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A POLYMORPHISM IN THE RESISTIN GENE IS ASSOCIATED WITH EARLY ADVERSE METABOLIC OUTCOME AND PREDICTS FUTURE FAT LOSS ON HAART: PHARMACOGENETIC ASSOCIATION STUDY OF ACTG A5005s

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BACKGROUND: The genetic basis of change in body fat associated with highly active antiretroviral therapy (HAART) is poorly understood. We sought single nucleotide polymorphisms (SNP) in select candidate genes associated with higher risk for changes in body fat after initiating HAART.

METHODS: We genotyped 189 HIV+ subjects (mean age 38 years, 88% male, 56% Caucasian, 28% Black and 14% Hispanic) from ACTG 5005s for whom DNA samples, biochemical profiles and body composition by dual X-ray absorptiometry were available prior to HAART and up to 64 weeks on therapy. Cluster analysis of metabolic variables measured at week 32 was used to identify a sub-group of patients who developed adverse metabolic changes. SNP association with cluster membership was analysed by Fisher's exact test and differences in metabolic variables and body composition between clusters were analysed by Kruskal-Wallis test or repeated measures ANOVA.

RESULTS: Cluster analysis revealed two subgroups of patients. At baseline, biochemical profiles (lipids and HOMA insulin resistance index) and trunk-to-limb fat ratios were comparable (1.16 versus 1.18, $P=0.7$) between the two groups. At 32 weeks of HAART, both groups experienced similar gains in total, trunk and limb fat, but by 64 weeks they lost fat. However, relative to the lowrisk cluster ($n=54$), the high-risk cluster ($n=22$) had significantly more limb fat loss (0.1 versus 2.1 kg, $P=0.003$), resulting in a significantly higher increase in the trunk-to-limb fat ratio (1.36 versus 1.62, $P=0.004$). A C→T SNP in the second intron of the resistin gene was significantly associated with

cluster membership ($P=0.001$). Heterozygotes ($n=31$; odds ratio=5.7; 95% C.I. 1.7–15.5) were at increased risk relative to wild-type ($n=43$) of being in the high-risk cluster. Both rare homozygotes were classified as high-risk.

CONCLUSIONS: In this exploratory pharmacogenetic study, a single variant of the resistin gene was associated with the cluster of patients with adverse metabolic changes that also experienced greater limb fat loss on HAART. Confirmation in other cohorts and relationship to individual antiretroviral agents are required.

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