HHS Public Access

Author manuscript

HIV Med. Author manuscript; available in PMC 2015 July 30.

Published in final edited form as:

HIV Med. 2013 October ; 14(9): 530–539. doi:10.1111/hiv.12046.

Omega-3 fatty acid therapy reduces triglycerides and interleukin-6 in hypertriglyeridemic HIV patients

TS Metkus[1], **J Timpone**[2], **D Leaf**[3], **M Bidwell Goetz**[4], **WS Harris**[5], and **TT Brown**[6]

[1]Division of Cardiology, Johns Hopkins University, Baltimore, MD

[2]Division of Infectious Diseases, Georgetown University, Washington, DC

[3]Division of General Internal Medicine, Veterans Administration Medical Center, Los Angeles, CA

[4]Division of Infectious Diseases, Veterans Administration Medical Center, Los Angeles, CA

[5]Department of Medicine, Sanford School of Medicine, University of South Dakota, and OmegaQuant Analytics, LLC; Sioux Falls, SD

[6]Division of Endocrinology and Metabolism, Johns Hopkins University, Baltimore, MD, USA

Abstract

Objectives—Cardiovascular disease and osteoporosis are common in HIV-infected patients and residual systemic inflammation is thought to contribute to both of these disorders. We performed a randomized placebo-controlled trial of omega-3-acid (O3A) ethyl esters in HIV-infected patients with hypertriglyceridaemia, hypothesizing that O3A would decrease the concentration of triglycerides, markers of systemic inflammation, and markers of bone turnover.

Methods—HIV-infected patients (*n*=48 recruited at three sites) with CD4 count > 200 cells/μL, suppressed viral load, and triglycerides > 200 mg/dL were randomized to placebo or 3.6 g/d of O3A. Fasting lipid profiles and markers of inflammation and bone turnover were assessed at baseline and after 8 weeks of treatment.

Results—Baseline HIV status, lipid profile, bone metabolism and cardiovascular risk factors were similar between the groups. Inflammatory markers were similar between the treatment groups at baseline, except for interleukin (IL)-6 and tumour necrosis factor (TNF)-α, which were higher in the O3A group. The concentration of triglycerides in patients receiving O3A decreased by a median (interquartile range (IQR)) of −34 (−149, 9.5) mg/dL versus a median increase of 46.5 (−51, 123) mg/dL in the placebo group (p=0.01). The median percentage change in IL-6 was greater in the O3A group compared with the placebo group [−39% (−63, 12%) versus 29% (10, 177%), respectively; p=0.006]. Similar results were observed for TNF-α, but not other inflammatory or bone turnover markers.

Conclusions—O3A ethyl esters decreased the concentrations of triglycerides, IL-6 and TNF-α in patients with well-controlled HIV infection and hypertriglyceridaemia. Larger studies are required to confirm these findings and investigate their clinical significance.

Correspondence: Dr Todd T. Brown, Division of Endocrinology and Metabolism, Johns Hopkins University, 1830 East Monument Street, Suite 333, Baltimore, MD 21287, USA. Tel : 410 502 6888; fax: 410 955 8172.tbrown27@jhmi.edu.

Keywords

Dyslipidemia; systemic inflammation; cardiovascular risk; omega-3 fatty acids; hypertriglyceridemia; HIV

Introduction

Antiretroviral therapy (ART) has resulted in increased life expectancy of patients with HIV infection [1, 2]; however, these patients are increasingly vulnerable to diseases of aging, including disordered bone metabolism and cardiovascular disease [3–6]. Increased cardiac risk in HIV-infected patients may be mediated in part by the chronic inflammatory state associated with HIV itself, metabolic changes induced by specific HIV treatments[7], and the abnormal lipid profiles associated with both HIV and its treatment[8, 9]. Novel strategies for managing cardiac risk factors and decreasing inflammation in HIV-infected patients are of paramount importance.

Hypertriglyceridaemia is common in HIV-infected patients, as are increased levels of pro-inflammatory cytokines[9], both ideal targets for the reduction of cardiovascular risk. Omega-3 fatty acids (O3As) have beneficial effects on triglycerides and systemic inflammation[10]. The effects of O3A on systemic inflammation are probably mediated through multiple mechanisms, including the reduction of pro-inflammatory eicosanoids from arachidonic acid, the metabolism of O3A into anti-inflammatory lipid modulators (resolvin and protectin), and a decrease in the activation of nuclear factor kappa B (NFκB) by inflammatory stimuli, such as lipopolysaccaride [11]. In addition, salutatory effects of O3A on bone metabolism [12, 13], insulin resistance [14, 15] and platelet function [16] have been postulated. O3As, therefore, are potentially well suited to treat the metabolic and skeletal complications of HIV infection; however, data on the use of O3As to treat HIV-associated dyslipidaemia have been heterogeneous [17–20].

We performed a randomized trial of O3A supplementation in patients with HIV infection, preserved CD4 count and hypertriglyceridaemia. We hypothesized that O3A would improve dyslipidaemia, systemic inflammation, insulin resistance, platelet function and markers of bone turnover.

Methods

Study population

HIV-infected persons 18 years of age or older with a CD4 count > 200 cells/μL and a concentration of triglycerides > 200 mg/dL who had been on stable antiretroviral medications for 3 months were eligible for recruitment from HIV specialty clinics at Johns Hopkins Hospital (Baltimore, MD), Veteran's Administration Greater Los Angeles Healthcare System (Los Angeles, CA), and the Georgetown University Hospital (Washington, DC). Eligible female subjects had normal menstrual periods for 6 months with a negative pregnancy test. Exclusion criteria included (1) creatinine > 3 times the upper limit of normal (ULN), transaminases >3 times ULN, haematocrit < 25%, absolute neutrophil count < 1.5×10^9 cells/L, platelets < 100×10^9 cells/L or haemoglobin < 8.0 gm/dL; (2)

untreated endocrinopathy; (3) use of glucocorticoids within the last year; (4) high alcohol intake (men > 3 drinks/day; women > 2 drinks/day), abuse or dependence; (5) injecting drug use within the last 3 months; (6) anti-coagulant use; (7) use of oral contraceptives, (8) use of prescription-strength vitamin A preparations; (9) post-menopausal status, and (9) clinical evidence of an acute infection. All participants provided informed consent, and the study was approved by the Institutional Review Board at each site. The study was registered at ClinicalTrials.gov (NCT00346697).

Treatment

Treatment was with O3A esters (LOVAZA®; GlaxoSmithKline, Inc.). Each 1000 mg O3A capsule contained 465 mg of eicosapentaenoic acid (EPA) and 365 mg of docosahexaenoic acid (DHA) (plus 60 mg of other long-chain O3As). Four O3A capsules were administered daily to achieve a daily dose of 3.6 g of O3As. The placebo capsule contained corn oil and was identical to the active treatment in size, colour, taste and caloric content. Randomization tables were generated by the statistician and provided to the investigational pharmacist who distributed the blinded pills on the day of randomization and at the 4-week visit.

Each subject received three nutritional counselling sessions, in which a diet containing 50–60% carbohydrate, 15% protein and 25–35% fat, with < 10% of calories from saturated fat, was recommended. No specific recommendations about fish intake were given. Active treatment was initiated after a 4-week dietary run-in phase. Compliance was assessed by pill count, and percentage adherence was calculated in the following manner: [(pills dispensed − pills returned)/expected number taken] × 100.

Study evaluations

Subjects were assessed at five visits over a 12-week period, including a screening visit. History and physical examination were completed at the baseline visit. Whole blood was drawn after an overnight fast at baseline, at 8 weeks and at 12 weeks (i.e. 4 weeks after the intervention period had concluded). Lipid profile was measured using a standard colorimetric enzymatic assay (Quest Diagnostics, Baltimore, MD). The CD4 cell count was measured by flow cytometry. Liver function testing, complete blood count, and coagulation profile were performed at the screening visit and at the 8-week follow-up visit. Platelet function testing using the PFA-100 assay (Siemens Healthcare Diagnostics, Tarrytown, NY, USA) was performed in the subset of patients recruited at Johns Hopkins. C-terminal telopeptide of type I collagen (CTX) was measured using an enzyme-linked immunosorbent assay (Osteometer BioTech, Herlev, Denmark) and amino-terminal propeptide of type I collagen (P1NP) was measured using an immuno-radiometric assay (IDS, Inc., Scottsdale, AZ). Median intra-assay coefficients of variation were 8.15 and 4.14%, respectively, and the median inter-assay coefficients of variation were 0.01 and 2.74%, respectively. The normal values for CTX are 0.115–0.748 ng/ml in men and 0.112–0.738 ng/ml in pre-menopausal women. Tumour necrosis factor (TNF)-α, TNF-α soluble receptors 1 and 2 (sTNFR1 and sTNFR2, respectively), interleukin (IL)-6 and high-sensitivity C-reactive protein (hsCRP) were measured in duplicate using commercially available enzyme-labelled immunosorbent sandwich assays and values were averaged for analysis. The intra-assay precision of these assays ranged from a coefficient of variation of 4.4 to 7.6% (average 5.6%). The sensitivity

of this assay system for these cytokines ranged from 0.5 to 16 pg/mL. Fasting glucose and insulin were used to determine the homeostasis model assessment of insulin resistance (HOMA-IR) [21]. HOMA-IR > 4 is considered elevated. Erythrocyte membrane fatty acid composition analysis by gas chromatography was performed with calculation of the omega-3 index (O3I) as the proportion of eicosapentaenoic acid and docosahexaenoic acid/ total fatty acid. O3I was categorized as low (<4%), intermediate (5–8%) and desirable (>8%) [22].

Statistical methods

Our sample size calculations were based on differences in mean change in serum triglycerides between the active fish oil group and the placebo group. With 24 subjects enrolled in each study arm, and allowing for a 10% drop-out rate over the course of the trial, we anticipated 21 evaluable subjects with analysable data points in each of the two study arms. Assuming alpha=0.05 and a log-transformed common standard deviation of 0.74, there is 90% power to detect a 12% difference in serum triglycerides between the active treatment and the placebo groups. The χ^2 test and Wilcoxon rank-sum test were used to compare baseline subject characteristics. The absolute change and the percentage change in the outcome measures were compared using the nonparametric Wilcoxon rank-sum test, given the nonnormal distributions of the variables. Similar testing was performed to compare changes in outcome measures from week 8 to week 12 (off treatment). *P*-values < 0.05 were considered statistically significant. There was no correction for multiple comparisons. All analyses were carried out with STATA 10.0 (STATA Corporation, College Station, TX).

Results

Subject characteristics

Of the 83 patients screened, 48 were randomized (Figure 1). The groups were similar with respect to age, sex, race, baseline cardiovascular risk factors and baseline lipid treatment (Table 1). Sixty-seven per cent of patients were receiving other lipid-lowering drugs. The median CD4 cell count was similar between the groups and 96% had an HIV RNA < 400 HIV-1 RNA copies/mL. Protease inhibitor (PI) use was more common among those randomized to the active treatment group compared with the placebo group (88% versus 54%, respectively) and efavirenz (EFV) use was less common (29% versus 54%, respectively). Of the 48 subjects randomized, 47 completed the week 8 assessment.

Effect of O3A ethyl esters on lipid parameters

For the 47 randomized subjects who completed the week 8 assessment, the median concentrations of total cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol and low-density lipoprotein (LDL) cholesterol were similar between groups (Table 1). After 8 weeks, the median change in triglycerides was significantly different between the active treatment and placebo groups (p=0.01). No differences were observed in the other lipid parameters. Similar results were observed when percentage change was used as the outcome variable (Figure 2). The concentration of triglycerides decreased by a median of −9% [interquartile range (IQR) 47, 2%] in the active treatment group (within-group

p=0.01), but was not significantly different from baseline in the placebo group [median change 15% (IQR −19, 40%); within-group p=0.24] (between-group p=0.03). The median percentage change in triglycerides among those in the active treatment group was similar between the subset who were statin-treated (n=17) and those who were not treated with statins (n=7) (−8.7% versus −9.5%, respectively), between those who were fibrate-treated (n=9) and those who were fibrate-untreated (n=15) (−5.8% versus −9.4%, respectively), between those who were PI-treated (n=21) and those who were not PI-treated (n=3) (−9.4% versus 12.1%, respectively; p=0.11) and between those who were EFV-treated (n=7) and those who were not EFV-treated (n=17) (2.8% versus −26.1%, respectively; p=0.11). After 4 weeks off treatment, the concentration of triglycerides increased significantly in those who had been randomized to active treatment [median change 63.5 mg/dL (IQR 10, 108 mg/dL); within-group p=0.01] and was no different from baseline values (p=0.63).

Effect of O3A ethyl esters on markers of systemic inflammation

At baseline, hsCRP, sTNFR1 and sTNFR2 concentrations were similar between the groups, whereas median IL-6 and TNF-α concentrations were significantly higher in the active treatment group than in the placebo group (Table 2). After 8 weeks of treatment, the median change in IL-6 was significantly different between the active treatment and placebo groups [−0.62 (IQR −1.19, 0.13) pg/mL versus 0.185 (IQR −0.13, 1.65) pg/mL, respectively; p=0.006] (Table 2). Similarly, the median change in TNF-α over 8 weeks was significantly different [−0.36 (IQR −2.27, 0.014) pg/mL versus 0.58 (IQR −1.15, 2.25) pg/mL, respectively; p=0.04]. Similar results were observed when percentage change was used as the outcome variable (Figure 2b) [IL-6: active treatment group −39% (IQR −63, 12%) versus placebo group 29% (IQR 10, 177%); between-group p=0.006; TNF-α: active treatment group −10% (IQR −32, 0.5%) versus placebo group 16% (IQR −27, 51%); between-group p=0.02]. Among the active treatment group, there were no differences in the percentage change in IL-6 or TNF-α between the subset treated with statins and those not treated with statins, or between the subset treated with fibrates and those not treated with fibrates (all p>0.48; data not shown). The percentage change in IL-6 was similar in those participants randomized to the active treatment group who were receiving a PI and those not receiving a PI (p=0.36) and between those receiving and not receiving EFV (p=0.89). Whereas the percentage change in TNF-α was similar regardless of EFV use (p=0.73), those in the active treatment group who were receiving a PI had a larger decrease in TNF-α compared with those who were not (−12% versus 1.6%, respectively; p=0.03). The percentage change in triglycerides was not correlated to the percentage change in IL-6 (Spearman's rho=0.04; p=0.84) or TNF-α (Spearman's rho=0.02; p=0.91) among those in the active treatment group.

Because of the chance imbalances in IL-6 and TNF-α between the active treatment and placebo groups at baseline, we conducted several supplementary analyses. Using linear regression with percentage change as the outcome and adjusting for baseline concentration, we found a greater percentage change in IL-6 in the active treatment group versus the placebo group (p=0.05). Similarly, TNF-α tended (p=0.07) to be reduced in the active treatment group compared with the placebo group. In a separate analysis, we log-transformed baseline and week 8 values and used the week 8 values as the outcome,

adjusting for the baseline values. We found that log IL-6 at 8 weeks tended to be lower in the active treatment group compared with the placebo group (p=0.06). However, the week 8 log TNF-α concentrations were similar between treatment groups (p=0.65).

After 4 weeks off treatment, IL-6 concentrations remained stable and decreases in TNF-α and sTNFR2 concentrations were observed in the active treatment group (n=18). In the placebo group (n=18), hsCRP, IL-6 and sTNFR2 concentrations decreased significantly in the placebo group (Table 2). The changes in hsCRP concentrations in the 4 weeks off treatment were greater in the placebo group compared with the active treatment group, and changes also tended to be greater in the placebo group for IL-6 and sTNFR1. No differences in the median concentrations of any of the inflammatory markers were observed at the post-treatment visit (data not shown).

Effect of O3A ethyl esters on bone turnover, insulin resistance and platelet function

Markers of bone formation (P1NP) and bone resorption (CTX) were similar between the groups at baseline and showed no change in either group during follow-up (Table 2). At baseline, 8% (four of 44; three in the active treatment group and one in the placebo group) had CTX concentrations above the normal range. While insulin resistance was common in this population (57% had HOMA-IR >4), HOMA-IR did not change in either group over follow-up. A subset of patients had platelet function assessed over the treatment period (n=18 in the active treatment group and n=16 in the placebo group), and no differences were observed by treatment group.

Adherence and effect on omega-3 fatty acid index

Median adherence over 8 weeks of treatment by pill count was 94% (IQR: 86, 98%) in the active treatment group and 96.5% (91.5, 100%) in the placebo group. The red blood cell O3I was similar in the two arms at baseline (Table 2) and increased by a median of 3.5% (IQR 1, 4%) in the active treatment group but showed no change in the placebo group (between-group difference, p<0.001). At baseline, the proportions of O3I values in the low (<4%), intermediate (5–8%) and desirable (>8%) categories were 14, 85 and 0% in the active treatment arm and 26, 73 and 0% in the placebo arm. After 8 weeks of treatment, the distribution shifted in the active treatment arm [low (<4%), 5%; intermediate (5–8%), 35%; desirable (>8%), 60%], but remained unchanged in the placebo group. At baseline, concentrations of lipid parameters, inflammatory markers or bone markers were not associated the O3I. In addition, among those randomized to active treatment, the change in the O3I was not associated with the percentage change in the outcome variables (data not shown).

Adverse events

The intervention was well tolerated in both groups. Three patients in the active treatment arm experienced gastrointestinal side effects including dyspepsia, bloating or fishy taste as compared with six patients in the placebo arm. One patient in the active treatment arm reported rash versus two patients in the placebo arm. None of these adverse events required treatment discontinuation. There were no other significant adverse events reported.

Discussion

We performed a randomized, placebo-controlled trial of O3A supplementation in patients with well-controlled HIV infection and hypertriglyceridaemia. We found a statistically significant but clinically modest decrease in the concentration of serum triglycerides associated with active treatment as well as decreases in IL-6 and TNF-α concentrations, but not other markers of inflammation. Our study adds to the evidence base regarding the use of O3As to treat primary hypertriglyceridaemia and as a treatment strategy to reduce systemic inflammation in patients with well-controlled HIV infection.

Baseline triglyceride levels were elevated in both groups, connoting elevated cardiovascular risk [23]. In unselected patients, O3A supplementation has been shown to reduce triglyceride levels by 20–50%[23]; however, in our study, the concentration of triglycerides decreased by less than 10% in the active treatment arm, but by 24% versus placebo. This is consistent with the triglyceride reduction observed in studies of O3A supplementation in dysglycaemia [24] but less than the approximately 100 mg/dL decrease observed in a meta-analysis of omega-3 supplementation in patients with HIV infection [19]. The change in triglycerides that we observed, while statistically significant, is clinically modest [23]. HIV-infected patients with dyslipidaemia may be resistant to traditional lipid-lowering treatment, although the mechanisms remain unknown. Treatment of dyslipidemia in patients with HIV may incur risks [25], and alternative therapies to treat triglyceridaemia in HIV-positive patients should be explored, including exercise training, Mediterranean diet or alternative ART.

Although the effect of O3A therapy on triglycerides was modest, the O3I increased. This index has been proposed as a novel marker of beneficial cardiovascular health [22]. Although prospective data are lacking, low O3I has been associated with sudden cardiac death [26] and myocardial infarction[27]. Sixty per cent of patients with active drug supplementation had an increase from suboptimal to optimal levels of O3I. The discrepancy between the increased O3I and the modest effect on triglycerides remains unexplained and is an area for future study.

Perhaps our most provocative finding was that O3A treatment was associated with a median 39% reduction in IL-6 and a 10% reduction in TNF-α. The interpretation of this finding is made difficult by the chance imbalance in these markers between the treatment groups at baseline, raising the possibility that the observed effect was a result of regression to the mean. However, we found similar results when percentage change rather than absolute change was used as the outcome measure which, at least in part, takes the baseline value into account. We also found similar results when the percentage change in these markers was modeled and the baseline value was included in the regression model. While these results provide some support for a true effect, larger studies are required to confirm our findings.

We also investigated the effects of 4 weeks of O3A treatment discontinuation on lipids and markers of systemic inflammation. In contrast to the effect on triglycerides, which increased back to baseline values after 4 weeks off O3A treatment, IL-6 concentrations remained unchanged off treatment and TNF-α concentrations showed further decreases. In addition,

another inflammatory marker, sTNFr2, showed significant decreases after O3A discontinuation. While these findings may suggest durability of the anti-inflammatory effects of O3A, caution should be exercised when interpreting these results because post-treatment data were only available for 75% of randomized participants and there were unexpected decreases in hsCRP, IL-6 and sTNFr2 among those randomized to placebo. It is therefore possible that the stability of, or decreases in, some inflammatory markers in the O3A group after treatment discontinuation could be attributable to lifestyle changes or other factors which may have been present in both arms.

Higher concentrations of IL-6 and inflammatory biomarkers are strongly associated with all-cause mortality [28] and non-AIDS-related comorbidities [29], suggesting that strategies to reduce systemic inflammation may improve the health of HIV-infected persons. The anti-inflammatory properties of O3A are well established [30]. EPA and DHA have been shown to decrease inflammation by suppressing the production of arachidonic-acid-derived eicosanoids [31], and EPA inhibits both cycloxygenase and 5-lipoxygenase [32]. O3As also alter the activity of peroxisome proliferator activator receptor alpha [33] and NFκB [34]. In rheumatoid arthritis, another disease associated with systemic inflammation, O3As have been associated with reductions in inflammatory markers and disease severity [35].

There are fewer data regarding O3A in HIV-infected populations. Hileman *et al*. recently reported a significant reduction in sTNFRI, but not IL-6, sTNFR2 or CRP, in HIV-infected persons randomized to 1 g twice daily of omega-3 fatty acids (51.6% EPA and 40.5% DHA), but no effect on endothelial function or triglycerides [18]. With a similar dosage and product to those used in our trial, Thusgaard reported an increased formation of the anti-inflammatory leukotriene B5, but no effect on CRP in HIV-infected patients randomized to O3As [36]. In a single-arm study evaluating the effect of O3A, hsCRP decreased by a median of 34.5% and IL-6 decreased by 28.6% [37].

O3A did not have any effect on bone turnover in our study. In previous studies, O3As have been shown to decrease markers of bone resorption [38]. It is possible that our study duration was too short to observe an effect, but, in general, bone turnover markers change very quickly after interventions that increase bone turnover (e.g. ART initiation) or decrease bone turnover (e.g. bisphosphonate therapy) [39, 40]. In addition, our population was selected on the presence of hypertriglyceridaemia, rather than metabolic bone disease, and indeed the majority of participants at baseline had bone resorption markers within the normal range. It is possible that the effect of O3A may be different in a population with higher bone turnover.

We did not observe any effect of O3A on platelet function or insulin sensitivity. Previous studies in HIV-uninfected populations have suggested that O3As decrease platelet aggregability and platelet response to collagen [41], but have shown conflicting results regarding their effect on insulin sensitivity [42, 43]. Although we cannot rule out the possibility of a smaller effect which could have been observed with a larger sample size, our findings may provide some reassurance regarding concerns about increased risk of bleeding or deterioration of glucose metabolism with O3A treatment.

Limitations of our study include a small sample size and short duration of follow-up. In addition, the majority of our patients were male which may limit generalizability, particularly given the debate regarding differential effects of lipid therapy in women versus men. Future studies should include both men and women with sufficient follow-up to detect clinical endpoints. Patients with hypertriglyceridaemia are at higher cardiovascular risk than patients without it, and hence this population remains an important population for future studies to target. It is unclear whether the observed effect on inflammatory markers would also be observed in HIV-infected persons without hypertriglyceridaemia, and further studies should address this question.

In conclusion, O3A supplementation resulted in a statistically significant but clinically modest decrease in triglyceride levels among HIV-infected patients with well-controlled HIV infection and hypertriglyceridaemia. We also found a significant effect of O3A in decreasing IL-6 and TNF-α concentrations. Given the potential importance of residual systemic inflammation in the pathogenesis of non-AIDS comorbidities, further studies of O3A in HIV-infected populations are warranted.

Acknowledgments

This study was supported in part by an Investigator Initiated Grant from GlaxoSmithKline, NIH (NCCAM) K23AT002862 to TTB, Johns Hopkins Bayview Advanced Chemistry Laboratory (NIH ICTR 5UL1RR025005). We gratefully acknowledge the participating subjects.

Bibliography

1. Sax PE. Assessing risk for cardiovascular disease in patients with human immunodeficiency virus: Why it matters. Circulation. 2010; 121(5):620–2. [PubMed: 20100977]
2. Lohse N, et al. Improved survival in HIV-infected persons: consequences and perspectives. J Antimicrob Chemother. 2007; 60(3):461–3. [PubMed: 17609196]
3. Brown TT, Glesby MJ. Management of the metabolic effects of HIV and HIV drugs. Nat Rev Endocrinol. 2012; 8(1):11–21. [PubMed: 21931374]
4. Sackoff JE, et al. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City. Ann Intern Med. 2006; 145(6):397–406. [PubMed: 16983127]
5. d'Ettorre G, et al. Significant coronary stenosis detected by coronary computed angiography in asymptomatic HIV infected subjects. J Infect. 2012; 64(1):82–8. [PubMed: 21983631]
6. Triant VA, et al. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrinol Metab. 2007; 92(7):2506–12. [PubMed: 17456578]
7. Burdo TH, et al. Soluble CD163, a novel marker of activated macrophages, is elevated and associated with noncalcified coronary plaque in HIV-infected patients. J Infect Dis. 2011; 204(8): 1227–36. [PubMed: 21917896]
8. Janiszewski PM, et al. Hypertriglyceridemia and waist circumference predict cardiovascular risk among HIV patients: a cross-sectional study. PLoS One. 2011; 6(9):e25032. [PubMed: 21966404]
9. Morse CG, Kovacs JA. Metabolic and skeletal complications of HIV infection: the price of success. JAMA. 2006; 296(7):844–54. [PubMed: 16905789]
10. Mozaffarian D, Wu JH. Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol. 2011; 58(20):2047–67. [PubMed: 22051327]
11. Calder PC. The role of marine omega-3 (n-3) fatty acids in inflammatory processes, atherosclerosis and plaque stability. Mol Nutr Food Res. 2012; 56(7):1073–80. [PubMed: 22760980]

12. Sun D, et al. Dietary n-3 fatty acids decrease osteoclastogenesis and loss of bone mass in ovariectomized mice. J Bone Miner Res. 2003; 18(7):1206–16. [PubMed: 12854830]
13. Kruger MC, et al. Calcium, gamma-linolenic acid and eicosapentaenoic acid supplementation in senile osteoporosis. Aging (Milano). 1998; 10(5):385–94. [PubMed: 9932142]
14. Yamazaki RK, et al. Low fish oil intake improves insulin sensitivity, lipid profile and muscle metabolism on insulin resistant MSG-obese rats. Lipids Health Dis. 2011; 10:66. [PubMed: 21526994]
15. Parra D, et al. A diet rich in long chain omega-3 fatty acids modulates satiety in overweight and obese volunteers during weight loss. Appetite. 2008; 51(3):676–80. [PubMed: 18602429]
16. Harris WS, et al. Omega-3 fatty acids and coronary heart disease risk: clinical and mechanistic perspectives. Atherosclerosis. 2008; 197(1):12–24. [PubMed: 18160071]
17. De Truchis P, et al. Reduction in triglyceride level with N-3 polyunsaturated fatty acids in HIV-infected patients taking potent antiretroviral therapy: a randomized prospective study. J Acquir Immune Defic Syndr. 2007; 44(3):278–85. [PubMed: 17179770]
18. Hileman CO, et al. Omega-3 Fatty Acids Do Not Improve Endothelial Function In Virologically Suppressed HIV-Infected Men: A Randomized Placebo-Controlled Trial. AIDS Res Hum Retroviruses. 2012; 28(7):649–55. [PubMed: 21870979]
19. Oliveira JM, Rondo PH. Omega-3 fatty acids and hypertriglyceridemia in HIV-infected subjects on antiretroviral therapy: systematic review and meta-analysis. HIV Clin Trials. 2011; 12(5):268–74. [PubMed: 22180524]
20. Wohl DA, et al. Randomized study of the safety and efficacy of fish oil (omega-3 fatty acid) supplementation with dietary and exercise counseling for the treatment of antiretroviral therapy-associated hypertriglyceridemia. Clin Infect Dis. 2005; 41(10):1498–504. [PubMed: 16231263]
21. Matthews DR, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28(7):412–9. [PubMed: 3899825]
22. Harris WS. The omega-3 index: clinical utility for therapeutic intervention. Curr Cardiol Rep. 2010; 12(6):503–8. [PubMed: 20809235]
23. Miller M, et al. Triglycerides and cardiovascular disease: a scientific statement from the American Heart Association. Circulation. 2011; 123(20):2292–333. [PubMed: 21502576]
24. Bosch J, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012; 367(4):309–18. [PubMed: 22686415]
25. Boccara F, et al. HIV and coronary heart disease: time for a better understanding. J Am Coll Cardiol. 2013; 61(5):511–23. [PubMed: 23369416]
26. Aarsetoey H, et al. Low levels of the omega-3 index are associated with sudden cardiac arrest and remain stable in survivors in the subacute phase. Lipids. 2011; 46(2):151–61. [PubMed: 21234696]
27. Park Y, et al. Erythrocyte fatty acid profiles can predict acute non-fatal myocardial infarction. Br J Nutr. 2009; 102(9):1355–61. [PubMed: 19505347]
28. Kuller LH, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 2008; 5(10):e203. [PubMed: 18942885]
29. McComsey, GA.; KD; Sax, PE.; Tierney, C.; Jahed, NC.; Melbourne, K.; Ha, B.; Brown, TT.; Bloom, A.; Fedarko, N.; Daar, ES. Associations of inflammatory markers with AIDS and non-AIDS clinical events after initiation of antiretroviral therapy (ART): AIDS Clinical Trials Group A5224s, a substudy of ACTG A5202. XIX International AIDS Conference; July 22–27, 2012; Washington, DC. Abstract THLBB06
30. Rangel-Huerta OD, et al. Omega-3 long-chain polyunsaturated fatty acids supplementation on inflammatory biomakers: a systematic review of randomised clinical trials. Br J Nutr. 2012; 107(Suppl 2):S159–70. [PubMed: 22591890]
31. Calder PC. n-3 polyunsaturated fatty acids, inflammation, and inflammatory diseases. Am J Clin Nutr. 2006; 83(6 Suppl):1505S–1519S. [PubMed: 16841861]
32. Calder PC. n-3 polyunsaturated fatty acids as pharmacologic agents: a fishy tale? Nutrition. 1997; 13(11–12):1002–4. [PubMed: 9433724]

33. Sethi S. Inhibition of leukocyte-endothelial interactions by oxidized omega-3 fatty acids: a novel mechanism for the anti-inflammatory effects of omega-3 fatty acids in fish oil. Redox Rep. 2002; 7(6):369–78. [PubMed: 12625944]
34. Novak TE, et al. NF-kappa B inhibition by omega -3 fatty acids modulates LPS-stimulated macrophage TNF-alpha transcription. Am J Physiol Lung Cell Mol Physiol. 2003; 284(1):L84–9. [PubMed: 12388359]
35. Lee YH, Bae SC, Song GG. Omega-3 Polyunsaturated Fatty Acids and Rheumatoid Arthritis Treatment: A Meta-analysis. Arch Med Res. 2012
36. Thusgaard M, et al. Effect of fish oil (n-3 polyunsaturated fatty acids) on plasma lipids, lipoproteins and inflammatory markers in HIV-infected patients treated with antiretroviral therapy: a randomized, double-blind, placebo-controlled study. Scand J Infect Dis. 2009; 41(10):760–6. [PubMed: 19685375]
37. Ross, L.; Zhao, H.; Pappa, K. A Pilot Study of the Impart of Switch of Fosamprenavir and Addition of LOVAZA for Treatment of Hypertriglyceridemia in HIV-infected Sujects on Antiretroviral Therapy. Program of the 13th International Workshop on Adverse Drug Reactions and Co-Morbidities in HIV; 2011; Rome.
38. Orchard TS, et al. A systematic review of omega-3 fatty acids and osteoporosis. Br J Nutr. 2012; 107(Suppl 2):S253–60. [PubMed: 22591899]
39. van Vonderen, M.; MP; Murray, B.; Doran, P.; van Agtmael, M.; Danner, S.; Lips, P.; Reiss, P. for MEDICLAS Study Group. Changes in Bone Biomarkers in ARV-naïve HIV+ Men Randomized to NVP/LPV/r or AZT/3TC/LPV/r Help Explain Limited Loss of Bone Mineral Density over the First 12 Months after ART Initiation. Program and Abstracts of the 18th Conference on Retroviruses and Opportunistic Infections; p. #833
40. Saag K, et al. A single zoledronic acid infusion reduces bone resorption markers more rapidly than weekly oral alendronate in postmenopausal women with low bone mineral density. Bone. 2007; 40(5):1238–43. [PubMed: 17347063]
41. von Schacky C. A review of omega-3 ethyl esters for cardiovascular prevention and treatment of increased blood triglyceride levels. Vasc Health Risk Manag. 2006; 2(3):251–62. [PubMed: 17326331]
42. Tsitouras PD, et al. High omega-3 fat intake improves insulin sensitivity and reduces CRP and IL6, but does not affect other endocrine axes in healthy older adults. Horm Metab Res. 2008; 40(3): 199–205. [PubMed: 18348080]
43. Ahren B, et al. Effects of conjugated linoleic acid plus n-3 polyunsaturated fatty acids on insulin secretion and estimated insulin sensitivity in men. Eur J Clin Nutr. 2009; 63(6):778–86. [PubMed: 18772894]

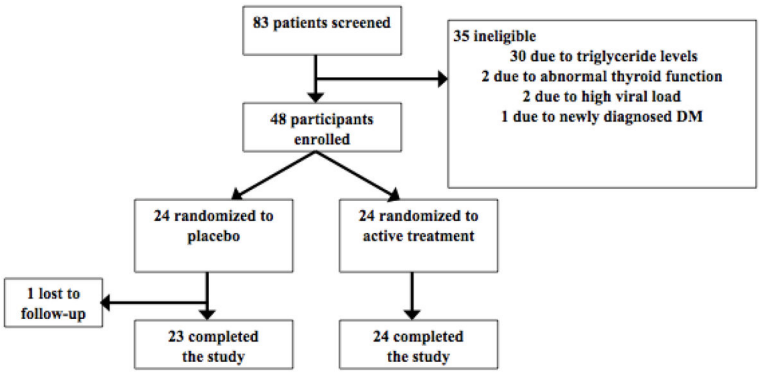

Fig. 1.

Flow chart for the study. DM, diabetes mellitus.

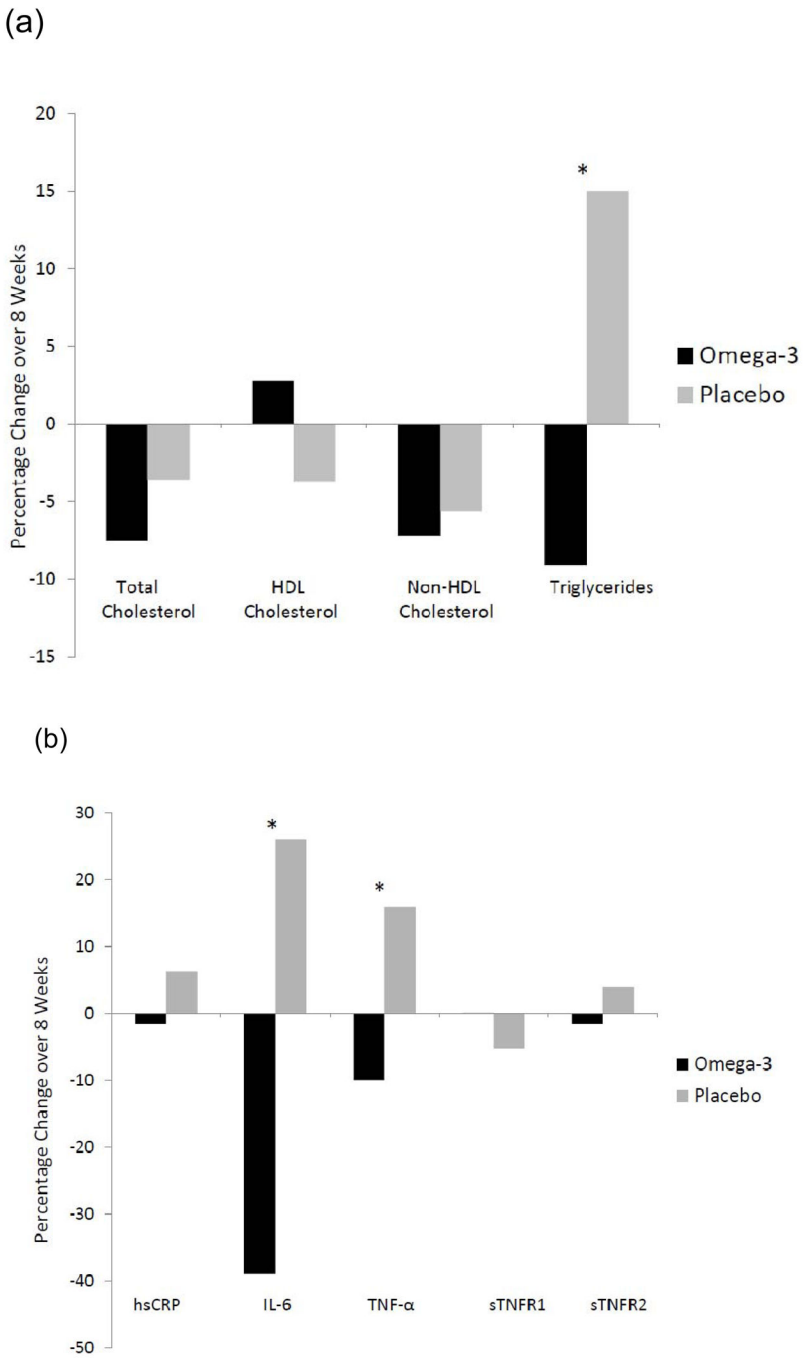

Fig. 2.

Percentage change in (a) Lipids and (b) inflammatory markers after 8 weeks of omega-3-acid ethyl ester treatment or placebo. *A between-arm difference with $p<0.05$ and within-arm change with $p<0.05$ in the omega-3 group. HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; sTNFR, TNF-α soluble receptor; TNF, tumour necrosis factor.

Table 1

Characteristics of subjects at baseline

	Active treatment (*n*=24)	**Placebo (*n*=24)**	***P*-value**
Age (years) [median (Q1, Q3)]	50 (47.0, 52.5)	48 (41.5, 52.5)	0.27
Male sex [*n* (%)]	21 (91)	22 (92)	0.96
Race [*n* (%)]			
Caucasian	11 (46)	12 (50)	0.79
African American	11 (46)	11 (26)	
Hispanic	1 (4)	0 (0)	
Other	1 (4)	1 (4)	
Current smoking [*n* (%)]	5 (21)	10 (42)	0.24
Diabetes mellitus [*n* (%)]	4 (17)	2 (8)	0.38
Hypertension [*n* (%)]	15 (63)	12 (50)	0.38
Coronary artery disease [*n* (%)]	2 (8)	1 (4)	0.55
Lipid therapy [*n* (%)]			
Any	17 (71)	15 (63)	0.54
Statin	17 (71)	14 (58)	0.36
Fibrate	9 (38)	7 (29)	0.54
Niacin	2 (8)	0 (0)	0.15
Ezetimibe	3 (13)	1 (4)	0.30
HIV parameters			
CD4 count (cells/μL) [median (Q1, Q3)]	477 (437, 710) (*n*=23)	531 (361, 661) (*n*=23)	0.89
Suppressed viral load (< 400 copies/ml) [*n* (%)]	23 (96)	22 (96) (*n*=23)	0.74
CD4 count nadir (cells/μL) [median (Q1, Q3)]	181 (46, 300) (*n*=22)	170.5 (69, 298) (*n*=24)	0.68
Duration of known HIV infection (years)	13.3 (10.9, 21) (*n*=23)	13.3 (7.38, 11.55) (*n*=24)	0.07
Antiretroviral therapy			
Duration (years)	9.9 (8.1, 11.1) (*n*=23)	8.9 (4.5, 10.4) (*n*=24)	0.16
Current PI use [*n* (%)]	21 (88)	13 (54)	0.01
Current efavirenz use [*n* (%)]	7 (29)	13 (54)	0.07
Hepatitis C [*n* (%)]	5 (21)	9 (38)	0.20

PI, protease inhibitor; Q1, Q3, first and third quartiles.

Table 2

Absolute changes in lipids, inflammatory markers, bone turnover markers, platelet function and insulin resistance after 8 weeks of omega-3-acid ethyl ester treatment or placebo and after 4 weeks off treatment

	Baseline			Change after 8 weeks			Change after 4 weeks off treatment		
	Omega-3 (*n*=24)	**Placebo (*n*=24)**	***P***	**Omega-3 (*n*=24)**	**Placebo (*n*=23)**	***P***	**Omega-3 (*n*=22)**	**Placebo (*n*=20)**	***P***
Total cholesterol (mg/dL)	198 (168, 226)	184 (151, 252)	0.83	−16 (−31, 23)	−5 (−25, 19)	0.80	2.5 (−15, 31)	6.5 (−15, 21)	0.98
HDL-c (mg/dL)	44 (31, 51)	38 (30, 50)	0.28	1.5 (−2, 4)	−1 (−6, 3)	0.16	0 (−4, 3)	0.5 (−1.5, 5.5)	0.42
Non-HDL-c (mg/dL)	160 (121, 181)	152 (132, 205)	0.72	−12.5 (−30, 17)	−9 (−23, 21)	0.72	7.5 (−23, 28)	7.5 (−17, 24)	0.94
Triglycerides (mg/dL)	327 (223, 463)	298 (246, 384)	0.79	−34 (−149, 9.5)*	40 (−51, 123)	0.01	63.5 (10, 108)*	−76.5 (−178, 72)	0.01
Omega-3 fatty acid index	5.1 (4.6, 6.3)	5.1 (3.7, 6.4)	0.99	3.5 (1, 4)* (*n*=20)	0 (0, 0) (*n*=20)	0.0001			
Inflammatory markers	***n*=23**	***n*=22**		***n*=23**	***n*=22**		***n*=18**	***n*=18**	
hsCRP (ng/mL)	3.14 (1.8, 4.85)	1.80 (0.49, 8.6)	0.32	−0.04 (−1.19, 0.35)	0.17 (−0.38, 0.99)	0.20	0.80 (−0.49, 2.5)	−0.51(−1.31, 0.02)*	0.02
IL-6 (pg/mL)	2.25 (1.12, 4.76)	1.04 (0.78, 1.73)	0.01	−0.62 (−1.89, 0.13)*	0.185 (−0.13, 1.65)	0.006	0.002 (−0.85, 0.44)	−0.36 (−1.38, −0.08)*	0.07
TNF-α (pg/mL)	5.46 (4.13, 17.99)	4.39 (3.88, 7.49)	0.02	−0.36 (−2.27, 0.014)*	0.58 (−1.15, 2.25)	0.04	−0.60 (−3.4, 0.02)*	−0.64 (−2.7, −0.17)	0.66
sTNFR1 (pg/mL)	1334 (1135, 1546)	1397 (1159, 1698)	0.72	−0.90 (−91.8, 69.8)	−66.3(−189, 152)	0.89	−3.8 (−113, 143)	−127 (−229, 61)	0.07
sTNFR2 (pg/mL)	3299 (2840, 4202)	3810 (2498, 4955)	0.95	−63.5 (−371, 615)	118 (−499, 565)	0.89	−163 (−834, 39)*	−531 (−697, −226)*	0.51
Bone markers									
P1NP (ug/L)	50.3 (31.3, 69.8)	44.2 (28.4, 55.4)	0.20	−5.23 (−12.6, −0.16)	−2.12 (−8.7, 1.3)	0.14	3.7 (−1.9, 13.2)	2.6 (−2.1, 7.8)	0.52
CTX (ng/mL)	0.49 (0.32, 0.61)	0.37 (0.27, 0.53)	0.16	−0.02 (−0.08, 0.02)	0.03 (0.06, 0.09)	0.25	−0.02 (−0.09, 0.04)	0.005 (−0.05, 0.05)	0.73
Platelet function	***n*=19**	***n*=18**		***n*=18**	***n*=16**		***n*=18**	***n*=14**	
Collagen ADP (s)	76.5 (67, 92)	86 (69, 99)	0.34	6.5 (−3, 21)	−6 (−13, 9.5)	0.12	2 (−13, 6)	−7 (−18, 16)	0.76
Collagen Epinephrine (s)	152.5 (119, 201)	130 (106, 190)	0.45	5.5 (−6, 39)	−18 (−46.5, 28)	0.30	−3.5 (−34, 21)	11 (−28, 30)	0.36
Insulin resistance	***n*=23**	***n*=22**		***n*=23**	***n*=22**				
HOMA-IR	3.87 (2.82, 5.31)	5.55 (3.29, 10.84)	0.27	0.56 (−0.51, 3.6)	0.94 (−1.9, 4.0)	0.96			

P-values are for the between-group comparisons using the Wilcoxon rank-sum test.

*$P<0.05$ for within-group change. Values shown are median (interquartile range).

HDL-c, high-density lipoprotein cholesterol; P1NP, amino-terminal propeptide of type I collagen; CTX, C-terminal telopeptide of type I collagen;; hsCRP, high-sensitivity C-reactive protein; IL, interleukin; TNF, tumour necrosis factor; ;sTNFR, TNF-α soluble receptorADP, adenosine diphosphate; s, seconds ; HOMA-IR, homeostasis model assessment of insulin resistance.