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## **Role of Methamphetamine Induced Extracellular Vesicles in HIV Neuropathogenesis and Toxicity**

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Despite effective combinational antiretroviral therapy (cART), the high prevalence of HIV-1 associated neurocognitive disorders (HAND) are found in nearly one-third of patients and pose significant health management challenges. Methamphetamine (Meth) and related amphetamine compounds, which are potent psychostimulants, are among the most commonly used illicit drugs. Intriguingly, HIV-infected individuals who are Meth users have a comparatively higher rate of neuropsychological impairment and exhibit a higher plasma viral load than the infected individuals who do not abuse Meth. Effectively, all cell types secrete nanosized lipid membrane vesicles referred to as extracellular vesicles (EVs) that can function as intercellular communication to modulate the physiology and pathology of the cells. We found that the HIV-1-infected and Meth-treated monocytes secreted significantly higher numbers of EVs and Meth significantly upregulated genes involved in EV biogenesis. This study shows that EVs released from HIV-infected and Meth treated monocyte-derived macrophages (MDMs) enhance syncytia formation and HIV-1 pathogenesis. Further, our analysis revealed increased expression of intercellular adhesion molecule 1 (ICAM-1) and Nef protein in 10K and 100K EV's of Meth groups. When EVs are applied on MDMs for 3 hr, Meth group EVs significantly enhance cell clustering and syncytia formation. Overnight treatment of MDMs with anti-lymphocyte function-associated antigen 1 (LFA1) antibodies (Abs) substantially decreases the formation of multinucleated cells. Further, EVs treatment with anti-ICAM-1 Abs significantly blocked syncytia formation. Thus, our findings indicate the possible role of EVs and Meth in the exacerbation of HIV pathogenesis and HAND.