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

Colleen B Mistler,1,2 Roman Shrestha,1,3 John Gunstad,4 Linda Collins,5 Lynn Madden,6,7 Tania Huedo-Medina,1,8 Brian Sibilio,3 Nicholas M Copenhaver,1 Michael Copenhaver1,3

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,1 as people who inject drugs (PWID) have consistently contributed to 10% of new infections each year.1 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.2

Behavioural approaches have been shown to be efficacious across a wide range of substance use disorders,3-5 and compatible with several other treatment approaches, including medication for opioid use disorders (MOUD).6 7 and traditional counselling approaches.8 However, existing evidence-based interventions require participants to have intact cognitive functioning in order to process and use intervention content.9-14 The influence of cognitive dysfunction on such approaches has not been addressed despite growing evidence that it negatively impacts treatment outcomes among persons with...
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 that 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 2⁴), 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...
by 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.\(^3\)\(^3\)\(^4\) 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)\(^3\)\(^3\)\(^4\) 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.\(^3\)\(^8\)

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.\(^3\)\(^8\)

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

---

Figure 1 Conceptual model for compensatory components targeting information in the IMB model. IMB, information-motivation-behavioural skills; PrEP, pre-exposure prophylaxis.
Open access

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. Persons whose performance falls within the MCI range on the MoCA based on age, education, race and ethnicity 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, 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 trials 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) 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 (e.g., 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. 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 43–45; (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 58–63; (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 Assessment35 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 89 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

Figure 3 Information, motivation, behavioural skills (IMB) model.
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: DSM-IV 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 χ² tests of categorical items to evaluate pretest equivalence between and within the experimental conditions. Any variable, such as biological sex or MOUD 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. 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. 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. 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
Open access

a variety of intervention approaches targeting PWID. The primary goals of the Ending the HIV Epidemic from the Centers of Disease Control and Prevention 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 (including PrEP adherence issues) and HIV-associated comorbidities (neurological complications).

Author affiliations

1Department of Allied Health Sciences, University of Connecticut, Storrs, Connecticut, USA
2Department of Psychiatry, Yale School of Medicine, New Haven, Connecticut, USA
3University of Connecticut Institute for Collaboration on Health Intervention and Policy, Storrs, Connecticut, USA
4Department of Social and Behavioral Science, New York University College of Global Public Health, New York, New York, USA
5Department of Internal Medicine—AIDS, Yale University School of Medicine, New Haven, Connecticut, USA
6Department of Psychology, Kent State University, Kent, Ohio, USA
7Department of Social and Behavioral Science, New York University College of Global Public Health, New York, New York, USA
8Department of Internal Medicine—AIDS, Yale University School of Medicine, New Haven, Connecticut, USA
9Department of Psychological Science, New York University College of Global Public Health, New York, New York, USA
10Department of Psychopharmacology, Yale School of Medicine, New Haven, Connecticut, USA
11Department of Social and Behavioral Science, New York University College of Global Public Health, New York, New York, USA
12Department of Social and Behavioral Science, New York University College of Global Public Health, New York, New York, USA
13Department of Clinical, Health Psychology and Research Methods, University of the Basque Country, Bilbao, Spain

Twitter Colleen B Mistler @ColleenMistler

Contributors CBM, MC, RS, JG and LC contributed to the conception and design of this work. CM, MC and RS drafted the article. LC and TM provided data analytical skills. NMC, BS and LM provided a critical revision of the article.

Funding

This work was supported by career development [K24-DA051344 to MMC and K01-DA051346 to RS], research [R01-DA055334 to MMC and training [T32-DA019426 to CM] awards from the National Institute on Drug Abuse. The funding sources are not responsible for data collection, data management, data analysis, interpretation of data or writing of the report.

Competing interests

None declared.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not applicable.

Provenance and peer review

Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Supplemental material

This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

Open access

This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID iD

Colleen B Mistler http://orcid.org/0000-0002-9681-0252

REFERENCES

18 Verdejo-Garcia A, Pérez Garcia M. Profile of executive deficits in cocaine and heroin Polysubstance users: common and differential...


BMJ Open: first published as 10.1136/bmjopen-2023-071688 on 30 June 2023. Downloaded from http://bmjopen.bmj.com/ on September 23, 2023 by guest. Protected by copyright.


