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Identifying Cell-Type-Specific Transcriptional Changes in Midbrain in the Context of Substance Use Disorder and Long-Term HIV Infection: A Cohort Study at the Manhattan HIV Brain Bank

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For individuals living with substance use disorder (SUD), HIV is both a prevalent comorbidity and an important neurological risk factor. In 2022, those who injected drugs worldwide were 35 times more likely to contract HIV than others, and long-term HIV infection (managed with antiretroviral therapy [ART]) may significantly alter brain function in the dopaminergic pathways impacted by SUD: HIV that integrates into brain DNA during initial infection persists in reservoir cells (like microglia) through ART, with increased burden in dopaminergic regions. Chronically, HIV-associated neurological disorders occur in ~50% of patients.

The cell-level changes associated with chronic SUD or HIV infection, or their co-occurrence, are not well described, although such information would be valuable for shaping future interventions.

Here, we explore cell-type-specific alterations in gene expression in the context of HIV and SUD involving opioids, cocaine, or both, specifically in the striatonigral dopaminergic pathway. We performed single-nucleus RNA sequencing on ventral midbrain tissue from 91 individuals either with or without HIV/SUD (41 HIV+/SUD+; 17 HIV+/SUD-; 20 HIV-/SUD+; 13 HIV-/SUD-), focusing on expression of 20,000 highly varying genes. We identified glial, neuronal, immune, and
blood-brain-barrier cell types, and explored expression differences by type, incorporating clinical information about HIV/SUD severity, demographic factors, and comorbidities.

We find that multiple cell types, including astrocytes, microglia, and oligodendrocyte precursor cells, contain highly distinct expression subsets suggestive of inflammatory/trauma responses. We also report on genes dysregulated in SUD for three levels of HIV infection (negative, positive but undetectable, positive and detectable).

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