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Transcriptome-wide association analyses identify genes associated with HIV latent reservoir and cocaine abuse

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Illicit drug use is known to impact HIV treatment and progression. Understanding and eliminating the HIV latent reservoir (HLR), the replication competent but silenced HIV provirus integrated into host cells' DNA, is key to an HIV cure. To better understand how gene expression relates to HLR and whether cocaine abuse (CA) effects HLR-associated expression, we quantified the CD4 T-cell HLR by intact proviral DNA assay among HIV-infected cART (combination anti-retroviral therapy) adherent participants with CA (n=160) and without CA (n=274) in the Women's Interagency HIV Study (WIHS). From these data, we identified an association between CA and increased HLR (p=0.004). We used CD4 T-cell RNAseq data from a subset of these WIHS participants to perform separate transcriptome-wide association studies (TWAS) of HLR (N=246) and CA status (N=259). We discovered 101 and 1,631 significant genes (FDR <0.1) in the HLR and CA TWAS, respectively, of which 47 were significant in both. GO term overrepresentation analysis of the 47 overlapping significant genes identified enriched terms related to GTPase activity and regulation of organelle assembly (FDR <0.1). We assessed whether expression at these 47 genes mediated the effect of CA status on HLR, and 31 showed nominal evidence of mediation (p <0.05) with *EPSTI1* mediation remaining statistically significant following multiple testing correction (Bonferroni p <0.05). *EPSTI1* is known to be activated by HIV-1 Tat protein in CD4 T-cells and plays a role in the translocation of NFkB to the nucleus. Overall, our results provide evidence that gene dysregulation in CA impacts HLR-associated genes.