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Drugs of abuse as drivers of epigenetic change in HIV-1 infection

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HIV-associated neurocognitive disorders (HAND) impact nearly one-half of HIV infected patients. There is considerable evidence in the literature that HIV positive substance abusers are at greater risk for HAND and generally have a heightened pathology compared to non-drug abusers.

Epigenetic control of HIV-1 transcription underlies the establishment and maintenance of latency. During this latent state, multiple factors associate with the viral LTR and repress transcription. Among these factors are the histone deacetylases (HDACs), RUNX1 other chromatin modifying proteins that alter the chromatin structure of the integrated viral promoter to prevent access and binding by positive transcription factors. We hypothesize that changes in chromatin modification driven by drugs of abuse have a role to play in the long term detrimental effects seen in drug abusers and are a confounding factor in latency reversal.

We have addressed this hypothesis by examining the effect of two classes of abused substances on HIV-1 latency and epigenetic changes in the nucleus. Our data shows that exposure to opiates drives changes in nuclear architecture and renders cells resistant to the activating effects of HDAC inhibitors. Further, we show that clinically prescribed benzodiazepines suppress RUNX1 activity and can be used to reactivate latent HIV-1. Using a novel high-resolution microscopy technique we have imaged epigenetic changes in cells exposed to opiates and benzodiazepines. Our data suggest that substances of abuse may be both affecting HIV-1 transcription and having an effect on the chromatin state of the host cell.