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Hepatotoxicity in a 52-week randomized trial of short-term versus long-term treatment with buprenorphine/naloxone in HIV-negative injection opioid users in China and Thailand*

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The protocol for the parent trial, HIV Prevention Trials Network 058 is available at http://www.hptn.org/Web%20Documents/HPTN_Protocols/HPTN058v2.pdf

Contributors

Authors DM, DDC, JBJ, AA, YS, GML, and DD designed the parent study and wrote the protocol. Authors AA, YS, YR, WL, LF, JM oversaw participant enrollment. PR oversaw laboratory testing. DB served as the protocol safety officer. AY and DD conducted the statistical analysis. GML wrote the initial draft of the manuscript and oversaw manuscript revisions. All authors contributed to and have approved the manuscript.

Conflict of Interest

No author has a conflict of interest with the material in the manuscript.

Abstract

Background—Buprenorphine/naloxone (BUP/NX), an effective treatment for opioid dependence, has been implicated in hepatic toxicity. However, as persons taking BUP/NX have multiple hepatic risk factors, comparative data are needed to quantify the risk of hepatotoxicity with BUP/NX.

Methods—We compared rates of alanine aminotransferase (ALT) elevation grade 3 (ALT 5.1 times the upper limit of normal) and graded bilirubin elevations in HIV-negative opioid injectors randomized to long-term (52 weeks) or short-term (18 days) medication assisted treatment (LT-MAT and ST-MAT, respectively) with BUP/NX in a multisite trial conducted in China and Thailand. ALT and bilirubin were measured at baseline, 12, 26, 40 and 52 weeks, times temporally remote from BUP/NX exposure in the ST-MAT participants.

Results—Among 1036 subjects with at least one laboratory follow-up measurement, 76 (7%) participants experienced ALT elevation grade 3. In an intent-to-treat analysis, the risk of ALT events was similar in participants randomized to LT-MAT compared with ST-MAT (adjusted hazard ratio 1.25, 95% confidence interval 0.79 to 1.98). This finding was supported by an as-treated analysis, in which actual exposure to BUP/NX was considered. Hepatitis C seroconversion during follow-up was strongly associated with ALT events. Bilirubin elevations grade 2 occurred in 2% of subjects, with no significant difference between arms.

Conclusions—Over 52-week follow-up, the risk of hepatotoxicity was similar in opioid injectors receiving brief and prolonged treatment with BUP/NX. These data suggest that most hepatotoxic events observed during treatment with BUP/NX are due to other factors.

Keywords

buprenorphine/naloxone; injection drug use; opioid dependence; HIV prevention; safety; hepatotoxicity; alanine aminotransferase; hepatitis C virus

1. INTRODUCTION

Buprenorphine (BUP) and buprenorphine/naloxone (BUP/NX) are effective for the treatment of opioid dependence and are widely used worldwide. In the combination preparation, the opioid antagonist naloxone is co-formulated with BUP to reduce the risk of misuse by injection. Compared with methadone, a systematic review reported BUP to be equally efficacious in decreasing opioid use as determined by urine drug tests, but less effective at retaining opioid-dependent individuals to treatment (Mattick et al., 2008). As a partial opioid μ -receptor agonist, BUP poses lower risk of respiratory depression or overdose compared with a full agonist (e.g., methadone; Substance Abuse and Mental Health Services Administration, 2004). In the United States, the Drug Addiction Treatment Act enables physicians to obtain a Drug Enforcement Agency waiver and prescribe BUP or BUP/NX for opioid dependence (Sullivan and Fiellin, 2008). In contrast, only regulated opioid treatment programs may provide methadone for the treatment of opioid dependence.

Case reports have raised concern about severe hepatitis with or without acute kidney injury among individuals who were taking BUP or BUP/NX sublingually as directed or misusing it

by overdose or injection (Berson et al., 2001b; Herve et al., 2004; Houdret et al., 1999; Zuin et al., 2009). Additionally, short-term uncontrolled studies comparing transaminase levels before and after treatment with BUP or BUP/NX have noted statistically significant increases in transaminase levels (Lucas et al., 2011; Petry et al., 2000). An in vitro study suggested that high doses of BUP may impair mitochondrial respiration, leading to hepatotoxicity (Berson et al., 2001a).

Despite these concerns, a recent trial, in which opioid-dependent participants were randomized to BUP/NX or methadone and monitored for changes in liver indices for 24 weeks, found relatively low rates of liver toxicity and no differences by study arm (Saxon et al., 2013). The HIV Prevention Trials Network (HPTN) 058 trial randomized HIV-negative opioid injectors to BUP/NX maintenance therapy or short-term BUP/NX detoxification, each combined with drug and risk reduction counseling, with the goal of comparing HIV seroconversion and death in the two study conditions. The objective of the secondary data analysis reported herein was to compare laboratory indicators of hepatic damage in subjects randomized to brief or prolonged exposure to BUP/NX.

2. METHODS

2.1 Study design and participants

HPTN 058 was a phase 3 randomized controlled trial (ClinicalTrials.gov identifier: NCT00270257) in which HIV-seronegative opioid-dependent injectors were randomized in a 1:1 ratio to either short-term or long-term medication assisted therapy with BUP/NX (ST-MAT and LT-MAT, respectively), each in combination with behavioral drug and risk-reduction counseling (Metzger et al., 2012). Drug and risk reduction counseling was rooted in cognitive behavioral theory and was delivered in 30-45 minute sessions by trained counsellors. Counseling sessions were delivered weekly for the first 12 weeks, followed by sessions approximately every month through week 52. The primary endpoint for HPTN 058 was HIV infection or death by the 104-week visit. The study was conducted at sites in 3 sites in China (Nanning and Heng County in Guangxi province and Urumqi in Xinjiang province) and in Chiang Mai, Thailand.

Participants were recruited to the study through outreach workers, recruitment flyers, and chain referral. Individuals were eligible for HPTN 058 if they were at least 18 years old, HIV-seronegative, met Diagnostic and Statistical Manual of Mental Disorder, fourth edition (DSM-IV) criteria for opioid dependence (American Psychiatric Association, 1994), had a positive urine drug test for opiates, and reported opioid injection 12 or more times in the prior 28 days. HIV testing was done with US Food and Drug Administration-approved or HPTN-validated rapid HIV test kits, with positive results confirmed at the HPTN central laboratory. Exclusion criteria included current or recent use of MAT in a clinician-guided program, allergy to BUP/NX, alcohol or benzodiazepine dependence by DSM-IV criteria, pregnancy, breastfeeding, or unwillingness to use birth control if female, alanine aminotransferase (ALT) > 3 times upper limit of normal (ULN), hemoglobin < 8g/dL (if male) or < 7g/dL (if female), bilirubin > 2.5 times ULN, or platelet count < 50 K/mm³.

The Statistical Center the HPTN generated a randomization sequence in blocks of 30, stratified by site. Study arm allocations were assigned sequentially as participants were enrolled with an envelope randomization system. Participants and study staff were not masked to treatment assignments.

All subjects began a 3-day induction to BUP/NX on the day of randomization (day 1). Study clinicians adjusted the BUP/NX dose during induction to relieve opioid withdrawal symptoms according to a protocol. Subjects assigned to LT-MAT received daily observed BUP/NX for 3 weeks, and then were converted to thrice-weekly observed BUP/NX through week 46, and were tapered from BUP/NX in weeks 47 to 52. Subjects assigned to ST-MAT began dose tapering at day 4 and discontinued BUP/NX by day 18. ST-MAT subjects were offered a second 18-day detoxification at study week 26 if they had relapsed to opioid use.

HPTN 058 began enrolling participants in May 2007. In October 2011, based on available study data, the independent data and safety monitoring board concluded that due to lower than anticipated HIV infection rates, the study would be unable to achieve its primary objective. At the recommendation of the board, HPTN 058 discontinued new enrollment and began a phased closeout.

2.2 Funding and support

This trial was funded by the National Institutes of Health through the HIV Prevention Trials Network. The BUP/NX used in this study was provided by the manufacturer, Reckitt Benckiser Pharmaceuticals, Inc.

2.3 Ethics statement

This study was approved by institutional review boards at all participating sites (listed in acknowledgments). Study participants provided written informed consent.

2.4 Study follow-up and laboratory testing

Serum concentrations of ALT and total bilirubin were measured in study participants at screening/baseline, 12 weeks, 26 weeks, 40 weeks, and 52 weeks. Notably, none of the scheduled laboratory assessments coincided with current or recent BUP/NX use in the ST-MAT arm. ALT and bilirubin were measured locally with laboratory equipment and commercial assays that were subject to routine proficiency testing and external monitoring according to HPTN Network Laboratory protocol. Urine drug tests for opiates and other drugs were performed at screening/baseline and follow-up visits using a commercial point-of-care test. Adverse laboratory events were categorized and graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events (available at <http://rsc.techres.com/safetyandpharmacovigilance>). For ALT level, grade 2 was defined as 2.6 – 5.0 times ULN, grade 3 as 5.1 – 10.0 times ULN, and grade 4 as >10.0 times ULN. For total bilirubin, grade 2 was defined 1.6 – 2.5 times ULN, grade 3 as 2.6 – 5.0 times ULN, and grade 4 as > 5.0 times ULN.

2.5 Statistical analysis

Participants were included in analyses if they were in the intent-to-treat cohort and had at least one ALT or bilirubin measurement at the 12-, 26-, 40- or 52-week study visits. Changes from baseline in ALT and bilirubin through week 52 were first compared between study arms, adjusted for time on study, using the generalized estimating equation (GEE) method to account for intra-subject correlations. Second, for the occurrence of ALT elevation grade 3 and total bilirubin elevation grade 3, we compared time to first occurrence in the ST-MAT and LT-MAT arms with an intent-to-treat approach, using Kaplan-Meier survival plots and the log rank test. Third, univariate and multivariate Cox proportional hazards models were used to examine potential associations between baseline factors and the risk of first occurrence of ALT elevation grade 3. Covariates included study arm, age, sex, study site, hepatitis C serostatus, hepatitis B surface antigen status, alcohol use, and baseline ALT.

Finally, we conducted an 'as-treated' analysis to assess for a dose-response relationship between three levels of actual BUP/NX use in LT-MAT subjects at the 12-, 26-, and 40-week study visits and the risk of ALT events, compared to ST-MAT subjects. The average daily dose of BUP/NX in the 7 days prior to study visits in subjects assigned to LT-MAT (expressed as mg of BUP) was categorized as none (i.e., had discontinued BUP/NX), < 12 mg, or ≥ 12 mg. We assessed alternative dose cutoffs in sensitivity analyses. Data from the 52-week visit were not included in this analysis because BUP/NX had been discontinued in all subjects prior to this assessment. We used logistic regression with GEE to account for repeated measures to compare the odds of ALT elevations grade 3 in the exposure groups. We also assessed the association between opioid detection in urine drug testing at each visit and ALT events.

3. RESULTS

3.1 Baseline characteristics and follow-up

Among 2,268 individuals that were assessed for eligibility, 1,018 were excluded (621 for failure to meet behavioral criteria, 207 for elevated ALT, 189 for HIV-positive status, and 1 for a protocol violation following randomization). A total of 1,250 (out of a planned enrollment of 1,500) were enrolled and randomized prior to trial discontinuation. Of the 1,250 randomized participants, 1,036 (83%) had at least one ALT or bilirubin value measured at a follow-up visit and were included in the present analysis. Of the 214 remaining participants that did not have a follow-up liver function measure, 109 (51%) had not yet reached their 12-week visit when the trial was halted (i.e., were administratively censored) and 105 (49%) had made it to the 12-week visit window or beyond but did not complete any follow-up laboratory visits (i.e., lost-to-follow-up).

The baseline characteristics of ST-MAT and LT-MAT subjects included in the analysis were similar (Table 1). Among the 1,036 subjects included in the present analysis and randomized to ST-MAT and LT-MAT, respectively, 427 (84%) and 470 (89%) completed the 12-week visit, 439 (86%) and 457 (87%) completed the 26-week visit, 272 (53%) and 322 (61%) completed the 40-week visit, and 338 (66%) and 355 (67%) completed the 52-week visit. Of

the 1,036 subjects included in our analysis, 270 were administratively censored prior to reaching week 52 (i.e., did not have the opportunity to complete all visits). Of the 766 that had the opportunity to complete all study visits, 468 (61%) completed all visits and 298 (39%) missed at least one visit. Compared with the subjects that completed all visits, those that missed visits were significantly more likely to be younger, have injected opioids for fewer years, to inject heroin (and less likely to inject opium), to have benzodiazepine-positive urine toxicology at baseline, and to be in the ST-MAT arm. There were no statistically significant differences in study site, baseline ALT, hepatitis C status, hepatitis B status, or alcohol use in subjects that completed all visits compared with those that missed visits (Table S1¹).

In the ST-MAT and LT-MAT arms, the median number of days (interquartile range) from the last dose of BUP/NX were 60 (56, 65) and 0 (0,0) at the 12-week visit, 145 (138, 156) and 0 (0, 13) at the 26-week visit, 252 (94, 259) and 0 (0,0) at the 40-week visit, and 335 (183, 345) and 2 (0,128) at the 52-week visit, respectively.

3.2 Average changes in ALT and bilirubin

Changes in ALT values were measured from baseline to the 12-, 26-, 40-, and 52-week study visits (Figure 1). The average change (95% confidence interval [CI]) from baseline in ALT during follow-up was 26 U/L (18, 33) in the LT-MAT arm and 21 U/L (1, 28) in the ST-MAT arm (difference of 4 U/L; 95% CI, -3, 12; $P=0.27$). The average change (95% CI) from baseline in total bilirubin during follow-up was 0.09 mg/dL (0.06, 0.12) in LT-MAT and 0.05 mg/dL (0.01, 0.09) in ST-MAT (difference, 0.04; 95% CI, 0.007, 0.07; $P=0.02$; data not shown).

3.3 Graded ALT and bilirubin events and baseline factors associated with ALT events

The distributions of highest elevations of ALT and bilirubin were similar in the two study arms over 52 weeks of follow-up, counting each participant's highest grade event (Table 2). ALT elevation grade 3 occurred in 34 ST-MAT participants and 42 LT-MAT participants with no significant difference between arms in the time to first ALT event (Figure 2, $P=0.28$ log rank test). The distributions of graded bilirubin elevations were similar between study arms ($P=0.45$, Fischer's exact test), and only a single subject (LT-MAT arm) had a bilirubin elevation grade 3. None of the ALT or bilirubin elevations grade 3 resulted in or was associated with death or hospitalization.

Unadjusted and adjusted associations of baseline characteristics with the risk of ALT elevation grade 3 during follow-up are shown in Table 3. Study arm was not statistically significantly associated with the risk of ALT events in unadjusted or adjusted analyses. Factors that were statistically significantly associated with increased risk of ALT events in the adjusted analysis included female gender, enrollment at a Chinese study site compared with the Thai site, hepatitis C seronegative status, and baseline ALT > ULN. There were no statistically significant interactions between these covariates and study arm (data not shown). Twenty out of 225 subjects (9%) that were hepatitis C negative at baseline had ALT

¹Supplementary material can be found by accessing the online version of this paper at <http://dx.doi.org> and by entering doi:...

> ULN, compared with 361 out of 807 (45%) hepatitis C positive subjects. When ALT level was removed from the multivariate model in Table 3, the hazard ratio (95% CI) for hepatitis C seropositive status was 0.62 (0.37, 1.05), intermediate between the unadjusted estimate and the estimate from the full model. Hepatitis B surface antigen status and self-reported alcohol use were not statistically significantly associated with ALT elevation grade 3.

3.4 Characterization of ALT events

Among the 42 LT-MAT and 34 ST-MAT subjects with ALT elevations grade 3, the median (range) ALT values were 306 U/L (203, 2714) and 381 U/L (237, 868) and the median (range) concurrent total bilirubin values were 0.8 mg/dL (0.2, 2.8) and 0.8 mg/dL (0.4, 1.7), respectively. Of these same 76 subjects with ALT elevations grade 3, 61 (35 in LT-MAT and 26 in ST-MAT) had one or more ALT measurements after the index measurement, with the last available ALT measurement a median (range) of 192 days (50, 462) after the index measurement. Among these, the last available ALT value remained grade 3 in 9 (16%; 4 in LT-MAT and 5 in ST-MAT).

Of the 42 LT-MAT subjects that had ALT elevation grade 3, 11 were not taking BUP/NX at the time of the event. Of the 31 LT-MAT participants who were taking BUP/NX at the time of ALT event, 20 continued at the same or higher dose of BUP/NX, and 11 continued at a lower dose of BUP/NX or completed an end-of-intervention taper.

Among subjects that were hepatitis C seronegative at baseline, hepatitis C seroconversion was strongly associated with ALT events. Among 42 hepatitis C seroconverters, 14 (34%) (7 in LT-MAT and 7 in ST-MAT) had ALT elevations grade 3 during follow-up. In contrast, among 223 baseline hepatitis C seronegative participants that did not seroconvert, only 6 (3%) (3 each in LT-MAT and ST-MAT) had ALT elevations grade 3 ($P<0.0001$ for comparison with hepatitis C seroconverters). No subjects with ALT elevation grade 3 were observed to acquire new hepatitis B infection during follow-up. We did not find evidence that allocation to ST-MAT or LT-MAT modified the relationship between baseline hepatitis C status and the risk of ALT events ($P=0.58$ for interaction).

3.5 As-treated analysis of ALT events

There were a total of 2,389 participant visits at weeks 12, 26, and 40 in which BUP/NX in the preceding week could be characterized as 1) ST-MAT (i.e., no BUP/NX received in the prior week), 2) LT-MAT but received no BUP/NX in the prior week (i.e., discontinued treatment), 3) LT-MAT received average daily dose < 12 mg in the prior week, and 4) LT-MAT received average daily dose $\geq$ 12 mg in the prior week. Table 4 compares the odds of ALT elevations grade 3 according to these exposure groups. Compared with the ST-MAT observations, the odds of ALT elevations were similar for LT-MAT participants that had discontinued BUP/NX, that were taking BUP/NX at an average daily dose < 12 mg, and that were taking BUP/NX at an average daily dose $\geq$ 12 mg. These results were unchanged in sensitivity analyses where we used alternative BUP/NX daily dose cutoffs of 14 mg and 16 mg (data not shown). In a separate model, the risk of ALT events was not significantly increased at visits where the urine drug test was positive for opiates compared to negative for opiates (OR 0.72, 95% CI 0.44, 1.16).

4. DISCUSSION

While BUP/NX is an effective therapy for opioid dependence, this preparation and buprenorphine mono-product have been associated with cytolytic hepatitis in case reports and with ALT increases in longitudinal, non-comparative studies (Berson et al., 2001b; Herve et al., 2004; Houdret et al., 1999; Lucas et al., 2011; Petry et al., 2000; Zuin et al., 2009). However, opioid dependent individuals are at increased risk of hepatotoxicity from multiple causes, particularly viral hepatitis and drug or alcohol use. In this analysis of data from a large, multisite, randomized trial, we found no evidence that treatment with BUP/NX increased the risk of hepatic events above background risk in the study population. Additionally, the 7% of subjects in HPTN 058 that experienced ALT elevation grade 3 was similar to the 10% of hepatitis C-infected injection drug users followed in a large community-based cohort that were observed to have transaminase elevations of this magnitude over a median follow-up of 6.4 years (Mehta et al., 2005).

In the intent-to-treat analysis, there was no significant difference in the risk of ALT elevation grade 3 between the two arms, in unadjusted or adjusted analyses. Additionally, compared with ST-MAT participants in an as-treated analysis, there were no significant differences in the odds of ALT elevation grade 3 in LT-MAT subjects who had discontinued BUP/NX, who were receiving BUP/NX at an average daily dose < 12 mg, or who were receiving BP/NX at an average daily dose 12 mg. Participants in LT-MAT had a statistically significantly larger increase in total bilirubin compared with those in ST-MAT, although the magnitude of the difference (<0.1 mg/dl) was not clinically significant. Graded bilirubin events were uncommon, with no significant difference between study arms.

Our results support and extend findings from recent publications. In a randomized trial of 152 opioid-dependent adolescents and young adults, the risk of transaminase elevation above the ULN was similar in participants assigned to a 2-week BUP/NX detoxification and in those assigned to 12 weeks of BUP/NX treatment (Bogenschutz et al., 2010). Similarly, a large phase 4 hepatic safety study conducted by the Clinical Trials Network, found no difference in the risk of transaminase elevations in opioid-dependent participants randomized to treatment with methadone or BUP/NX (Saxon et al., 2013).

Some non-comparative longitudinal studies, including a report from the safety phase of this trial, have reported statistically significant increases in transaminase levels in individuals initiating treatment with BUP/NX (Lucas et al., 2011; Petry et al., 2000), although another study of HIV-infected individuals starting BUP/NX found no significant increase in transaminase levels (Vergara-Rodriguez et al., 2011). In the current study, we observed that ALT concentrations increased by an average of approximately 20 U/L at follow-up visits compared with baseline, with no significant difference between arms. The pattern we observed in both arms - of increased ALT values between baseline and week 12 followed by stabilization thereafter - is likely to be a regression to the mean artifact resulting from high intra-person variability in ALT values and exclusion of individuals with ALT > 3 times ULN at screening.

In an adjusted model of baseline factors, we found that women, subjects from Chinese sites compared to the Thai site, and subjects with ALT levels > ULN at baseline were at statistically significantly higher risk of ALT elevation grade 3. Unexpectedly, we found that hepatitis C seronegative status at baseline was associated with a significantly higher risk of ALT events in the multivariate analysis. This may be because 42 hepatitis C seroconversions were observed during follow-up, and these seroconversions were strongly associated with ALT elevations grade 3. Other studies have reported hepatitis C positive status to be associated with an increased risk of transaminase abnormalities (Petry et al., 2000; Saxon et al., 2013). Consequently, we believe that our findings support the importance of hepatitis C (underlying or newly acquired) in sporadic ALT elevations among drug injectors. We found no evidence that treatment arm modified the association between hepatitis C status and risk of ALT elevation, as was reported in one small study (Bogenschutz et al., 2010).

It is not clear what accounted for the higher risk of ALT events at the Chinese sites compared with the Thai site. Since ALT events were based on fold-change relative to the ULN, which was locally determined, it is possible that site differences in the normal range accounted for this difference. Alternatively, the difference may reflect genetic differences in hepatocellular injury, although we are aware of no data to support this. Additionally, it is not clear why women were at twice the risk of ALT events compared with men, however, this finding persisted in multivariate analysis. Study arm did not modify the association between sex and risk of ALT events. In contrast with our finding, a community-based cohort of 1059 hepatitis C-infected injection drug users reported that women had a lower risk of transaminase elevations than men (Mehta et al., 2005).

Our study has notable strengths including a randomized design, large sample size, 52-week follow-up and direct observation of BUP/NX dosing. Additionally, neither BUP/NX nor BUP mono-drug were approved for clinical use in China or Thailand at the time this study was conducted, decreasing the likelihood participants randomized to ST-MAT received this drug from outside sources.

Our study also has limitations. First, the trial was conducted in China and Thailand and the results may not apply to non-Asian populations. Second, after a dose stabilization period, participants assigned to LT-MAT were transitioned to thrice-weekly, directly-observed dosing (maximum dose 48 mg buprenorphine component). While pharmacological data and some clinical trial data support the efficacy of thrice-weekly BUP/NX or BUP mono-drug dosing (Amass et al., 2001; Schottenfeld et al., 2000), the clinical experience with this dosing regimen is limited. In the US, Europe, and Australia BUP/NX prescriptions are dispensed by pharmacies and patients generally take doses once daily (Sullivan and Fiellin, 2008). Based on animal data (Berson et al., 2001a), it can be hypothesized that larger intermittent doses of BUP/NX would be more prone to cause hepatotoxicity than smaller daily doses. So in this regard, our failure to find increased rates of hepatotoxicity with thrice-weekly dosing compared to ST-MAT may be viewed as reassuring. Third, we did not have information on concurrent medication use.

In summary, ALT elevations grade 3 were observed in approximately 7% of HIV-negative, opioid-dependent injectors in this 52-week clinical trial. However, there was no association between randomization to brief or extended treatment with BUP/NX and the risk of ALT events. Additionally, most ALT elevations grade 3 resolved and BUP/NX was generally continued in subjects taking BUP/NX at the time of an ALT event. Graded bilirubin elevations were uncommon, with no significant difference between arms. Although these data do not exclude BUP/NX as a possible cause of cytolytic hepatitis, they do support the conclusion that BUP/NX is generally safe in opioid injectors with a high prevalence of viral hepatitis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Average changes from baseline in alanine aminotransferase concentrations according to study arm in HIV Prevention Network Trials Network 058. I-bars represent 95% confidence intervals. ALT, alanine aminotransferase; LT-MAT, long-term medication assisted treatment; ST-MAT, short-term medication assisted treatment.

Figure 2.

Kaplan-Meier plot showing time to first alanine aminotransferase elevation grade 3 (≥ 5.1 times the upper limit of normal) in the long-term and short-term medication assisted treatment arms of HIV Prevention Trials Network 058.

Table 1

Baseline characteristics of HIV-negative Chinese and Thai opioid injectors enrolled in HIV Prevention Trials Network 058

Characteristics	ST-MAT (n=508)	LT-MAT (n=528)	P value
Study site, n (%)			0.98
Xinjiang, China	202 (40)	203 (38)	
Heng County, China	161 (32)	171 (32)	
Nanning, China	50 (10)	54 (10)	
Chiang Mai, Thailand	95 (19)	100 (19)	
Age (years), median (P ₂₅ , P ₇₅)	35 (28, 39)	34 (28, 39)	0.31
Male, n (%)	470 (93%)	485 (92%)	0.69
Hepatitis B surface antigen positive, n (%)	70 (14)	79 (15)	0.59
Hepatitis C antibody positive, n (%)	387 (76%)	420 (80%)	0.19
Duration of opioid injection (years), median (P ₂₅ , P ₇₅)	7 (3, 12)	7 (3, 12)	0.59
Days injected in prior month, median (P ₂₅ , P ₇₅)	30 (30, 30)	30 (30, 30)	0.74
Opioid injected ¹ , n (%)			
Heroin	444 (87)	464 (88)	0.82
Opium	67 (13)	67 (13)	0.81
Urine drug test positive ¹ , n (%)			
Opiate	508 (100)	528 (100)	.2
Benzodiazepine	94 (19)	87 (16)	0.39
Methadone	11 (2)	18 (3)	0.23
Amphetamine	9 (2)	5 (1)	0.25
Drank alcohol in prior 6 months, n (%)	247 (49)	241 (46)	0.34
Baseline laboratory values, median (P ₂₅ , P ₇₅)			
Hemoglobin (g/dL)	14.7 (13.7, 15.6)	14.7 (13.7, 15.7)	0.70
Platelets (K/mm ³)	230 (184, 278)	231 (188, 272)	0.97
White blood cell count (K/mm ³)	7.4 (6.1, 9.0)	7.5 (6.3, 9.1)	0.27
Creatinine (mg/dL)	0.8 (0.7, 0.9)	0.8 (0.7, 0.9)	0.35
Alanine aminotransferase (U/L)	37 (21, 63)	39 (22, 64)	0.24
Total bilirubin (mg/dL)	0.6 (0.4, 0.7)	0.6 (0.4, 0.7)	0.98
BUP/NX exposure during study			
Day 3 dose (mg) ³ , median (P ₂₅ , P ₇₅)	18 (16, 24)	16 (12, 20)	0.03
Total days dosed, median (P ₂₅ , P ₇₅)	15 (11, 20)	101 (57, 150)	<0.0001

ST-MAT, short-term medication assisted treatment; LT-MAT, long-term medication assisted treatment; P₂₅ and P₇₅, 25th and 75th percentiles, respectively; BUP/NX, buprenorphine/naloxone.

¹ Categories not mutually exclusive.

² Opiate positive urine drug screen required for enrollment.

³Dose expressed in mg of buprenorphine component.

Table 2

Highest recorded alanine aminotransferase and total bilirubin adverse laboratory events, stratified by study arm and severity grade

	Total (N=1036)	ST-MAT (n=508)	LT-MAT (n=528)	P value
ALT ¹ , n (%)				0.45
None/Grade 1	796 (77)	400 (79)	396 (79)	
Grade 2	164 (16)	74 (14)	90 (14)	
Grade 3	57 (5)	24 (5)	33 (5)	
Grade 4	19 (2)	10 (2)	9 (1)	
Total bilirubin ² , n (%)				0.45
None/Grade 1	1019 (98)	502 (99)	517 (98)	
Grade 2	16 (2)		10 (2)	
Grade 3	0 (0)	0 (0)	0 (0)	
Grade 4	1 (0)	0 (0)	1 (0)	

ST-MAT, short-term medication assisted treatment; LT-MAT, long-term medication assisted treatment; ALT, alanine aminotransferase.

¹ Grades 2, 3, and 4 ALT were defined as values 2.6 – 5.0 times upper limit of normal (ULN), 5.1 – 10.0 times ULN, and > 10.0 times ULN, respectively.

² Grades 2, 3, and 4 total bilirubin were defined as values 1.6 – 2.5 times ULN, 2.6 – 5.0 times ULN, and > 5.0 times ULN, respectively.

Table 3

Associations of baseline factors with risk of grade 3 or higher alanine aminotransferase elevations during 52-week follow-up

Factor	Frequency (%)	Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)
Arm			
ST-MAT	34 (7)	1.0	1.0
LT-MAT	42 (8)	1.24 (0.79, 1.95)	1.25 (0.79, 1.98)
Age, per 10 years	-	0.70 (0.52, 0.94)	0.97 (0.94, 1.00)
Sex			
Male	65 (7)	1.0	1.0
Female	11 (14)	2.11 (1.11, 4.01)	2.38 (1.24, 4.58)
Study site			
Chiang Mai, Thailand	4 (2)	1.0	1.0
Heng County, China	23 (7)	4.31 (1.49, 12.47)	3.40 (1.13, 10.23)
Nanning, China	4 (4)	3.01 (0.75, 12.06)	3.77 (0.91, 15.62)
Xinjiang, China	45 (11)	7.45 (2.67, 20.77)	5.67 (1.93, 16.69)
Hepatitis C antibody			
Negative	20 (9)	1.0	1.0
Positive	56 (7)	0.78 (0.47, 1.31)	0.39 (0.22, 0.70)
Hepatitis B surface antigen			
Negative	67 (8)	1.0	1.0
Positive	9 (6)	0.79 (0.40, 1.59)	0.87 (0.43, 1.76)
Drank alcohol in 6 months prior to enrollment			
No	50 (9)	1.0	1.0
Yes	26 (5)	0.60 (0.37, 0.96)	0.91 (0.53, 1.56)
Baseline alanine aminotransferase			
upper limit of normal	31 (5)	1.0	1.0
> upper limit of normal	45 (12)	2.76 (1.75, 4.37)	2.74 (1.63, 4.62)

ST-MAT, short-term medication assisted treatment; LT-MAT, long-term medication assisted treatment; CI, confidence interval. Estimates shown in bold are statistically significant (P<0.05).

Table 4

Relative odds of grade 3 or higher alanine aminotransferase elevations in subjects in the LT-MAT arm according to prior week use of BUP/NX compared with subjects in the ST-MAT arm

Study arm/current BUP/NX use category	ALT grade 3 / number of visits	Odds ratio (95% CI)	P value
ST-MAT	37/1137	1.0	-
LT-MAT, discontinued BUP/NX	8/233	1.00 (0.45, 2.25)	0.99
LT-MAT, taking BUP/NX at average daily dose < 12 mg ^I	16/414	1.15 (0.61, 2.16)	0.66
LT-MAT, taking BUP/NX at average daily dose ≥ 12 mg ^I	18/605	0.96 (0.52, 1.77)	0.89

BUP/NX, buprenorphine/naloxone; LT-MAT, long-term medication-assisted therapy; ST-MAT, short-term medication-assisted therapy

^I Dose expressed in buprenorphine component