University of California, Los Angeles
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Clinical Research Protocol

Expression of stress markers in MSM living with HIV receiving contingency management for methamphetamine use disorder (a.k.a. "EXPRESS+")

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Coordinating Center:	UCLA

Approval:

07/08/2022

PI or Sponsor Signature (Name and Title) *Date*

PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing National Institutes of Health with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number:

Protocol Title: Expression of stress markers in MSM living with HIV receiving contingency management for methamphetamine use disorder (a.k.a. "EXPRESS+")

Protocol Date: 07/08/2022

07/08/2022

Investigator Signature *Date*

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Table of Contents

AE	adverse event
CFR	Code of Federal Regulations
CRF	case report form
CTRA	conserved transcriptional response to adversity
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MA	methamphetamine
MSM	men who have sex with men
MUD	methamphetamine use disorder
PI	Principal Investigator
SAE	serious adverse experience
SCID-5	The Structured Clinical Interview for DSM-5
VL	viral load

PROTOCOL SYNOPSIS

TITLE	Expression of stress markers in MSM living with HIV receiving contingency management for methamphetamine use disorder (a.k.a. "EXPRESS+")
SPONSOR	Michael Li, PhD, MPH
FUNDING ORGANIZATION	
NUMBER OF SITES	1
RATIONALE	Determining whether a patient is both feeling better and improving physiologically when treating people living with HIV (PLWH) for methamphetamine use disorder requires identification of a clinically significant measure separate from abstinence. This study will to address this challenge by testing a gene expression (mRNA) pattern identified by the field of social genomics, which may provide insight into both psychosocial health and biological processes that impact chronic disease risk in PLWH receiving MUD treatment.
STUDY DESIGN	This is a within-subjects, two-arm clinical trial with 35 HIV-positive MSM receiving contingency management for treatment of methamphetamine use disorder and 20 HIV-positive MSM serving as a non-substance-using healthy control (N=55 total).
PRIMARY OBJECTIVE	To investigate whether differences in CTRA expression (mRNA) coincide with differences in methamphetamine use and viral load over the course of 12 weeks in HIV-positive MSM with and without methamphetamine use disorder.

SECONDARY OBJECTIVES	• To investigate whether differences in seven psychosocial dimensions of drug addiction (Short Inventory of Problems Revised (SIP-R))—physical, social, intrapersonal, interpersonal, impulse control—are associated with differences in CTRA gene expression. • To conduct an exploratory pilot investigation to determine the degree to which CTRA mediates the association between METH use and viral suppression.
NUMBER OF SUBJECTS	55
SUBJECT SELECTION CRITERIA	**Inclusion Criteria** <u>HIV-positive MSM with MUD in the contingency management condition (N = 35)</u> 1. Assigned male sex at birth 2. 18 to 45 years of age 3. Reports having sex with men in the past 12 months. 4. HIV-positive (confirmed by certification or by HIV rapid test) 5. Has an HIV care provider (last seen in the past 12 months) 6. Has a current antiretroviral prescription 7. Meets the DSM-5 criteria for MUD using SCID-5 8. Urine test is positive for MA within 30 days of their screening visit 9. Seeking treatment for MUD. 10. Ability to attend twice weekly appointments for drug testing and treatment <u>HIV-positive MSM non-substance-using control (N = 20)</u> 1. Assigned male sex at birth 2. 18 to 45 years of age 3. Reports having sex with men in the past 12 months. 4. HIV-positive (confirmed by certification or by HIV rapid test) 5. Has an HIV care provider (last seen in the past 12 months)

	6. Has a current antiretroviral prescription **Exclusion Criteria** HIV-positive MSM with MUD in the contingency management condition (N = 35) 1. Identifies as (cis- or transgender) female 2. Reports another current or past substance use disorder 3. Reports being in another intervention or clinical trial for substance use 4. Positive test for opioids, cocaine, and/or MDMA HIV-positive MSM non-substance-using control (N = 20) 1. Identifies as (cis- or transgender) female 2. Positive test for MA, opioids, cocaine, and/or MDMA. 3. Reports substance use (MA, opioids, cocaine, MDMA, hallucinogens, heavy alcohol use, and/or tobacco) in the past 6 months 4. Reports past or current substance use disorder
BEHAVIORAL INTERVENTION	Those with MUD (MA+/HIV+) will receive contingency management, a positive reinforcement behavioral treatment with escalating rewards for escalating rewards for consecutive negative urine tests, capped at a maximum of $30 per negative result.
CONTROL GROUP	Those in the non-substance-using control condition (MA-/HIV+) will only not receive an intervention. They will only attend four appointments total after their screening to provide blood draws, urine samples, and complete their behavioral surveys.

DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	Each subject will be on study for up to 17 weeks **Screening period:** 1-4 weeks **Baseline assessment:** 1 week **Treatment:** 8 weeks **Follow-up:** 4 weeks after end of treatment The total duration of the study is expected to be 4 years. 1 year of rolling subject recruitment, 1 year for final subject follow-up, 1 year of biospecimen processing, and 1 year of analysis.
CONCOMITANT MEDICATIONS	NONE
EFFICACY EVALUATIONS	
PRIMARY ENDPOINT	• A gene expression (mRNA) pattern called the conserved transcriptional response to adversity (CTRA) will be measured using transcriptome profiling of leukocytes.
SECONDARY ENDPOINTS	• Negative urine tests for methamphetamine • HIV viral load from plasma
OTHER EVALUATIONS	• Plasma concentration of methamphetamine • Short Inventory of Problems Revised (SIP-R) • Sociodemographics – age, race, education level, sexual orientation, housing status, body mass index (BMI), smoking history, and heavy alcohol use history
SAFETY EVALUATIONS	• MA use frequency based on urine tests • HIV viral load • Incidence of adverse events
PLANNED INTERIM ANALYSES	This will be an NIH-funded study through the K01 mechanism. We have just received requested for Just In Time. When approximately

	50% of patients have completed the study through Week 4, an interim analysis for safety will be conducted when 25% of participants complete Week 4. Serious adverse events will be monitored by the investigators on an ongoing basis throughout the study.
STATISTICS	
Primary Analysis Plan	Using a linear mixed effects regression, we will test whether a negative MA urine test is associated with reductions in CTRA contrast scores across four time points—Visits B, 4.2 (Week 4), 8.2 (Week 8), and 12.0 (Week 12 follow-up). We will use a time (days) by MA urine result interaction term to estimate difference in change in CTRA as a function of MA test result. Using a mixed effects logistic regression, we will test whether CTRA expression is associated with viral suppression (<200c/mL) across three time points— Visits B, 4.2 (Week 4), 8.2 (Week 8), and 12.0 (Week 12 follow-up). We will include a time (days) by CTRA expression interaction term to test this association longitudinally.
Rationale for Number of Subjects	Power analysis for this pilot study indicates that a minimum of 135 person-observations will be sufficient to test whether MA use or the psychosocial Short Inventory of Problems (SIP-R) are associated with CTRA expression, assuming a medium effect size of 0.15 and power level of .80. Additionally, a logistic model testing whether CTRA is associated with viral suppression would require a minimum of 154 person-observations, assuming a power level of .80, a CTRA standard deviation of 1.44, mean centering of CTRA, and an odds ratio of 1.5. When modeling viral load as a continuous outcome, 135 person-observations is the minimum to test whether CTRA is associated with viral load (c/mL), assuming a medium effect size of 0.15 and power level of .80. These analyses will include 55 participants over four measurements of CTRA, for a total of 220 person-observations (176 person-observations at 80% retention), which is sufficient for these thresholds.

1 BACKGROUND

Contingency management (CM), which provides incentives that escalate in value for provision of consecutive biomarkers demonstrating drug abstinence, is an effective positive reinforcement approach to promoting abstinence from methamphetamine (MA) and other substances.

1.1 Treatment of methamphetamine use disorder and management of HIV

Use of MA is disproportionately higher among men who have sex with men (MSM) than the general U.S. population (5.9% in HIV-negative MSM and 12.3% in HIV-positive MSM) (1, 2). Chronic MA use is linked to myriad health conditions including psychiatric disorders, cardiovascular disease, social problems, and infectious diseases such as HIV (25). MA use reduces adherence to antiretroviral therapy (ART) and engagement in HIV care (3, 4), and induces immune dysfunction (5). All of these factors can hamper people living with HIV (PLWH) from achieving and sustaining viral suppression, which contributes to forward HIV transmission. Reducing MA use is essential to managing HIV, reducing transmission, and maintaining health in PLWH with MA use disorder (MUD).

There are no effective pharmacological treatments in place for MUD (40). The most robust treatments use behavioral approaches (41-43). Research in substance use intervention has demonstrated that contingency management (CM), which provides incentives that escalate in value for provision of consecutive biomarkers demonstrating drug abstinence, is an effective positive reinforcement approach to promoting abstinence from MA and other substances (6, 43-49). CM is based on the theory that MUD or other substance disorder is due to sustained, high-value drug reinforcement and that providing incentives that compete with drug reinforcement can successfully alter drug taking and produce sustained drug abstinence (15).

1.2 A social transcriptomics perspective on MA treatment and HIV

With support from this K01, I will conduct a pilot investigation to determine whether a neurally regulated “stress” gene expression profile (mRNA) observable in circulating blood cells can serve as a clinically meaningful, non-abstinence-based endpoint for contingency management (CM) for MA use disorder (MUD) in MSM living with HIV. Ensuring that a patient is both feeling better and improving physiologically are fundamental tasks to addiction treatment, yet abstinence alone—based on urine tests—has been the standard clinical outcome for MA treatment (7, 32, 33). However, this outcome is incomplete, especially when seeking to determine whether treatment improved psychosocial health and attenuated the adverse biological processes linking drug use to chronic disease (33). Both of these aspects of health are important to understanding substance use treatment efficacy. Promoting psychosocial health and reducing

distress may be important to long-term recovery from MUD, especially for PLWH with MUD (6, 7). Assessing biological patterns linked to MA use and pathogenesis may help in identifying individuals at particularly high risk for severe addiction and for development of MA-related chronic disease (8, 9). Moreover, the lack of a currently accepted clinical endpoint beyond abstinence may be limiting the number of approved therapies for MUD, yet identification of such an endpoint remains a challenge for researchers (32, 33).

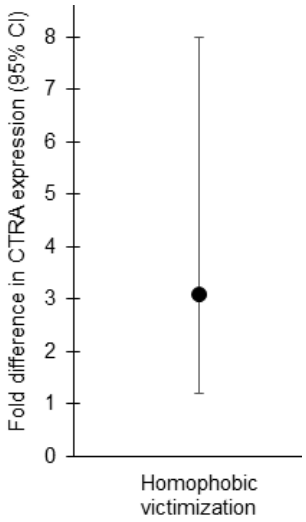

Figure 1. CTRA expression in HIV-negative MSM who experienced homophobic victimization (10)

I propose to assess a gene expression (mRNA) pattern called the conserved transcriptional response to adversity (CTRA), which may provide insight into changes in both psychosocial health and pathogenesis over the course of MA treatment. According to the field of social genomics, the CTRA is an intracellular pattern is marked by upregulated expression of pro-inflammatory genes (i.e., increases in mRNA) and downregulated expression of Type I interferon (IFN-I) and antibody-synthesis genes (i.e., decreases in mRNA) (9, 11-14) in response to negative psychosocial experiences such as emotional distress, isolation, and rejection, as well as compulsive and addictive behaviors (9, 11-14) (see Table 1). In contrast, experiences of eudaimonic well-being and sense of purpose and meaning are associated with low CTRA levels (15, 16). The CTRA is mediated by neurally-induced upregulation of inflammatory transcription factor activity (cAMP response element binding protein (CREB), nuclear factor kappa B (NF-κB), and activator protein 1 (AP-1)), and downregulated activity of interferon responsive transcription factors (IRF), which proximally induce these empirical differences in gene expression. As such, the CTRA profile can be assessed either by quantifying the activity of pre-specified sets of inflammatory and interferon-related genes (i.e., mRNA transcripts), or by bioinformatic measures of transcription factor activation derived from genome-wide transcriptional profiling.

It is important to note that although CTRA measurement involves the use of basic science techniques, its application largely lies in behavioral and psychosocial sciences that aim to expand understanding of the stress-disease relationship (9). Evaluation of this CTRA profile with MA addiction treatment outcomes represents a significant advancement and offers the opportunity to describe health enhancements from treatment beyond that offered solely by behavioral markers of abstinence.

Many of the psychosocial problems that are comorbid with MA use are associated with CTRA expression. Socioeconomic challenges, discrimination, childhood trauma, and interpersonal conflict are associated with chronic MA use in MSM (34, 50-56) and are known drivers of CTRA expression (12, 14, 57-60). My pilot research has shown three-fold elevations

Table 1. CTRA gene expression and transcription factor activation in response to stress vs. well-being

Stress response	Well-being response	Transcription factor	Genes expressed
↑	↓	CREB, NF-κB, AP-1	Inflammatory: IL1A, IL1B, IL6, IL8, TNF, PTGS1, PTGS2, FOS, FOSB, FOSL1, FOSL2, JUN, JUNB, JUND, NFKB1, NFKB2, REL, RELA, and RELB
↓	↑	IRF	Interferon: GBP1, IFI16, IFI27, IFI27L1-2, IFI30, IFI35, IFI44, IFI44L, IFI6, IFIH1, IFIT1-3, IFIT5, IFIT1L, IFITM1-3, IFITM4P, IFITM5, IFNB1, IRF2, IRF7-8, MX1-2, OAS1-3, and OASL Antibody synthesis: IGJ, IGLL1, and IGLL3

in CTRA expression in HIV-negative MSM who experienced homophobic victimization (Figure 1) (10), a problem also comorbid with MA use in MSM (34). The CTRA has also been shown to be related to the development of depressive and anxiety-related disorders (18-22), which are highly comorbid with MA use (23-25). Research on compulsive gaming also may suggest that CTRA is linked to addictive behaviors and dynamics (16). Participants who experienced internet gaming as compulsive

, isolating, or dissatisfying had increases in their CTRA gene expression, while those who felt accomplishment and connectedness with online gamers had low CTRA levels (16).

The CTRA also involves some of same gene regulatory pathways that contribute to MA-related pathogenesis, such as those involving inflammation and innate antiviral responses (particularly relevant to PLWH). Chronic MA use in pre-clinical experiments and stimulation of inflammation using lipopolysaccharide (LPS) was shown to induce anxiety-like and sickness behaviors in adult rats, while neonatal exposure to LPS-induced inflammation was linked to behavioral sensitization to MA self-administration during adulthood (23, 24, 61, 62). Chronic MA use is also associated with increased CREB, AP-1, and NF-κB activation, transcription factors driving CTRA gene expression and likely involved in MA-induced inflammation (8, 28-31). The CTRA has also been epidemiologically linked to inflammatory health problems such as cardiovascular disease (26, 27), a common cause of mortality in people with MUD (63, 64).

Both chronic MA use and comorbid psychosocial problems such as HIV stigma and depression have been linked to the progression of HIV (65-67). One explanation for this may be their impact on poorer ART adherence (68), while another possibility is the mediating role of inflammation and/or impaired antiviral response on viremia (67, 69-73). Prior research has demonstrated that greater cytokine levels and activation of CTRA-related transcription factors such as NF-κB and CREB induce replication of HIV and predict increases in viral load (30, 74-77). Conversely, HIV itself induces chronic inflammation and enhances risk of inflammatory-related health conditions such as cardiovascular disease (78-80) and depression (81). Risk of these inflammatory conditions in PLWH is further exacerbated by comorbid MA use (69, 70).

For these reasons, measuring inflammatory patterns in CTRA may have clinical relevance to management of HIV and related chronic conditions in the context of MA treatment.

However, the impact of IFN-I activity on HIV disease progression is less clear (82, 83). While IFN-I responses to acute HIV are involved in initial reduction of the virus (71, 72), prolonged IFN-1 activation can lead to immune dysregulation and T-cell exhaustion, and in turn, increased viral load (82, 83). As stated previously, CTRA gene expression involves threat/stress-induced increases in inflammatory gene expression and decreases in IFN-1 and antibody gene expression, all of which are markers linked to HIV viral load. Whether physiologic patterns of IFN gene expression underlie the link between psychosocial health and the body's management of HIV warrants investigation.

2 STUDY RATIONALE

There is a need for a biomarker measure than can serve as a clinically meaningful, non-abstinence-based endpoint for contingency management (CM) for MA reduction in HIV-positive MSM with MA use disorder. MA use disorder is frequently comorbid with HIV infection in MSM, and adversely impacts management of HIV. Abstinence determined by urine testing has been the only standard clinical outcome for MA treatment, but provides an incomplete picture of patient recovery. The potential benefit of measuring the CTRA as a biomarker outcome linked to MA abstinence is that this measure may provide insight into both psychosocial health and biological patterns of pathogenesis as MSM living with HIV change their MA use. While MA abstinence is currently the primary outcome for treatment, the CTRA is a valid measure of both biological and psychosocial aspects of health, both of which are important to documenting substance use treatment efficacy. Promoting psychosocial health and reducing distress may be important to long-term recovery from MA use disorder, especially in PLWH (6, 7). Moreover, assessing biological patterns linked to MA use and pathogenesis may help in identifying individuals at particularly high risk for addiction and for development of MA-related chronic disease (8, 9).

Despite the CTRA's scope and nature, CTRA measurement should not be a substitute for directly asking MA-dependent patients how they are feeling/functioning. Rather, CTRA measurement should complement psychosocial self-reports and urine tests in substance use research, because it may help to identify patients who require additional intervention beyond the any single treatment approach (7, 32, 33). Assessing CTRA may also offset inaccuracies in self-report measures caused by limited recall, social desirability bias, power of suggestion, or other misconceptions (9, 32). Methods used to measure CTRA are accessible using common technologies like those used to quantify HIV viral load. Findings from my proposed research

may offer a framework to apply CTRA assessment to the treatment of more generalized populations affected by MUD, or for assessing outcomes in people receiving treatment for other substances such as opioids or other stimulants. Outside of addiction, CTRA assessment may also provide insight into stress-biology processes connecting HIV stigma, mental health problems, and chronic disease, challenges that to extend to broader communities of PLWH (84-86).

2.1 Risk / Benefit Assessment

Risks

Contingency management. Some clinicians may deem the use of monetary incentives to be too tempting for some patients to receive money, who may then go out and purchase drugs. This risk is mitigated by the lack of earnings from not being able to provide a urine sample negative for drug metabolite. That said, all participants are aware that they must abstain for the entire period of 8 weeks to earn the maximum amount, which can then be used to buy consumptive goods such as food, other essential items for their families, or hedonistic goods, such as tickets to movie theaters, to meals at restaurants or for other recreational activities. Most people with MUD seek treatment to improve their lives, for themselves and for their families, and so we will help to incentivize the money to be spent on life-improving factors as opposed to drugs. There is also risk that participants with MUD 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. Li) will discuss participant follow-up care as needed (see Data and Safety Monitoring Plan).

Blood Draws. The risks of the blood draws include pain, lightheadedness, fainting, and on rare occasions, infection. Possible bruising at the site of the needle puncture may also occur, and it will heal and disappear within days (several weeks at most.) Rarely, the vein may clot. The risk and discomfort are slight. Good venipuncture practices reduce the pain and likelihood of bruising and secondary infection. Precautions will be taken with participants who have a history of fainting during blood draws, such as having the patient lie down during the procedure.

Urine testing for substance misuse. There are minimal risks to urine testing that include embarrassment or emotional discomfort following positive urine test results.

Survey assessments. There is minor risk that completion of survey assessments may induce distress. Social consequences of research participation. The PI, Dr. Li, and the study site will make every effort to protect participant's privacy and confidentiality. 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

There is minor risk that completion of survey assessments may induce distress. In such instances, participants will meet with study staff members for debriefing. The PI, Dr. Li, will keep a record of the number and type of cases that require invoking a rescue protocol and discuss these with the Medical Director, Dr. Jesse Clark and mentor Dr. Steve Shoptaw for participant follow-up. Dr. Shoptaw is a licensed psychologist and will be on call in the rare case that mental health intervention is required.

There is a risk that some participants may have a MA addiction that is too severe to be adequately treated on an outpatient basis or that for any reason does not respond to the CM program. At all points during the trial participants have access to treatment facilities instead of or in addition to the CM program. Those 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 specimen collection, survey administration, or the contingency management program that caused harm and/or that affects the risk to all participants in the research will be reported on an annual basis to the IRB.

Potential benefits

Contingency management has been shown to effectively reduce relapse rates in those with substance abuse disorder, yet the specific underlying neurobiological mechanism of action for abstinence using this procedure is currently unknown. While other researchers have examined the effect of strengthening cognitive control of impulses in the executive function system of the prefrontal cortex, contingency management conversely aims to introduce new conditioned schedules within the mesolimbic reward system. Thus, we aim to see whether the receipt of money, as opposed to drugs can become more salient, and thus be linked to function of the reward system in those who have been dependent on MA.

We do not anticipate any benefits to participants in the non-substance-using control condition.

Importance of the knowledge to be gained

Information gathered from this study will help to determine whether socially regulated gene expression can serve as a clinically meaningful, non-abstinence-based endpoint for contingency management (CM) for MUD in MSM living with HIV. The potential benefit of this measure as a non-abstinence endpoint to CM for MUD is that it provides information about both psychosocial health and the underlying stress-biology that exacerbates risk of chronic disease. Both of these aspects of health are important to understanding substance use treatment efficacy on a holistic level. Promoting psychosocial health and reducing distress may be important to long-term recovery from MUD, especially for PLWH with MUD. Assessing molecular patterns

linked to MA use and pathogenesis may help in identifying risk and preventing development of MA-related chronic disease. Moreover, identification of a clinical endpoint beyond abstinence may facilitate future approval of therapies for MUD.

3 STUDY OBJECTIVES

3.1 Primary Objective

To investigate whether changes in CTRA gene expression coincide with changes in MA use and viral load over the course of 12 weeks in HIV-positive MSM with and without MUD.

3.2 Secondary Objectives

- To investigate whether differences in seven psychosocial dimensions of drug addiction (Short Inventory of Problems Revised (SIP-R))—physical, social, intrapersonal, interpersonal, impulse control—are associated with differences in CTRA gene expression.
- To conduct an exploratory pilot investigation to determine the degree to which CTRA mediates the association between MA use and viral suppression.

4 STUDY DESIGN

4.1 Study Overview

The proposed study will be a two-arm clinical trial design of 55 MSM living with HIV, of whom 35 HIV-positive MSM with MUD (MA+/HIV+) will receive contingency management for MA reduction, and 20 HIV-positive, non-substance-using MSM (MA-/HIV+) will participate as a control. There is extensive evidence that CM has greater efficacy than a non-contingent condition in the treatment of MUD (41-44, 46-49, 88), so it may raise ethical concerns to withhold CM from people with MUD who are willing to receive treatment. For this reason, this study uses a control of non-substance using HIV-positive (MA-/HIV+) MSM rather than a non-contingent yoked control of HIV-positive MSM with MUD (89). The use of a non-substance-using HIV-positive control will provide a baseline level of CTRA among HIV-positive MSM who do not have MUD or use other substances, which can be compared against CTRA levels in those with MUD. Screening data will be reviewed to determine subject eligibility. Subjects who meet all inclusion criteria and none of the exclusion criteria will be entered into the study. The following treatment regimens will be used:

- Contingency management twice weekly for 8 weeks, with post-treatment follow-up at Week 12.

- Non-substance-using control will not receive a treatment, but will be evaluated at Baseline, Weeks 4, 8, and 12.

The total duration of subject participation will be 14 weeks. The total duration of the study is expected to be 4 years: 1 year of rolling subject recruitment, 1 year for final subject follow-up, 1 year of biospecimen processing, and 1 year of analysis.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

The primary efficacy endpoint is a gene expression pattern called the conserved transcriptional response to adversity (CTRA), measured using transcriptome profiling of leukocytes. We will test whether this gene expression pattern coincides with changes in MA use and psychosocial domains of addiction severity.

5.2 Secondary Efficacy Endpoints

We will conduct negative urine tests for MA as a measure of abstinence. HIV viral load from will be quantified from plasma.

5.3 Safety Evaluations

We will evaluate patients on MA use patterns using thrice weekly urine tests. Viral load will be taken at baseline, Week 4, Week 8, and Week 12 to determine HIV disease progression. We will report on incidence of adverse events

5.4 Other Evaluations

We will assess psychosocial problems with substance use using the Short Inventory of Problems-Revised (SIP-R). Sociodemographics – age, race, education level, sexual orientation, housing status, body mass index (BMI), smoking history, and heavy alcohol use history.

6 SUBJECT SELECTION

6.1 Study Population

We plan to recruit 55 cisgender men who have sex with men (MSM) aged 18-45 living with HIV (confirmed by certification or by a 5th generation HIV screening assay) who reside in Los Angeles County who enroll into this study. Of these participants, 35 must meet the DSM-5 criteria for methamphetamine (MA) use disorder (MUD) (via Structured Clinical

Interview for DSM-5 (SCID-5)) and have a positive urine test for METH during screening (MA+/HIV+), and 20 participants must qualify as a non-substance-using control (MA-/HIV+).

6.2 Inclusion Criteria

HIV-positive MSM with MUD in the contingency management condition (N = 35)

1. Assigned male sex at birth
2. 18 to 45 years of age
3. Reports having sex with men in the past 12 months.
4. HIV-positive (confirmed by certification or by HIV rapid test)
5. Has an HIV care provider (last seen in the past 12 months)
6. Has a current antiretroviral prescription
7. Meets the DSM-5 criteria for MUD using SCID-5
8. Urine test is positive for MA within 30 days of their screening visit
9. Seeking treatment for MUD.
10. Ability to attend twice weekly appointments for drug testing and treatment

HIV-positive MSM non-substance-using control (N = 20)

1. Assigned male sex at birth
2. 18 to 45 years of age
3. Reports having sex with men in the past 12 months.
4. HIV-positive (confirmed by certification or by HIV rapid test)
5. Has an HIV care provider (last seen in the past 12 months)
6. Has a current antiretroviral prescription

6.3 Exclusion Criteria

HIV-positive MSM with MUD in the contingency management condition (N = 35)

1. Identifies as (cis- or transgender) female
2. Reports another current or past substance use disorder
3. Reports being in another intervention or clinical trial for substance use
4. Positive test for opioids and/or cocaine

HIV-positive MSM non-substance-using control (N = 20)

1. Identifies as (cis- or transgender) female
2. Positive test for MA, opioids, cocaine, and/or MDMA.
3. Reports substance use (MA, opioids, cocaine, MDMA, hallucinogens, heavy alcohol use, and/or tobacco) in the past 6 months
4. Reports past or current substance use disorder

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 HIV (i.e., antiretroviral therapy) is encouraged.

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

This is a non-randomized behavioral trial with a non-substance-using control group. HIV-positive MSM with methamphetamine use disorder who meet the criteria described above will be assigned to the contingency management treatment group. HIV-positive MSM who do not use substances and meet the criteria described above will be assigned to the non-substance-using control group.

8.2 Treatment Schedule

For those with METH use disorder (MA+/HIV+), treatment with CM commences at Visit 1.1, and visits will occur 2x weekly from Weeks 1-8 for regularly urine drug tests (see Table 2). Those in the CM condition will receive escalating rewards for each consecutive negative urine test (Table 2)starting at $10 and capping at $40. Participants will receive a $10 gift card for each visit brief visit where they provide urine tests. Each participant will be allowed to reschedule one appointment 24 hours or more in advance, to take place within 24 hours of the original appointment. Following a missed appointment or relapse, a rapid reset to the participant's highest reward level will take place by the second consecutive negative urine result. Cash compensation will be provided for key assessment visits at Baseline, Weeks 4, 8, and 12 as shown in Table 2.

Table 2. Compensation for study visits and contingent rewards for negative urine tests

	Visit	Cash for Assessment Visit	Gift Card for Urine Test Only Visit	Consecutive Negative Urine Tests	Contingent Reward
Screen	S	$40			
Baseline	B	$50			
Week 1	1.1		$10	1	$10
	1.2		$10	2	$12
Week 2	2.1		$10	3	$14
	2.2		$10	4	$16
Week 3	3.1		$10	5	$18
	3.2		$10	6	$20
Week 4	4.1		$10	7	$22
	4.2	$60		8	$24
Week 5	5.1		$10	9	$26
	5.2		$10	10	$28
Week 6	6.1		$10	11	$30
	6.2		$10	12	$32
Week 7	7.1		$10	13	$34
	7.2		$10	14	$36
Week 8	8.1		$10	15	$38
	8.2	$80		16	$40
Week 12	12.0	$100			
	Subtotal	$330	$140		$400

Those in the non-substance-using control condition (MA-/HIV+) will only attend four appointments total after their screening—one appointment each week at baseline, and Weeks 4, 8, and 12. At these appointments, MA-/HIV+ controls will provide blood draws, urine samples, and complete their behavioral surveys. They will receive attendance compensation at these key visits identical to the CM group (Table 2).

8.3 Measures of Treatment Compliance

Treatment compliance will be based on attendance and urine drug tests, thrice weekly for 8 weeks. Each participant will be allowed to reschedule one appointment 24 hours or more in advance, to take place within 24 hours of the original appointment. Missed visits will be counted as a positive drug test. We will use the in vitro urine drug testing for rapid, simultaneous detection of MA, amphetamine, cocaine, opioids, and MDMA in urine.

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.

9.1 Clinical Assessments

9.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at Screening, Baseline, and at Visits 4.2, 8.2, and 12.0. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.2 Demographics

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

9.1.3 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 drug will be recorded on the case report form (CRF).

9.2 Clinical Laboratory Measurements

9.2.1 Urine drug testing

We will use in vitro urine drug testing for rapid, simultaneous detection of MA, amphetamine, cocaine, opioid, and MDMA in urine. At their screening visit and baseline visit (the week prior to intervention start), participants will provide a urine sample for drug testing. From Week 1 to Week 8, urine drug tests will be conducted 2x a week. One final urine drug test will be taken Week 12. Each participant will be allowed to reschedule one appointment 24 hours or more in advance, to take place within 24 hours of the original appointment. Prior to providing the urine specimen, participants empty their pockets and leave bags with a clinic staff member. To minimize attempts to provide false specimens, the participant will provide the urine sample while the pass-through specimen cabinet is open, prior to washing his hands. A temperature strip will verify the sample was provided in real-time, near body temperature.

9.2.2 HIV viral load

We will quantify viral load as count per milliliter of blood based on HIV RNA obtained from blood samples, and obtained at Visits B, 4.2, 8.2, and 12.0 (see Table 2). We will also compute a dichotomous variable of viral suppression, set at less than 200 c/mL.

9.2.3 COVID-19 immunoassay

We will conduct testing for SARS-CoV-2 (COVID-19) nucleocapsid at baseline and Visit 8.2 (Week 8) as part of health monitoring and to assess for confounding by COVID-19 infection either before or during the study.

9.3 Research Laboratory Measurements

9.3.1 Leukocyte Transcriptome Profiling – Conserved transcriptional response to adversity (CTRA)

Biomarkers of immune functioning will be measured based on leukocyte transcriptome profiling from PBMCs. To quantify abundance of genes expressed, my collaborators and I will conduct

supervised transcriptional profiling of participants from PBMCs using methods previously established and validated procedures of CTRA profiling (11, 90). Blood draws will be obtained via venipuncture at 4 visits: Baseline, Visit 4.2 (Week 4), Visit 8.2 (Week 8), and Visit 12.0 (Week 12). PBMCs will be extracted at an external laboratory and stored at -70°C. The PBMC samples will be transferred to our clinical collaborators, Dr. Steven Cole and the UCLA Social Genomics Core Laboratory, where mRNA will be extracted using Qiagen RNeasy standard methods, converted to cDNA libraries using the mRNA-targeted Lexogen QuantSeq 3' FWD enzyme system, and sequenced on an Illumina HiSeq 4000 instrument in the UCLA Neuroscience Genomics Core Laboratory, all following the manufacturers' standard protocols. Sequencing will target >10 million 65 nt forward strand reads per sample, which will be mapped to the human transcriptome using the STAR aligner, quantified as gene transcripts per million mapped reads, log2-transformed for analysis, and further normalized if needed to standardize the expression of 11 pre-established housekeeping gene transcripts (91).

10 EVALUATIONS BY VISIT

Below is the schedule of study elements by study arm (i.e., contingency management group vs. non-substance using control (Table 3). Both groups have a screening and baseline visit.

Table 3. Schedule of study elements by study arm

	Visit																		
Element	**S**	**B**	**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**	**8.1**	**8.2**	**12.0**
SCID-5	▲◊																		
Screening survey and locator form	▲◊																		
Urine drug test (MA, AMP, opioids, MDMA, cannabis)	▲◊	▲◊	▲	▲	▲	▲	▲	▲	▲	▲◊	▲	▲	▲	▲	▲	▲	▲	▲◊	▲◊
Record/review HIV medications	▲◊	▲◊								▲◊								▲◊	▲◊
HIV rapid test or certification	▲◊																		
Contingent Rewards			▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Plasma (for Viral load)		▲◊								▲◊								▲◊	▲◊
PBMC (for transcriptome profiling)		▲◊								▲◊								▲◊	▲◊

Serum (for COVID-19 immunoassay)		▲◊																▲◊	
Behavioral survey		▲◊								▲◊								▲◊	▲◊
▲ = Contingency management (CM) for HIV-positive MSM with METH use disorder. ◊ = Non-substance-using control of HIV-positive MSM.																			

I. Those in the Contingency Management group will have the following visit activities:

10.1 Screening (Visit S)

1. Review the study with the subject and obtain written informed consent
2. Assign the subject a unique screening number
3. Screening survey (self-reported demographics, behavior, and health data) and locator form
4. Urine drug screening (participants must have a positive MA test within 30 days of this screening visit)
5. Receive certification of HIV diagnosis or HIV rapid test
6. Record HIV medications based on bottle(s) brought by participant
7. Perform SCID-5 for DSM-5 diagnosis of methamphetamine use disorder
8. Assign subject to contingency management or non-substance-using control.
9. If necessary, participants may return within 30 days to complete any screening elements if not possible to complete in the main screening visit.

10.2 Baseline (Visit B, one week before Visit 1.1)

1. Urine drug test
2. Behavioral survey
3. Blood draws (~50 mL total) for:
    a. PBMCs for transcriptome profiling (~34 mL)
    b. HIV viral load (~6 mL)
    c. COVID-19 immunoassay (~8.5 mL)
4. HIV medications review
5. Measure weight and height
6. Record any adverse events

10.3 Weeks 1-3 (Visits 1.1-3.2)

1. Urine drug test
2. Contingent rewards for negative urine test

10.4 Week 4 (Visits 4.1-4.2)

Visit 4.1

1. Urine drug test
2. Contingent rewards for negative urine test

Visit 4.2

1. Urine drug test
2. Contingent rewards for negative urine test
3. Behavioral survey
4. Blood draws (~40 mL total) for:
    a. PBMCs for transcriptome profiling (~34 mL)
    b. HIV viral load (~6 mL)
5. HIV medications review
6. Record any adverse events

10.5 Weeks 5-7 (Visits 5.1-7.2)

1. Urine drug test
2. Contingent rewards for negative urine test

10.6 Week 8 (Visits 8.1-8.2)

Visit 8.1

1. Urine drug test
2. Contingent rewards for negative urine test

Visit 8.2

1. Urine drug test
2. Contingent rewards for negative urine test
3. Behavioral survey
4. Blood draws (~50 mL total) for:
    a. PBMCs for transcriptome profiling (~34 mL)
    b. HIV viral load (~6 mL)
    c. COVID-19 immunoassay (~8.5 mL)

5. HIV medications review
6. Record any adverse events

10.7 Week 12 (Visit 12.0)

1. Urine drug test
2. Behavioral survey
3. Blood draws (~40 mL total) for:
    a. PBMCs for transcriptome profiling (~34 mL)
    b. HIV viral load (~6 mL)
4. HIV medications review
5. Record any adverse events

10.8 Early withdrawal appointment

1. Record any adverse events
2. Record reason for withdrawal if initiated by 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., phone or email)

II. <u>Those in the Non-substance-using Control group will only have 4 visits, which will have the same components listed below:</u>

10.9 Baseline, Week 4, Week 8, and Week 12 (Only control group)

1. Urine drug test
2. Behavioral survey
3. Blood draws (~50 mL total) for:
    a. PBMCs for transcriptome profiling (~34 mL)
    b. Plasma for HIV viral load (~6 mL)
    c. Serum for COVID-19 immunoassay (~8.5 mL)
4. HIV medications review
5. Record any adverse events

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 a pharmaceutical product 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 investigational product, whether or not related to that investigational product. An unexpected AE is one of a type not identified in nature, severity, or frequency in the current Investigator's Brochure or of greater severity or frequency than expected based on the information in the Investigator's Brochure.

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

AE severity will be based on the table below.

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 Behavioral Intervention

The risk of monetary rewards exacerbating meth use disorder is unlikely because participants cannot get money unless you test negative for drugs. A participant can only get the full amount of money if they abstain for all 8 weeks, so it is unlikely that the rewards will support further drug use. This money can be used to buy essential items, things to help family and friends, and things for enjoyment like restaurant meals and move tickets. Most people with METH dependence seek treatment to improve their lives, for themselves and for their families, and so we will help to incentivize the money to be spent on life-improving factors as opposed to drugs. There is also some risk that participants will not improve or possibly worsen during treatment, but because this is not a drug or biomedical treatment, it is difficult to attribute any adverse health events to the contingency management intervention. The relationship of an AE to the behavioral intervention should be assessed using the following the guidelines in Table 2.

Table 2. AE Relationship to Treatment

Relationship to Intervention	Comment
Possibly	There is no study drug. 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 drug) 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

Jesse Clark, MD should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Phone: 310-557-2273

Pager: Call (310) 825-6301, provide operator with pager number 24690.

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Behavioral Intervention

A subject may be discontinued from the contingency management intervention at any time if the subject, the investigator, or the Sponsor 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
- Sponsor request for early termination of study

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, the investigator, or the Sponsor 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 Visit 5.2) should have an early discontinuation visit, especially if initiated by the investigator. Refer to Section 10 for early termination procedures. Subjects who withdraw after Visit 5.2 should be encouraged to come in for a final visit (and the procedures to be followed would include those for their next scheduled visit).

12.4 Replacement of Subjects

Subjects who withdraw from the study before Visit 5.2 will be replaced.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor 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. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

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 by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

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 Principal Investigator (Dr. Li), and key personnel will monitor the practical aspects of 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 IRB of the University of California, Los Angeles (UCLA) (a.k.a., Office of the Human Research Protection Program (OHRPP)), and will use secure, HIPAA-compliant technology per UCLA Health Sciences information and technology (DGIT) standards. Dr. Li and key personnel will communicate regularly with UCLA OHRPP for coordinated review of ethical practices, safety procedures, and adherence to confidentiality/privacy agreements.

Dr. Li will prepare administrative reports every month or more frequently as requested describing study progress including the following to review with primary mentor, Dr. Shoptaw, and co-mentor Dr. Clark:

- Actual versus expected enrollment figures
- Demographic and clinical characteristics
- Missing visits and case report forms
- Number and type of clinically significant/adverse events (CSEs), AEs and UPs
- 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

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

15.1 Data Sets Analyzed

All eligible patients who are enrolled into the study and attend the first study visit (the Safety Population) will be included in the safety analysis.

15.2 Demographic and Baseline Characteristics

Sociodemographic and behavioral covariates will include age, race, education level, sexual orientation, employment, income, body mass index (BMI) which is a known risk factor for inflammatory gene expression and a standard biological covariate in social genomics analysis (11, 98-100), smoking history, heavy alcohol use history.

15.3 Analysis of Primary Endpoint

Using mixed effects linear regression and marginal plots, we will estimate, graph, and compare trajectories of CTRA gene expression between those with methamphetamine use disorder in the contingency management (MA+/HIV+) and non-substance-using control (MA-/HIV+) conditions.

15.4 Analysis of Secondary Endpoints

Using two separate mixed effects logistic regressions and marginal plots, we will estimate, graph, and compare probabilities of a negative urine test and viral suppression over time between those with methamphetamine use disorder in the contingency management (MA+/HIV+) and non-substance-using control (MA-/HIV+) conditions.

15.5 Interim Analysis

Interim analysis will take place on the primary and secondary endpoints after all participants complete of Week 4 of the study using the modeling approaches described above. Additionally, an interim analysis for safety will be conducted when 25% of participants complete Week 4.

15.6 Multivariate Analysis for Associations Between Endpoints

Associations between MA use, CTRA gene expression, and viral suppression. All models in Aim 1 will adjust for age, race, education, employment, housing, and mRNA encoding markers of major leukocyte subsets (e.g., CD4). We will also assess for confounding by COVID-19 infection detected by immunoassay, liver function, and type of ART prescription. MA use and CTRA. Using a linear mixed effects regression, we will test whether a negative MA urine test is associated with reductions in CTRA contrast scores across four time points—Visits B, 4.2, 8.2, and 12.0. We will use a time (days) by MA urine result interaction term to estimate difference in change in CTRA as

a function of MA test result. CTRA and viral load. Using a mixed effects logistic regression, we will test whether CTRA gene expression is associated with viral suppression (<200c/mL) across three time points—Visits B, 4.2, 8.2, and 12.0. We will include a time (days) by CTRA gene expression interaction term to test this association longitudinally. We will also test whether CTRA and viral load are reciprocally associated using dynamic panel data modeling with maximum likelihood (102-104). This approach will allow us to simultaneously test whether CTRA is associated with viral load at subsequent observations, and account for whether CTRA is affected by prior values of viral load (102-104).

Associations between psychosocial indicators of substance use severity and CTRA. Using a linear mixed effects regression, I will test whether the seven domains of the Addiction Severity Index (ASI) is associated with reductions in CTRA contrast scores across four time points—Visits B, 4.2, 8.2, and 12.0. I will use a time (days) by ASI domain score interaction term to estimate change in CTRA as a function of changes in ASI scoring. We will control for age, race, education, and mRNA markers of major leukocyte subsets.

Indirect associations between MA use, CTRA, and viral suppression. I will use propensity scores to test the degree to which CTRA mediates the association between MA use and viral suppression (105, 106). The general theory is that we would compute propensity score for CTRA—the probability of having a particular CTRA level—to compare participants who used MA with those who would have had the same value of the CTRA had they used MA.

15.7 Sample Size and Randomization

This study will enroll 55 participants, who will be evaluated for the course of 14 weeks, including screening. Power analysis for this pilot study indicates that a minimum of 135 person-observations will be sufficient to test whether MA use or the psychosocial Addiction Severity Index (ASI) are associated with CTRA gene expression, assuming a medium effect size of 0.15 and power level of .80. Additionally, a logistic model testing whether CTRA is associated with viral suppression would require a minimum of 154 person-observations, assuming a power level of .80, a CTRA standard deviation of 1.44, mean centering of CTRA, and an odds ratio of 1.5. When modeling viral load as a continuous outcome, 135 person-observations is the minimum to test whether CTRA is associated with viral load (c/mL), assuming a medium effect size of 0.15 and power level of .80. These analyses will include 55 participants over four measurements of CTRA, for a total of 220 person-observations (176 person-observations at 80% retention), which is sufficient for these thresholds.

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 treated with the study drug.

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 by the Sponsor (or designee), but will be identified by a site name, subject number and initials.

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 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 of the Sponsor (or designee), 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.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

16.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and 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/name, subject number and subject initials will identify all study subjects on CRFs and other documentation submitted to the Sponsor. 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, except as necessary for monitoring by the FDA. 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 PI: Li. 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, Investigator's Brochure, 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 transmitted by the Investigator to the Sponsor or designee 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 provide the documents to the Sponsor or designee for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Sponsor and 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 send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (or designee) 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 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 among the study Sponsor and 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 IND 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. COMPENSATION AND REWARDS

Compensation for study visits and contingent rewards for negative urine tests

	Visit	Cash for Assessment Visit	Gift Card for Urine Test Only Visit	Consecutive Negative Urine Tests	Contingent Reward
Screen	S	$40			
Baseline	B	$50			
Week 1	1.1		$10	1	$10
	1.2		$10	2	$12
Week 2	2.1		$10	3	$14
	2.2		$10	4	$16
Week 3	3.1		$10	5	$18
	3.2		$10	6	$20
Week 4	4.1		$10	7	$22
	4.2	$60		8	$24
Week 5	5.1		$10	9	$26
	5.2		$10	10	$28
Week 6	6.1		$10	11	$30
	6.2		$10	12	$32
Week 7	7.1		$10	13	$34
	7.2		$10	14	$36
Week 8	8.1		$10	15	$38
	8.2	$80		16	$40
Week 12	12.0	$100			
	Subtotal	$330	$140		$400

APPENDIX 2. STUDY ELEMENTS

Schedule of study elements by study arm and visit number

	Visit																		
Element	**S**	**B**	**1.1**	**1.2**	**2.1**	**2.2**	**3.1**	**3.2**	**4.1**	**4.2**	**5.1**	**5.2**	**6.1**	**6.2**	**7.1**	**7.2**	**8.1**	**8.2**	**12.0**
SCID-5	▲◊																		
Screening survey and locator form	▲◊																		
Urine drug test (MA, AMP, opioids, MDMA, cannabis)	▲◊	▲◊	▲	▲	▲	▲	▲	▲	▲	▲◊	▲	▲	▲	▲	▲	▲	▲	▲◊	▲◊
Record/review HIV medications	▲◊	▲◊								▲◊								▲◊	▲◊
HIV rapid test or certification	▲◊																		
Contingent Rewards			▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲	▲
Plasma (for Viral load)		▲◊								▲◊								▲◊	▲◊
PBMC (for transcriptome profiling)		▲◊								▲◊								▲◊	▲◊
Serum (for COVID-19 immunoassay)		▲◊																▲◊	
Behavioral survey		▲◊								▲◊								▲◊	▲◊
▲ = Contingency management (CM) for HIV-positive MSM with METH use disorder. ◊ = Non-substance-using control of HIV-positive MSM.																			

UNIVERSITY OF CALIFORNIA LOS ANGELES
CONSENT TO PARTICIPATE IN RESEARCH

Expression of stress markers in MSM living with HIV receiving contingency management for methamphetamine use disorder (a.k.a. "EXPRESS+")

Short Title: EXPRESS+

INTRODUCTION

Michael Li, PhD, UCLA Vine Street Clinic, and the UCLA Center for Behavioral and Addiction Medicine are conducting a research study on methamphetamine treatment and its impact on immune function and mental health. This study is being funded by the National Institute on Drug Abuse (NIDA), which is part of the National Institutes of Health.

Research studies are voluntary and include only people who choose to take part. Please take your time about deciding whether to participate in this study. Before deciding, you can:

- Discuss this study with family and friends
- Discuss it with a regular physician or request a second opinion

If you have any questions, you can ask the researchers for more information before deciding to participate. Contact information is provided at the end of this document.

KEY INFORMATION:

The following is a short summary of this study to help you decide whether or not to be a part of this study. More detailed information is listed later on in this form.

WHY AM I BEING INVITED TO TAKE PART IN A RESEARCH STUDY?

We invite you to take part in a research study because you:

- were assigned male at birth and do not identify as (cis- or transgender) female
- are between 18 and 45 years of age
- reports having sex with men in the past 12 months
- are HIV-positive
- have an HIV care doctor who you saw in the past 12 months
- have a current prescription for HIV medication

To receive treatment for meth use in this study, you must:

- be willing to participate in a behavioral treatment, which involves 2 visits a week for 8 weeks
- meet the diagnosis for meth use disorder
- have a positive urine test for meth
- NOT be in treatment for another substance disorder
- NOT have another past or current substance use disorder (i.e., other than meth)
- test negative for opioids and cocaine

To be a part of the non-substance using group, you must:

- test negative for meth, opioids, cocaine, and MDMA
- report NO substance use (meth, opioids, cocaine, MDMA, hallucinogens, heavy alcohol and/or tobacco) in the past 6 months
- report NO past or current substance use disorder

WHAT SHOULD I KNOW ABOUT A RESEARCH STUDY?

- Someone will explain this research study to you.
- Whether or not you take part is up to you.
- You can choose not to take part.
- You can agree to take part and later change your mind.
- Your decision will not be held against you.
- You can ask all the questions you want before you decide.
- You can discuss this study with friends and family.
- You can also discuss it with your health care doctor or request a second opinion.

WHY IS THIS RESEARCH BEING DONE?

It is important to understand whether a patient is feeling better and whether their health is improving as they go through treatment for methamphetamine use disorder. This is especially important in people living with HIV impacted by meth use. This study uses a behavioral treatment called “contingency management”, which motivates and rewards quitting meth. This study will look also at immune markers in the blood to see how the immune system reacts to treatment.

HOW LONG WILL THE RESEARCH LAST AND WHAT WILL I NEED TO DO?

We expect that you will be in this research study for 14 weeks. If you qualify for treatment for meth use disorder, you will visit the clinic 2 days a week for 8 weeks during treatment, then come back for a check-up 4 weeks after the end of treatment. You have a urine test at each visit. You will get a blood test and take a survey at 4 of those visits.

If you do not use any drugs and qualify for the control group, you will only have 4 visits, about 4 weeks apart. At these visits, you will get a urine test, blood test, and take a survey.

More detailed information about the study procedures can be found under *“*WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?*”*

WHAT KINDS OF RISKS OR DISCOMFORTS COULD I EXPECT?

Contingency management: Some people may think that rewarding patients with money for abstaining from drugs is too tempting, and will be used to purchase drugs. This risk is unlikely because you cannot get money unless you test negative for drugs. That said, you can only get the full amount of money if you abstain for all 8 weeks. This money can be used to buy essential items, things to help family and friends, and things for enjoyment like restaurant meals and

move tickets. Most people with METH dependence seek treatment to improve their lives, for themselves and for their families, and so we will help to incentivize the money to be spent on life-improving factors as opposed to drugs. There is also some risk that you will not improve or possibly worsen during treatment. We will refer you to additional services if they require further care following the study and discuss this plan with Dr. Li as needed.

Blood draws. The risks of the blood draws include pain, lightheadedness, fainting, and on rare occasions, infection. Possible bruising at the site of the needle puncture may also occur, and it will heal and disappear within days (several weeks at most.) Rarely, the vein may clot. The risk and discomfort are slight. Good venipuncture practices reduce the pain and likelihood of bruising and secondary infection. Precautions will be taken with you if you have a history of fainting during blood draws, such as having the patient lie down during the procedure.

Urine testing for substance use: There are minimal risks to urine testing that include embarrassment or emotional discomfort following positive urine test results.

Survey assessments: There is minor risk that completion of survey assessments may induce distress.

Social consequences of research participation: Dr. Li and the research team will make every effort to protect your privacy and confidentiality. 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 other people. All guidelines for the protection of Personal Health Identifiers will be followed.

ARE THERE ANY BENEFITS IF I PARTICIPATE?

Contingency management has been shown to effectively reduce relapse rates in those with meth use disorder, yet the specific way this affects the brain is not fully understood. We aim to see whether money can be more appealing than drugs, and activate the brain's rewards system in those who have been dependent on methamphetamine. We do not anticipate any benefits to participants in the non-substance-using control condition.

Information gathered from this study will help identify other ways to monitor response to meth treatment besides just abstinence. This study will look at immune markers in the blood, which may help clinicians and scientist monitor risk of disease and improvement in the body. Also, having another way to measure treatment response may help in the approval of new therapies for meth use disorder.

WHAT OTHER CHOICES DO I HAVE IF I DO NOT WANT TO PARTICIPATE?

Your participation in this research is voluntary. If you choose not to participate, this will not affect your relationship with your doctor or your access to other services. If you choose to participate now, you can change your mind and withdraw from the study at any time.

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

55 people will take part in this study at UCLA.

WHAT WILL HAPPEN IF I TAKE PART IN THIS STUDY?

Before you begin the study:
Before you begin the study, you will need to review this form carefully, ask any questions, and sign this form.

During the study:

Screening (Visit S)
If you agree to participate in this study, you will continue with the Screening. This will take about 1-2 hours, and include the following:

- Confirm HIV status based on paperwork or HIV rapid test (oral swab optional)
- Urine drug test
- Short survey about your background, behavior, and mental and physical health
- Interview about your meth use (only if you report a meth use problem)
- Record HIV medications and doctor
- A research associate may suggest scheduling you again within 30 days of this screening visit to complete any activities that could not be feasibly completed at this visit.

Baseline (Visit B)
This visit will take about 1-2 hours, and include the following:

- Urine drug test
- Blood draws (50 mL total) to check:
    - HIV viral load (6 mL)
    - Immune functioning (34 mL)
    - Past COVID-19 infection (8.5 mL)
- Detailed survey about your background, behavior, and mental and physical health
- Review of HIV medications

If you meet the criteria for treatment of meth use disorder you will have standard contingency management visits for treatment. These should be brief and take between 20-40 minutes. You will have 2 visits a week (Monday + Thursday or Tuesday + Friday) for 8 weeks, which will include the following:

- Urine drug test. You will get a $10 gift card for providing a urine test at these visits, regardless of the result.
- Cash reward for negative tests. You will get $10 for your first negative drug test. For each negative test you get in a row, the reward will increase by $2, capped at a maximum of $40 per negative test. If you get a positive drug test or miss a visit, you will not get a cash reward and the next reward will reset to $10. Your reward level will go back to your highest level by the second negative test in a row. You are allowed to reschedule 1 visit with 24 hours or more notice, which must take place within 24 hours of the original appointment.

The second visit of Week 4. You will have:

- Urine drug test
    - If in the contingency management group, this includes rewards for negative urine tests as described above.
- Blood draws (40 mL total) to check:
    - HIV viral load (6 mL)
    - Immune functioning (34 mL)

- Detailed survey about your background, behavior, and mental and physical health
- Review of HIV medications

The second visit of Week 8. You will have:

- Urine drug test
  - If in the contingency management group, this includes rewards for negative urine tests as described above.
- Blood draws (~50 mL total) to check:
  - HIV viral load (6 mL)
  - Immune functioning (34 mL)
  - Past COVID-19 infection (8.5 mL)
- Detailed survey about your background, behavior, and mental and physical health
- Review of HIV medications

Week 12 follow-up. Four weeks after the last day of treatment, you will have one last check-up visit with:

- Urine drug test
- Blood draws (40 mL) to check:
  - HIV viral load (6 mL)
  - Immune functioning (34 mL)
- Detailed survey about your background, behavior, and mental and physical health
- Review of HIV medications

The study procedures include routine tests for treating and monitoring your condition and the results of these routine tests will be provided to you.

CAN THE RESEARCHERS REMOVE ME FROM THIS STUDY?

The researchers may end your participation in this study for a number of reasons, such as if your safety and welfare are at risk, if you do not follow instructions or if you miss scheduled visits. The researchers or the study sponsor might also decide to stop the study at any time.

If you decide to stop being in the study, or are removed from the study, or the study is stopped the researcher may ask you to come in for one final visit or complete an exit interview over the phone.

HOW WILL INFORMATION ABOUT ME AND MY PARTICIPATION BE KEPT CONFIDENTIAL?

The researchers will do their best to make sure that your private information is kept confidential. Information about you will be handled as confidentially as possible, but participating in research may involve a loss of privacy and the potential for a breach in confidentiality. Study data will be physically and electronically secured. As with any use of electronic means to store data, there is a risk of breach of data security.

Use of personal information that can identify you:

All data collection procedures will take place at the UCLA Vine Street Clinic. Each blood sample, urine sample, and survey response will be given a unique identifier code, which will link separately to personal information such as the participant's name, date of birth, contact information, and visit notes.

How information about you will be stored:
Paper copies of this highly confidential information will be maintained in locked storage, accessible to key research personnel in at UCLA Vine Street Clinic, and given the ID code as a reference. All assayed samples will refer to the ID code only, and personal information will be kept separately in secure storage within a locked medical record room. Blood draws of 125 mL will be taken via venipuncture and labeled with the UIC. PBMCs will be extracted, ID code labeled, and stored at -70°C at UCLA Vine Street Clinic's biorepository. The PBMC samples will be transferred our clinical collaborators, Dr. Steven Cole and the UCLA Social Genomics Core Laboratory for assaying. Urine samples will also be ID code-labeled and tested for simultaneous detection of METH, cocaine, opiates, and cannabis in urine using in vitro drug screen by CLIA-waived, Inc. Electronic survey data will refer to the ID code, and will be saved in a password protected folder on external back-up hardware, accessible only to key research personnel while data are being collected. Datasets used for statistical analysis will only refer to the ID code.

People and agencies that will have access to your information:

The research team, authorized UCLA personnel, the study sponsor, and regulatory agencies such as the Food and Drug Administration (FDA), may have access to study data and records to monitor the study. Research records provided to authorized, non-UCLA personnel will not contain identifiable information about you. Publications and/or presentations that result from this study will not identify you by name.

Employees of the University may have access to identifiable information as part of routine processing of your information, such as lab work or processing payment. However, University employees are bound by strict rules of confidentiality.

How long information from the study will be kept:

The researchers intend to keep the research data and records until the study is over and then transfer the data to a research database, which will be kept indefinitely for future research. This database will be housed by the UCLA Center for Behavioral and Addiction Medicine in a locked UCLA Health Secure hard drive and/or UCLA Health Secure cloud storage.

USE OF DATA AND SPECIMENS FOR FUTURE RESEARCH

My data and/or specimens, including de-identified data and/or specimens may be kept for use in future research.

WILL I BE PAID FOR MY PARTICIPATION?

You will be compensated for your time and effort for study visits in cash or gift card equivalent, for the following visits:

- $40 for Screening
- $50 for Baseline

- $60 for Week 4 (for those getting contingency management, Friday, Visit 4.2)
- $80 for Week 8 (for those getting contingency management, Friday, Visit 8.2)
- $100 for Week 12 (follow-up)

Use of My Specimens:

- Any specimens (e.g., blood, urine) obtained for the purposes of this study will become the property of the University of California. Once you provide the specimens you will not have access to them. The University may share your specimens in the future with other researchers or outside institutions. Information that identifies you will not be shared with anyone outside of UCLA. The specimens will be used for research and such use may result in inventions or discoveries that could become the basis for new products or diagnostic or therapeutic agents. In some instances, these inventions and discoveries may be of potential commercial value and may be patented and licensed by the University. You will not receive any money or other benefits derived from any commercial or other products that may be developed from use of the specimens.

WHO CAN I CONTACT IF I HAVE QUESTIONS ABOUT THIS STUDY?

The Research Team:
You may contact Dr. Michael Li at (310) 794-8530 with any questions or concerns about the research or your participation in this study. Additionally, you may contact mSTUDY staff at the UCLA Vine Street Clinic at (323) 461-3106 with any questions or concerns.

UCLA Office of the Human Research Protection Program (OHRPP):
If you have questions about your rights while taking part in this study, or you have concerns or suggestions and you want to talk to someone other than the researchers about the study, you may contact the UCLA OHRPP by phone: (310) 206-2040; by email: participants@research.ucla.edu or U.S. mail: UCLA OHRPP, Box 951406, Los Angeles, CA 90095-1406.

Public Information about this Study:
ClinicalTrials.gov is a website that provides information about federally and privately supported clinical trials. A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

WHAT ARE MY RIGHTS IF I TAKE PART IN THIS STUDY?

Taking part in this study is your choice. You can choose whether or not you want to participate. Whatever decision you make, there will be no penalty to you and you will not lose any of your regular benefits.

- You have a right to have all of your questions answered before deciding whether to take part.
- Your decision will not affect the medical care you receive from UCLA.
- If you decide to take part, you can leave the study at any time.

- If you decide to stop being in this study you should notify the research team right away. The researchers may ask you to complete some procedures in order to protect your safety.
- If you decide not to take part, you can still get medical care from UCLA.

HOW DO I INDICATE MY AGREEMENT TO PARTICIPATE?

If you want to participate in this study you should sign and date below. You have been given a copy of this consent form and the Research Participant's Bill of Rights to keep. You will be asked to sign a separate form authorizing access, use, creation, or disclosure of health information about you.

SIGNATURE OF THE PARTICIPANT

_____
Name of Participant

_____ _____
Signature of Participant Date

SIGNATURE OF PERSON OBTAINING CONSENT

_____ _____
Name of Person Obtaining Consent Phone

_____ _____
Signature of Person Obtaining Consent Date