

# Protease Inhibitors, Apolipoprotein C-III Polymorphisms and Atherogenic Dyslipidemia in HIV

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Adult AIDS  
Clinical Trials Group

## BACKGROUND

Atherogenic dyslipidemia is common in ART-treated patients, particularly those on protease inhibitors (PI). We sought to identify single nucleotide polymorphisms (SNPs) in candidate lipoprotein genes that predict dyslipidemia in subjects on PI containing ART (PI-ART) compared to those on non PI-ART.

## METHODS

HIV subjects (n=626, mean age 42 years, 89% male, 60% Caucasian) with fasting lipids measured while on stable PI-ART\* (n= 457; 40% IDV, 33% NFV, 5% RTV; median exposure 971 days (IQR= 231,1240)) or non PI-ART\*\* (n= 154; 65% EFV, 11% NVP) were studied from the following ACTG protocols: ACTG372, A5005s, A5068, A5087 and A5116. The following apolipoprotein C-III (ApoCIII) and ApoA SNPs were examined: Apo CIII -455C/T, -482C/T, ApoCIII Intron 1, ApoCIII Gly34Gly, ApoCIII Ssl(3238C/G) and ApoA1 XmnI(-2500T/C). Primary lipid outcome was triglycerides (TG) and secondary outcomes included HDL-Cholesterol (HDL-C) and LDL-C.

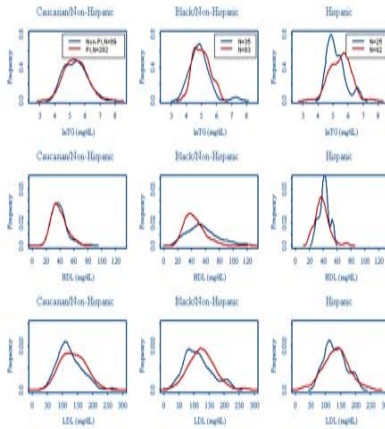
**Statistical Methods:** Multivariable regression models were fit using Splus for Windows, Version 6.2. TGs were natural log transformed to achieve normality. F-test and Wald-test statistics were used to assess significance. Adjustment for multiple testing in the context of genotype analysis was achieved through a permutation-based test and by control of the False Discovery Rate (Benjamini and Hochberg, 1995.) Haplotype based analysis was performed using the haplo.stats library in R, Version 2.0.0.

\*13 subjects with less than 90 days of PI exposure were removed from analysis. \*\*2 subjects with exposure to a PI within the last 30 days were also excluded.

## RESULTS

MEDIAN LIPIDS (IQ RANGE)		TG	HDL	LDL
Race/ Ethnicity	Caucasian/ Non-Hispanic (N=378, 60.4%)	207 (120,341)	37 (31,44)	129 (103,160)
	Black / Non-Hispanic (N=121, 19.3%)	139 (91,215)	44 (34,55)	117 (91,149)
	Hispanic (N=112, 17.9%)	239 (129,339)	38 (33,44)	135 (108,156)
PI	Yes (N=457)	195 (119,335)	37 (32,46)	132 (105,160)
	No (N=154)	163 (107,279)	40 (32,49)	114 (98,148)

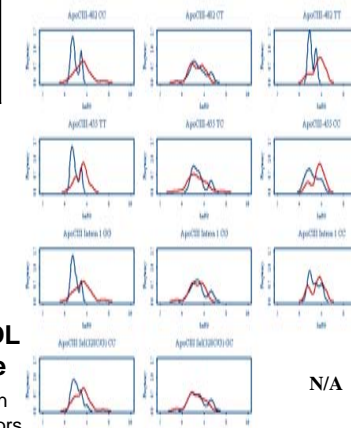
**Table 1: Median TG, HDL and LDL by Race/Ethnicity and PI exposure.** Race/ethnicity was a highly statistically significant predictor of lipid levels even after controlling for sex, age, study, lipid lowering therapy, CD4 count, ART drug exposure and apoC-III/apoA-I genotypes with Black/non-Hispanics subjects having lower TGs (overall p=0.001) and higher HDL (p=0.004) cholesterol than Caucasians/non-Hispanics and Hispanics.



**Figure 1: Estimated Distribution of lnTG, HDL and LDL by PI-exposure within Race/Ethnicity.** In fully adjusted analysis (for all factors listed above) that did not account for potential differences in PI-effects on lipids across genotype, no differences in TGs, HDL and LDL by PI-use are detectable within race/ethnicity groups, with the exception of LDL in Caucasians (p=0.009). This underscores the need for consideration of differential responses across genotypes within race/ethnicity groups, as shown in Figure 2.

**Table 2: Genotype frequencies by Race/Ethnicity.** SNP and haplotype frequencies varied markedly by race/ethnicity. Significant departures from Hardy Weinberg Equilibrium were not observed within race/ethnicity groups.

Genotype Prevalences	ApoCIII-482			ApoCIII-455			ApoCIII Intron 1			ApoCIII Ssl(3238C/G)		
	CC	CT	TT	TT	TC	CC	GG	CG	CC	CC	GC	GG
Race/Ethnicity:	CC	CT	TT	TT	TC	CC	GG	CG	CC	CC	GC	GG
Caucasian/Non-Hispanic	0.54	0.38	0.08	0.38	0.47	0.15	0.49	0.41	0.09	0.83	0.16	0.01
Black/Non-Hispanic	0.09	0.50	0.42	0.09	0.44	0.48	0.04	0.32	0.64	0.75	0.24	0.01
Hispanic	0.36	0.49	0.15	0.32	0.46	0.22	0.38	0.43	0.19	0.66	0.30	0.04



**Figure 2: Estimated Distribution of lnTG by ApoCIII genotypes within Hispanics.** The effect of PI on TG was different across genotypes in Hispanics (2-way PI-gene interaction: p=0.008, p=0.015, p=0.011, p=0.033 for ApoCIII -482, -455, Intron 1 and Ssl(3238C/G), respectively), but not Caucasians or Blacks. The difference in TGs between PI and non-PI exposed Hispanic subjects was most dramatic for the homozygous wild-type APOCIII-482 (CC), -455 (TT), Intron 1 (GG) and Ssl(3238C/G) (CC) genotypes. Test statistics remained significant after correction for multiple tests. Haplotype analysis did not reveal haplotype effects or haplotype-PI interactions.

## CONCLUSIONS

This study found evidence that (a) race/ethnicity independently predicts lipid levels with Black/non-Hispanics having the least atherogenic lipid profiles and (b) apoC-III gene variants modify PI-ART associated hypertriglyceridemia differentially across race/ethnicity, with evidence for genotype-PI interactions in Hispanics. These findings have important implications for the use of genetic strategies for identification of HIV infected subjects at greatest risk for metabolic complications and highlight the requirement for appropriate studies within ethnic strata when assessing gene-drug interactions.