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Gene expression regulation for persons with HIV who inject drugs

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Injection drug use (IDU) significantly impacts the course of HIV progression. However, little is known about the mechanisms of the adverse effects of IDU on HIV infection. We hypothesize that IDU dysregulates gene expression in the host transcriptome and the differentially expressed genes are associated with worse HIV outcomes. To test the hypothesis, we performed a transcriptome-wide association study in 176 individuals with HIV (IDU=83, non-IDU=93) from the Veteran Aging Cohort Study. Total RNA was extracted from peripheral blood mononuclear cells and sequenced. We used the *Salmon* package for transcriptome mapping and *Deseq2* package to identify differentially expressed genes. Compared to non-IDU, IDU displayed increased expression of 38 genes and decreased expression of 7 genes (False Discovery Rate, FDR < 0.05). Significant genes included *HIF1A*, a gene associated with increased HIV-1 replication and latency, and *NFKB1B*, an important gene for inflammatory signaling. In an enrichment analysis using the top 687 genes with FDR<0.2, we identified multiple statistically significant perturbation of Gene Ontology (GO) pathways associated with IDU. The identified GO pathways included immune system activation, cytokine and intracellular signal transduction, cell development/differentiation/migration, cell stress/apoptotic process, transcription regulation, and double strand break repair (FDR<0.05). When Enriched in the Reactome database, the significant pathways for IDU included immune/TLR/Interleukin response, GPCR signaling, and cell growth signaling. The DNA repair system pathway showed a net down regulation among IDU compared to non-IDU. Overall, the results indicated that IDU impacts the immune and inflammation signaling systems, which may contribute to accelerated HIV disease progression.