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Retention in clinical trials after prison release: results from a clinical trial with incarcerated men with HIV and opioid dependence in Malaysia

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Abstract

Background: Study retention is a major challenge in HIV clinical trials conducted with persons recruited from correctional facilities.

Objective: To examine study retention in a trial of within-prison methadone initiation and a behavioral intervention among incarcerated men living with HIV and opioid dependence in Malaysia.

Methods: In this 2×2 factorial trial, 296 incarcerated men with HIV and opioid dependence were allocated to 1) an HIV risk reduction intervention, the Holistic Health Recovery Program for Malaysia (HHRP-M), 2) pre-release methadone initiation, 3) both interventions, or 4) standard care (). Here we estimate effects of these interventions on linkage to the study after prison release and completion of post-release study visits.

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Compliance with Ethical Standards: All procedures involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

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Results: Most participants (68.9%) completed at least one post-release study visit but few (18.6%) completed all twelve. HHRP-M was associated with a 13.5% (95% CI 3.8%, 23.2%) increased probability of completing at least one post-release study visit. Although not associated with linkage, methadone treatment was associated with an 11% (95% CI 2.0%, 20.6%) increased probability of completing all twelve post-release study visits. Being subject to forced relocation outside Kuala Lumpur after prison release decreased retention by 43.3% (95% CI -51.9%, -34.8%). **Conclusions:** Retaining study participants in HIV clinical trials following prison release is challenging and potentially related to the broader challenges that participants experience during community reentry. Researchers conducting clinical trials with this population may want to consider methadone and HHRP as means to improve post-release retention, even in clinical trials where these interventions are not being directly evaluated.

Keywords

clinical trials; criminal justice; HIV; prisoners; substance use; study retention

1. INTRODUCTION

More than 10.7 million people are incarcerated worldwide.¹ People who spend time in correctional facilities are disproportionately at risk for numerous communicable and chronic diseases including HIV and opioid use disorder (OUD).^{2,3} Despite interventions developed to treat HIV and substance use disorders (SUDs) in prisoners,⁴ treatment effectiveness diminishes quickly after prison release.⁵ During the transition from prison to the community, people with HIV (PWH) and/or OUD often find it challenging to adhere to prescribed medical treatments^{6,7} or abstain from drugs and alcohol.^{8,9} Moreover, correctional facilities may intensify health disparities after prison release through persistent institutional effects.¹⁰ Evidence from high-income settings suggests that exposure to the prison environment elevates the risk of treatment non-adherence¹¹ and reduces lifespan in a dose-response fashion.^{12,13} PWH with frequent and repeated criminal justice system exposure appear especially vulnerable.⁷

Given the higher prevalence of HIV and OUD in criminal justice populations, correctional facilities are important settings in which to offer interventions to improve treatment of HIV and OUD during community reentry.^{14,15} Several recent clinical trials have examined the effectiveness of interventions to improve health outcomes in PWH returning to the community, including case management,¹⁶ directly-observed antiretroviral therapy (ART),¹⁷ methadone,^{18,19} buprenorphine,^{20,21} and extended-release naltrexone.^{22,23} These studies provide encouraging evidence that starting treatment for OUD in prison may increase treatment uptake and reduce drug-related risk behaviors after prison release.^{19,24,25}

A main challenge for generating high-quality evidence from these studies is the ability to retain research participants after they are released from correctional facilities. Incomplete retention can introduce bias, decrease statistical power, and limit the ability to make causal inferences.²⁶ Studies with persons transitioning from prisons demonstrate lower retention rates (40% to 74%) relative to studies conducted solely within the community (86%).²⁷⁻²⁹ For example, in two recent studies involving prisoners, one third to one half of the original

samples were lost to follow-up within six months after prison release.^{16,22} Understanding participant characteristics and study-related factors associated with higher retention rates may lead to more effective retention strategies and improve the quality of longitudinal research with persons recruited in correctional facilities.

This study examined predictors of study linkage and retention after prison release in a randomized controlled trial (RCT) conducted with incarcerated persons with HIV and OUD in Malaysia.³⁰ We hypothesized that interventions targeting substance use and HIV transmission risk behaviors might also influence patterns of study retention following prison release. We examined the effects of two experimental interventions (pharmacological and behavioral) delivered within prison on linkage and retention in the study during the year after prison release.

2. METHODS

2.1 Study Design

The study design has been described previously.³⁰ Briefly, HIV-positive and opioid-dependent incarcerated men enrolled in a RCT that utilized a 2×2 factorial design to evaluate the effects of two interventions on HIV transmission risk behaviors following prison release: 1) methadone treatment initiated prior to prison release with linkage to subsidized methadone in the community, and 2) the Holistic Health Recovery Program (HHRP), a behavioral intervention that was adapted for the Malaysian prison setting (HHRP-M).³¹ All subjects were randomized 1:1 to HHRP-M or no HHRP-M. Subjects were initially also randomized to methadone, however, due to changing standards of care and strong individual preferences, protocols were adjusted during the early stages of recruitment to allow subjects to be allocated to methadone or no methadone based on their individual preferences. Eligible participants were Malaysian citizens 18 years of age, HIV-infected and opioid dependent, within 6 months of prison release, and planning to return to Greater Kuala Lumpur after prison release. Figure 1 presents a study flow diagram. This analysis utilizes data from 296 participants who were successfully allocated to one of the study's four groups and survived until prison release. Analyzed participants included n=105 allocated to methadone only, n=35 allocated to HHRP-M only, n=113 allocated to both HHRP-M and methadone, and n=43 allocated to standard care (Figure 1). Summing across the two interventions, this represents n=218 allocated to methadone and n=78 not allocated to methadone, and n=148 allocated to HHRP-M and n=148 allocated to no HHRP-M.

2.2 Study Setting

Malaysia is an ethnically and culturally diverse upper-middle-income country where HIV, addiction, and incarceration are syndemic.³² Although the number of new HIV infections has decreased,³³ HIV prevalence remains high in key populations including people who inject drugs (PWID).³⁴ Criminalization of drug use has concentrated PWID into prisons where HIV testing is compulsory and PWH are segregated. Despite high HIV prevalence, healthcare resources within these facilities are often inadequate to address the complex health needs of patients.³⁵ This study was set in Greater Kuala Lumpur. Subjects were

recruited from Malaysia's largest prison facility, which is located within the Klang Valley, houses approximately 4,000 prisoners, and has an HIV prevalence of 5%.³⁰

2.3 Standard Care

At the time of the study, all HIV-diagnosed patients were under the care of a physician, screened for tuberculosis, and ART eligible according to Ministry of Health guidelines (CD4<350 cells/ μ L), although standards evolved over time.³⁰ Faith-based counseling was offered to prisoners seeking help for addiction. Initially, access to methadone for those not enrolled in the study was extremely limited, although the prison gradually expanded its MMT program during the study. Before release, all participants were referred for HIV care and temporary housing assistance, and efforts were made to link all participants to HIV care after release.

2.4 Experimental Conditions

2.4.1 Pharmacological treatment with methadone—Protocols for within-prison MMT initiation were based on a pilot study showing that a methadone dose 80 mg/day at the time of release was associated with higher retention in substance use treatment.³⁶ All participants screened negative for opiates on urine drug testing at enrollment and were started on a 5mg daily initial methadone dose that was increased by 5 mg weekly to reach a target daily dose of 80 mg. Subjects allocated to methadone were linked to fully subsidized treatment in the community. Methadone dosing was directly observed in prison and throughout the first month after release. Protocols for methadone dosing and titration were actively monitored by a study clinician within prison and throughout the 12-month post-release follow-up period.

2.4.2 The Holistic Health Recovery Program, Malaysia (HHRP-M)—The Holistic Health Recovery Program (HHRP-M) is an evidence-based HIV risk reduction intervention³⁷ that was adapted for the Malaysian prison setting.³¹ HHRP-M consisted of eight two-hour group sessions conducted within prison with an optional individual “booster session” scheduled 1 month after release. Topics included accessing health care, reducing HIV transmission risk behaviors, preventing drug relapse, overcoming stigma, moving beyond grief, and achieving personal goals.³¹

2.5 Study Procedures

Participants who gave informed consent completed questionnaires, confirmatory HIV testing, CD4+ T-cell and viral load quantification, and were allocated using block randomization to one of four treatment groups: 1) methadone, 2) HHRP-M, 3) methadone + HHRP-M, or 4) standard care, with deviation from random assignment to methadone as described above. Participants were reenrolled into the study on their release date or the date of their first post-release study visit. Participants were followed for one year after prison release and completed monthly visits in the community. On their release date, participants met with a research assistant who updated their contact information and provided transportation to study-affiliated clinics if needed. Between post-release study visits, researchers maintained contact with participants by phone and SMS text messages or by locating participants at their residential address or “hangouts” in the community where they

agreed to be contacted by researchers. Missing one or more post-release study visits did not preclude participation in future visits. For their time, participants received RM130 (\$31 USD) on their release date, RM50 (\$12 USD) at quarterly follow-up visits, and RM40 (\$10 USD) at monthly follow-up visits.

2.6 Study Measures

2.6.1 Dependent Variable—To estimate the effects of study interventions on retention, we chose three operational definitions. *Linkage* was defined as having completed at least one follow-up study visit in the community after prison release, irrespective of time since release. *Retention* was measured as a continuous variable, using each of the twelve monthly follow-up visits as repeated measures; and as a dichotomous variable, categorizing participants who completed all 12 monthly follow-up visits as having *sustained retention*.

2.6.2 Independent Variables—Baseline variables used in analysis were selected *a priori* based on previous research and substantive expertise. Demographic variables included a participant's age, highest level of education, and whether the participant anticipated a permanent living arrangement after release (i.e. stable housing). Incarceration variables included sentence length and relocation status, which assessed whether the participant was subject to legally enforced deportation from Kuala Lumpur to another Malaysian state after prison release under the Prevention of Crimes Act (PCA). HIV treatment variables included years since HIV diagnosis, baseline CD4⁺ T-cell count and previous ART use.

Social support was measured using the Medical Outcomes Study (MOS) Social Support survey,³⁸ which included 19 Likert-type items assessing participants emotional/informational support, tangible support, affectionate support, and positive social interaction. Composite scores were calculated by averaging item responses and transformed linearly (0–100), with higher scores representing higher levels of perceived social support.

HIV stigma was measured using the Berger Stigma Scale,³⁹ a 40 item scale that measures personalized stigma, disclosure concerns, negative self-image, and perceived public attitudes towards PWH using a 4-point Likert-type scale. One item with low reliability, *people don't want me around their children once they know I have HIV*, was dropped. Total scores were calculated by averaging responses to the remaining 39-items (39–159), with higher scores indicating higher perceived stigma.

Health-related quality of life (HRQoL) was assessed using the 5-item general health scale on the Short-Form 36 (SF-36) survey.⁴⁰ The general health composite score was generated from sub-scale average scores.

Depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D),⁴¹ which uses 20 items to assess the frequency of depression symptoms in the previous two weeks from 1) *rarely or not at all* to 4) *most or all of the time*. Composite scores are calculated as the sum of responses to all 20 items, with scores ≥ 16 indicating clinically significant depressive symptomology.

Substance use variables included substance use and drug injection during the participant's lifetime and 30 days before incarceration. Pre-incarceration alcohol use was assessed using the 10-item World Health Organization Alcohol Use Disorders Identification Test (AUDIT).⁴² Scores ranging from 8–40 indicate the presence of an alcohol use disorder.

Pre-incarceration addiction severity was measured using the Addiction Severity Index (ASI) drug subscale,⁴³ which measures social and health consequences of substance use. Composite scores ranged from 0.0 to 0.52, with higher scores indicating greater addiction severity.

To improve validity, all survey measures underwent rigorous forward-backward translation by bilinguals⁴⁴ and were piloted with the first 10 participants to ensure understanding. Mean scores were imputed for measures with missing data.

2.7 Statistical Analyses

To estimate the effects of methadone and HHRP-M on retention, we used multiple estimation strategies. For the fully randomized HHRP-M, we present results from unadjusted non- or semi-parametric estimators; for methadone, we present adjusted estimates that attempt to correct for potential selection bias from non-random allocation. Excluded from our analyses were 14 subjects who withdrew from the study (n=3), were determined to be ineligible (n=4), or who died (n=7) after allocation and before prison release.

2.7.1 Estimating intervention effects on study linkage and sustained retention after prison release—For both dichotomous measures of retention—linkage and sustained retention—we first present unadjusted point estimates for HHRP-M and methadone accompanied by a non-parametric estimator of the variance⁴⁵ for HHRP-M and a T-statistic-based estimator of the variance for methadone. The unadjusted simple difference-in-means estimator is unbiased for the fully-randomized HHRP-M and subject to selection bias for methadone because most participants were allocated to methadone based on their personal preference. To increase precision and decrease bias, we also present three model-assisted treatment effect estimators that adjust for all the baseline characteristics shown in Table 1. These estimators include OLS regression, inverse propensity score weighting (IPW) with weights estimated using logistic regression and stabilized by the marginal probability of receiving methadone,^{46,47} and a doubly-robust estimator that incorporates both of these two approaches.^{48,49} The non-parametric bootstrap was used to estimate uncertainty for the model-assisted estimators.⁵⁰

2.7.2 Estimating intervention effects on retention—To estimate intervention effects on retention across all twelve study visits, we used generalized estimating equations (GEE) with an exchangeable covariance structure and the robust sandwich estimator of the variance.⁵¹ We present unadjusted GEE models for HHRP-M and methadone as well as a model adjusting for all the baseline covariates shown in Table 1. Additional models examining the effects of time and interactions between the interventions are presented in the supplemental appendix. GEE models were fit using the *R* package *geepack*.⁵²

2.8 Ethical Approval

The study protocol was approved by institutional review boards at University of Malaya and Yale University, with additional oversight by the Office of Human Research Protection at the U.S. Department of Health and Human Services. All participants provided informed consent prior to enrollment and again at their first post-release study visit. The trial is registered at clinicaltrials.gov ().

3. RESULTS

3.1 Participant characteristics

Table 1 shows baseline characteristics of the 296 study participants by treatment group. Participants randomized to HHRP-M and no HHRP-M did not differ on the baseline characteristics shown in Table 1, with the exception of pre-incarceration heroin use ($p=0.03$). Participants allocated to methadone and no methadone differed only on ASI drug severity score ($p=0.002$).

3.2 Effects of interventions on linkage

Overall, two thirds of participants (68.9%) completed at least one post-release study visit. We estimate that HHRP-M increased the probability of completing at least one post-release study visit by 13.5% (95% CI 3.8%, 23.2%), based on the unadjusted estimate and a non-parametric estimator of the variance. For HHRP-M, model-assisted estimators adjusting for baseline covariates yielded similar estimates (Table 2). The unadjusted estimate of the effect of pre-release methadone on completion of at least one post-release study visit was 10.0% (95% CI -2.5%, 22.6%). Model-assisted estimators adjusting for baseline covariates produced similar estimates with confidence intervals that were also compatible with a null effect (Table 2).

3.3 Effects of interventions on retention

Participation declined sharply in the first month after prison release (57.8%) and continued to decline until the final study visit (34.8%). Across all twelve study visits, we estimate that HHRP-M increased retention by 6.6% (95% CI -2.6%, 15.8%) using an unadjusted GEE model, though this confidence interval is compatible with a null effect (Table 3, Model 1). The adjusted model yielded a similar estimate of HHRP-M's effect, also with a confidence interval compatible with a null effect (Table 3, Model 3). Across all study visits, we estimate that methadone increased retention by 10.8% (0.8%, 20.8%) using the GEE model adjusting for baseline covariates (Table 3, Model 3).

3.4 Effects of interventions on sustained retention

We also estimated the effects of HHRP-M and methadone on the probability of sustained retention, defined as attending all 12 monthly post-release study visits (Table 4). The estimated effect of HHRP-M on the probability of sustained retention was 3.4% (95% CI -5.3%, 12.0%) in unadjusted analysis, with the confidence intervals from unadjusted and adjusted analyses broadly overlapping with zero. Methadone was associated with an increased probability of sustained retention in analyses adjusting for baseline characteristics,

with the confidence intervals overlapping with zero for the OLS estimator (9.5%, 95% CI -0.5%, 19.5%) and not overlapping with zero for the inverse propensity score weighting (11.3%, 95% CI 2.6%, 19.5%) and doubly robust (11.0%, 95% CI 2.0%, 20.6%) estimators.

3.5 Temporal trends, interaction effects, and correlates of retention

We plotted retention and fit several additional GEE models to examine temporal trends, interaction effects, and correlates of retention. Participation declined over time, as shown in Figure 2 and demonstrated by the significant effect of time in all GEE models in which it was included (Supplemental Appendix, Table S1). Trends in intervention effects over time differed for HHRP-M and methadone. The interaction between HHRP and time was not associated with retention in a basic interaction model (95% CI -1.2%, 0.9%; Supplemental Appendix, Table S1). Similarly, the difference in retention between HHRP-M and no HHRP-M participants was small and remained relatively constant over time (Figure 2, Panel B). The interaction between methadone and time, however, was positively associated with retention (95% CI 0.5%, 2.9%; Supplemental Appendix, Table S1). As shown in Panel C of Figure 2, participants allocated to methadone were lost to follow-up at a slower rate compared to participants not allocated to methadone.

To examine the interaction between the two interventions, we fit a model including HHRP-M, methadone, their interaction, and the set of baseline covariates (Supplemental Appendix, Table S2). The coefficient for the interaction of HHRP-M and methadone (-12.5%, 95% CI -31.5%, 6.4%) had a similar magnitude to and opposite sign of the coefficients for both HHRP-M (14.5%, 95% CI -1.6%, 30.7%) and methadone (16.5%, 95% CI 3.3%, 29.7%), suggesting that any increased retention due to either HHRP-M or methadone might not have been further increased by receiving both interventions. This trend can also be seen in Panel D of Figure 2 showing that retention rates among those receiving HHRP-M, methadone, or both interventions were similar and potentially greater than retention rates among those who received neither intervention.

Among baseline measures evaluated, PCA relocation status – police enforced relocation after prison release - was the strongest predictor of retention, associated with a 43.3% decreased (95% CI -51.9%, -34.8%) probability of retention over all study visits (Table 3, Model 3).

4. DISCUSSION

Successful post-release follow-up of participants recruited in correctional facilities is essential for developing effective interventions to improve health outcomes in people with HIV (PWH) and opioid use disorder (OUD). In this study, we examined the effects of within-prison methadone initiation and a behavioral HIV risk reduction intervention on study retention in men with HIV and OUD recently released from prison in Malaysia. Participation declined rapidly after prison release and continued to decline over time, with only 18.6% completing all twelve post-release study visits. Concerning was the amount of missing post-release data (>50%), which reduces power and makes unbiased estimation of treatment effects challenging.²⁹ Although consistent with retention rates in similar studies, 16,19,22,25,27,29,53,54 findings here demonstrate the challenges of retaining study participants

recruited from correctional facilities in long-term follow-up and the need for more effective retention strategies in this population.

Two possible explanations for the rapid loss to follow-up in this group of prisoners with OUD and HIV are relapse to opioids and HIV-related mortality. Relapse to opioids may occur in up to 90% of released prisoners within one year, with much of the relapse occurring in the first 1 to 2 weeks after release,^{55,56} and contributes greatly to the high mortality rates (8.5 deaths per 1,000 person-years) observed in released prisoners globally.⁵⁷ Another potential explanation for the high rates of attrition observed is mortality attributable to HIV-related opportunistic infections, which may surpass drug overdose as a leading cause of death in released prisoners in low-to-middle income countries where HIV treatment post-release is not adequately supported.^{58,59} In this study, subjects who were ART-experienced when they enrolled into the study were no more or less likely to be retained after prison release. Unknown, however, is whether subjects who initiated or were adherent to ART after their enrollment date were more likely to be retained.

Findings here suggest that in addition to reducing drug relapse and mortality, interventions to address infectious disease and substance use during reentry may also improve retention rates.⁶⁰ While receiving HHRP-M was associated with linkage to the study (completion of at least one study visit), only methadone was associated with study retention, both when defined as a repeated measure or as sustained retention to all visits. One explanation for the effect of HHRP-M on linkage is that HHRP-M participants were offered an optional individual “booster” session 4 weeks after prison release for which they received additional compensation. Moreover, subjects allocated to the HHRP-M intervention received more structured interaction with research staff in the form of eight intervention sessions. As a result, HHRP-M participants may have been more engaged and may have developed a greater interest in participating in the study due to stronger relationships with research staff.⁶¹ Such characteristics of the HHRP-M intervention have been shown to improve retention in previous studies.^{28,60,62}

One explanation for the increased retention in the methadone arm is that methadone, which has been repeatedly demonstrated to improve HIV-related health outcomes,⁶³ including among prisoners,⁶⁴ and in supervised settings in Malaysia,⁶⁵ may have improved study retention by preventing drug relapse and improving social functioning.⁶⁶ Additionally, increased retention in the methadone arm could have been due to the proximity of interview sites to methadone treatment facilities or to increased ability of research staff to locate participants engaged in methadone therapy, both of which could bias treatment effect estimates.⁶⁷ Regardless of the mechanism, interventions to address infectious disease and substance use in this population are not only the evolving standard of care, but also may be an important aspect of study design that improves retention rates even in studies that are not specifically designed to test the effects of these interventions.

In addition to elevated health risks, persons recruited from correctional facilities may encounter numerous practical barriers to study participation before and after prison release. First, research staff may have difficulty maintaining contact with incarcerated subjects. Cell phones, for example, which could be used to send contact reminders and update contact

information, are contraband. Second, prisoners may not know their post-release contact details such as their residential address, phone number, or emergency contact until the day of release or afterwards when they are re-established in the community. Third, incarcerated subjects may have their release date changed or be transferred to another correctional facility, and have difficulty communicating these changes to research staff. Fourth, participants recruited in correctional facilities may remain incarcerated for many months/years after enrollment and may misplace study contact information or forget that they are involved with a study. Even when study contact information is included with a person's discharge paperwork, it may become lost or misplaced. Finally, participants released from correctional facilities may be justifiably more concerned with meeting their immediate physiological and safety needs than with contacting researchers. For these reasons, we recommend that researchers actively engage participants throughout the study and collaborate with prison administrators to remain aware of release plans.^{28,62}

Finally, although all participants planned to return to Kuala Lumpur after prison release, some were subject to an antiquated provision under Malaysia's Prevention of Crime Act (PCA) of 1959, which significantly reduced study retention. Under the PCA of 1959, persons may be forcefully relocated to other cities after prison release at the discretion of law enforcement.⁶⁸ Although this law was repealed in 2011, some study participants (9% of this sample) were evidently subject to forced relocation and possibly prevented from returning to Kuala Lumpur to be able to continue their participation in the study. Deleterious law enforcement practices not only impede study retention but also destabilize individuals, hampering their ability to reintegrate into the community and denying them the very resources they may need to be healthy.

Although this study provides important insights into longitudinal research with released prisoners, there are nevertheless some important limitations. First, we did not estimate the effects of post-release HIV treatment and substance use outcomes on study retention due to incomplete post-release data. Beyond the scope of the present study and requiring further investigation were other possible reasons for post-release attrition, including disability, hospitalization, death, loss of interest in the study, concerns about stigmatization from study participation, or moving outside the study catchment area. Additionally, we did not account for other study-related factors such as the completeness and quality of participant locator information or frequency of contact with research staff as variables that may influence retention.²⁷ These limitations notwithstanding, this study is one of the first to examine study attrition following prison release in a low-to-middle-income country and, as such, contributes to research with persons recruited in correctional facilities who represent an especially important population for HIV and SUD clinical trials.

5. CONCLUSION

Retaining study participants in HIV clinical trials after prison release is challenging and potentially related to the broader health and social challenges that participants experience during community reentry. By improving health outcomes and social functioning, interventions targeting HIV and substance use during reentry may also increase retention rates. Even in studies that do not directly evaluate HIV and substance use outcomes,

researchers may need to consider whether study protocols adequately address the overall burden of infectious disease and SUD as factors potentially contributing to study attrition after prison release. Improved coordination with prison administrators also is needed to address restrictions on communication and mobility within prison and after release that may adversely influence study retention and social reintegration during reentry.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:
Study flow diagram

Figure 2:
Retention of study participants after prison release by treatment allocation

Table 1.

Participants characteristics at enrollment by treatment group (N=296)

Variable	HHRP-M ^a		Methadone ^a	
	Treatment (n=148) n (%)	Control (n=148) n (%)	Treatment (n=218) n (%)	Control (n=78) n (%)
Demographic characteristics				
Mean age (SD)	38.9 ± 6.9	39.2 ± 6.5	38.7 ± 6.6	40.1 ± 6.7
Completed upper secondary education	45 (30.4)	47 (31.8)	70 (32.1)	22 (28.2)
Stable housing before incarceration ^c	104 (70.3)	97 (65.5)	148 (67.9)	53 (67.9)
Incarceration factors				
Mean years of prison sentence (SD)	3.1 ± 4.4	2.6 ± 3.9	2.8 ± 4.0	3.2 ± 4.6
Relocation status ^d	13 (8.80)	14 (9.50)	18 (8.3)	9 (11.5)
Psychosocial characteristics				
Social support mean score (SD)	50.6 ± 20.4	50.1 ± 18.8	50.1 ± 19.2	51.1 ± 20.8
HIV stigma mean score (SD)	99.6 ± 12.0	97.8 ± 11.7	98.6 ± 12.2	99.0 ± 11.1
SF-36 general health (SD)	61.3 ± 16.0	60.4 ± 14.6	61.2 ± 16.0	59.8 ± 13.2
Clinical characteristics				
Mean years since HIV diagnosis (SD)	8.4 ± 5.2	8.1 ± 5.5	8.5 ± 5.4	7.8 ± 5.2
Mean CD4 ⁺ T-cells/ μ L (SD)	442 ± 275	460 ± 293	439 ± 277	483 ± 301
ART experienced	26 (17.6)	33 (22.3)	41 (18.8)	18 (23.1)
Depression mean score (SD)	12.6 ± 6.6	12.2 ± 6.8	12.1 ± 6.2	13.2 ± 7.9
Substance use				
Addiction severity mean score (SD)	0.26 ± 0.10	0.27 ± 0.10	0.26 ± 0.10	0.30 ± 0.10
Alcohol use disorder	26 (17.6)	23 (15.5)	34 (15.6)	15 (19.2)
Lifetime drug injection	131 (88.5)	140 (94.6)	199 (91.3)	72 (92.3)
Pre-incarceration heroin use ^d	143 (96.6)	133 (89.9)	202 (92.7)	74 (94.9)
Pre-incarceration amphetamine use ^d	81 (54.7)	84 (56.8)	124 (56.9)	41 (52.6)

Legend:^aSome subjects were allocated to receive both methadone and HHRP-M;

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^b Chi-squared/Fishers Exact p-value reported for categorical predictors; KS test p-value reported for continuous predictors;

^c Variable assessed for the 30 days before incarceration;

^d Participant was subject to legally enforced relocation to another Malaysian state after prison release.

Abbreviations: SD, standard deviation; HHRP-M, Holistic Health Recovery Program, Malaysia; ART, antiretroviral therapy

Estimated effects of HHRP-M and pre-release methadone initiation on reenrollment completion of 1 post-release study visit within 12 months of prison release)

Table 2.

Treatment Effect Estimator	HHRP-M		Methadone	
	Estimate	95% CI	Estimate	95% CI
Unadjusted estimator				
Difference in means	13.5%	3.8, 23.2% ^b	10.0%	-2.5, 22.6% ^c
Adjusted estimators ^a				
Outcome regression (OLS)	12.9%	3.1, 22.5%	10.2%	-1.8, 22.9%
Inverse probability weighting	13.1%	2.8, 23.6%	12.1%	-4.9, 29.8%
Doubly-robust	12.8%	2.6, 23.0%	10.4%	-5.8, 26.4%

Legend:

^a Adjusting for all covariates shown in Table 1; standard errors estimated with the non-parametric bootstrap.

^b Non-parametric variance estimator

^c T-statistic based confidence interval

Abbreviations: CI, confidence interval; OLS, ordinary least squares

Estimated effects of HHRP-M and pre-release methadone initiation on post-release retention across all time points using generalized estimating equations

Variable	Unadjusted			Adjusted		
	Model 1	Model 2		Model 3		
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
Interventions						
HHRP-M	0.06 (−0.02, 0.15)	0.160			0.05 (−0.01, 0.13)	0.220
Methadone			0.09 (−0.001, 0.20)	0.053	0.10 (0.008, 0.20)	0.034
Demographic						
Mean age					0.003 (−0.004, 0.01)	0.391
Completed upper secondary education					0.08 (−0.006, 0.17)	0.067
Length of prison sentence					−0.008 (−0.01, 0.002)	0.112
Relocation status ^a					−0.43 (−0.51, −0.34)	<0.001
Psychosocial factors						
Stable housing ^b					−0.01 (−0.11, 0.08)	0.783
Social support score					0.002 (−0.001, 0.004)	0.173
HIV stigma score					−0.003 (−0.007, 0.001)	0.113
Clinical factors						
SF-36 general health					−0.001 (−0.004, 0.002)	0.436
Years since HIV diagnosis					0.001 (−0.007, 0.009)	0.781
CD4 ⁺ T-cells/ μ L ^c					0.004 (−0.01, 0.02)	0.621
ART experienced					−0.02 (−0.13, 0.08)	0.707
Depression score					0.008 (−0.0002, 0.01)	0.055
Substance use						
Addiction severity score					0.03 (−0.40 − 0.46)	0.895
Alcohol use disorder					0.01 (−0.09, 0.12)	0.790
Lifetime drug injection					−0.09 (−0.25, 0.05)	0.221
Heroin use ^b					0.08 (−0.09, 0.25)	0.372
Methamphetamine use [†]					−0.08 (−0.16, 0.006)	0.069
Study-related factors						

Variable	Unadjusted			Adjusted		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
	p value	p value	p value	p value	p value	p value
Elapsed time ^d				-0.002 (-0.006, 0.002)		0.392

Legend:

^aParticipant was subject to legally enforced relocation to another Malaysian state after prison release;

^bVariable assessed for the 30 days before incarceration;

^cCoefficients represent 100-cell/ μ L change in baseline count;

^dElapsed time between study start date and participant enrollment date;

Abbreviations: β , unstandardized coefficients; CI, confidence interval

Estimated effects of HHRP-M and pre-release methadone initiation on sustained retention, defined as completion of all 12 monthly follow-up visits

Table 4.

Treatment Effect Estimator	HHRP-M		Methadone	
	Estimate	95% CI	Estimate	95% CI
Unadjusted estimator				
Difference in means	3.4%	-5.3, 12.0% ^a	7.8%	-1.5, 17.1% ^b
Adjusted estimators[*]				
Outcome regression (OLS)	3.6%	-5.4, 12.5%	9.5%	-0.5, 19.5%
Inverse probability weighting	3.1%	-6.1, 12.7%	11.3%	2.6, 19.5%
Doubly-robust	2.7%	-6.1, 11.6%	11.0%	2.0, 20.6%

Legend: Adjusting for all covariates shown in Table 1; standard errors estimated with the non-parametric bootstrap.

^aNon-parametric variance estimator

^bT-statistic based confidence interval