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Impact of Methamphetamine Use and Rectal STIs on Systemic and Rectal Mucosal Inflammation

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Abstract

Background: Methamphetamine (MA) use is associated with sexual risk behavior as well as systemic and mucosal inflammation, suggesting parallel biological and behavioral mechanisms of HIV transmission among men who have sex with men (MSM) who use MA. Data evaluating the combined biological effects of MA use with concomitant rectal gonococcal and/or chlamydial (GC/CT) infection on inflammation are limited.

Setting: Secondary analysis of stored rectal and plasma specimens from 100 MSM participating in a NIDA-funded longitudinal cohort in Los Angeles, California.

Methods: This cross-sectional analysis evaluated systemic and rectal inflammatory markers under two conditions: 1) recent MA use (by urine drug screen) and 2) rectal GC/CT infection. We evaluated 50 participants with recent MA use (25 with and 25 without rectal GC/CT) and 50 MSM without MA use (25 with and 25 without rectal GC/CT). Log-transformed plasma and rectal immune markers were regressed on MA exposure and rectal GC/CT, controlling for HIV status and age.

Results: Median age was 32 (range 19–45) and 58% of participants were living with HIV. Plasma tumor necrosis factor (TNF)- α , interleukin (IL)-6, IL-8, IL-1 β , and rectal IL-6 were associated with rectal GC/CT and MA use, independent of HIV status. Higher levels of rectal TNF- α , IL-1 β , and IL-17a were associated with rectal GC/CT.

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Conclusions: Systemic and rectal inflammation was positively associated with rectal GC/CT and MA use. Condomless sex in the setting of GC/CT- and MA-induced immune activation may provide a basis for synergistic bio-behavioral mechanisms that promote HIV/STI transmission among MSM who use MA.

Keywords

sexually transmitted infection; systemic inflammation; rectal inflammation; rectal cytokines; MSM; substance use

INTRODUCTION:

Methamphetamine (MA) use is an important driver of HIV transmission and sexually transmitted infections (STIs) among men who have sex with men (MSM) ^{1,2}. Rectal gonorrhea and chlamydia (GC/CT) are associated with MA use ^{3,4} and are key risk factors for HIV transmission, producing rectal mucosal inflammation that facilitates HIV acquisition ^{5,6}. Inflammation caused by GC/CT infection increases risk for HIV transmission through local recruitment of HIV-susceptible cells, such as macrophages and T-lymphocytes, and disruption of mucosal barrier integrity ^{7,8}. This risk is potentiated by increased viral shedding due to GC/CT-mediated mucosal inflammation among individuals living with HIV, independent of systemic viral load ⁹. MA exposure is also independently associated with systemic and mucosal inflammation ^{12–15}, which may possibly be due to MA-associated changes in central and peripheral catecholamine levels ^{16–18}. While MA use has classically been associated with HIV/STI transmission through increased sexual risk behavior ^{10,11}, these findings suggest a parallel biological mechanism for HIV transmission among MSM who use MA.

While both MA use and rectal STIs have been independently linked to immune dysregulation which may predispose to HIV transmission, there is a paucity of data exploring the combined impact of MA use and concomitant rectal GC/CT on systemic and mucosal inflammation. Understanding the impact of MA use and rectal GC/CT on inflammation in these different compartments is important from a public health standpoint, as MA-associated sexual risk behavior occurring in the context of MA- and GC/CT-associated immune dysregulation may represent an important bio-behavioral mechanism for ongoing HIV transmission within sexual networks of MSM who use MA. To improve our understanding of these biological factors, this cross-sectional study sought to understand the impact of MA use and rectal GC/CT on systemic and rectal mucosal inflammatory markers using stored biological specimens and behavioral data from a NIDA-funded longitudinal cohort of MSM. In this project, we hypothesize that both MA use and rectal GC/CT will be associated with elevated systemic and mucosal inflammatory markers.

METHODS:

Participants and Recruitment

We conducted a cross-sectional, secondary analysis of stored specimens and behavioral data of MSM enrolled in the mSTUDY, a longitudinal cohort designed to evaluate the

immunological and epidemiological impacts of substance use and HIV on a cohort of racially/ethnically diverse MSM. The mSTUDY has been described previously^{12,19,20}. Briefly, study enrollment started in August 2014 and participants were recruited from a community-based university research clinic as well as a community-based organization that provide resources for the lesbian, gay, bisexual, and transgender community in Los Angeles, California. Visits occur every 6 months, and the cohort consists of one half MSM with active substance use (the other not); one half MSM living with HIV (the other not) at enrollment. Inclusion criteria for the cohort include: 1) aged 18–45 years at study enrollment, 2) assigned male sex at birth, and 3) condomless anal intercourse with a male partner in the past 6 months (if HIV-negative).

Study Procedures

At each study visit, participants completed a computer-assisted self-interview survey that collected data on demographics, sexual behavior, and substance use. Participants were provided a list of drugs (MA, cocaine, ecstasy, cannabis, and opiates) and were asked to specify the frequency with which they used each drug in the last 6 months (daily, weekly, monthly, less often than monthly, once, or never). At each visit, urine drug screens were performed that tested for the following: MA, amphetamines, ecstasy, cocaine, opiates, nitrites, cannabis, and fentanyl. Urine samples as well as rectal and pharyngeal swabs were collected at each study visit and tested for GC/CT with nucleic acid amplification testing (Aptima Combo 2, Hologic, San Diego, CA). Plasma samples, collected via phlebotomy, and rectal sponges, collected via anoscopy, were obtained at each visit and were stored at –80°C until batch processing. Study personnel assisted with notifying participants of their STI testing results and facilitated linkage to care for positive results. Written informed consent was provided before enrollment. The study was reviewed and approved by the Office of Human Research Participant Protection (OHRPP) at UCLA.

This analysis was limited to specimens from 100 randomly selected participants that comprised four groups (n=25 for each group): 1) MA-positive, rectal GC/CT negative; 2) MA-positive, rectal GC/CT positive; 3) MA-negative, rectal GC/CT negative; and 4) MA-negative, rectal GC/CT positive. MA-positive was defined as a positive urine drug screen for MA at a given visit that was negative for other drugs (except for amphetamines, ecstasy, and cannabis due to high frequency of polysubstance use in the cohort) and accompanied by self-reported MA use within the past 6 months at the same visit. MA-negative was defined as a negative urine drug screen and self-report of daily, weekly or monthly stimulant use (MA, ecstasy, or cocaine) in the past 6 months. Rectal GC/CT positive was defined as nucleic acid testing being positive for GC and/or CT at a given visit.

Sample Collection and Cytokine Quantification

Plasma was prepared by centrifugation from whole blood. Rectal secretions were collected using polyvinyl acetate sponges (Merocel, Beaver Visitec, Waltham, MA) introduced into the rectum via anoscopy and held against the rectal mucosa for 2 minutes^{21,22}. For processing, sponges were thawed on ice and sponge tips were transferred to a 2-mL Spin-X column (Corning, Corning, NY) from which the acetate membrane was removed. Rectal secretions were eluted twice with 250µL of cold elution buffer [PBS containing

0.25% bovine serum albumin, 1% Igepal (Sigma Chemicals), and protease inhibitor cocktail (Sigma Chemicals)] by centrifugation (10,000 rpm for 30 minutes at 4°C). Tumor necrosis factor (TNF)- α , interleukin (IL)-1 β , IL-6, IL-8, IL-17a, CD14, CD163, and CXCL10 were measured in plasma and rectal specimens using custom Luminex multiplex assays (R&D Systems, Minneapolis, MN) according to manufacturer's instructions. Samples were run in duplicate and repeated if the coefficient of variation (%CV) was >25%.

Data Analysis

The purpose of this analysis was to evaluate whether MA use and presence of rectal GC/CT infection were associated with increased systemic and rectal inflammatory markers. Log-transformed immune markers were regressed on MA exposure and rectal GC/CT, controlling for HIV status and age. Models for rectal inflammatory markers also controlled for self-reported receptive anal intercourse in the past week²³. The Benjamin-Hochberg procedure with a false discovery rate of <0.2 was used to adjust for multiple comparisons. All analyses were conducted using Stata 15.0 (StataCorp, College Town, TX).

RESULTS:

Study visits occurred from October 2014 to December 2017. The median age of participants was 32 years (IQR 27–37.5), and participants with recent MA use tended to be older (median age 33 years; IQR 29–40) than those without recent MA use (28.5 years; 25–33; $p=0.001$). Most participants self-identified their race/ethnicity as Latinx ($n=58$), followed by Black ($n=33$), and non-Black/non-Latinx ($n=9$). The most common mode of using MA was smoking ($n=41$), followed by injection ($n=11$), intranasal ($n=5$), and anal insertion ($n=1$). Among participants with recent MA use, 36% had rectal GC ($n=18/50$) and 28% had rectal CT ($n=14/50$). Among MA-negative participants, 18% had rectal GC ($n=9/50$) and 38% ($n=19/50$) had rectal CT (Table 1). Median plasma and rectal inflammatory marker concentrations are in Supplemental Table 1.

In adjusted models, recent MA use was associated with elevated systemic levels of CD14, TNF- α , IL-1 β , IL-6, IL-8, and CD27 (Table 2, unadjusted models in Supplementary Table 2). Rectal GC/CT was associated with elevated systemic levels of TNF- α , IL-1 β , IL-6, IL-8, and CD163. Living with HIV was positively associated with CXCL10, CD163, and CD27 but was not associated with any interleukin levels. In the rectal mucosa, rectal GC/CT was associated with elevated rectal levels of TNF- α , IL-1 β , IL-6, and IL-17a. Recent MA use was associated with elevated rectal levels of IL-6, but no associations were observed between MA use and rectal levels of TNF- α , IL-1 β , and IL-17a. HIV status was not associated with increased levels of any rectal inflammatory markers tested.

DISCUSSION:

To the best of our knowledge, this study is the first to evaluate the association of recent MA use and rectal GC/CT with systemic and rectal mucosal inflammation. Our findings demonstrate that markers of both systemic and mucosal inflammation were positively associated with MA use and rectal GC/CT. As MA-associated sexual risk behavior often facilitates rectal GC/CT infection⁴, our results suggest parallel biological and behavioral

mechanisms that may contribute to ongoing HIV transmission within the sexual networks of MSM who use MA. Both MA use and rectal GC/CT were associated with elevated systemic levels of IL-1 β , IL-6, IL-8, and TNF- α . These findings have implications for HIV transmission as systemic inflammation has been associated with increased risk of HIV acquisition^{24,25}. Among individuals living with HIV, elevated systemic levels of IL-1 β and IL-6 are associated with increased risk of cardiovascular disease and mortality^{26,27}. Furthermore, increased systemic levels of IL-6 and TNF- α , have been shown to enhance HIV replication, impairing virologic control and promoting HIV transmission^{28,29}.

Rectal GC/CT infection was associated with increased rectal mucosal levels of all cytokines tested, which is congruent with the commonly accepted paradigm that mucosal inflammation from rectal STIs contributes to HIV transmission³⁰. However, our results add to the body of knowledge as this mechanism is largely extrapolated from cervical mucosal data in the setting of genital GC/CT infection^{31,32}. Data on rectal mucosal cytokine levels in the setting of rectal STIs is limited, consisting of one cross-sectional study evaluating the joint effects of CT infection and HIV⁶. These findings are notable as imbalances in systemic and mucosal inflammation have been associated increased HIV acquisition risk³³. While MA use was only associated with elevated rectal IL-6 levels, these findings are significant as IL-6 has been demonstrated to increase susceptibility of monocyte-derived macrophages to HIV infection, potentially increasing vulnerability to acquisition and progression of HIV³⁴. Additionally, RAI was more frequently reported among participants who reported MA use, which has been demonstrated to alter the rectal inflammatory environment and may contribute to inflammation in this group³⁵. Collectively, our findings demonstrate that inflammation resulting from recent MA use in the setting of rectal GC/CT infection may promote HIV transmission within the sexual networks of MSM who use MA. Our results demonstrate the importance of regular STI screening and treatment among MSM who use MA and highlight the potential utility of interventions that combine substance use treatment with HIV/STI treatment and prevention within this population.

Our findings must be interpreted within the context of several limitations. Given the small sample size of this analysis, our study may not be adequately powered to detect small differences in cytokine concentrations. This consideration is particularly relevant given the cross-sectional design of this study and the substantial variation observed in cytokine levels, which may partially explain why systemic levels of IL-6 and IL-1 β were not associated with HIV status^{36,37}. Larger longitudinal analyses will be needed to confirm these findings. Additionally, this sample contained high rates of polysubstance use (such as cannabis), which may have influenced our results. However, rates of polysubstance use in our cohort are consistent with what has been reported among other populations of MSM who use MA in the literature³⁸. Symptomatic proctitis was not included in our models, given the small sample size and to prevent overspecification of our models. We did conduct a sensitivity analysis that included symptomatic proctitis in our models (Supplemental Table 3), which did not influence our results. It is also important to note that social genomic factors should be considered when interpreting our findings. MSM who use MA often experience high rates of social adversity, such as homophobia, racial/ethnic discrimination, stigma, and socioeconomic marginalization^{39–42}, which has been associated with epigenetic alterations that are linked to systemic inflammation and cellular aging^{43–46}. As both systemic and

mucosal inflammation have been associated with increased risk of HIV/STI transmission, future studies further evaluating the impacts of MA use and rectal GC/CT on immune dysregulation in these different compartments are warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Participant characteristics and sexual risk behaviors among men who have sex with men in the mSTUDY cohort stratified by recent methamphetamine (MA) use; Los Angeles, California 2014–17 (N=100)

	<u>Recent MA Use (n=50)</u>		<u>No Recent MA Use (n=50)</u>		<u>p-value</u> [†]
	<u>n</u>	<u>%</u>	<u>n</u>	<u>%</u>	
Age [‡]	33 (29–40)		28.5 (25–33)		0.001
Race/Ethnicity					
Latinx	30	60	28	56	0.40
Black	14	28	19	38	
Non-Black/Latinx	6	12	3	6	
HIV					
HIV-negative	13	26	29	58	0.001
Living with HIV	37	74	21	42	
Rectal GC					
Negative	32	64	41	82	0.043
Positive	18	36	9	18	
Rectal CT					
Negative	36	72	31	62	0.29
Positive	14	28	19	38	
RAI last 7 days					
No	12	24	27	54	0.002
Yes	38	76	23	46	
Symptomatic proctitis					
No	41	82	44	88	0.40
Yes	9	18	6	12	
Cannabis ^{§§}					
Negative	33	66	50	100	--
Positive	17	34	--	--	
Ecstasy ^{§§}					
Negative	38	76	50	100	--
Positive	12	24	--	--	

[†] Calculated using Fisher's exact or Kruskal-Wallis tests

[‡] Median (interquartile range)

^{§§} Urine toxicology screen

MA = methamphetamine; GC = gonorrhea; CT = chlamydia; RAI = receptive anal intercourse

Table 2:

Adjusted regression models evaluating associations between HIV status, rectal gonorrhea/chlamydia (GC/CT), and methamphetamine (MA) use with rectal and plasma inflammatory markers among a cohort of men who have sex with men (N=100)^{§§}

	MA use	Rectal GC/CT	HIV
	Adjusted β (95% CI)	Adjusted β (95% CI)	Adjusted β (95% CI)
Plasma			
CD14	0.26 (0.01–0.51)*	0.01 (–0.22–0.23)	0.11 (–0.13–0.36)
TNF- α	0.53 (0.09–0.98)*	0.52 (0.12–0.92)*	0.29 (–0.15–0.72)
IL-6	0.75 (0.29–1.20)**	0.94 (0.53–1.36)***	0.19 (–0.26–0.63)
IL-8	0.60 (0.15–1.04)**	0.86 (0.46–1.27)***	0.15 (–0.29–0.58)
CXCL10	0.27 (–0.08–0.61)	0.19 (–0.13–0.50)	0.61 (0.28–0.95)***
CD163	–0.08 (–0.34–0.18)	0.36 (0.13–0.59)**	0.45 (0.20–0.70)***
IL-1 β	2.10 (0.24–3.95)*	4.13 (2.45–5.82)***	1.08 (–0.73–2.90)
CD27	0.28 (0.05–0.50)*	–0.01 (–0.22–0.20)	0.46 (0.24–0.69)***
Rectal			
TNF- α	0.54 (–0.15–1.24)	1.36 (0.75–1.98)***	–0.26 (–0.90–0.38)
IL-1 β	0.41 (–0.55–1.37)	2.19 (1.35–3.03)***	–0.45 (–1.31–0.41)
IL-6	0.92 (0.11–1.74)*	2.03 (1.30–2.75)***	0.23 (–0.52–0.98)
IL-17a	–0.05 (–0.53–0.44)	0.85 (0.42–1.28)***	–0.07 (–0.51–0.37)

* p<0.05

** p<0.01

*** p<0.001

MA=methamphetamine; GC/CT=gonorrhea/chlamydia; TNF=Tumor Necrosis Factor; IL=Interleukin

^{§§} Calculated using linear regression where log-transformed inflammatory markers were regressed on MA use, rectal GC/CT, and HIV status, controlling for age (continuous) and receptive anal intercourse in past week (for rectal samples only). Multiple comparisons adjusted for with the Benjamin-Hochberg procedure with a false discovery rate of <0.2.