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Expanding substance use treatment options for HIV prevention with Buprenorphine-Naloxone: HIV Prevention Trials Network 058 (HPTN 058)

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For the HPTN 058 Protocol team

Abstract

Background—Injection opioid use plays a significant role in the transmission of HIV infection in many communities and several regions of the world. Access to evidence-based treatments for opioid use disorders is extremely limited.

Methods—HPTN 058 was a randomized controlled trial designed to compare the impact of two medication assisted treatment (MAT) strategies on HIV incidence or death among opioid dependent people who inject drugs (PWID). HIV-negative opiate dependent PWID were recruited from four communities in Thailand and China with historically high prevalence of HIV among PWID. 1251 participants were randomly assigned to either; 1) a one year intervention consisting of two opportunities for a 15 day detoxification with buprenorphine/naloxone (BUP/NX) combined with up to 21 sessions of behavioral drug and risk counseling (Short Term Medication Assisted Treatment: ST-MAT) or, 2) thrice weekly dosing for 48 weeks with BUP/NX and up to 21 counseling sessions (Long Term Medication Assisted Treatment: LT-MAT) followed by dose tapering. All participants were followed for 52 weeks after treatment completion to assess durability of impact.

Results—While the study was stopped early due to lower than expected occurrence of the primary endpoints, sufficient data were available to assess the impact of the interventions on drug use and injection related risk behavior. At weeks 26, 22% of ST-MAT participants had negative urinalyses for opioids compared to 57% in the LT-MAT ($p<0.001$). Differences disappeared in the year following treatment: at week 78, 35% in ST-MAT and 32% in the LT-MAT had negative urinalyses. Injection related risk behaviors were significantly reduced in both groups following randomization.

Conclusions—Participants receiving BUP/NX three times weekly were more likely to reduce opioid injection while on active treatment. Both treatment strategies were considered safe and associated with reductions in injection related risk behavior. These data support the use of thrice weekly BUP/NX as a way to reduce exposure to HIV risk. Continued access to BUP/NX may be required to sustain reductions in opioid use.

Introduction

Globally, the number of people who inject drugs (PWID) is relatively small, rarely exceeding 1% of total population in any country. Yet, in many communities and several regions, particularly Eastern Europe, Central and Southeast Asia, injection drug use remains a primary driver in the AIDS epidemic.[1–5] Outside of sub-Saharan Africa, injection drug use accounts for about one third of all new HIV infections and approximately three million PWID are estimated to be infected with HIV.[1,5] PWID are estimated to have twenty-two times the prevalence of HIV infection relative to the general population.[6] Since most of these infections are related to the injection of heroin or other opioids, alone or in combination with stimulants or benzodiazepines, effective treatments for opioid dependence have important potential for preventing new HIV infections. Although there have been no randomized controlled trials, over 20 years of observational data on the impact of methadone maintenance treatment (MMT) provide “proof of concept” on the ability of medication assisted treatment (MAT) to reduce opioid use, injection related risk behaviors, and HIV infections.[7–16] Yet, despite evidence of the efficacy of methadone treatment as an HIV prevention strategy, access remains extremely limited.[3,13,17] Only a small proportion of PWID are currently receiving MAT and most drug users at risk of HIV infection have no access to any form of evidence based treatments for opioid use.[5,18]

The use of buprenorphine/naloxone (BUP/NX) has expanded rapidly since its approval as a treatment for opioid addiction in the US in 2002. Buprenorphine is a partial opioid agonist with strong affinity to the *mu* opioid receptors of the central nervous system resulting in an active half-life of up to 60 hours, making dosing intervals of up to three days possible.[19,20] While buprenorphine alone was first introduced for opioid dependence treatment in Europe in 1996, naloxone was included in the tablet formulation as a deterrent to diversion and injection.[21] When absorbed sublingually, buprenorphine maintains adequate bioavailability while naloxone poorly absorbed and rapidly metabolized. However, if a BUP/NX tablet is dissolved for use by injection, naloxone will remain active and precipitate withdrawal. Overdose from BUP/NX alone is uncommon and withdrawal symptoms following dose reduction are less severe in intensity and duration than pure agonist medications.[22–24]

Similar to other opioids, side effects include nausea, vomiting, constipation, sedation and temporary elevations in liver transaminases.

Given the critical need to expand MAT options for HIV prevention among opioid injectors, HPTN 058 was designed to compare two novel, one year, community-based opioid treatment strategies using BUP/NX and counseling to reduce incident HIV infections and mortality among opioid dependent injectors.

Methods

HPTN 058, a 1:1 randomized open label trial, compared two twelve month opioid treatment strategies combining medication and drug counseling in opioid dependent PWID in China and Thailand. Those assigned to the short-term medication assisted treatment arm (ST-MAT) received a three day induction to BUP/NX followed by up to 15 days of dose reduction detoxification. ST-MAT participants also received weekly drug counseling for the first three months of treatment and then offered monthly for the remaining nine months of the intervention.[25,26] Recognizing that opioid dependence is a chronic disease with a high likelihood of relapse, at week 26, participants in the ST-MAT arm were offered a second opportunity for detoxification. The LT-MAT arm received BUP/NX induction and dosage stabilization followed by directly observed BUP/NX administration in the clinic three times per week for 46 weeks. At week 47 BUP/NX dose tapering began with final dosing completed by the end of week 52. LT-MAT participants received twelve months of drug counseling on the same schedule as the ST-MAT arm. Both study arms were followed for an additional 52 weeks after treatment completion to evaluate long term impact. The primary endpoint of the study was incident HIV infection or death at week 104, one year after the completion of the intervention. The protocol was designed to measure impact during the intervention year and to assess durability of effect following treatment completion. Interim monitoring rules established prior to the initiation of the study included planned analyses by the independent DSMB after 25%, 50% and 75% of the participants had completed the 104 week assessment. The protocol was reviewed and approved by ethics committees and IRBs at each local site and affiliated institutions.

Study population

Study participants were active opioid injectors recruited from the community at four sites: Chiang Mai, Thailand (n= 202); Nanning (n=161) and Heng County (n=411) in Guangxi, China and Urumqi (n=477), in Xinjiang, China. Sites were selected based on prior evidence of HIV incidence among PWID ranging from 2% to 9% per year.[27,28] All study sites had access to methadone treatment, harm reduction services, and HIV treatment. Targeted outreach and recruitment activities were guided by local epidemiologic information and knowledge of the drug using community.

Individuals were eligible if they were at least 18 years old, HIV-seronegative, met criteria for opioid dependence (DSM-IV)[29], had a positive urine drug test for opioids, and reported injecting 12 or more times in the prior 28 days. Exclusion criteria included enrollment in MMT, known allergy to BUP/NX, current alcohol or benzodiazepine dependence, pregnancy or breastfeeding, unwillingness to use contraception if female, alanine

aminotransferase (ALT) > 3 times upper limit of normal (ULN), hemoglobin < 8 g/dL (if male) or 7 g/dL (if female), bilirubin > 2.5 times ULN, or platelet count < 50,000/mm^3.

HPTN 058 represented the first use of BUP/NX in both Thailand and China. Consequently, recruitment of participants included activities and materials devoted to community and participant education. Each site had an active community advisory board (CAB) that included representatives from local advocacy groups, family members, public health, and criminal justice agencies. Prior to project implementation, CABs and community representatives were invited to participate in formal meetings designed to solicit feedback on the purpose of the study, its procedures, the interventions, and the strategies used to protect the safety and confidentiality of study participants. The design included a safety phase and review at each site after the first 50 participants completed one month of treatment. No unexpected safety concerns were identified at any site and enrollment proceeded uninterrupted.[30]

Medication management

Participants in both study arms began with a three day, outpatient induction period. In accordance with established clinical guidelines, participants were instructed not to use opioids for 24 hours prior to induction which must be initiated during withdrawal. Withdrawal symptoms were assessed using the Clinical Opioid Withdrawal Scale (COWS).[31,32] Those with a score of 8 or greater were judged ready for induction, and received a 4 mg dose of sublingual BUP/NX. At one hour post-dose, if the COWS score was 2 or greater a second 4 mg dose was given. Days two and three followed similar procedures with provision for up to 16 mg and 32 mg respectively. Following induction, participants assigned to ST-MAT completed detoxification with an average dose tapering of 2 mgs per day for up to 15 days. Participants assigned to LT-MAT, after establishing the maintenance dose that prevented the emergence of withdrawal symptoms, continued receiving BUP/NX for 48 weeks, attending the clinic three times each week for directly observed dosing. At week 48, tapering of BUP/NX began, with dose reduction of 1–2 mgs per day with all medication administration completed prior to week 52. Dosing visits were carefully monitored and re-induction was required if more than three consecutive visits were missed. Women who became pregnant during the BUP/NX treatment phase were tapered from the medication and referred to MMT but continued in the counseling intervention and were followed through delivery and the completion of the study. At the week 26 assessment, participants in the ST-MAT arm who had relapsed to opioid use were offered a second induction and detoxification.

Counseling intervention

All study participants received behavioral drug and risk counseling (BDRC).[25,26] BDRC is rooted in cognitive behavioral theory and focused on helping participants understand their addiction as a manageable medical condition. Counseling was delivered in individual sessions of 30–45 minutes, guided by a manual and designed to help participants develop and implement meaningful strategies for controlling drug use and avoiding injection and sexual risk. Counselors helped participants establish short term behavioral goals that promoted completion of BUP/NX administration visits, risk reduction, avoidance of

"triggers" for craving and use, and initiation of rewarding behaviors incompatible with continued drug use. Counselors developed behavioral contracts to guide goal directed behavior between counseling sessions.

Assessments

All participants completed interviewer administered assessments of injection and non-injection drug use, sexual and drug related risk behaviors, community treatment utilization, HIV testing and plasma storage every 26 weeks throughout the study. At baseline and weeks 12, 26, 40 and 52 specimens were collected to assess liver function (ALT and total bilirubin). Testing for Hepatitis B and C was performed at screening and week 26, additional testing for Hepatitis C was performed at subsequent semi-annual follow up visits if previously negative. Urine drug screens and pregnancy tests were assessed monthly and semi-annually during the 12 month intervention period. Participants were followed for a minimum of 104 weeks, and a maximum of 156 weeks based upon their time of enrollment.

Laboratory methods

HIV testing was completed using two locally available rapid HIV test kits that had undergone full validation and were subject to routine proficiency testing according to HPTN protocol. Baseline HIV status and all new HIV infections were verified by the HPTN Network Laboratory using stored plasma and Food and Drug Administration (FDA) approved HIV methodologies. A commercial point of care test with a sensitivity of 300ng/mL was used for detection of urine opioids and other drugs (Integrated E-Z Split Key Cup, ACON Laboratories, San Diego, CA).

Statistical analysis

The study had 90% power to detect a 50% reduction in cumulative HIV infection and death at 104 weeks, assuming an HIV infection risk such that 7.25% of the ST-MAT arm would be infected or have died by 104 weeks.

The study was reviewed at least annually by an independent Data Safety and Monitoring Board (DSMB) appointed by the sponsor. At the first scheduled interim analyses, occurring October 4, 2011, when 25% of the participants had completed 104 weeks on study, the DSMB halted the study due to futility as a result of lower than anticipated HIV incidence rates. The present analysis includes data from visits up through October 4, 2011.

Cumulative incidence rates and confidence intervals were calculated based on Poisson distribution with time to infection or death. Cox proportional hazards model was used to compute hazards ratios. Monthly urine screens and injection and related risk behaviors were compared between arms using logistic regression at each visit, adjusted for site.

Results

A total of 2268 PWID were screened for eligibility and 1251 were enrolled and randomized between May 2007 and October 2011, 627 on the ST-MAT and 623 on the LT-MAT (Figure 1). At the time the study was halted, 470 ST-MAT participants and 477 in the LT-MAT

completed at least one follow-up HIV test and are included in the primary intent to treat (ITT) analysis.

As shown in Table 1, participants were predominantly (92%) male with a median age of 33 years. Over 40% were from ethnic minorities and a slight majority were married and living with a spouse or partner. Participants had been injecting for a median of 7 years with a median age at first injection of 25 years. During the month prior to enrollment, 90% reported injecting heroin, 11% reported injecting opium. The median number of injections in the month prior to enrollment was 84 (IQR: 60–90), or about 3 times per day. As required for enrollment, 100% of the participants tested positive for opioids. Methadone (3%), amphetamine (2%) and benzodiazepines (19%) were detected by urine drug screen.

Intervention exposure

The 3 day induction was initiated by all participants (with one exception) and completed by 89% (88% in the ST-MAT and 91% in the LT-MAT arm) (Table 2). In the ST-MAT arm, 80% of participants completed detoxification. At week 26, 153 of 440 (35%) ST-MAT participants initiated a second detoxification; 85% of these completed this detoxification. LT-MAT participants received observed BUP/NX doses for a median (IQR) of 170 days (IQR, 63, 308).

Among the LT-MAT participants, 74% were retained in treatment through weeks 25–28, (i.e. completed BUP/NX medication visits during or after the period) with 55% receiving at least 75% of expected doses in this time window. By the final month of intervention (weeks 45–48), 55% remained in treatment, with 43% receiving at least 75% of expected doses.

Among those assigned to ST-MAT, 66% completed at least 9 of 12 weekly counseling sessions, compared to 84% in the LT-MAT arm ($p < 0.001$). Similarly, 59% of those in the ST-MAT arm completed 6 of 9 monthly counseling sessions compared to 70% of the LT-MAT ($p < 0.001$)

HIV infection and Death

Through week 104, 5 incident HIV infections and 9 deaths were identified among those in the ST-MAT arm and 2 incident HIV infections and 8 deaths among LT-MAT participants. With 642 person years (PY) in the ST-MAT arm and 658 in the LT-MAT arm, the composite rates of HIV infection or death were 1.9 (95% CI: 1.0–3.3) and 1.5 (95% CI: 0.7–2.8) per 100 PY, for a hazard ratio of LT-MAT vs. ST-MAT of 0.69 (CI: 0.31–1.56, $p = 0.38$).

Drug use outcomes

Monthly and semi-annual urine toxicology tests are shown in Figure 2. At week 24, 23% (103/445) in the ST-MAT arm and 56% (257/461) in the LT-MAT tested negative for opioids ($p<0.001$). At the initiation of dose tapering in week 48, opioid negative toxicology results were found in 33% (78/237) of ST-MAT compared to 58% (155/268) of LT-MAT participants ($p<0.001$); at completion of tapering (week 52), this remained at 32% (107/338) among ST-MAT participants but decreased to 46% (163/357) in the LT-MAT arm (p<

0.001). By 78 and 104 weeks, ST-MAT and LT-MAT arms had similar rates of opioid-negative tests: at week 78, 35% (100/283) in the ST-MAT and 32% (89/279) in the LT-MAT arm ($p = 0.38$); at week 104, 30% and 34% in the ST-MAT and LT-MAT arms respectively ($p = 0.43$).

As shown in Figure 3A, self-reported drug use was consistent with urinalyses results; at week 26, 26% of participants in the ST-MAT arm and 58% in the LT-MAT arm reported no injection in the prior 30 days ($p \leq 0.001$). At the end of the treatment phase of the study (week 52), 43% of the ST-MAT and 59% of the LT-MAT participants reported no injection during the prior month ($p \leq 0.001$). No significant differences between arms were found during the second year: at 78 weeks 48% of ST-MAT and 50% of LT-MAT participants reported no injection ($p = 0.7$) and at 104 weeks, 53% of ST-MAT and 49% of LT-MAT reported no injection use ($p = 0.4$).

Risk behavior outcomes

Self-reported injection related risk behaviors showed significant reduction in both arms following baseline that was sustained through the treatment phase and the subsequent year of follow-up. Figures 3B, 3C, and 3D show this pattern for injecting with more than one person, use of the same syringe/needle after another PWID, and sharing cookers, cottons, and rinse water. Significantly fewer injections were reported by LT-MAT participants at week 26 and 52. Also, fewer LT-MAT participants reported injecting with more than one person compared to ST-MAT.

Discussion

Due to the small number of new HIV infections observed in the study, we were unable to evaluate whether one year of BUP/NX and counseling was more effective in preventing HIV infection and death than short term BUP/NX and counseling. Despite this, those with one year of access to BUP/NX in the LT-MAT arm had a significantly higher, sustained reduction in opioid use and injection compared to those in the ST-MAT arm, as measured by both urinalyses and self-report, indicating a reduced risk of exposure to HIV. The differential rates of opioid use between arms disappeared by week 78, although 30% or more participants remained opioid free.

The study was designed to assess the durability of the LT-MAT intervention following one year of treatment and it is apparent that relapse to opioid use commenced as soon as the tapering began. Thrice-weekly access to BUP/NX achieved significant reductions in opioid use and injection during treatment. Since these reductions were not sustained after cessation of BUP/NX and counseling, our data clearly demonstrate the necessity of continued access to medication beyond one year to sustain reductions in opioid use for many PWID.

The reduction in opioid use among participants in the LT-MAT arm during the treatment phase has important implications for HIV prevention. Research conducted over the past 20 years clearly demonstrates that reduced opioid use and injection related risk behaviors among opioid users in MAT are associated with lower risk of HIV acquisition.[16] In addition, access to and retention in MAT by HIV positive individuals has been associated with

increased retention in antiretroviral treatment and viral suppression, which itself has been associated with a reduced risk of HIV transmission.[33–36] Past research among PWID has demonstrated that continued drug use inhibits these objectives. Cessation of injection through effective treatments (similar to that reported here) has been shown to increase access and improve retention and adherence to antiretroviral treatment.[35,37–42] Importantly, these positive impacts occur among injectors who cease injection and not merely stop sharing syringes or enter treatment.[38]

Injection related risk behaviors were reduced among participants in both arms. Significant reductions in self -reports of injection, frequency of injection, needle sharing (reuse of a syringe after another injector), injection with others and sharing of cookers, cotton, and rinse water were observed between baseline and the assessment at six months in both arms. These behavioral changes were sustained through the intervention year and extended throughout the year following cessation of BUP/NX and counseling. The self-reported reductions in drug use and risk behavior among participants in both groups are consistent with the low rate of HIV incidence observed during the study.

Reductions in injection related risk behaviors must be considered in light of the counseling intervention that was available to participants in both arms. The approach and content were the same and attendance had potential to be clinically meaningful. Those assigned to the LT-MAT arm completed significantly more counseling sessions, suggesting that the regular contact required for medication administration also facilitated counseling attendance. Since participants in both arms received the same counseling, it is not possible to directly measure its impact on drug use and risk behaviors in this study. However, both arms displayed similar patterns of risk reduction. The data reported here support the perception that behavior change can occur among drug users who continue to use drugs.

Study sites were chosen based on earlier studies in these same communities that found HIV incidence rates as high as 8% per year.[27,28] During the intervening time, HIV testing was expanded, access to antiretroviral treatment was scaled up and methadone treatment was introduced in each of the three communities in China. It is likely that these public health programs contributed to the low HIV incidence observed in HPTN 058.

The findings reported here should be considered in light of several limitations. First, participants in this study were recruited from the community and volunteered to receive treatment for their addiction. Consequently, data from this trial may not generalize to all opioid dependent injectors. Despite efforts to include women, 92% of the participants were men and we cannot be certain that the treatment outcomes apply to female opioid dependent injectors. Data on frequency of injection, injections with others, and sharing of syringes and other injection equipment can only be measured by self-report. However, it is important to note that we observed a high correlation between self-reported opioid use and urine toxicology results. Additionally, the decline in opioid use and injection in both arms of the study may reflect a regression to the mean bias since all participants had to have a positive opioid test in order to be enrolled. Finally, the study was discontinued prematurely due to lower than expected event rates in both arms of the study and we were unable to address the primary outcome of the trial.

Medication Assisted Treatment (MAT) approaches are based upon a body of evidence showing that drug dependence is most effectively treated when viewed as a chronic medical condition with both biological and behavioral components. As in the treatment of other chronic medical conditions disease management is more likely to be successful when appropriate medications are used in combination with behavioral interventions. In the United States, data on the efficacy of BUP/NX treatment coupled with its safety profile led to FDA approval for administration through office-based practice in which physicians with brief training can provide prescriptions for pharmacy distribution and self-administration. For some opioid dependent individuals however, the clinic based, directly observed medication administration used in HPTN 058 may be a more effective delivery strategy and lead to increased adherence and participation in counseling.

The participation we achieved in both medication and counseling is comparable or superior to that seen in other drug treatment modalities and provides evidence of the feasibility and acceptability of this strategy.[33] Thrice weekly directly observed dosing, combined with counseling has a much lower burden on both patients and staff than daily MMT and has not previously been assessed in a large scale community-based trial. This intervention was safe and effective for reducing both opioid dependence and injection related risk. Access to MATs for opioid dependent individuals who are at risk for HIV and other blood borne infections is extremely limited, particularly in areas where HIV transmission is most commonly linked to injection drug use.[5,17] It is hoped that the success of the BUP/NX strategy tested in HPTN 058 will lead to expanded coverage of effective MAT as HIV prevention.

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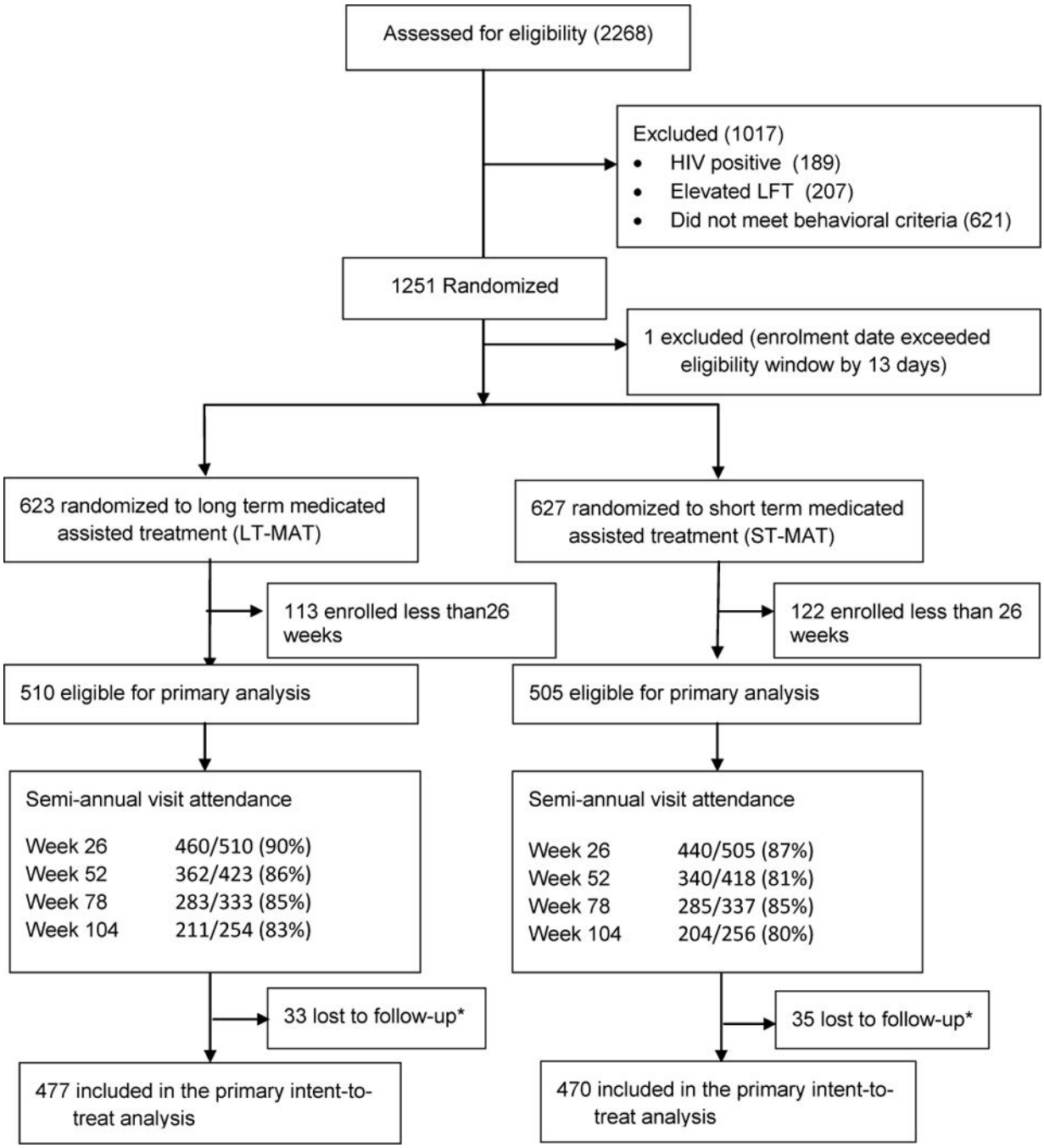
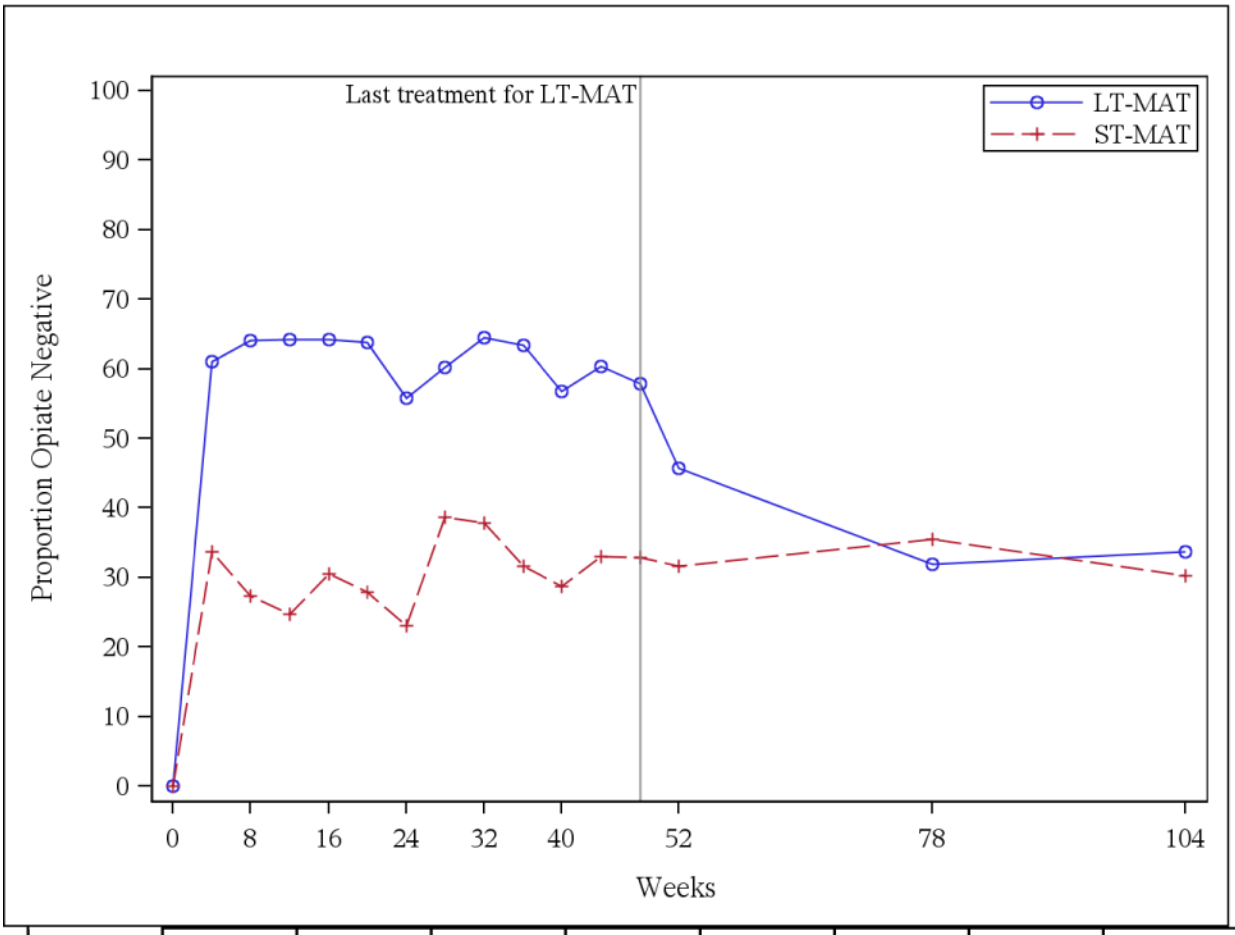


Figure 1. Enrollment and follow-up of study participants

*participants enrolled for at least 26 weeks with no follow-up assessment of primary endpoint at the time of study closure



	Baseline	Week 12	Week 24	Week 36	Week 48	Week 52	Week 78	Week 104
LT-MAT	0/623 0%	304/473 64%	257/461 56%	201/317 63%	155/268 58%	163/357 46%	89/279 32%	70/208 34%
ST-MAT	0/627 0%	106/429 25%	103/445 23%	91/288 32%	78/237 32%	107/338 32%	100/282 35%	61/202 30%

Figure 2.

Opiate negative urinalyses by study arm during monthly screening and semi-annual follow-up

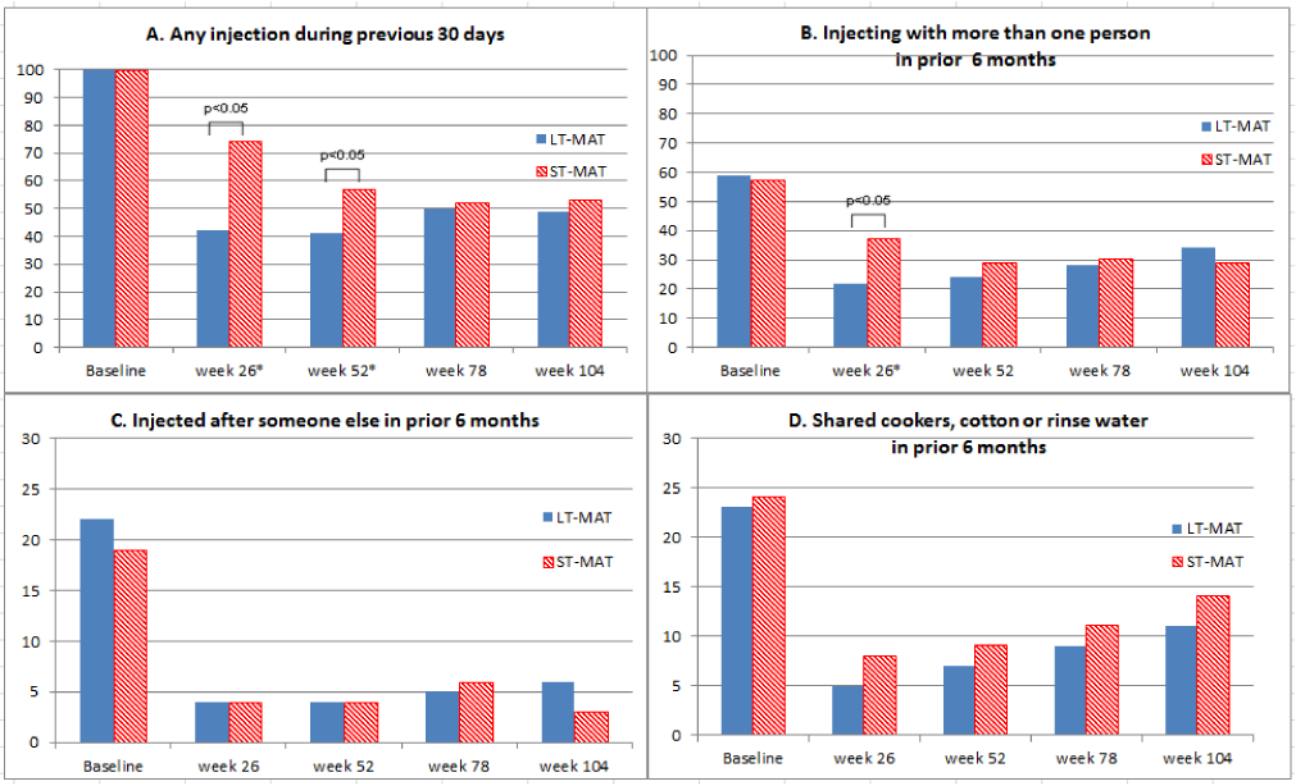


Figure 3.
Self-reported injection and related risk behaviors

Table 1

Baseline characteristics by arm

	N (%) or median (IQR)	
	LT-MAT (N = 623)	**ST-MAT (N = 627)**
Demographic characteristics		
Age	33 (27,39)	34 (28,39)
Male	574 (92%)	577 (92%)
Ethnic minority[1]	262 (42%)	260 (41%)
Married/Living with Partner	321 (51%)	327 (52%)
Days employed (prior 30 days)	15 (0,28)	16 (0,27)
Injection drug use behaviors		
Used needle/syringe after someone in the prior 6 months	136 (22%)	121 (19%)
Age at first injection	24 (21, 30)	25 (20, 31)
Years of injection	7 (3, 12)	7 (3, 12)
Self-reported drugs injected (prior 30 days)		
Heroin	556 (90%)	556 (89%)
Opium	66 (11%)	69 (11%)
Amphetamine	0 (0%)	0 (0%)
Methadone	3 (1%)	0 (0%)
Benzodiazepine	5 (1%)	10 (2%)
Median number of injections (prior 30 days)	84 (60, 90)	84 (60, 90)
Urine drug screen		
Opioid	623 (100%)	627 (100%)
Amphetamine	8 (1%)	12 (2%)
Methadone	25 (4%)	18 (3%)
Benzodiazepine	111 (18%)	124 (20%)

[1] Ethnic minority are participants who did not identify as Han in China or Thai in Thailand

Table 2

Delivery of the medication assisted treatment for opioid dependence

	Initiated BUP/NX induction	Completed induction	Completed detoxification	Weekly counseling[1] (≥75% sessions weeks 1–12)	Monthly counseling[1] (≥75% sessions months 4–12)
Initial induction/detoxification and counseling					
ST-MAT	626/627 (100%)	554/627 (88%)	502/627 (80%)	361/545 (66%)	215/366 (59%)
LT-MAT	623/623 (100%)	564/623 (91%)	N/A	453/541 (84%)	271/385 (70%)
Significance				p<.001	p<.001
ST-MAT: BUP/NX dosing during follow-up					
26 week induction (optional)	153/440 (35%)	137/153 (90%)	130/153 (85%)		
LT-MAT: BUP/NX dosing during follow-up					
	Weeks 1–4	**Weeks 13–16**	**Weeks 25–28**	**Weeks 33–36**	**Weeks 45–48**
Received ≥75% of doses[2]	519/612 (85%)	331/552 (60%)	275/499 (55%)	245/474 (52%)	187/432 (43%)
Received any BUP/NX dose[3]	590/612 (96%)	416/552 (75%)	345/499 (69%)	294/474 (62%)	239/432 (55%)
Retained in BUP/NX treatment[4]	597/612 (98%)	449/552 (81%)	370/499 (74%)	317/474 (67%)	239/432 (55%)

ST-MATMAT = Short term medication assisted arm, LT-MAT = Long term medication assisted arm,

[1] At the time the study was halted, 1087 had completed the 12 weekly and 751 the 9 monthly counseling sessions

[2] Received at least 75% of thrice weekly dosing throughout the period

[3] Received any BUP/NX dose in the period

[4] Received BUP/NX dose at any point during or after the period