Application of the multiphase optimisation strategy (MOST) to optimise HIV prevention targeting people on medication for opioid use disorder (MOUD) who have cognitive dysfunction: protocol for a MOST study

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ABSTRACT

Introduction People who inject drugs (PWID) have remained a contributor to the consistent HIV incidence rates in the US for decades. Pre-exposure prophylaxis (PrEP) is a promising biomedical intervention for HIV prevention among individuals at risk for HIV infection, including PWID. However, PWID report the lowest rates of PrEP uptake and adherence among at-risk groups. Tailored HIV prevention interventions must include strategies that compensate for cognitive dysfunction among PWID.

Methods and analysis Using the multiphase optimisation strategy, we will be conducting a 16-condition factorial experiment to investigate the effects of four different accommodation strategy components to compensate for cognitive dysfunction among 256 PWID on medication for opioid use disorder. This innovative approach will inform optimisation of a highly effective intervention to enhance PWID’s ability to process and utilise HIV prevention content to improve PrEP adherence and HIV risk reduction in a drug treatment setting.

Ethics and dissemination The institutional review board at the University of Connecticut approved this protocol (H22-0122) with an institutional reliance agreement with APT Foundation Inc. All participants are required to sign an informed consent form prior to engaging in any study protocols. The results of this study will be disseminated on national and international platforms through presentations at major conferences and journals.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The use of the multiphase optimisation strategy tailored for the first time to optimise an intervention aimed at HIV prevention in an extremely high-risk population.
⇒ A biomarker blood sample used to determine adherence to pre-exposure prophylaxis.
⇒ An innovative and highly efficient factorial experiment to test four different accommodation strategy components to compensate for cognitive dysfunction among persons with opioid use disorder.
⇒ A double-consent process to determine eligibility into the study.
⇒ The integration of HIV prevention among people who inject drugs, newly entering drug treatment for opioid use disorder, limits generalisability to other drug-using populations.

INTRODUCTION

HIV incidence in the US has remained largely stagnant for the past 15 years, as people who inject drugs (PWID) have consistently contributed to 10% of new infections each year. Pre-exposure prophylaxis (PrEP) can provide primary HIV prevention to persons at-risk for HIV. HIV prevention interventions involving PrEP should appropriately target the highest-risk groups, rather than applying a one-size-fits-all approach. PrEP uptake and adherence among PWID, however, have remained alarmingly low, despite increased PrEP promotion efforts.

Behavioural approaches have been shown to be efficacious across a wide range of substance use disorders, and compatible with several other treatment approaches, including medication for opioid use disorders (MOUD) and traditional counselling approaches. However, existing evidence-based interventions require participants to have intact cognitive functioning in order to process and use intervention content. The influence of cognitive dysfunction on such approaches has not been addressed despite growing evidence that it negatively impacts treatment outcomes among persons with
substance use disorders. In particular, people with OUD, particularly those on MOUD, are often characterised by cognitive dysfunction, which can impact PrEP adoption and subsequent adherence. This complication may impede individuals’ ability to process and use information as needed for higher levels of adherence, making the requirement for near-perfect adherence to daily oral PrEP a significant barrier to wide-scale PrEP usage among PWID. Thus, maintaining optimal PrEP adherence represents a formidable challenge for treatment providers and PWID on MOUD, unless approaches accommodate those with diverse levels of cognitive dysfunction. Interventions must now focus on optimising evidence-based primary HIV prevention, including the development of PrEP-focused interventions that compensate for cognitive dysfunction among PWID.

A number of promising compensatory strategies can be integrated to accommodate the significant levels of cognitive dysfunction that often characterises PWID to maximise PrEP adherence and thereby improve HIV prevention benefits. Recent studies comparing objective and self-report cognitive assessments (eg, NIH toolbox) show that approximately 67% of PWID experience substantial levels of cognitive dysfunction across tasks involving attention, executive function, memory and information processing, that, in turn, disrupt the expected outcomes. Studies have found a majority of PWID on MOUD experience cognitive dysfunction and may benefit from an intervention approach that incorporates compensatory strategies (ie, ‘work around’ strategies) to accommodate their cognitive dysfunction. Compensatory strategies have been successfully applied to other patient populations (eg, traumatic brain injury, Attention-deficit/hyperactivity disorder, Alzheimer’s/dementia) to improve daily function and adherence to medical recommendations even without the goal of directly improving cognitive function. Integrating such compensatory accommodation strategies can also improve HIV risk reduction skills among PWID.

To date, no studies have examined the impact of incorporating such compensatory strategies, individually or in various combinations, in improving PrEP uptake and adherence among people on MOUD who have cognitive dysfunction.

A more appropriately tailored evidence-based approach could advance HIV prevention science by enabling more effective prevention of HIV transmission. The multi-phase optimisation strategy (MOST) is an innovative, engineering-inspired framework used to develop highly efficacious, affordable, scalable and efficient interventions. In this context, the MOST framework can provide in-depth analysis to inform what combination of cognitive dysfunction accommodation strategies best improves PrEP adoption and adherence among PWID on MOUD. The purpose of this project is to apply the MOST framework to an evidence-based behavioural intervention (ie, community-friendly health recovery programme: CHRP) to identify which combination of compensatory cognitive strategies (ie, attention, executive function, memory and information processing) best improves HIV prevention outcomes among highly diverse patients with OUD. The CHRP is an evidence-based behavioural intervention designed to reduce sex-related and drug-related HIV risk behaviour for opioid-dependent individuals. The CHRP intervention is based on the information-motivation-behavioural skills (IMB) model and is designed for implementation within community-based drug treatment settings, where large numbers of high-risk drug users routinely participate in treatment. The iterative approach in this study will help optimise and build a highly effective intervention to enhance PWID’s ability to process and use HIV prevention content that may improve PrEP adherence.

METHODS AND ANALYSIS

Study design: MOST

MOST consists of three phases of research: preparation, optimisation and evaluation. The primary activity of the preparation phase is developing a detailed conceptual model that expresses how each component is expected to impact the process—in this case, the uptake of primary HIV prevention behaviours. The preparation phase was completed in our preliminary work, which resulted in the identification of four compensatory components (ie, attention, executive functioning, memory and information processing) that show promise in terms of enhancing participants’ ability to process and use primary HIV prevention intervention information (table 1).

As shown in the conceptual model (figure 1), we have integrated four compensatory components into our evidence-based intervention in an effort to target and enhance the information construct within the IMB model based on what has worked well in interventions with other patient populations.

In the present study, we are beginning the next phase of MOST, optimisation, in which the performance of these four components will be assessed in a highly efficient optimisation trial. Components will then be selected for inclusion in a final intervention package based on the results of the optimisation trial and also considering the ‘optimisation objective’. In this case, the optimisation objective is to identify the components that contribute most to enhanced PrEP adherence (primary outcome) and HIV risk reduction (secondary outcomes).

Using a factorial design that includes 16 experimental conditions (2×2×2×2 or 2^4), we will be conducting an optimisation trial among PWID on MOUD (N=256), with an expected small-medium effect size equivalent to the uptake of 65% in the ‘yes’ versus the ‘no’ levels of each component (figure 2). The purpose of the factorial design is to estimate the main effect of each component (its effect on average across all experimental conditions) and interactions among components (whether the performance of a component is enhanced or diminished...
The presence or absence of other components. The 16 experimental conditions vary only by including varied combinations of compensatory components incorporated into the core components of the CHRP intervention.33-34 Having experimental conditions that include standard-of-care drug treatment (standardised MOUD protocol and clinical contact) and core components of an evidence-based HIV prevention programme (CHRP)33-34 protect against differential attrition and differential demand characteristics, thus bolstering the internal validity of the experimental design. Furthermore, we believe that it may be unethical to offer participants anything less than a standard of care intervention, such as no treatment or a delayed treatment condition.38

All participants will be assessed at baseline, immediately postintervention (ie, 4 weeks) and follow-ups at 3-month, 6-month and 9-month postintervention measurement points. This time frame allows us to examine the 16 intervention conditions in the short term as well as the trajectory of PrEP adherence and HIV risk reduction over time. Importantly, this approach also allows for a clear examination of the decay and/or emergence of effects.38

### Study procedures

#### Recruitment and randomisation

Recruitment for this study began on 1 March 2023. Anticipated completion date of this study is 1 January 2027. Participants will continue to be recruited using client interest sheets located within intake packets that are completed when entering methadone maintenance treatment at APT Foundation Inc. in New Haven, CT as well as clinic-based advertisements and flyers, word-of-mouth

### Table 1 Four components of accommodation strategies

<table>
<thead>
<tr>
<th>Components</th>
<th>Intervention tasks</th>
<th>Sample strategies</th>
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| **Attention**       | 1. Sustained attention and concentration  
  2. Motivation to engage  
  3. Listening skills  
  4. Emotion regulation | 1. Increase frequency of sessions (more than once per week)  
  2. Distributed practice (spreading out information across sessions)  
  3. Structured sessions (well-organised objectives shared with patients)  
  4. Introduce new information during closure (foreshadow content of next session) |
| **Executive function** | 1. Anticipate consequences  
  2. Executive planning skills  
  3. Decisional balance  
  4. Self-regulation | 1. Associate behaviour with situational cues (anticipate risky situations)  
  2. Link actions to a triggering cue (storytelling techniques using imagery)  
  3. Planning (identify and organise steps required to meet goal)  
  4. Value future events (recognise the benefits of drug treatment) |
| **Memory**          | 1. Recall past behaviour  
  2. Remembering behavioural cues  
  3. Recollect intervention content  
  4. Learning new info | 1. Memory aids (reminders and cues to be used between sessions)  
  2. Summarise/reiterate information (frequent review throughout sessions)  
  3. Prospective memory (emphasise routine, develop cues, elaborate on positive behaviours)  
  4. Environmental engineering (prepare for adverse events) |
| **Information processing** | 1. Processing written info  
  2. Manage complex language  
  3. Interpreting feedback  
  4. Consequences of behaviour | 1. Mixed methods of presentation (verbal, visual and hands-on)  
  2. Simple language (clear, concrete examples aligned with health literacy)  
  3. Present content slowly (allow extra time for responses)  
  4. Immediate feedback (oral and written clarification of material) |

Figure 1 Conceptual model for compensatory components targeting information in the IMB model. IMB, information-motivation-behavioural skills; PrEP, pre-exposure prophylaxis.
and direct referral from counsellors at APT. Eligibility criteria include: (1) being 18 years or older; (2) meeting Diagnostic and Statistical Manual of Mental Disorders (DSM)-V criteria for opioid dependence and entering MOUD drug treatment (eg, methadone, buprenorphine) at APT; (3) showing mild cognitive impairment (MCI) based on the Montreal cognitive assessment (MoCA) screening; (4) having initiated PrEP within the past week; (5) confirming HIV-negative status through proof of PrEP prescription; (6) reporting unsafe injection drug use practices or unprotected sex within the past 3 months; (7) having a cell phone and (8) being able to read and understand in English. Individuals who are newly enrolled patients on MOUD and are interested in PrEP will be referred to a local PrEP provider within our PrEP prescriber network. Patients will sign an initial informed consent (online supplemental file 1) when they are screened for cognitive dysfunction using the MoCA, a brief (<10 min) and well-validated measure of global cognitive function.39 40 Persons whose performance falls within the MCI range on the MoCA based on age, education, race and ethnicity41 42 will be eligible for study inclusion. Individuals with scores suggestive of dementia, adjusting for these factors, will be excluded. Based on our work showing high rates of participants meeting criteria for MCI on a comprehensive test battery and the known agreement between the MoCA and similar testing,9–12 14 39 we anticipate that approximately 60%–65% of screened individuals will be categorised as having MCI. Additionally, individuals who cannot provide consent or are actively suicidal, homicidal or psychotic are excluded.

After confirming eligibility criteria and providing additional informed consent (online supplemental file 2), all enrolled participants will undergo a baseline assessment. After completing the baseline assessment, enrolled participants are randomised to one of the 16 conditions, using single blind protocols. All participants assigned to a given condition will receive the same components. Based on the recruitment pace in prior trials34 and resource constraints at APT, block randomisation will be used with four participants per block, with two active conditions at a given time, and blocks repeated until each condition meets the planned sample size.

**Intervention**

**Standard of drug treatment care**

Participants in all conditions will receive routine services as part of their enrolment in MOUD at APT, which includes daily methadone and case management consisting of a minimum of 1 hour of monthly contact with a counsellor/case manager.

**Experimental conditions**

All participants will attend 4 weekly 50 min HIV risk reduction and PrEP adherence group sessions (ie, CHRP)33 34 led by two facilitators trained and supervised by a licensed clinical psychologist. The group sessions include: (a) making the most of PrEP as an active health manager;
(b) reducing drug risk and taking PrEP; (c) PrEP adherence and sex risk reduction strategies and (d) negotiating partner support for HIV prevention. The groups use a coping skill training approach to primary prevention (eg, problem solving, identifying triggers, goal setting) and are delivered in a small group by two trained intervention facilitators using a motivational enhancement therapeutic style.

In addition to receiving the core components of CHRP (described above), participants will receive one of the 16 combinations of four compensatory components. The compensatory components are not part of the original evidence-based CHRP but have shown promise in enhancing participants’ ability to process and use HIV prevention content.13 The Attention component includes:

- (a) increasing frequency of sessions (more than once per week)24 43 44; (b) distributed practice (spreading out information across sessions)24 45–45; (c) more structured sessions (well-organised objectives shared with patients)46–50 and (d) introducing new information during closure (foreshadow content of next session).50 51

The Executive Function component includes the following strategies:

- (a) associating behaviour with situational cues (anticipate risky situations)52 53; (b) linking actions to a triggering cue (storytelling techniques using imagery)52; (c) planning (identify and organise steps required to meet goal)53 54 and (d) valuing future events (recognise the benefits of drug treatment).54 Similarly, the Memory component involves:

- (a) memory aids (reminders and cues to be used between sessions)24 46 55–63; (b) summarising/reiterating information (frequent review throughout sessions)24 53 58; (c) prospective memory (emphasise routine, develop cues, elaborate on positive behaviours)50 52 53 64 and (d) environmental engineering (prepare for adverse events).50 53 64 65

Finally, the Information Processing component includes:

- (a) multimodal presentation of content (verbal, visual and hands-on)24 46 66–70; (b) simple language (clear, concrete examples aligned with health literacy level)46 48 53 59 70–72; (c) slowly presenting information (allow extra time for responses)24 46 48 53 59 68 72 73 and (d) assessment with immediate feedback (oral/written).46 74–78

### Assessment procedures

The baseline assessment, which takes approximately 90 min to complete, will be conducted prior to week 1 of participation and repeated following week 4 and at all follow-up measurement points. Participants will be reimbursed at the market rate of USD $45 for the time required to complete the assessment. Assessments are administered with Qualtrics, a computer-driven questionnaire system that gives participants a greater sense of anonymity.

### Measurement of outcomes

The primary outcome is PrEP adherence. Secondary outcomes include reducing sex-related and drug-related HIV risk. Furthermore, we will assess participants’ knowledge, motivation and behavioural skills related to outcomes of interest based on the IMB framework.35

PrEP adherence will be assessed using biomedical and behavioural approaches at postintervention and the 3-month, 6-month and 9-month postintervention follow-ups. For the biomedical assessment, we will quantify the tenofovir-diphosphate fumarate (TDF; used in Truvada for PrEP) or the tenofovir alafenamide (TAF; used in Descovy for PrEP) in participants’ red blood cell counts, measured with dried blood spots, as a validated adherence measure.79 80 This test assesses cumulative adherence because TDF/TAF in red blood cells exhibits a 17-day half-life and 25-fold accumulation. This enables assessment using a standardised nomogram of cumulative TDF/TAF exposure (adherence) over the preceding 1–2 months.81–83 Self-reported PrEP adherence will be collected using a visual analogue scale (VAS).84 The VAS is an empirically validated tool that effectively measures a ‘difference’ in adherence that changes in response to an intervention (despite consistently under-reporting adherence). In addition, pharmacy refill data will be used as an additional objective data source. As used in current studies,85 86 releases of information to obtain pharmacy data from both Medicaid and individual pharmacies are deployed. This will allow us to triangulate PrEP adherence, assessing the correlation between biomedical, self-report, and pharmacy refill data.

### HIV-risk and risk reduction behaviour

We will use the adapted version of the NIDA’s Risk Behaviour Assessment87 to measure several aspects of HIV risk behaviours, including measurement of ‘any’ high-risk behaviour (sexual or drug-related) as well as measurements of event-level (ie, partner-by-partner) behaviours. ‘Any’ risk behaviour will be dichotomously parsed as those who have engaged in HIV transmission risk behaviours with those of unknown HIV status or with people living with HIV (PLWH).35 88 Event-level data will be measured as a continuous variable analysed using Poisson regression to examine the magnitude of risk behaviours for a small number of individuals who engage in large numbers of events with unknown HIV status and with PLWH. These measures have been used in our prior clinical trials,84 88 confirming high test–retest reliability (0.88 to 0.98).90

### IMB construct measures

Data collected at all assessment points will be included in our measure of IMB model constructs (figure 3).35
including (a) information—HIV risk-related and PrEP-related knowledge; (b) motivation—readiness to change and intentions to change PrEP adherence and change HIV risk behaviour; (c) behavioural skills—PrEP adherence skills and HIV risk reduction skills and (d) behavioural outcomes—HIV risk and HIV risk reduction behaviours and PrEP adherence. Behavioural skills will also be assessed, as in prior trials, by having participants demonstrate the specific steps necessary to properly clean a needle/syringe and the specific steps to properly select and apply a male and female condom using replicas. Ratings of audiotaped demonstrations of these procedures by staff blind to treatment assignment have shown excellent inter-rater reliability (inter-rater reliability = 0.98). The demonstrated behavioural skills score is derived from calculating the percentage of steps performed correctly on each skill.

**Urine toxicology**

Five-panel (ie, heroin, cocaine, oxycodone, fentanyl and benzodiazepine) immunoassay urinalyses (with confirmation of positive results) will be conducted at baseline, two times weekly during the 4-week intervention phase, and at 3-month, 6-month and 9-month follow-ups to detect the most use of common illicit substances in this group. Urine samples are analysed using the Abbott Tdx method.

**Potential covariates**

A number of covariates will be measured to examine the differential impact of characteristics that might influence primary outcomes. Demographic variables (eg, gender) have been found to influence HIV prevention outcomes and are, therefore, measured and closely examined. Factors associated with PrEP non-adherence and HIV risk-taking include: MOUD treatment dropout, depressive symptoms, active drug use, alcohol use disorder (AUD), social support, patient–physician relationships, destabilised living circumstances, etc. We will measure these variables using standardised instruments, including: DSMIV criteria for substance use disorders (M.I.N.I.), mental illness (M.I.N.I.), depressive symptoms based on the Center for Epidemiological Studies-Depression scale (CES-D), AUD based on the Alcohol Use Disorder Identification Test (AUDIT), social support (Medical Outcomes Study Social Support Survey), patient–physician relationships (Trust in Physician Scale) and active drug use (urine toxicology screening using the NIDA-5 panel).

**Weekly assessments**

During the 4-week intervention period, weekly urine toxicology will be performed to detect the use of an illicit substance. In addition, a weekly self-report of illicit drug use, other high-risk behaviours and PrEP adherence measures will be obtained. Our team has used a similar instrument in an randomized controlled trial (RCT) at the research performance site. Using a time-line follow-back technique, patients report on: (a) quantity, frequency and route of administration of illicit drugs, including heroin and cocaine; (b) frequency and type of other HIV risk behaviours, including needle sharing, unsafe needle cleaning and unsafe sexual practices, (c) frequency of harm reduction practices, such as the use of needle exchange programmes and purchase of needles and use of male and female condoms and (d) adherence to PrEP as prescribed. In addition, following each intervention group session, a quiz will be administered to assess the acquisition of intervention content. As in prior trials, attendance, engagement and satisfaction information is also collected. The number of group sessions will be monitored and audio recorded weekly. Patient participation will be assessed by a cofacilitator on a scale from 0 (not at all engaged) to 4 (extremely engaged). Additionally, a satisfaction measure is completed by participants as an indication of the perceived strengths and weaknesses of intervention content, delivery and overall usefulness. These measures complement qualitative implementation data to support the assessment of intervention barriers/facilitators.

**Strategies to minimise attrition**

We will continue to use multiple procedures which we have found to enhance compliance and retention within drug treatment programmes in order to minimise participant dropout. These procedures include rapid assignment to study conditions after informed consent (usually the same day), thorough explanation of study conditions, close monitoring of participants’ clinical status, integration of the research with the clinical programme and accessibility to patients of study staff for questions and problems. We will also use a subject locator that has been used in many of our community-based trials of active drug users, where retention has ranged from 86% to 93% (average 91%). Retention in this trial may be higher because the majority of participants are on a stable dose of methadone and have multiple contact points. Attrition rates will be monitored yearly, and the sample size will be increased if retention rates are unexpectedly lower than in prior trials, as needed to ensure adequate power to conduct the proposed outcome analyses.

**Minimising contamination across conditions**

We will use several procedures to guard against potential threats to internal validity. Contamination is minimised in several ways: (1) as in our prior NIDA-funded work, we will use a detailed intervention manual that includes session outlines and all other supporting materials needed to conduct the intervention sessions; (2) all the intervention condition sessions are delivered at different times within the same treatment facility and by the same facilitators; (3) participants in each condition are assessed independently, thus avoiding direct participant interaction when assessed and (3) only one individual per household is recruited. Thus, interactions among participants do not differ from what would occur under natural circumstances in the programme.
**Statistical analysis**

All data will be deidentified and stored on secure servers. Prior to analysing outcomes, the degree of pretest equivalence between experimental conditions at baseline will be evaluated for key variables, including demographics and clinical characteristics. Baseline data are evaluated via Analysis of Variance (ANOVA) on numerical items when normal or Mann-Whitney test when we have a non-normal distribution of those items and \( \chi^2 \) tests of categorical items to evaluate pretest equivalence between and within the experimental conditions. Any variable, such as biological sex or OUD treatment dropout, for which inequality across conditions is identified at baseline and entered as a covariate in subsequent analyses to address potential non-equivalence across conditions.\(^{27,101,102}\) Differential attrition analyses will be conducted to assess differential attrition by condition between baseline and subsequent measurements. Any variable influencing differential attrition will be included as a covariate in subsequent analyses.

Mixed-effects modelling with log as the function and time points clustered within individuals will be used to estimate the effects of components on the odds of PrEP adherence. Experimental factors are effect coded to estimate the main effects and two-way interactions of the four candidate components over time. The coefficient for the main effect term, multiplied by 2 and exponentiated, will be used to estimate the effect of the component on the odds of the primary outcome, PrEP adherence. Similarly, the coefficient for an interaction term, multiplied by 2 and exponentiated, will be used to estimate interaction effects between candidate components on the odds of PrEP adherence. Similar logistic or linear (depending on the numerical or dichotomous outcome) regression analyses will be used to estimate the effects of components on the secondary outcomes. Mixed-effects linear models (or GLM if normality is not met) will be used to estimate the effects of components on HIV risk reduction behaviour, absolute adherence levels and retention in care as well as the interaction effects of components on these outcomes.

Mediators and moderators of intervention component efficacy will be examined based on the IMB model of health behaviour change by assessing participants’ knowledge, motivation and behavioural skills related to the primary outcome (PrEP adherence) at all measurement points. Generalised linear model (GLM) analysis will be used to determine impacts of intervention components on mediators.\(^{103,104}\) Probit regression, used to estimate indirect effects, will be used to determine which mediators are related to PrEP adherence, after controlling for intervention components received. Intervention components may not be equally efficacious for all participants. Other factors may modify the relation between condition and outcomes, including: age, gender, minority status and substance use.

**Sample size calculation**

Power was computed for a probability of superiority, ‘yes’ vs ‘no’ of 65%, a small–medium effect for medication adherence and HIV risk reduction, based on similar intervention studies in this facility.\(^{34}\) Participants are randomised equally to 16 different intervention conditions over 44 weeks. We will use a two-tailed test with an alpha of 0.05, which means an effect in either direction is interpreted. Given these assumptions (for the effect size) and criteria (for alpha and tails), the study demonstrates a power of 85% to yield a statistically significant result. The study will allow us to report the effect size (d) with an SE of approximately 0.089. To maintain that power level, we aim to retain 246 participants postintervention, 236 at 3-month follow-up, 220 participants at 6-month follow-up and 191 participants at 9-month follow-up. Even if only 71% of participants complete the final 9-month follow-up assessment (a conservative estimate based on previous trials in this facility), the proposed sample size will provide sufficient power (83%) to detect the expected main effects and interaction effects.

**Data safety and monitoring**

A data safety and monitoring committee will serve to protect the safety of human subjects and the validity of this research. This committee is independent from the sponsor and will provide oversight throughout all study procedures. All adverse events will be reported to the ethics committee and IRB of the affiliated university. Decisions to postpone, suspend or terminate any study procedures will be determined by the ethics committee and data safety and monitoring committee.

**Patient and public involvement**

None.

**ETHICS AND DISSEMINATION**

The institutional review board at the University of Connecticut approved this protocol (H22-0122) with an institutional reliance agreement with APT Foundation Inc. This study is registered at ClinicalTrials.gov. Any modification to the protocol will be submitted as an amendment to the ethics committees for approval. Informed consent is obtained from all participants before the study enrolment. Participant information is always kept confidential. The principal investigator may grant access to the final data set and statistical code to any responsible parties, on request. Findings will be submitted for publication in leading international peer-reviewed journals. In addition, the results will be disseminated on national and international platforms through presentations at major conferences.

**DISCUSSION**

Information gleaned from this innovative optimisation trial should have a significant public health impact across
a variety of intervention approaches targeting PWID. The primary goals of the Ending the HIV Epidemic\textsuperscript{105} from the Centers of Disease Control and Prevention\textsuperscript{105} are to diagnose all people with HIV as early as possible, treat people with HIV rapidly and effectively, prevent new HIV transmissions and respond quickly to potential HIV outbreaks. There is a high likelihood that these goals can be met through this line of research. If this trial leads to the optimisation of a PrEP-focused primary HIV prevention intervention among high-risk PWID with cognitive dysfunction, it is likely to become a resource-efficient approach for use in treatment settings targeting PWID. Although the sample population of this study may limit generalisability to other drug-using populations, the benefits of a tailored biobehavioural interventions for people with OUD are likely to improve drug treatment outcomes and reduce HIV transmission among PWID. This will be the first MOST-framed optimisation trial to examine intervention components designed to compensate for cognitive features that are characteristic of PWID on MOUD. Additionally, this is among the first optimisation trials among PWID on MOUD that aligns with high-priority research areas of reducing the incidence of HIV/AIDS (methods of delivery, especially those that mitigate PrEP adherence issues) and HIV-associated comorbidities (neuropsychological complications).

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Consent Form for Participation in a Research Study

Principal Investigator: Dr. Michael Copenhaver
Study Title: Optimizing evidence-based HIV prevention targeting people who inject drugs (PWID) on PrEP
Sponsor: National Institute on Drug Abuse (NIDA)

Overview of the Research

This form is used for you to provide consent to complete a brief cognitive screening. This will help us decide if you qualify to participate in the main research study. Participation is voluntary. You can say yes or no. If you say yes now you can still change your mind later. There are no penalties for withdrawing from this study at any time and your status at the APT Foundation treatment program will not be affected in any way. Some key points to consider are summarized in this overview, but you should consider all of the information in this document carefully before making your decision. The cognitive screening is being done because we want to make sure to include people who have at least some cognitive challenges, like difficulty concentrating or remembering information. This will help us learn to improve how we deliver HIV prevention groups while people are in drug treatment. Your participation will take about 10 minutes. Risks are described in more detail later in this form. There may also be benefits from participation. We believe that we will gain a better understanding of the cognitive challenges faced by patients while in drug treatment. Before making a decision about whether to participate you should know that there are other options available to you. For example, you may choose to seek a different cognitive assessment study.

A more detailed description of this research follows.

Introduction

First of all, thank you for taking the time to look over this invitation to participate in this cognitive screening study. You are invited to participate in this research study that may qualify you for our main study, which will help us learn the best ways of delivering HIV prevention groups while people are in drug treatment. You have been asked to participate because you are HIV-negative, enrolled in drug treatment at the APT Foundation, and have expressed interest in our flyer.

In order to decide whether or not you want to be a part of this study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and potential benefits. We also encourage you to ask...
questions now and at any time. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this consent form, and you will be given a copy.

**Why is this study being done?**

The purpose of this research study is to determine whether your cognitive performance qualifies you for our main study, which will include only people with some cognitive challenges, like difficulty concentrating or remembering information. We plan to enroll 256 participants in this study for this purpose. In addition to helping us screen for cognitive challenges, we will be able to identify how common cognitive challenges are for patients in drug treatment at this facility. This will help us develop better ways to deliver HIV prevention groups to patients while they are in drug treatment.

**What are the study procedures? What will I be asked to do?**

If you agree to participate in this cognitive screening study, a trained member of our research team will ask you a set of questions from the Montreal Cognitive Assessment (MoCA). This instrument is used for many different types of patients to help decide whether they have common difficulties that can affect their daily life, such as with concentration or memory. Taking the MoCA will take about 10 minutes. After that, you will be given feedback about your performance. Then we will discuss with you whether your score qualifies you for the main study. We will also answer any questions you may have about the screening. If your brief cognitive screening results suggest more than mild cognitive challenges, we will discuss this with you. After discussing your results with you, if you want, we can connect you to a treatment provider of your choice to follow up on your condition. As part of your enrollment, we expect that you will complete the questionnaire. The Principal Investigator may discontinue you from this study if you are unable or unwilling to complete the questionnaire.

**What are the risks or inconveniences of the study?**

The procedures involved in this screening study may involve risks that are currently unforeseeable. Possible risks associated with this study include being identified as a participant in a research study by other patients or staff. Inconveniences may include taking time to respond to the questions required in the cognitive screening. You are free not to answer such questions and also to withdraw yourself from participating in the research process at any time you like to do so. If you would like to talk to a counselor about your feelings at any time, we can connect you with a counselor at the APT Foundation.

A research team member will tell you about any important new information that we learn during the course of this study that might affect your condition or your willingness to participate. You should also know that study identifiers may be removed from our records in the future, and after such removal, the study information may be used for future research studies or given to another investigator for future research studies without asking you to sign another informed consent form.
What other options are there?

If you choose not to participate in this study, we will discuss other options with you such as other possible cognitive assessment studies or another treatment provider of your choice if you are interested in getting more information about your cognitive performance.

What are the benefits of the study?

We do not know that this cognitive screening will be helpful in general, and we do not know whether it will be of any help to you in particular. However, we believe that this screening process has the potential to help us understand how common it is for patients in this facility to have cognitive challenges and to design better HIV prevention groups. It is also possible that, in the future, results from this study may help individuals who participate in healthcare like the APT Foundation program.

Will I receive payment for participation? Are there costs to participate?

Your participation is purely voluntary. For your participation you will be reimbursed a total of $5 in the form of a prepaid debit card for the time we expect it to take for you to participate in the screening.

How will my personal information be protected?

We will make every effort to insure your privacy and confidentiality. If you do not choose to participate in this study, all information that you have given us will be destroyed immediately. If you do choose to participate, in all of our study records, you will be identified by a number and your name will be known only to the researcher. Your name will not appear in any publication or be released to anyone without your written consent. You should understand, however, that there is a risk that you will be recognized by other patients or staff involved in the study and that you may be recognized as a participant in a research program. But this is no greater than the usual risk of identification that occurs in your clinical care.

The following procedures will be used to protect the confidentiality of your data. The researchers will keep all study records (including any codes to your data) locked in a secure location. Research records will be labeled with a code. The code will be derived from a number (e.g. sequential 3-digit code) that reflects how many people have enrolled in the study. A master key that links names and codes will be maintained in a separate and secure location. Any audio-recordings will be viewed and transcribed only by research staff members for accuracy and consistency purposes. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected. Any computer hosting such files will also have password protection to prevent access by unauthorized users. Only the members of the research staff will have access to the passwords. The master key, audio-recordings, and data will be destroyed 3 years after the completion of this study. Data that will be shared with others will be coded as described above to help protect your identity. At the conclusion of this study, the researchers may publish their
findings. Information will be presented in summary format and you will not be identified in any publications or presentations.

Data that we collect from you may be shared with other researchers in the future, but only after your name and all identifying information have been removed.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

We will do our best to protect the confidentiality of the information we gather from you but we cannot guarantee 100% confidentiality. Your confidentiality cannot be guaranteed if your record is subpoenaed in a court of law or in the event the researcher determines that you are a clear and imminent danger to yourself and/or others. In addition, confidentiality cannot be guaranteed if you disclose that you are intending to or currently sexually or physically abusing a child or an elderly person.

We have a Certificate of Confidentiality from the National Institute on Drug Abuse (NIDA). This Certificate will protect the investigators from being forced to release any research data in which you are identified, even under a court order or subpoena. This protection, however, is not absolute. For example, if we the researchers learn about serious harm that could come to you or to someone else, we would take steps to protect the person or persons endangered even if it required telling the authorities without your permission. If that happened, we would only disclose information to the extent necessary to prevent harm to the person(s) believed to be endangered. When the results of this study are published, your name will not be used.

You should also know that the UConn Institutional Review Board (IRB) and Research Compliance Services and the APT Foundation research board may inspect study records as part of its auditing program, but these reviews will only focus on the researchers and not on your responses or involvement. The IRB is a group of people who review research studies to protect the rights and welfare of research participants.

Can I stop being in the study and what are my rights?

You do not have to be in this study if you do not want to. If you agree to be in the study, but later change your mind, you may drop out at any time for any reason. There are no penalties or consequences of any kind if you decide that you do not want to participate. You will be notified of all significant new findings during the course of the study that may affect your willingness to continue. You do not have to answer any question that you do not want to answer.

Whom do I contact if I have questions about the study?

Take as long as you like before you make a decision. We will be happy to answer any question you have about this study. If you have further questions about this study or if you have a research-related problem, you may contact the principal investigator, Dr. Michael Copenhaver at (203) 781-4690. If you have any questions concerning your rights as a research participant, you may contact the University of Connecticut Institutional Review Board (IRB) at 860-486-8802.
**Documentation of Consent:**
I have read this form and decided that I will participate in the project described above. Its general purposes, the particulars of involvement and possible risks and inconveniences have been explained to my satisfaction. I understand that I can withdraw at any time. My signature also indicates that I have received a copy of this consent form.

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Participant Signature: ____________________ Print Name: ____________________ Date: __________

Signature of Person Obtaining Consent: ____________________ Print Name: ____________________ Date: __________
Consent Form for Participation in a Research Study

Principal Investigator: Michael Copenhaver  
Student Researcher: 
Study Title: Optimizing evidence-based HIV prevention targeting people who inject drugs (PWID) on PrEP  
Sponsor: National Institute on Drug Abuse (NIDA)

Overview of the Research

You are being asked to provide consent to participate in a research study. Participation is voluntary. You can say yes or no. If you say yes now you can still change your mind later. There are no penalties for withdrawing from this study at any time and your status at the APT Foundation treatment program will not be affected in any way. Some key points to consider are summarized in this overview, but you should consider all of the information in this document carefully before making your decision. This research study is being done to help us learn the best ways of delivering HIV prevention groups for people who have some cognitive challenges, like difficulty concentrating or remembering information. Improving how we deliver these groups may assist in helping you reduce health risks while you’re in drug treatment. Participation will involve approximately 90 minutes of your time per interview, with a total of 5 interviews. We also require 1 hour of your time each week after your initial interview to attend groups, and this will continue weekly for 4 weeks until intervention completion. You will be asked to answer person drug and sex related questions, and provide a skills demonstration all 5 interview time points, we will also ask you to supply a blood spot at post, and the 3 follow-up time points. Risks include group participants breaching confidentiality, being identified as a participant in a research study by other patients or staff, feeling upset by some of the material brought up in the group meetings, or by knowing that the meetings are being audio-taped. Risks are described in more detail later in this form. There may also be benefits from participation. We believe that these groups have the potential to be helpful for reducing health risks related to getting infected or transmitting HIV. Before making a decision about whether to participate in this research you should know that there are other options available to you. You may choose to participate in a different harm reduction study that you feel suits your needs better.

A more detailed description of this research follows.

Introduction

First of all, thank you for taking the time to look over this invitation to participate in our study. You are invited to participate in a research study designed to help us learn the best ways of delivering
HIV prevention groups to help you reduce health risks while you’re in drug treatment. You have been asked to participate because you are HIV-negative, enrolled in drug treatment at the APT Foundation, and have reported mild cognitive impairment.

In order to decide whether or not you want to be a part of this study, you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and potential benefits. We also encourage you to ask questions now and at any time. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this consent form, and you will be given a copy.

Why is this study being done?

The purpose of this research study is to help us understand better methods to use in delivering HIV prevention groups to patients in drug treatment so they will better adhere to pre-exposure prophylaxis (PrEP) and lower their risk of getting HIV. We plan to enroll 256 participants in this study for this purpose. The intervention group meetings will focus on ways people can lower their risks of being infected with HIV and ways they can improve their adherence to PrEP medication. We hope that we can help patients reduce their risks for HIV by improving our methods.

What are the study procedures? What will I be asked to do?

If you agree to participate in this study, you will be randomly assigned to one of sixteen different study conditions that will use different ways of teaching HIV prevention. All conditions will involve attending weekly group meetings for four weeks. The meetings will last 60 minutes each and will be held in a private room at the APT Foundation. Each meeting is aimed at teaching different health-related topics, and what you can do to reduce health risks. The content of the topics will include sensitive and explicit information about sexual behavior and substance use. You should know that each meeting also provides information and skills that you may use to reduce health risks. Each meeting will be audio-taped to ensure that the group topics are properly covered by the group leaders. Urine toxicology screens for opiates and cocaine (benzoylecgonine) will also be performed to detect illicit substance use at pre-, post- and at all follow-up assessment points as well as twice weekly during the four week intervention phase of the study. The urine screens will be collected in the clinic and used as data for the study. There are no penalties for using illicit drugs while participating in the study and your results will not be shared with your counselor unless you request it. Additionally, we will collect dried blood spots (DBS) to help us measure the amount of PrEP in your blood. We will ask to do a ‘finger stick’ in order to collect a drop or two of blood from your finger at post-intervention, and at all follow-up assessments. You will be asked to complete several questionnaires on a computer just before you start your first group meeting and just after you complete your last group meeting and then again about 3 months, and 6 months after your last group meeting. In addition to the assessments listed above, we will also ask that you complete a short computerized questionnaire once per week during the four-week intervention period. We will ask for your contact information for future interviews. The questionnaires on the computer will ask about any health risks over the past week due to drug use or sexual behavior as well as how you have been taking PrEP. You may skip any question that you would rather not answer. Completing the questionnaires will take
about 90 minutes each time. As part of your enrollment in this study, we expect that you will show good participation. The Principal Investigator may discontinue you from the study if your attendance is too low at groups, appointments, and bi-weekly urine measures.

**What are the risks or inconveniences of the study?**

The procedures involved in this study may involve risks that are currently unforeseeable. Possible risks associated with this study include group participants breaching confidentiality, being identified as a participant in a research study by other patients or staff, feeling upset by some of the material brought up in the group meetings, or by knowing that the meetings are being audio-taped. Inconveniences may include taking time to complete the questionnaires and the possibility of experiencing discomfort regarding questions related to drug use and sexual risk behaviors in the questionnaires. You are free not to answer such questions and also to withdraw yourself from participating in the research process at any time you like to do so. If you would like to talk to a counselor about your feelings at any time, we can connect you with a counselor at the APT Foundation. As mentioned, in one of our study measures, we will need to collect one or two drops of blood using a finger stick. To do this, we will make a small prick on your finger using a finger-stick with a lancet. You will feel a slight pain when the needle pricks your finger and your fingertips may be sore for a day or two. The biospecimens that we collect will not include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

Our research team will tell you about any important new information that we learn during the course of this study that might affect your condition or your willingness to continue participating. You should also know that study identifiers may be removed from our records in the future, and after such removal, the study information may be used for future research studies or given to another investigator for future research studies without asking you to sign another informed consent form.

**What other options are there?**

If you choose not to participate in this study, we will discuss other options with you such as individual meetings with a counselor to discuss HIV-prevention related care.

**What are the benefits of the study?**

We do not know that these groups will be shown to be effective in general, and we do not know whether they will be of any help to you in particular. However, we believe that this study has the potential to help us understand the best ways that HIV prevention can be delivered so that we can help you reduce health risks related to HIV. It is possible that, in the future, results from this study may help individuals who participate in healthcare like the APT Foundation program.

**Will I receive payment for participation? Are there costs to participate?**
Your participation is purely voluntary. For your participation you may be reimbursed a total of $325 in the form of a prepaid debit card for the time we expect it to take for you to participate in all the assessments. This amount will be pro-rated so participants will be reimbursed $25 per week for time spent completing each of four weekly brief assessments during the intervention period of participation and $45 each for assessments conducted at baseline, post-intervention, and at 3-month, 6-month, and 9-month follow-up assessments.

**How will my personal information be protected?**

We will make every effort to ensure your privacy and confidentiality. If you do not choose to participate in this study, all information that you have given us will be destroyed immediately. If you do choose to participate, in all of our study records, you will be identified by a number and your name will be known only to the researcher. Your name will not appear in any publication or be released to anyone without your written consent. You should understand, however, that there is a risk that you will be recognized by other patients or staff involved in the study and that you may be recognized as a participant in a research program. But this is no greater than the usual risk of identification that occurs in your clinical care.

The following procedures will be used to protect the confidentiality of your data. The researchers will keep all study records (including any codes to your data) locked in a secure location. Research records will be labeled with a code. The code will be derived from a number (e.g. sequential 3-digit code) that reflects how many people have enrolled in the study. A master key that links names and codes will be maintained in a separate and secure location. Any audio-recordings will be viewed and transcribed only by research staff members for accuracy and consistency purposes. All electronic files (e.g., database, spreadsheet, etc.) containing identifiable information will be password protected. Any computer hosting such files will also have password protection to prevent access by unauthorized users. Only the members of the research staff will have access to the passwords. The master key, audio-recordings, and data will be destroyed 3 years after the completion of this study. Data that will be shared with others will be coded as described above to help protect your identity. At the conclusion of this study, the researchers may publish their findings. Information will be presented in summary format and you will not be identified in any publications or presentations.

Data that we collect from you may be shared with other researchers in the future, but only after your name and all identifying information have been removed.

A description of this clinical trial will be available on [http://www.ClinicalTrials.gov](http://www.ClinicalTrials.gov), as required by U.S. Law. This web site will not include information that can identify you. At most, the web site will include a summary of the results. You can search this web site at any time.

We will do our best to protect the confidentiality of the information we gather from you but we cannot guarantee 100% confidentiality. Your confidentiality cannot be guaranteed if your record is subpoenaed in a court of law or in the event the researcher determines that you are a clear and imminent danger to yourself and/or others. In addition, confidentiality cannot be guaranteed if you disclose that you are intending to or currently sexually or physically abusing a child or an elderly person.
We have a Certificate of Confidentiality from the National Institute on Drug Abuse (NIDA). This Certificate will protect the investigators from being forced to release any research data in which you are identified, even under a court order or subpoena. This protection, however, is not absolute. For example, if we the researchers learn about serious harm that could come to you or to someone else, we would take steps to protect the person or persons endangered even if it required telling the authorities without your permission. If that happened, we would only disclose information to the extent necessary to prevent harm to the person(s) believed to be endangered. When the results of this study are published, your name will not be used.

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Can I stop being in the study and what are my rights?

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Whom do I contact if I have questions about the study?

Take as long as you like before you make a decision. We will be happy to answer any question you have about this study. If you have further questions about this study or if you have a research-related problem, you may contact the principal investigator, Dr. Michael Copenhaver at (203) 781-4690. If you have any questions concerning your rights as a research participant, you may contact the University of Connecticut Institutional Review Board (IRB) at 860-486-8802.

Documentation of Consent:

I have read this form and decided that I will participate in the project described above. Its general purposes, the particulars of involvement and possible risks and inconveniences have been explained to my satisfaction. I understand that I can withdraw at any time. My signature also indicates that I have received a copy of this consent form.

____________________ ____________________ __________
Participant Signature: Print Name: Date:

____________________ ____________________ __________
Signature of Person Print Name: Date:
Obtaining Consent