Published in final edited form as:

Contemp Clin Trials. 2017 August ; 59: 1–12. doi:10.1016/j.cct.2017.05.006.

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

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Abstract

Incarcerated people living with HIV and opioid dependence face enormous challenges to accessing evidence-based treatment during incarceration and after release into the community, placing them at risk of poor HIV treatment outcomes, relapse to opioid use and accompanying HIV transmission risk behaviors. Here we describe in detail the design and implementation of Project *Harapan*, a prospective clinical trial conducted among people living with HIV and opioid dependence who transitioned from prison to the community in Malaysia from 2010 to 2014. This trial involved 2 interventions: within-prison initiation of methadone maintenance therapy and an evidence-based behavioral intervention adapted to the Malaysian context (the Holistic Health Recovery Program for Malaysia, HHRP-M). Individuals were recruited and received the interventions while incarcerated and were followed for 12 months after release to assess post-release HIV transmission risk behaviors and a range of other health-related outcomes. Project *Harapan* was designed as a fully randomized 2×2 factorial trial where individuals would be allocated in equal proportions to methadone maintenance therapy and HHRP-M, methadone maintenance therapy alone, HHRP-M alone, or control. Partway through study implementation, allocation to methadone maintenance therapy was changed from randomization to participant choice; randomization to HHRP-M continued throughout. We describe the justification for this study; the development and implementation of these interventions; changes to the protocol; and

screening, enrollment, treatment receipt, and retention of study participants. Logistical, ethical, and analytic issues associated with the implementation of this study are discussed.

Keywords

HIV; opioid dependence; methadone maintenance therapy; prisoner health; Malaysia

1. Introduction*

Globally, HIV prevalence is elevated among people who use drugs, particularly among those who inject.^{1–3} Criminalization of drug use results in large numbers of people living with HIV (PLH) and substance use disorders cycling through the criminal justice system.^{1,2,4} People with substance use disorders and PLH face enormous barriers to receiving evidence-based treatments both while incarcerated and during the tumultuous period after release.^{5–9} While some criminal justice systems offer evidence-based treatment, the most common approach to the treatment of prisoners with opioid use disorders is forced abstinence.^{6,10} Data show that even after periods of forced abstinence during incarceration, the majority of untreated individuals with pre-incarceration opioid dependence relapse to opioid use within a year, and many relapse in the first month.^{11–15} After prison release, PLH also are at risk for suboptimal linkage to HIV care, poor adherence to antiretroviral therapy (ART), loss of viral suppression, and engagement in HIV transmission risk behaviors.^{16,17} Interventions targeting the transition from prison to the community have the potential to improve individual health and social outcomes and reduce HIV transmission in the communities to which prisoners return.^{18,19}

Decades of evidence support the use of opioid agonist therapies (OAT) in community settings for the treatment of opioid use disorders and reduction of HIV risk behaviors.^{20,21} One randomized controlled trial in the US examined the impact of initiating OAT during incarceration on post-release outcomes and found positive effects on linkage to community-based MMT, substance use, and HIV risk behaviors, but did not include PLH.^{12,22,23} Compared to passive referral to post-release MMT, initiating MMT during incarceration and offering subsidized treatment after release resulted in a significantly greater proportion of people entering community-based treatment (68.6% vs. 7.8%, $p<0.05$) and fewer testing positive for opioids (27.6% vs. 62.9%, $p<0.05$) one month after release.¹² Initiating OAT among prisoners who are not physiologically dependent is merited because of the chronic, relapsing nature of opioid dependence; without treatment, relapse risk among recently released prisoners is extraordinarily high.^{11–15} Prison-based OAT has not been evaluated specifically among PLH, but evidence from PLH with opioid use disorders in the community suggests that OAT can reduce HIV risk behaviors and improve HIV-related clinical outcomes.^{24–28}

* **Abbreviations:** people living with HIV, PLH; antiretroviral therapy, ART; opioid agonist therapy, OAT; Holistic Health Recovery Program for HIV-infected persons, HHRP+; Holistic Health Recovery Program for Malaysia, HHRP-M; methadone maintenance therapy, MMT.

Some behavioral interventions have also been shown to reduce HIV risk behaviors and improve health among people with substance use disorders.^{29,30} Although behavioral risk reduction interventions may be more effective when they specifically target PLH,³¹ few effective behavioral interventions exist for PLH who use drugs in the community and even fewer for those in the criminal justice system.^{32–36} The Holistic Health Recovery Program for HIV-infected persons (HHRP+) is one of the only evidence-based behavioral HIV risk reduction and ART adherence interventions that has been adapted for use in criminal justice settings with people who use drugs.^{32,33,37} In a randomized controlled trial in the community, HHRP+ significantly reduced substance use and HIV risk behaviors and improved ART adherence.³²

In Malaysia, illicit opioid use is widespread, and the prevalence of injection drug use may be among the highest globally.^{38–40} The HIV epidemic in Malaysia is concentrated among people who inject drugs and in the criminal justice system,^{38,41–44} yet programs for treating substance use disorders and HIV in prison and linking individuals to care after release remain limited.^{45,46} In Project *Harapan* (Bahasa Malaysia for “hope”), HHRP+ was adapted for prisoners living with HIV and opioid dependence in Malaysia (HHRP-M).⁴⁷ Project *Harapan* was designed as a 2×2 factorial randomized controlled trial to evaluate the efficacy of pre-release initiation of methadone maintenance therapy (MMT) and HHRP-M alone and in combination on post-release HIV transmission behaviors, drug use, and a range of other health and social outcomes.

2. Methods

2.1. Trial design overview

Project *Harapan* was designed as a 2×2 factorial trial in which opioid-dependent, incarcerated individuals living with HIV were to be randomized in equal proportions to receive either within-prison MMT, HHRP-M, both MMT and HHRP-M, or no study intervention. Partway through recruitment, the design was changed from randomizing participants to MMT to allowing them to choose MMT or not; randomization to HHRP-M continued throughout. Participants receiving MMT in prison were linked to fully subsidized MMT in the community. Details are described below.

2.2. Study setting

Malaysia’s incarceration rate is 171 per 100,000 people, with approximately 39,000 sentenced prisoners located in 35 prisons nationwide.⁴⁸ HIV prevalence in the prison system is approximately 2%, 5-fold higher than in the general population, and prevalence in the Kajang prison is even higher at 5%.^{49–51} Crimes directly and indirectly associated with drug use significantly contribute to imprisonment, and drug-related sentences typically include judicial corporal punishment (“caning”).^{44,52}

Participants were recruited and enrolled from the men’s prison in Kajang, Malaysia’s largest prison located approximately 30 km from the capital city of Kuala Lumpur. During recruitment, Kajang Prison housed approximately 4,000 male prisoners, operating well over its capacity.⁵³ All persons incarcerated at Kajang undergo mandatory rapid HIV-1/2

antibody testing upon entry and all PLH are segregated into a dedicated housing unit. The prison has an inpatient and outpatient medical unit.

In the prison, all study-related activities were conducted in private rooms reserved for Project *Harapan* within the prison medical unit, including interview rooms with Plexiglas windows, a group counseling room, a methadone dispensing room, and a waiting room. For participants' convenience, study evaluations in the community were conducted at a research facility, in a methadone clinic, or in other private locations (e.g. participants' homes).

HIV care was initially provided by Ministry of Health clinicians in the prison clinic and later also by study clinicians.⁵⁴ CD4+ T-lymphocyte count was measured on all participants and viral load was measured on those participants receiving ART. Results were provided to the prison doctors. Upon release, study participants were provided written referrals to their choice of one of Kuala Lumpur's few public or private HIV specialty clinics. All first-line ART medications are fully subsidized by the Ministry of Health. For those receiving ART in prison, a supply of medication for the period after release was provided only inconsistently because prisoners were sometimes released before or after their scheduled release date without informing medical staff. Major changes to HIV care in the prison over the course of the study are described in the discussion section.

2.3. Study interventions

2.3.1. Methadone maintenance therapy

2.3.1.a. Intervention development: pilot study of methadone initiation before prison release: Before beginning recruitment for the trial, two pilot studies initiating PLH on MMT before release were conducted in Kajang and Pengkalan Chepa Prisons to pilot and refine clinical and research procedures.^{55,56} One finding from the pilot studies was that participants receiving daily methadone doses 80 mg at the time of release were significantly more likely to be retained on MMT compared to those receiving doses <80 mg.⁵⁶ It was also found that MMT dosage typically could not be increased by more than 5 mg per week without precipitating side effects in this population with limited opioid tolerance.⁵⁵ Barriers to implementing MMT in the prison and actions taken to overcome them have been previously described.⁵⁵

2.3.1.b. Description of methadone maintenance therapy protocol

Methadone maintenance therapy in prison: Recruitment targeted eligible participants between 4 and 6 months before release from prison. To inform initial dose titration, participants underwent urine drug testing for opioids before starting methadone; however, opioids were not detected in any participant. The starting dose was 5 mg, which was increased by 5 mg weekly to reach a target dosage of 80 mg. Participants' dosage was reviewed whenever they requested an adjustment (e.g. due to continued cravings), whenever they reported difficulty tolerating methadone (i.e., symptoms of opioid excess, including vomiting, excessive drowsiness, and constipation) or when their ART regimen was changed. Methadone dosing and titration was performed by a study physician. Methadone was dispensed by a study nurse 7 days per week with all doses consumed within the prison medical clinic.

Methadone maintenance therapy in the community: Participants who received MMT in prison were offered fully subsidized MMT at a study-specific community MMT clinic upon release. The study MMT clinic was originally a small clinic that only provided MMT to research participants. Later, MMT for participants was provided at a combined MMT and medical clinic jointly operated by the research team and Malaysia's Anti-Drug Agency. If participants chose to receive MMT at a non-affiliated clinic, a referral was made but subsidization was not guaranteed. In the community, participants' dosage was readily reviewed by study clinicians at the request of participants. Take-home doses for up to one week were generally provided after one month of directly observed dosing, but exceptions were made to allow take-home doses after a shorter period of directly observed dosing for respondents who worked or lived far from the study clinic. Participants not allocated to MMT in prison were not restricted from accessing MMT in community clinics where some government-subsidized treatment slots were available for PLH.

2.3.2. Holistic Health Recovery Program for Malaysia

2.3.2.a. Intervention development: selection and adaptation of HHRP: The process of selecting an evidence-based intervention and adapting it to the Malaysian context is detailed elsewhere.⁴⁷ Briefly, the Holistic Health Recovery Program for PLH (HHRP+) was selected because of its demonstrated efficacy in reducing sexual and drug-related HIV risk behaviors, drug use, and addiction severity, and in improving adherence to ART among opioid-dependent people who inject drugs living with HIV as well as because of the feasibility of adapting it for implementation in the prison setting.^{32,47} Formative work involved critical examination of established evidence-based interventions complemented by data from structured interviews and focus groups with key stakeholders, members of the target population, and their family members. Based on this work, the original HHRP+ intervention was adapted to consist of 8 sessions designed to address challenges to reducing HIV risk behaviors and adhering to ART faced by incarcerated PLH in the Malaysian correctional system as they transition back to the community. The adapted intervention is called the Holistic Health Recovery Program for Malaysia, HHRP-M.⁴⁷

2.3.2.b. Description of HHRP-M protocol: HHRP-M consisted of 8 two-hour group sessions in prison. Sessions addressed healthcare participation, reducing individual sexual and drug-related risk behaviors and negotiating risk reduction with partners, healthy lifestyle choices, preventing relapse, overcoming HIV and drug use stigma, motivation for changing HIV risk behaviors, moving beyond grief, and achieving personal goals.⁴⁷ One optional individual "booster" session was offered to HHRP-M participants in the first month after their release. This session was tailored to the individual's needs and designed to review and maintain HIV risk reduction and ART adherence skills.

2.3.3. Control conditions—The control arm did not receive any addiction treatment intervention from the study but did receive health-related services that were the standard of care in the prison. The approach to addiction treatment in the prison was primarily faith-based counseling provided by Islamic clerics. This was delivered weekly to all participants and non-participants in the cell block where PLH were housed. The prison offered MMT on a limited basis, and study participation did not preclude participation in this program. All

participants received an informational packet on where to access HIV prevention services, temporary housing assistance, and HIV-specific medical care after release.

2.4. Eligibility criteria

Eligibility criteria were: (i) 18 years of age; (ii) HIV-positive, initially determined by self-report and confirmed by a rapid whole-blood antibody test; (iii) opioid-dependent in the 12 months prior to incarceration, determined initially by an abbreviated screening based on DSM-IV criteria and confirmed with a clinician-administered assessment of DSM-IV criteria in the Mini International Neuropsychiatric Interview;^{57,58} (iv) Malaysian citizenship, to assure availability of subsidized methadone and ART after release; (v) planning to return to Greater Kuala Lumpur; and (vi) within 6 months of anticipated release from prison but not less than 4 weeks.

2.5. Recruitment

Prison officers provided lists of all PLH in the dedicated HIV housing block after removing names of those who were not Malaysian, sentenced to life in prison, or were awaiting execution. These individuals were invited by prison staff to voluntarily attend group information sessions about the study conducted by study-employed research assistants. Interested individuals added their name to a list to schedule a private meeting with the research assistant to learn more about the study and undergo screening and informed consent. Individuals were offered the opportunity to attend the informational sessions and undergo screening multiple times in order to recruit those who were not originally eligible because they were more than 6 months from their release date. The majority of those who attended these sessions were screened for eligibility, though the number of unique individuals who attended the sessions was not recorded to protect confidentiality.

2.6. Treatment assignment

2.6.1. Randomization procedures—A random allocation sequence was generated with Random Allocation Software.⁵⁹ Blocking was used to ensure balance in the number of participants assigned to each group. Block size was varied randomly. Eligible, consented participants were assigned sequential study identification numbers, after which point the random allocation sequence was consulted to reveal what study arm was assigned to this number. Only one study staff member, who was not involved with recruitment, had access to the random allocation sequence. This individual informed the recruiting research assistants of the study arm associated with a participant's identification number only after they consented to participate. Blinding was not employed.

2.6.2. Changes to trial design—In February 2011, after 63 (15.8%) of the target sample size of 400 participants were enrolled in the fully randomized 2×2 factorial trial, MMT assignment was changed from randomization to participant choice.²² This change was due to strong individual preferences for or against methadone, which slowed recruitment, and an evolving standard of care within the prison during the course of the trial that resulted in increased access to MMT among prisoners.

First, despite 2 pilot studies and the adaptation of the intervention to the Malaysian context,^{47,55,56} initial enrollment proceeded much slower than anticipated. This was attributed in part to strong individual preferences for or against MMT,⁶⁰ resulting in many declining to enroll due to concerns that they would be randomized to a study arm they did not desire. Second, the standard of care for opioid treatment within the prison changed over time. Early in the study, the Ministry of Health offered MMT in the prison through a new and highly restrictive program. Few people received MMT through the prison-operated program because of restrictive criteria, including requirements that prisoners' families consent to MMT and agree to provide "social support" after release and that patients undergo hepatic transaminase testing that was often unavailable in the prison. As the prison gradually expanded its own MMT program, concerns about recruitment rate were compounded by concerns related to randomizing participants to not receive methadone when it was available, albeit on a limited basis, outside the study. Randomization to HHRP-M or no HHRP-M continued throughout the study.

2.7. Measures

2.7.1. Outcomes

2.7.1.a. Pre-specified primary and secondary outcomes: The primary outcome was HIV risk behaviors after prison release, defined as the number of potential transmission events from unprotected vaginal and anal sex and needle and syringe sharing during the 12-month post-release period. Secondary outcomes were (i) health-related quality of life, operationalized by the 36-Item Short Form Health Survey (SF-36);^{61–63} (ii) post-release relapse to illicit opioid use, defined as time to drug relapse and mean duration of time drug-free and measured by urine opioid testing and self-report; (iii) psychosocial functioning related to addiction severity, assessed with the Addiction Severity Index; (iv) reincarceration, including time to reincarceration and proportion reincarcerated by 12 months after release, assessed from a central database maintained by the prisons; (v) linkage to and engagement in HIV treatment post-release; and mortality using data from death records.

2.7.2. Ascertainment of outcomes and covariates—A detailed timeline of study activities is presented in Table 1.

2.7.2.a. Behavioral data: Behavioral outcomes and relevant covariates were ascertained with a battery of instruments administered at monthly study interviews. Study measurements included instruments evaluating addiction severity (Addiction Severity Index 5th edition, ASI),⁶⁴ mental health (psychiatrist-administered Mini International Neuropsychiatric Interview, MINI,⁵⁸ and the Center for Epidemiological Studies Depression Scale, CES-D,⁶⁵ alcohol use disorders (WHO AUDIT),⁶⁶ neuropsychological impairment,^{67,68} HIV symptoms,⁶⁹ health-related quality of life (SF-36),^{61–63} social support (MOS social support survey),⁷⁰ HIV stigma (Berger HIV stigma scale),⁷¹ trust in physicians,⁷² sexual and drug-related HIV risk behaviors, medical and drug treatment history, involvement with the criminal justice system, and attitudes toward drug treatment.

2.7.2.b. Biological data: All participants were tested for CD4+ lymphocyte count, hepatic transaminases, hepatitis B and C virus, and tuberculosis at baseline. CD4 testing was

repeated quarterly after release from prison. HIV viral load testing was also repeated quarterly for those on ART. Urine opiate testing was conducted monthly after release.

2.7.2.c. Administrative data: Some outcomes were ascertained from administrative databases without direct contact with participants. Participants consented to this in advance. These outcomes included mortality, which was ascertained by querying the government database of death records; linkage to and retention in HIV care, which was ascertained by reviewing medical records at clinics that provide HIV care in the study catchment area (targeted facilities were selected using study team knowledge and participant self-report during follow-up); and reincarceration, which was ascertained from a database maintained by the Malaysian Prison Department. Data on post-release MMT linkage, retention, and dosage was only available for the study-affiliated methadone clinic and was ascertained from medical or dispensing records, when available, or attendance records kept by study or clinic staff.

2.8. Follow-up Procedures

On the day of release, the consent process was repeated to ensure that participation was voluntary. All participants were offered transportation to the research site (where interview rooms were available) or another private location more convenient to study participants and to an HIV clinic for registration. Participants allocated to MMT were specifically transported to a methadone provider affiliated with the study. Contact with participants was minimally maintained by phone. Research assistants engaged in intensive efforts to locate participants lost to follow-up, including reaching out to a list of multiple contacts provided by participants and visiting shelter homes and public spaces frequented by people who use drugs in Kuala Lumpur. For their time and transportation costs, participants received RM130 (\$31 US) on their day of release, RM50 (\$12 US) at quarterly follow-up visits, and RM40 (\$10 US) at all other monthly visits.

2.9. Sample size and power calculations

Target enrollment was 400 participants, based on the original sample size calculations for the fully randomized design with 100 participants per treatment arm. These calculations were based on detecting a difference in the number of high-risk events during the period after release, assessing the effects of MMT and HHRP-M separately and not the interaction between the two treatments.^{73,74} We estimated that the number of such events in the control group would be Poisson distributed with a mean of one per week and that 73 subjects would be required in each arm (292 total) to achieve 85% power to detect a 10% difference in the rate of risky events with a type I error rate of 0.05 in the pairwise comparisons within each of the two interventions.⁷⁵ With a retention rate of 80%, a sample size of 365 would be needed. Target sample size was increased by an additional 10% to account for attenuated effects resulting from subjects not randomized to MMT choosing to enroll on their own after prison release, thus giving a final target sample size of 400 participants, 100 per study arm.

2.10. Planned Analyses

Given analytic issues arising from changes in the treatment allocation procedure for methadone, failure to reach target enrollment, and unexpectedly high rates of attrition to

behavioral follow-up, we do not present our pre-specified analysis plan, as it is no longer valid for the analysis of the primary outcome. Analyses of the effects of methadone will present raw data separately for randomized and non-randomized participants alongside pooled estimates to facilitate extraction of data for future meta-analysis.

2.11. Ethical oversight

This protocol was approved by institutional review boards at University of Malaya Medical Centre and Yale University. As this study involved federally funded research with prisoners, the protocol was also reviewed and approved by the Office of Human Research Protection at the U.S. Department of Health and Human Services. This study is registered at clinicaltrials.gov (NCT02396979).

3. PARTICIPANT FLOW

3.1. Screening

Figures 1A and 1B show participant flow from screening to treatment receipt for MMT and HHRP-M, respectively. Figure 1C shows participant flow for MMT, pooling over the randomized and treatment choice phases of the study. Between March 2010 and September 2013, 605 individuals were screened for eligibility. Of these, 310 (51.2%) were preliminarily deemed eligible and interested in participating and 295 (48.8%) were deemed ineligible or uninterested in participating.

Of the 295 screened individuals who did not enroll, 185 had a recorded reason for not enrolling. Reasons for ineligibility (multiple possible for each person) included: self-reported HIV-negative (n=10), screened negative for pre-incarceration opioid dependence (n=32), anticipated place of residence after release outside study catchment area (n=22), and too little or too much time remained in their sentence (n=132). Thirty-four individuals were not interested in participating after completing the screening.

Of the 310 individuals who initially were determined to be eligible and consented to participate, 3 were later found to be HIV-negative on confirmatory HIV screening (n=1 in the MMT randomization phase and n=2 in the MMT choice phase) and 1 was deemed not to have been opioid dependent in the 12 months prior to incarceration based on a clinician-administered screening (from the MMT choice phase). An additional 5 of these 310 individuals (all from the MMT choice phase) left the study before completing a baseline evaluation or receiving any intervention (n=3 withdrew shortly after screening, n=2 died in prison shortly after screening). Our final sample size was 301.

3.2. Treatment Allocation

Among those 63 participants enrolled during the MMT randomization phase, 32 (50.1%) were eligible and allocated to MMT and 31 (49.2%) were eligible and allocated to no MMT (Figure 1A). Among the 237 eligible participants in the MMT choice phase, 189 (79.7%) chose MMT and 48 (20.3%) chose no MMT (Figure 1A). HHRP-M was randomly assigned throughout, with 150 participants (49.8%) randomized to HHRP-M and 151 participants (50.2%) randomized to no HHRP-M (Figure 1B). Across the MMT randomization and

choice phases, a total of 221 participants (73.4%) were allocated to receive MMT (Figure 1C). Overall, 116 participants were allocated to HHRP and MMT (114 after exclusions), 37 were allocated to HHRP and no MMT (36 after exclusions), 113 were allocated to MMT and no HHRP (107 after exclusions), and 44 were allocated to neither HHRP nor MMT (none excluded). Post-allocation exclusions are shown in Figures 1A, 1B and 1C.

3.3. Receipt of and fidelity to interventions

3.3.1. Receipt of within-prison methadone maintenance therapy—From survey data and clinical records, we confirmed that 215 of the 221 participants eligible and allocated to receive MMT (97.3%) were initiated on methadone within prison (i.e. received at least one dose), including 100% of those randomly assigned to MMT and 96.8% of those who chose to receive MMT. Also by survey data and clinical records, we confirmed that 209 of the 221 (94.6%) received at least one dose of methadone in the 30 days prior to release, including 31 of 32 (96.9%) participants randomly assigned to MMT and 178 of 189 (94.2%) participants who chose to receive MMT.

Clinical methadone records were available for 192 of the 221 (86.9%) participants eligible and allocated to receive MMT, though some of these records were incomplete. Recorded doses in the 7 days before release were found for 54.8% of participants (121 of 221) and recorded doses in the 30 days before release were found for 72.4% (160 of 221). Among the 160 participants who had doses recorded in the 30 days prior to release, the average maximum dose was 60.8 mg (SD 33.8 mg); 64 (40.0%) achieved the target daily dosage of 80 mg of methadone and 98 (61.3%) received at least 60 mg. Obstacles to achieving the target daily dose of 80 mg included medication side effects (e.g. sedation) resulting in a slower titration schedule and insufficient time before release from prison, which was similar to results from pilot studies.^{55,56}

3.3.2. Receipt of HHRP Intervention—While there were no records to confirm how many HHRP-M sessions were attended by participants allocated to receive this intervention, facilitators reported consistently high levels of attendance.

3.4. Follow-up and Attrition

Behavioral follow-up occurred through December 2014, 12 months after the release of the last participant. Of the final sample of 301, 5 (1.7%) died before release (4 from infectious causes and 1 from liver failure). Immediately upon release from the prison, 27 participants (9.0%) were lost to follow-up without completing a day-of-release interview because they were issued a “police corrective order/action.” This involved the police taking custody of the participant on the day of release, forcibly relocating him to a location outside of Greater Kuala Lumpur and previously unknown to the individual or his family, and prohibiting him from returning to Greater Kuala Lumpur for a period of time. Only 2 of these 27 participants eventually returned to Greater Kuala Lumpur and completed a study interview. Overall, 268 participants (89.0%) completed an interview on the day of release, and 204 participants (67.8%) completed at least 1 additional behavioral follow-up visit from months 1 to 12 (Figure 2). Follow-up at 12-months was achieved by 103 participants (34.2%), and 55 (18.3%) completed all 12 monthly interviews.

Figure 2 displays retention overall and by treatment group. Some significant differences were observed across methadone allocation groups. At 12 months, 38.5% of those allocated to MMT and 22.5% of those not allocated to MMT were interviewed (t-test, $p=0.005$); significantly more participants allocated to MMT were also interviewed at month 9 ($p=0.007$), but this difference was not significant at 3-month or 6-month interviews ($p=0.565$ and $p=0.314$, respectively). No significant differences in retention at quarterly interviews were detected between people randomized to HHRP-M and those randomized to no HHRP-M. At 12 months, 39.3% of those randomized to HHRP-M and 29.1% of those not randomized to HHRP-M were interviewed ($p=0.063$); differences in retention at 3, 6, and 9 months also were not significant ($p=0.095$, $p=0.529$, and $p=0.178$; respectively).

4. DISCUSSION

Project *Harapan* was the first trial of within-prison MMT specifically for people living with HIV and of the HHRP-M behavioral intervention. Below we recount several of the challenges to study implementation we faced as well as the lessons learned from them and their implications for analysis.

4.1. Recruitment issues and patient preferences

The recruitment target of 400 participants was not reached during the study period for several reasons. Fewer people living with HIV and opioid dependence were incarcerated during the study period than anticipated, many individuals in the Kajang Prison were due to be released in regions outside the catchment area, and release rates were lower than anticipated, leaving a smaller population from which to recruit. Additionally, strong patient preferences for and against MMT, which have been previously documented in Malaysia,^{60,76} may have discouraged participation. At the outset of our trial, evidence from a preliminary study of prisoners with HIV and opioid dependence suggested that attitudes toward MMT were truly mixed, with 51% believing that opioid maintenance therapy would be helpful and 33% believing that they needed it to prevent relapse after release.⁶⁰ Anecdotally, research staff reported that during the early phase of recruitment, there was widespread suspicion toward methadone among prisoners, and that this suspicion abated over time as prisoners interacted with research participants receiving methadone. This change in perceptions toward MMT is best explained by the contact hypothesis, which posits that prejudice toward marginalized groups or even to treatments with which individuals do not identify, may be reduced via personal interaction with those groups (e.g., those taking MMT).^{77–79} Despite this evidence of mixed attitudes and early reports of resistance to MMT, overall most people preferred to receive MMT, as was evident when 80% of participants chose MMT when given the choice. A significant minority (20%) chose not to receive MMT. A Baltimore study of within-prison MMT also reported implementation issues related to strong preferences, which were primarily in favor of MMT: 25.7% of individuals randomized to receive only counseling withdrew because they had wanted to receive MMT and only 3% of those randomized to receive within-prison MMT withdrew because they had not wanted to receive MMT.¹²

Strong preferences may have led individuals in our study to refuse to participate altogether in the early phase of the study because they did not want to be randomized to MMT. This is an example of how strong treatment preferences—even in the setting of clinical equipoise—can adversely impact clinical trial participation. Furthermore, even when individuals are willing to undergo randomization, strong preferences can also threaten the external validity of a study if individuals who participate are those who would never select a particular intervention in a non-experimental setting.

Another challenge was in recruiting women. Although we did not intend to recruit only men, we were not provided access to the women's prison or to transgender women housed in solitary confinement within the men's prison. The reason given by the prison for not providing access to the women's facility was that all incarcerated women living with HIV were not Malaysian citizens and were facing extradition, a justification that we were not able to independently verify. This unfortunately continues a pattern of underrepresentation of incarcerated women and women who use drugs from research in Malaysia, despite the burden of disease in this population.⁸⁰

4.2. Expansion of treatment for opioid dependence in the prison

Study activities resulted in the expansion of MMT in the prison and a positive shift in prison staff attitudes toward medication-assisted therapies for opioid dependence. At the time of study implementation, MMT was available on a very limited basis through a newly established Ministry of Health program. Study activities resulted in an expansion of the prison clinic to accommodate increased provision of MMT and the training of medical staff in evidence-based guidelines for opioid agonist therapy. As described elsewhere, receipt of support from the Director General of the prison and implementation of regular trainings were critical for MMT implementation and for minimizing resistance among medical staff and correctional officers.⁵⁵

4.3. Expansion of medical care in the prison

Assuring that participants consistently received evidence-based HIV care was a challenge throughout the study. HIV care in the prison was under the purview of the Ministry of Health, the guidelines of which restricted ART to individuals whose CD4 lymphocyte counts were <350 cells/ μ L and pneumocystis pneumonia prophylaxis to those whose CD4 lymphocyte counts were <200 cells/ μ L. Initially, HIV care was not consistently provided to all PLH in the prison. For example, CD4 lymphocyte testing could only be conducted at a nearby government hospital and monitoring and testing was not routine. ART initiation remained contingent on physician discretion, medication stockouts occurred periodically, and high morbidity and mortality among PLH in the prison were observed.^{54,81} In 2011, the research team worked with prison staff to establish a dedicated HIV clinic with staffing support from physicians affiliated with University of Malaya and Yale, which led to the expansion of evidence-based HIV care in the prison.⁵⁴ Rapid, point-of-care CD4 testing was introduced to the prison clinic. Subsequently, all PLH, regardless of study participation, received CD4 and viral load testing and a comprehensive clinical assessment and medical record review. Specialty care skills were transferred to prison medical staff. In the 18 months

after the study ended, study staff continued to provide telemedicine consults and training in infectious diseases for Ministry of Health staff working in the prison.⁸¹

Early on in the study, tuberculosis care in the prison consisted of referring symptomatic individuals to a government hospital for diagnosis and treatment and then follow-up care within the prison. Because of tuberculosis-related deaths observed in the prison early in the study period, we initiated tuberculosis screening and treatment for latent tuberculosis infection within the prison HIV clinic. Details of the tuberculosis screening and treatment program are described elsewhere.^{54,82,83}

In part, as a result of these interventions, all-cause mortality in the prison decreased by 50.0% from 2011 to 2014.⁵⁴ Overall, there was significant transfer of clinical knowledge from research staff to prison medical staff, including through ongoing tele-educational programs delivered using Project ECHO strategies,^{84,85} that improved the quality of care in the prison. Continual turnover of staff and directors, however, poses a challenge to sustaining these benefits.

4.4. Ethical considerations

4.4.1. Coercion and consent—Research in correctional settings requires extra attention to concerns of coercion and consent. Because initial contact was with prison staff (correctional officers), there was concern that prisoners might be coerced to join the study or that correctional officers might preferentially select inmates in exchange for favors. To minimize the risk of actual or perceived coercion or selection bias, the lead investigators met with prison leadership quarterly and the research team conducted training sessions with prison staff to educate them on the importance of adherence to ethical standards in the conduct of this study. These standards included the importance of ensuring the privacy of potential or enrolled participants' health-related information, guaranteeing that all potentially eligible participants had the same opportunity to agree or disagree to enrolling in the study, and awareness of the potential for prison staff to intentionally or unintentionally engage in coercive behavior toward prisoners regarding study related activities. As part of this process, the prison personnel recommended installation of plexiglass windows on all rooms where research activities occurred that would ensure the research team's safety, but also protect participant self-reported responses and interactions. Voluntariness of participation was stressed at each phase of recruitment. All interested individuals underwent a detailed informed consent process in private and away from any correctional staff. The consent process was repeated after release from prison.

4.4.2. Ethical concerns within the prison system, independent of study activities—Research can offer a window into otherwise-closed, highly controlled environments, such as prisons, that reveal ethical issues independent of study activities. Several such issues arose while conducting this study; we note two here since they may diverge from expectations about prison research in other countries. First, prisoners were subjected to mandatory HIV testing, and PLH were segregated into an HIV-specific housing unit, thereby compromising the confidentiality of their HIV status. Research staff insisted on procedures to maintain participant confidentiality when communicating with participants

and providing medical care, but prison policy made it nearly impossible for participants' HIV status to remain confidential from other prisoners. Second, judicial corporal punishment is typically a component of drug-related sentences.^{44,52} Many of our participants were subjected to “caning” during incarceration.

4.5. Analytic challenges

Changing from randomizing participants in the MMT intervention to allowing them to choose poses a unique analytic challenge. In addition to the need to control for treatment selection bias among non-randomized participants, it may also be necessary to account for differences between participants in the randomized and non-randomized phases of the trial. It may be useful to account for heterogeneity of treatment effects between these phases by, for example, including a dummy variable for study phase and its interaction with treatment in a regression of the outcome on the covariates.

An additional challenge is the reduced power to detect treatment effects. Since the target enrollment was not reached within the study period, the power to detect treatment effects is lower than that originally estimated. Power issues related to not reaching the target sample size are potentially compounded by the change in the allocation mechanism for MMT. In estimating the effects of MMT, power may be further reduced by statistical adjustments needed to account for treatment selection bias. We will use strategies that make use of pre-treatment variables to increase efficiency in treatment effect estimation.

Another threat to both power and unbiased estimation of treatment effects on behavioral outcomes is the high degree of attrition. Retention rates were lowest among control participants, which has been documented in other clinical trials with released prisoners.^{15,22,86} Differential attrition rates between treatment groups and the large proportion of participants missing behavioral follow-up data can lead to biased treatment effect estimates for behavioral outcomes. We will use inverse probability weighting to handle missing behavioral outcome data. Secondary outcomes from administrative datasets are more complete. For example, less than 5% of participants were missing mortality data. Data on HIV care utilization are available for those participants who followed up at the clinics in Kuala Lumpur where subsidized treatment is available; it is possible but less likely that participants accessed care at private clinics at their own expense, which could lead to ascertainment bias.

5. CONCLUSION

Project *Harapan* is the first prospective trial of prison-based, pre-release MMT specifically for incarcerated people living with HIV and the first prospective evaluation of the behavioral intervention HHRP-M. Data from this trial will be used to evaluate the effects of within-prison MMT and HHRP-M on post-release HIV transmission behaviors and a range of key health-related outcomes. This study led to additional indirect benefits to prisoner health through improvements in HIV, tuberculosis, and opioid dependence treatment resulting from the study implementation process.

Acknowledgments

This work was supported by grants for research (R01 DA025943 [FLA, AK, MMC]), career development (K24 DA017072 [RA], K01 DA038529 [JAW]), and training (F30 DA039716 [ARB], T32 GM07205 [ARB], F30 MH105153 [MPW]) from the National Institute of Health and a training grant from Doris Duke Charitable Foundation (MPW). Funders had no role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; nor in the decision to submit the article for publication.

We would like to gratefully acknowledge the contributions made by the following people to study implementation and administration: Ezra Mohd Akbar, Nuruljannah Nor Azmi, Maria Theresa Anthony, Paula Dellamura, Samuel Haquin, Maua Herme, Nor Akma Ibrahim, Tunku Noor Hayati Tunku Abdul, Rusli Ismail, Lianna Khairuddin, Clayton Koh, Iqa Mohd Salleh, Rumana Saifi, Jayanthi Venugopal, Ilias Adam Yee, Muhammad Muhsin Zahari.

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A. Participant flow diagram, methadone maintenance therapy

B. Participant flow diagram, Holistic Health Recovery Program for Malaysia (HHRP-M)

C. Allocation to methadone, pooled over randomization and treatment choice phases.

Figure 1.

A. Participant flow diagram, methadone maintenance therapy

▲Methadone assignment change from randomization to participant choice.

*Reasons for exclusion not mutually exclusive.

**All post randomization withdrawals and deaths occurred shortly after screening and before intervention receipt.

B. Participant flow diagram, Holistic Health Recovery Program for Malaysia (HHRP-M)

*Reasons for exclusion not mutually exclusive.

**All post randomization withdrawals and deaths occurred shortly after screening and before intervention receipt.

C. Allocation to methadone, pooled over randomization and treatment choice phases.

*All post randomization withdrawals and deaths occurred shortly after screening and before intervention receipt.

Figure 2. Retention to behavioral follow-up.

Bars represent the fraction of participants completing an evaluation at different times in the study, from the pre-release interview (PRE), the day of release interview (DOR), to the monthly follow-up interviews (M1 to M12).

Table 1

Timeline of study activities.

	Prison																		Community											
Timeline (months)	Pre-Intervention	-6 to -4	-3	-2	-1	0*	1	2	3	4	5	6	7	8	9	10	11	12												
Study activity																														
Screening for eligibility	X																													
Informed consent	X				X																									
Treatment assignment	X	X																												
Interventions																														
HHRP-M				X	X		X																							
Methadone initiation and dose escalation (within prison)																														
Methadone maintenance (community)		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X												
Clinical assessments																		X												
HIV antibody/antigen confirmatory test	X																													
HIV-1 RNA (viral load) %	X					X			X			X			X			X												
CD4 lymphocyte count	X								X			X			X			X												
Hepatitis B and C antibody testing	X																													
Hepatic transaminases (AST and ALT)	X																													
Tuberculin skin testing (TST)	X																													
Urine drug testing (opioids)							X	X	X	X	X	X	X	X	X	X	X	X												
Research interviews																														
Medical assessment	X																													
HIV symptom index	X				X				X			X			X			X												
Chronic illness history	X				X				X			X			X			X												
HIV and other medical care utilization	X					X	X	X	X	X	X	X	X	X	X	X	X	X												
Psychiatric evaluation (MINI)	X																													
Neuropsychological impairment scale	X																													
Depressive symptoms (CES-D)	X								X			X			X			X												

	Prison					Community												
	Pre-Intervention	-6 to -4	-3	-2	-1	0*	1	2	3	4	5	6	7	8	9	10	11	12
Timeline (months)																		
Addiction severity index	X					X	X		X			X			X			X
Alcohol use disorders screening (AUDIT)	X																	
Drug use and risk behaviors, previous 30d +	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Sex and related risk behaviors, previous 30d +	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Previous experience with addiction treatment						X	X	X	X	X	X	X	X	X	X	X	X	X
Methadone knowledge and attitudes	X								X			X			X			X
Adherence support preferences	X																	
Health-related quality of life (SF-36)	X					X												
Social support scale	X						X		X			X			X			X
Berger HIV stigma scale	X								X			X			X			X
Information-Motivation-Behavioral skills for risk behaviors	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Adherence support preferences	X																	
Re-entry challenges and recidivism	X					X	X	X	X	X	X	X	X	X	X	X	X	X
Police Harassment assessment									X			X			X			X
Outcomes assessed using administrative datasets																		
Re-incarceration						X	X	X	X	X	X	X	X	X	X	X	X	X
Linkage to HIV Care						X	X	X	X	X	X	X	X	X	X	X	X	X
Mortality			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Community MMT clinical data						X	X	X	X	X	X	X	X	X	X	X	X	X
Payment for participation						X	X	X	X	X	X	X	X	X	X	X	X	X

* Time 0 refers to interview conducted in the community on the day of release.

⁺ Risk behaviors in 30 days prior to incarceration assessed at baseline interview. Risk behaviors during incarceration assessed outside of prison on the day of release.

% Only participants on ARVs received viral load testing.

[^] Community methadone data only available from study-affiliated methadone clinic.