International Journal of Drug Policy 137 (2025) 104733

Contents lists available at ScienceDirect

International Journal of Drug Policy

journal homepage: www.elsevier.com/locate/drugpo

Research Paper

Prescribing methadone in prison predicts linkage to HIV care after release from prison: A randomized and patient preference trial

Allison M. Mobley [a,b,c,1], Martin P. Wegman [d,2], Alexander R. Bazazi [e,2], Sheela V. Shenoi [c,f], Daniel J. Bromberg [f], Ahsan Ahmad [c,f], Adeeba Kamarulzaman [c,3], Frederick L. Altice [b,c,f,*]

[a] University of Chicago Pritzker School of Medicine, Chicago, IL, USA
[b] Yale School of Public Health, Department of Epidemiology of Microbial Diseases, 60 College Street, New Haven, CT, USA
[c] Faculty of Medicine, Centre of Excellence for Research in AIDS (CERiA) University of Malaya, Level 17, Wisma R&D, Kalan Pantai Baharu, 59990, Kuala Lumpur, Malaysia
[d] HCA Florida Orange Park Hospital, Orange Park, FL, USA
[e] Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, 675 18th Street, San Francisco, CA, USA
[f] Yale University School of Medicine, Department of Internal Medicine, Section of Infectious Diseases, AIDS Program, 333 Cedar Street, New Haven, CT, USA

ARTICLE INFO

Keywords:
Medications for opioids use disorder (MOUD)
HIV
Linkage to care
Methadone
Malaysia
Prison
Preference study

ABSTRACT

Purpose: The transition from prison is hazardous, especially for people with HIV and opioid use disorder. To determine the impact of methadone on linkage to HIV care in people with HIV and opioid use disorder, we prospectively compared those allocated to pre-release methadone or not.

Methods: A prospective, open-label trial of 310 people with HIV and opioid use disorder at Malaysia's largest prison were allocated to pre-release methadone up to 24 weeks before release or not by randomization ($n = 64$) or preference ($n = 246$); 296 were included in the final analytical sample. Directed acyclic graphing was used to theorize the relationship between pre-release methadone and post-release linkage to HIV care and identify confounding variables. An inverse probability weighted Cox proportional hazards model estimated the impact of pre-release methadone on linkage to HIV care through 360 days after release.

Results: Overall, 218 (73.6 %) of 296 study participants initiated methadone before release. Receiving pre-release methadone significantly predicted linkage to HIV care at all time points through 360 days (aHR = 1.87; 95 % CI 1.15–2.85) after release. The corresponding numbers needed to treat with pre-release methadone for one increased linkage to HIV care at 30 and 360 days were 14 (95 % CI 9.2–62.4) and 5 (95 % CI 3.4–22.0), respectively.

Conclusions: While treatment with methadone should be available to everyone with opioid use disorder, it should especially be included as part of an HIV treatment-as-prevention strategy for people in prisons, especially by the time of release. It can optimize HIV treatment outcomes by jumpstarting the HIV treatment cascade.

Introduction

Increasing incarceration (UNODC, 2021) and criminalization of drug use concentrate people with communicable (e.g., HIV, HCV, tuberculosis) (Dolan et al., 2016; Kamarulzaman et al., 2016) and non-communicable (e.g., substance use disorders) diseases in prison. In the absence of effective decarceration efforts, strategies to mitigate the harms of incarceration are needed, especially during the dangerous transition to the community (Borschmann et al., 2024a,b; Macdonald et al., 2024) where people with opioid use disorder (OUD) and HIV (PWH) experience heightened risk for overdose and death, discontinuation of antiretroviral therapy (ART) and elevated HIV risk behaviors due to disruptions in risk networks (Altice et al., 2016).

For PWH, linkage to Loeliger et al. (2018a,b,c) and retention Loeliger

* Corresponding author at: 135 College Street, Suite 323, New Haven, CT, USA.
E-mail address: Frederick.altice@yale.edu (F.L. Altice).
[1] Department of Medicine, University of Washington, 1959 NE Pacific Street, Box 356421, Seattle WA, USA.
[2] MPW and ARB contributed equally to this manuscript.
[3] Monash University (Malaysia), Jalan Lagoon Selatan, Bandar Sunway, 47500 Subang Jaya, Selangor, Malaysia.

https://doi.org/10.1016/j.drugpo.2025.104733

Available online 8 February 2025

et al. (2018d) in HIV care after release from prison has been especially challenging. Similar reports are documented for people with opioid use disorder (Kinlock et al., 2009; Macdonald et al., 2024). Concomitant HIV and OUD are synergistic and result in especially adverse outcomes, including low linkage to and retention in HIV care and heightened post-release mortality from both HIV and OUD (Borschmann et al., 2024a,b; Loeliger et al., 2018a,b,c, 2018d; Bosworth et al., 2022). Early linkage to HIV care after release from prison in high-income countries (HICs) increases the likelihood that PWH maintain viral suppression (Loeliger et al., 2018a,b,c), potentially reducing opportunities for HIV transmission. Initiating medications for opioid use disorder (MOUD) at the time of release, like extended-release naltrexone, is associated with higher viral suppression levels six months after release for people in prison with HIV and OUD in HICs, where antiretroviral therapy (ART) coverage and viral suppression levels are high (Springer et al., 2018a,b); similar findings for PWH and alcohol use disorder treated with extended-release naltrexone have been described (Springer et al., 2018a, b). Initiating methadone before release, however, is more complicated and requires a gradual induction process to achieve an adequate dose, preferably over 80 mg per day (Wickersham et al., 2013b), which is associated with longer retention on treatment after release (Ahmad et al., 2024; Bachireddy et al., 2022; Wickersham et al., 2013). Systematic reviews from community settings confirm that PWH and OUD have substantially better HIV treatment outcomes along the HIV treatment cascade when prescribed MOUD (Bromberg et al., 2024; Low et al., 2016; Mazhnaya et al., 2018). The extent to which any MOUD improves linkage to HIV care, the first step in the treatment cascade after release from prison, however, remains unknown. We hypothesized that initiating methadone before release in PWH and OUD would decrease drug use and promote social stabilization after release, thereby supporting an individual's engagement with HIV care. We therefore analyzed data from a prospective trial of incarcerated PWH and OUD who were transitioning to the community to test whether methadone, an evidence-based treatment for OUD, influenced the likelihood of linking to HIV care.

Methods

Study context

Malaysia is a middle-income country in Southeast Asia with an HIV epidemic concentrated in people who inject drugs (PWID), primarily of opioids (Suleiman et al., 2015). Its proscriptive drug policies have resulted in high levels of incarceration of PWH and OUD, with high (4.0 %) HIV prevalence, 10-fold higher than in the community (0.4 %). HIV testing is mandatory upon entry to prisons in Malaysia, and PWH are housed in a segregated housing unit. The Malaysian Ministry of Health is responsible for the treatment of PWH. Treatment for HIV and MOUD in Malaysia is free in all Ministry of Health clinics. At the time of the study, this care was provided at specialty care settings that were not co-located. HIV and MOUD is now decentralized and available in some, but not all primary care clinics. There are no restrictions in accessing these services. Though methadone was introduced in governmental clinics in 2005, pilot studies of methadone in prisons did not occur until 2010 (Wickersham et al., 2013a,b), allowing for the conduct of the current prospective, randomized controlled trial (RCT).

Study design and eligibility criteria

The details of the trial conducted in Malaysia's largest prison from 2010 to 2014 have been described previously (Bazazi et al., 2017). Briefly, incarcerated men with HIV and OUD were initially randomized ($n = 64$) to receive either pre-release methadone, a risk-reduction behavioral intervention, neither, or both as part of a 2×2 factorial RCT. The behavioral intervention, the Holistic Health Recovery Program for Malaysia (HHRP-M), was adapted for the Malaysian context (Copenhaver et al., 2011). Due to an evolving standard-of-care based on other trials and strong participant preference, data monitors recommended altering the methadone arm allocation in February 2011 to a preference design based on ethical principles, allowing participants to select methadone or no methadone. No participants enrolled during the randomization period switched arms. Enrollment into HHRP-M remained randomized throughout the study. Random allocation software generated the randomization sequences and blocking was employed, with randomly varying block sizes (Bazazi et al., 2017). One research staff member, not involved with study recruitment, linked the participant identification with the allocation sequence. Only the outcome assessor was blinded.

Based on the major content of the HHRP-M intervention, the pre-specified primary trial outcome was HIV transmission risks such as unprotected sex or sharing of injection equipment during the first twelve months post-release. Linkage to HIV care was a pre-specified secondary study outcome, which is the focus of this analysis. Early in the study, only those with CD4 <350 cells/mL could receive antiretroviral therapy (ART) medication (Bazazi et al., 2017). Malaysian guidelines aligned with WHO recommendations in 2012 and allowed universal ART coverage. All Malaysian citizens in the HIV-specific housing unit, except those sentenced for life or to execution, were targeted for recruitment (Bazazi et al., 2017). Participant eligibility included: Malaysian citizenship, age ≥18 years, confirmed HIV positive status, opioid dependence using DSM-IV criteria for the twelve months before incarceration (Wickersham et al., 2015), and being between 4 and 24 weeks before anticipated release. Anyone meeting the pre-incarceration criteria for opioid dependence was eligible to initiate methadone maintenance therapy. While sex was not an inclusion criterion, research access was granted only to the men's prison as all women with HIV during the time of the study were not citizens of Malaysia; gender was screened for as male, female, or transgender.

Interventions

A secondary analysis found attaining a daily dose of methadone of ≥80 mg increased retention on treatment after release (Ahmad et al., 2024; Wickersham et al., 2013a,b), making this dose the study's target dose before release. An initial dose of 5 mg was increased by 5 mg weekly, subject to clinical judgment. All participants, irrespective of allocation, were provided a resource guide to find community services after release, including for methadone, HIV care, and social services. All participants allocated to methadone, however, due to the necessary timeliness of linking to methadone to avoid symptoms of opioid withdrawal, were provided more detailed information about where and how to find the nearest program to their home or work and were assisted with transportation (e.g., bus routes, maps, etc.) for the first visit at free methadone treatment programs in the community. The behavioral intervention, HHRP-M, is an evidence-based HIV risk reduction risk reduction intervention that was first shortened from the 12-session (Margolin et al., 2003) Holistic Health Recovery Program (HHRP) to the 4-session intervention (Copenhaver et al., 2011; Zelenev et al., 2024). It was also adapted to the prison context (Copenhaver et al., 2009) and then further adapted to the Malaysian prison context (Copenhaver et al., 2011). HHRP-M entailed four one-hour group sessions that were administered in two, two-hour blocks during incarceration. The content involved interactive sessions on sexual- and injection-related risk reduction, adherence to antiretroviral therapy, and strategies to assist in coping and strengthening relationships. A one-hour booster session was provided one month after release. All participants allocated to HHRP-M received the entire intervention before release; however, the post-release booster session attendance was not recorded. In this analysis, we sought to estimate the impact of receiving methadone before release on linkage to HIV care after release. HHRP-M was not included as a covariate given as it was not considered a potential confounder of the relationship between methadone and

linkage (see covariate selection below).

Primary outcome of this study: linkage to HIV care

Linkage to HIV care was a pre-specified, secondary outcome and the focus of this analysis. It was defined a priori as either an outpatient HIV clinic visit, laboratory testing for CD4 T-lymphocyte count, or HIV-1 RNA after release from prison (Croxford et al., 2018). Using a standardized abstraction tool for all participants enrolled in this study through one year following release from prison, charts were reviewed at all clinics and hospitals that provide HIV care in the greater Kuala Lumpur area, including date of visit or laboratory testing, and any diagnoses recorded in the clinical record. All patients consented for chart review before release as part of the informed consent process.

Covariate selection

Allocation to and prescription of pre-release methadone, either by randomization or patient preference, was the primary explanatory variable. Informed by application of the Behavioral Model for Vulnerable Populations for healthcare utilization (Fig. A.1), we created a directed acyclic graph (DAG) to theorize and represent causal pathways between variables and identify potential confounders of the relationship between selection of methadone and linkage to HIV care (Fig. 2) (Textor et al., 2017). The Behavioral Model theorizes that predisposing, enabling, and patient need factors influence a vulnerable person's healthcare utilization (i.e., linkage) (Gelberg et al., 2000). Covariates are further detailed in the appendix.

Statistical analysis

Data from all 296 participants enrolled during the randomization and preference phases for analysis of time to linkage to HIV care after release from prison were combined to maximize power, as the clinical trial was powered to the primary outcome variable (Bazazi et al., 2017). Mortality data were available for participants from the Malaysian Ministry of Health and were used to censor participants at time of death (Bazazi et al., 2022). Given that some participants self-selected methadone or no methadone, the two treatment groups were compared on baseline characteristics using the student's *t*-test and chi-squared test for dichotomous and continuous variables and categorical variables, respectively, to control for the allocation strategy.

We used a doubly-robust estimation strategy incorporating inverse probability of treatment weighting (IPW) and Cox proportional hazards regression to mitigate potential selection bias due to nonrandom allocation during the preference portion of the trial (Zhang & Schaubel, 2012). For participants in the preference phase, we estimated the probability of methadone allocation using logistic regression with a set of potential baseline confounders identified with the DAG. HHRP-M in the DAG was not predicted to predict linkage to HIV. Participants in the methadone randomization phase were assigned a weight of 0.5, consistent with randomization. We performed conventional diagnostics to confirm positivity and improved group balance (Cole & Hernán, 2008; Xiao et al., 2013). For the primary analysis, weights were stabilized and truncated to the 99th percentile, a well-established strategy to reduce variance and promote positivity (Cole & Hernán, 2008). We then fit a Cox proportional hazards model for linkage to care over the 360 days following release with our theorized covariates and estimated weights. The start and origin time was considered the day of release from prison and event time as the day of linkage, censored at 360 days. We assessed the Cox regression linearity assumption. From the final model, we calculated the risk difference and number needed to treat for one additional linkage at pre-specified post-release time points (30, 90, 180 and 360 days) (Austin, 2010; Zhang et al., 2018). Though the DAG did not suggest including HHRP-M in the model, HHRP-M was designed to enhance motivation (mostly to reduce HIV risk-taking). Forcing HHRP-M into the model did not significantly influence linkage to HIV care (adjusted hazards ratio = 0.97 [0.40–2.35]) and reduced the goodness of fit.

We estimated confidence intervals via bootstrapping to promote improved variance accuracy while easing the unrealistic assumption of proportional hazard ratios (Stensrud & Hernán, 2020). Multivariate imputation by chained equations was employed for baseline covariates with missing data. All covariates had less than 2 % of values missing prior to imputation and were assumed to be missing at random. Imputation impacted only 39 participants in the sample, and for 31 (79 %) of these, it involved only self-reported TB screening. For sensitivity analyses, we modified the stabilized and unstabilized inverse probability of treatment weights: (1) no trimming or truncation; (2) trimming at 99th percentile; (3) truncation at 95th percentile; (4) trimming at 95th percentile. We also calculated the effect estimate separately for those randomly allocated to treatment ($n = 64$). To aid in visualization, we computed unadjusted and inverse propensity score weight-adjusted survival curves. The data were analyzed using R Statistical Software (R Core Team, 2022).

Ethical considerations

Institutional review boards at the University of Malaya and Yale University approved this clinical trial (ClinicalTrials.gov: NCT02396979). The Office of Human Research Protection at the U.S. Department of Health and Human Services also provided approval. Potential participants were provided a brief description of the study; if interested, study procedures were reviewed in detail, and informed consent was offered. All enrollment procedures were conducted privately in Malay by trained research personnel and repeated after release (Bazazi et al., 2017). The study's funder had no role in the design, data collection, statistical analysis, results interpretation, or report writing.

Results

Among the 605 people in prison screened from March 2010 to September 2013 (Fig. 1), 310 met eligibility for the trial and were enrolled. From March 29, 2010 to January 25, 2011, 64 participants underwent randomization to methadone or not. Thereafter, 246 participants selected their preferred treatment. In the final analytical sample ($n = 296$), 218 were allocated to methadone (32 randomization, 186 preference), and 78 were allocated to no methadone (30 randomization, 48 preference). There were no significant differences in baseline characteristics between the methadone and no methadone groups, aside from the time at which they enrolled (Table 1). Appendix Table A.1 summarizes the descriptive characteristics of the inverse probability weights, stratified by treatment group and stabilization, truncation, or trimming strategy. Distributions of the propensity scores for both groups are also presented in the appendix (Appendix A.3). Good overlap was observed for those weights trimmed or truncated to the 99th percentile. Additionally, inverse propensity score weighting achieved improved, satisfactory standardized mean differences between the methadone and the no methadone groups (all $p < 0.1$) (Appendix Fig. A.4).

We estimated the effect of receiving methadone before release on linkage to HIV care after release. Raw linkage rates were 45 % for the no methadone group and 54 % for the methadone group at 360 days and the unadjusted hazard ratio (HR) estimate for the effect of methadone was 1.38 (95 % CI 0.97–1.96) at 360 days. The aHR, however, was 1.87 (95 % CI 1.15–2.85) at 360 days (Table 2). Those receiving methadone before release were 8 % (95 % CI 2.0–11 %) and 21 % (95 % CI 5.0–30 %) more likely to link to HIV care 30 days and 360 days after release than those not prescribed methadone, respectively (Table 3). At 30 days after release, our analysis demonstrated the number needed to treat with methadone of 14 for one increased HIV linkage event (95 % CI 9.2–62.4) (Table 3). This decreased to 5 people needed to treat to achieve one more linkage by 360 days (95 % CI 3.4–22.0) (Table 3). Survival curves

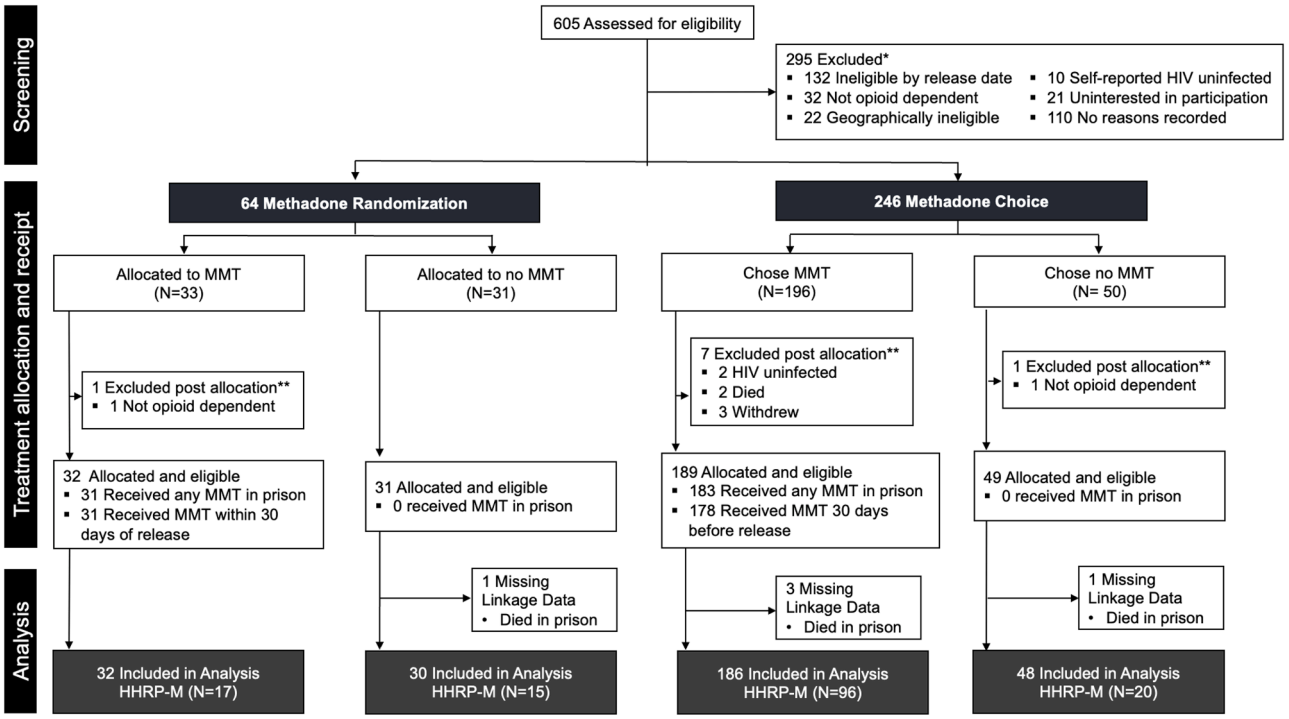

Fig. 1. Consort diagram: participant recruitment and disposition regarding allocation to pre-release methadone.
* These withdrawals and deaths occurred briefly following randomization but before receipt of the intervention.

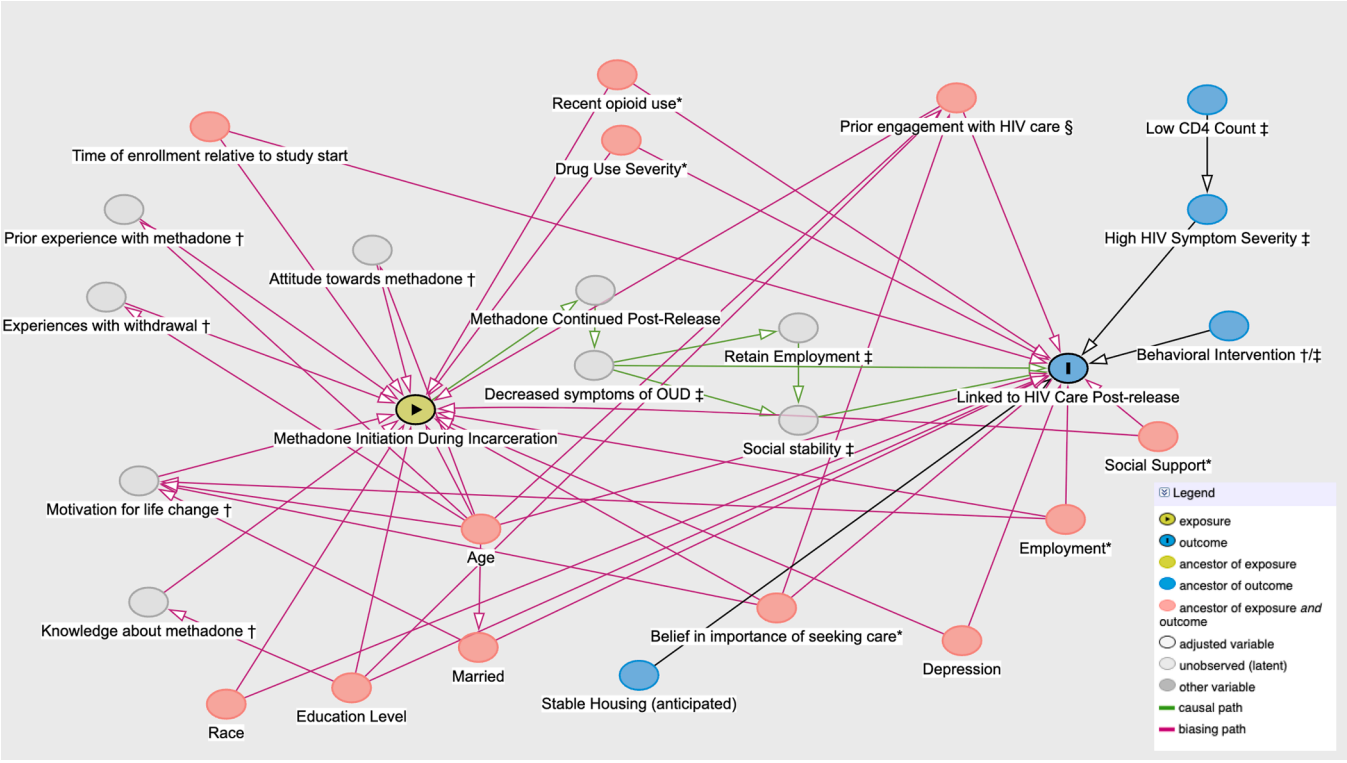

Fig. 2. Directed acyclic graph for the relationship between choice of methadone during incarceration and linkage to HIV care after release.
Caption: Graphing software courtesy of daggity.net (1). Time frames for when variables were theorized or measured: *prior to incarceration; † during incarceration; ‡ after incarceration. § Prior prescription of antiretroviral therapy as a proxy for this variable.

displaying the unadjusted and inverse probability weight adjusted linkage to HIV care through one year following release can be found in Fig. 3.

Sensitivity analyses trimming the weights at the 99th and 95th percentile and truncating at the 95th percentile were conducted with stabilized and unstabilized weights (Appendix Tables A.2–A.4). Our

Table 1
Baseline characteristics of participants, aggregate and stratified by prescription of methadone ($N = 296$).

			Prescribed methadone				
			No		Yes		
Study specific variables	Total $N = 296$	(%)	$N = 78$	(%)	$(N = 218)$	(%)	*p*-value *
Time since study initiation (months)							
Mean (SD)	22.5	12.8	17.1	11.9	24.4	12.6	<0.001
Predisposing factors							
Age (years)†							
Mean (SD)	39.0	6.6	40.1	6.7	38.7	6.6	0.118
Malay ethnicity							
No	82	27.7	25	32.1	57	26.1	..
Yes	214	72.3	53	67.9	161	73.9	0.394
Completed secondary education							
No	45	15.2	13	16.7	32	14.7	..
Yes	251	84.8	65	83.3	186	85.3	0.814
Married, currently							
No	264	89.2	72	92.3	192	88.1	..
Yes	32	10.8	6	7.7	26	11.9	0.412
Moderate/severe depression							
No	156	52.7	40	51.3	116	53.2	..
Yes	140	47.3	38	48.7	102	46.8	0.872
Importance of seeking medical care							
High	83	28.0	26	33.3	57	26.1	..
Low	213	72.0	52	66.7	161	73.9	0.287
Enabling resources							
Social support							
Low	93	31.4	26	33.3	67	30.7	..
Moderate	92	31.1	18	23.1	74	33.9	..
High	111	37.5	34	43.6	77	35.3	0.187
Previous employment‡							
No	108	36.5	34	43.6	74	33.9	..
Yes	188	63.5	44	56.4	144	66.1	0.167
Need factors							
Previously prescribed antiretroviral therapy							
No	237	80.1	60	76.9	177	81.2	..
Yes	59	19.9	18	23.1	41	18.8	0.519
Addiction severity, drug use scale							
Mean (SD)	15.7	17.5	15.9	17.2	15.6	17.6	0.905
Opioids used 30 days prior to incarceration							
No	20	6.8	4	5.1	16	7.3	..
Yes	276	93.2	74	94.9	202	92.7	0.686

* Student's *t*-test was used for comparison between groups with dichotomous and continuous variables; Chi-squared tests for categorical data; assumptions for these tests were investigated including normality and homogeneity of variance for the *t*-test and the expected values for the chi-squared test.
† Further descriptive statistics for Age: median is 39; IQR is 35.0–44.0.
‡ Within six months prior to incarceration and includes full and part-time employment.

Table 2
Predictors of linkage to HIV Care in 360 days after release: Hazard ratios estimated from Cox proportional hazards model ($N = 296$).

Variable	Adjusted hazard ratio	95 % confidence interval*	
Prescribed methadone before release	**1.87**	**1.15**	**2.85**
Age	1.04	1.00	1.07
Opioids used 30 days prior to incarceration	0.54	0.30	1.50
Social support—Middle tertile	1.25	0.63	1.52
Social support—Upper tertile	1.20	0.62	1.45
Employed 6 months prior to incarceration	0.94	0.66	1.33
Time since study start (months)	0.98	0.97	1.00
Drug severity (ASI†)	1.00	0.98	1.01
Married	0.55	0.35	1.19
Education level	0.84	0.57	1.36
Malay ethnicity	1.03	0.86	1.92
Depression	1.09	0.88	1.88
Prior prescription of antiretroviral therapy	1.56	1.05	2.83
Importance of seeking care	1.30	0.68	1.60

* Bootstrapped confidence interval; HRs estimates from multivariate Cox model with weights stabilized and truncated at 99th percentile.
† Addiction severity index.

Table 3
The estimated effect of treatment with methadone on linkage to HIV care at 30, 90, 180 and 360 days: Risk difference and number needed to treat ($N = 296$).

Timepoint (days)	Risk Difference for linkage to care, methadone vs. no methadone	95 % CI		Number needed to treat with methadone	95 % CI	
30	8 %	2 %	11 %	14	9.2	62.4
90	15 %	3 %	21 %	7	4.9	35.0
180	20 %	4 %	27 %	6	3.7	23.6
360	21 %	5 %	30 %	5	3.4	22.0

Caption: Risk difference calculated from Cox model including all variables in Table 1 as covariates with inverse probability weighting truncated at the 99th percentile and stabilized; confidence intervals estimated using non-parametric bootstrap.

main finding of the positive impact of pre-release methadone on post-release linkage to HIV care was robust to all iterations except for that of trimming to the 95th percentile ($N = 281$) (Appendix Tables A.2, A.4). In the sub-sample of the 64 randomized participants (24 randomized to methadone and 30 randomized to no methadone), the unadjusted HR for the effect of pre-release methadone on linkage was 1.66 (95 % CI 0.88–3.13) at 360 days.

Discussion

To our knowledge, this is the first prospective clinical trial of people in prison with HIV and OUD that examined the impact of initiating methadone before release on linkage to HIV care after release, the first step of the HIV treatment cascade for people who are leaving prison. Receiving methadone before release significantly increased linkage to HIV care through 360 days, with the number needed to treat for one additional linkage to HIV care decreasing from 14 at 30 days to 5 at 360 days. As MOUD is under-implemented globally in prisons, and particularly in low- and middle-income countries (LMICs), this is one of few clinical trials to focus on MOUD provision in an LMIC prison and one of the extremely few to examine HIV outcomes in this context.

These results demonstrate the importance of MOUD for PWH and OUD during the hazardous transition from prison to the community. Opioid-related mortality is the most common cause of death for all people leaving prison globally, including in HICs and LMICs (Borschmann et al., 2024a,b), but specifically for PWH leaving prison, mortality rates are driven most by untreated HIV disease followed by untreated opioid use disorder (Bazazi et al., 2022; Culbert et al., 2017; Loeliger et al., 2018a,b,c). Early linkage to MOUD serves the multi-purpose of reducing overdose, death, and criminal behavior, and also supporting participants to gain employment and connect with family (Altice et al., 2010; Degenhardt et al., 2019; Macdonald et al., 2024). In the case where HIV-related causes contribute the most to post-release mortality, PWH transitioning from prison to the community benefit substantially from early linkage to HIV care to assure access to ART and viral suppression. Mathematical modeling using community data suggests MOUD would reduce HIV transmission and death for PWH leaving prison (Altice et al., 2016; Stone et al., 2021). Our study contributes substantial new evidence supporting the initiation of MOUD within prison to promote post-release linkage to HIV care in LMICs.

Unlike studies of other types of MOUD that improve viral suppression levels, like extended-release naltrexone (Springer et al., 2018a) or

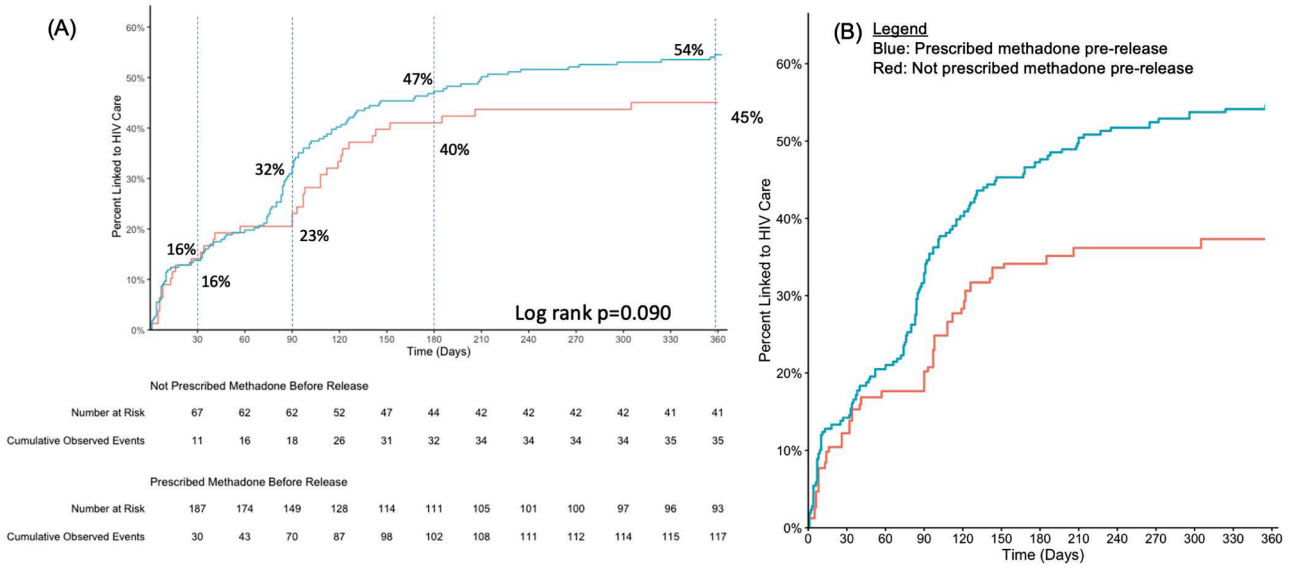

Fig. 3. Linkage to HIV care over 360 days after release from prison, stratified by pre-release methadone prescription ($N = 296$). (A) Unadjusted Kaplan–Meier survival curves. (B) Survival curves adjusted for covariates in Table 1 using inverse probability weighting.
Caption: Log rank test at 360 days.

sublingual buprenorphine (Springer et al., 2012) administered on the day of release, patients receiving methadone, as in our study, require substantial time to achieve an optimal dose. These other studies of MOUD in PWH transitioning to the community were comparatively small and did not examine the first step in the HIV care continuum, linkage to HIV care, though this outcome may be implicit.

For studies involving people in prison receiving MOUD, recent data show that achieving methadone doses of ≥80 mg before release results in substantially higher linkage to and retention in treatment with methadone after release (Ahmad et al., 2024; Bachireddy et al., 2022). This finding is aligned with community studies suggesting that higher dosages are associated with retention on treatment (Amato et al., 2005; Dumchev et al., 2017; Farnum et al., 2021; Ivasiy et al., 2022). Dosages in PWH during this era may have needed to be substantially higher as many common antiretroviral medications diminish methadone bioavailability (Altice et al., 2010). Recommendations for MOUD treatment throughout incarceration, allowing time to achieve an optimal dose, are aligned with studies supporting continuity of methadone between communities and criminal-legal settings (Rich et al., 2015). With increasing MOUD options, future studies should compare these options and incorporate study designs that align with patient preferences for the type of treatment (Bromberg et al., 2024; Liberman et al., 2021; Muthulingam et al., 2023).

The low level of linkage to HIV care is similar to other studies from the era before widespread universal ART for all PWH, irrespective of CD4. This may have influenced the rate and manner with which all Malaysians with HIV, including those in our study population, engaged in care; however, this would impact our treatment and control arms equally. Moreover, our use of inverse probability weighting addresses residual differences between groups regarding the type of allocation related to enrollment date (Appendix Fig. A.4).

Limitations

Despite these important findings, there are limitations. The design change from randomization to preference for methadone potentially introduced bias in our effect estimates. Deploying the doubly-robust estimation strategy, however, partially mitigates this concern with weighting applied to non-randomized participants. While we used a DAG informed by the literature to identify potential confounders, there are possibly unmeasured factors resulting in residual confounding. In particular, not being able to measure length of incarceration potentially confounds other variables. Our finding of a similar point estimate in a sensitivity analysis with the randomized subsample of participants (albeit with a broad confidence interval likely attributable to the sample size) reinforces the robustness of our analytic approach.

Ascertainment bias may have been introduced by relying on chart review data for the primary outcome. There are, however, few HIV clinics in Kuala Lumpur, making this less concerning aside from the few patients who may have moved to another region, with this outcome being underestimated. Ascertainment bias, however, would be similar for both groups. This study only examined the first step of the HIV cascade. Future studies should explore the entire HIV care continuum. Last, no women were recruited, potentially limiting generalizability. Though women account for a minority of people in prison, they are incarcerated at higher rates than men for drug-related offenses and have higher HIV prevalence and worse HIV-related outcomes (Erickson et al., 2019). Women must be included in future research on HIV and OUD.

Conclusion

Notwithstanding these limitations, findings from this prospective clinical trial highlight the vital role of pre-release MOUD, specifically methadone, on facilitating the HIV treatment cascade after release from prison. These findings should strengthen the level of international recommendations for managing HIV and OUD among people in prison in LMICs. Providing access to methadone voluntarily, after a complete discussion of benefits and risks, should be the expectation for PWH and OUD who are in prison. Malaysia remains far below UNAIDS 95-95-95 targets. Universal access to methadone, or other types of MOUD for people in prison with HIV and OUD, is one key strategy to reduce this gap. Findings here support methadone as a strategy to link PWH and OUD to HIV care after release with the opportunity to improve health outcomes for people in prison in LMICs.

Funding

This work was supported by the National Institutes on Drug Abuse at the National Institute for Health for research [R01DA025943; FLA] and [R01DA041271; SVS and FLA] and career development awards

[F31DA054861; DJB] and [F30 DA039716; ARB], the Fogarty International Center of the National Institutes of Health [D43TW011324; FLA and AK] and [D43TW010540; AMM], and the National Institute of Mental Health at the National Institute of Health [F30 MH105153; MPW]. MPW also received support from the Doris Duke Charitable Foundation International Clinical Research Fellowship.

Data sharing statement

Individual level participant data and a corresponding codebook will be published through NAHDAP upon acceptance of publication of this manuscript. Blank copies of the participant consent forms, and blank copies of the data collection instruments will be published as well. The study protocol has already been published under the title, "Design and implementation of a factorial randomized controlled trial of methadone maintenance therapy and an evidence-based behavioral intervention for incarcerated people living with HIV and opioid dependence in Malaysia" by Bazazi et al. The data will be made available at a DOI supplied by NAHDAP. Access will be in line with NAHDAP criteria and is anticipated to be public-use, downloadable, and free-of-cost.

CRediT authorship contribution statement

Allison M. Mobley: Writing – review & editing, Writing – original draft, Software, Formal analysis. **Martin P. Wegman:** Writing – review & editing, Validation, Software, Formal analysis, Data curation. **Alexander R. Bazazi:** Writing – review & editing, Software, Formal analysis, Data curation. **Sheela V. Shenoi:** Writing – review & editing, Supervision. **Daniel J. Bromberg:** Writing – review & editing, Validation, Software, Formal analysis. **Ahsan Ahmad:** Writing – review & editing, Data curation. **Adeeba Kamarulzaman:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Frederick L. Altice:** Writing – review & editing, Supervision, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

SVS's spouse worked for Merck pharmaceuticals 1997–2007 and retains company stock in his retirement account. There is no conflict of interest, but it is included in the interest of full disclosure. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We extend our thanks for all study participants, as well as the custodial and medical staff at Kajang prison. We give thanks also to all the research staff at the University of Malaya Centre of Excellence for Research in AIDS, in particular Basyirah Azmi, Prahaladhan Sivalingam, Jayanthi Venugopal, Clayton Koh, and N. Akma Ibriham, and all those at Yale University who provided vital support to this project.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.drugpo.2025.104733.

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