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IMMUNOGENETICS AND IMMUNE RECONSTITUTION DURING POTENT ANTIRETROVIRAL THERAPY: NWCS 233, AN ANALYSIS OF AACTG PROTOCOL A5001

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INTRODUCTION: During potent antiretroviral therapy (ART) CD4 cell increases are modest in many patients. We explored whether single nucleotide polymorphisms (SNPs) in genes involved in T-cell expansion, survival, and apoptosis are associated with CD4 cell increases during ART.

METHODS: We studied previously ART-naïve subjects who had <400 plasma HIV-1 RNA copies/mL sustained for at least 48 weeks after initiating ART during Adult AIDS Clinical Trials Group (AACTG) trials. Eligible subjects participated in Protocol A5001, and contributed specimens to the AACTG Human DNA Repository via A5128. We characterized 137 SNPs in 17 genes by PCR-sequencing. Genes important for T-cell proliferation and survival encoded IL-15, IL-15 receptor α chain, IL-2/IL-15 receptor β chain, IL-2, IL-2 receptor common γ chain, IL-7, IL-7 receptor γ chain, TNF- α , IFN- α , and IFN- β . Genes important for T-cell apoptosis encoded TNF receptors I and II, FAS, FAS ligand, TRAIL, caspase 8, and BIM. The outcome variable was <200 CD4 cells/mm³ increase from baseline with 48 weeks of virologic control. There was no correction for multiple comparisons.

RESULTS: The 880 study subjects included 52% whites, 26% blacks, 20% Hispanics. 18% were female. 47% had CD4 change <200 cells/mm³. By univariate analyses, CD4 increases were associated with SNPs in genes encoding IL-15, IL-15 receptor α chain, IL-2/IL-15 receptor β chain, IL-7 receptor γ chain, TNF- α , TRAIL, and BIM ($P < 0.05$ for each). In analyses that controlled for race, baseline CD4 count, viral load, HBsAg

positivity, and sex, SNPs in genes encoding IL-15, IL-15 receptor α chain, TNF- α , TRAIL, and BIM were associated with CD4 rise at $P < 0.05$.

CONCLUSIONS: Allelic variants in genes important for CD4 cell expansion, survival, and apoptosis may affect interindividual variability in immune reconstitution during ART. Characterizing these variants, variants in additional genes implicated in T-cell biology, and gene-gene interactions, may suggest novel interventions to enhance immune reconstitution.

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