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Multi-Omic Network Analysis Identifies Gene Modules Linked to Both Frequent Cocaine Use and the HIV Reservoir in CD4+ T Cells

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Cocaine is frequently used among people living with HIV, and cocaine use is known to impact HIV treatment and progression. Understanding the molecular biology linking cocaine use to the HIV reservoir (HR) is critical for improving treatment and cure efforts. To identify dysregulated gene modules associated with both cocaine use and HR, we constructed a fully connected gene network using data from 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. All study participants were virally suppressed and antiretroviral therapy adherent. We quantified the CD4+ T-cell HR (HR-CD4) by intact proviral HIV DNA assay. For our fully connected gene network, we removed weak gene-gene connections and identified 8 densely connected gene modules using the Louvain community detection algorithm. To assess the functional relevance of these modules to cocaine use and HR-CD4, we used a hypergeometric test to evaluate whether differentially expressed genes for cocaine use and CpG-linked EWAS genes for HR-CD4 size were statistically enriched in any module. One module, comprised of 49 genes, exhibited significant enrichment for both cocaine use and HR-CD4 associated genes ($p<0.01$). Using Gene Set Enrichment Analysis, we observed genes in this module to be strongly enriched for defense response to viral infection, including multiple interferon genes and their downstream targets. Using our multi-omic network-based framework, we provide evidence of cocaine use impacting gene dysregulation within interferon signaling pathways associated with HR.