Dysregulated Synthesis of Neurotransmitters in Methamphetamine Users Living with HIV

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BACKGROUND

- People living with HIV display elevations in the kynurenine/tryptophan (K/T) ratio
- K/T elevations are only partially reversed by effective treatment and predict faster clinical HIV progression
- K/T elevations disrupt serotonin synthesis, increasing risk for depression and other psychiatric comorbidities
- Less is known about the mechanisms of HIV-associated increases in the phenylalanine/tyrosine (P/T) ratio
- A greater P/T ratio is associated with disruptions in the synthesis of catecholamines such as dopamine
- This 15-month longitudinal study examined what specific HIV-associated pathophysiologic processes predict greater K/T and P/T ratios in methamphetamine users

METHODS

- In total, 110 sexual minority men living with HIV who use methamphetamine were enrolled in a RCT
- Study visits that included plasma sample collection were conducted at baseline, 6, 12, and 15 months

Outcomes

- **K/T and P/T ratios:** measured using stored plasma samples with high performance liquid chromatography
- **Depression:** Centers for the Epidemiology Study of Depression (CES-D) scores ≥ 16

Exposures

- LPS Binding Protein (LBP) – Baseline Only
- Soluble CD14 (sCD14)
- Proviral HIV DNA – Baseline only
- Detectable HIV Viral Load
- Reactive Urine Toxicology Results for Stimulants

Analyses

- Marginal models were constructed to analyze predictors of the time-varying K/T and P/T across 15 months
- Generalized Estimating Equations (GEE) were used to test the probability of CES-D ≥ 16
- **Model 1:** Tested each independent variable separately adjusting only for age and time
- **Model 2:** Adjusted for age, time, and all independent variables

Higher *proviral HIV DNA* and *recent stimulant use* independently predict a greater P/T ratio

RESULTS

- Most participants were ethnic minorities (57%) and middle-aged (mean = 43.2 years; SD = 8.9)
- Approximately three-fourths (74%) had an undetectable HIV viral load at baseline and71% screened positive for depression at baseline
- As shown in the Table below (model 2), greater time-varying sCD14 and time-varying detectable viral load were independently associated with a higher K/T ratio
- As shown in the Table below (model 2), higher proviral HIV DNA at baseline and time-varying recent stimulant use were independently associated with a greater P/T ratio
- There were no intervention effects on the K/T or P/T ratios, and neither was significantly associated with screening positive for depression
- Only time-varying recent stimulant use was associated with more than 2-fold greater odds of screening positive for depression (AOR = 2.26; 95% CI = 1.06 – 4.80; p – 0.043)

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	K/T Ratio		P/T Ratio	
	Model 1	Model 2	Model 1	Model 2
	β	β	β	β
Age	0.10	0.16	0.01	-0.01
Time Point	0.004	0.03*	-0.01	0.02
Proviral HIV DNA	-0.03	-0.07	**0.31*** **	**0.33*** **
LBP	0.17	0.05	0.05	-0.09
sCD14	**0.21*** **	**0.13***	0.17**	0.11
PI	-0.05	0.06	-0.04	0.12
Efavirenz	-0.64*	-1.01**	-0.53	-0.21
Detectable Viral Load	**0.33****	**0.74*** **	0.08	-0.20
Self-Reported Adherence ≥ 90%	-0.02	-0.04	-0.05	0.09
Recent Stimulant Use	-0.11	-0.08	0.20	**0.52*** **

CONCLUSIONS

- To our knowledge, *this study is among the first* to observe that greater HIV persistence and recent stimulant use are independently associated with a higher P/T ratio
- Markers of HIV persistence in immune cells such as higher proviral HIV DNA may stimulate intracellular inflammatory mechanisms such as cGAS-STING, Toll-Like Receptor 9 and residual transcription of Tat proteins
- HIV-associated pathophysiologic alterations could contribute to *endogenous depletion* of catecholamines, including dopamine in sexual minority men
- Observed associations of markers of microbial translocation and immune activation with a higher K/T ratio support findings from previous studies
- Future studies could address some of the limitations of this study by measuring proviral HIV DNA and cell-associated HIV RNA longitudinally as well as examining these pathways in HIV-negative stimulant users
- Other key confounders to be more carefully examined in future research include nadir CD4+ T-cell count, biomarker levels in CSF, and impaired liver function
- Findings will inform subsequent clinical research testing targeted pharmacologic treatments to mitigate dysregulated catecholamine synthesis in those who co-occurring HIV and stimulant use disorders.

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