Low-Dose Methamphetamine (MA) Triggers Inflammasome Activation in MA-naïve People with HIV under ART

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BACKGROUND

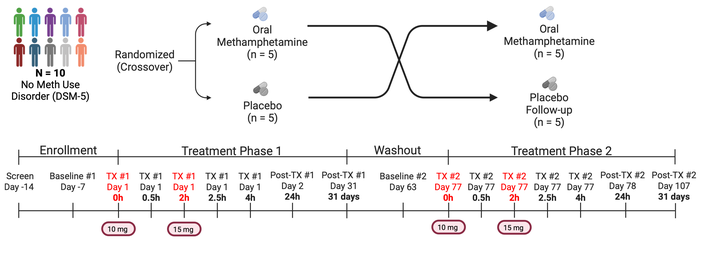
Substance use disorders (SUD) adversely affect the prognosis of people with HIV (PWH) by impairing immune responses, reducing adherence to antiretroviral therapy (ART), and increasing the burden of comorbidities. Our previous findings showed that methamphetamine (MA) exposure in PWH under ART was associated with activation of the inflammasome cascade in both innate and adaptive immune cells, as well as increased HIV transcription, which could be upstream of their worse prognosis. To validate the direct effect of MA on the modulation of the inflammasome pathway, we conducted a randomized, placebo-controlled crossover trial (NCT03825536), investigating the effects of low-dose oral MA in ART-suppressed PWH without history of MA use disorder.

METHODS

Participants (n=10) received an FDA-approved pediatric dose of oral MA (given as two doses, 10 mg + 15 mg) vs. placebo. Blood samples were collected at baseline, 0.5, 2, 2.5, 4, 24 hours, and 31 days post-intervention. Serum MA levels, plasma cytokine concentrations, and cellular HIV Pol transcript quantifications were performed. Immunophenotyping of peripheral blood mononuclear cells (PBMCs) was performed by flow cytometry *ex vivo*.

Characteristics	PWH MA- (N = 10)
Age (years)	44.5 (36.5 - 50.8)
Sex at birth (% male)	10 (100%)
Race/Ethnicity (self-reported)	
African American (%)	1 (10%)
Asian (%)	1 (10%)
White/Hispanic/Latino (%)	3 (30%)
White/European American (%)	5 (50%)
Nadir CD4+ T cell count (cells/mm³)	252 (199 - 370)
Study Baseline CD4+ T cell count (cells/mm³)	665.5 (517.3 - 688.8)
Study Baseline CD4:CD8 ratio	1.2 (1.1 - 1.2)

Figure 1. Crossover clinical trial design.



Methamphetamine is an upstream inducer of inflammasome activation in innate and adaptive cells from PWH

RESULTS

Figure 2. MA was detected in the serum of all participants 30 minutes after the first dose and continued to increase, reaching a peak at 4 hours post-intervention (74.6 ng/ml ±9.74), followed by a decline at 24 hours (26 ng/ml ±7.82). No MA was detected in the serum during placebo administration.

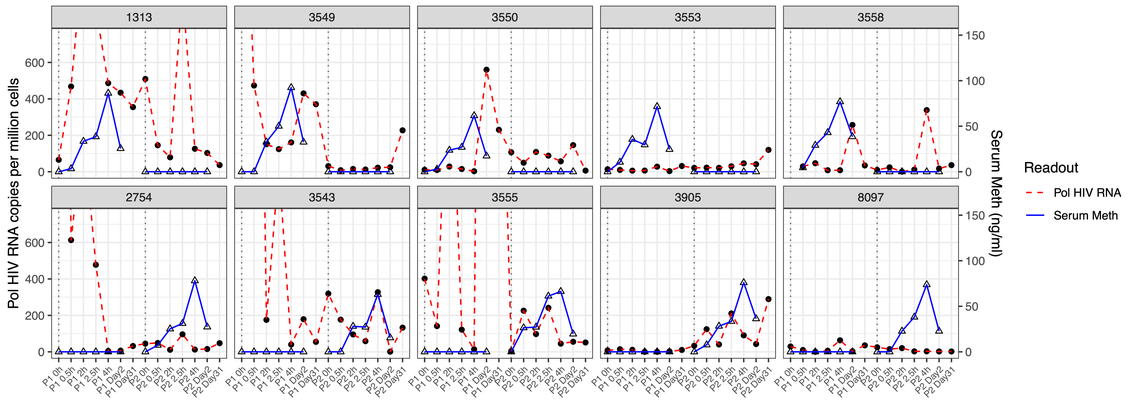


Figure 3. Inflammasome markers, NLRP3, FLICA, ASC, and IL-1β, are increased in lymphocytes and non-classical monocytes (CD14^{dim}CD16^{+}) from PBMCs 4 hours post-intervention. Paired linear regression analysis (FDR p < 0.2). Solid lines show the longitudinal trend estimated by local polynomial regression method.

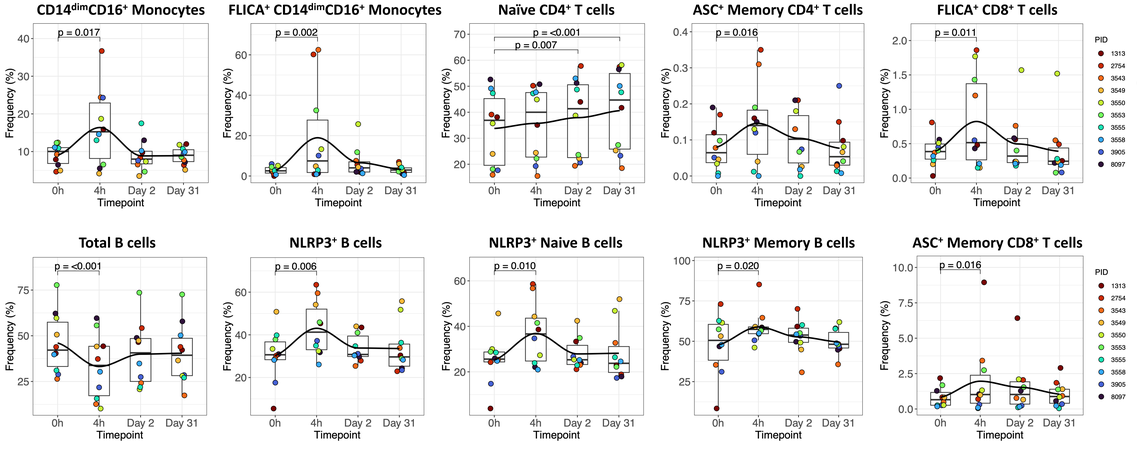
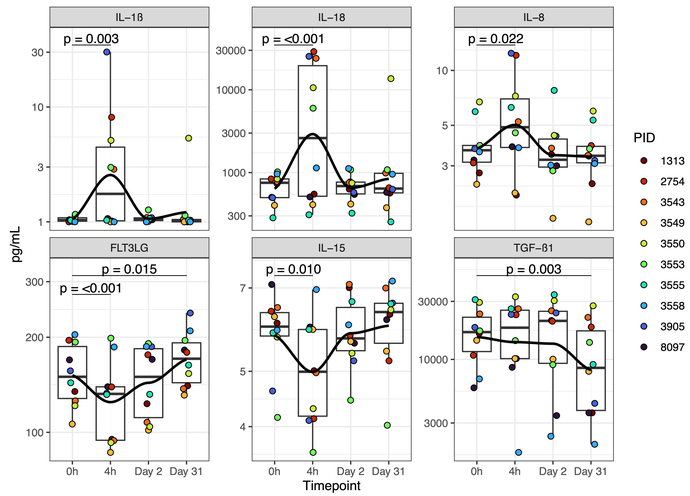


Figure 4. Proinflammatory cytokines (IL-1β, IL-18, IL-8) increased 4 hours post-intervention, along with decrease in FLT3GLG and IL-15. These cytokines returned to baseline levels 24 hours-intervention. TGFβ-1, an anti-inflammatory cytokine, decreased 31 days post intervention. Analysis and visualization were performed as in Fig. 3.



CONCLUSIONS

- Low-dose oral MA administration in PWH under ART, without history of MA use, induced a transient inflammasome activation in innate and adaptive cells. This was accompanied by increased plasma levels of inflammatory cytokines.
- Our results validate MA as the upstream inducer of inflammasome activation, reshaping immunity. This result corroborates previous observations that MA use disorder in PWH-ART is associated with inflammasome activation leading to HIV reservoir activation.
- These findings suggest that targeting this pathway may offer a potential strategy to restore homeostasis in PWH-ART with MA use disorder.

FINANCIAL SUPPORT

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NIH National Institute on Drug Abuse

PLAIN LANGUAGE SUMMARY

Participants with ART-suppressed HIV, and no history of methamphetamine (MA) use, received a low dose of MA. The increase in the blood levels of MA was associated with elevation in markers of inflammation.