

Submitter Name: Susan Ribeiro
PI Name: Sulggi Lee

Submitted Email: susan.pereira.ribeiro@emory.edu
PI Email: sulggi.lee@ucsf.edu

Methamphetamine Use in People with HIV on Antiretroviral Therapy is Associated with Elevated Systemic Inflammation and HIV Reservoir Transcription

Susan P. Ribeiro¹, Fernanda C. Coirada¹, Sun Jin Kim², Maria Sophia Donaire³, Sannidhi Sarvadhavabhatla³, Vivian Pae³, Alton Barbehenn³, Cassandra Yun⁴, John C. Halifax⁴, Nitasha A. Kumar⁵, Paula J. Lum³, Kara L. Lynch⁴, Steven A. Yukl², Rafick P. Sekaly¹, Sulggi A. Lee³

¹Department of Pathology and Laboratory Medicine, Emory School of Medicine, Atlanta, GA 30322, USA;

²San Francisco Veterans Affairs Medical Center and Department of Medicine, University of California San Francisco, San Francisco, CA 94121 USA;

³Department of Medicine, Division of HIV, Infectious Diseases & Global Medicine, University of California San Francisco, San Francisco, CA 94110, USA;

⁴Department of Laboratory Medicine, University of California San Francisco, San Francisco, CA 94110, US;

⁵Department of Medicine, Division of Experimental Medicine, University of California San Francisco, San Francisco, CA 94110, USA.

Despite over four decades of research, we still do not have an HIV cure. While antiretroviral therapy (ART) can suppress virus, it is not a cure; virus rebounds from latently-infected cells (“the HIV reservoir”) within weeks after ART interruption. High-risk PWH, such as individuals who use methamphetamine (MA), are most likely to benefit from HIV cure strategies, but often have suboptimal ART adherence which may contribute to abnormally high levels of inflammation and residual viral transcription. We studied 20 ART-suppressed (>1 year) PWH with and without MA use (10 HIV+MA+, 10 HIV+MA-). MA concentrations were quantified from plasma using a clinically validated LC-MS/MS assay. Plasma cytokines (43 analytes) were quantified using a multi-plex immunoassay (MesoScale). PBMCs were used to measure the HIV reservoir using RT-ddPCR assays to quantify sequentially produced HIV RNA transcripts: transcriptional initiation (TAR), elongation (Long LTR), mid-transcription (Pol), distal transcription (Nef), completion (PolyA), and multiple splicing (Tat-Rev). Plasma TNF- α , TNF- β , IL-6, and MIP-1 α , and IFN- β were significantly higher in HIV+MA+ vs. HIV+MA- individuals, and these associations (except IFN- β) remained statistically significant in multivariate models adjusted for nadir CD4+ T cell count and duration of ART (P<0.05). HIV Pol transcripts were significantly higher in 8 HIV+MA+ vs. 9 HIV+MA- participants. This is the first human study to evaluate MA use on circulating cytokine levels and the HIV reservoir. Our findings suggest that even during ART, PWH who use MA have elevated inflammation and residual HIV transcription, posing potential additional challenges in eliciting HIV cure in this critical population.