Name: Mudit Tyagi Email: mudit.tyagi@jefferson.edu

# Cocaine by co-stimulating NF-kB, NFAT, and AP-1 enhances CD4+ T-cells metabolism; thus, sensitizes partially active cells for HIV infection

Adhikarimayum Lakhikumar Sharma[1] and Mudit Tyagi[1]

[1]Center for Translational Medicine, Department of Medicine, Thomas Jefferson Univeristy

**Background:** Illicit drug users are at significant risk of contracting the Human Immunodeficiency Virus (HIV). A strong correlation exists between prohibited drugs use and an increase rate of HIV transmission.

**Rationale/significance:** Cocaine is one of the most widely abused drugs in the United States, which both impairs the normal functioning of brain cells and also augments HIV gene-expression in the central nervous system (CNS), even in the presence of effective antiretroviral therapy (ART).

**Hypothesis:** HIV replication depends primarily on the metabolic state of the host cell. Higher cell metabolisms allow the availability of required building blocks for viral progeny. We hypothesized that cocaine-induced signaling pathways leads to the stimulation of transcription factors, including NFAT, NF-kB and AP-1, which besides augmenting overall cell metabolism, promotes HIV gene expression and replication.

**Results and discussion:** We discovered that cocaine enhances overall metabolism of CD4+ T-cells by co-stimulating transcription factors, primarily NFAT, NF-kB and AP-1. We validated the upregulation of certain crucial cell activation markers following cocaine treatment. Additionally, cocaine treatment besides enhancing HIV transcription and replication, augments overall cellular transcription. We found higher recruitment of NFAT, NF-kB and AP-1 at HIV LTR. Subsequently, we noted that cocaine-induced AP-1 cooperates with both NFAT and NF-kB, in enhancing HIV transcription, also marked with enhanced RNA polymerase II C-terminal domain phosphorylation. We also confirmed the presence of euchromatin structures at HIV LTR. The obtained knowledge may be beneficial in designing novel highly specific therapies to counter cocaine and HIV effects in illicit drug-using population.