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Extended-Release Niacin Versus Fenofibrate in HIV-Infected Participants With Low High-Density Lipoprotein Cholesterol: Effects on Endothelial Function, Lipoproteins, and Inflammation

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Background.   Low levels of high-density lipoprotein cholesterol (HDL-C) are common in individuals with human immunodeficiency virus (HIV) infection, persist during antiretroviral therapy (ART), and are associated with increased cardiovascular disease (CVD) risk.

Methods.   Virologically controlled participants without CVD on stable ART with low HDL-C (men <40 mg/dL, women <50 mg/dL) and triglycerides >150 mg/dL were randomized to receive open-label extended-release niacin 1500 mg/day with aspirin 325 mg/day or fenofibrate 200 mg/day for 24 weeks. The primary endpoint was the week 24 within-arm change in brachial artery flow-mediated dilation (FMD) in participants with complete follow-up scans.

Results.   Of 99 participants, 74 had complete data (35 niacin, 39 fenofibrate). Median age was 45 years, 77% were male, median CD4$^+$ count was 561 cells/μL, and brachial FMD was 4.2%. Median HDL-C was 32 mg/dL for men and 38 mg/dL for women, low-density lipoprotein cholesterol was 103 mg/dL, and triglycerides were 232 mg/dL. In men, HDL-C increased a median of 3 mg/dL with niacin and 6.5 mg/dL with fenofibrate ($P < .001$ for both). In women, HDL-C increased a median of 16 mg/dL with niacin and 8 mg/dL with fenofibrate ($P = .08$ for both). After 24 weeks, there was no significant change in FMD in either arm; the median (interquartile range) change was +0.6% (−1.6 to 2.3) with niacin ($P = .28$) and +0.5% (−1.0 to 3.0) with fenofibrate ($P = .19$). Neither treatment significantly affected C-reactive protein, interleukin 6, or D-dimer levels.

Conclusions.   Despite improvements in lipids, niacin or fenofibrate treatment for 24 weeks did not improve endothelial function or inflammatory markers in participants with well-controlled HIV infection and low HDL-C.

Clinical Trials Registration.   NCT01426438.

Keywords.   HIV; niacin; fenofibrate; high-density lipoprotein; endothelial function.

In individuals infected with human immunodeficiency virus (HIV), low high-density lipoprotein cholesterol (HDL-C) is very common and is associated with disease progression, greater immunosuppression, and immune activation [1]. Antiretroviral therapy (ART) generally increases HDL-C levels; however, HDL-C levels do not return to normal even with prolonged ART. In the Multicenter AIDS Cohort Study, 55% of men had depressed HDL-C levels (<40 mg/dL) after 6–7 years of ART [2].

Depressed HDL-C levels predict future cardiovascular disease (CVD) events in HIV-infected patients [3, 4]

and in the general population [5, 6]. However, current guidelines for managing dyslipidemia in the general [7] and in the HIV-infected population [8, 9] do not recommend drug intervention for low HDL-C; they focus on treating elevated levels of low-density lipoprotein cholesterol (LDL-C) and severe hypertriglyceridemia. Indeed, the clinical benefits of HDL-increasing therapies such as niacin and fibrates are not proven. Trials of fenofibrate [10, 11] and niacin [12, 13] among non-HIV-infected participants with well-controlled LDL-C on statins have not demonstrated a benefit on CVD events, and genetic studies have questioned the relationship between HDL-C and CVD risk [14–16].

Extended-release niacin [17–19] and fenofibrate [20, 21] are well tolerated and increase HDL-C and HDL particles in HIV-infected persons. Both drugs also reduce apolipoprotein B [17, 21], non–HDL-C, and triglyceride levels [17, 21, 22]. A pilot study of niacin in HIV-infected individuals [18] suggested that its use improved brachial artery endothelial function. To determine if treatment with extended-release niacin or fenofibrate could improve arterial endothelial function and cardiovascular inflammatory biomarkers, we performed a 24-week, open-label randomized trial in HIV-infected participants with low HDL-C and elevated triglycerides.

MATERIALS AND METHODS

Participants

HIV-infected individuals aged ≥18 years with a CD4+ count >100 cells/μL were eligible if they had fasting HDL-C <40 mg/dL (men) or <50 mg/dL (women) and also had fasting triglycerides 150–800 mg/dL and LDL-C <160 mg/dL. Participants were required to be on continuous ART for ≥48 weeks with no regimen changes within the prior 12 weeks, planned on continuing with their current regimen, and had HIV RNA below the limit of detection. Laboratory criteria included fasting glucose level <126 mg/dL, platelet count ≥50 000/μL, absolute neutrophil count >750 cells/μL, hemoglobin level >8 g/dL, liver aminotransferases <2.5 times the upper limit of normal, estimated creatinine clearance ≥60 mL/minute (Cockcroft-Gault), and uric acid <1.3 times the upper limit of normal. Participants were excluded if they had known coronary heart disease or a coronary heart disease risk equivalent condition [23], class III or IV heart failure, uncontrolled hypertension, acute gout, active peptic ulcer disease, untreated hypothyroidism, active or symptomatic gallbladder disease within the past year, active cancer within the past year, currently used any prescription or nonprescription lipid-lowering agents other than statins, or using niacin-containing products that contain >100 mg daily, systemic glucocorticoids above replacement levels, current or planned hepatitis C treatment during the study period, known intolerance of any of the study medications, severe substance abuse, active opportunistic infection, or other acute illness.

Participants were randomized equally to niacin plus aspirin or fenofibrate with stratification by ongoing statin use and by screening HDL-C level (<30 vs 30–40 mg/dL for men, <40 vs 40–50 mg/dL for women). Those receiving a statin were required to be on a stable dose for at least 90 days prior to entry. All participants were provided with lipid-lowering diet and activity recommendations. Institutional review boards at each site approved the study. All participants provided written informed consent.

Drug Treatment

Extended-release niacin (Niaspan, AbbVie) was supplied as 500-mg tablets. All participants initiated extended-release niacin at 500 mg before bedtime with 325 mg of plain aspirin daily. At weeks 4 and 8, they increased their doses to 1000 mg (2 tablets) and 1500 mg (3 tablets) daily, respectively, before bedtime. This dose was chosen because 95% of participants were able to tolerate it in our prior work, whereas only 70% tolerated 2000 mg/day [17]. Those who were unable to tolerate an increase continued at the previously tolerated dose for the duration of the study. Aspirin-intolerant participants had the option to use naproxen 225 mg instead of aspirin. Fenofibrate was supplied as 200-mg capsules. One capsule was taken orally once daily without regard to meals. No dosage adjustments were allowed.

Evaluations

Fasting serum glucose (defined as at least 8 hours with no food or beverage other than water), uric acid, creatinine and aminotransferase levels, inflammatory biomarkers, and standard lipid profiles were each obtained at entry and weeks 12 and 24. Adherence assessments were performed at weeks 4, 8, 12, and 24. A myopathy questionnaire [24] was administered at baseline and weeks 4, 8, 12, 16, and 24.

Assays

Centrally performed assays used specimens stored at −70°C and shipped on dry ice. Advanced lipoprotein testing used nuclear magnetic resonance spectroscopy [25] on ethylenediaminetetraacetic acid plasma (LipoScience NMR Lipoprofile, Raleigh, North Carolina). High-sensitivity C-reactive protein (hs-CRP) was measured by nephelometry (Siemens BNII Nephelometer, Siemens Health Care, Indianapolis, Indiana), at the University of Vermont Laboratory for Clinical Biochemistry, as were interleukin 6 (IL-6) and D-dimers. Plasma glucose, liver aminotransferase, and uric acid concentrations were measured locally at sites. All other assays were performed at the AIDS Clinical Trials Group central metabolic laboratory (Quest Diagnostics, Baltimore, Maryland). Serum insulin concentration was measured by an enzyme-labeled immunometric assay (DPC Immulite 2000). Total cholesterol, HDL-C, and triglycerides were measured enzymatically. LDL-C was calculated by the following

equation: Total cholesterol - HDL cholesterol - Triglycerides/5 when triglycerides were <400 mg/dL. Non–HDL-C was calculated as total cholesterol minus HDL-C.

Brachial Artery Reactivity Testing

Brachial artery flow-mediated dilation (FMD) was measured by ultrasound prior to study treatment, then again after 12 and 24 weeks, as previously described [26, 27]. Participants were required to fast, not smoke, and not drink caffeinated products for at least 8 hours prior to testing. After resting supine for 10 minutes in a temperature-controlled room, a blood pressure cuff was placed on the widest part of the proximal right forearm approximately 1 cm distal to the antecubital fossa. Using a high-resolution linear array vascular ultrasound transducer, the brachial artery was located above the elbow and scanned in longitudinal sections with the focus zone set to the depth of the far wall. Extravascular landmarks were identified and labeled to assure that the imaged segment of the brachial artery was reproduced within and between studies. After recording baseline B-mode images of the brachial artery and spectral Doppler images of flow, the forearm cuff was inflated to 250 mm Hg for 5 minutes to induce reactive hyperemia. Immediately after deflation, spectral Doppler images are obtained to verify hyperemia. FMD of the brachial artery was measured 60 and 90 seconds after cuff deflation. FMD (%) was calculated as the ratio between the largest postcuff release and the baseline diameter. Images were sent electronically to the University of Wisconsin core laboratory for quality control and interpretation by a single, experienced technician using Access Point Web software (Freeland Systems, Westminster, Colorado). Blinded, paired readings of 25 FMD studies performed by sonographers in this study showed a median difference of 0.20% (1st–3rd quartile, −0.47% to 0.49%) [26].

Statistical Analysis

The primary hypothesis was that 24 weeks of treatment of low HDL-C with either extended-release niacin or fenofibrate will improve brachial artery FMD. The study had 80% power to detect a clinically relevant 1.5% mean difference in FMD within each arm after 24 weeks with 38 participants per arm. The primary analysis was as-treated and limited to participants with useable ultrasound scans at entry and week 24 and who were on study treatment at the time of the their week 24 scan. All values are reported as median (interquartile range [IQR]). Absolute changes over 24 weeks are reported from baseline. The Wilcoxon signed-rank test was used to assess within-arm changes. For the primary endpoint, a stratified, exact Wilcoxon signed-rank test was used. Between-group statistical comparisons used the Wilcoxon rank-sum test. Spearman correlations evaluated the relationship between pairs of continuous variables. The analysis did not adjust for multiple comparisons. A P value <.05 was considered statistically significant.

RESULTS

Participant flow through the study is shown in Figure 1. Fifty participants were assigned to niacin and 49 to fenofibrate. Nine participants discontinued niacin (mostly due to flushing) and 3 stopped fenofibrate (1 due to rash, 1 increased creatinine, 1 participant decision). Results are reported for the 35 niacin recipients and the 39 fenofibrate recipients who had complete data and completed study therapy. Baseline characteristics of participants not included in the primary analysis were similar (data not shown). Among the 40 participants who still were on niacin at week 24 (completed treatment), 1 was taking 500 mg, 4 were taking 1000 mg, and 35 were taking the full 1500-mg dose per day. Of the 9 who stopped niacin due to toxicity, 2 were taking the 500-mg dose, 3 the 1000-mg dose, and 4 the 1500-mg dose. Four participants switched from aspirin to naproxen because of flushing. All 49 participants receiving fenofibrate received 200 mg per day throughout the study; 3 stopped for toxicity and 3 for other reasons, and 43 completed treatment.

Baseline demographic, clinical, and laboratory features are shown in Table 1. Participants had a median age of 45 years (IQR, 38–51) years and 35% were smokers. Nine (12%) were receiving a statin at entry and none had a prior diagnosis of diabetes mellitus. Median time on current ART regimen was about 3 years. Approximately half of participants were taking a protease inhibitor. All participants had undetectable HIV RNA at entry. Median CD4 cell counts and hemoglobin levels were relatively normal, indicating a generally healthy population. Approximately 30% of participants had a very low HDL-C level. The median 10-year risk of coronary heart disease death or myocardial infarction was low at 3% (IQR, 1%–8%); only 15 (21%) had an estimated 10-year risk >10%.

Lipids and Lipoproteins

Baseline values and their changes after 24 weeks are shown in Table 2. Triglyceride decreases were similar with both treatments: −65 mg/dL (IQR, −163 to 8 mg/dL) with niacin ($P = .002$) and −54 mg/dL (IQR, −113 to −10 mg/dL) with fenofibrate ($P < .001$). LDL-C did not change with either drug, nor did total LDL particles. Small LDL particles were high at entry, at levels comparable to the 90th percentile in the general population [28], and decreased significantly with both drugs, whereas LDL particle size increased with both treatments. Among men, HDL-C levels increased modestly in both groups, by a median of 3 mg/dL (IQR, 0–9 mg/dL) with niacin ($P < .001$) and by 6.5 mg/dL (IQR, 0–12 mg/dL) with fenofibrate ($P < .001$; $P = .37$ for between-groups difference). Women had numerically greater increases in HDL-C: 16 mg/dL (IQR, −1 to 22 mg/dL) with niacin and 8 mg/dL (IQR, 5–13 mg/dL) with fenofibrate ($P = .08$ for both), but these changes were based on only 16 female participants. Total HDL particles decreased significantly only with
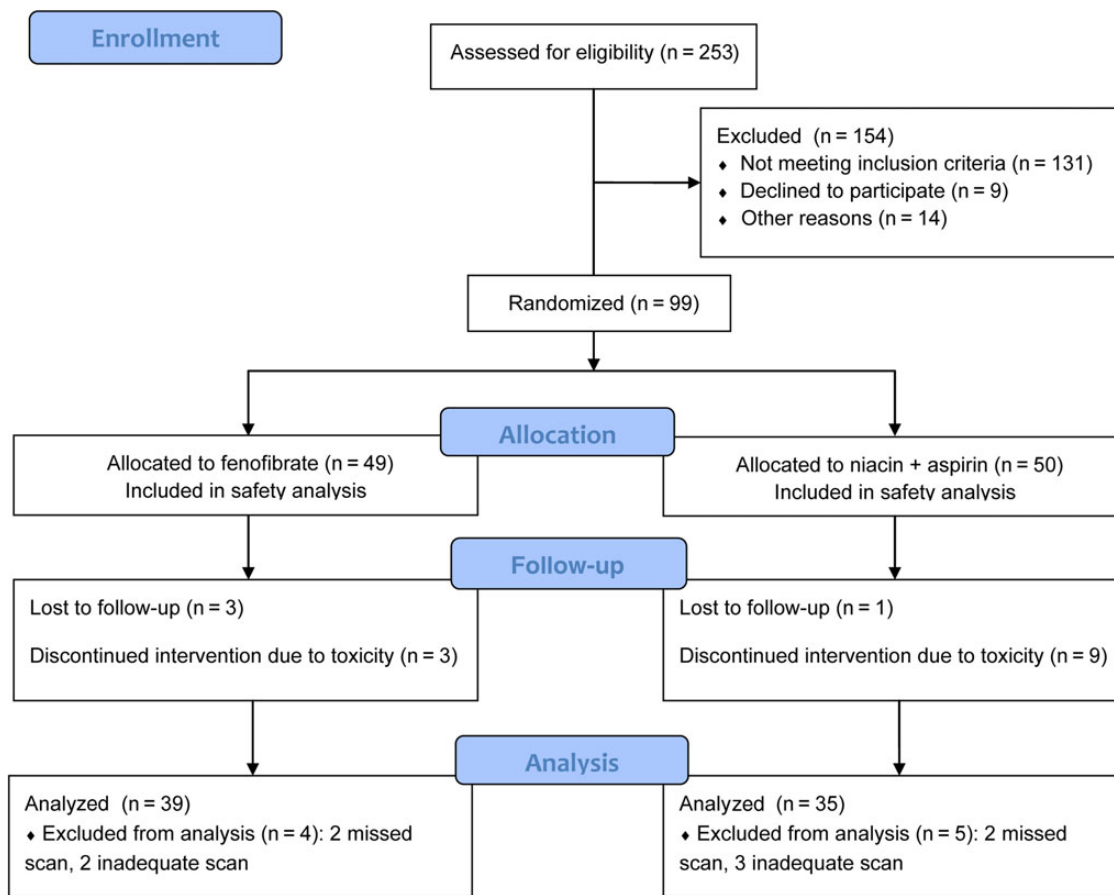
Figure 1. Consolidated Standards of Reporting Trials (CONSORT) diagram.

fenofibrate, whereas large HDL increased significantly only with niacin. Non–HDL-C decreased significantly only with niacin. Large very low-density lipoprotein (VLDL) particles decreased with both drugs.

Inflammatory Biomarkers, Glucose Metabolism, and Renal Function

There were no statistically significant changes in the levels of D-dimer, IL-6, or hs-CRP with either drug treatment (Table 3). Baseline values for these biomarkers were not elevated. GlycA, a novel biomarker that reflects enzymatically glycated acute phase proteins [29, 30], decreased significantly with fenofibrate, whereas levels of GlycB increased with niacin and aspirin. Fasting glucose, insulin, and the homeostasis model assessment–insulin resistance (HOMA-IR) index increased significantly with niacin, consistent with other reports [17], and did not change with fenofibrate. Estimated creatinine clearance decreased by 13.1 mL/minute (IQR, −25.4 to −9.5) with fenofibrate (P < .001), consistent with the known reversible renal effects of fenofibrate [31, 32]. Only 1 participant stopped fenofibrate due to increased creatinine levels.

Brachial Artery FMD

FMD over time is shown in Figure 2. Baseline FMD was normal and similar in both groups at baseline and did not change over time with niacin (+0.60% [IQR, −1.6 to 2.3]; P = .28]) or with fenofibrate (+0.50% [IQR, −1.0 to 3.0]; P = .19]) (Table 4). The standard deviation of the change in the week 24 relative FMD of 3.2% was consistent with the assumptions in our sample size estimates. There were no changes in brachial artery diameter, peak hyperemic flow velocity after cuff deflation, systolic or diastolic blood pressure, or heart rate with either drug treatment. In post hoc analyses, the change in FMD at week 24 did not differ by the HDL-C stratification factor at entry (<30 vs 30–40 mg/dL for men, <40 vs 40–50 mg/dL for women), the change in HDL-C at week 24 categorized into tertiles, protease inhibitor use, abacavir use, smoking status, antihypertensive medication use, or concurrent statin use (data not shown).

Correlations Between Changes in Variables and Changes in FMD

The strongest correlations with changes in FMD were for changes in non–HDL-C ($r = -0.43$, $P < .001$), total cholesterol ($r = -0.40$, $P < .001$), and total LDL particles ($r = -0.39$,

Table 1. Demographics and Baseline Characteristics: As-Treated, Primary Analysis Population

Characteristic	Niacin + Aspirin (n = 35)	Fenofibrate (n = 39)
Age, median (IQR)	46 (37–50)	45 (38–51)
Male sex	27 (77)	30 (77)
Race/ethnicity		
Hispanic	15 (43)	17 (44)
White non-Hispanic	15 (43)	15 (38)
Black non-Hispanic	5 (14)	6 (15)
Other	0	1 (3)
CD4$^+$ cells/µL, median (IQR)	580 (421–798)	539 (393–777)
Months on current ART (IQR)	38 (28–62)	34 (16–63)
Protease inhibitor–containing regimen	19 (54)	17 (44)
Abacavir-containing regimen	4 (11)	6 (15)
Current smoker	10 (29)	16 (41)
Statin use	4 (11)	5 (13)
Use of antihypertensive medications	10 (29)	9 (23)
Very low HDL-C (<30 mg/dL men, <40 mg/dL women)	10 (29)	12 (31)
LDL-C mg/dL, median (IQR)	103 (88–117)	101 (83–120)
Hemoglobin g/dL, median (IQR)	15 (14–15)	15 (14–16)
Body mass index kg/m^2, median (IQR)	26.9 (25.9–31.5)	28.3 (24.6–34.4)
10-year Framingham coronary heart disease risk, median (IQR)	3% (1–6)	3% (1–10)

Data are presented as No. (%) unless otherwise specified.

Abbreviations: ART, antiretroviral therapy; HDL-C, high-density lipoprotein cholesterol; IQR, interquartile range; LDL-C, low-density lipoprotein cholesterol.

$P < .001$) (Table 5). However, the correlation of change in FMD with change in HDL-C was weak ($r = 0.23$, $P = .046$). There was no statistically significant correlation between changes in FMD and changes in HDL particles, large HDL particles, HDL size, large VLDL particles, LDL size, HOMA-IR, estimated creatinine clearance, GlycA, GlycB, IL-6, hs-CRP, or D-dimer.

Tolerability

All participants who were randomized were included in the safety analysis. There were no grade 4 safety events. Thirty-six of 50 participants (72%) in the niacin arm reported at least 1 primary event of interest. In the fenofibrate arm, 21 of 49 participants (43%) reported at least 1 primary event ($P = .007$ compared with niacin). The most frequent, prespecified targeted event was flushing, which was experienced by 13 participants (26%) in the niacin arm. Five participants in the niacin arm had possible myopathy, as did 2 participants in the fenofibrate arm. There were no persistent symptoms of myopathy in either arm and there were no treatment discontinuations due to possible myopathy. There were no episodes of myositis.

DISCUSSION

In participants with well-controlled HIV infection and low HDL-C, 24 weeks of either niacin or fenofibrate led to significant improvements in HDL-C and atherogenic lipoproteins. However, despite these potentially beneficial effects, neither intervention improved endothelial function or most inflammatory biomarkers. The reasons for this lack of benefit are not clear, but these results are consistent with recent large-scale studies of the addition of niacin [12, 13] or fenofibrate [10, 11] to statin therapy as secondary CVD prevention among individuals with well-controlled LDL-C but without HIV infection. The current study had few participants who were receiving statins (12%) and had relatively normal levels of LDL-C but had high levels of small LDL particles and low levels of HDL-C. Despite improvements in these parameters with both study interventions, there still was no appreciable benefit in arterial endothelial function or cardiovascular inflammatory biomarkers. As such, it is unlikely that use of either intervention for patients with HIV infection with low levels of HDL–C will favorably impact CVD risk.

Published studies in the general population with niacin [33–38] and fenofibrate [39–50] generally have supported a benefit with regard to their effects on endothelial function, albeit at higher doses of niacin and in individuals with more severe dyslipidemia. A recent meta-analysis of randomized niacin trials [51] suggests an overall benefit of niacin on FMD, particularly when used at doses ≥2000 mg/day and when used in primary CVD prevention. In meta-regression, observed improvements in FMD with niacin were not related to changes in atherogenic lipoproteins [51]. We identified significant correlations between changes in atherogenic lipoproteins and FMD, but no significant effect of either treatment on FMD and no major differences between the arms. The reason for the lack of FMD benefit in our study may be related to the moderate dose of niacin used, or that the milieu of inflammation and immune activation in patients with treated HIV infection is not amenable to intervention with either niacin or fenofibrate. Alternatively, it is possible that the relatively low CVD risk of our participants contributed to the null result.

The magnitude of lipid and lipoprotein changes in this trial were similar to other studies involving HIV-infected participants using niacin [17], fenofibrate [20], or both [52]. Differing participant populations, treatment durations, methods of data presentation, and drug dosages, however, make direct comparisons between these studies difficult. In the Heart Positive study, a trial that compared a usual-care group to an intensive diet and exercise intervention combined with fenofibrate, niacin, both drugs, or placebo, the combination of fenofibrate and niacin had the greatest increases in HDL-C and decreases in non–HDL-C [52]. However, no cardiovascular imaging was included

Table 2. Lipid and Lipoprotein Values

Variable	Niacin + Aspirin (n = 35)			Fenofibrate (n = 39)			Between-Groups P Value for Week 24 Change
	Baseline	Week 24 Change	P Value	Baseline	Week 24 Change	P Value	
Total cholesterol, mg/dL	184.5 (171.0–212.0)	9 (–26 to 3)	**.037**	184 (159–211)	–2 (–28 to 25)	.93	.17
Triglycerides	253.5 (198.0–360.0)	–65 (–163 to 8)	**.002**	206 (171–293)	–54 (–113 to –10)	**<.001**	.80
LDL cholesterol	103 (88–117)	–1 (–14 to 12)	.95	101.0 (83.5–120.0)	7 (–13 to 26)	.20	.38
Total LDL particles, nmol/L	1231 (1088–1470)	–113 (–273 to 62)	.07	1394 (1088–1560)	35 (–123 to 225)	.77	.15
Small LDL particles	1018 (803–1133)	–176 (–410 to –19)	**<.001**	1052 (823–1222)	–119 (–320 to –17)	**<.001**	.52
LDL size, nm	19.7 (19.6–20.0)	0.4 (0.0–1.0)	**<.001**	19.9 (19.7–20.3)	0.6 (0.4–1.0)	**<.001**	.26
HDL cholesterol, men, mg/dL	32 (30–35) (n = 27)	3 (0–9)	**<.001**	36 (29–39) (n = 30)	6.5 (0.0–12.0)	**<.001**	.37
HDL cholesterol, women, mg/dL	37 (36–49) (n = 7)	16 (–1 to 22)	.08	38 (35–42) (n = 9)	8 (5–13)	.07	0.17
Total HDL particles, μmol/L	31.8 (28.4–35.4)	–1.7 (–4.3 to 2.1)	.14	30.2 (26.7–33.2)	4.3 (1.8–7.2)	**<.001**	**<.001**
Large HDL particles	2.1 (1.4–3.2)	0.9 (0.1–3.3)	**<.001**	2.6 (1.5–3.7)	–0.3 (–0.9 to 0.5)	.27	**<.001**
HDL size, nm	8.8 (8.5–9.0)	0.2 (0.0–0.4)	**<.001**	8.7 (8.6–9.0)	–0.2 (–0.4 to 0.0)	**.007**	**<.001**
Non-HDL cholesterol, mg/dL	150 (135–169)	–17 (–29 to 4)	**.002**	153 (123–175)	–4 (–28 to 17)	.27	.26
Large VLDL particles, nmol/L	12.1 (7.8–24.9)	–5.4 (–12.2 to 0.6)	**<.001**	8.7 (3.4–14.6)	–1.7 (–6.5 to 0.7)	**.009**	.13

Data are presented as median (interquartile range). Significant P values are shown in bold.

Abbreviations: HDL, high-density lipoprotein; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein.

Table 3. Inflammatory Biomarkers, Renal Function, and Insulin Resistance

Variable	Niacin + Aspirin (n = 35)			Fenofibrate (n = 39)			Change at Week 24 Between Groups P Value
	Baseline	Week 24 Change	P Value	Baseline	Week 24 Change	P Value	
Glucose, mg/dL	91 (84–99)	3 (–2 to 13)	**.005**	92 (89–97)	–4 (–10 to 6)	.45	**.006**
Insulin, μIU/mL	12 (9–23)	6 (1–11)	**<.001**	14 (12–24)	–1 (–5 to 5)	.79	**.016**
HOMA-IR	2.5 (1.9–4.5)	1.3 (0.0–3.0)	**<.001**	3.2 (2.6–5.3)	0.3 (–1.2 to 1.2)	.74	**<.001**
Estimated creatinine clearance, mL/min[a]	112.6 (91.9–142.8)	0.0 (–11.9 to 6.8)	.99	119.8 (90.7–167.3)	–13.1 (–25.4 to –9.5)	**<.001**	**<.001**
hs-CRP, mg/L	1.9 (1.0–5.4)	–0.6 (–3.0 to 2.6)	.16	1.5 (0.7–3.9)	0.7 (–2.1 to 2.7)	.27	.09
D-dimer, pg/mL	0.3 (0.2–0.4)	0.1 (–0.1 to 0.2)	.18	0.3 (0.2–0.5)	0.1 (–0.2 to 0.3)	.39	.90
Interleukin 6, pg/mL	1.1 (0.8–2.2)	0.1 (–1.1 to 0.8)	.99	1.5 (0.8–2.2)	0.2 (–0.7 to 1.1)	.33	.41
GlycA, μmol/L	405.7 (372.7–447.5)	7.0 (–24.3 to 40.3)	.45	400.3 (354.7–459.6)	–31.5 (–51.2 to –4.9)	**<.001**	**.002**
GlycB, μmol/L	112.6 (104.1–120.5)	10.1 (–3.1 to 18.5)	**.003**	120.2 (100.7–135.1)	7.1 (–8.5 to 14.9)	.29	.25

Data are presented as median (interquartile range). Significant P values are shown in bold.

Abbreviations: HOMA-IR, homeostasis model assessment–insulin resistance; hs-CRP, high-sensitivity C-reactive protein.

[a] Estimated creatinine clearance by Cockroft-Gault.

Table 4. Brachial Ultrasound and Cardiovascular Measurements

Variable	Niacin + Aspirin (n = 35)			Fenofibrate (n = 39)			Between-Groups P Value for Week 24 Change
	Baseline	Week 24 Change	P Value	Baseline	Week 24 Change	P Value	
Brachial flow mediated dilation, %	4.38 (2.88–6.76)	0.60 (–1.58 to 2.28)	.28	3.93 (2.61–8.05)	0.50 (–0.97 to 2.28)	.19	.99
Brachial artery diameter, mm	4.25 (3.88–4.66)	0.08 (–0.11 to 0.21)	.22	4.46 (4.19–4.74)	–0.03 (–0.15 to 0.11)	.35	.08
Relative hyperemia brachial flow, mL/min	801 (621–1040)	–7 (–130 to 142)	.84	857 (592–1100)	22 (–106 to 126)	.97	.77
Systolic blood pressure, mm Hg	120 (110–129)	0 (–5 to 4)	.74	119 (114–124)	–2 (–14 to 10)	.74	.66
Diastolic blood pressure, mm Hg	76 (72–81)	–1 (–7 to 3)	.22	76 (71–82)	–2 (–8 to 5)	.32	.89
Heart rate, beats/min	69 (60–77)	–1 (–5 to 5)	.68	64 (58–71)	2 (–5 to 6)	.49	.45

Data are presented as median (interquartile range).

in that study. We did not include a combination niacin plus fenofibrate treatment group in our study.

Endothelial dysfunction is associated with increased CVD risk and adverse risk factors in individuals with HIV infection [18, 26, 27]. We were unable to confirm the results of Chow et al with the same dose of extended-release niacin plus aspirin, in a very similar HIV-infected study population, and using the same FMD methods and core reading center [18]. The increase in FMD with 12 weeks of niacin in that study was 0.91%, which was not statistically different from the change in controls and was not dramatically different than that seen at 24 weeks in the present study with niacin (0.60%). However, that study was small (N = 19) and of only 12 weeks' duration, the control arm experienced a decrease in FMD, and the between-arms

difference was of borderline statistical significance and only emerged after adjustment, suggesting that the observations of Chow et al [18] may have been due to chance.

We observed relatively strong correlations (r = 0.39–0.43) between changes in total cholesterol, non–HDL-C, and LDL particles and changes in FMD. However, the association of changes

Table 5. Spearman Correlations Between the Week 24 Change in Brachial Flow-Mediated Dilation and the Week 24 Changes in Lipid, Lipoprotein, Glucose Metabolism, and Inflammatory Markers

Study Variable	No.	Spearman ρ	P Value
Total cholesterol	73	–0.40	<.001
Triglycerides	73	–0.26	.03
LDL cholesterol	62	–0.28	.03
Total LDL particles	74	–0.39	<.001
Small LDL particles	74	–0.24	.04
LDL size	74	0.12	.31
HDL cholesterol	73	0.23	.05
Total HDL particles	74	–0.08	.50
Large HDL particles	74	0.21	.07
HDL size	74	0.18	.13
Non-HDL cholesterol	73	–0.43	<.001
Large VLDL particles	74	–0.15	.20
HOMA-IR	69	–0.04	.77
Estimated creatinine clearance	72	–0.05	.68
High sensitivity C-reactive protein	74	–0.02	.86
D-dimer	73	–0.04	.76
Interleukin 6	65	–0.09	.46
GlycA	74	0.10	.39
GlycB	74	0.19	.10

Abbreviations: HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment–insulin resistance; LDL, low-density lipoprotein; VLDL, very low-density lipoprotein cholesterol.
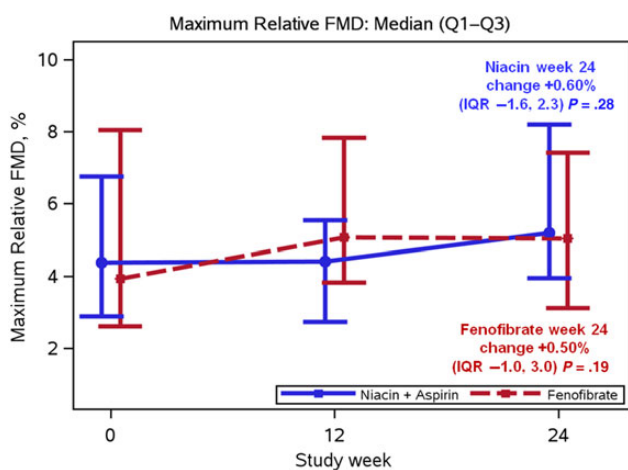

Figure 2. Median brachial artery flow-mediated dilation (FMD) with interquartile range (IQR) over 24 weeks among evaluable participants receiving either extended-release niacin plus aspirin (n = 35) or fenofibrate (n = 39).

in HDL-C with change in FMD was weak and only of border-line statistical significance. This suggests that changes in athero-genic lipoproteins such as non–HDL-C may influence endothelial function more so than changes in HDL-C. Thus, interventions with greater non–HDL-C–lowering potency should be considered for study in this population.

Limitations of our trial include lack of a blinded placebo con-trol arm and the variability inherent in a multicenter study that employs precise ultrasound measurements. However, we were not able to demonstrate a benefit with either therapy even with an as-treated analysis using an objective endpoint. Test variability is less of a concern given that the standard deviation of the change in FMD that we observed was within the expected range, the longitudinal within-subject nature of the primary endpoint, and central reading of brachial ultrasound scans with excellent reproducibility. We also identified expected rela-tionships between changes in lipids and changes in FMD. It is possible, although unlikely, that use of aspirin and/or naproxen in the niacin arm may have masked a salutary effect of niacin.

The approach to patients with well-controlled HIV infection who are not candidates for a statin, yet have low levels of HDL-C, is unclear. A consensus statement from the National Lipid Association [53] and current treatment guidelines in the general population [7] do not consider low HDL-C to be a therapeutic target with currently available interventions. In view of these and recent trials in secondary CVD prevention [10–13], as well as the current study, there appears to be no major role for either niacin or fenofibrate for treatment of low HDL-C in patients with HIV.

Notes

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