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Transcriptomic analyses identify genes mediating frequent cocaine use effects on HIV latent reservoir quantity

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Cocaine 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 cocaine affects HLR through gene expression, we conduct transcriptome-wide association studies (TWAS) of cocaine use and HLR in virally suppressed, combination antiretroviral therapy (ART) adherent women living with HIV who frequently used cocaine (at least once/week or greater; n=60) or did not (n=178) within 6 months prior to blood draw. We quantified the $CD4^+$ T-cell HLR by intact proviral DNA assay. Using negative binomial regression, we identified 804 (cocaine use) and 141 (HLR) differentially expressed genes (FDR<0.1) with 63 genes associated with both phenotypes. Gene set overrepresentation analysis of the overlapping genes identified enriched biological pathway terms related to cell morphology, immune cell signaling, and apoptosis (FDR<0.1). We assessed whether expression of the 63 genes mediates the effect of cocaine use on HLR, and 4 genes were identified as potential mediators (FDR<0.05): *EPSTI1*, *GALNT2*, *GFOD1*, and *PSMD1*. *EPSTI1*, the gene with the largest estimated average causal mediation effect from our study, is activated by HIV-1 Tat protein in $CD4^+$ T cells and plays a role in the translocation of NFKB to the nucleus. DNA methylation sites proximal to this gene were previously reported to mediate the effect of cocaine use on HIV severity. Overall, our results provide evidence that gene dysregulation in cocaine use impacts genes associated with HLR quantity.