Extended-Release Naltrexone Improves Viral Suppression Among Incarcerated Persons Living With HIV With Opioid Use Disorders Transitioning to the Community: Results of a Double-Blind, Placebo-Controlled Randomized Trial

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Objective: To determine whether extended-release naltrexone (XR-NTX) would improve or maintain viral suppression (VS) among prisoners or jail detainees with HIV and opioid use disorder (OUD) transitioning to the community.

Design: A 4-site, prospective randomized double-blind, placebo-controlled trial was conducted among prison and jail inmates with HIV and OUD transitioning to the community from September 2010 through March 2016.

Methods: Eligible participants (N = 93) were randomized 2:1 to receive 6 monthly injections of XR-NTX (n = 66) or placebo (n = 27) starting at release and observed for 6 months. The primary outcome was the proportion that maintained or improved VS (<50 copies/mL) from baseline to 6 months.

Results: Participants allocated to XR-NTX significantly improved to VS (<50 copies/mL) from baseline (37.9%) to 6 months (60.6%) (P = 0.002), whereas the placebo group did not (55.6% at baseline to 40.7% at 6 months P = 0.294). There was, however, no statistical significant difference in VS levels at 6 months between XR-NTX (60.6%) vs. placebo (40.7%) (P = 0.087). After controlling for other factors, only allocation to XR-NTX (adjusted odds ratio = 2.90; 95% confidence interval = 1.04 to 8.14, P = 0.043) was associated with the primary outcome. Trajectories in VS from baseline to 6 months differed significantly (P = 0.017) between treatment groups, and the differences in the discordant values were significantly different as well (P = 0.041): the XR-NTX group was more likely than the placebo group to improve VS (30.3% vs. 18.5%), maintain VS (30.3% vs. 27.3), and less likely to lose VS (7.6% vs. 33.3%) by 6 months.

Conclusions: XR-NTX improves or maintains VS after release to the community for incarcerated people living with HIV with OUD.

Key Words: HIV, viral load, HIV-1 RNA, opioid use disorder, extended-release naltrexone, prisoners, jail, criminal justice system, randomized controlled trial

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INTRODUCTION

To increase the likelihood of viral suppression (VS), international guidelines recommend directly administered antiretroviral therapy for prisoners with HIV transitioning to the community, and in community settings, HIV patients with opioid use disorder (OUD) should be offered methadone or buprenorphine with or without directly administered antiretroviral therapy.[1] Such guidelines have not been updated in recent years.

Both HIV and OUD are highly prevalent among persons within the criminal justice system.[2–5] Release to the community for people living with HIV (PLH) is associated with loss of HIV VS, despite high levels attained during the incarceration.[3,4,6,7] Moreover, for released prisoners with OUD, relapse exceeds 85%, mostly within the first 2 weeks and is associated with overdose and death.[8–10] Inadequately treated OUD interrupts HIV treatment adherence with resultant loss of VS.[11,12]

Three evidence-based medication treatments for OUD are available, including 2 opioid agonists (methadone and buprenorphine) and 1 opioid antagonist [injectable extended-release naltrexone (XR-NTX); Vivitrol Alkermes, Inc., Waltham, MA]. Unlike opioid agonists, XR-NTX is not

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a controlled substance, does not require regulatory licensing for prescription, also treats alcohol use disorders, and is without diversion concerns.[13–19] In criminal justice–involved persons with OUD, XR-NTX has been associated with decreased opioid use after release.[20] Recent randomized controlled trials confirm its equivalence in treatment of OUD with buprenorphine in community settings.[21,22] Despite data suggesting that buprenorphine maintains or improves VS in released prisoners with HIV,[11,12] the use of XR-NTX has not been tested on HIV VS.

We therefore sought to examine in a multisite study whether treatment with XR-NTX would improve or maintain VS levels after release in prisoners and jail detainees with HIV and OUD using a double blind, placebo-controlled trial.

METHODS

Study Design

The study protocol and detailed methods have previously been published,[13] along with preliminary safety data,[17] and early postrelease retention data.[16] This multisite, double-blind, placebo-controlled trial was conducted between September 1, 2010, and March 31, 2016, and compared XR-NTX with placebo among incarcerated PLH with OUD transitioning to the community over a 6-month period.

Ethical Oversight

All study procedures were reviewed and approved by the institutional review boards (IRBs) at all 4 study sites, the Office of Human Research Protections at the Department of Health and Human Services, and research committees at Hampden County Correctional Centers, and the Connecticut Department of Correction. A Certificate of Confidentiality was obtained for additional participant protections. The study is registered at www.clinicaltrials.gov (NCT01246401).

Recruitment

Recruitment occurred between September 2010 and August 2015. Initial referrals were made by nursing and transitional care staff within prison or jail with confirmatory screening and informed consent by study personnel.

Study Eligibility Criteria

Inclusion Criteria

(1) HIV-seropositive; (2) returning to 3 sites in Connecticut (New Haven, Hartford, and Waterbury) or Springfield, MA; (3) DSM-IV criteria for opioid dependence; (4) able to provide informed consent; (5) speaks English or Spanish; (6) age ≥18 years; (7) not receiving methadone or buprenorphine or involved in an antiretroviral treatment (ART) adherence trial in the previous 30 days; and (8) within 30 days of release from prison or jail.

Exclusion Criteria

(1) Threatening behavior toward research staff or other participants; (2) other pending charges; (3) receiving opioid pain medications or expressing a need for them; (4) known hypersensitivity to naltrexone or its diluent components; and (5) study medication contraindications that included: (a) aspartate aminotransferase or alanine aminotransferase elevations (>5× upper limit of normal); (b) evidence of Child Pugh Class C cirrhosis; or (c) breastfeeding, pregnant, or unwilling to use contraception for female participants.

Informed Consent Process and Enrollment

Study personnel completed informed consent procedures with eligible and interested individuals; consent was repeated immediately after release to prevent real or perceived coercion.

Randomization

Participants were then randomly allocated 2:1 to receive 380 mg of XR-NTX or placebo (provided in-kind by Alkermes, Inc.), administered intramuscularly every 4 weeks for 6 months. A covariate adaptive stratified block randomization was performed[23–25] using the study site and whether ART was prescribed or not.

Study Measures

After enrollment, participants underwent baseline assessments, monthly follow-up interviews, and laboratory assessments for 6 months[13] using a computer-assisted survey instrument.[26,27] Structured interviews included demographic information, housing and health care status, mental health comorbidities (Mini-International Neuropsychiatric Interview),[28,29] depressive symptoms (Brief Symptom Inventory-18),[30] quality of life (12-item Short Form Health Survey),[31] Alcohol Use Disorder Identification Test,[32] and daily opioid use reports using a structured Timeline Followback (TLFB).[33,34] Biological measures included: monthly urine drug toxicology screens, urine pregnancy tests for female participants, and quarterly phlebotomy to assess HIV-1 RNA levels. Tolerability and adverse events were monitored monthly using the Systemic Assessment For Treatment Emergent Effects Intervention,[35] and also included liver function tests and injection site reaction assessments.

Study Procedures

Study injections were administered within 1 week before or on the day of release and then monthly for 5 additional months (N = 6 potential injections). During injection procedures, all participants received a brief 15-minute medical management counseling intervention.[36] Optional individual drug counseling sessions and 12-step group counseling meetings were available to all participants. Participants were compensated for contributing their time to the research activities and not for receiving study medication.

Sample Size and Power Calculations

We calculated an original sample size of 150 (XR-NTX = 100 and placebo = 50) needed to detect a statistically

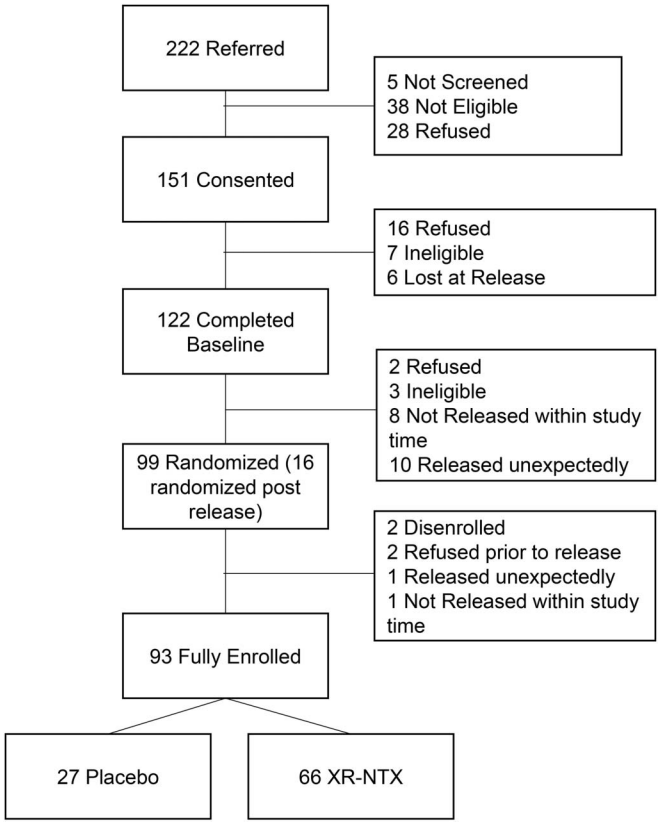

FIGURE 1. Study enrollment flow chart.

significant difference in the primary outcome at 6 months between the 2 groups. This incorporated a 2-sided alpha = 0.05, beta = 0.20, and a compound symmetry true correlation structure of 0.5 (the most conservative, based on our results from earlier studies where our prison-release data suggested that 59% of HIV+ inmates leave prison with VS[6,37]). Calculations also included oversampling (2:1 randomization) those receiving XR-NTX due to potential adverse events.

Participant Disposition

Of the 222 PLH referred to the study, 151 consented and 93 were included in the final analytical sample, 66 were randomized to receive XR-NTX, and 27 to receive placebo. The CONSORT diagram is depicted in Figure 1.

STATISTICAL ANALYSIS

Baseline Characteristics

Baseline characteristics were compared between the 2 study treatment groups using paired *t*-tests, Fisher exact, analysis of variance, and χ^2 to assess for differences using SPSS and R.

Missingness Analysis

Overall, 14.1% of participants had missing HIV-1 RNA data at 6 months postrelease. Using Little MCAR ("Missing Completely at Random") test[38] using the *BaylorEdPsych* package in R,[39] we explored the structure of the missing data to determine whether the data were MCAR and not related to the dependent or independent variables. The highly nonsignificant results ($P = 0.560$) suggested that the missing data were not statistically related to the main outcome (VS), viral load (VL) at baseline, nor any of the variables used in the analysis, most importantly, treatment assignment or number of XR-NTX injections. High *P*-values for Little MCAR test suggest that further missingness inquiries using sensitivity analysis are not merited because the data were clearly neither Missing at Random nor Not Missing at Random.[40,41] Consequently, we were able to maintain the most conservative standard intention-to-treat (ITT) assumption that missingness from participant attrition equals viral nonsuppression (missing = failure). This is the standard analytic method for regulatory submission of HIV-1 RNA data to the U.S. Food and Drug Administration,[42] which provides the most sensitive and conservative detection limits available and used previously in prospective trials of PLH where HIV-1 RNA is the outcome. We did, however, make adjustments such that if a participant had both VS confirmed at 3 months and 9 months (before or after the 6-month censor period of data analysis), then that data was considered in the 6-month missing outcome evaluation and not simply denoted as "failure." Of note, there was no statistically significant difference in available VL data between treatment groups at 6 months (88.9% placebo, 84.9% XR-NTX, $P = 0.597$).

Outcome Variables

Primary Outcome: ITT Analysis of Viral Suppression From Baseline to 6 Months

The original predetermined primary outcomes were VS defined as HIV-1 RNA <400 copies/mL and <50 copies/mL after 6 months of intervention. The choice of VS at <400 copies/mL at the study start was because our previous studies of released HIV prisoners had a lower limit of VS at <400 copies/mL.[6,13,37] After finalizing study protocols, standard clinical practice used more stringent VS cut-offs (<50 copies/mL) as the lower limit of detection. We therefore report findings the predetermined outcome of using maximal VS (<50 copies/mL) as sole the primary outcome;[43] however, VS <400 copies/mL is also reported. Using an ITT strategy, the primary outcomes involved a comparison of the changes in maximal VS levels (<50 copies/mL) from baseline to 6 months after release. Our hypothesis was that effective treatment of OUD would maintain VS for those already on ART, and for those not on it at the time of enrollment (either by preference while incarcerated due to confidentiality concerns), they might be more likely to initiate it.[11,44] Consequently, the change in VS from baseline to 6 months best reflected how participants would do over time either with or without effective treatment of OUD. After dichotomizing VS as suppressed (<50 copies/mL) or not, changes in VS were assessed using Welch *t* test using R statistical software,[45] with $P < 0.05$ as being statistically significant.

In addition, the principal outcome of VS required a further more nuanced analysis because 4 possible VS

TABLE 1. Baseline Characteristics

Variable	XR-NTX, N = 66 (%)	Placebo, N = 27 (%)	Total, N = 93 (%)	*P*
Sex				0.562
Male	55 (83.3)	21 (77.8)	76 (81.7)	
Female	11 (16.7)	6 (22.2)	17 (18.3)	
Ethnicity				
Black	17 (25.8)	6 (22.2)	23 (24.7)	0.806
Hispanic	42 (63.3)	19 (70.4)	61 (65.6)	
White	7 (10.6)	2 (7.4)	9 (9.7)	
Age in years, mean (SD)	46.6 (8.3)	43.9 (7.8)	45.8 (8.2)	0.147
Completed GED or high school	37 (56.1)	12 (44.4)	49 (52.7)	0.308
Referred from				
Prison	14 (21.2)	7 (25.7)	21 (22.6)	0.729
Jail	49 (74.2)	18 (66.7)	67 (72.0)	
Community	3 (5.4)	2 (7.4)	5 (5.4)	
Mean incarceration (months; SD)	8.5 (10.0)	9.3 (12.0)	8.8 (10.5)	0.735
Study site				
Greater New Haven	24 (36.4)	10 (37.0)	34 (36.6)	0.668
Greater Hartford	32 (48.5)	11 (40.7)	43 (46.2)	
Greater Springfield	10 (15.2)	6 (22.2)	16 (17.2)	
Housing status				
Stable	23 (34.8)	11 (40.7)	34 (36.6)	0.365
Unstable	19 (28.8)	4 (14.8)	23 (24.7)	
Homeless	24 (36.4)	12 (44.4)	36 (38.7)	
Chronic hepatitis C (N = 79)	46 (83.6)	20 (83.3)	66 (83.5)	1.000
Currently prescribed ART	58 (89.2)	24 (88.9)	82 (89.1)	1.000
Prescribed ART-based regimen (N = 82)				
Protease inhibitor (PIs)	26 (44.8)	5 (20.8)	31 (37.8)	0.105
Nonnucleoside reverse transcriptase inhibitors	17 (29.3)	13 (54.2)	30 (36.6)	
Integrase inhibitors	7 (12.1)	4 (16.7)	11 (13.4)	
Combination	8 (13.8)	2 (8.3)	10 (12.2)	
HIV-RNA VL (copies/mL) (N = 93)				
<400	42 (63.6)	18 (66.7)	60 (64.5)	0.784
<200	37 (56.1)	17 (63.0)	54 (58.1)	0.544
<50	25 (37.9)	15 (55.6)	40 (43.0)	0.129
HIV-RNA VL (copies/mL)				
Mean (SD)	21,439 (85,004)	4535 (13,238)	16,478 (72,054)	0.308
Log_{10} mean (SD)	2.47 (1.3)	2.18 (1.1)	2.38 (1.2)	0.313
Mean CD4 count (SD)	465.2 (273.8)	580.8 (336.8)	498.8 (296.3)	0.088
M.I.N.I.				
Bipolar disorder	9 (14.8)	2 (8.3)	11 (12.9)	0.721
Major depressive disorder	15 (24.6)	9 (37.5)	24 (28.2)	0.234
PTSD	10 (16.4)	5 (20.0)	15 (17.4)	0.757
Generalized anxiety disorder	9 (14.8)	4 (16.0)	13 (15.1)	1.000
Brief Symptom Index, depression (N = 89)	25 (38.5)	11 (45.8)	36 (40.4)	0.529
Addiction Severity (ASI) scores, median (range)				
Drug composite scores	0.40 (0.00–0.66)	0.46 (0.16–0.78)	0.43 (0.00–0.78)	0.173
Alcohol composite scores	0.00 (0.00–0.97)	0.00 (0.00–0.65)	0.00 (0.00–0.97)	0.242
Quality of life, SF-12, median (range)				
Physical composite scores	52.5 (26.0–62.7)	50.8 (23.5–59.7)	51.7 (23.5–62.7)	0.441
Mental composite scores	42.2 (15.3–66.3)	42.7 (17.9–59.8)	42.6 (15.3–66.3)	0.950
Alcohol use severity (by AUDIT score)				
Abstinent or low-risk drinking	42 (64.6)	23 (85.2)	65 (70.7)	0.097
Hazardous drinking	11 (16.9)	2 (7.4)	13 (14.1)	
Harmful drinking	2 (3.1)	0 (0.0)	2 (2.2)	
Dependent drinking	10 (15.4)	2 (7.4)	12 (13.0)	
Opioid craving (scale of 0–10)				
Mean (SD)	3.2 (3.6)	3.5 (3.8)	3.3 (3.6)	0.700

TABLE 1. (*Continued*) Baseline Characteristics

Variable	XR-NTX, N = 66 (%)	Placebo, N = 27 (%)	Total, N = 93 (%)	*P*
Substance use, ASI, (years; SD)				
Alcohol mean	13.5 (15.2)	9.2 (11.6)	12.2 (14.3)	0.186
Cannabis mean	14.0 (14.3)	12.8 (12.5)	13.6 (13.7)	0.705
Cocaine mean	17.5 (11.4)	18.7 (8.6)	17.9 (10.6)	0.634
Heroin mean	20.1 (11.2)	18.4 (10.2)	19.6 (10.9)	0.491
Other opioids	2.8 (7.2)	3.2 (5.4)	2.9 (6.7)	0.818
Positive urine toxicology result				
Opioids	8 (12.1)	3 (11.1)	11 (11.8)	0.968
Cocaine	11 (16.7)	5 (18.5)	16 (17.3)	0.739
Substance use disorder using M.I.N.I.				
Alcohol use disorder	18 (29.5)	5 (20.0)	23 (26.7)	0.366
Cannabis use disorder	16 (26.2)	6 (25.0)	22 (25.9)	0.907
Cocaine use disorder	47 (77.0)	21 (87.5)	68 (80.0)	0.373
Previous experience with MAT	51 (77.3)	19 (70.4)	70 (75.3)	0.484
Methadone lifetime	43 (84.3)	17 (89.5)	60 (85.7)	0.717
Methadone past 30 days	16 (37.2)	5 (29.4)	21 (35.0)	0.568
Buprenorphine lifetime	34 (66.7)	11 (57.9)	45 (64.3)	0.496
Buprenorphine past 30 days	14 (41.2)	6 (54.5)	20 (44.4)	0.500
Injections received				
0–2	44 (66.7)	18 (66.7)	62 (66.7)	0.91
3–6	24 (36.4)	9 (33.3)	33 (35.5)	
Cumulative injections received				
1	45 (68.2)	17 (63.0)	62 (66.7)	0.628
2	28 (42.4)	10 (37.0)	38 (40.9)	0.631
3	24 (36.4)	9 (33.3)	33 (35.5)	0.782
4	15 (22.7)	7 (25.9)	22 (23.7)	0.742
5	9 (13.6)	5 (18.5)	14 (15.1)	0.550
6	10 (15.2)	4 (14.8)	14 (15.1)	0.967

ASI, addiction severity index; AUDIT, Alcohol Use Disorders Identification Test; M.I.N.I., Mini-International Neuropsychiatric Interview; MAT, medication-assisted therapy; PTSD, posttraumatic stress disorder; SF-12, Short Form 12.

suppression trajectories were possible from baseline to 6 months: (1) maintained VS; (2) improved to VS; (3) lost VS from baseline to 6 months; and (4) remained detectable at baseline and 6 months. Using Pearson χ^2 test, we compared the distribution of the placebo with the XR-NTX arms across these 4 possible outcomes. To further capture changes in VS from baseline to 6 months, we applied McNemar χ^2 test using the *exact2x2*[46–48] package in *R* to the discordant outcomes where VS status had changed.

The mean change in VL (copies/mL) was also analyzed between treatment arms comparing the baseline with 6-month time points. The negative values for changes in the XR-NTX group precluded the usual log transformation; thus, we used the original data and reported the mean changes.

Multiple Logistic Regression Analysis of Predictors of Viral Suppression at 6 Months

After confirming that a statistically significant difference was found for changes in VS, we explored predictive variables guided by the literature,[7,16] including treatment group assignment and the number of injections received to further explain independent predictors for maximal VS (<50 copies/mL). A backward stepwise model selection *"step"* algorithm in *R* then sequentially eliminated variables until we achieved models with the best goodness-of-fit using the Akaike information criterion, as they yielded the most parsimonious results.

Other Secondary Outcomes Statistical Analysis Methods

Opioid Abstinence and Time to Relapse to Opioid Use

Daily opioid use was assessed for the 30 days before incarceration and monthly throughout the study follow-up period using the TLFB.[49] Variables generated from this tool included the number of consecutive days abstinent or time to first opioid use at the end of the 6-month intervention period. We performed a Kaplan–Meier test for time to first opioid use, or more specifically as an adjustment for the censoring of the end of the observation period at 6 months, using the study's TLFB self-reported data and monthly urine toxicology screens. We considered the observations "reported days of consecutive abstinence in 6 months." Those who dropped out of the study were most conservatively assumed to have resumed opioid use. The participants with missing data therefore reported no days of abstinence. Because previous

studies have confirmed the effect of XR-NTX on opioid relapse and abstinence, this study was not powered to detect this outcome, but instead was intended for use as a planned "as treated" to complement the ITT analysis. We grouped participants into those (1) who had received 3 or more injections of XR-NTX (N = 22 participants) and (2) those who received 2 or fewer XR-NTX injections or were in the placebo group (N = 71) in the other group. Statistical significance was tested using the log rank test and Welch *t* test for days of continuous reported abstinence.

Adverse Events

Chi-squared analyses were used to explore the differences in side effects between the treatment groups.

RESULTS

Baseline Characteristics

There were no differences in baseline characteristics between treatment arms (Table 1). Participants were on average in their mid-40s, mostly men (81.7%), racial/ethnic minorities (85.7%), homeless or unstably housed (63.4%), prescribed ART (89.1%), coinfected with chronic hepatitis C virus (83.5%), had previous preincarceration experience with methadone and/or buprenorphine (75.3%), and were incarcerated for a mean duration of 8.8 months. Central to the analysis, baseline VS levels at <400, <200, and <50 copies/mL were 64.5%, 58.1%, and 43.0%, respectively, and not statistically significantly different. There were also no differences in mean baseline CD4 count (465 vs. 581 cells/mL; $P = 0.088$).

HIV Treatment Retention

There were no statistically significant differences between the 2 groups at 6 months in the proportion of those: with HIV VL data (XR-NTX = 84.9%, placebo = 88.9%; $P = 0.597$); who completed 6-month study interviews (XR-NTX = 49.5%, placebo = 50.5%; $P = 0.822$, Fig. 2); or who were retained for study injections (66.7% received 2 or fewer study injections and 35.5% received 3–6 study injections; Table 1).

Primary Outcome: Viral Suppression at 6 Months

Compared with the placebo group that decreased VS levels over time (55.6% at baseline to 40.7% at 6 months, $P = 0.294$), the XR-NTX group had a statistically significant improvement in the proportion who maintained or achieved VS at <50 copies/mL from baseline (37.9%) to 6 months (60.6%) ($P = 0.002$) (Fig. 3). A direct comparison of VS levels at 6 months between the 2 treatment groups, however, approached statistical significance (XR-NTX = 60.6%, placebo = 40.7%; $P = 0.08$). For higher VS levels (<400 copies/mL), there were no time differences in VS levels for the XR-NTX (63.6% at baseline to 68.2% at 6 months; $P = 0.47$) or placebo (66.7% at baseline to 59.3% at 6 months; $P = 0.574$). Similarly, for this level of VS, the XR-NTX and placebo groups did not differ significantly at 6 months (68.2% vs. 59.3%; $P = 0.43$, respectively).

When comparing the distribution of the 4 possible outcomes (Fig. 4): (1) the XR-NTX group was significantly more likely to improve to VS (<50 copies/mL) levels at 6 months compared with placebo (30.3% vs. 18.5%): (2) maintain VS at 6 months (30.3% vs. 27.3%); and (3) less likely to lose VS (7.6% vs. 33.3%) at 6 months (Pearson χ^2 $P = 0.017$; McNemar χ^2, $P = 0.043$). Additionally, when evaluating further the participants who had a (Fig. 4) detectable VL at the time of release to 6 months, the XR-NTX group also statistically significantly reduced the mean VL by −6515.7 copies/mL, whereas the placebo group increased the mean VL by +9081.4 copies/mL ($P = 0.031$).

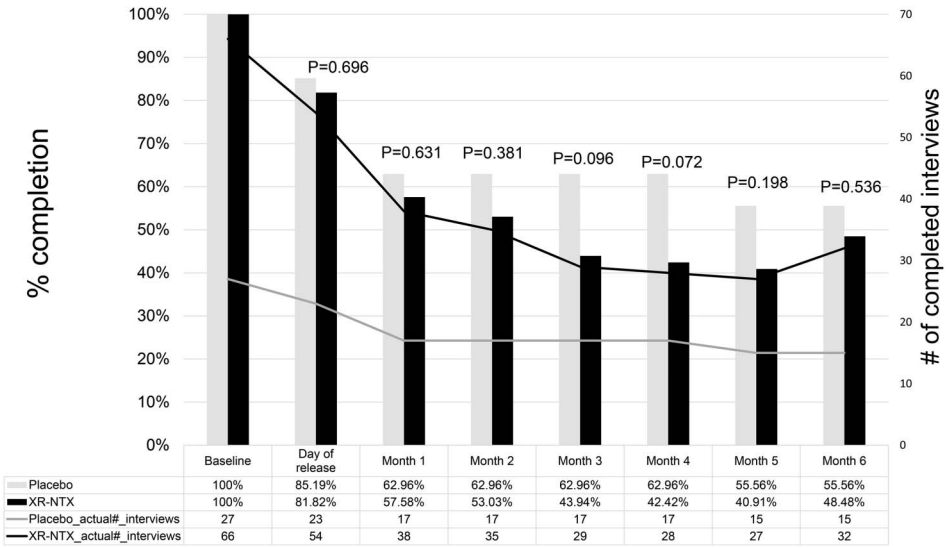

FIGURE 2 Six-month study retention.

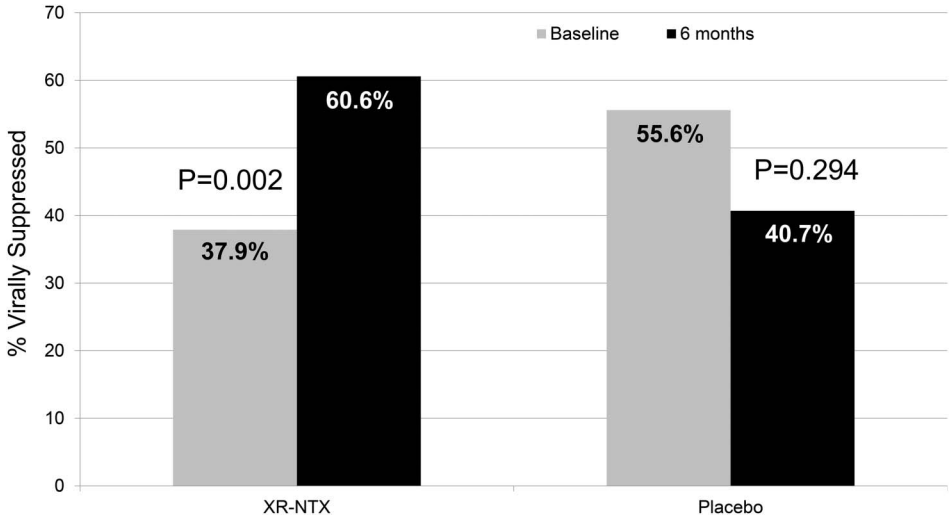

FIGURE 3. Change in VS (<50 copies/mL) from baseline to 6 months.

Multivariate Analysis of Independent Predictors of Achieving Viral Suppression

When controlling for potential confounders (Table 2), assignment to the XR-NTX group remained significantly associated with the primary outcome. No other variables, including cocaine use disorder, homeless and unstably housed status, and number of injections received, were significant.

Time to First Opioid Use

The ITT analysis revealed no statistically significant difference in time to first opioid use (continuous days of opioid abstinence) between treatment arms (XR-NTX mean = 78.0 days, placebo mean = 63.7 days; $P = 0.110$) (Fig. 5A). In the as-treated analysis (Fig. 5B), those who received 3 or more XR-NTX injections had a statistically significantly longer time of continuous days of opioid abstinence (mean = 136.4 vs. 53.2 days; $P = 0.002$) compared with those who received any number of placebo injections or 2 or fewer XR-NTX injections.

Adverse Events

No serious grade 3 or 4 hepatic events or any serious injection site or other adverse events occurred in either treatment group. The most common reported side effect (13%) was immediate injection site reaction (redness, soreness) and fatigue (8%), with no statistically significant differences between the groups (Table 3). The study did not evaluate nonfatal opioid overdoses. One participant in the XR-NTX group experienced a fatal opioid overdose 128 days after his last injection, but was determined not to be a study-related treatment serious adverse event by the Yale School of Medicine IRB, correctional system IRBs,

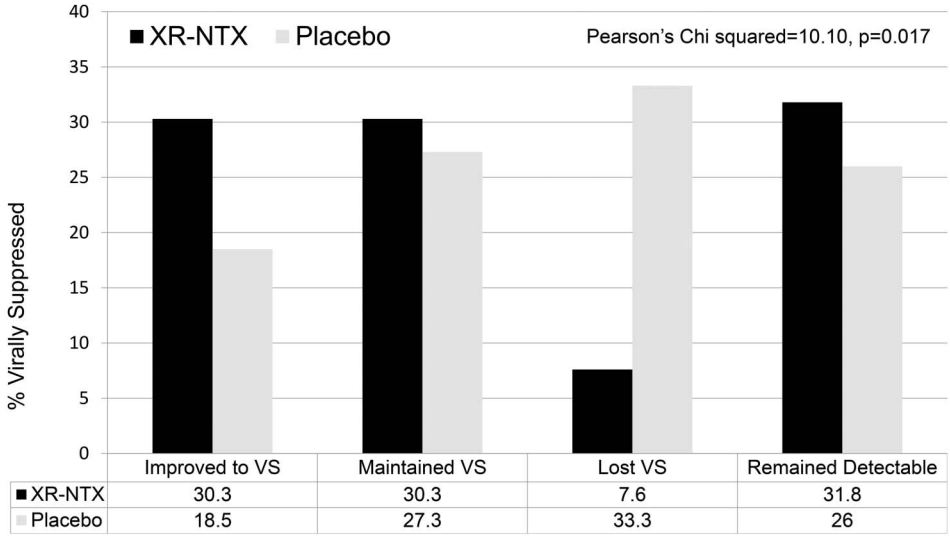

FIGURE 4. Distribution of VS (<50 copies/mL) category by treatment group from baseline to 6 months. Pearson χ^2 was evaluating difference in distribution of observations for the 4 categories between groups and was statistically significant ($P = 0.017$). Discordant observation over time within groups and between groups was evaluated using McNemar's χ^2 test, and was statistically significant ($P = 0.041$).

TABLE 2. Multivariate Models Predictive of Viral Suppression at <50 Copies/mL

Variables	aOR (95% CI)	*P*
Intercept	0.192 (0.052 to 0.704)	0.129
Treatment arm		
Placebo	Referent	
XR-NTX	**2.902 (1.035 to 8.137)**	**0.043**
Cocaine use disorder	2.031 (0.753 to 5.482)	0.162
Insecure housing	1.956 (0.740 to 5.170)	0.207
Number of injections		
2 or less	Referent	
3 or more	1.860 (0.710 to 4.872)	0.207

Akaike information criterion= 118.
Bold represents statistically significant.
aOR, adjusted odds ratio; CI, 95% confidence interval.

Baystate Medical Center IRB, Alkermes Inc. review board, or by NIDA.

DISCUSSION

To the best of our knowledge, this is the first randomized, placebo-controlled, double-blind trial that examined whether an evidence-based pharmacotherapy to treat OUD, XR-NTX, resulted in improved viral suppression levels in prisoners and jail detainees with HIV who were released from prison or jail. The key findings from this trial were that maximal viral suppression (<50 copies/mL) was maintained or improved from the time of release to the end of the 6-month treatment intervention in those who received XR-NTX, whereas those who received placebo had decreasing VS levels over time. Furthermore, receiving XR-NTX was statistically associated with a lower proportion of persons losing VS as compared to placebo. After controlling for other factors associated with poor HIV treatment outcomes after release, assignment to XR-NTX alone predicted VS at 6 months after release. These findings have important implications for individual management of PLH with OUD being released from a criminal justice system setting and from a public health perspective.

Recent longitudinal data suggest that in the absence of treatment of OUD, linkage to HIV care after release is poor and associated with poor VS levels that decrease over time.[50] Strategies that optimize VS over time are more likely to promote individual health, but also public health through treatment as prevention efforts.

These findings are especially relevant, given the volatile opioid epidemic and associated transmission of HIV and HCV. For prisoners and jail detainees with OUD, including those with HIV, relapse to opioid use exceeds 85%, often within the first 2 weeks,[10] and results in interruptions in HIV care,[11] overdose, and death.[7] In prisoners without HIV, XR-NTX markedly reduces opioid relapse and use.[20] This study extends these findings and documents for the first time that XR-NTX stabilizes PLH sufficiently to stabilize them so that they can continue and adhere to ART and maintain or achieve VS.

The mechanism by which XR-NTX maintained or improved VS is not fully understood. In another study of prisoners with HIV and alcohol use disorders, XR-NTX significantly reduced alcohol consumption and exerted its effect on VS.[51] The current trial was not powered to demonstrate a difference in opioid relapse outcomes, which were measured using more complex metrics in previous studies of XR-NTX.[14,20] In the current trial, however, the only opioid use outcome measured was time to opioid relapse, which was not statistically different between those receiving XR-NTX or placebo in the ITT analysis. A more robust opioid use outcome variable, which might have

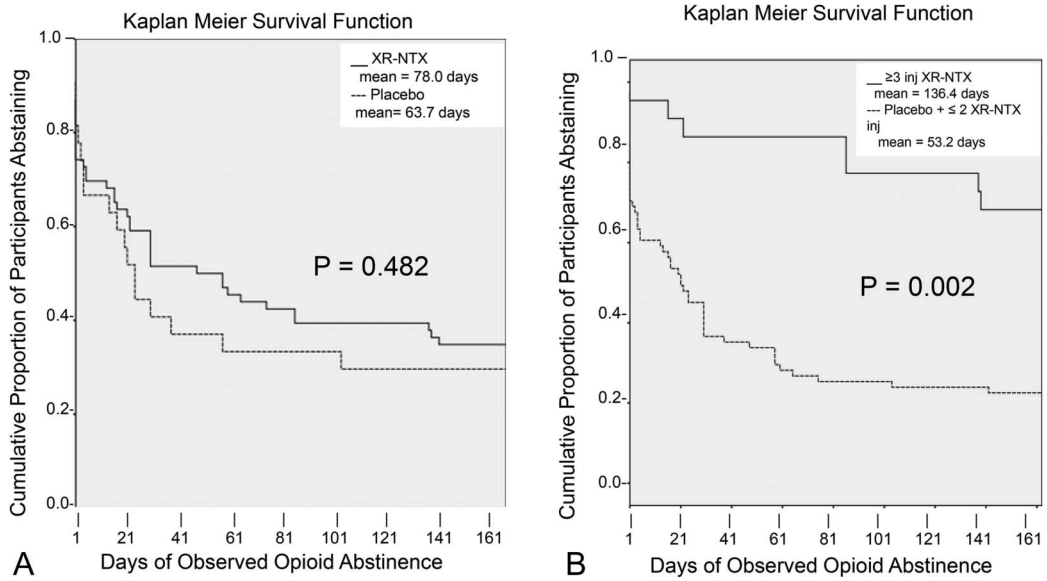

FIGURE 5. Kaplan–Meier curve days of continuous opioid abstinence. A, Intention to treat analysis. B, As-treated analysis by treatment grouping.

TABLE 3. Adverse Events

Adverse Event	XR-NTX	Placebo	Total Sample	*P*
Transaminase level 5× upper limit of normal				
Aspartate aminotransferase				
Baseline; N = 85	1% (1)	0% (0)	1% (1)	1.000
Month 6; N = 39	0% (0)	0% (0)	0% (0)	N/A
Alanine transaminase				
Baseline; N = 86	1% (1)	0% (0)	1% (1)	1.000
Month 6; N = 39	7% (2)	0% (0)	5% (2)	1.000
Other Adverse Events	**N = 66**	**N = 27**	**N = 93**	***P***
Skin and soft tissue infection	3% (2)	1% (1)	3% (3)	1.000
Signs of edema	3% (2)	4% (2)	2% (4)	0.577
Immediate injection reaction	15% (10)	4% (2)	13% (12)	0.498
Injection site reaction	3% (2)	0% (0)	2% (2)	1.000
Nausea	2% (1)	4% (1)	2% (2)	0.500
Vomiting	2% (1)	0% (0)	1% (1)	1.000
Diarrhea	5% (3)	0% (0)	3% (3)	0.554
Decreased appetite	3% (2)	4% (1)	3% (3)	1.000
Increased appetite	3% (2)	4% (1)	3% (3)	1.000
Headache	8% (5)	0% (0)	5% (5)	0.317
Dizziness	0% (0)	0% (0)	0% (0)	N/A
Fatigue	9% (6)	4% (1)	8% (7)	0.669

included a combination of time to relapse, days of opioid use, or continuous days of opioid use might have provided insights into how XR-NTX might have exerted its influence.

In addition, despite a low number of participants, retention on XR-NTX was associated with a longer time to relapse (continued abstinence). Participants who received 3 or more XR-NTX injections had a significantly longer time of continuous abstinence compared to those who received any number of placebo injections or those who received 2 or fewer injections of XR-NTX. This finding supports longitudinal studies of released prisoners with HIV and OUD who had better HIV treatment outcomes if they were able to remain on buprenorphine longer,[11] a medication-assisted treatment for OUD that is a partial opioid agonist/antagonist. Strategies that improve retention on OUD treatment are therefore crucial to optimize VS levels and are especially challenging when using antagonist-based treatments such as XR-NTX.[16] Cohort studies of released prisoners with HIV, irrespective of having an OUD, suggest that VS levels markedly decrease within the first 3 months after release.[3,4,6,50] This period is therefore especially crucial to ensure adequate treatment for both HIV and OUD. Given the chronic and relapsing nature of both HIV and OUD, each of which need a lifetime of treatment, future studies should not only treat and observe patients longer, but should be conducted using other medication-assisted therapies for OUD, such as methadone and buprenorphine.

In addition to efficacy outcomes, treatment with XR-NTX is safe, especially given that 80% of the sample had chronic HCV infection. The fatal overdose that occurred that was not related to the study, however, remains concerning and has been raised as a concern in other studies of XR-NTX.[52] Death occurred in one participant in the XR-NTX group 128 days after the last injection. This finding is consistent with all other studies of treatment of OUD where discontinuation of treatment, irrespective of the medication, is associated with increased overdose-related death.[53–56] Previous studies have shown that XR-NTX protects against opioid overdose.[20]

Despite the important findings and implications of these research findings, some limitations remain. The lower-than-anticipated sample size concerns have been discussed elsewhere,[13,16] but related to introduction of methadone in Connecticut and alternatives to incarceration strategies resulting in fewer numbers of PLH in prison in Connecticut and Massachusetts. Attrition from the study was high, but similar to other studies of released prisoners with OUD.[6,57] Despite attrition from the study, VL measurements were high resulting in relatively few missing data that were MCAR, allowing for imputation of conservative missing = failure assumptions. This assumption, however, is typically what is considered in "real-world" treatment settings of PLH where the association between poor retention, particularly "no-show" behavior, and poorer biological outcomes is evidenced by virological failure and mortality.[58,59] Despite the missing data and lower-than-expected sample size, the findings remain robust. A larger sample size and better measures of opioid use might have provided better insights into additional factors that might have contributed to VS in this sample.

CONCLUSIONS

Findings from this study inform guidelines for treating transitioning prisoners with HIV and OUD with XR-NTX to improve HIV treatment outcomes. Future strategies, however, must optimize treatment retention to reduce opioid use and maintain or increase VS. When XR-NTX is initiated just before release and maintained thereafter, it results in both improved individual and public health benefits. Not only was XR-NTX found to be efficacious, it was also safe in PLH and high levels of HCV.

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