

# An Evaluation a PrEP-Focused HIV Prevention Intervention Tailored for Individuals with Opioid Use Disorder and Cognitive Dysfunction

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**Purpose:** This study aimed to test the efficacy of the 4-week Bio-behavioral Community-Friendly Health Recovery Program (CHRP-BB) at improving HIV prevention outcomes among individuals receiving medication for opioid use disorder (MOUD) and to examine the extent to which cognitive dysfunction impacts outcomes.

**Patients and Methods:** This randomized controlled trial included 237 individuals receiving MOUD and Pre-Exposure Prophylaxis (PrEP) in New Haven, CT. We conducted a longitudinal regression analysis to evaluate the impact of the intervention on HIV risk behaviors and PrEP-related outcomes over time. We estimated the effect of treatment on the outcome variables that include PrEP knowledge and adherence skills, HIV risk behavior, Syringe cleaning skills, and Condom skills using a difference-in-differences framework across four time periods (Post-intervention, and 3-, 6-, and 9-month follow-ups).

**Results:** The CHRP-BB intervention exerted a positive effect on experimental group participants across a range of key outcomes, particularly among shorter term IDUs. Improvements that were the most pronounced included PrEP outcomes (knowledge and adherence skills) and syringe cleaning skills. Most outcomes were not significantly disrupted by cognitive dysfunction.

**Conclusion:** Outcomes from this trial highlight the efficacy of the CHRP-BB intervention, including the use of cognitive dysfunction compensatory strategies, to significantly improve HIV prevention efforts among individuals on MOUD. We suggest that future efforts focus on refining and testing additional strategies that can further optimize intervention effects across a broader range of outcomes and MOUD patients.

**Keywords:** cognitive dysfunction, people who inject drugs, pre-exposure prophylaxis, HIV prevention, opioid use disorder, medication for opioid use disorder

## Introduction

The opioid epidemic in the US has halted HIV prevention progress, as one in ten new HIV infections are attributed to people who inject drugs (PWID).<sup>1</sup> Evidence-based HIV prevention interventions for people with opioid use disorder (OUD) typically consist of individual or group behavioral counseling sessions to improve HIV risk perception, HIV prevention knowledge, and HIV risk reduction behaviors.<sup>2</sup> These sessions, by nature, require participants to have intact cognitive functioning in order to fully participate and maximize efficacy. People with OUD often demonstrate cognitive dysfunction, with the pattern and severity of deficits similar to those found in persons with attention deficit hyperactivity disorder (ADHD) and traumatic brain injury (TBI). Deficits often include dysfunction in executive functioning, attention, memory, and information processing.<sup>3-5</sup> This specific cognitive profile can disrupt treatment engagement and retention,<sup>5</sup>

lead to increased HIV risk behaviors, increased risk of HIV transmission, and decreased adherence to medications.<sup>6,7</sup> While the prevalence of cognitive dysfunction among people with OUD is disproportionately higher than in the general population, it is often overlooked in HIV prevention and addiction treatment efforts.<sup>8,9</sup>

In a 2013 study, a new HIV prevention medication strategy, Pre-exposure prophylaxis (PrEP), demonstrated efficacy in reducing HIV transmission by almost 50% among very high-risk HIV-negative people who inject drugs (PWID).<sup>10</sup> This HIV prevention medication strategy was supported by the use of behavioral counseling and medication for opioid use disorder (MOUD).<sup>10</sup> Despite the efficacy of PrEP at preventing HIV transmission, PrEP uptake and adherence has been disturbingly low among PWID in the US (0–3%).<sup>11</sup> PrEP is most effective at preventing HIV transmission when taken precisely as prescribed; the pill requires daily adherence, and the long-acting injectable (LAI) requires bi-monthly injections.<sup>12</sup> The cognitive challenges of many high-risk individuals receiving MOUD, however, contribute to the low uptake and adherence to PrEP among this risk group. There is also evidence that other patient attributes, such as the extent of injection drug use history, influences how patients respond to harm reduction strategies.<sup>13</sup> Thus, PrEP-focused evidence-based behavioral interventions must be tailored to accommodate a range of patient attributes that are common among individuals on MOUD.

Integrating PrEP services into existing substance use treatment settings and syringe service programs has shown feasibility, acceptability, and preliminary efficacy in improving PrEP interest and uptake among individuals with OUD.<sup>14–19</sup> One such integrated intervention approach is the Bio-behavioral Community-Friendly Health Recovery Program (CHRP-BB),<sup>20,21</sup> designed for implementation in real-world substance use treatment settings. Although preliminary research on the Bio-Behavioral Community-friendly Health Recovery Program (CHRP-BB) demonstrated acceptability and feasibility of improving adherence to PrEP and reducing HIV risk in PWID, its efficacy has not been evaluated across a diverse sample of patients on MOUD. Therefore, this study seeks to evaluate the efficacy of CHRP-BB at improving HIV prevention outcomes among individuals receiving MOUD, and to examine the extent to which patient attributes (eg, cognitive dysfunction, IDU history), influence HIV prevention outcomes.

Based on the information, motivation, and behavioral skills (IMB) model,<sup>22</sup> this intervention was adapted and tailored to accommodate the cognitive profiles of individuals receiving MOUD with the aim of optimizing PrEP interest, uptake, adherence, and HIV risk reduction among people receiving MOUD. The CHRP-BB approach addresses cognitive dysfunction through a variety of compensatory strategies that are incorporated into the brief HIV prevention group sessions.<sup>5</sup> A number of evidence-based strategies are implemented, including the use of structured sessions with a written agenda, a multi-modal presentation of information, hands-on activities, immediate feedback, and memory aids (eg, daily text message reminders).

In the present study, a fully powered randomized controlled clinical trial of the CHRP-BB intervention was conducted to test its efficacy at improving PrEP- and HIV risk reduction-related outcomes among individuals receiving MOUD. Differences were also assessed between participants with intact vs impaired cognitive functioning. We hypothesized that participants who received the 4-week bio-behavioral intervention would demonstrate significantly greater improvements in PrEP and HIV risk reduction outcomes compared to participants who received treatment as usual (TAU) care in a substance use treatment program.

## Material and Methods

### Recruitment and Sample

A purposive sample was recruited through an opioid replacement substance use treatment program in New Haven, CT, via clinic-based advertisements and flyers, word-of-mouth, and direct referrals from their counselors. Participants were included in the study if they met the following criteria: a) DSM-V criteria for opioid use disorder (OUD); b) enrolled in opioid substitution therapy for OUD; c) self-reported being HIV negative; d) at least 18 years or older; e) reported unsafe injection drug use practices or unprotected sex within (past 3 months); f) have a cell phone; g) able to understand, speak, and read English; and h) willing to initiate PrEP use; and i) able to communicate (read, write and speak) in English. Participants were excluded if they were a) unable to attend all intervention and follow-up assessment sessions; and/or b) actively suicidal, psychotic, and/or homicidal.

## Procedures

### Study Design

Participants were randomized into one of the two conditions: CHRP-BB intervention (experimental condition) vs a time- and attention-matched control condition. The power analysis was computed for an effect size ( $d$ ) of 0.37, a small-medium effect size to be conservative, based on similar intervention studies in similar facilities comparing groups in terms of high levels of medication adherence and changes in HIV risk behavior. The computations assumed an intra-class correlation (ICC) of 0.500. All participants were linked to PrEP services, and after confirmation of PrEP prescription, they completed baseline assessments. Participants in the experimental condition attended 4-weekly 50-minute group sessions and one 8-week booster session, in which two trained facilitators provided HIV prevention sessions using a multimodal presentation style. Intervention fidelity was measured by an independent reviewer's checklist to ensure that each session was delivered in a standardized manner. Any discrepancies were discussed weekly by the facilitators and the reviewer. The 4 weekly sessions topics included: 'Making the Most of PrEP as an Active Health Manager', 'Reducing Drug Risk and Taking PrEP', 'PrEP Adherence and Sex Risk Reduction Strategies', and Negotiating Partner Support for HIV Prevention. A detailed overview of this intervention and associated protocols has been reported elsewhere.<sup>21</sup> Participants in the control condition received TAU, consisting of ongoing MOUD and a matching amount of group counseling time and attention routinely offered by the substance use treatment program. After 8-weeks, all participants completed a post-assessment and then 3-, 6-, and 9-month follow-up assessments.

During the initial intake session, participants completed self-report surveys to collect data on their demographics, as well as PrEP and HIV risk reduction constructs<sup>22</sup> using Qualtrics survey software.<sup>23</sup> Participants also completed a risk reduction skills assessment at the intake session.<sup>24–26</sup> The surveys and skills assessments were also completed at the 8-week post and at 3-, 6-, and 9-month follow-ups. Cognitive status was assessed retrospectively using a combination of electronic medical records review and self-reported cognitive functioning items.<sup>27</sup> The study was approved by the University of Connecticut Institutional Review Board (IRB; H17-200) and the APT foundation, Inc., a substance use treatment program. This study complies with the Declaration of Helsinki principles; all participants provided fully informed consent prior to their enrollment in the study. This study was registered at ClinicalTrials.gov (# NCT03282890).

## Material and Methods

### Demographics

Participants were asked to report their age, gender, racial-ethnic identity, sexual identity, marital status, education level, primary language, employment status, yearly income, and health insurance status.

### Cognitive Dysfunction Risk Score (CDRS)

The CDRS consists of a total score of 11-items designed to assess cognitive functioning among individuals with opioid use disorder (OUD) who are enrolled in opioid replacement therapy (ORT).<sup>27</sup> Each of the following demographic/medical variables were converted to binary indicators, which are equal to "1" if a condition is met, and "0" otherwise:  $\geq 50$  years of age, education less than high school graduate, non-white, history of head injury, any other psychological diagnosis (ie, in addition to OUD), history of overdose, history of polysubstance use in past two years. Self-reported questions required participants to respond to the following questions on a four-point Likert Scale ranging from not at all, slightly, somewhat, moderately, and extremely: If they count with their fingers, forget the names of common things, drop things frequently, and if part of their body feels numb. These items were recoded for "not at all" and "slightly" to equal 0, and for "somewhat", "moderately", and "extremely" to equal 1. A total score was calculated using these 11 items, ranging from 0–11. Scores of 0–4 were categorized as "Intact cognitive functioning", and 5–11 as "Impaired cognitive functioning."

### PrEP-Related Measures

PrEP-related measures included 12 items focused on each participant's PrEP Knowledge as well as 11 items designed to assess their PrEP Adherence Skills.<sup>22,28</sup> The 12 PrEP Knowledge items (eg, "PrEP provides protection against other sexually transmitted infections") required participants to indicate whether the items were true, false, or if they were unsure. The 11

PrEP Adherence Skills items (eg, “How confident are you that you could make PrEP part of your daily routine?”) required participants to indicate either: not at all, somewhat confident, moderately confident, very confident, or completely confident.

### HIV Risk Reduction Measures

Categorical HIV risk reduction measures<sup>22,28</sup> consisted of Information, Motivation, and Behavioral skills questions based on the IMB model of health behavior change. Four information (knowledge) variables included questions such as “If an HIV+ person only has sex with another HIV+ person, they don’t need to use a condom”. Participants were asked to indicate if the four questions were true, false, or if they were unsure. Eight motivation items included questions on readiness to change and intentions to change HIV risk behavior, such as “I plan not to have sex during the next 3 months”. Participants were asked to indicate whether the eight statements were very true, somewhat true, neither true nor untrue, somewhat untrue, or very untrue. Four behavioral skills items related to self-efficacy about risk reduction skills, such as “How hard would it be for you to always use condoms or latex protection if you have oral, vaginal, or anal sex?” Participants were asked to indicate whether these behaviors would be very hard to do, fairly, hard to do, neither hard nor easy to do, somewhat easy to do, or very easy to do.

### Behavioral Skills

Participants’ HIV risk reduction behavioral skills were systematically assessed as in prior randomized controlled trials<sup>24–26</sup> by having participants demonstrate the 16 steps necessary to properly clean a syringe, 17 steps necessary to properly use a male condom, and 15 steps necessary to properly use a female condom. Ratings of audio-taped demonstrations of these standardized procedures have shown high inter-rater reliability in similar prior trials (inter-rater reliability = 0.98).<sup>25</sup> A total score was calculated for each of the three HIV risk reduction skills assessments; a higher total score indicated a greater HIV risk reduction skill level.

## Data Analysis

First, *t*-tests and Chi-squared tests were conducted to determine if there were any significant differences between conditions for all demographic variables at baseline. Second, to assess the impact of the intervention on HIV risk behaviors and PrEP-related outcomes, we conducted a longitudinal regression analysis. More specifically, we estimated the effect of treatment on the outcome variables across four time periods (Post-intervention, and 3-, 6-, and 9-month follow-ups) using a difference-in-differences framework.<sup>29</sup> The model includes a Time indicator, equal to unity for each post-intervention period and “0” otherwise, a Group indicator identifying intervention group, and interaction terms between Group and Time. Based on prior research,<sup>13</sup> we also included injection drug use (IDU) history as a moderator variable, categorized as longer term IDU (above the median in years) and shorter term IDU (below the median in years). Two-way interaction terms between IDU history and Time and three-way interactions between IDU history, Group, and Time were also included to assess differential treatment effects by IDU history. The statistical significance was evaluated using *t*-tests, with inference drawn from robust clustered standard errors to adjust for the correlated structure resulting from repeated longitudinal measures. CDRS, and IDU history by Group, and Time interactions were also used to test the possible moderation effect of the intervention due to the intact or impaired cognitive functioning of participants, and IDU history. PrEP- and HIV risk-related variables were recoded to standardize the scales using reverse coding as applicable to make the results more intuitive, as higher scores indicate better HIV risk reduction information, motivation, and behavioral skills. Missing data were assumed to be missing at random and multiple imputations with chained equations, using the Markov chain Monte Carlo (MCMC) method to impute the missing data.<sup>30</sup> Data analyses were conducted using SPSS v. 28<sup>31</sup> and Stata.<sup>32</sup>

## Results

### Demographics

The average age of the 237 participants was 43 years old (S.D. = 10.06), and 51% of the sample identified as male. Those identifying as White made up 61% of the sample population; participants identifying as African American or Black made up 21%, 15% identified as Hispanic/Latinx, and 3% identified as Others. Most participants identified as heterosexual (79%) and having health insurance (99%). More than half of the participants had at least a high school diploma / GED (74%), and more than half reported having less than \$10,000 annual income (79%). Participants with intact cognitive functioning comprised 58% of the

sample, while 42% had impaired cognitive functioning. Approximately half of the sample reported an injection drug use (IDU) history of greater than 20 years. There was a statistically significant difference between conditions in terms of Ethnicity (Table 1), so that variable was controlled in all analyses.

**Table 1** Baseline Characteristics and Demographic Variables

Demographic	Total Sample		Experimental Condition (BB)		Control Condition		Pearson Chi-Squared 2-Sided p-Value
	(n = 237)		(n=120)		(n=117)		
	n / m*	% / S.D.*	n / m*	% / S.D.*	n / m*	% / S.D.*	
Age (average)*	43.64	10.06	43.63	10.06	43.66	10.10	0.980
Methadone Dose (average)*	86.28	31.05	85.52	29.67	87.07	32.52	0.701
<b>Gender</b>							0.607
Male	122	51.5%	61	50.8%	61	52.1%	
Female	114	48.1%	58	48.3%	56	47.9%	
Neutral	1	0.4%	1	0.8%	0	0.0%	
<b>Racial-Ethnic Identity</b>							0.025
White	144	60.8%	76	63.3%	68	58.1%	
African American or Black	49	20.7%	20	16.7%	29	24.8%	
Hispanic or Latinx	36	15.2%	23	19.2%	13	11.1%	
Other	8	3.4%	1	0.8%	7	6.0%	
<b>Sexual Identity</b>							0.304
Heterosexual or Straight	187	78.9%	96	80.0%	91	77.8%	
Homosexual, Gay, or Lesbian	11	4.6%	5	4.2%	6	5.1%	
Bisexual	36	15.2%	16	13.3%	20	17.1%	
Other	3	1.3%	3	2.5%	0	0.0%	
<b>Current Marital Status</b>							0.485
Currently married or living with partner	44	18.6%	21	17.5%	23	19.7%	
Divorced	45	19.0%	27	22.5%	18	15.4%	
Separated	20	8.4%	12	10.0%	8	6.8%	
Widowed	8	3.4%	3	2.5%	5	4.3%	
Never married	120	50.6%	57	47.5%	63	53.8%	
<b>Education level</b>							0.276
Middle School	12	5.1%	6	5.0%	6	5.1%	
Some high school, no degree	48	20.3%	25	20.8%	23	19.7%	
High school Graduate / GED	105	44.3%	49	40.8%	56	47.9%	
2-year college degree	7	3.0%	1	0.8%	6	5.1%	

(Continued)

**Table 1** (Continued).

Demographic	Total Sample		Experimental Condition (BB)		Control Condition		Pearson Chi-Squared 2-Sided p-Value
	(n = 237)		(n=120)		(n=117)		
	n / m*	% / S.D.*	n / m*	% / S.D.*	n / m*	% / S.D.*	
Technical / Trade / Vocational	28	11.8%	18	15.0%	10	8.5%	
4-year college degree	27	11.4%	17	14.2%	10	8.5%	
Graduate degree	8	3.4%	3	2.5%	5	4.3%	
Masters or PhD	2	0.8%	1	0.8%	1	0.9%	
<b>Primary Language</b>							0.615
English	223	94.1%	112	93.3%	111	94.9%	
Spanish	14	5.9%	8	6.7%	6	5.1%	
<b>Current Employment Status</b>							0.964
Currently working	27	11.4%	14	11.7%	13	11.1%	
Only temporarily laid off, sick leave or maternity leave	3	1.3%	1	0.8%	2	1.7%	
Unemployed and looking for work	89	37.6%	47	39.2%	42	35.9%	
Retired	10	4.2%	4	3.3%	6	5.1%	
Disabled, permanently or temporarily	63	26.6%	31	25.8%	32	27.4%	
Keeping house (full-time homemaker)	4	1.7%	2	1.7%	2	1.7%	
Student	4	1.7%	2	1.7%	2	1.7%	
Unemployed and not looking for work	21	8.9%	9	7.5%	12	10.3%	
Other	16	6.8%	10	8.3%	6	5.1%	
<b>Current Yearly Income</b>							0.441
less than \$10,000	188	79.3%	96	80.0%	92	78.6%	
\$10,000 - \$19,999	33	13.9%	16	13.3%	17	14.5%	
\$20,000 - \$29,999	11	4.6%	7	5.8%	4	3.4%	
\$30,000 or more	5	2.1%	1	0.8%	4	3.4%	
<b>Health Insurance</b>							0.546
No	3	1.3%	1	0.8%	2	1.7%	
Yes	234	98.7%	119	99.2%	115	98.3%	
<b>Cognitive Functioning</b>							0.793
Intact	137	57.8%	68	56.7%	69	59.0%	
Impaired	100	42.2%	52	43.3%	48	41.0%	

(Continued)

**Table 1** (Continued).

Demographic	Total Sample		Experimental Condition (BB)		Control Condition		Pearson Chi-Squared 2-Sided p-Value
	(n = 237)		(n=120)		(n=117)		
	n / m*	% / S.D.*	n / m*	% / S.D.*	n / m*	% / S.D.*	
<b>Years of Injection Drug Use (IDU)</b>							
< 20 years	107	54.9%	54	45.0%	53	45.0%	0.963
≥ 20 years	130	45.1%	66	55.0%	64	55.0%	

Notes: \* = t-test results; m = mean, S.D. = standard deviation.

## Intervention Outcomes

### PrEP Outcomes (Knowledge and Adherence Skills)

Participants in the intervention group with a shorter IDU history showed statistically significant improvements in PrEP Knowledge scores at the Post ( $\beta = 1.15$ ,  $p < 0.01$ ), 6-month ( $\beta = 0.84$ ,  $p = 0.06$ ) and 9-month points following the intervention ( $\beta = 1.09$ ,  $p < 0.01$ ). By contrast, individuals with a longer IDU history had lower PrEP Knowledge scores in both the control and intervention group ( $\beta = -0.368$ ,  $p = 0.07$ ). At 9-months, shorter IDU history was associated with higher PrEP Knowledge scores in the intervention group, as evidenced by the 3-way interaction term ( $\beta = -1.00$ ,  $p = 0.02$ ).

As evidenced by the two way and three way interactions, cognitive dysfunction did tend to disrupt the treatment effect on PrEP Knowledge, but only at the Post and 3-month follow-up points ( $\beta = -1.17$ ,  $p < 0.01$  and  $\beta = -0.92$ ,  $p = 0.034$ ). At the 6- and 9-month points, the intervention effect was not significantly impacted by cognitive dysfunction relative to baseline ( $\beta = -0.44$ ,  $p = 0.34$  and  $\beta = -0.30$ ,  $p = 0.50$ ).

For the PrEP Adherence Skills outcome, we tested the presence of a moderator effect of IDU history and found no evidence that the intervention had a differential impact on PrEP adherence skills based on the length of participants' IDU history. Thus, we excluded the IDU history moderator from the model based on the relative goodness of fit metric, adjusted  $R^2$ . Participants in the intervention group showed statistically significant improvements in PrEP adherence skills at 6-months ( $\beta = 5.15$ ,  $p = 0.04$ ) and 9-months following the intervention ( $\beta = 5.16$ ,  $p = 0.08$ ). We found evidence that this effect was moderated by cognitive dysfunction at 6 months and 9 months, such that the impact of the intervention was reduced by the presence of cognitive dysfunction, as evidence by the interaction between cognitive dysfunction, intervention and the 6 and 9-month time indicators ( $\beta = -6.42$ ,  $p = 0.06$ ) and ( $\beta = -6.65$ ,  $p = 0.06$ ), respectively (Table 2).

**Table 2** Intervention Effects for PrEP Knowledge and PrEP Adherence Behavior Outcomes (n = 237)

Parameter	PrEP Knowledge			PrEP Behavior		
	Estimate	p-Value	95% Confidence Interval	Estimate	p-Value	95% Confidence Interval
Intercept	7.73	0.000	(7.31, 8.15)	28.34	0.00	(26.12, 30.56)
Posttest	0.00	0.998	(-0.70, 0.70)	-3.92	0.02	(-7.24, -0.60)
3 Month FUP	0.55	0.091	(-0.09, 1.19)	-6.74	0.00	(-10.53, -2.96)
6 Month FUP	0.34	0.352	(-0.38, 1.05)	-5.07	0.01	(-8.62, -1.53)
9 Month FUP	0.54	0.096	(-0.10, 1.17)	-8.02	0.00	(-12.57, -3.48)
Arm	-0.02	0.938	(-0.42, 0.38)	1.15	0.25	(-0.80, 3.09)
Arm * Posttest	1.15	0.006	(0.34, 1.96)	1.44	0.51	(-2.86, 5.74)
Arm * 3 Month FUP	0.54	0.176	(-0.24, 1.33)	3.05	0.19	(-1.51, 7.61)
Arm * 6 Month FUP	0.84	0.055	(-0.02, 1.70)	5.15	0.04	(0.20, 10.10)

(Continued)



**Table 2** (Continued).

Parameter	PrEP Knowledge			PrEP Behavior		
	Estimate	p-Value	95% Confidence Interval	Estimate	p-Value	95% Confidence Interval
Arm * 9 Month FUP	1.09	0.004	(0.34, 1.83)	5.16	0.08	(-0.71, 11.02)
Ethnicity	-0.33	0.000	(-0.44, -0.21)	1.04	0.02	(0.17, 1.92)
Cognitive Dysfunction: Impaired	-0.46	0.027	(-0.86, -0.05)	-1.51	0.13	(-3.46, 0.44)
Cognitive Dysfunction * Posttest	0.85	0.030	(0.09, 1.62)	-0.25	0.91	(-4.68, 4.18)
Cognitive Dysfunction * 3 months FUP	0.60	0.105	(-0.12, 1.32)	3.30	0.22	(-2.05, 8.64)
Cognitive Dysfunction * 6 months FUP	0.32	0.437	(-0.48, 1.12)	1.50	0.55	(-3.45, 6.45)
Cognitive Dysfunction * 9 months FUP	0.25	0.527	(-0.53, 1.03)	3.06	0.24	(-2.10, 8.22)
Cognitive Dysfunction * Arm * Posttest	-1.17	0.006	(-2.00, -0.34)	-1.19	0.67	(-6.65, 4.27)
Cognitive Dysfunction * Arm * 3 months FUP	-0.92	0.034	(-1.77, -0.07)	-2.91	0.34	(-8.98, 3.15)
Cognitive Dysfunction * Arm * 6 months FUP	-0.44	0.336	(-1.34, 0.46)	-6.42	0.06	(-13.21, 0.38)
Cognitive Dysfunction * Arm * 9 months FUP	-0.30	0.499	(-1.16, 0.56)	-6.65	0.06	(-13.66, 0.35)
Years IDU: ≥20 years	-0.37	0.069	(-0.77, 0.03)			
Years IDU * Posttest	0.03	0.941	(-0.75, 0.81)			
Years IDU * 3 months FUP	0.03	0.938	(-0.69, 0.75)			
Years IDU * 6 months FUP	0.22	0.588	(-0.58, 1.02)			
Years IDU * 9 months FUP	0.33	0.391	(-0.42, 1.08)			
Years IDU * Arm * Posttest	-0.35	0.405	(-1.18, 0.48)			
Years IDU * Arm * 3 months FUP	-0.27	0.528	(-1.09, 0.56)			
Years IDU * Arm * 6 months FUP	-0.45	0.315	(-1.34, 0.43)			
Years IDU * Arm * 9 months FUP	-1.00	0.016	(-1.81, -0.19)			

**Notes:** Intercept = Average estimated PrEP Knowledge and PrEP Behavior score among non-White participants with intact cognition and < 20 years of IDU in the control group at baseline. FUP = Follow-up.

### HIV Risk Reduction Outcomes

The intervention group showed a significant improvement in HIV Risk reduction behavior scores at the 9-month follow-up point ( $\beta = 2.39$ ,  $p = 0.012$ ), while scores at the other time points showed positive but non-significant intervention effects in the predicted direction (Table 3). The coefficients for the Time variables were positive and significant, indicating that the HIV risk behavior scores increased over time in both the control and intervention groups relative to baseline. In addition, cognitive dysfunction did not have a statistically significant association with HIV risk behavior

**Table 3** Intervention Effects for HIV Risk Reduction Behaviors and Syringe Cleaning Skills Outcomes (n = 237)

Parameter	HIV Risk Reduction Behaviors			Syringe Cleaning Skills		
	Estimate	p-Value	95% Confidence Interval	Estimate	p-Value	95% Confidence Interval
Intercept	12.91	0.000	(11.93, 13.89)	42.37	0.000	(35.39, 49.34)
Posttest	2.01	0.008	(0.54, 3.48)	20.64	0.000	(9.59, 31.70)
3 Month FUP	2.97	0.000	(1.41, 4.53)	33.60	0.000	(22.52, 44.69)
6 Month FUP	3.53	0.000	(2.10, 4.97)	32.66	0.000	(21.60, 43.72)
9 Month FUP	3.18	0.000	(1.62, 4.73)	32.93	0.000	(21.62, 44.24)
Arm	0.21	0.655	(-0.71, 1.13)	-1.54	0.621	(-7.64, 4.57)
Arm * Posttest	1.51	0.132	(-0.46, 3.47)	16.77	0.014	(3.36, 30.19)
Arm * 3 Month FUP	1.19	0.229	(-0.75, 3.14)	6.16	0.375	(-7.48, 19.80)
Arm * 6 Month FUP	1.50	0.109	(-0.33, 3.33)	15.59	0.015	(2.98, 28.20)
Arm * 9 Month FUP	2.39	0.012	(0.54, 4.25)	22.47	0.001	(9.82, 35.12)

(Continued)



**Table 3** (Continued).

Parameter	HIV Risk Reduction Behaviors			Syringe Cleaning Skills		
	Estimate	p-Value	95% Confidence Interval	Estimate	p-Value	95% Confidence Interval
Years IDU: $\geq 20$ years	-0.96	0.041	(-1.88, -0.04)	3.44	0.275	(-2.74, 9.63)
Years IDU * Posttest	0.24	0.804	(-1.64, 2.11)	-0.92	0.890	(-13.93, 12.09)
Years IDU * 3 months FUP	1.10	0.246	(-0.76, 2.97)	-3.79	0.561	(-16.58, 9.00)
Years IDU * 6 months FUP	-0.32	0.733	(-2.18, 1.53)	-1.43	0.825	(-14.18, 11.31)
Years IDU * 9 months FUP	1.10	0.250	(-0.77, 2.97)	-1.50	0.820	(-14.38, 11.39)
Years IDU * Arm * Posttest	-0.68	0.566	(-3.01, 1.65)	1.48	0.846	(-13.49, 16.45)
Years IDU * Arm * 3 months FUP	-1.60	0.159	(-3.84, 0.63)	-6.68	0.408	(-22.50, 9.14)
Years IDU * Arm * 6 months FUP	-0.41	0.710	(-2.59, 1.76)	-11.23	0.125	(-25.56, 3.11)
Years IDU * Arm * 9 months FUP	-1.58	0.136	(-3.67, 0.50)	-14.59	0.047	(-29.00, -0.19)
Ethnicity	0.00	0.982	(-0.26, 0.25)	-2.70	0.001	(-4.27, -1.14)
Cognitive Dysfunction: Impaired	-0.50	0.299	(-1.44, 0.44)	-7.56	0.015	(-13.63, -1.50)
Cognitive Dysfunction * Time	0.48	0.448	(-0.76, 1.73)	3.92	0.355	(-4.41, 12.25)
Cognitive Dysfunction * Arm * Time	-0.95	0.097	(-2.08, 0.17)	-0.55	0.888	(-8.17, 7.08)

**Notes:** Intercept = Average estimated HIV Risk Reduction Behavior score and Syringe Cleaning score among non-White participants with intact cognition and < 20 years of IDU in the control group at baseline. FUP = Follow-up.

scores. Participants with a shorter IDU history had lower HIV risk behavior scores at baseline ( $\beta = -0.96$ ,  $p = 0.041$ ), but the interactions between IDU history and time indicators were not statistically significant. We found no statistical difference over time between groups in terms of changes in HIV risk reduction knowledge ([Table S1](#)).

## Behavioral Skills

### Syringe Cleaning Skills

The intervention effect on syringe cleaning skills showed that participants in the intervention group demonstrated statistically significant improvements in syringe cleaning skills over time relative to the control group at Post ( $\beta = 16.77$ ,  $p = 0.014$ ), 6-months ( $\beta = 15.59$ ,  $p = 0.015$ ), and 9-months ( $\beta = 22.47$ ,  $p = 0.001$ ). A significant three-way interaction between Group, IDU history, and 9-month period ( $\beta = -14.59$ ,  $p = 0.047$ ) showed that longer-term IDUs had significantly smaller improvements stemming from the intervention effect relative to those with shorter-term IDUs.

In addition, White participants ( $\beta = -2.70$ ,  $p = 0.001$ ) and those with cognitive dysfunction ( $\beta = -7.56$ ,  $p = 0.015$ ) showed lower syringe cleaning skill scores at baseline in both control and intervention groups. We did not find any significant evidence that cognitive dysfunction disrupted syringe cleaning skills in the intervention group over time.

### Male Condom Application Skills

The intervention effect on male condom application skills was statistically significant at the 9-month point ( $\beta = 6.92$ ,  $p = 0.031$ ), indicating that shorter term IDUs in the intervention group demonstrated greater improvements in male condom application skills at 9 months compared to those in the control group. Individuals with a longer IDU history showed less improvements in male condom skills compared to shorter term IDUs in the treatment group at 9-months ( $\beta = -6.58$ ,  $p = 0.032$ ). At the other time points, the difference between control and intervention groups was not statistically significant. Both the control and intervention groups, however, exhibited positive effects at all time points ( $p < 0.01$ ) indicating that male condom application skills improved over time relative to baseline. In addition, White participants ( $\beta = -1.35$ ,  $p = 0.009$ ) and those with cognitive dysfunction ( $\beta = -5.55$ ,  $p = 0.009$ ) demonstrated significantly lower male condom application skill scores across time. There was also a statistically significant Cognitive Dysfunction  $\times$  Time interaction ( $\beta = 5.19$ ,  $p = 0.042$ ), suggesting that cognitively impaired participants in both conditions made some improvements at posttest ([Table 4](#)).

### Female Condom Application Skills

The intervention effect on female condom application skills was statistically significant at the 9-month point ( $\beta = 9.6$ ,  $p =$

**Table 4** Intervention Effects for Female Condom Skills and Male Condom Skills Outcomes (n =237)

Parameter	Female Condom Skills			Male Condom Skills		
	Estimate	p-Value	95% Confidence Interval	Estimate	p-Value	95% Confidence Interval
Intercept	56.23	0.000	(65.69, 75.25)	70.47	0.000	(50.02, 62.45)
Posttest	23.91	0.000	(7.68, 21.05)	14.36	0.000	(15.60, 32.22)
3 Month FUP	29.78	0.000	(14.73, 26.49)	20.61	0.000	(21.68, 37.87)
6 Month FUP	29.61	0.000	(14.47, 26.56)	20.51	0.000	(21.41, 37.81)
9 Month FUP	30.17	0.000	(14.89, 26.82)	20.85	0.000	(22.32, 38.03)
Arm	2.35	0.399	(-2.75, 5.64)	1.44	0.500	(-3.12, 7.82)
Arm * Posttest	5.68	0.205	(-1.26, 13.37)	6.06	0.105	(-3.11, 14.46)
Arm * 3 Month FUP	2.55	0.563	(-6.99, 6.21)	-0.39	0.907	(-6.09, 11.19)
Arm * 6 Month FUP	6.15	0.156	(-4.02, 9.53)	2.76	0.425	(-2.34, 14.63)
Arm * 9 Month FUP	9.06	0.027	(0.63, 13.21)	6.92	0.031	(1.01, 17.11)
Years IDU: ≥20 years	0.03	0.990	(-1.68, 6.70)	2.51	0.239	(-5.51, 5.58)
Years IDU * Posttest	-6.80	0.182	(-10.08, 4.94)	-2.57	0.502	(-16.79, 3.19)
Years IDU * 3 months FUP	-2.42	0.605	(-9.69, 3.49)	-3.10	0.357	(-11.58, 6.74)
Years IDU * 6 months FUP	-0.03	0.995	(-9.32, 3.84)	-2.74	0.414	(-8.84, 8.78)
Years IDU * 9 months FUP	1.52	0.720	(-6.83, 5.82)	-0.50	0.876	(-6.78, 9.81)
Years IDU * Arm * Posttest	1.27	0.810	(-9.32, 6.58)	-1.37	0.735	(-9.12, 11.67)
Years IDU * Arm * 3 months FUP	-2.62	0.568	(-6.93, 7.26)	0.16	0.964	(-11.64, 6.39)
Years IDU * Arm * 6 months FUP	-4.77	0.250	(-10.29, 3.81)	-3.24	0.368	(-12.90, 3.36)
Years IDU * Arm * 9 months FUP	-8.48	0.034	(-12.59, -0.57)	-6.58	0.032	(-16.30, -0.66)
Ethnicity	-1.29	0.029	(-2.37, -0.33)	-1.35	0.009	(-2.45, -0.14)
Cognitive Dysfunction: Impaired	-0.74	0.794	(-9.73, -1.37)	-5.55	0.009	(-6.28, 4.80)
Cognitive Dysfunction * Time	0.31	0.928	(0.19, 10.19)	5.19	0.042	(-6.32, 6.93)
Cognitive Dysfunction * Arm * Time	-2.72	0.242	(-6.30, 0.99)	-2.66	0.153	(-7.28, 1.84)

**Notes:** Intercept = Average estimated skills score among non-White participants with intact cognition and < 20 years of IDU in the control group at baseline.  
FUP = Follow-up.

0.03), indicating that shorter-term IDUs in the intervention group demonstrated greater improvements in female condom application skills at 9 months compared to those in control group. At other time points, the difference between groups was not statistically significant. Both control and intervention groups exhibited positive effects at all time points ( $p < 0.01$ ), indicating that female condom skills improved over time relative to the baseline. The 3-way interaction between IDU history, intervention group, and 9-month time period was statistically significant, such that individuals with a longer IDU history demonstrated less improvement in female condom skills compared to shorter term IDUs at 9-months ( $\beta = -8.4$ ,  $p = 0.03$ ). In addition, White participants ( $\beta = -1.2$ ,  $p = 0.03$ ) demonstrated significantly lower female condom skill scores across time. There was no statistically significant association between cognitive dysfunction and intervention; thus, there was no significant difference in female condom application skill changes due to cognitive dysfunction.

## Discussion

The design and focus of this study was guided by recommendations from the Substance Abuse and Mental Health Services Administration (SAMHSA), which promotes the need to review patients' psychosocial history and cognitive functioning in order to properly design behavioral interventions.<sup>33</sup> Our preliminary work<sup>3-5</sup> also provided the rationale for adapting an existing evidence-based intervention to better accommodate the cognitive profiles of individuals with OUD receiving MOUD. Following adaptation and feasibility testing,<sup>34,35</sup> the present study tested the impact of the experimental CHRP-BB intervention, a PrEP-focused HIV risk reduction approach specifically tailored for individuals on MOUD, many of whom demonstrate mild to moderate cognitive dysfunction. The CHRP-BB approach includes compensatory strategies specifically designed to enhance participants' ability to process and utilize intervention content.

Encouraging outcomes were found in terms of improvements in PrEP-related knowledge, PrEP adherence skills, HIV risk reduction, and various HIV prevention skills stemming from the CHRP-BB intervention approach relative to the time-and-attention-matched control condition. Interestingly, certain outcomes were most pronounced among a subgroup of patients with a shorter history of injection drug use, including significantly greater improvements in PrEP Knowledge, male condom application skills, and female condom application skills. This is consistent with prior work showing that diverse samples of IDUs tend to exhibit differential responses to harm reduction strategies based on their injection history, which may be a proxy for a host of other unmeasured attributes.<sup>13</sup> Although there was no evidence that cognitive dysfunction impeded improvements in male and female condom application skills, it did attenuate the intervention effect on PrEP Knowledge at the Post and 3-month period, and PrEP adherence skills at the 6 and 9-month periods. This points toward the potential benefit of incorporating more potent compensatory intervention strategies to enhance PrEP-focused outcomes.

In contrast, the intervention effects on syringe cleaning skills and HIV risk reduction outcomes did not diverge based on cognitive dysfunction or IDU history. Thus, the CHRP-BB approach tended to exert positive outcomes on intervention group participants regardless of cognitive dysfunction. It is particularly encouraging that the experimental intervention strategies that were designed to compensate for (ie, work around) cognitive dysfunction may have enhanced many participants' ability to accrue the expected intervention effects in this case, as intended.<sup>36</sup> Interestingly, although the pattern of syringe cleaning skills and HIV risk reduction outcomes were in the predicted direction earlier, they reached significance only at the latter time point. We note, however, that delayed emergence of treatment effects is not unusual in response to behavioral interventions, and is arguably even more important than early treatment success that often decays rapidly.<sup>37</sup>

Overall, the pattern of findings suggests that the CHRP-BB intervention may benefit from further refinement in order to optimize a broader range of PrEP-focused outcomes and a more diverse range of patients on MOUD, including those with a more extensive history of IDU. Relatedly, continuing along this line of research, it would be helpful to determine which specific compensatory strategies – alone or in varied combinations – are the most potent in terms of boosting HIV prevention outcomes in this priority population.

## Limitations

While this study examines an innovative approach, as the first PrEP-focused intervention tailored to the cognitive profiles of individuals receiving MOUD, there are some limitations worth mentioning. This study only recruited participants who could understand, speak, and read the English language, and participants who had a phone for communicating daily text messages in English. Therefore, we may have missed the opportunity to test the impacts of this intervention on non-English speakers, which presents a sample-selection bias. Cognitive functioning was measured via a validated item;<sup>27</sup> however, this cognitive dysfunction risk score provides a score based on a one-time measurement that does not account for fluctuations in daily cognitive function or extraneous variables that may influence cognitive functioning. Future studies should measure cognitive functioning more frequently in order to improve the precision of this measurement. While this intervention was designed for implementation within a common type of opioid replacement drug treatment setting, the generalizability to other clinical settings may be reduced. Despite a time- and attention-match control condition, the benefits of this particular intervention should be further researched using an active control condition. In addition, despite efforts for equal distribution of demographic variables between conditions there were significant differences between the two intervention conditions regarding ethnicity. Thus, findings should be interpreted in the context of these limitations.

## Conclusion

This study used a randomized controlled trial designed to test a novel experimental intervention approach – CHRP-BB,<sup>20,21</sup> a PrEP-focused adapted evidence-based HIV prevention intervention, vs a time- and attention-matched control condition. The CHRP-BB intervention was specifically tailored to accommodate the mild to moderate cognitive dysfunction found in many patients enrolled in MOUD treatment. In terms of treatment outcomes, a key reason that cognitive dysfunction is relevant to this patient population is that it can disrupt patients' ability to fully process and utilize intervention content. Not surprisingly, prior studies have shown differential outcomes when comparing those classified as having cognitive dysfunction relative to their counterparts classified with intact cognitive functioning.<sup>38</sup> Thus, our aim in developing CHRP-BB was to

enhance HIV prevention outcomes by integrating proven compensatory strategies to work around their common cognitive challenges, which would allow them to accrue the expected intervention benefits.

Overall, our outcomes suggest that the CHRP-BB intervention exerted an important positive effect on experimental group participants across a range of key outcomes, and the level of improvement went well beyond what was evidenced among participants in the active control condition, particularly among shorter term IDUs. Improvements that were the most pronounced included PrEP behavior (adherence skills) and syringe cleaning skills. Of significant interest, the intervention effect on some PrEP-related outcomes was disrupted to a degree, suggesting the need to continue refining more potent compensatory strategies in this case. It is encouraging, however, that the majority of improvements were not hampered by cognitive dysfunction, as that was our objective in designing the CHRP-BB intervention approach.

We suggest that future efforts focus on refining and testing intervention strategies that can further optimize intervention effects across a broader range of outcomes and MOUD patients, including those characterized by a longer history of IDU. It is plausible that additional compensatory strategies that have been successful in other patient populations<sup>5</sup> may also be successfully applied to a wider range of patients on MOUD and cognitive dysfunction. Furthermore, it may be useful to apply other research designs, such as a Multiphase Optimization Strategy (MOST),<sup>39,40</sup> to more precisely investigate how to maximize the potency of various combinations of evidence-based intervention strategies targeting patients on MOUD who are impeded by cognitive dysfunction.

## Data Sharing Statement

The authors intend to share individual de-identified participant data, upon request to the first author's contact information. The authors are also willing to share intervention manuals, recruitment flyers, and data collection measurement tools upon request.

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## Disclosure

The authors report no conflicts of interest in this work.

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