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Research Protocol

INFLAMMATION IN METHAMPHETAMINE AND STIS (AKA “IMSTI”)

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LIST OF ABBREVIATIONS

ACSA	Amphetamine Cessation Symptom Assessment
AE	Adverse Event
BAI	Beck Anxiety Inventory
BDI-II	Beck Depression Inventory-II
BQA-II	Behavioral Questionnaire-Amphetamine II
BUN	blood urea nitrogen
CAI	Condomless Anal Intercourse
CFR	Code of Federal Regulations
CM	Contingency Management
CT	<i>Chlamydia trachomatis</i>
CRF	case report form
DMC	Data Monitoring Committee
DSM-5	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Data Safety Monitoring Board
EDC	Electronic Data Capture
F	Friday
FDA	Food and Drug Administration
GC	<i>Neisseria gonorrhoeae</i>
GCP	Good Clinical Practice
GLMM	Generalized Linear Mixed Models
HIPAA	Health Insurance Portability and Accountability Act of 1996
HIV	Human Immunodeficiency Virus
ICF	informed consent form
ICH	International Conference on Harmonization
IMSTI	Inflammation in Methamphetamine and STIs
IRB	Institutional Review Board
IEC	Independent Ethics Committee
IL-1β	Interleukin-1 beta
IL-2	Interleukin-2
IL-2R	Interleukin-2 receptor
IL-6	Interleukin-6
IL-8	Interleukin-8
IL-10	Interleukin-10
IL-12	Interleukin-12
IFN-γ	Interferon gamma
IRB	Institutional Review Board
M	Monday

MA	Methamphetamine
MSM	Men who have sex with men
mSTUDY	MSM and Substances Cohort at UCLA Linking Infections Noting Effects
MUD	Methamphetamine Use Disorder
PI	Principal Investigator
PMH	Past Medical History
PrEP	HIV Pre-exposure Prophylaxis
RAI	Receptive Anal Intercourse
RANTES	Regulated on Activation, Normal T-cell Expressed and Secreted
RPR	Rapid Plasma Reagin
STI	Sexually Transmitted Infection
TNF-α	Tumor Necrosis Factor alpha
TPPA	<i>Treponema pallidum</i> particle agglutination test
Tr	Thursday
Tu	Tuesday
UPIC	Unique Participant Identification Code

PROTOCOL SYNOPSIS

TITLE	Inflammation in methamphetamine and STIs (aka “IMSTI”)
NUMBER OF SITES	1
RATIONALE	This project will evaluate the joint effects of MA use, sexual risk behavior, and rectal GC/CT on rectal and systemic inflammation (e.g., cytokines) – a key step to designing potent prevention interventions. Our overarching hypothesis is that continued MA exposure results in persistent immune dysregulation that, when combined with the synergistic effects of sexual risk behaviors and rectal GC/CT on rectal inflammation, confers increased bio-behavioral risk for HIV/STI transmission, the duration of which is attenuated by reduced MA exposure.
STUDY DESIGN	The proposed study will consist of 40 MSM (20 with rectal GC/CT, 20 without rectal GC/CT) who meet clinical criteria for MA use disorder (MUD). Participants will receive contingency management (CM) to promote MA reduction and to evaluate associations of decreased MA use frequency on systemic and rectal inflammation and risk behaviors.
PRIMARY OBJECTIVE	To identify the effects of MA exposure and concomitant rectal GC/CT on rectal cytokine concentrations over the course of 8 weeks
SECONDARY OBJECTIVES	<ul style="list-style-type: none"> • To evaluate the impact of changes in MA use frequency on systemic cytokine concentrations over the course of 8 weeks • To identify the impact of MA withdrawal symptoms on systemic cytokine concentrations over an 8-week period, adjusting for MA use frequency • To investigate the association of MA use frequency with sexual risk behaviors (partnership types and number, serodiscordant receptive CAI) in the setting of rectal inflammation.
NUMBER OF SUBJECTS	40
SUBJECT SELECTION CRITERIA	<p><u>MSM with MA use disorder (N=40)</u></p> <p><u>Inclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Cisgender male 2. 18 years of age or older 3. Understand written and spoken English 4. Condomless receptive anal intercourse in past 90 days 5. Meet DSM-5 criteria for MUD 6. Positive urine toxicology screen for MA metabolites at study entry 7. Negative rectal GC/CT screen (n=20) <u>or</u> Positive rectal GC and/or CT screen (n=20) <p><u>Exclusion criteria:</u></p> <ol style="list-style-type: none"> 1. Reports current treatment for another substance use disorder 2. Positive test for opioids, cocaine, and/or hallucinogens 3. GC/CT treatment in past 3 months

BEHAVIORAL INTERVENTION	Participants will receive contingency management, a behavioral intervention that provides positive reinforcement for MA abstinence. Participants will receive escalating rewards for consecutive negative urine tests, rewards are capped at a maximum of \$30 per negative test.
DURATION OF SUBJECT PARTICIPANT AND DURATION OF STUDY	<p>Each subject will be on study for up to 10 weeks</p> <p>Screening: 7 days</p> <p>Baseline assessment: 7 days</p> <p>Treatment: 8 weeks</p> <p>The total duration of the study is expected to last up to 4 years and will consist of 1 year of subject recruitment, 1 year for final subject follow-up, 1 year for biospecimen processing, and 1 year of analysis.</p>
PRIMARY ENDPOINT	<ul style="list-style-type: none"> Rectal cytokine concentrations over the course of 8 weeks
SECONDARY ENDPOINTS	<ul style="list-style-type: none"> Systemic cytokine concentrations Negative urine tests for methamphetamine Frequency of serodiscordant receptive CAI MA use frequency
OTHER EVALUATIONS	<ul style="list-style-type: none"> Co-substance use (opiates, stimulants, hallucinogens, alcohol, cannabis) MA withdrawal symptoms, measured by the Amphetamine Cessation Symptom Assessment (ACSA) Last 7-day sexual risk behaviors (number sexual partners, partnership type, substance use during intercourse, transactional sex) Demographics (age, race/ethnicity, income, unstable housing, education)
SAFETY EVALUATIONS	<ul style="list-style-type: none"> MA use frequency based on urine tests Incidence of adverse events
PLANNED INTERIM ANALYSES	When approximately 25% of participants have completed the study through Week 4, an interim analysis for safety will be conducted. Serious adverse events will be monitored by the investigators on an ongoing basis throughout the study.
STATISTICS	We will use longitudinal random effects models to compare differences in log-transformed rectal cytokine concentrations as functions of 1) rectal GC/CT diagnosis and 2) number MA abstinent days. We will use longitudinal generalized linear mixed models (GLMMs) and a difference in difference analysis to evaluate rate of normalization in cytokines following rectal GC/CT treatment, controlling for RAI in last 24 hours, MA use frequency, and HIV status. We will also use longitudinal GLMMs to evaluate MA use frequency (times/week) as a function of last 7-day sexual risk behavior (e.g., sexual partnerships [number and type], serodiscordant CAI) and log-transformed rectal cytokine concentrations, controlling for demographics, co-substance use, GC/CT diagnosis, HIV status, and RAI in last 24 hours.

<p>RATIONALE FOR NUMBER OF SUBJECTS</p>	<p>Power analyses assume an alpha of 0.05 (two-sided) and 0.8 power. Cytokines tend to be highly skewed, so we will transform by adding a small non-zero constant and then taking a log (base e) before analysis. We assume a 10% loss to follow-up at 3 months, based on previous CM studies involving MA-using MSM (1). We anticipate being able to detect a log difference of 1.1-1.7 in either arm (n=18) between two time points with the pilot data generated. To compare differences in differences between the two groups (with GC/CT vs without GC/CT), the log difference increases by 0.6. As we will use repeated measures and a GLMM for analysis, we will have additional power beyond what is reported. This pilot study is not designed as a confirmatory trial, but to estimate the size of the signal of MA use and biomarker links to inform a fully powered R01 trial.</p>
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1 BACKGROUND

Methamphetamine (MA) use is common among MSM and is an important driver of the HIV/STI epidemic – understanding the biological and behavioral risk factors that drive ongoing HIV/STI transmission among MA-using MSM is critical to designing potent HIV prevention interventions. Prevalence of MA use is substantially higher among MSM (5.9% among HIV-negative MSM and 12.3% among MSM living with HIV) than the general population (0.7%) (2,3), with a 707% increase in MA-related mortality in Los Angeles County over the past decade (4). MA is ingrained into the MSM party scene and frequently consumed at sex clubs, circuit parties, and bath houses (5-7). MA use is a significant risk factor for HIV/STI transmission and is temporally related to sexual risk-taking, such as receptive condomless anal intercourse (CAI) with HIV-serodiscordant partners and transactional sex (8-11). These contexts govern MA's contribution to the ongoing HIV/STI epidemic among MSM, yet prior research consists predominantly of association studies linking MA use with risk behaviors (10,12-17). Understanding the real-time impact of reductions in MA exposure on sexual risk behaviors and substance use contexts is crucial toward a complete understanding of the relationship between MA use and sexual risk, an important gap in the literature that is addressed by this proposal. This knowledge is critical to develop effective HIV prevention interventions among MA-using MSM and to measure impacts of substance use treatment efforts on the HIV/STI epidemic.

MA use is associated with increased risk for HIV/STI acquisition and impaired HIV virologic control. MA-using MSM have up to 7 times higher HIV incidence than MSM without MA use (18). Recent stimulant use was attributed to 32.7% of HIV seroconversions among MSM enrolled in a multi-institutional cohort (19). Bacterial STIs (e.g., gonorrhea, chlamydia [GC/CT] and syphilis) are independently associated with HIV seroconversion (20,21) and linked to MA use, driven in part by increased sexual risk behavior and high-risk networks (22-24). Further compounding HIV transmission risk, MA use is associated with impaired HIV virologic control due to ART non-adherence (25,26), impaired immune cell function (27-29), and enhanced intracellular HIV replication (30,31) and cell entry (32,33). Lack of HIV virologic control among HIV-positive MA-using MSM, combined with increased HIV/STI prevalence within their sexual networks, contributes to ongoing HIV/STI transmission. As MA use is associated with high-risk behavior, it is importantly pressing to study the impacts of MA use on the biological and behavioral factors that are driving HIV/STI transmission among MSM.

MA causes systemic inflammation that predisposes to HIV seroconversion. MA causes immunological changes resulting in a pro-inflammatory state (34-36) that increases susceptibility to infections (37,38). Dysfunction in adaptive immunity from MA use is caused by reduction in CD4 lymphocytes (39), disruption of T-cell proliferation (38,40), and T-cell mitochondrial oxidative damage (41). MA increases systemic cytokines, such as interleukin-2 (IL-2), IL-10, IL-12, interferon (IFN)- γ and tumor necrosis factor (TNF)- α (42-44), which are associated with HIV seroconversion (45,46) and suggest that MA-induced immune dysregulation increases HIV acquisition risk. Additionally, elevations in IL-8 are associated with worsened MA-withdrawal symptoms, suggesting that MA-associated inflammation may contribute to addiction (47). Furthermore, MA-induced immune dysfunction is associated with neurotoxicity and development of age-related diseases, such as cardiovascular disease (48,49) and stroke (50,51). While the effects of MA use on immune dysregulation have been explored, existing studies are predominantly cross-sectional – the longitudinal effects of MA-induced systemic immune dysregulation have not been established and will be addressed by this application. Evaluating the longitudinal effects of systemic inflammation associated with MA use has important implications as it

contextualizes 1) the time period where individuals are at highest risk for HIV acquisition and 2) the cumulative effect of MA use on longitudinal outcomes, such as cardiovascular disease and stroke.

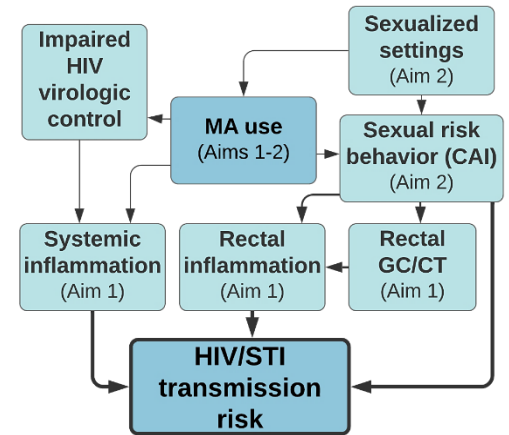
STIs and rectal inflammation are associated with HIV transmission. STIs promote HIV transmission through two routes: increased susceptibility of the HIV-negative person and increased viral shedding among individuals with HIV (52-55). Rectal STIs result in mucosal inflammation which disrupts mucosal epithelial integrity and increases risk for HIV infection (56-58). Data evaluating the effects of genital GC/CT on cervical mucosal inflammation demonstrate elevated mucosal concentrations of IL-1 β , IL-6, IL-8, IL-10, TNF- α , and IFN- γ , which facilitate immune cell migration and activation, increasing risk for HIV transmission (59-61).

Inflammation from rectal GC/CT is a dominant mechanism for HIV transmission among MSM (62-66). Yet, data evaluating mucosal inflammation from rectal STIs is scant, limited to one cross-sectional study (67). This proposal addresses this gap by evaluating rectal cytokine concentrations following STI diagnosis prospectively. Cross-sectional data demonstrates that MA use is associated with elevated rectal levels of IL-6 and TNF- α (68), increasing risk for HIV acquisition. This risk is potentiated by abundant levels of CD4 and dendritic cells, key target cells for HIV, in the rectal mucosa (58). MA exposure intensifies cytokine elevation in response to bacterial lipopolysaccharide (69), suggesting that MA may potentiate GC/CT-associated inflammation. However, no longitudinal studies have evaluated the effect of MA use on rectal inflammation and with concomitant rectal GC/CT. Determining the longitudinal impact of MA-induced rectal inflammation is important for contextualizing HIV/STI transmission among MA-using MSM. This objective is particularly relevant as persistent MA-induced immune dysregulation following MA use may continue to leave MSM vulnerable to HIV/STI acquisition, when risk compensation strategies may not occur due to low perceived HIV/STI risk (70).

2 STUDY RATIONALE

Study rationale: the bio-behavioral synergy of MA-induced systemic and mucosal inflammation, combined with risky sexual behavior, results in a modifiable period of high HIV/STI acquisition risk that contributes to ongoing HIV/STI transmission among MA-using MSM and that can potentially be managed through new prevention technologies (Figure 1). MA is linked with HIV/STI transmission through increased risk behaviors (10,12), use in sexualized settings (7,71), and high HIV/STI prevalence within sexual networks of MA-using MSM (18,24), yet the longitudinal and real-time effects of changes in MA use on sexual risk behaviors and substance use contexts have not been determined. We propose that MA-induced systemic and mucosal inflammation, both of which predispose individuals to HIV/STI acquisition and are exacerbated by concomitant rectal GC/CT, act synergistically with sexual risk behaviors to drive ongoing HIV/STI transmission among MA-using MSM. However, the duration and contexts of MA-associated bio-behavioral HIV/STI risk have not been determined and have

Figure 1. Conceptual model for bio-behavioral HIV/STI acquisition risk associated with MA use



important implications for HIV prevention, such as determining which drivers of ongoing HIV/STI transmission need to be prioritized in interventions.

2.1 Risk / Benefit Assessment

Potential risks:

HIV/STI screening. Risks associated with HIV/STI screening are minimal. Blood draws to test for HIV and syphilis include possible bruising at the venipuncture site, pain, lightheadedness, fainting, and rarely infection or clotting of the vein. Risk and discomfort are minimal. All precautions will be taken to minimize pain and risk of infection during venipuncture. If participants have a history of fainting during blood draw, precautions will be taken to minimize risk of fainting, such as providing water to consume immediately following the procedure or having the participant lie down during the procedure. An additional risk associated with HIV/STI screening is related to emotional discomfort, distress, or embarrassment related to a positive diagnosis. Participants will receive referrals to emotional support services should they require further care during the study. If potential participants test positive for HIV during screening, they will receive linkages to HIV-related care and support services.

Urine testing for substance use. Risks for urine drug screening are minimal and include emotional discomfort or embarrassment following positive urine test results or by the process of providing a urine specimen itself.

Behavioral surveys. There is minor risk that completion of behavioral surveys may cause emotional discomfort or distress. Administration of surveys through a computer-assisted self-interview is designed to minimize these potential risks as the participant will not be required to interact with study staff during survey completion.

Anoscopy and rectal swabs. Rectal secretions will be collected from swabs that are self-collected by the participant and introduced into the rectum via anoscopy. Anoscopy is a minimally invasive procedure that is generally well tolerated. Minor risks include mild discomfort during and immediately following the procedure. Additional minor risks include abrasion or tearing of the perianal skin or mucosa as well as the risk of infection, though occurrence is very rare. Risks of discomfort and abrasion will be minimized as much as possible through adequate use of lubricants.

Saliva collection. Risks for saliva collection are minimal and may include embarrassment with providing the sample or dry mouth.

Contingency management. The use of monetary incentives may be considered by some clinicians to be too tempting, given concerns that participants may then purchase drugs with the money they receive through contingency management. This risk is mitigated by the lack of earnings from not being able to provide a negative urine sample for drug metabolites. All participants will be aware that they must abstain for the entire period of 8 weeks to earn the maximum amount, which can be used to purchase consumptive goods, such as food, other essential items for their families, or hedonistic goods, such as tickets to movie theaters, meals at restaurants, or other recreational activities. Most individuals with MA dependence seek treatment to improve their lives, for both themselves as well as their families, and we will help to incentivize the money to be spent on life-improving factors as opposed to drugs. There is also the risk that participants with MA use disorder will not improve or possibly worsen during CM

participation. Participants will receive referrals to additional services if they require further care following the study, and the PI (Dr. Blair) will discuss participant follow-up care as needed.

Social consequences of research participation. The PI (Dr. Blair) and the study site will make every effort to protect participant's confidentiality and privacy. However, it is possible that involvement in the study could become known to others and that social harms may result such as unfair or discriminatory treatment from the participant's social network. All guidelines for the protection of personal health identifiers will be followed.

Protection Against Risks:

Informed Consent and Confidentiality. Potential participants will be provided with a detailed description of the study design, risks and benefits, and an opportunity to ask questions about the study at the initial in-person visit. It will be emphasized that participation in this study is voluntary and the decision to not participate, or to decline to participate at any point in the study, will not affect their medical care or consideration for future studies in any way. All prospective study candidates will receive a copy of the informed consent(s) and, if they elect to participate, will sign the form(s) before beginning study screening. Participants will also receive a copy of the "California Subjects Bill of Rights" as required by the UCLA IRB. A Certificate of Confidentiality covering the research project will be received prior to starting any recruitment. Participants will be informed of procedures for ensuring their confidentiality, which will include: 1) storage of data locked filing cabinets in locked rooms or in password protected, encrypted servers behind UCLA firewalls and 2) use of non-personally identified unique participant identification codes (UPIC) instead of names on lab tests and research data. At the initial visit, participants will complete a contact information form that will assist key personnel with contacting participants to inform/remind them of their next study visit. These contact information forms will be collected and maintained separately from any other identifying information. Participants may be contacted by key personnel by e-mail or telephone about study-oriented issues or timing for study visits. Participants will be contacted in a confidential manner and according to their pre-arranged instructions. All contact with participants using their name or e-mail address will not include their UPIC in order to prevent linking of data. All participants will be provided with a 24-hour emergency number as well as the contact numbers of the PI (Dr. Blair) and IRB Chairs to answer questions about one's rights as a human subject or the study.

HIV/STI screening. There is a minor risk that HIV/STI screening may cause emotional discomfort, distress, or embarrassment related to a positive diagnosis. In such instances, participants will receive referrals to emotional support services should they require further care during the study. If potential participants test positive for HIV during screening, they will receive linkages to HIV-related care and support services.

Behavioral surveys. There is minor risk that completion of behavioral surveys may cause emotional discomfort or distress. In such instances, participants will meet with study staff members for debriefing. Linkages to emotional support or mental health services will be made in the rare case that a mental health intervention is required.

Anoscopy and rectal swabs. While anoscopy is generally well tolerated, there is the minor risk of discomfort as well as abrasions or tearing of the perianal skin or mucosa. Risks of discomfort and

abrasion will be minimized as much as possible through adequate use of lubricants.

Contingency management and MA use disorder. There is a risk that some participants may have MA addiction that is too severe to be adequately treated as an outpatient or that does not respond to the CM program. At all points during the trial, participants will have access to treatment facilities instead of or in addition to the CM program. Participants who wish to focus solely on treatment and not on research can withdraw from study participation at any time. Any unexpected events that arise during survey administration, specimen collection, or the contingency management program that caused harm and/or affects the risk to all participants in the research will be reported immediately to the IRB.

Potential Benefits:

Reduction in relapse rates among those with substance use disorder has been demonstrated with contingency management, which is thought to be due to the introduction of new conditioned schedules within the mesolimbic reward system. Therefore, there is the potential benefit that individuals who participate in the contingency management intervention may become abstinent from MA or reduce their MA-use frequency, which may be a lasting effect.

Importance of Knowledge to be Gained:

As MA use is an important driver of HIV transmission and the burgeoning STI epidemic among MSM, this study will provide important information regarding the biological and behavioral risks associated with HIV/STI transmission among MA-using MSM. These findings may help guide future shared decision-making between individuals who use MA, providers, and key stakeholders. Additionally, this research is that it will help to gain an understanding of the interaction of biological and behavioral risk factors for HIV/STI acquisition that can be used to develop a comprehensive risk reduction profile for MA-using MSM which will be incorporated into multimodal integrated HIV prevention strategies in future projects. The benefit of these findings will be to future MA-using MSM who are at risk for HIV/STI acquisition.

3 STUDY OBJECTIVES

3.1 Primary Objective

- The primary objective of this study will be to identify the effects of MA exposure and concomitant rectal GC/CT on rectal cytokine concentrations over an 8-week period.

3.2 Secondary Objectives

- To evaluate the impact of changes in MA use frequency on systemic cytokine concentrations over the course of 8 weeks
- To identify the impact of MA withdrawal symptoms on systemic cytokine concentrations over an 8-week period, adjusting for MA use frequency

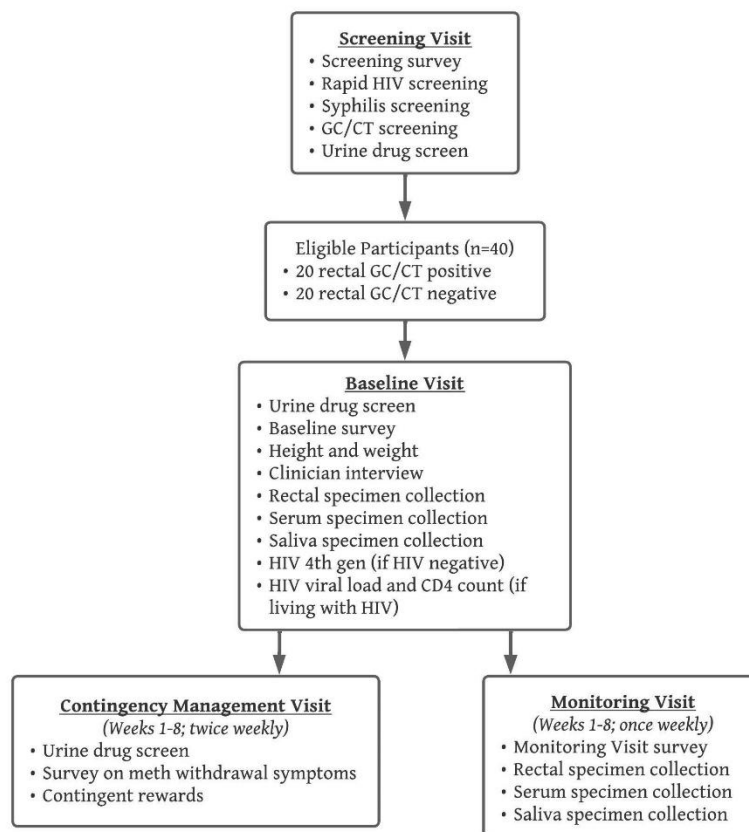
- To investigate the association of MA use frequency with sexual risk behaviors (partnership types and number, serodiscordant receptive CAI) in the setting of rectal inflammation.

4 STUDY DESIGN

4.1 Study Overview

The proposed study will consist of 40 MSM (20 with rectal GC/CT, 20 without rectal GC/CT) who meet clinical criteria for MA use disorder (MUD). Participants will receive contingency management (CM) to promote MA reduction and to evaluate associations of decreased MA use frequency on systemic and rectal inflammation (Aim 1) as well as risk behavior (Aim 2). Rectal and serum specimens will be obtained at baseline and measured weekly over 8 weeks. Participants will also complete weekly questionnaires that assess sexual risk behaviors and co-substance use.

Figure 2. Participant recruitment, enrollment, and monitoring flowchart



4.2 Intervention

Contingency management (CM), an evidence-based intervention with proven efficacy that provides increasing rewards for consecutive biomarkers confirming drug abstinence (72,73), will be used to promote MA abstinence – this is not a CM efficacy trial. CM will be used as it is an evidence-based, non-pharmacologic treatment for MUD that can be used to manipulate MA use, as the impact of pharmacologic interventions on cytokine levels is unknown and may cause unintended bias. CM will start at the first visit in Week 1 and participants will have twice weekly (Monday/Thursday [M/Tr] or Tuesday/Friday [Tu/F]) urine drug screens for MA metabolites during Weeks 1-8. Individuals providing urine samples negative for MA metabolites will earn rewards that will start at \$6 and will escalate in value by \$2 for each successive negative sample, capped at a maximum of \$30 per negative result (1). If abstinence is maintained for the entire study, participants could receive a maximum amount of \$564. Following relapse or missed appointment, rewards will be recalibrated back to the participant's highest level by the third consecutive negative result (rapid reset to sustain motivation). If a sample is positive for MA or missing, a reward will not be issued. Participants will be allowed to reschedule one appointment at least 24 hours in advance, to occur within 24 hours of the original appointment. Participants will complete twice weekly drug tests which will test urine for MA, cocaine, amphetamines, and opiates. Participants will provide a urine sample for drug testing at the following visits: Screening, Baseline, and Weeks 1-8 (twice weekly [M/Th or Tu/F]). Participants will leave their belongings with clinic staff and empty their pockets prior to urine specimen collection. Samples will be provided to clinic staff while the pass-through cabinet door is open and before hands are washed, to minimize attempts to provide false specimens. To ensure specimens are provided in real time, a temperature strip will confirm that urine samples are near body temperature at time of collection.

Total duration of subject participation will up to 10 weeks. Total duration of the study is expected to be 4 years.

5 CRITERIA FOR EVALUATION

5.1 Primary Endpoint

The primary endpoint for this study is rectal cytokine concentrations that are measured from rectal secretions that are obtained weekly during this study over the course of 8 weeks. We will test the effects of MA exposure and concomitant rectal GC/CT on rectal inflammation over the course of 8 weeks.

5.2 Secondary Endpoints

- We will measure systemic cytokine concentrations over the course of 8 weeks.
- We will evaluate number of negative urine tests for methamphetamine over 8 weeks.
- Frequency of self-reported serodiscordant receptive CAI over 8 weeks
- MA use frequency measured by number of positive urine tests for methamphetamine over 8 weeks.
- Self-reported MA withdrawal symptoms over the course of 8 weeks.

5.3 Safety Evaluations

- We will evaluate methamphetamine use patterns using twice weekly urine tests. Participants will participate in Monitoring Visits once weekly during Weeks 1-8. We will report on the incidence of adverse events.

5.4 Other Evaluations

- Co-substance use (opiates, stimulants, hallucinogens, alcohol, cannabis)
- MA withdrawal symptoms, measured by the Amphetamine Cessation Symptom Assessment (ACSA)
- Last 7-day sexual risk behaviors (number sexual partners, partnership type, substance use during intercourse, transactional sex)
- Partnership types (sexual partnerships, drug use partnerships)
- Demographics (age, race/ethnicity, income, unstable housing, education)

6 SUBJECT SELECTION

6.1 Study Population

40 MSM who meet criteria for MUD and who meet the inclusion and exclusion criteria will be eligible for participation in this study. At study enrollment, 20 participants will have a positive rectal GC/CT screen and 20 participants will have a negative rectal GC/CT screen at enrollment.

6.2 Inclusion Criteria

Inclusion criteria:

1. Cisgender male
2. 18 years of age or older
3. Understand written and spoken English
4. CAI in past 90 days
5. Meet DSM-5 criteria for MUD
6. Positive urine toxicology screen for MA metabolites at study entry
7. Negative rectal GC/CT screen (n=20) *or* Positive rectal GC and/or CT screen (n=20)
8. Written informed consent obtained from subject or subject's legal representative and ability for subject to comply with the requirements of the study.

6.3 Exclusion Criteria

Exclusion criteria:

1. Reports current treatment for another substance use disorder
2. Positive test for opioids, cocaine, and/or hallucinogens
3. GC/CT treatment in past 3 months
4. Presence of a condition or abnormality that in the opinion of the Investigator would compromise the safety of the patient or the quality of the data.

7 CONCURRENT MEDICATIONS

All subjects should be maintained on the same medications throughout the entire study period, as medically feasible, with no introduction of new chronic therapies.

7.1 Allowed Medications and Treatments

Standard therapy for any medical condition is allowed except for current treatments for substance use disorders as noted in the exclusion criteria described above.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

This is a non-randomized behavioral trial that will consist of 20 MSM without rectal GC/CT at study entry and 20 MSM with rectal GC and/or CT at study entry as per the inclusion criteria detailed above, for a total of 40 participants. All participants will receive the same behavioral intervention (contingency management) and will participate in the same assessments (questionnaires and specimen collection) throughout the duration of the study.

8.2 Study Treatment – Contingency Management

Contingency management (CM), an evidence-based intervention with proven efficacy that provides increasing rewards for consecutive biomarkers confirming drug abstinence (72,73), will be used to promote MA abstinence – this is not a CM efficacy trial. CM will be used as it is an evidence-based, non-pharmacologic treatment for MUD that can be used to manipulate MA use, as the impact of pharmacologic interventions on cytokine levels is unknown and may cause unintended bias. CM will start at the first visit in Week 1 and participants will have twice weekly (M/Th or Tu/F) urine drug screens for MA metabolites during Weeks 1-8. Individuals providing urine samples negative for MA metabolites will earn rewards that will start at \$6 and will escalate in value by \$2 for each successive negative sample, capped at a maximum of \$30 per negative result (1). If abstinence is maintained for the entire study, participants could receive a maximum amount of \$654 (not including compensation for attending CM Visits and Monitoring Visits). Following relapse or missed appointment, rewards will be recalibrated back to the participant's highest level by the third consecutive negative result (rapid reset to sustain motivation). If a sample is positive for MA or missing, a reward will not be issued. Participants will be allowed to reschedule one appointment at least 24 hours in advance, to occur within 24 hours of the original appointment. Participants will complete twice weekly drug tests which will test urine for MA, cocaine, amphetamines, and opiates. Participants will provide a urine sample for drug testing at the following visits: Screening, Baseline, and Weeks 1-8 (twice weekly [M/Th or Tu/F]). Participants will leave their belongings with clinic staff and empty their pockets prior to urine specimen collection. Samples will be provided to clinic staff while the pass-through cabinet door is open and before hands are washed, to minimize attempts to provide false specimens. To ensure specimens are provided in real time, a temperature strip will confirm that urine samples are near body temperature at time of collection.

8.3 Measures of Treatment Compliance

Treatment compliance will be based on visit attendance and urine drug tests, which will occur twice weekly for 8 weeks. Participants will be allowed to reschedule one appointment at least 24 hours in advance, to occur within 24 hours of the original appointment. Participants will complete twice weekly drug tests using which will test urine for MA, cocaine, amphetamines, and opiates.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject.

Prior to conducting study activities and enrollment of participants, surveys will be piloted with up to 10 individuals from the study population to ensure that questions are easy to comprehend. Participants who pilot study surveys will undergo a separate informed consent process, will be compensated \$20 for their time, and data obtained from piloting the surveys will not be used for data analysis.

9.1 Participant Recruitment

Potential participants will be recruited from existing participant pools from previous and ongoing studies that have been conducted at the UCLA Vine Street Clinic. Potential participants will only be contacted only if they consent to be notified about future research studies. To increase the likelihood of recruitment of participants with positive GC/CT testing, subjects who are enrolled in ongoing trials at the UCLA Vine Street Clinic and screen positive for an STI during that trial will be prioritized for potential enrollment and screening in this study and will be encouraged to inform their sexual partners of the study. Participants will also be recruited through flyers that will be placed at HIV/STI clinics throughout Los Angeles as well as community sites that are frequented by the LGBT community. Potential participants will also be recruited using referral cards from individuals who have screened for the study or agreed to be contacted for future studies. These referral cards will provide individuals with a referral bonus for each individual who screens and enrolls in the study. Prior to attending the Screening Visit, participants will undergo telephone pre-screening that will be conducted by study staff with a phone screening script. Participants who are eligible for the in-person Screening Visit will be male, aged 18 years or older, not have been treated for an STI in the past 3 months, used MA in the past week, and agree to return to the study site twice a week for 8 weeks.

9.2 Clinical Assessments

9.2.1 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

9.2.2 Adverse Events

Information regarding occurrence of adverse events will be captured throughout the study. Duration (start and stop dates), severity/grade, outcome, treatment and relation to study intervention will be recorded on the case report form (CRF).

9.3 Clinical Laboratory Measurements

9.3.1 Urine drug testing

Participants will complete urine drug tests, which will test urine for MA, cocaine, amphetamines, and opiates. Participants will provide a urine sample for drug testing at the following visits: Screening, Baseline, and Weeks 1-8 (twice weekly [M/Th or Tu/F]). Participants will leave their belongings with clinic staff and empty their pockets prior to urine specimen collection. Samples will be provided to clinic staff while the pass-through cabinet door is open and before hands are washed, to minimize attempts to provide false specimens. To ensure specimens are provided in real time, a temperature strip will confirm that urine samples are near body temperature at time of collection.

9.3.2 HIV Screening

Participants will be screened for HIV using rapid HIV testing using whole blood at the Screening Visit to ensure that participants will have access to their HIV testing results on the same day as their Screening Visit. At the Baseline visit, blood will be obtained and sent the UCLA clinical lab to screen for HIV using HIV 4th generation testing for confirmation testing.

9.3.3 HIV Testing and CD4 Count

For participants who are living with HIV, blood will be obtained and sent to the clinical lab for HIV viral load testing at Baseline and at Week 4. Blood obtained for CD4 counts will be obtained at Baseline.

9.3.4 Syphilis Screening

Blood will be obtained and sent the clinical lab to screen for syphilis using rapid plasma reagin (RPR) with confirmatory testing via the Treponema pallidum particle agglutination test (TPPA). Syphilis screening will occur at the Screening Visit.

9.3.5 GC/CT Screening

Pharyngeal and rectal swabs as well as urine will be obtained and sent to the clinical lab to test for GC/CT. Pharyngeal, urethral, and rectal GC/CT testing will occur at the Screening Visit.

9.4 Research Laboratory Measurements

9.4.1 Serum Cytokine Measurements

Serum for measurement of interleukin-1 β (IL-1 β), IL-2, IL-2R, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES). Blood draws of 20mL will be obtained via venipuncture at 9 visits: Baseline and once weekly during Weeks 1-8. Serum will be extracted, labeled, and stored at -70°C at UCLA Vine Street Clinic's biorepository. The samples will then be transferred to our research collaborators, Dr. Jennifer Fulcher and Dr. Grace Aldrovandi, where serum cytokine concentrations will be measured using Luminex Multiplex Cytokine assays (Luminex, Austin, TX).

9.4.2 Rectal Cytokine Measurements

Rectal secretions will be obtained to measure interleukin-1 β (IL-1 β), IL-2, IL-2R, IL-6, IL-8, IL-10, IL-12, tumor necrosis factor (TNF)- α , interferon (IFN)- γ , and Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES). Rectal secretions will be obtained at 9 visits: Baseline and once weekly during Weeks 1-8. A study clinician will perform an anoscopy, and a rectal sponge will be inserted by the clinician and held against the rectum for 2 minutes to collect rectal secretions. Rectal sponges will be labeled and stored at -70°C at UCLA Vine Street Clinic's biorepository. The samples will then be transferred to our research collaborators, Dr. Jennifer Fulcher and Dr. Grace Aldrovandi, where specimens will be processed and rectal cytokine concentrations will be measured using Luminex Multiplex Cytokine assays (Luminex, Austin, TX).

9.4.3 Saliva Cytokine Measurements

Saliva specimens will be obtained to measure cytokine levels. Saliva specimens will be obtained at 9 visits: Baseline and once weekly during Weeks 1-8. Participants will be asked to provide 2-3mL saliva via passive drool method into a specimen collection cup. Saliva specimens will be labeled and stored at -70°C at UCLA Vine Street Clinic's biorepository. The samples will then be transferred to our research collaborators, Dr. Jennifer Fulcher and Dr. Grace Aldrovandi, where specimens will be processed and cytokine concentrations will be measured using Luminex Multiplex Cytokine assays (Luminex, Austin, TX).

10 EVALUATIONS BY VISIT

10.1 Screening Visit (Visit S)

1. Review the study with the subject and obtain written informed consent
2. Assign the subject a unique screening number.
3. Record of self-reported demographics, behavior, substance use, and health data.
4. Urine drug screening
5. HIV rapid test, if no available medical information of HIV status
6. Syphilis screening, if no syphilis testing results available

7. GC/CT screening, if no GC/CT testing results available in past 3 months
8. Screen for MA use disorder using DSM-5 criteria
9. Refer participant to free/low-cost sexual wellness clinic if participant demonstrates interest in HIV pre-exposure prophylaxis (PrEP) or HIV treatment

10.2 Baseline Visit (Visit B)

1. Urine drug test
2. Behavioral survey
3. Measurement of height and weight
4. Blood draw for HIV 4th generation testing (if HIV-negative) or HIV viral load and CD4 count (if living with HIV)
5. Blood draw for serum cytokine measurements
6. Anoscopy and collection of rectal secretions for rectal cytokine measurements
 - a. Collection rectal sponges by clinician via anoscopy
 - b. Collection rectal swabs by clinician via anoscopy
7. Saliva sample collection
8. Clinician review of past medical history, current medications, STI history, antibiotic use in past 3 months, probiotic use in past 3 months

10.3 Contingency Management (Weeks 1-8, twice weekly Monday + Thursday or Tuesday + Friday)

1. Urine drug test
2. Contingent rewards for negative urine test
3. Brief survey on MA withdrawal symptoms

10.4 Monitoring Visits (Weeks 1-8, once weekly immediately following CM visit)

1. Behavioral survey
2. Blood draw for serum cytokine measurements
 - a. At Week 4, blood draw for HIV viral load (if living with HIV)
3. Anoscopy and collection of rectal secretions for rectal cytokine measurements
 - a. Collection of rectal sponges by clinician via anoscopy
 - b. Collection of rectal swabs by clinician via anoscopy
4. Saliva sample collection
5. Record any adverse events

10.5 Early Withdrawal Visit

1. Record any adverse events

2. Record reason for withdrawal if initiated by the participant
3. Discuss reason for withdrawal if initiated by investigator
4. Note that participant-initiated withdrawals do not have to occur in person and can occur over remote communication (e.g., email or phone)

11 ADVERSE EXPERIENCE REPORTING AND DOCUMENTATION

11.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a clinical investigation of a patient administered an intervention and that does not necessarily have a causal relationship with the treatment. An AE is therefore any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration of an intervention, whether or not related to that intervention. The Investigator will probe, via discussion with the subject, for the occurrence of AEs during each subject visit and record the information in the site's source documents. Adverse events will be recorded in the patient CRF. Adverse events will be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study drug, or if unrelated, the cause.

AE Severity

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. The modified criteria can be found in the study manual. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible.
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

AE Relationship to Study Intervention

The relationship of an AE to the study intervention should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Study Intervention

Relationship to Intervention	Comment
Possibly	An event that follows a reasonable temporal sequence from administration of the contingency management intervention; that follows a common negative response pattern among some individuals treated with this intervention, but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study intervention.

11.2 Serious Adverse Experiences (SAE)

An SAE is defined as any AE occurring at any dose that results in any of the following outcomes:

- death
- a life-threatening adverse experience
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant disability/incapacity

Other important medical events may also be considered an SAE when, based on appropriate medical judgment, they jeopardize the subject or require intervention to prevent one of the outcomes listed.

11.2.1 Serious Adverse Experience Reporting

Study sites will document all SAEs that occur (whether or not related to study intervention) per [UCLA OHRPP Guidelines](#). The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local Institutional Review Board (IRB)/Independent Ethics Committee (IEC), the site investigator will report SAEs to the IRB/IEC.

11.3 Medical Monitoring

Cherie Blair, MD, PhD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: (323) 461-3106
Pager: (310) 825-6301

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Intervention

A subject may be discontinued from the contingency management intervention at any time if the subject or the investigator feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Refer to Section 10 for early termination procedures.

12.3 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject or the investigator feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. As noted above, subjects who discontinue study treatment early (i.e., they withdraw prior to the final Week 8 visit) should have an early discontinuation visit, especially if initiated by the investigator. Refer to Section 10 for early termination procedures. Subjects who withdraw after Week 1 but prior to Week 8 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

If participants miss more than two consecutive weeks of study visits, participants will be withdrawn from the study. Participants who withdraw from the study will be provided an opportunity to re-screen and re-enroll if they choose to re-enter the study.

12.4 Replacement of Subjects

Subjects who withdraw from the study treatment will be replaced.

Subjects who withdraw from the study will be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject or investigator fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited treatment/intervention

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed the Investigator. A copy of the form will be filed in the site's regulatory binder.

14 DATA SAFETY MONITORING

A data and safety monitoring plan (DSMP) will be used to monitor good clinical research procedures regarding data and safety of participants. During data collection, the investigator and key personnel will monitor the project to ensure that participants and the data are being protected, especially in conducting quality assurance of all informed consent documents in real time. All standard safety procedures and ethical practices will be adhered to per the Office of Human Research Protection Program (OHRPP) of UCLA and will use secure, HIPAA-compliant technology per UCLA Health Sciences information and technology standards. The investigator and key personnel will communicate regularly with UCLA OHRPP for coordinated review of ethical practices, safety procedures, and adherence to confidentiality/privacy agreements.

Administrative reports will be prepared every month or more frequently as requested describing study progress. Such reports will include the following:

- Demographic and clinical characteristics
- Actual versus expected enrollment figures
- Missing visits and case report forms
- Number and type of clinically significant and/or adverse events
- Randomly audited consent forms of five participants to determine whether they are available and properly executed
- Aggregate values of clinical laboratory results

15 STATISTICAL METHODS AND CONSIDERATIONS

The following SAP will describe statistical analyses.

15.1 Data Sets Analyzed

Participants who miss no more than 2 monitoring visits will be considered enrolled for statistical purposes.

15.2 Demographic and Baseline Characteristics

Sociodemographic and behavioral characteristics will include age, race/ethnicity, education level, sexual orientation, employment, income, smoking history, heavy alcohol use history, and self-reported co-substance use (cocaine, ecstasy, opiates, cannabis, hallucinogens).

15.3 Analysis of Primary Endpoint

Longitudinal random effects models will be used to compare differences in log-transformed rectal cytokine concentrations as functions of 1) rectal GC/CT diagnosis and 2) number MA abstinent days. Longitudinal generalized linear mixed models (GLMMs) and a difference in difference analysis to evaluate rate of normalization in cytokines following rectal GC/CT treatment, controlling for RAI in last 24 hours, HIV status, and MA use frequency.

15.4 Analysis of Secondary Endpoints

- Longitudinal GLMMs will be used to evaluate MA use frequency (times/week) as a function of last 7-day sexual risk behavior (e.g., sexual partnerships [number and type], serodiscordant CAI) and log-transformed rectal cytokine concentrations, controlling for demographics, co-substance use, GC/CT diagnosis, HIV status, and receptive anal intercourse (RAI) in last 24 hours.
- Longitudinal random effects models will be used to compare differences in log-transformed systemic cytokine concentrations as a function of number MA abstinent days.
- GLMMs will also be used to evaluate MA withdrawal symptoms as a function of log-transformed systemic cytokine levels, controlling for demographics, co-substance use, depression/anxiety symptoms, MA use frequency (times/week), HIV status, and days elapsed from last MA use. Additionally, the temporal association between systemic cytokine levels, MA use, and MA withdrawal will be examined with GLMMs that will evaluate log-transformed systemic cytokine levels as a function of days elapsed from last MA use and MA withdrawal symptoms.

15.5 Sample Size

Power analyses assume an alpha of 0.05 (two-sided) and 0.8 power. Cytokines tend to be highly skewed, so we will transform by adding a small non-zero constant and then taking a log (base e) before analysis. We assume a 10% loss to follow-up at 3 months, based on previous CM studies involving MA-using MSM (1). We anticipate being able to detect a log difference of 1.1-1.7 in either arm (n=18) between two time points with the pilot data generated. To compare differences in differences between the two groups (with GC/CT vs without GC/CT), the log difference increases by 0.6. As we will use repeated measures and a GLMM for analysis, we will have additional power beyond what is reported. This pilot study is not

designed as a confirmatory trial, but to estimate the size of the signal of MA use and biomarker links to inform a fully powered R01 trial.

16 DATA COLLECTION, RETENTION AND MONITORING

16.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject receiving the behavioral intervention.

Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific electronic Case Report Form (eCRF) OR paper CRF when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected but will be identified by a unique participant identification code and initials. All surveys will be administered via computer assisted self-interview via Qualtrics on a UCLA encrypted server.

For eCRFs: If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and creates an electronic audit trail. *For paper CRFs:* If a correction is made on a CRF, the study staff member will line through the incorrect data, write in the correct data and initial and date the change.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator. A copy of the CRF will remain at the Investigator's site at the completion of the study.

16.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

16.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. Queries are entered, tracked, and resolved through the electronic data capture (EDC) system directly. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

16.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

16.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives, IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

16.6 Monitoring

By signing this protocol, the Investigator grants permission to the appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

16.7 Subject Confidentiality

In order to maintain subject confidentiality, only a site number, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to regulatory authorities. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

17 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

17.1 Protocol Amendments

Any amendment to the protocol will be written by the primary investigator. Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRBs are notified within five working days.

17.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC of each participating center prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the

Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be obtained by the Investigator prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

17.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and will submit these materials to the IRB/IEC. The consent form generated by the Investigator must be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will maintain an IRB/IEC-approved copy of the Informed Consent Form for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

17.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement with the participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

17.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (or designee), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or investigation).
3. Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
4. Report to the Sponsor or designee any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
5. Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
6. Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (or designee).
7. Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
8. Promptly report to the IRB and the Sponsor (or designee) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and safety reports).
9. Seek IRB approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
10. Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.

APPENDIX 1. EXAMPLE OF SCHEDULE OF STUDY VISITS

	S	B	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8
Informed Consent	X									
Assign unique participant ID	X									
Screening Visit survey	X									
Urine drug screen	X	X								
HIV rapid test	X									
Syphilis screening	X									
GC/CT screening	X									
HIV 4 th gen (HIV negative)		X								
HIV viral load (living with HIV)		X				X				
CD4 count (living with HIV)		X								
Height, Weight		X								
Baseline Visit survey		X								
Clinician screening questionnaire		X								
Contingency Management survey ^a		X	X	X	X	X	X	X	X	X
Contingent rewards ^a		X	X	X	X	X	X	X	X	X
Drug screen for contingent rewards ^a		X	X	X	X	X	X	X	X	X
Anoscopy and rectal samples ^b		X	X	X	X	X	X	X	X	X
Saliva specimen ^b		X	X	X	X	X	X	X	X	X
Serum for cytokine measurements ^b		X	X	X	X	X	X	X	X	X
Monitoring Visit survey ^b			X	X	X	X	X	X	X	X

^aTwice weekly on Monday and Thursday or Tuesday and Friday; ^bonce weekly
S = Screening Visit; B = Baseline Visit

APPENDIX 2. VISIT COMPENSATION SCHEDULE

Visit Compensation Schedule					
	Visit	Visit payment	Specimen collection*	Serial negative urine tests	Contingency management incentive
Screen	S	\$50			
Baseline	B	\$50			
Week 1	1.1	\$20	\$20	1	\$6
	1.2	\$20		2	\$8
Week 2	2.1	\$20	\$20	3	\$10
	2.2	\$20		4	\$12
Week 3	3.1	\$20	\$20	5	\$14
	3.2	\$20		6	\$16
Week 4	4.1	\$20	\$20	7	\$18
	4.2	\$20		8	\$20
Week 5	5.1	\$20	\$20	9	\$22
	5.2	\$20		10	\$24
Week 6	6.1	\$20	\$20	11	\$26
	6.2	\$20		12	\$28
Week 7	7.1	\$20	\$20	13	\$30
	7.2	\$20		14	\$30
Week 8	8.1	\$20	\$20	15	\$30
	8.2	\$20		16	\$30
*Specimen collection refers to additional compensation for participating in once weekly Monitoring visits					

REFERENCES

1. Landovitz RJ, Fletcher JB, Inzhakova G, Lake JE, Shoptaw S, Reback CJ. A novel combination HIV prevention strategy: post-exposure prophylaxis with contingency management for substance abuse treatment among methamphetamine-using men who have sex with men. *AIDS Patient Care STDS*. 2012;26(6):320-8. Epub 2012/06/12. doi: 10.1089/apc.2011.0432. PubMed PMID: 22680280; PMCID: PMC3366332.
2. Substance Abuse and Mental Health Services Administration. 2018 National Survey on Drug Use and Health: lesbian, gay, and bisexual (LGB) adults: US Department of Health and Human Services; 2019. Available from: https://www.samhsa.gov/data/sites/default/files/reports/rpt23252/7_LGB_2020_01_14_508.pdf.
3. Centers for Disease Control and Prevention. HIV infection risk, prevention, and testing behaviors among men who have sex with men - National HIV Behavioral Surveillance, 23 U.S. cities, 2017. 2019.
4. Los Angeles County Department of Public Health. Meth in LA Los Angeles CA: Los Angeles County Department of Public Health, Substance Abuse Prevention and Control; 2019. Available from: <http://publichealth.lacounty.gov/sapc/public/meth/?lang=en#meth-in-la>.
5. Reback CJ, Larkins S, Shoptaw S. Changes in the meaning of sexual risk behaviors among gay and bisexual male methamphetamine abusers before and after drug treatment. *AIDS Behav*. 2004;8(1):87-98. doi: 10.1023/B:AIBE.0000017528.39338.75.
6. Drumright LN, Patterson TL, Strathdee SA. Club drugs as causal risk factors for HIV acquisition among men who have sex with men: a review. *Subst Use Misuse*. 2006;41(10-12):1551-601. Epub 2006/09/28. doi: 10.1080/10826080600847894. PubMed PMID: 17002993.
7. Giorgetti R, Tagliabracci A, Schifano F, Zaami S, Marinelli E, Busardò FP. When "chems" meet sex: a rising phenomenon called "chemsex". *Curr Neuropharmacol*. 2017;15(5):762-70. Epub 2016/11/20. doi: 10.2174/1570159x15666161117151148. PubMed PMID: 27855594; PMCID: PMC5771052.
8. Garofalo R, Mustanski BS, McKirnan DJ, Herrick A, Donenberg GR. Methamphetamine and young men who have sex with men: understanding patterns and correlates of use and the association with HIV-related sexual risk. *Arch Pediatr Adolesc Med*. 2007;161(6):591-6. doi: 10.1001/archpedi.161.6.591.
9. Brennan-Ing M, Porter KE, Seidel L, Karpiak SE. Substance use and sexual risk differences among older bisexual and gay men with HIV. *Behav Med*. 2014;40(3):108-15. Epub 2014/08/05. doi: 10.1080/08964289.2014.889069. PubMed PMID: 25090363.
10. Hoenigl M, Chaillon A, Moore DJ, Morris SR, Smith DM, Little SJ. Clear links between starting methamphetamine and increasing sexual risk behavior: a cohort study among men who have sex with men. *J Acquir Immune Defic Syndr*. 2016;71(5):551-7. Epub 2015/11/05. doi: 10.1097/qai.0000000000000888. PubMed PMID: 26536321; PMCID: PMC4788567.
11. Loza O, Curiel ZV, Beltran O, Ramos R. Methamphetamine use and sexual risk behaviors among men who have sex with men in a Mexico-US border city. *Am J Addict*. 2020;29(2):111-9. Epub 2020/01/08. doi: 10.1111/ajad.12985. PubMed PMID: 31908109.
12. Santos G-M, Coffin PO, Das M, Matheson T, DeMicco E, Raiford JL, Vittinghoff E, Dilley JW, Colfax G, Herbst JH. Dose-response associations between number and frequency of substance use and high-risk sexual behaviors among HIV-negative substance-using men who have sex with men

- (SUMSM) in San Francisco. *J Acquir Immune Defic Syndr*. 2013;63(4):540-4. doi: 10.1097/QAI.0b013e318293f10b. PubMed PMID: 23572012.
13. McCarty-Caplan D, Jantz I, Swartz J. MSM and drug use: a latent class analysis of drug use and related sexual risk behaviors. *AIDS Behav*. 2014;18(7):1339-51. doi: 10.1007/s10461-013-0622-x.
 14. Wohl AR, Frye DM, Johnson DF. Demographic characteristics and sexual behaviors associated with methamphetamine use among MSM and non-MSM diagnosed with AIDS in Los Angeles County. *AIDS Behav*. 2008;12(5):705-12. doi: 10.1007/s10461-007-9315-7.
 15. Halkitis PN, Levy MD, Solomon TM. Temporal relations between methamphetamine use and HIV seroconversion in gay, bisexual, and other men who have sex with men. *J Health Psychol*. 2016;21(1):93-9. Epub 2014/03/01. doi: 10.1177/1359105314522675. PubMed PMID: 24578373.
 16. Vu NT, Maher L, Zablotska I. Amphetamine-type stimulants and HIV infection among men who have sex with men: implications on HIV research and prevention from a systematic review and meta-analysis. *J Int AIDS Soc*. 2015;18(1):19273. Epub 2015/01/23. doi: 10.7448/ias.18.1.19273. PubMed PMID: 25609214; PMCID: PMC4302169.
 17. Nerlander LMC, Hoots BE, Bradley H, Broz D, Thorson A, Paz-Bailey G. HIV infection among MSM who inject methamphetamine in 8 US cities. *Drug Alcohol Depend*. 2018;190:216-23. Epub 2018/07/29. doi: 10.1016/j.drugalcdep.2018.06.017. PubMed PMID: 30055426.
 18. Reback CJ, Fletcher JB. Elevated HIV and STI prevalence and incidence among methamphetamine-using men who have sex with men in Los Angeles County. *AIDS Educ Prev*. 2018;30(4):350-6. Epub 2018/08/28. doi: 10.1521/aeap.2018.30.4.350. PubMed PMID: 30148668; PMCID: PMC6298741.
 19. Ostrow DG, Plankey MW, Cox C, Li X, Shoptaw S, Jacobson LP, Stall RC. Specific sex drug combinations contribute to the majority of recent HIV seroconversions among MSM in the MACS. *J Acquir Immune Defic Syndr*. 2009;51(3):349-55. doi: 10.1097/QAI.0b013e3181a24b20. PubMed PMID: 19387357.
 20. Barbee LA, Khosropour CM, Dombrowski JC, Golden MR. New human immunodeficiency virus diagnosis independently associated with rectal gonorrhea and chlamydia in men who have sex with men. *Sex Transm Dis*. 2017;44(7):385-9. Epub 2017/06/14. doi: 10.1097/olq.0000000000000614. PubMed PMID: 28608786; PMCID: PMC5481158.
 21. Katz DA, Dombrowski JC, Bell TR, Kerani RP, Golden MR. HIV incidence among men who have sex with men after diagnosis with sexually transmitted infections. *Sex Transm Dis*. 2016;43(4):249-54. Epub 2016/03/12. doi: 10.1097/olq.0000000000000423. PubMed PMID: 26967302; PMCID: PMC4789769.
 22. Freeman P, Walker BC, Harris DR, Garofalo R, Willard N, Ellen JM, Adolescent Trials Network for HIVAIBT. Methamphetamine use and risk for HIV among young men who have sex with men in 8 US cities. *Arch Pediatr Adolesc Med*. 2011;165(8):736-40. doi: 10.1001/archpediatrics.2011.118. PubMed PMID: 21810635.
 23. Goddard SL, Poynten IM, Petoumenous K, Jin F, Hillman RJ, Law C, Roberts JM, Fairley CK, Garland SM, Grulich AE, Templeton DJ. Prevalence, incidence and predictors of anal Chlamydia trachomatis, anal Neisseria gonorrhoeae and syphilis among older gay and bisexual men in the longitudinal Study for the Prevention of Anal Cancer (SPANC). *Sex Transm Infect*. 2019;95(7):477-83. Epub 2019/04/26. doi: 10.1136/sextrans-2019-054011. PubMed PMID: 31018992.
 24. Sanchez TH, Zlotorzynska M, Sineath RC, Kahle E, Tregear S, Sullivan PS. National trends in sexual behavior, substance use and HIV testing among United States men who have sex with men recruited

- online, 2013 through 2017. *AIDS Behav.* 2018;22(8):2413-25. Epub 2018/06/28. doi: 10.1007/s10461-018-2168-4. PubMed PMID: 29948340.
25. Starks TJ, Millar BM, Lassiter JM, Parsons JT. Preintervention profiles of information, motivational, and behavioral self-efficacy for methamphetamine use and HIV medication adherence among gay and bisexual men. *AIDS Patient Care STDS.* 2017;31(2):78-86. Epub 2017/01/17. doi: 10.1089/apc.2016.0196. PubMed PMID: 28092450; PMCID: PMC5312573.
 26. Lai HH, Kuo YC, Kuo CJ, Lai YJ, Chen M, Chen YT, Chen CC, Yen MY, Hu BS, Wang TH, Wang CC, Kuo LL, Yen TF, Chuang PH, Yen YF. Methamphetamine use associated with non-adherence to antiretroviral treatment in men who have sex with men. *Sci Rep.* 2020;10(1):7131. Epub 2020/04/30. doi: 10.1038/s41598-020-64069-2. PubMed PMID: 32346081; PMCID: PMC7188802.
 27. Cen P, Ye L, Su QJ, Wang X, Li JL, Lin XQ, Liang H, Ho WZ. Methamphetamine inhibits Toll-like receptor 9-mediated anti-HIV activity in macrophages. *AIDS Res Hum Retroviruses.* 2013;29(8):1129-37. Epub 2013/06/12. doi: 10.1089/aid.2012.0264. PubMed PMID: 23751096; PMCID: PMC3715810.
 28. House RV, Thomas PT, Bhargava HN. Comparison of immune functional parameters following in vitro exposure to natural and synthetic amphetamines. *Immunopharmacol Immunotoxicol.* 1994;16(1):1-21. doi: 10.3109/08923979409029897.
 29. Iwasa M, Maeno Y, Inoue H, Koyama H, Matoba R. Induction of apoptotic cell death in rat thymus and spleen after a bolus injection of methamphetamine. *Int J Legal Med.* 1996;109(1):23-8. doi: 10.1007/BF01369597.
 30. Liang H, Wang X, Chen H, Song L, Ye L, Wang SH, Wang YJ, Zhou L, Ho WZ. Methamphetamine enhances HIV infection of macrophages. *Am J Pathol.* 2008;172(6):1617-24. Epub 2008/05/07. doi: 10.2353/ajpath.2008.070971. PubMed PMID: 18458095; PMCID: PMC2408421.
 31. Lawson KS, Prasad A, Groopman JE. Methamphetamine enhances HIV-1 replication in CD4+ T-cells via a novel IL-1 β auto-regulatory loop. *Front Immunol.* 2020;11:136.
 32. Nair MP, Saiyed ZM. Effect of methamphetamine on expression of HIV coreceptors and CC-chemokines by dendritic cells. *Life Sci.* 2011;88(21-22):987-94. Epub 2010/10/12. doi: 10.1016/j.lfs.2010.09.019. PubMed PMID: 20932494; PMCID: PMC3044785.
 33. Nair MPN, Saiyed ZM, Nair N, Gandhi NH, Rodriguez JW, Boukli N, Provencio-Vasquez E, Malow RM, Miguez-Burbano MJ. Methamphetamine enhances HIV-1 infectivity in monocyte derived dendritic cells. *J Neuroimmune Pharmacol.* 2009;4(1):129-39. doi: 10.1007/s11481-008-9128-0.
 34. Papageorgiou M, Raza A, Fraser S, Nurgali K, Apostolopoulos V. Methamphetamine and its immune-modulating effects. *Maturitas.* 2019;121:13-21. Epub 2019/02/02. doi: 10.1016/j.maturitas.2018.12.003. PubMed PMID: 30704560.
 35. Mahajan SD, Hu Z, Reynolds JL, Aalinkeel R, Schwartz SA, Nair MPN. Methamphetamine modulates gene expression patterns in monocyte derived mature dendritic cells. *Mol Diagn Ther.* 2006;10(4):257-69. doi: 10.1007/BF03256465.
 36. Sriram U, Halder B, Cenna J, Gofman L, Potula R. Methamphetamine mediates immune dysregulation in a murine model of chronic viral infection. *Front Microbiol.* 2015;6(793). doi: 10.3389/fmicb.2015.00793.
 37. Harms R, Morsey B, Boyer CW, Fox HS, Sarvetnick N. Methamphetamine administration targets multiple immune subsets and induces phenotypic alterations suggestive of immunosuppression. *PLoS One.* 2012;7(12):e49897. doi: 10.1371/journal.pone.0049897.

38. Peerzada H, Gandhi JA, Guimaraes AJ, Nosanchuk JD, Martinez LR. Methamphetamine administration modifies leukocyte proliferation and cytokine production in murine tissues. *Immunobiology*. 2013;218(8):1063-8. doi: 10.1016/j.imbio.2013.02.001.
39. Mata MM, Napier TC, Graves SM, Mahmood F, Raesi S, Baum LL. Methamphetamine decreases CD4 T cell frequency and alters pro-inflammatory cytokine production in a model of drug abuse. *Eur J Pharmacol*. 2015;752:26-33. Epub 2015/02/14. doi: 10.1016/j.ejphar.2015.02.002. PubMed PMID: 25678251; PMCID: PMC4396630.
40. Potula R, Haldar B, Cenna JM, Sriram U, Fan S. Methamphetamine alters T cell cycle entry and progression: role in immune dysfunction. *Cell Death Discov*. 2018;4(1):44. doi: 10.1038/s41420-018-0045-6.
41. Potula R, Hawkins BJ, Cenna JM, Fan S, Dykstra H, Ramirez SH, Morsey B, Brodie MR, Persidsky Y. Methamphetamine causes mitochondrial oxidative damage in human T lymphocytes leading to functional impairment. *J Immunol*. 2010;185(5):2867. doi: 10.4049/jimmunol.0903691.
42. Loftis JM, Choi D, Hoffman W, Huckans MS. Methamphetamine causes persistent immune dysregulation: a cross-species, translational report. *Neurotox Res*. 2011;20(1):59-68. Epub 2010/10/19. doi: 10.1007/s12640-010-9223-x. PubMed PMID: 20953917; PMCID: PMC3081419.
43. Prakash MD, Tangalakakis K, Antonipillai J, Stojanovska L, Nurgali K, Apostolopoulos V. Methamphetamine: effects on the brain, gut and immune system. *Pharmacol Res*. 2017;120:60-7. doi: 10.1016/j.phrs.2017.03.009.
44. Permpoonputtana K, Govitrapong P. The anti-inflammatory effect of melatonin on methamphetamine-induced proinflammatory mediators in human neuroblastoma dopamine SH-SY5Y cell lines. *Neurotox Res*. 2013;23(2):189-99. doi: 10.1007/s12640-012-9350-7.
45. Kahle EM, Bolton M, Hughes JP, Donnell D, Celum C, Lingappa JR, Ronald A, Cohen CR, de Bruyn G, Fong Y, Katabira E, McElrath MJ, Baeten JM. Plasma cytokine levels and risk of HIV type 1 (HIV-1) transmission and acquisition: a nested case-control study among HIV-1-serodiscordant couples. *J Infect Dis*. 2015;211(9):1451-60. Epub 2014/11/13. doi: 10.1093/infdis/jiu621. PubMed PMID: 25389306; PMCID: PMC4447828.
46. Naranbhai V, Abdool Karim SS, Altfeld M, Samsunder N, Durgiah R, Sibeko S, Abdool Karim Q, Carr WH. Innate immune activation enhances HIV acquisition in women, diminishing the effectiveness of tenofovir microbicide gel. *J Infect Dis*. 2012;206(7):993-1001. Epub 2012/07/26. doi: 10.1093/infdis/jis465. PubMed PMID: 22829639; PMCID: PMC3501691.
47. Feng L, He W, Lin S, Ruan Y, Yuan C, Qiu H, Ren W, He J. The association between interleukin-8 levels and the development of withdrawal symptoms during methamphetamine abstinence. *Hum Psychopharmacol*. 2020:e2736.
48. Kevil CG, Goeders NE, Woolard MD, Bhuiyan MS, Dominic P, Kolluru GK, Arnold CL, Traylor JG, Orr AW. Methamphetamine use and cardiovascular disease: in search of answers. *Arterioscler Thromb Vasc Biol*. 2019;39(9):1739-46.
49. Schürer S, Klingel K, Sandri M, Majunke N, Besler C, Kandolf R, Lurz P, Luck M, Hertel P, Schuler G, Linke A, Mangner N. Clinical characteristics, histopathological features, and clinical outcome of methamphetamine-associated cardiomyopathy. *JACC Heart Fail*. 2017;5(6):435-45. doi: 10.1016/j.jchf.2017.02.017.
50. Lappin JM, Darke S, Farrell M. Stroke and methamphetamine use in young adults: a review. *J Neurol Neurosurg Psychiatry*. 2017;88(12):1079-91.

51. Winslow BT, Voorhees KI, Pehl KA. Methamphetamine abuse. *Am Fam Physician*. 2007;76(8):1169-74. Epub 2007/11/10. PubMed PMID: 17990840.
52. Cohen MS, Council OD, Chen JS. Sexually transmitted infections and HIV in the era of antiretroviral treatment and prevention: the biologic basis for epidemiologic synergy. *J Int AIDS Soc*. 2019;22 Suppl 6(Suppl Suppl 6):e25355. Epub 2019/08/31. doi: 10.1002/jia2.25355. PubMed PMID: 31468737; PMCID: PMC6715951.
53. Cohen MS, Hoffman IF, Royce RA, Kazembe P, Dyer JR, Daly CC, Zimba D, Vernazza PL, Maida M, Fiscus SA, Eron JJ, Jr. Reduction of concentration of HIV-1 in semen after treatment of urethritis: implications for prevention of sexual transmission of HIV-1. *Lancet*. 1997;349(9069):1868-73. Epub 1997/06/28. doi: 10.1016/s0140-6736(97)02190-9. PubMed PMID: 9217758.
54. Price MA, Zimba D, Hoffman IF, Kaydos-Daniels SC, Miller WC, Martinson F, Chilongozi D, Kip E, Msowoya E, Hobbs MM, Kazembe PN, Cohen MS. Addition of treatment for trichomoniasis to syndromic management of urethritis in Malawi: a randomized clinical trial. *Sex Transm Dis*. 2003;30(6):516-22. doi: 10.1097/00007435-200306000-00009. PubMed PMID: 12782954.
55. Blish CA, McClelland RS, Richardson BA, Jaoko W, Mandaliya K, Baeten JM, Overbaugh J. Genital inflammation predicts HIV-1 shedding independent of plasma viral load and systemic inflammation. *J Acquir Immune Defic Syndr*. 2012;61(4):436-40. doi: 10.1097/QAI.0b013e31826c2edd. PubMed PMID: 22878424.
56. Passmore JA, Jaspan HB, Masson L. Genital inflammation, immune activation and risk of sexual HIV acquisition. *Curr Opin HIV AIDS*. 2016;11(2):156-62. Epub 2015/12/03. doi: 10.1097/coh.0000000000000232. PubMed PMID: 26628324; PMCID: PMC6194860.
57. Mayer KH, Venkatesh KK. Interactions of HIV, other sexually transmitted diseases, and genital tract inflammation facilitating local pathogen transmission and acquisition. *Am J Reprod Immunol*. 2011;65(3):308-16. Epub 2011/01/11. doi: 10.1111/j.1600-0897.2010.00942.x. PubMed PMID: 21214660; PMCID: PMC3077541.
58. Burgener A, McGowan I, Klatt NR. HIV and mucosal barrier interactions: consequences for transmission and pathogenesis. *Curr Opin Immunol*. 2015;36:22-30. Epub 2015/07/08. doi: 10.1016/j.coi.2015.06.004. PubMed PMID: 26151777.
59. Henning TR, Butler K, Hanson D, Sturdevant G, Ellis S, Sweeney EM, Mitchell J, Deyoungs F, Phillips C, Farshy C, Fakile Y, Papp J, Evan Secor W, Caldwell H, Patton D, McNicholl JM, N. Kersh E. Increased susceptibility to vaginal simian/human immunodeficiency virus transmission in pig-tailed macaques coinfecting with *Chlamydia trachomatis* and *Trichomonas vaginalis*. *J Infect Dis*. 2014;210(8):1239-47. doi: 10.1093/infdis/jiu240.
60. Kaul R, Pettengell C, Sheth PM, Sunderji S, Biringer A, MacDonald K, Walmsley S, Rebbapragada A. The genital tract immune milieu: an important determinant of HIV susceptibility and secondary transmission. *J Reprod Immunol*. 2008;77(1):32-40. doi: 10.1016/j.jri.2007.02.002.
61. Sanyal A, Shen C, Ding M, Reinhart TA, Chen Y, Sankapal S, Gupta P. *Neisseria gonorrhoeae* uses cellular proteins CXCL10 and IL8 to enhance HIV-1 transmission across cervical mucosa. *Am J Reprod Immunol*. 2019;81(6):e13111. Epub 2019/03/25. doi: 10.1111/aji.13111. PubMed PMID: 30903720; PMCID: PMC6540971.
62. Fox J, Fidler S. Sexual transmission of HIV-1. *Antiviral Res*. 2010;85(1):276-85. Epub 2009/10/31. doi: 10.1016/j.antiviral.2009.10.012. PubMed PMID: 19874852.

63. Bernstein KT, Marcus JL, Nieri G, Philip SS, Klausner JD. Rectal gonorrhea and chlamydia reinfection is associated with increased risk of HIV seroconversion. *J Acquir Immune Defic Syndr*. 2010;53(4).
64. Craib KJ, Meddings DR, Strathdee SA, Hogg RS, Montaner JS, Shaughnessy MV, Schechter MT. Rectal gonorrhoea as an independent risk factor for HIV infection in a cohort of homosexual men. *Genitourin Med*. 1995;71(3):150. doi: 10.1136/sti.71.3.150.
65. Kelley CF, Kraft CS, de Man TJ, Duphare C, Lee HW, Yang J, Easley KA, Tharp GK, Mulligan MJ, Sullivan PS, Bosinger SE, Amara RR. The rectal mucosa and condomless receptive anal intercourse in HIV-negative MSM: implications for HIV transmission and prevention. *Mucosal Immunol*. 2017;10(4):996-1007. doi: 10.1038/mi.2016.97.
66. Vieira VA, Avelino-Silva VI, Cerqueira NB, Costa DA, Costa PR, Vasconcelos RP, Madruga VR, Moreira RI, Hoagland B, Veloso VG, Grinsztejn B, Kallás EG, for the Pr EPBST. Asymptomatic anorectal Chlamydia trachomatis and Neisseria gonorrhoeae infections are associated with systemic CD8+ T-cell activation. *AIDS*. 2017;31(15).
67. Heiligenberg M, Lutter R, Pajkrt D, Adams K, De Vries H, Heijman T, Schim van der Loeff MF, Geerlings S. Effect of HIV and chlamydia infection on rectal inflammation and cytokine concentrations in men who have sex with men. *Clin Vaccine Immunol*. 2013;20(10):1517-23. Epub 2013/08/02. doi: 10.1128/cvi.00763-12. PubMed PMID: 23904458; PMCID: PMC3807186.
68. Fulcher JA, Shoptaw S, Makgoeng SB, Elliott J, Ibarrondo FJ, Ragsdale A, Brookmeyer R, Anton PA, Gorbach PM. Recent methamphetamine use is associated with increased rectal mucosal inflammatory cytokines, regardless of HIV-1 serostatus. *J Acquir Immune Defic Syndr*. 2018;78(1):119-23. Epub 2018/02/09. doi: 10.1097/qai.0000000000001643. PubMed PMID: 29419567; PMCID: PMC5810127.
69. Buchanan JB, Sparkman NL, Johnson RW. A neurotoxic regimen of methamphetamine exacerbates the febrile and neuroinflammatory response to a subsequent peripheral immune stimulus. *J Neuroinflammation*. 2010;7(1):82. doi: 10.1186/1742-2094-7-82.
70. Blair CS, Segura ER, Perez-Brumer AG, Sanchez J, Lama JR, Clark JL. Sexual orientation, gender identity and perceived source of infection among men who have sex with men (MSM) and transgender women (TW) recently diagnosed with HIV and/or STI in Lima, Peru. *AIDS Behav*. 2016;20(10):2178-85. Epub 2016/01/16. doi: 10.1007/s10461-015-1276-7. PubMed PMID: 26767533; PMCID: PMC4945472.
71. Tomkins A, George R, Kliner M. Sexualised drug taking among men who have sex with men: a systematic review. *Perspect Public Health*. 2018;139(1):23-33. doi: 10.1177/1757913918778872.
72. Roll JM. Contingency management: an evidence-based component of methamphetamine use disorder treatments. *Addiction*. 2007;102 Suppl 1:114-20. Epub 2007/05/12. doi: 10.1111/j.1360-0443.2006.01774.x. PubMed PMID: 17493060.
73. Shoptaw S, Reback CJ, Peck JA, Yang X, Rotheram-Fuller E, Larkins S, Veniegas RC, Freese TE, Hucks-Ortiz C. Behavioral treatment approaches for methamphetamine dependence and HIV-related sexual risk behaviors among urban gay and bisexual men. *Drug Alcohol Depend*. 2005;78(2):125-34. Epub 2005/04/23. doi: 10.1016/j.drugalcdep.2004.10.004. PubMed PMID: 15845315.