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An evaluation of hepatic enzyme elevations among HIV-infected released prisoners enrolled in two randomized placebo-controlled trials of extended release naltrexone

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ABSTRACT

Extended-release naltrexone (XR-NTX), an approved treatment for opioid or alcohol dependence, is a once-monthly injectable formulation of naltrexone. Hepatotoxicity concerns have limited its use, necessitating further investigation. This study aims to examine hepatic enzyme levels in participants of 2 randomized placebo-controlled trials (RCTs) of XR-NTX. Hepatic transaminases were measured in 85 patients enrolled in RCTs of XR-NTX among HIV-infected prisoners, transitioning to the community and receiving treatment for either dependence on alcohol (52.9%), opioids (44.7%) or both (16.5%). Baseline characteristics included HCV co-infection (55.7%), antiretroviral therapy (81%), mental illness (39%) and receiving psychiatric medications (34.1%). Levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma glutamyl transferase (GGT) were not statistically different between persons randomized to placebo ($N = 24$) and XR-NTX ($N = 61$) arms. These results confirm that XR-NTX is safe to use among opioid and alcohol dependent HIV-infected released prisoners receiving ART with high rates of co-morbid HCV infection and mental illness.

1. Introduction

HIV and HCV infections are both highly concentrated in criminal justice settings (CJS) (Spaulding, Seals, et al., 2009). Similarly, alcohol use disorders (AUDs) and opioid dependence are also concentrated within these settings (Springer, Azar, et al., 2011; Springer, Chen, et al., 2010) and magnified further among those with HIV due to the increased risk of alcohol/intravenous drug use (IDU) on HIV transmission and alcohol's and opioids' role in contributing to poor HIV treatment outcomes (Springer, Qiu, et al., 2012). Recent data from treating opioid dependence using medication-assisted therapies (MAT) in HIV-infected patients transitioning to the community has been associated with sustained HIV and substance abuse treatment outcomes post-release, especially if patients can be retained on MAT (Altice, Kamarulzaman, et al., 2010; Springer et al., 2011, 2012). The extent to which MAT for treating AUDs improves alcohol and HIV treatment outcomes among HIV-infected prisoners transitioning to the community is currently unknown.

In randomized controlled trials for treating AUDs in HIV uninfected patients, MAT using naltrexone (NTX) has been the most effective treatment (Anton, O'Malley, et al., 2006). A newer, injectable extended release formulation (XR-NTX) has been more recently approved for alcohol dependence (Garbutt, Kranzler, et al., 2005) as well as opioid dependence (Krupitsky, Nunes, et al., 2011) and may have adherence advantages over daily medication self-administration (Garbutt et al., 2005). Though longitudinal cohort data in HIV-infected patients preliminarily suggest it to be safe (Lucey, Silverman, et al., 2008; Sax, Kornetsky, et al., 1994; Yen, Ko, et al., 2006), NTX using either formulation has not been empirically tested solely in HIV-infected patients, many of whom are also co-infected with HCV, and who are simultaneously prescribed antiretroviral therapy (ART). Potentially, HIV-infected prisoners with AUDs and opioid dependence who are transitioning to the community may be at multiple risks for hepatotoxicity from the additional treatment using XR-NTX and without empirical testing, decrease the likelihood that clinicians will prescribe XR-NTX for HIV-infected patients on ART for fear of excessive toxicity. To address this issue directly, we examine the various contributions to hepatotoxicity among HIV-infected prisoners prescribed ART and transitioning to the community who are enrolled in two placebo-controlled trials of XR-NTX.

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2. Materials and methods

2.1. Ethical considerations

Both studies (R01AA018944 and R01DA030762) are approved by the Institutional Review Board at Yale University, with additional approval by the Connecticut Department of Correction, and for R01DA030762, at the Hampden Country Correctional Clinic (HCCC) and additional participating hospitals (Waterbury Hospital, Waterbury, CT; Baystate Medical Center, Springfield, MA). Additionally both studies were registered at www.clinicaltrials.gov (R01AA018944: NCT10177310; R01DA04762: NCT01246401). Because the trials involved prisoners with substance use disorders, additional protections were afforded by the Office of Human Research Protections (OHRP) at the Department of Health and Human Services, and Certificates of Confidentiality were obtained from the National Institutes of Health (NIH). All participants gave verbal and written informed consent prior to enrollment while incarcerated and again on day of release.

2.2. Design

Projects NEW HOPE (R01DA030762) and INSPIRE (R01AA018944) (Springer, Altice, et al., 2013) are two NIH-funded double-blinded randomized placebo-controlled trials of XR-NTX among incarcerated HIV-infected men and women with opioid or alcohol dependence, respectively, who are transitioning to the community. The studies are being conducted in Connecticut cities (New Haven, Hartford, Waterbury) and Massachusetts (Springfield) and seek to evaluate the impact of XR-NTX on HIV-related treatment outcomes among HIV-infected participants with substance use disorders. XR-NTX and placebo are provided by Alkermes Pharmaceuticals, Inc. (Cambridge, MA) through Investigator-Initiated applications. Project INSPIRE began in September 2009 and will end in September 2014. Project NEW HOPE began in September 2010 and will end in September 2015.

2.3. Participants

Eligibility criteria for the parent trials included: (1) documented HIV-infection, (2) currently incarcerated or within 30 days after release from prison/jail; (3) release from incarceration to specific areas (New Haven and Hartford; additionally for NEW HOPE: Waterbury and Springfield); (4) LFTs under 5 times the upper limit of normal (ULN values: AST: 35, ALT 39, GGT 95 IU/mL); (5) problem drinking or DSM-IV criteria for alcohol dependence (INSPIRE) or DSM-IV criteria for opioid dependence (NEW HOPE); (6) 18 years of age or older, and (7) able to provide informed consent. Exclusion criteria include: (1) pregnancy/breastfeeding or unwilling to use contraception; (2) Child–Pugh's class C liver cirrhosis; (3) prescribed opioid medications or having a pain condition requiring them; and (4) prescribed other form of MAT for alcohol/opioid dependence. All participants were abstinent during incarceration, for a mean of 13 months, confirmed with negative urine drug toxicology screens for drugs and phosphatidyl ethanol test (PEth) testing for alcohol.

2.4. Treatment

Participants were randomized 2:1 to XR-NTX or placebo to ensure adequate sample size to assess safety. The intervention involves 6 monthly injections of 380 mg XR-NTX or placebo (microspheres), administered intramuscularly by a study nurse, with the first being administered within 1 week prior to release from prison/jail, followed by 5 monthly injections after release in the community, administered at the study sites.

2.5. Measures

A number of study measures were included for the parent studies, but for the purposes of this analysis, we evaluated the information obtained from baseline demographic assessments; confirmed opioid and alcohol dependency as well as other SUD and psychiatric disorders using the M.I.N.I. (Mini International Neuropsychiatric Interview) (Sheehan, Lecrubier, et al., 1998), and problem drinking using the Alcohol Use Disorder Identification Test (AUDIT) (Bohn, 1995) ($\geq$4 women and $\geq$8 for men); as well as retention with monthly injections and transaminase assessments measured at baseline, the day of release and weeks 2, 4, 8, 12, 16, 20 and 24. Hepatic enzymes were analyzed by Quest Laboratories. The upper limit of normal (ULN) values was 35 IU/mL for AST, 39 IU/mL for ALT and 95 IU/mL for GGT. Values of more than 10 times ULN were considered adverse events, were reportable to the IRB and were reasons for un-blinding participants and study drug discontinuation; however, participation in the study interviews was allowed to continue.

Medical records from the correctional health systems (CT/MA) were reviewed for confirming HIV infection and ART prescription, as well as HCV antibody testing results, prior to first injection. Prior to receiving an injection, a study clinician evaluated the patient to ensure no contraindications to receiving injection, as well as to evaluate for any prior injection site reactions. Other adverse events were evaluated monthly using the Systematic Assessment for Treatment Emergent Events (SAFTEE) (Johnson, Ait-Daoud, et al., 2005). An interim analysis was conducted as part of the data safety monitoring plan to examine the hepatic safety of XR-NTX compared to placebo among study participants in both investigations. Data were combined from both studies to allow sufficient power to detect differences.

Table 1
Participant demographics at baseline: Totals, XR-NTX and placebo arms. p-Value refers to comparisons between XR-NTX and placebo arms.

Variable	Total, $n = 85$	XR-NTX, $n = 61$	Placebo, $n = 24$	p-Value
Age (median, years)	46	47	44	0.081
Gender (*n*, %); male	67 (78.8)	48 (78.7)	19 (71.2)	0.860
Female	13 (15.3)	9 (14.8)	4 (16.7)	
Race (*n*, %); White	16 (18.8)	13 (21.3)	3 (12.5)	0.720
Black	39 (45.9)	27 (44.3)	12 (50)	
Hispanic	29 (34.1)	20 (32.8)	9 (37.5)	
Other	1 (0)	1 (1.6)	0 (0)	
HIV viral load (median) copies/mL	209	234	200	0.987
Undetectable HIV VL (<50 copies/mL) (*n*, %)	17 (20)	12 (19.7)	5 (20.8)	0.917
HIV VL <400 copies/mL (*n*, %)	45 (52.9)	33 (54.1)	12 (50)	0.700
On ART (*n*, %)	69 (81.2)	47 (77)	22 (91.7)	0.121
NNRTI[1]-based ART regimen (*n*, %)	28 (32.9)	18 (29.5)	10 (41.7)	0.396
NRTI[2]-based ART regimen (*n*, %)	0 (0)	0 (0)	0 (0)	-
PI[3]-based ART regimen (*n*, %)	41 (48.2)	30 (49.2)	11 (45.8)	0.386
II[4]-based ART regimen (*n*, %)	2 (2.4)	1 (1.6)	1 (4.2)	0.442
CD4 count cells/mL (median, SD)	433 (290)	407 (271)	530 (320)	0.086
HCV AB positive (*n*, %)	44 (55.7)	31 (56.4)	13 (54.2)	0.857
AUDIT[5] score (mean, SD)	22 (13)	25 (12)	21 (13)	0.222
Homeless (*n*, %)	21 (24.7)	17 (27.9)	4 (16.7)	0.210
Incarceration period (mean in months, SD)	14.4 (29)	15.6 (32.7)	11.2 (16.2)	0.548
Alcohol dependence (*n*, %)	45 (52.9)	29 (47.5)	16 (66.7)	0.092
Opioid dependence (*n*, %)	38 (44.7)	29 (47.5)	9 (37.5)	0.367
Alcohol & opioid dependence (*n*, %)	14 (16.5)	9 (14.8)	5 (20.8)	0.496
Cocaine dependence (*n*, %)	49 (57.6)	37 (60.7)	12 (50)	0.203
Depressive disorder (*n*, %)	33 (38.8)	25 (41)	8 (33.3)	0.505
Manic disorder (*n*, %)	12 (14.1)	10 (16.4)	2 (8.3)	0.337
Psychiatric meds (*n*, %)	29 (34.1)	23 (37.7)	6 (25.0)	0.504
Person-days of observation	-	5,190	2,350	-

[1] NNRTI: Non-nucleoside reverse transcriptase inhibitor.
[2] NRTI: Nucleoside reverse transcriptase inhibitor.
[3] PI: Protease inhibitor.
[4] II: Integrase inhibitor.
[5] AUDIT: Alcohol Use Disorders Identification Test.

2.6. Data analysis

Eighty-five participants who received at least one XR-NTX (or placebo) injection were included in this analysis. Participants from both studies were analyzed together because they all received the exact same treatment (XR-NTX or placebo), and the main goal of this analysis was to evaluate hepatic enzyme elevations for an interim safety evaluation only. Three hepatic enzymes were evaluated in this analysis: AST, ALT and GGT. Enzyme levels were analyzed using the NIH Division of AIDS (DAIDS) grade 3 and 4 criteria (>5× ULN) (National Institutes of Health, 2004). Chi-square tests were used to determine whether there were statistically significant differences in hepatic enzyme levels between the XR-NTX and the placebo arms. Kaplan–Meier survival analyses and Cox regressions were conducted to assess hepatic enzyme levels longitudinally: in the first analysis, any value >5× ULN was considered a "failure"; in the second analysis, any two grade (DAIDS criteria) elevation was considered a "failure". At baseline, chi-square tests, t-tests and non-parametric Mann–Whitney tests were used to assess potential differences between the two groups. It should be noted that no participants withdrew from the study due to hepatic side effects.

3. Results

3.1. Baseline demographics

Comparison of demographics and baseline characteristics of the 85 participants, between the placebo ($n = 24$) and XR-NTX ($n = 61$) arms, showed no significant differences (Table 1). The median age was 46 years, 55.7% were HCV antibody positive (HCV RNA testing was not available), predominantly African American (46%), male (79%), and most had a co-morbid DSM-IV Axis I mental illness (38.8% major depression, 14.1% manic episode, 16.5% hypomanic episode, 15.3% post-traumatic stress disorder), 51.7% were alcohol dependent, 44.7% were opioid dependent, 16.5% were both alcohol and opioid dependent and 57.6% were cocaine dependent. Mean incarceration length was 14 months for both groups. Median baseline CD4 counts were similar between groups, as were the HIV VLs and the percentages of participants with undetectable HIV VL (<50 copies/mL and <400 copies/mL). Thirty-four percent of participants were prescribed psychiatric medications. Eighty-one percent of participants were prescribed ART. Our data represent 5,190 person–days of XR-NTX use (assuming every monthly injection corresponds to 30 days of XR-NTX use).

3.2. Hepatic enzyme results

The levels of AST, ALT and GGT were compared between placebo and XR-NTX arms at baseline, and 3- and 6-months post first monthly injection (Fig. 1). We compared HEE levels based on DAIDS classifications (Fig. 1): Grades 1 and 2 were considered as the first category (less clinically relevant), whereas grades 3 and 4 were considered as the second category (clinically relevant). Grades 1 and 2 refer to enzyme levels up to 5× ULN. Grades 3 and 4 refer to enzyme levels >5× ULN. At baseline, 3 or 6 months post first injection, there were no significant differences observed between placebo and XR-NTX.

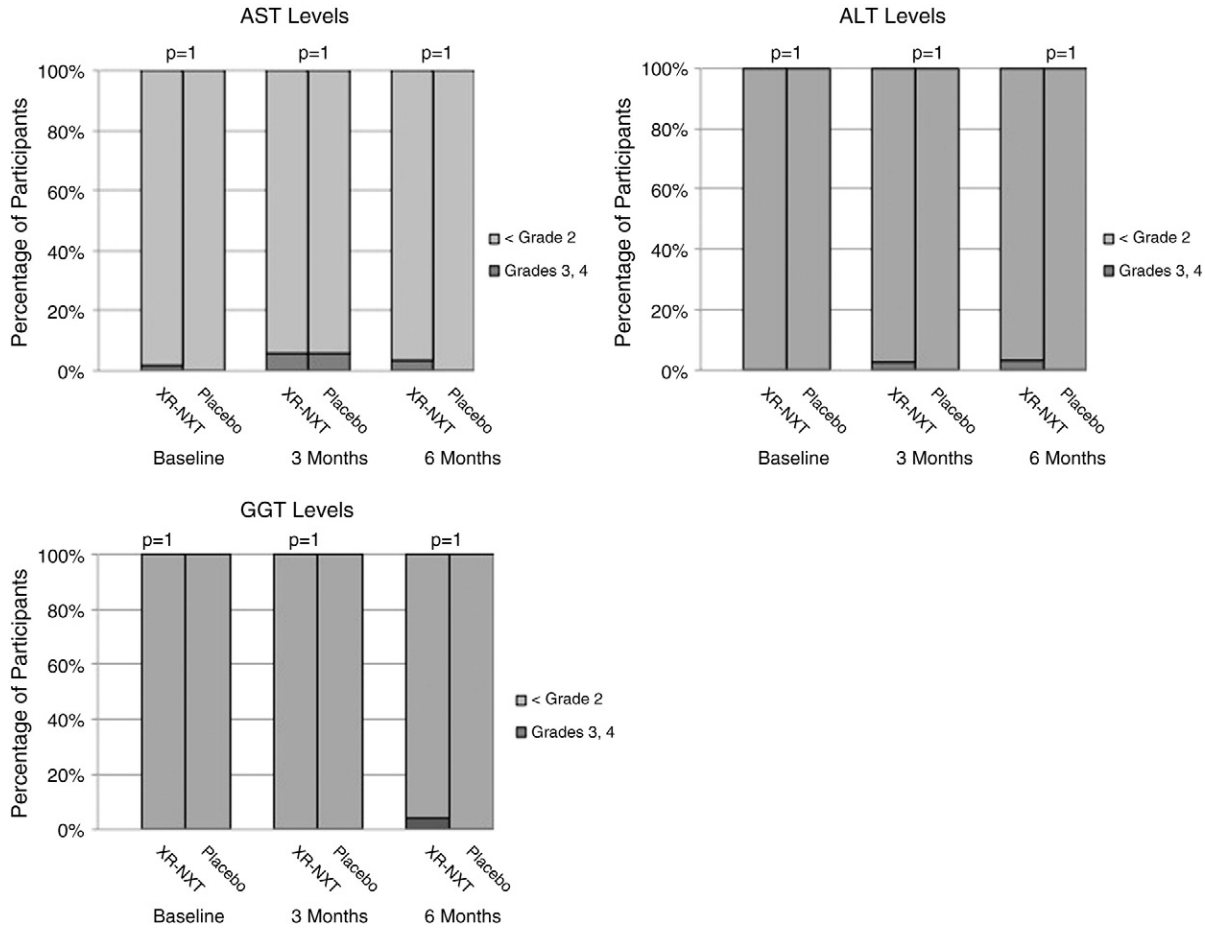

Fig. 1. Hepatic Enzyme Elevations (HEE) among participants in the XR-NTX and placebo arms, comparing NIH/DAIDS[1] definitions of HEE: Grades 1, 2: elevations up to 5× ULN[2]; Grades 3, 4: elevations ≥5× ULN. 1 Division of AIDS. 2 Upper limit of normal.

One subject was unblinded from Project NEW HOPE for having hepatic enzyme values > 10 × ULN. The participant was a 43 year-old female with HCV co-infection and opioid dependence who was prescribed ART (Atripla®). Her baseline LFTs, prior to first injection, were AST: 29 IU/mL and ALT: 27 IU/mL (no GGT information). She received 4 injections prior to when her enzyme values rose to AST: 419 IU/mL and ALT: 394 IU/mL. She did not have any clinical symptoms or signs of hepatic failure, nor did she require hospitalization. The Yale IRB, DSMB and Alkermes Inc., were notified; the patient was unblinded and found to be in the XR-NTX arm. This was deemed not to be a serious pharmacologic adverse event, as there were no clinical signs or symptoms of hepatic disease. According to IRB regulations at the time, injections were stopped. Hepatic enzymes spontaneously decreased to AST: 86 IU/mL and ALT: 98 IU/mL within 18 days post last injection. Since that event, the IRB protocol has been modified and approved to recommend unblinding only if the participant with enzyme levels > 10 × ULN has either clinical signs or symptoms of hepatic disease or requires hospitalization or an ER visit. Since that update, there have been no further reports of enzyme levels > 10 × ULN, nor have any more patients been unblinded, as of September 2013. Furthermore no patients have withdrawn from the parent studies due to hepatic safety or other severe adverse side effects.

To additionally assess enzyme levels over time, two distinct Kaplan–Meier survival analyses were conducted (Fig. 2). First, hepatic enzyme values > grade 3 or 4 (>5× ULN), according to the DAIDS classification, were considered a "failure"/censored (Fig. 2A). A limitation of this analysis was that once a failure was recorded, that participant was censored at that point, ignoring subsequent "normal" tests, making this an even more conservative estimate. Nevertheless, no statistically significant differences were observed between the placebo and XR-NTX arms, over time for any enzyme. Subsequently, an additional analysis was performed where a participant was censored if he/she had any elevation of two grades (according to the DAIDS classification) or more between two time-points. For example, an elevation between grade 1 and 3 or between 2 and 4 (Fig. 2B) was censored. This analysis aimed to capture not just clinically relevant HEEs (grades 3, 4), but any marked (two grades or more) elevation that occurred. Again, there were no statistically significant differences between the placebo and XR-NTX arms for any hepatic enzyme evaluation. Finally, Cox regression analysis was used to obtain hazard ratios for the survival analysis (Table 2). Similar to the Kaplan–Meier procedure, no significant differences were observed between XR-NTX and placebo (all HRs straddled 1).

4. Discussion

The combined data from these two prospective, placebo controlled trials provide the first empiric hepatic enzyme safety data for XR-NTX in alcohol and opioid dependent HIV-infected patients, most of whom were prescribed ART, with significant co-morbidity, including HCV co-infection, and DSM-IV axis-I psychiatric illness. Projects INSPIRE and NEW HOPE are among the first randomized placebo-controlled trials of XR-NTX to be conducted for the treatment of alcohol or opioid dependence among HIV-infected prisoners who are being released from the CJS. Additionally, these trials are the first to exclusively enroll HIV-infected participants. In a previous RCT of XR-NTX, conducted in Russia, approximately 40% of participants were HIV-infected (Krupitsky et al., 2011). Concerns have previously been raised on the hepatic safety of naltrexone (Bonacini, 2004; Pfohl, Allen, et al., 1986; Tetrault, Tate, et al., 2012), although these concerns have focused on

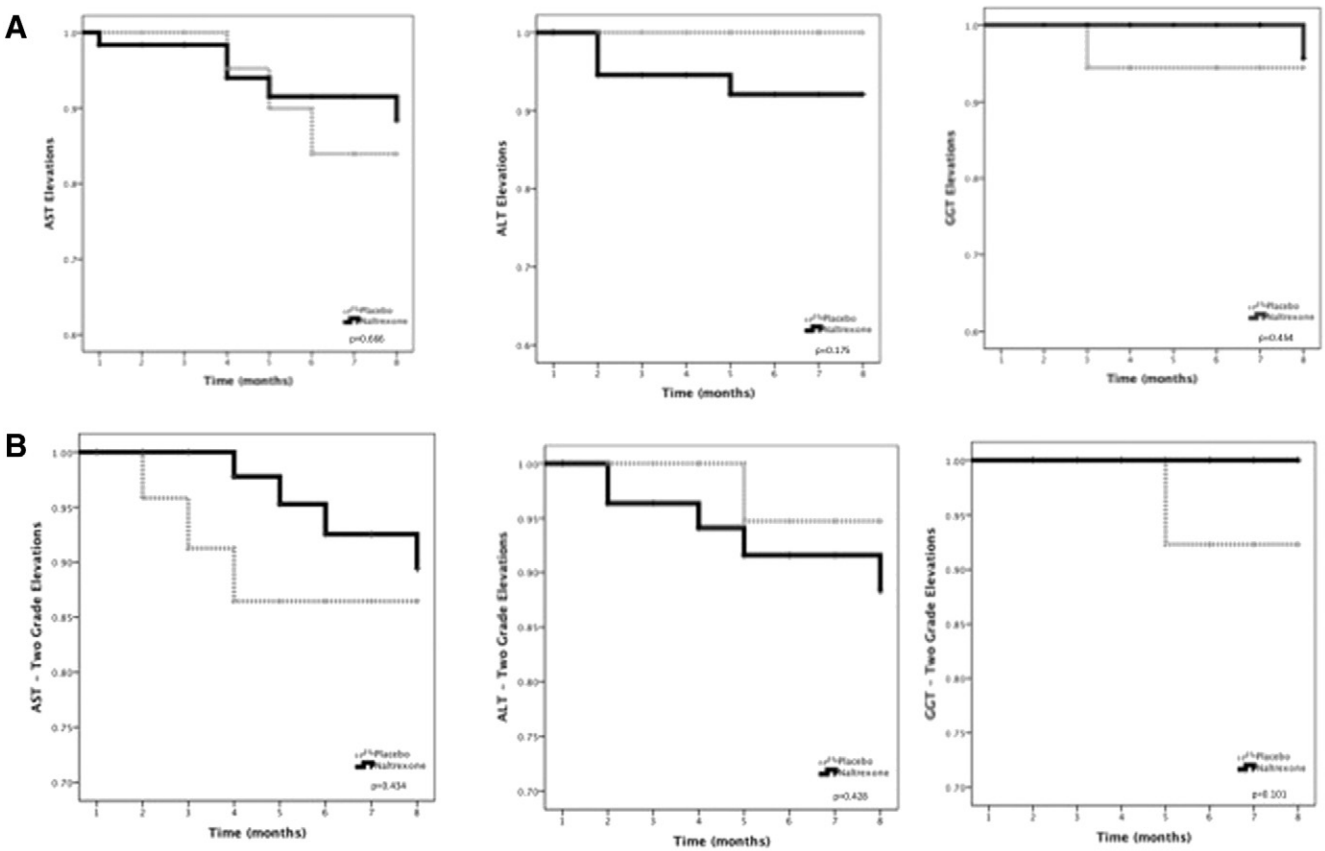

Fig. 2. Kaplan–Meier curves depicting liver enzyme (AST, ALT, and GGT) levels over time, for placebo and naltrexone arms. A) HEE >5× ULN (DAIDS Grades 3, 4) were censored; B) HEE of two DAIDS Grades magnitude were censored.

Table 2
Relative hazards, in the survival analysis, obtained through Cox regression. N/a: no HR available due to lack of censored events for one of the conditions (XR-NTX or placebo).

	HEE >5× ULN		HEE >2 DAIDS Grades	
	Hazard ratio	95% CI	Hazard ratio	95% CI
AST	1.366	0.326–5.728	1.800	0.403–8.045
ALT	n/a	-	0.432	0.050–3.704
GGT	2.769	0.171–44.719	n/a	-

the oral formulation. Subsequent evaluations of XR-NTX have been conducted (Lucey et al., 2008; Mitchell, Memisoglu, et al., 2012), however these were conducted primarily among HIV uninfected patients with alcohol dependence (Lucey et al., 2008; Yen et al., 2006) and later among opioid dependent persons of whom only 40% were HIV-infected and none were receiving ART (Krupitsky et al., 2011; Mitchell et al., 2012). It was therefore of great interest to establish whether XR-NTX has any impact on the liver function of exclusively HIV-infected persons with comorbid substance use disorders, mental illness and hepatitis C predominantly receiving ART and being released from a criminal justice setting, given the significant concern for potential greater hepatotoxicity of XR-NTX due to their substantial comorbidities, as compared with participants in previous studies of hepatic enzyme changes in persons receiving XR-NTX.

At the time of data analysis, 85 HIV-infected persons who were being released to the community from prison/jail in CT and MA with opioid and/or alcohol dependence had been enrolled in these two double-blind RCTs and had received at least one XR-NTX injection. More than 50% of the sample was HCV antibody positive and 39% had an axis I DSM-IV mental illness with 34% prescribed psychiatric medications, both additional hepatotoxic risk factors identified previously among persons receiving NTX (Krupitsky et al., 2011). The majority (81%) were receiving ART for their HIV infection, another important potential hepatotoxic risk factor. All analyses revealed no significant differences between the placebo and XR-NTX arms, in spite of the multiple co-morbidities of this heavily afflicted population.

Our results confirm those of a very small number of previous studies evaluating the hepatic safety of XR-NTX (Lucey et al., 2008; Mitchell et al., 2012; Tetrault et al., 2012). A study among alcohol dependent patients demonstrated no statistically significant differences among LFT enzyme levels between placebo and XR-NTX arms, but all of the participants were HIV-uninfected (Lucey et al., 2008). An analysis of LFTs of participants from the Krupitsky trial (Krupitsky et al., 2011) in Russia, evaluating the use of XR-NTX for opioid dependency, also showed no significant differences between the placebo and XR-NTX arms (Mitchell et al., 2012), however only 40% of these participants were HIV infected, although ART prescription was not reported. A small number of additional studies examined HEE among patients receiving the oral formulation of naltrexone. A study among alcohol dependent men and women prescribed oral naltrexone did not observe HEE; this study however did not compare the participants to a control group, nor did they have any additional significant co-morbidities (Yen et al., 2006). A similar observational study followed patients with Huntington's Disease who were prescribed oral naltrexone and again did not observe HEE (Sax et al., 1994). A recent retrospective cohort study among HIV-positive patients involved in the Veterans Administration Healthy care system who were alcohol dependent also found no differences in hepatic enzyme levels among placebo and the oral naltrexone arms (Tetrault et al., 2012).

Together with the previously published studies mentioned above, our results support that XR-NTX is safe from a hepatic standpoint, for use in the treatment of opioid and/or alcohol dependence, even among HIV-infected patients prescribed ART, half of whom were co-infected with HCV and who are being released from the criminal justice system. Our study is the first to study XR-NTX among a group of incarcerated HIV-infected opioid and/or alcohol dependent individuals with significant additional co-morbidities, including HCV, mental illness, receipt of ART and involved with the CJS. The previously suggested safety concerns, mainly referring to oral naltrexone, have not been confirmed in our studies thus far, as well as in previously published studies, one of which also enrolled a subgroup of HIV-infected patients. Thus far, it appears that XR-NTX is safe to administer among HIV-infected opioid and/or alcohol dependent persons with HCV co-infection and mental illness, who are receiving ART. Expanded clinical use of XR-NTX among similar populations is recommended. Careful monitoring of patients, however, remains important including regular hepatic enzyme levels, as well as monitoring for clinical side effects and symptoms, while persons are on treatment.

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