

**Transcriptome analysis of Peripheral Blood Mononuclear Cells from individuals with HIV-1 associated neurocognitive disorder identifies key players associated with neuropathogenesis and Marijuana use.**

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**Abstract:** HIV-1 associated neurocognitive disorder (HAND) is a major co-morbidity of HIV infection. Viral proteins and host proinflammatory factors have a direct role in neuronal toxicity in *in vitro* studies, but the contribution of these factors *in vivo* is not fully understood. Outcome is determined by complex interaction of multiple host and viral factors that are either neuroprotective or neurotoxic. Further illicit drug abuse, such as marijuana is highly prevalent in HIV-1 infected population. However, the effects of cannabinoids on HAND development are poorly understood. Here, we performed a systematic evaluation of global transcriptome of peripheral blood mononuclear cells (PBMC) obtained from HIV-1 seronegative individuals and from HIV-1 positive

individuals without neurocognitive symptoms, or with mild neurocognitive disorder (MND) or HIV-associated dementia (HAD) who either use or do not use Marijuana. MND and HAD were associated with specific changes in mRNA transcripts in PBMCs and these changes in transcriptome suggest progressive dysregulation of genes in MND and HAD, that are highly related. Similarly, a higher percentage of overlap was observed in microRNAs that are significantly dysregulated in MND and HAD, compared to cognitively asymptomatic HIV-1 subjects. Systems Biology Analysis identified specific cellular factors associated with MND and HAD, while HIV-1 viral proteins played a greater role in HAD. Grouping the individuals based on Marijuana use further identified specific changes associated with Marijuana use in HAND. Specifically, inflammatory factors such as TNF, IL1B, IFNG were significantly up regulated, whereas, IL6 and SOCS1 were down regulated in subjects who use Marijuana compared to non-users. Additionally, expression of specific microRNAs – miR-124-3p, miR-15a, miR-210-5p, miR-17-5p and others were identified to correlate with mRNA gene expression and may have a potential protective role in cognitively asymptomatic HIV-1 seropositive individuals by regulating critical chemokine and cytokine mediated downstream signaling. Together, results identified signature transcriptome changes in PBMCs associated with stages of HAND and shed light on the potential contribution of host cellular factors, HIV-1 viral proteins and Marijuana use in HAND development.