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## **High Content Transcriptomics Screen to Explore Pathway Crosstalk between Morphine and Antiretroviral Therapy Drug Combinations**

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Patients with HIV who use illicit drugs are more likely to experience side effects and toxicities associated with antiretroviral therapy (ART). However, little is known about the molecular mechanisms of the interaction between opioids and various combinations of ART prescriptions. Here, we employed a systems pharmacology approach to systematically analyze changes in gene expression in human cell lines when ART regimens are applied in various combinations and concentrations in the presence or absence of morphine and discover novel molecular mechanisms of drug interaction. We profiled transcriptional responses of the four human cell lines to 15 common ART drugs in 50 distinct combinations at two time points with or without morphine using the L1000 gene expression array. In total, we generated data from 2496 experiments across 800 conditions.

Global analysis established consensus signatures and identified patterns linked to known adverse events. Examining the overlap between differentially expressed genes associated with morphine exposure in combination with ART and previously reported genetic signatures associated with cardiometabolic, renal, and bone phenotypes identified unique genes that may begin to explain the clinical manifestations of specific observed adverse events and comorbidities. Understanding the interaction between opioids and commonly used combination ART regimens can help identify targets to mitigate side effects and toxicities and optimize therapy for patients with HIV who use illicit drugs or are in need of prescription opioids for pain relief.