



# A Randomized, Open-Label Trial of Omega-3-Fatty Acid (Fish Oil) Supplementation Along with Diet and Exercise in HIV+ Patients with Hypertriglyceridemia

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## Introduction

•Hypertriglyceridemia is common among HIV-infected persons and, along with elevation of LDL cholesterol, has been observed to be exacerbated by antiretroviral therapy.

•Recent reports suggest combination antiretroviral therapy may increase the risk of cardiovascular disease.

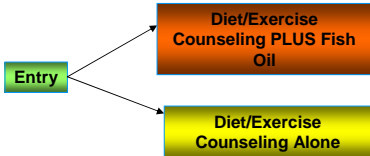
•Omega-3 fatty acids have been shown in epidemiological and clinical trials to reduce the incidence of CVD<sup>1</sup> and prospective secondary prevention studies suggests that marine-derived omega-3 fatty acid (EPA+DHA) supplementation ranging from 0.5 to 1.8 g/d (either as fatty fish or supplements) significantly reduces subsequent cardiac and all-cause mortality<sup>2</sup>.

•The American Heart Association (AHA) recommends persons with coronary heart disease consume ~1 g of omega-3 EPA+DHA (fish oil) per day, preferably from oily fish or via supplementation if dietary intake is insufficient. Patients with hypertriglyceridemia may consider supplementation with 2-4 g/d of EPA+DHA<sup>3</sup>.

•The efficacy and safety of omega-3 fatty acid supplementation for hypertriglyceridemia in the setting of HIV infection is not known.

## Methods

Design: Randomized controlled open-label 16 week trial.



### Interventions:

•Omega-3 fatty acid: Coromega® (European Reference Botanical Laboratories Inc.) containing 1750 mg EPA + 1150 mg DHA mg was administered orally daily. This formulation is a liquid and was chosen due to its pleasant taste and available bioavailability data

•Diet and Exercise Counseling: Certified nutritionist-administered individual counseling in accordance with American Heart Association recommendations for diet and exercise were conducted at Entry and weeks 4 and 16

## Methods (cont)

### Inclusion Criteria:

- Fasting serum triglycerides 200-2000 mg/dL
- Stable HAART for 3 months
- Not receiving a fibrate
- If receiving a statin, to remain on agent without modification during the study
- Karnofsky status score ≥70

### Evaluations at Entry and Week 4 and Week 16:

- Fasting (> 8 h) triglycerides, total, LDL and HDL cholesterol – UNC Clinical Lab
- Direct LDL cholesterol, Lp(a) – VAP (Atherotech Inc.)
- 2h Oral Glucose Tolerance Test UNC Clinical Lab
- Platelet Function Assay – UNC Clinical Lab
- AACTG Self-Reported Adherence Survey

### Statistical Methods:

The primary objective was to compare the change in fasting triglyceride levels at week 4 among subjects randomized to Diet/Exercise alone versus with the addition of Fish Oil.

For the primary analysis triglyceride values were log transformed and the paired t-test employed. For descriptive purposes, the original values were also analyzed prior to transformation to logarithm. Inter and intra-arm comparisons were performed.

## Results

- 52 subjects were randomized
- 8 subjects were lost to follow-up prior to week 4

Table 1 • Mean Baseline Characteristics

	Fish Oil (n=25)	Diet/Exercise (n=19)
Male (%)	88%	95%
Age (y)	42 (25-58)	44 (36-54)
Non-white (%)	64%	42%
Triglycerides (mg/dL)	454	553
Total Cholesterol (mg/dL)	230	254
HDL-C (mg/dL)	40	42
LDL-C (mg/dL)	112	117
Lp(a) (mg/dL)	10	12
CD4 cell count (/uL)	576	505
HIV RNA (log <sub>10</sub> c/mL)	38618	35110

Fig. 1 • Mean Percent and Log Change from Baseline in Triglyceride Levels

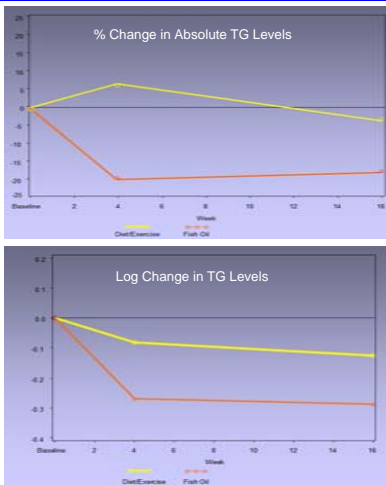


Table 2 • Mean Percent Change from Baseline in Triglycerides

	Fish Oil (95% CI)	Diet/Exer. Alone (95% CI)	P value between arms
Wk 4	-19.6% (-30.1, -9.0)	+6.4% (-23.3, +36.2)	0.049
Wk 16	-17.7% (-33.4, -2.0)	-3.5% (-25.7, +18.7)	0.134

Table 3 • Proportion of Subjects in Each Arm with Triglyceride Level <200 at weeks 4 and 16

	Fish Oil	Diet/Exercise Alone	P value
Wk 4	9 (36%)	2 (11%)	0.046
Wk 16	6 (27%)	4 (26%)	0.279

Fig. 2 • Mean Percent Change from Baseline in Total & LDL Cholesterol Levels

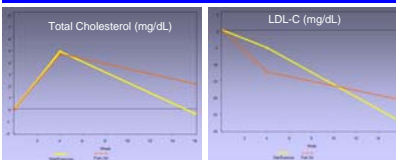


Table 4 • Mean Percent Change from Baseline in LDL, Total Cholesterol, Lp(a) Insulin and 2h OGTT Result

	Fish Oil	Diet/Exercise Alone
LDL-C Wk 4	-12.6% (-24.8, -0.3)	-5.3% (-20.0, +9.4)
LDL-C Wk 16	-21.0% (-38.2, -3.8)	-27.5% (-54.3, -0.7)
Total Cholesterol Wk 4	+4.7% (-1.1, +10.5)	+4.7% (-3.4, +13.1)
Total Cholesterol Wk 16	+2.1% (-7.5, +11.7)	-0.4% (-11.8, +10.9)
Lp(a) Wk 4	-0.3% (-114.7, +34.1)	+0.8% (-31.4, +32.9)
Lp(a) Wk 16	-4.5% (-115, +22.1)	-2.2% (-37.3, +32.9)
Insulin Wk 4	82.56% (+7.2, +158.0)	31.0% (-29, +90.9)
Insulin Wk 16	24.33% (-20.9, +69.5)	127.1% (-96, +350.2)
2 h OGTT Wk 4	-3.7% (-12.7, +5.4)	6.4% (-9.2, +22.0)
2 h OGTT Wk 16	-1.0% (-9.1, +7.2)	-3.7% (-12.7, +5.4)

## Fish Oil Self-Reported Adherence

- At week 4: 82.6% reported not missing fish oil in past 4 days
- At week 16: 87.0% reported not missing fish oil in the past 4 days

## Safety and Tolerability

- Fish oil was well tolerated:
  - No new grade 3+ clinical or laboratory toxicities
  - 1 subject discontinued Fish Oil due to nausea and vomiting associated with the agent
  - No change in platelet function assay results
  - No change in viral load or CD4+ cell count

## Conclusions

•Fish oil supplementation at a dose of ~3 grams/d coupled with diet and exercise counseling modestly reduced triglycerides in HIV-infected patients.

•However, a statistically significant difference in the decline of triglyceride levels was not observed between those assigned to diet/exercise counseling without fish oil supplementation in this small study.

•Fish oil was well tolerated. One subject had a treatment-limiting adverse event. No subject developed a grade 3 or higher clinical or laboratory toxicity.

•Given the trends observed in this pilot study, larger trials of fish oil supplementation for the treatment of HIV-associated hypertriglyceridemia are warranted.

### References

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2. Bucher HC, Hengstler P, Schindler C, et al. N-3 polyunsaturated fatty acids in coronary heart disease: a meta-analysis of randomized controlled trials. *Am J Med*. 2002; 112: 298-304
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