)	22 (55)	24 (50)	0.01
Hepatitis						
A	4 (13)	4 (11)	4 (10)	3 (8)	5 (12)	0.36
B	6 (20)	5 (13)	6 (15)	5 (13)	3 (7)	0.55
C	1 (3)	4 (11)	3 (7)	1 (3)	6 (14)	0.57

Data are expressed as mean ± SE, or number (percentage) unless described otherwise. UC, Usual care; D/E+F, D/E + fenofibrate; D/E+N, D/E + niacin; D/E+F+N, D/E + fenofibrate + niacin.

creased in groups 4 and 5 compared with group 2, but remained within the normoglycemic range. There were no group differences in HbA1c. HOMA-IR was higher, and the insulin sensitivity index was lower in groups 4 and 5 compared with group 2. Despite these indications of decreased insulin sensitivity with respect to glucose, groups 4 and 5 experienced markedly increased levels of adiponectin compared with groups 1 and 2, whereas

TABLE 2. Baseline characteristics: lipid, biochemical, and hormonal parameters

Parameter	Group 1 (UC)	Group 2 (D/E)	Group 3 (D/E+F)	Group 4 (D/E+N)	Group 5 (D/E+F+N)	*P*
Total cholesterol (mg/dl)	214.4 ± 8.6	220.3 ± 10.0	208.3 ± 8.1	207.2 ± 6.0	207.9 ± 7.3	0.74
Triglycerides (mg/dl)	313.5 ± 34.0	328.3 ± 34.1	297.7 ± 21.7	313.9 ± 26.8	283.1 ± 21.2	0.79
HDL-C (mg/dl)	40.5 ± 1.9	39.8 ± 1.6	39.4 ± 1.2	38.7 ± 1.3	40.0 ± 1.4	0.94
Non-HDL-C (mg/dl)	173.9 ± 7.7	180.5 ± 9.5	168.8 ± 7.5	168.5 ± 5.3	167.8 ± 6.5	0.71
TC:HDL-C ratio	5.4 ± 0.19	5.7 ± 0.24	5.3 ± 0.17	5.5 ± 0.14	5.3 ± 0.14	0.59
Fasting glucose (mg/dl)	93.4 ± 1.7	97.4 ± 2.9	91.4 ± 1.3	96.3 ± 1.7	96.3 ± 3.1	0.31
Fasting insulin (μU/ml)	12.6 ± 1.7	11.9 ± 1.3	13.4 ± 1.4	14.2 ± 1.9	25.0 ± 8.2	0.14
HbA1c (%)	5.21 ± 0.10	5.35 ± 0.07	5.19 ± 0.07	5.34 ± 0.12	5.43 ± 0.12	0.38
TSH (μIU/ml)	2.06 ± 0.29	2.13 ± 0.24	2.28 ± 0.23	1.63 ± 0.13	1.74 ± 0.15	0.13
Testosterone (ng/dl)	428.8 ± 47.8	497.5 ± 36.6	476.2 ± 57.7	467.3 ± 53.3	447.7 ± 54.4	0.92
FFA (mEq/liter)	0.41 ± 0.07	0.28 ± 0.03	0.33 ± 0.04	0.31 ± 0.03	0.31 ± 0.02	0.18
Leptin (ng/ml)	7.32 ± 1.10	6.13 ± 0.86	7.88 ± 1.14	5.50 ± 0.88	7.14 ± 0.98	0.44
Adiponectin (ng/ml)	6.1 ± 1.5	8.6 ± 1.4	7.6 ± 0.9	5.2 ± 0.8	5.3 ± 0.7	0.12
hsCRP (mg/liter)	3.39 ± 0.58	4.58 ± 1.35	4.39 ± 1.85	3.56 ± 0.85	3.62 ± 0.85	0.89
BUN (mg/dl)	14.8 ± 0.94	14.7 ± 0.73	15.0 ± 0.58	13.0 ± 0.62	14.1 ± 0.61	0.21
Creatinine (g/dl)	0.98 ± 0.04	0.96 ± 0.04	0.97 ± 0.04	0.94 ± 0.02	0.98 ± 0.02	0.83
ALT (U/liter)	33.4 ± 3.9	30.9 ± 1.9	31.7 ± 3.0	37.0 ± 3.3	25.9 ± 1.9	0.39
AST (U/liter)	27.2 ± 2.0	28.4 ± 1.5	28.4 ± 1.7	32.1 ± 3.4	26.5 ± 1.5	0.21
SBP (mm Hg)	128.3 ± 2.5	145.6 ± 14.5	127.3 ± 2.2	130.4 ± 2.5	125.8 ± 2.3	0.23
DBP (mm Hg)	82.1 ± 1.8	84.7 ± 1.7	81.3 ± 1.5	84.0 ± 1.7	80.7 ± 1.7	0.36

Data are expressed as mean ± SE. UC, Usual care; D/E+F, D/E + fenofibrate; D/E+N, D/E + niacin; D/E+F+N, D/E + fenofibrate + niacin; SBP, systolic blood pressure; DBP, diastolic blood pressure. For conversion to SI units: cholesterol × 0.0259; triglycerides × 0.0113; glucose × 0.0555; insulin × 6.945; testosterone × 0.0347; BUN × 0.357; creatinine × 88.4.

TABLE 3. Lipid outcomes: effects of fenofibrate or niacin

Parameter	Fenofibrate			Niacin			Fenofibrate × niacin interaction (*P*)
	No	Yes	*P*	No	Yes	*P*	
Total cholesterol							
All subjects	195.5 ± 4.9	181.2 ± 5.8	**0.02**	192.1 ± 5.4	184.6 ± 5.3	0.24	0.78
24-wk completers	202.6 ± 7.5	190.4 ± 7.0	0.06	201.1 ± 7.5	191.8 ± 7.0	0.18	0.97
Triglycerides							
All subjects	197.3 ± 18.7	154.4 ± 12.5	**0.002**	186.0 ± 17.0	156.6 ± 8.5	0.07	0.72
24-wk completers	247.6 ± 33.0	186.6 ± 22.5	**0.02**	236.9 ± 30.1	197.4 ± 22.7	0.06	0.77
HDL-C							
All subjects	40.3 ± 1.4	42.8 ± 1.4	0.16	39.7 ± 1.3	43.3 ± 1.5	**0.03**	0.84
24-wk completers	42.0 ± 2.0	43.5 ± 1.9	0.43	40.5 ± 1.8	45.0 ± 2.1	**0.02**	0.59
Non-HDL-C							
All subjects	159.7 ± 5.8	141.5 ± 5.3	**0.003**	155.6 ± 5.5	145.6 ± 5.7	0.11	0.81
24-wk completers	161.6 ± 6.8	148.4 ± 6.3	**0.03**	160.4 ± 6.3	149.6 ± 6.6	0.12	0.90
TC:HDL-C							
All subjects	4.9 ± 0.2	4.3 ± 0.1	**0.005**	4.8 ± 0.2	4.3 ± 0.2	**0.01**	0.95
24-wk completers	4.8 ± 0.3	4.4 ± 0.2	**0.04**	4.9 ± 0.3	4.3 ± 0.2	**0.004**	0.66

Data are expressed as mean ± SE. *Bold values* indicate $P < 0.05$.

group 3 had a slightly lower level of adiponectin than group 1. Creatinine was higher in groups 3 and 5 than in groups 1 and 2. There were no significant group differences in FFA or hsCRP levels. As intended in the weight-maintaining lifestyle intervention, there were no significant changes or group differences in weight or BMI.

Except for flushing, reported by 35–40% of those taking niacin, adverse events were infrequent and were not increased in those who received active drugs (Table 6).

Of the 191 subjects who completed 2 wk and were included in the final analysis, 64 did not complete the 24-wk protocol. The only differences between completers and noncompleters were that the former were slightly

TABLE 4. Lipid outcomes: comparisons with control groups 1 and 2

Parameter	Group 1 (UC)	Group 2 (D/E)	Group 3 (D/E+F)	Group 4 (D/E+N)	Group 5 (D/E+F+N)
All subjects					
Total cholesterol (mg/dl)	195.6 ± 7.7	200.1 ± 8.3	184.0 ± 6.9	190.8 ± 8.2	178.4 ± 7.0[a]
% attaining <200 mg/dl	57	47	63	58	62
Triglycerides (mg/dl)	199.0 ± 24.9	216.9 ± 28.6	155.1 ± 18.5	177.6 ± 24.2	135.6 ± 16.9[a,b]
% attaining <150 mg/dl	30	26	44	30	57
HDL-C (mg/dl)	37.1 ± 1.8	38.7 ± 1.9	40.7 ± 1.8	41.8 ± 2.2[a]	44.8 ± 2.1[a]
% attaining >40 mg/dl	40	45	44	58	76
Non-HDL-C (mg/dl)	162.2 ± 7.8	165.4 ± 8.1	145.8 ± 7.4	154.0 ± 8.3	137.1 ± 7.7[a]
% attaining <130 mg/dl	23	16	44	20	48
Total cholesterol:HDL-C	5.2 ± 0.3	5.1 ± 0.3	4.5 ± 0.2[a]	4.6 ± 0.3[a]	4.0 ± 0.2[a]
% attaining <3.5:1	10	5	20	15	31
24-wk completers					
Total cholesterol (mg/dl)	206.3 ± 10.0	206.9 ± 10.7	195.3 ± 10.6	198.2 ± 10.6	185.4 ± 9.1[a,b]
% attaining <200 mg/dl	47	32	44	35	48
Triglycerides (mg/dl)	256.0 ± 44.6	269.3 ± 49.8	204.4 ± 34.0	225.9 ± 43.2	168.8 ± 29.6[a]
% attaining <150 mg/dl	27	21	32	18	45
HDL cholesterol (mg/dl)	36.9 ± 2.3	39.9 ± 2.6	41.0 ± 2.4	44.0 ± 3.0[a]	46.0 ± 2.9[a,b]
% attaining >40 mg/dl	30	29	37	33	52
Non-HDL-C (mg/dl)	170.0 ± 8.9	166.2 ± 9.4	154.5 ± 8.5	156.9 ± 9.7	142.2 ± 9.0[a,b]
% attaining <130 mg/dl	7	5	20	8	31
Total cholesterol:HDL-C	5.4 ± 0.4	5.1 ± 0.4	4.7 ± 0.3	4.5 ± 0.3[a]	4.0 ± 0.3[a]
% attaining <3.5:1	20	13	37	13	40

Data are expressed as mean ± SE or percentage. Covariates in the analyses were: baseline values, ART strata, sex, ethnicity, smoking history, alcohol history, drug use history, and family history of diabetes. For "All subjects," n = 191 and mixed repeated measures model analysis results are displayed. Analysis by LOCF yielded similar results. For conversion to SI units: cholesterol × 0.0259; triglycerides × 0.0113. For "24-wk completers," n = 127. UC, Usual care; D/E+F, D/E + fenofibrate; D/E+N, D/E + niacin; D/E+F+N, D/E + fenofibrate + niacin.

[a] $P < 0.05$ compared to group 1.

[b] $P < 0.05$ compared to group 2.

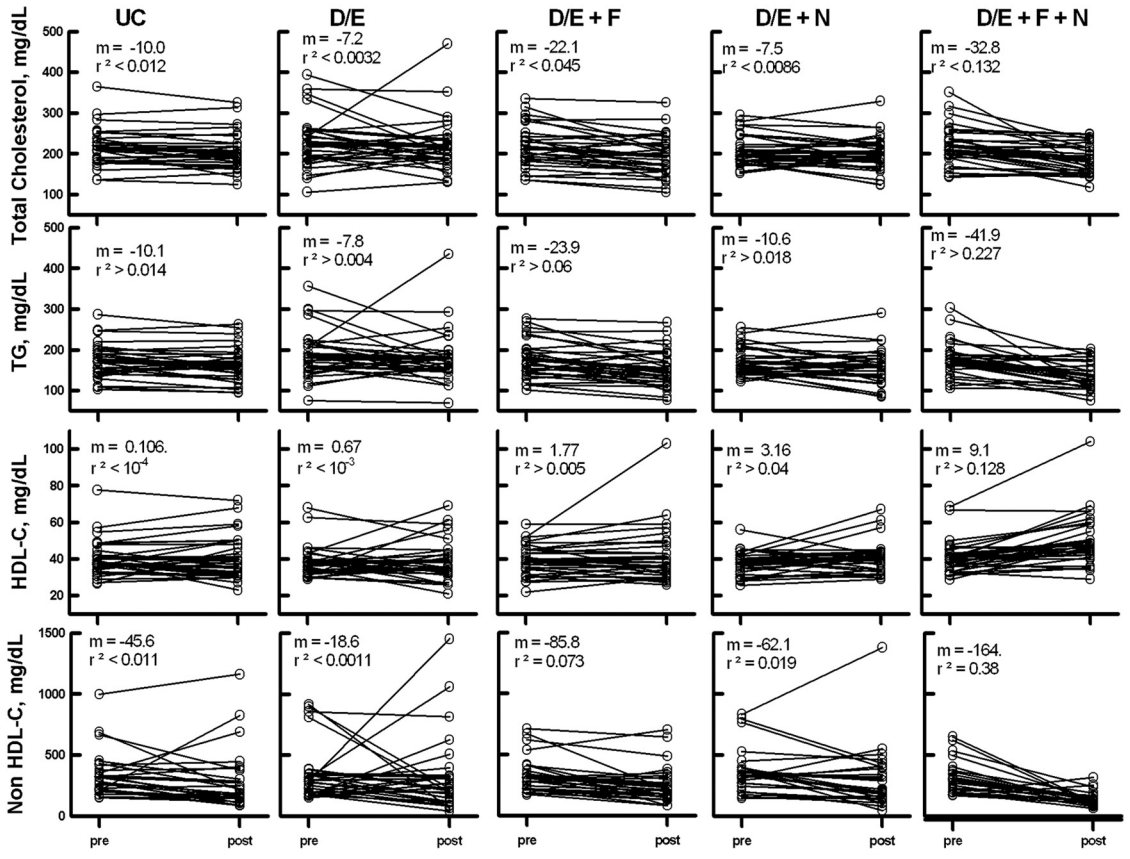

FIG. 2. Lipid changes within individual subjects, displayed by group. All 191 subjects included in the analysis are represented, and "post" refers to the last value measured in each subject. The slope (m) represents the magnitude of the mean group change (in milligrams per deciliter), and r^2 represents the correlation of the change with the treatment. The slope and correlation coefficients were calculated by linear regression analysis using SigmaPlot (Systat Software, Inc., San Jose, CA). TG, Triglyceride; UC, usual care; F, fenofibrate; N, niacin.

older (44.8 ± 8.6 yr compared with 41.3 ± 7.3 yr; $P = 0.006$) and had a lower frequency of family history of diabetes (37% compared with 53.1%; $P = 0.04$). The subject population was largely indigent (>90% participated in the Ryan White program for low-income, uninsured HIV patients), and approximately 30% had only transient addresses. Lack of permanent addresses or telephone connections made it difficult to ascertain reasons for dropout in 54 noncompleters. Ten subjects were removed from the study for problems unrelated to the interventions. Completion rates for groups 1–5 were 87, 63, 71, 53, and 67%, respectively. Dosage of niacin or placebo was decreased by prespecified algorithm for seven subjects with persistent flushing and two with ALT/AST elevations. The latter were hepatitis B or C positive and belonged to group 5—transaminase levels returned to baseline after dose reduction in one who completed the study, but remained elevated in the other until removal from the study. Review of medication use at refill visits revealed no group differences in compliance. Dietary compliance was reviewed, and guidelines were reiterated at each dietitian visit (wk 8, 16, and 24). Compliance with dietitian visits (number of total visits/number of expected visits for the duration of the subject in the program) was as follows: 55% completed 100%, 14% completed 75%, 4% completed 67%, 18% completed 50%, 6% completed 25%, and 3% completed 0%. Compliance with gym visits (number of total visits/week for the duration of the subject in the program) was 1.65 ± 0.26 visits (mean ± SD) per week.

The ART regime was altered in seven subjects by their HIV physicians. By prespecified policy, one subject was removed because this altered his ART stratum; the others were permitted to continue because the change did not alter their strata.

At the baseline OGTT, 17 subjects (three in group 1, one in group 2, two in group 3, six in group 4, and five in group 5) met criteria for diabetes. They were permitted to remain in the study with close monitoring of glucose levels. Six did not complete the study for reasons unrelated to glucose control and had no change in fasting glycemic levels while participating in the study. Of the 11 completers, seven belonged to a niacin arm; one showed a decrease in HbA1c by more than 0.2%, four showed no change, and one showed an increase in HbA1c by more than 0.2%. Four completers were in a non-niacin arm;

TABLE 5. Metabolic, hormonal, insulin sensitivity, body composition, energy expenditure, and virological outcomes: comparisons with control groups 1 and 2

Parameter	Group 1 (UC)	Group 2 (D/E)	Group 3 (D/E+F)	Group 4 (D/E+N)	Group 5 (D/E+F+N)
FFA (mEq/liter)	0.40 ± 0.05	0.37 ± 0.05	0.35 ± 0.05	0.34 ± 0.05	0.36 ± 0.05
HbA1c (%)	5.5 ± 0.9	5.3 ± 0.9[a]	5.3 ± 0.9[a]	5.4 ± 0.1	5.3 ± 0.1[a]
FPG (mg/dl)	90.9 ± 2.9	88.7 ± 3.0	88.4 ± 2.7	95.4 ± 3.2[b]	95.6 ± 3.0[b]
OGTT-AUC for glucose (mg/dl over 120 min)	17,318 ± 959	17,207 ± 1022	16,221 ± 852	18,113 ± 1,110	18,239 ± 1,086
Fasting plasma insulin (μU/ml)	8.7 ± 2.0	6.7 ± 1.6	9.5 ± 1.6	11.9 ± 3.0[b]	10.3 ± 2.5[b]
OGTT-AUC for insulin (μU/ml over 120 min)	10,051 ± 1,869	7,180 ± 1,430	9,141 ± 1,635	8,821 ± 1,838	10,066 ± 2,039
HOMA-IR	1.92 ± 0.47	1.38 ± 0.36	2.02 ± 0.47	2.76 ± 0.75[b]	2.38 ± 0.62[b]
Insulin sensitivity index	3.54 ± 0.73	4.95 ± 1.10	3.81 ± 0.76	2.88 ± 0.67[b]	3.12 ± 0.70[b]
Fasting plasma leptin (ng/ml)	4.22 ± 0.67	4.42 ± 0.76	4.47 ± 0.69	4.67 ± 0.81	4.11 ± 0.74
Adiponectin (μg/ml)	7.12 ± 1.09	6.04 ± 0.98	5.24 ± 0.76[a]	11.01 ± 1.87[a,b]	10.34 ± 1.67[a,b]
hsCRP (mg/liter)	1.75 ± 1.13	2.42 ± 1.19	1.42 ± 1.09	1.18 ± 1.24	2.62 ± 1.16
ALT (IU/liter)	25.9 ± 5.4	24.7 ± 5.2	26.6 ± 5.5	29.7 ± 5.9	25.4 ± 5.2
AST (IU/liter)	29.6 ± 6.1	25.4 ± 6.0	31.0 ± 5.9	29.3 ± 5.7	28.7 ± 6.0
BUN (mg/dl)	15.9 ± 1.9	14.3 ± 1.9	15.9 ± 1.9	15.5 ± 1.8	15.5 ± 1.9
Creatinine (g/dl)	1.09 ± 0.07	1.12 ± 0.07	1.22 ± 0.07[a,b]	1.16 ± 0.07	1.23 ± 0.07[a,b]
TSH (μU/ml)	1.24 ± 0.21	1.22 ± 0.22	1.31 ± 0.20	1.24 ± 0.23	1.10 ± 0.19
Testosterone (ng/dl)	499.9 ± 60.2	439.3 ± 60.3	436.7 ± 54.1	504.2 ± 62.9	460.3 ± 59.8
Weight (kg)	79.8 ± 2.2	79.5 ± 2.2	79.2 ± 2.1	78.7 ± 2.1	79.0 ± 2.2
BMI (kg/m^2)	26.9 ± 0.76	26.5 ± 0.75	26.5 ± 0.72	26.3 ± 0.72	26.7 ± 0.75
Systolic BP (mm Hg)	120.9 ± 5.3	122.8 ± 5.2	122.2 ± 5.1	125.6 ± 5.0	121.1 ± 5.2
Diastolic BP (mm Hg)	78.5 ± 3.9	80.1 ± 3.8	80.9 ± 3.8	81.8 ± 3.7	78.6 ± 3.8
Waist (cm)	90.5 ± 2.7	90.2 ± 2.2	89.4 ± 2.0	91.3 ± 2.2	89.3 ± 2.1
Hip (cm)	92.2 ± 4.3	92.3 ± 3.5	93.1 ± 3.2	91.0 ± 3.5	93.5 ± 3.3
Waist-hip ratio	0.91 ± 0.02	0.92 ± 0.02	0.92 ± 0.02	0.92 ± 0.02	0.90 ± 0.02
Body cell mass (kg)	59.6 ± 2.3	67.3 ± 2.0	66.6 ± 1.8	67.1 ± 2.1	68.2 ± 2.0
Fat mass (kg)	36.8 ± 1.9	37.5 ± 1.6	35.8 ± 1.5	37.7 ± 1.8	36.2 ± 1.7
Body fat (%)	24.1 ± 1.1	22.3 ± 0.9	22.1 ± 0.9	22.1 ± 1.0	22.3 ± 0.9
VCO_2 (ml/min)	218.3 ± 8.6	212.1 ± 8.4	216.7 ± 8.1	211.7 ± 9.7	202.8 ± 8.7
VO_2 (ml/min)	271.2 ± 10.6	256.3 ± 10.3	264.8 ± 9.8	262.6 ± 10.9	261.3 ± 10.7
RQ	0.83 ± 0.01	0.85 ± 0.01	0.857 ± 0.01	0.853 ± 0.01	0.82 ± 0.01
REE (kcal/24 h)	1,800 ± 94	1,663 ± 88	1,799 ± 86	1,765 ± 94	1,757 ± 93
CD4 count (per ml)	455 ± 51	429 ± 8	508 ± 5	490 ± 54	491 ± 53
Log VL	2.58 ± 0.16	2.45 ± 0.18	2.35 ± 0.17	2.55 ± 0.17	2.38 ± 0.17

Data are expressed as mean ± SE. Covariates in the analyses were: baseline values, ART strata, sex, ethnicity, smoking history, alcohol history, drug use history, and family history of diabetes. HOMA-IR = fasting glucose (mmol/liter) × fasting insulin (mU/liter)/22.5; insulin sensitivity index = 10,000/√[(fasting glucose × fasting insulin) × (mean glucose × mean insulin during the OGTT)]. For conversion to SI units: glucose × 0.0555; BUN × 0.357; creatinine × 88.4; testosterone × 0.0347. UC, Usual care; D/E+F, D/E + fenofibrate; D/E+N, D/E + niacin; D/E+F+N, D/E + fenofibrate + niacin; VCO_2, rate of elimination of CO_2; VO_2, rate of oxygen consumption; RQ, respiratory quotient; REE, resting energy expenditure.

[a] $P < 0.05$ compared to group 1.

[b] $P < 0.05$ compared to group 2.

one showed a decrease in HbA1c, two showed no change, and one showed an increase in HbA1c, using the same criteria.

Eight subjects who had nondiabetic baseline OGTT responses and completed the study crossed thresholds of glycemic control by the end of the trial. Three subjects in a non-niacin arm and one in a niacin arm moved from normal glucose tolerance to impaired glucose tolerance. One subject in a niacin arm moved from impaired glucose tolerance to diabetes. Two subjects in a non-niacin arm and one in a niacin arm moved from normal glucose tolerance to diabetes.

Discussion

The Heart Positive study demonstrated that, against a background of a low-saturated-fat diet and regular exercise, niacin increased HDL-C and fenofibrate decreased triglycerides in a multiethnic group of dyslipidemic HIV patients on ART. These drugs were selected, despite their overlapping lipid-lowering effects, for their ability to target distinct kinetic defects in HIV patients. A combination of the two was most effective in lowering triglycerides (−52% compared with usual care), increasing HDL-C (+12%), and lowering non-HDL-C (−18.5%). Indeed,

TABLE 6. Adverse events

Adverse events	Group 1 (UC)	Group 2 (D/E)	Group 3 (D/E+F)	Group 4 (D/E+N)	Group 5 (D/E+F+N)
Dizziness	2	1		1	1
Rash/itching	1			3	2
ALT/AST >3X ULN[a]	1	1		1	2
Flushing[b]	1	2	3	16	12
Diarrhea	3	1	2	2	
Nausea/vomiting	2	1	4		3
Chest pain/angina	1	1	1	1	
Abdominal pain	1	2		1	
Back pain				2	1
Fatigue	2			1	2
Triglyceride ≥1000 mg/dl	1	3		1	
Headache	5			2	
Muscle/body ache		1		1	2
Polyuria			1	1	
Elevated bilirubin[c]	3	5	4		2
Leg cramps		1			1
Creatinine >1.5 g/dl			1	1	1
Loss of appetite	1	1			1

Table lists the numbers of all events that occurred in at least 1% of the subjects. Other notable adverse events included: acute kidney injury (one subject in group 4), kidney stone (one subject in group 3), acute myocardial infarction (one subject in group 2), acute cholecystitis (one subject in group 4), and suicide attempt (one subject in group 4). UC, Usual care; D/E+F, D/E + fenofibrate; D/E+N, D/E + niacin; D/E+F+N, D/E + fenofibrate + niacin; ULN, upper limit of normal.

[a] Reasons: One subject in group 1 due to binge drinking—resolved, and subject completed study; one subject in group 2 due to taking oxandrolone—subject removed from study; one subject in group 4 for no clear reason 3 d after start of protocol—resolved spontaneously, and subject completed study; two subjects in group 5 likely due to study drug(s)—in one, the levels returned to baseline after decreasing dose of study drugs and he completed the study, whereas the other had persistently elevated levels after decreasing the dose, and he was removed from the study with return of levels to normal 1 month later.

[b] Includes all reports of flushing, regardless of severity.

[c] All subjects with elevated bilirubin were taking atazanavir (known to cause a Gilbert's-like syndrome) and had no clinical or biochemical evidence of hepatitis or obstructive jaundice.

postintervention mean levels for the group that received both drugs were in the normal range for triglycerides and HDL-C. Combination therapy also produced the lowest ratio of total cholesterol to HDL-C, a measure highly correlated with cardiovascular risk (24).

Prior studies of niacin or fibrates in HIV patients have been small and limited to monotherapy without lifestyle interventions. Dubé *et al.* (25) noted improvements in total cholesterol, triglycerides, HDL-C, and non-HDL-C in a 44-wk study of niacin in 30 patients. Fibrates produced modest improvements in low-density lipoprotein cholesterol, triglycerides (−30 to −33%), and HDL-C (+10 to +12%) in small, nonrandomized cohorts (26–28). A randomized trial of gemfibrozil in 36 patients demonstrated a 23% decrease in triglycerides after 12 wk (29). Response to gemfibrozil may be attenuated in HIV patients (30).

Evidence from non-HIV populations with hypertriglyceridemia and low HDL-C, treated with fibrates or niacin, suggests that the improvements observed in the Heart Positive study could be clinically meaningful. Niacin reduced myocardial infarction rates by 15% in the Coronary Drug Project (31), and decreased carotid atherosclerosis when added to a statin in the Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol trial (32). The Helsinki Heart Study showed that increases in HDL-C among patients on gemfibrozil were associated with coronary heart disease (CHD) risk reduction (33), and in the Veterans Administration HDL Intervention Trial, gemfibrozil raised HDL-C by 6% and reduced CHD by 20% (34). A recent meta-analysis indicated that every 1 mg/dl rise in HDL-C or reduction in non-HDL-C reduced CHD risk 1.5 and 1.4%, respectively (35). Thus, the approximately 9 mg/dl increase in HDL-C and 41 mg/dl decrease in non-HDL-C observed among group 5 subjects in the Heart Positive study might correspond to CHD risk reductions of 14.5 and 57%, respectively, or total risk reduction as much as 72%. However, the unique features of accelerated atherosclerosis in HIV patients dictate caution in extrapolating from outcomes in non-HIV populations. By analogy, patients with diabetes (who have a related form of metabolic syndrome and vascular inflammation) may not experience the same degree of CVD risk reduction as nondiabetic patients. The Fenofibrate Intervention and Event Lowering in Diabetes trial showed no significant effect of fenofibrate on coronary events among patients with type 2 diabetes (36). In the

Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, addition of fenofibrate to statins did not reduce cardiovascular events among patients with type 2 diabetes overall (37); however, there was a benefit for patients with both high triglycerides and low HDL-C, a subgroup with a lipid profile similar to that of HIV patients on ART.

As previously reported for hypertriglyceridemic HIV patients (38–40), baseline adiponectin levels were low. Adiponectin levels increased markedly in response to niacin (mean change, +111% from baseline to 11.01 ± 1.87 μg/ml in group 4, and +95% to 10.34 ± 1.67 μg/ml in group 5). This outcome is remarkable given that niacin produced mild increases in mean fasting glucose levels (but within the normoglycemic range), as well as in insulin levels and HOMA-IR, and it suggests a direct effect of niacin on adiponectin expression (41). This effect of niacin has been noted in HIV-negative persons (42, 43). The relationship between hypoadiponectinemia, hypertriglyceridemia, and poor clearance of triglyceride from very low-density lipoprotein, low-density lipoprotein, and HDL in dyslipidemic HIV patients also suggests an effect of adiponectin on lipoprotein metabolism (44). Collectively, these data suggest that niacin may induce a qualitative improvement in lipoprotein composition mediated by adiponectin in dyslipidemic HIV patients.

Despite interventions aimed at blunting lipolysis and increasing fat oxidation, fasting FFA levels did not improve. Impaired dietary fat disposal contributes markedly to fasting FFA levels in patients with HIV lipodystrophy (13); inability to lower FFA levels with a regime that included a 30% fat diet suggests that greater reductions in dietary fat may be necessary to overcome this defect. Consistent with this notion and a previous lifestyle study (45), D/E alone failed to improve fasting triglyceride levels.

Liver dysfunction was a concern with the use of niacin and fenofibrate in this population with high prevalence of viral hepatitis. The frequency of transaminase elevation was not increased among subjects receiving niacin or fenofibrate, but two patients who experienced (reversible) elevation of ALT/AST as a possible consequence of the interventions were positive for hepatitis B or C and received both drugs. Monitoring liver functions will be important when treating HIV patients with a niacin-fenofibrate combination. CD4 counts and VL were not altered by any study interventions.

Changes across thresholds of glycemic control were similar in subjects who received niacin compared with those who did not—among study completers, 6% of niacin users compared with 6.3% of non-niacin users had a combined incidence of impaired glucose tolerance or diabetes. Among the 17 subjects who were first diagnosed with diabetes at the time of the baseline OGTT, glycemic changes through the trial were similar between niacin users and nonusers. Flushing was a common side effect of niacin. Although aspirin or acetaminophen frequently alleviated the symptoms, it is possible that flushing contributed to dropouts among subjects in groups 4 and 5. Prostaglandin D2 receptor inhibitors that prevent flushing may facilitate niacin therapy (46).

The D/E intervention alone did not improve lipid levels or adiponectin or induce statistically significant change in any of the secondary outcomes. Changes in fitness and dietary behavior and their relationship to energy expenditure parameters will be reported separately.

Clinicians attempting to reduce CVD risk in HIV patients on ART face special therapeutic challenges; there are significant interactions between lipid medications and antiretroviral agents, and the unique origins and distinctive features of the dyslipidemia make it difficult to achieve NCEP targets using current algorithms. A rationally based, combinatorial approach using niacin and fenofibrate with low-saturated-fat diet and exercise is both effective and safe in improving the CVD risk factors of low HDL-C, elevated non-HDL-C, and hypertriglyceridemia among HIV patients on ART. Its effectiveness across different ethnic groups and ART regimes makes these results broadly applicable to dyslipidemic HIV patients, including ethnic minorities with increasing prevalence of HIV infection. An event-driven trial is required to determine whether this approach can improve cardiovascular outcomes and to compare it to the non-CYP3A4-metabolized statins currently recommended as initial therapy for dyslipidemia in HIV patients. Data from the Heart Positive study provide the rationale for such an investigation.

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References

1. **Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA** 1998 A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. AIDS 12:F51–F58
2. **Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, De Wit S, Law M, Monforte AD, Friis-Møller N, Kirk O, Fontas E, Weller I, Phillips A, Lundgren J** 2010 Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: the data collection on adverse events of anti-HIV drugs (D:A:D) study. J Infect Dis 201:318–330
3. **d'Arminio A, Sabin CA, Phillips AN, Reiss P, Weber R, Kirk O, El-Sadr W, De Wit S, Mateu S, Petoumenos K, Dabis F, Pradier C, Morfeldt L, Lundgren JD, Friis-Moller N, Writing Committee of the D:A:D Study Group** 2004 Cardio- and cerebrovascular events in HIV-infected persons. AIDS 18:1811–1817
4. **Flynn TE, Bricker LA** 1999 Myocardial infarction in HIV-infected men receiving protease inhibitors. Ann Intern Med 131:548
5. **Friis-Møller N, Weber R, Reiss P, Thiébaut R, Kirk O, d'Arminio Monforte A, Pradier C, Morfeldt L, Mateu S, Law M, El-Sadr W, De Wit S, Sabin CA, Phillips AN, Lundgren JD** 2003 Cardiovascular disease risk factors in HIV patients—association with antiretroviral therapy. Results from the DAD study. AIDS 17:1179–1193
6. **Varriale P, Saravi G, Hernandez E, Carbon F** 2004 Acute myocardial infarction in patients infected with human immunodeficiency virus. Am Heart J 147:55–59
7. **Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A** 2007 Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. Diabetes Care 30:113–119
8. **Rose H, Hoy J, Woolley I, Tchoua U, Bukrinsky M, Dart A, Sviridov D** 2008 HIV infection and high density lipoprotein metabolism. Atherosclerosis 199:79–86
9. **Tsiodras S, Mantzoros C, Hammer S, Samore M** 2000 Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. Arch Intern Med 160:2050–2056
10. **Sekhar RV, Jahoor F, White AC, Pownall HJ, Visnegarwala F, Rodriguez-Barradas MC, Sharma M, Reeds PJ, Balasubramanyam A** 2002 Metabolic basis of HIV-lipodystrophy syndrome. Am J Physiol Endocrinol Metab 283:E332–E337
11. **Hadigan C, Borgonha S, Rabe J, Young V, Grinspoon S** 2002 Increased rates of lipolysis among human immunodeficiency virus-infected men receiving highly active antiretroviral therapy. Metabolism 51:1143–1147
12. **Reeds DN, Mittendorfer B, Patterson BW, Powderly WG, Yarasheski KE, Klein S** 2003 Alterations in lipid kinetics in men with HIV-dyslipidemia. Am J Physiol Endocrinol Metab 285:E490–E497
13. **Sekhar RV, Jahoor F, Pownall HJ, Rehman K, Gaubatz J, Iyer D, Balasubramanyam A** 2005 Severely dysregulated disposal of postprandial triacylglycerols exacerbates hypertriacylglycerolemia in HIV lipodystrophy syndrome. Am J Clin Nutr 81:1405–1410
14. **Ware LJ, Wootton SA, Morlese JM, Gazzard BG, Jackson AA** 2002 The paradox of improved antiretroviral therapy in HIV: potential for nutritional modulation? Proc Nutr Soc 61:131–136
15. **Mujawar Z, Rose H, Morrow MP, Pushkarsky T, Dubrovsky L, Mukhamedova N, Fu Y, Dart A, Orenstein JM, Bobryshev YV, Bukrinsky M, Sviridov D** 2006 Human immunodeficiency virus impairs reverse cholesterol transport from macrophages. PLoS Biol 4:e365
16. **Tong Q, Sankalé JL, Hadigan CM, Tan G, Rosenberg ES, Kanki PJ, Grinspoon SK, Hotamisligil GS** 2003 Regulation of adiponectin in human immunodeficiency virus-infected patients: relationship to body composition and metabolic indices. J Clin Endocrinol Metab 88:1559–1564
17. **Vigouroux C, Maachi M, Nguyên TH, Coussieu C, Gharakhanian S, Funahashi T, Matsuzawa Y, Shimomura I, Rozenbaum W, Capeau J, Bastard JP** 2003 Serum adipocytokines are related to lipodystrophy and metabolic disorders in HIV-infected men under antiretroviral therapy. AIDS 17:1503–1511
18. **Dubé MP, Stein JH, Aberg JA, Fichtenbaum CJ, Gerber JG, Tashima KT, Henry WK, Currier JS, Sprecher D, Glesby MJ** 2003 Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. Clin Infect Dis 37:613–627
19. **Hulgan T, Sterling TR, Daugherty J, Arbogast PG, Raffanti S, Ray W** 2005 Prescribing of contraindicated protease inhibitor and statin combinations among HIV-infected persons. J Acquir Immune Defic Syndr 38:277–282
20. **Samson SL, Pownall HJ, Scott LW, Ballantyne CM, Smith EO, Sekhar RV, Balasubramanyam A** 2006 Heart Positive: design of a randomized controlled clinical trial of intensive lifestyle intervention, niacin and fenofibrate for HIV lipodystrophy/dyslipidemia. Contemp Clin Trials 27:518–530
21. **Brown BG, Zhao XQ, Chait A, Fisher LD, Cheung MC, Morse JS, Dowdy AA, Marino EK, Bolson EL, Alaupovic P, Frohlich J, Albers JJ** 2001 Simvastatin and niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. N Engl J Med 345:1583–1592
22. 1987 Atherosclerosis risk in communities (ARIC) study. Operations manual. Bethesda, MD: National Heart Lung and Blood Institute
23. **Siddiqui O, Hung HM, O'Neill R** 2009 MMRM vs. LOCF: a comprehensive comparison based on simulation study and 25 NDA datasets. J Biopharm Stat 19:227–246
24. **Ingelsson E, Schaefer EJ, Contois JH, McNamara JR, Sullivan L, Keyes MJ, Pencina MJ, Schoonmaker C, Wilson PW, D'Agostino RB, Vasan RS** 2007 Clinical utility of different lipid measures for prediction of coronary heart disease in men and women. JAMA 298:776–785
25. **Dubé MP, Wu JW, Aberg JA, Deeg MA, Alston-Smith BL, McGovern ME, Lee D, Shriver SL, Martinez AI, Greenwald M, Stein JH** 2006 Safety and efficacy of extended-release niacin for the treatment of dyslipidaemia in patients with HIV infection: AIDS Clinical Trials Group Study A5148. Antivir Ther 11:1081–1089

26. **Calza L, Manfredi R, Chiodo F** 2003 Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. AIDS 17:851–859
27. **Aberg JA, Zackin RA, Brobst SW, Evans SR, Alston BL, Henry WK, Glesby MJ, Torriani FJ, Yang Y, Owens SI, Fichtenbaum CJ; ACTG 5087 Study Team** 2005 A randomized trial of the efficacy and safety of fenofibrate versus pravastatin in HIV-infected subjects with lipid abnormalities: AIDS Clinical Trials Group Study 5087. AIDS Res Hum Retroviruses 21:757–767
28. **Badiou S, Merle De Boever C, Dupuy AM, Baillat V, Cristol JP, Reynes J** 2004 Fenofibrate improves the atherogenic lipid profile and enhances LDL resistance to oxidation in HIV-positive adults. Atherosclerosis 172:273–279
29. **Miller J, Brown D, Amin J, Kent-Hughes J, Law M, Kaldor J, Cooper DA, Carr A** 2002 A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. AIDS 16:2195–2200
30. **Silverberg MJ, Leyden W, Hurley L, Go AS, Quesenberry Jr CP, Klein D, Horberg MA** 2009 Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. Ann Intern Med 150:301–313
31. 2002 Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 106:3143–3421
32. **Taylor AJ, Sullenberger LE, Lee HJ, Lee JK, Grace KA** 2004 Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol (ARBITER) 2: a double-blind, placebo-controlled study of extended-release niacin on atherosclerosis progression in secondary prevention patients treated with statins. Circulation 110:3512–3517
33. **Manninen V, Elo MO, Frick MH, Haapa K, Heinonen OP, Heinsalmi P, Helo P, Huttunen JK, Kaitaniemi P, Koskinen P** 1988 Lipid alterations and decline in the incidence of coronary heart disease in the Helsinki Heart Study. JAMA 260:641–651
34. **Rubins HB, Robins SJ, Collins D, Fye CL, Anderson JW, Elam MB, Faas FH, Linares E, Schaefer EJ, Schectman G, Wilt TJ, Wittes J** 1999 Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high-density lipoprotein cholesterol. Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial Study Group. N Engl J Med 341:410–418
35. **Di Angelantonio E, Sarwar N, Perry P, Kaptoge S, Ray KK, Thompson A, Wood AM, Lewington S, Sattar N, Packard CJ, Collins R, Thompson SG, Danesh J** 2009 Major lipids, apolipoproteins, and risk of vascular disease. JAMA 302:1993–2000
36. **Keech A, Simes RJ, Barter P, Best J, Scott R, Taskinen MR, Forder P, Pillai A, Davis T, Glasziou P, Drury P, Kesäniemi YA, Sullivan D, Hunt D, Colman P, d'Emden M, Whiting M, Ehnholm C, Laakso M; FIELD study investigators** 2005 Effects of long-term fenofibrate therapy on cardiovascular events in 9795 people with type 2 diabetes mellitus (the FIELD study): randomised controlled trial. Lancet 366:1849–1861
37. **Ginsberg HN, Elam MB, Lovato LC, Crouse 3rd JR, Leiter LA, Linz P, Friedewald WT, Buse JB, Gerstein HC, Probstfield J, Grimm RH, Ismail-Beigi F, Bigger JT, Goff Jr DC, Cushman WC, Simons-Morton DG, Byington RP** 2010 Effects of combination lipid therapy in type 2 diabetes mellitus. N Engl J Med 362:1563–1574
38. **Lindegaard B, Keller P, Bruunsgaard H, Gerstoft J, Pedersen BK** 2004 Low plasma level of adiponectin is associated with stavudine treatment and lipodystrophy in HIV-infected patients. Clin Exp Immunol 135:273–279
39. **Falasca K, Manigrasso MR, Racciatti D, Zingariello P, Dalessandro M, Ucciferri C, Mancino P, Marinopiccoli M, Petrarca C, Conti P, Pizzigallo E, Guagnano MT, Vecchiet J** 2006 Associations between hypertriglyceridemia and serum ghrelin, adiponectin, and IL-18 levels in HIV-infected patients. Ann Clin Lab Sci 36:59–66
40. **Hadigan C, Yawetz S, Thomas A, Havers F, Sax PE, Grinspoon S** 2004 Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. Ann Intern Med 140:786–794
41. **Plaisance EP, Lukasova M, Offermanns S, Zhang Y, Cao G, Judd RL** 2009 Niacin stimulates adiponectin secretion through the GPR109A receptor. Am J Physiol Endocrinol Metab 296:E549–E558
42. **Westphal S, Borucki K, Taneva E, Makarova R, Luley C** 2007 Extended-release niacin raises adiponectin and leptin. Atherosclerosis 193:361–365
43. **Plaisance EP, Grandjean PW, Brunson BL, Judd RL** 2008 Increased total and high-molecular weight adiponectin after extended-release niacin. Metabolism 57:404–409
44. **Shahmanesh M, Das S, Stolinski M, Shojaee-Moradie F, Jackson NC, Jefferson W, Cramb R, Nightingale P, Umpleby AM** 2005 Antiretroviral treatment reduces very-low-density lipoprotein and intermediate-density lipoprotein apolipoprotein B fractional catabolic rate in human immunodeficiency virus-infected patients with mild dyslipidemia. J Clin Endocrinol Metab 90:755–760
45. **Fitch KV, Anderson EJ, Hubbard JL, Carpenter SJ, Waddell WR, Caliendo AM, Grinspoon SK** 2006 Effects of a lifestyle modification program in HIV-infected patients with the metabolic syndrome. AIDS 20:1843–1850
46. **Parhofer KG** 2009 Review of extended-release niacin/laropiprant fixed combination in the treatment of mixed dyslipidemia and primary hypercholesterolemia. Vasc Health Risk Manag 5:901–908