Extended-release Naltrexone Improves Viral Suppression Among Incarcerated Persons Living with HIV and Alcohol use Disorders Transitioning to the Community: Results From a Double-Blind, Placebo-Controlled Trial

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Objective: To determine whether extended-release naltrexone (XR-NTX) would improve or maintain viral suppression (VS) among incarcerated individuals with HIV and alcohol use disorders (AUDs) transitioning to the community.

Design: A randomized, double-blind, placebo-controlled trial was conducted among incarcerated individuals with HIV and AUDs transitioning to the community from 2010 through 2016.

Methods: Eligible participants (N = 100) were randomized 2:1 to receive 6 monthly injections of XR-NTX (n = 67) or placebo (n = 33) starting at release and continued for 6 months. The primary and secondary outcomes were the proportion that maintained or improved VS at <200 and <50 copies per milliliter from baseline to 6 months, respectively, using an intention-to-treat analysis.

Results: Participants allocated to XR-NTX improved VS from baseline to 6 months for <200 copies per milliliter (48.0%–64.2%, $P = 0.024$) and for <50 copies per milliliter (31.0%–56.7%, $P = 0.001$), whereas the placebo group did not (<200 copies/mL: 64%–42.4%, $P = 0.070$; <50 copies/mL: 42.0%–30.3%, $P = 0.292$). XR-NTX participants were more likely to achieve VS than the placebo group at 6 months (<200 copies/mL: 64.2% vs. 42.4%; $P = 0.041$; <50 copies/mL: 56.7% vs. 30.3%; $P = 0.015$). XR-NTX independently predicted VS [<200 copies/mL: adjusted odds ratio (aOR) = 2.68, 95% confidence interval (CI) = 1.01 to 7.09, $P = 0.047$; <50 copies/mL: aOR = 4.54; 95% CI = 1.43 to 14.43, $P = 0.009$] as did receipt of ≥3 injections (<200 copies/mL: aOR = 3.26; 95% CI = 1.26 to 8.47, $P = 0.010$; <50 copies/mL: aOR = 6.34; 95% CI = 2.08 to 19.29, $P = 0.001$). Reductions in alcohol consumption (aOR = 1.43, 95% CI = 1.03 to 1.98, $P = 0.033$) and white race (aOR = 5.37, 95% CI = 1.08 to 27.72, $P = 0.040$) also predicted VS at <50 copies per milliliter.

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

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

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INTRODUCTION

Globally, people living with HIV (PLH), and especially those with substance use disorders, are disproportionately concentrated in prisons and jails.[1] In the United States (US), one-sixth of the 1.2 million PLH cycle through these criminal justice settings annually, resulting in an HIV prevalence that is 3-fold higher than the community.[2] Despite high levels of viral suppression (VS) achieved during incarceration,[3] this transition is made tumultuous by low linkage to HIV care,[4] high rates of relapse to substance use,[5] homelessness,[6] and overdose.[7] Together, these factors undermine adherence to antiretroviral therapy (ART) after release and result in loss of VS.[4,8–10]

Alcohol use disorders (AUDs) are 8 times more prevalent in criminal justice populations than in the community, with relapse especially common and problematic after release.[11,12] In PLH, AUDs exacerbate ART nonadherence, resulting in suboptimal VS.[13] Most prisoners in the United States do not receive medication to treat AUDs or prevent relapse to alcohol use at the time of release.[11,14] Extended-release naltrexone (XR-NTX) is an evidence-based and Food and Drug Administration–approved treatment for AUDs, which delays and reduces alcohol consumption,[15] including

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for incarcerated PLH with AUDs and released to the community.[16] We therefore hypothesized that XR-NTX would reduce alcohol consumption in PLH with AUDs who are transitioning to the community and either maintain or improve VS after release, compared with those with untreated AUDs. We tested this hypothesis within a placebo-controlled trial using XR-NTX by specifically examining the influence of XR-NTX on achieving VS 6 months after release from prison or jail.

METHODS

A double-blind, placebo-controlled prospective trial of XR-NTX among PLH with AUDs who were transitioning to the community was conducted from September 2010 through February 2016 in 2 sites in Connecticut. Eligible participants were randomized 2:1 to XR-NTX or placebo, receiving their first injection within 1 week before release from prison or jail; treatment was continued for 6 months after release. Recruitment procedures and eligibility criteria,[17] early and final retention levels,[16–18] hepatic safety,[16,19] alcohol consumption outcomes,[16] and adverse events[16] have previously been reported.

Recruitment

After screening, 100 participants were ultimately recruited from prisons and jails within the Connecticut Department of Correction. Incarcerated PLH were first screened for self-reported hazardous drinking (≥4 drinks daily for women or ≥5 drinks daily for men),[20] followed by more detailed screening assessments.[17]

Screening, Eligibility, and Consent

Inclusion Criteria

(1) Documented HIV-infection; (2) adults aged 18 years and older; (3) transitioning to either New Haven or Hartford, Connecticut; (4) met the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV criteria for alcohol abuse or dependence using the Mini International Neuropsychiatric Interview[21] or hazardous drinking using the Alcohol Use Disorders Identification Test (score ≥4 for women and ≥8 for men)[22]; (5) provided informed consent; and (6) spoke English or Spanish.

Exclusion Criteria

(1) Prescribed opioid pain medications or reported a medical indication for them after release; (2) grade 3 or higher aspartate aminotransferase or alanine aminotransferase elevations (>5× upper limit of normal); (3) evidence of Childs-Pugh class C cirrhosis; (4) enrolled in another alcohol pharmacological or ART adherence study; or (5) breastfeeding, pregnant, or unwilling to use contraception (women only).

Eligible and interested prisoners then completed verbal and written informed consent procedures, which were repeated immediately after release to prevent real or perceived coercion.

Ethical Oversight

All study procedures were reviewed and approved by the institutional review board at Yale University, the Connecticut Department of Correction Research Advisory Committee, and the Office of Human Research Protections. A Certificate of Confidentiality was obtained from the National Institutes of Health. The study is registered at www.clinicaltrials.gov (NCT01077310).

Randomization

After consent, participants were randomly assigned 2:1 to receive 380 mg of XR-NTX (Vivitrol) or placebo (provided in-kind by Alkermes, Inc., Waltham, MA), administered intramuscularly every 4 weeks for 6 months. A covariate-adapted stratified block randomization was performed controlling for the presence or absence of concurrent opioid use disorder and whether prescribed ART or not.[17]

Study Measures

HIV-1 RNA levels, along with CD4 T-lymphocyte cell counts, were assessed at baseline, time of release, and at 3 and 6 months after release. Other study measures included demographic information (age, sex, race, and housing status), type of ART regimen (protease inhibitor, non-nucleoside reverse transcriptase inhibitor, or integrase strand transfer inhibitor regimens), health insurance status, duration of incarceration, symptoms of depression using the Brief Symptom Inventory (defined as a general T-score of ≥63 or any 2 primary dimension scores of ≥63),[23] alcohol and drug use, hepatitis C virus coinfection, and presence of comorbid mental illness and other substance use disorders using the Mini International Neuropsychiatric Interview. Our alcohol consumption variables[16] were derived from a timeline follow-back[24,25] that assessed self-reported daily totals of standard drinking units before incarceration and monthly for 6 months. Because drinking patterns are varied, we used a previously described alcohol improvement score to more comprehensively measure heterogeneous drinking patterns.[16] This score included the (1) time to first heavy drinking day; (2) total number of drinks per drinking day; (3) percent of heavy drinking days (≥5 drinks per day for men or ≥4 drinks per day for women); (4) preincarceration to postincarceration change in average drinks per day; and (5) total number of drinking days. Each of these 5 variables were combined and weighted equally with a score of "1" for favorable outcomes and combined into a unit-weighted composite score using previously described criteria.[16] This score generated a single summary measure that was more easily amenable to interpretation of heterogeneous drinking patterns and more sensitive to data variance and subtle changes by reducing floor and ceiling effects.[16]

Adverse events were also monitored monthly and included hepatic transaminase levels and injection site reactions. Previous reports from this trial found no differences in adverse events between the 2 groups nor were there any serious adverse events in either treatment group.[16]

Outcome Variables

The original preplanned primary outcomes were defined as the proportion that achieved or maintained HIV VS at the <400 and the <50 copies per milliliter levels from baseline to 6 months. The Department of Health and Human Services HIV treatment guidelines changed their definition of VS to <200 copies per milliliter as the goal of therapy soon after study initiation,[26] resulting in a change in one of the primary outcomes from <400 to <200 copies per milliliter.[17] The other preplanned coprimary outcome, change in maximal VS defined as <50 copies per milliliter, remained a clinically important outcome in real-world practice and is listed as a secondary outcome in this article. Using an intention-to-treat (ITT) strategy, the primary and secondary outcomes involved a comparison of the changes in VS levels of <200 and <50 copies per milliliter from baseline to 6 months after release in both treatment groups, respectively. This outcome best reflected how participants did over time (baseline to 6 months) because our hypothesis was that participants who received placebo would be more likely to lose VS after release, whereas those who benefited from XR-NTX would either maintain or improve VS levels, or if not on ART, initiate it because of increased postrelease stability.[27,28] In addition, the difference between groups in proportions with VS at the 6-month time point was assessed.

Sample Size and Power Calculations

We calculated an original sample size of 125 (XR-NTX = 83 and placebo = 42) needed to detect a statistically 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,[10] and where 28% of HIV prisoners with an AUD leaving prison have VS after 6 months).[29] Power calculations, as previously published,[17] also included oversampling (2:1 randomization) those receiving XR-NTX due to concern for potential increase in adverse events[30] in the XR-NTX group and were also based on aforementioned studies of released prisoners who had 80% retention after 6 months.[29,31]

Participants' Disposition

Of the 195 PLH referred to the study, 118 consented and completed baseline interviews, and 100 were fully reenrolled and randomized and included in the final analytical sample; 67 were randomized to receive XR-NTX and 33 to receive placebo. The CONSORT diagram is depicted in Figure 1. Study retention was not statistically different between study arms as reported in a previous article.[16]

Analytical Approach

Missingness Analysis

Overall, 13% of participants who were randomized had missing HIV-1 RNA data 6 months after release. Therefore, we explored the structure of the missing data to determine whether the data were "missing completely at random" (MCAR) and not related to the dependent or independent variables. The structure of the missing data was assessed using the Little MCAR[32] test implemented with code within the BaylorEdPsych package in *R* software.[33] The highly nonsignificant results for the Little MCAR test ($P = 0.560$) suggested that the missing data were not statistically related to the main outcome (VS), viral load 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 the Little MCAR test also suggested that further missingness inquiries using sensitivity analysis were not merited because the data were clearly neither missing at random nor not missing at random.[34,35] Although the MCAR result allowed for the application of multiple imputation, when this was performed, it gave inconsistent results because of colinearity of some variables. Consequently, we were able to maintain the most conservative standard 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 US Food and Drug Administration,[36] 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.

Intention to Treat Analysis of Viral Suppression From Baseline to 6 Months After release

An ITT analysis was conducted first by dichotomizing VS as suppressed or nonsuppressed, and comparing VS levels for primary and secondary outcomes at 6 months was performed using χ^2 testing. Furthermore, change in VS over time from baseline to 6 months was deployed to more accurately reflect the differences in VS levels. These analyses were conducted using T tests in *R* statistical software.

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

After confirming that a statistically significant difference was found for each level of VS both over time and at 6 months, we explored predictive variables guided by the literature that included receipt of ART,[9,18] as well as specific to this study, treatment assignment, and the number of injections received, to further explain independent predictors for the primary (VS <200 copies/mL) and secondary (VS <50 copies/mL) outcomes. Of note, most participants were receiving ART, and there was no difference in the number on ART with almost 90% receiving ART at the time of release. The number of injections was dichotomized as 2 or fewer injections vs. 3 or more to reflect better retention in the study because of previous studies showing that the first 3 months is enough time to lose VS after release.[8,10] A backward stepwise model selection "step" algorithm in *R* software then sequentially eliminated variables until we achieved models with the best goodness-of-fit using the Akaike information criterion (AIC) because they yielded the most parsimonious results. Of note, because of the number of potential variables, those with the best AIC are demonstrated.

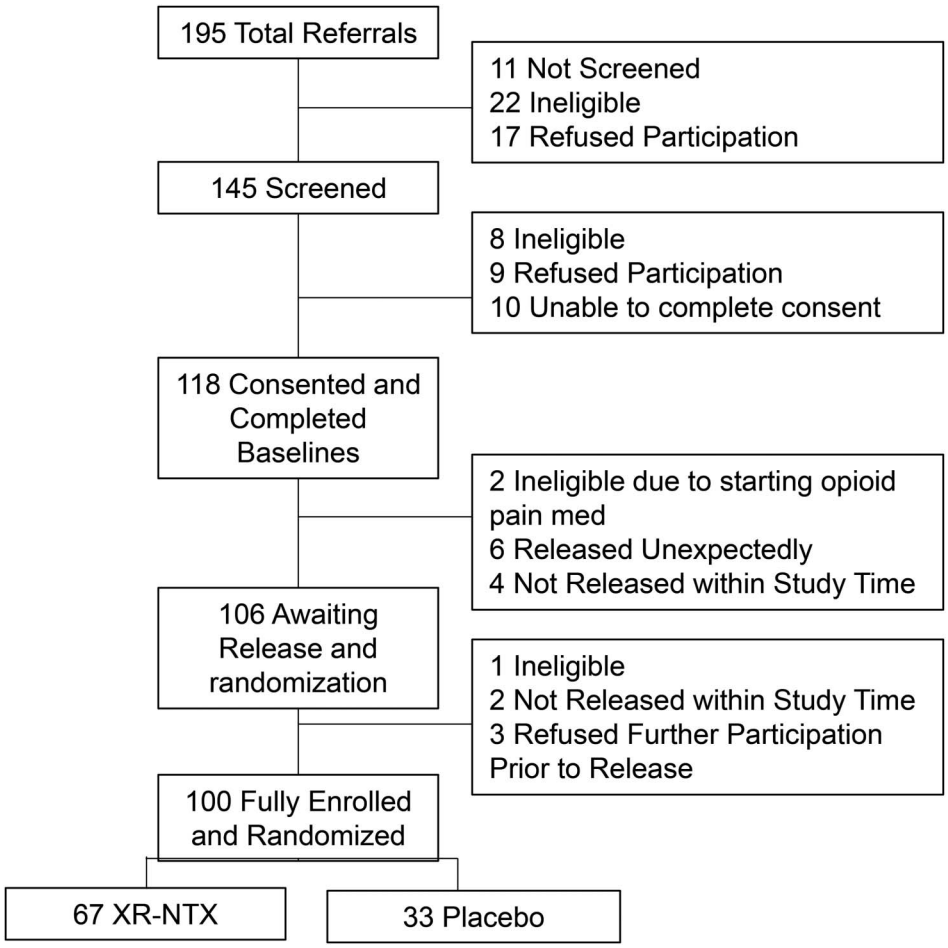

FIGURE 1. CONSORT flow diagram. XR-NTX, extended-release naltrexone.

RESULTS

Baseline Characteristics

The baseline characteristics are described in Table 1. Participants were on average in their mid-40s, mostly men (77%), racial/ethnic minorities (84%), homeless or unstably housed (63%), and prescribed ART (87%) and had major depression (75%). Central to the analysis, baseline VS levels at <200 and <50 copies per milliliter were 53% and 35%, respectively, and not significantly different (66% had VS < 400 copies/mL and not significantly different). The 2 treatment arms did not differ significantly for any baseline variable aside from median CD4 count (XR-NTX: 490 vs. placebo: 418 cells/mL; $P = 0.033$); however, 90% of participants in both groups had CD4 counts >200 cells/mL.

Intention to Treat Analysis: Comparison of Viral Suppression at Baseline and 6 Months After release

Figure 2 depicts the change in VS levels from baseline to 6 months after release using the ITT analysis in each treatment group and the between-group differences at the 6-month time point for both outcomes. At baseline as previously mentioned, there were no differences in VS levels for either the primary or secondary VS outcome as shown in Table 1. The primary VS outcome (<200 copies/mL) did not statistically significantly improve from baseline (64%) to 6 months (42.4%) for the placebo group ($P = 0.070$) nor did it for the secondary VS outcome (<50 copies/mL) (42.0% to 30.3%, $P = 0.292$); VS <400 copies/mL also did not improve for the placebo group from baseline (66.7%) to 6 months (42.4%, $P = 0.030$). The XR-NTX group significantly improved from baseline to 6 months for the primary VS outcome (<200 copies/mL) (48.0% to 64.2%, $P = 0.024$) and for the secondary VS outcome (<50 copies/mL) (31.0% to 56.7%, $P = 0.001$); VS <400 copies/mL in the XR-NTX group was maintained from baseline (63.6%) to 6 months (53.7%, $P = 0.260$). Furthermore, at 6 months, compared with placebo, participants who received XR-NTX were also significantly more likely to have VS for both the primary (<200 copies/mL) (64.2% XR-NTX vs. 42.4% placebo; $P = 0.041$) and secondary VS outcomes (<50 copies/mL) (56.7% XR-NTX vs. 30.3% placebo; $P = 0.015$). VS <400 copies/mL at 6 months was not significantly different between groups (53.7% XR-NTX vs. 42.2% placebo, $P = 0.289$). Of note, additional analyses found that no participants in the placebo group who were not on ART at baseline achieved VS, whereas 14.3% of those not on ART at baseline in the XR-NTX group did achieve VS at that level at the 6-month time point.

TABLE 1. Baseline Characteristics (N = 100)

Variable	XR-NTX, N = 67 (%)	Placebo, N = 33 (%)	Total, N = 100 (%)	*P*
Gender				
Male	50 (74.6)	27 (81.8)	77 (77.0)	0.422
Female	16 (23.9)	5 (15.2)	21 (21.0)	
Transgender	1 (1.5)	1 (3.0)	2 (2.0)	
Ethnicity				
Black	46 (68.7)	19 (57.6)	65 (65.0)	0.528
Hispanic	11 (16.4)	8 (24.2)	19 (19.0)	
White	10 (14.9)	6 (18.2)	16 (16.0)	
Mean age, yr	44·9 (SD ±8.12)	45·2 (SD ±8.92)	45·0 (SD ±8.35)	0.866
Completed high school (N = 99)	35 (53.0)	15 (45.5)	50 (50.5)	0.568
Referred from				
Prison	17 (25.4)	6 (18.2)	23 (23.0)	0.085
Jail	43 (64.2)	27 (81.2)	70 (70.0)	
Community (within 30 days)	7 (10.4)	0 (0)	7 (7.0)	
Duration of current incarceration (mo)	13.99 (SD ±30.32)	11·64 (SD ±18.05)	13·21 (SD ±26.82)	0.683
Study site				
New Haven	40 (59.7)	19 (57.6)	59 (59.0)	0.839
Hartford	27 (40.3)	14 (42.4)	41 (41.0)	
Housing status (N = 99)				
Stable	22 (33.3)	14 (42.4)	36 (36.4)	0.440
Unstable	17 (25.8)	10 (30.3)	27 (27.3)	
Homeless	27 (40.9)	9 (27.3)	36 (36.4)	
Chronic hepatitis C virus infection	29 (47.5)	16 (50.0)	45 (48.4)	0.822
Currently prescribed ART	57 (85.1)	30 (90.9)	87 (87.0)	0.470
Prescribed ART regimen				
Protease inhibitor	29 (51.7)	16 (55.2)	45 (51.7)	0.441
Non-nucleoside reverse transcriptase inhibitor	20 (35.7)	10 (34.4)	30 (34.5)	
Integrase inhibitor	5 (8.9)	3 (10.3)	8 (9.4)	
Combination	3 (5.4)	1 (3.4)	4 (4.7)	
HIV-RNA (copies/mL)				
<400	22 (63.6)	42 (67.7)	66 (66.0)	0.292
<200	32 (48.0)	21 (64.0)	53 (53.0)	0.135
<50	21 (31.0)	14 (42.0)	35 (35.0)	0.293
HIV-RNA (copies/mL)				
Mean (SD)	4427 (±14,386)	8119 (±37,959)	5683 (±24,884)	0.492
Log_{10} mean (SD)	2.43 (±1.03)	2.22 (±1.04)	2.36 (±1.03)	0.368
CD4 count ≥200 cells/mL (cells/mL)	60 (89.6)	30 (90.9)	90 (90.0)	0.832
Median CD4 count (cells/mL)	490	418	410	0.033
Psychiatric conditions‖				
Bipolar disorder	12 (18.8)	4 (12.1)	16 (16.5)	0.457
Major depressive disorder	10 (15.6)	4 (12.1)	14 (14.4)	0.481
PTSD	5 (7.8)	3 (9.1)	8 (8.2)	0.536
Panic disorder	6 (9.2)	1 (3.1)	7 (7.2)	0.260
Psychotic disorder	9 (14.1)	2 (6.1)	11 (11.3)	0.325
Brief symptom index, depression	46 (78.0)	22 (68.8)	68 (74.7)	0.334
Alcohol use severity§				
Abstinent or low-risk drinking	2 (3.0)	0 (0.0)	2 (2.0)	0.174
Hazardous drinking	5 (7.5)	2 (6.0)	7 (7.0)	
Harmful drinking	0 (0.0)	4 (12.1)	4 (4.0)	
Dependent drinking	60 (89.6)	27 (81.8)	87 (87.0)	
Opioid dependence*	15 (22.4)	7 (21.2)	22 (22.0)	0.894
Mean substance use duration (yr)†				
Cannabis (SD)	6.63 (±9.550)	4.14 (±7.395)	5.81 (±8.937)	0.424
Cocaine (SD)	8.68 (±9.939)	8.34 (±10.495)	8.67 (±10.074)	0.747
Heroin (SD) (N = 99)	3.06 (±7.512)	2.68 (±6.763)	2.94 (±7.239)	0.890
Substance use disorder from M.I.N.I‡				
Cannabis use disorder (N = 77)	9 (18.8)	3 (10.3)	12 (15.6)	0.259
Cocaine use disorder (N = 89)	38 (63.3)	15 (51.7)	53 (59.6)	0.324
Opioid use disorder (N = 87)	11 (19.6)	3 (9.7)	14 (16.1)	0.361
XR-NTX injections received				
0–3	40 (59.7)	19 (57.6)	59 (59.0)	0.839
4–6	27 (40.3)	14 (42.4)	41 (41.0)	
Cumulative injections received				
6	10 (14.9)	6 (18.2)	16 (16.0)	0.061
5	19 (28.4)	8 (24.2)	27 (27.0)	
4	27 (40.3)	14 (42.4)	41 (41.0)	
3	38 (56.7)	15 (45.5)	53 (53.0)	
2	49 (73.1)	17 (51.2)	66 (66.0)	
1	61 (91.0)	24 (72.7)	85 (85.0)	
Reincarcerations				
0	43 (64)	23 (70)	66 (66)	0.857
1	14 (21)	6 (18)	20 (20)	
2 or more	10 (15)	4 (12)	14 (14)	

*Using rapid opioid dependence screen.
†Using the Addiction Severity Index.
‡Mini International Neuropsychiatric Interview (M.I.N.I.).
§AUDIT (Alcohol Use Disorders Identification Test).
PTSD, post-traumatic stress disorder.
‖Psychiatric Conditions: based upon MINI.

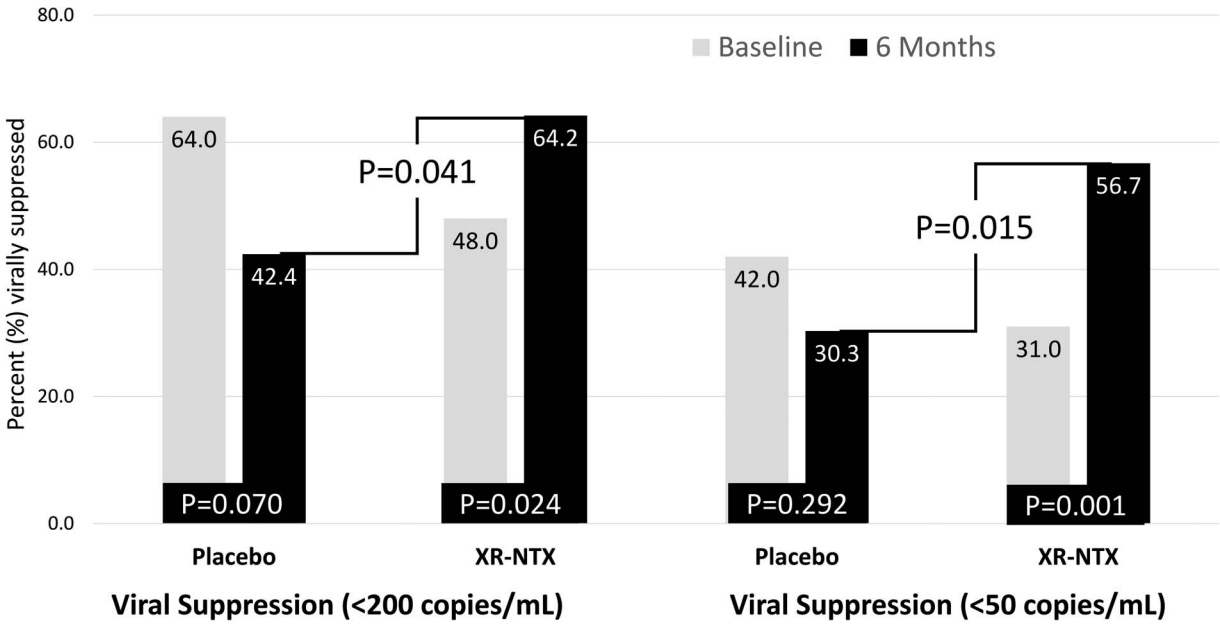

FIGURE 2. ITT analysis: comparison of VS levels at <200 and <50 copies per milliliter for participants receiving XR-NTX or placebo (N = 100).

Independent Predictors of Achieving VS

The independent correlates of achieving VS for the primary and secondary outcomes are provided in Table 2. For the primary outcome (VS <200 copies/mL), both allocation to receive XR-NTX [adjusted odds ratio (aOR): 2.68; 95% confidence interval = 1.01 to 7.09] and receipt of 3 or more injections (aOR: 3.26; 95% confidence interval = 1.26 to 8.47), irrespective of allocation, predicted VS at <200 copies per milliliter. Treatment allocation to XR-NTX, receiving 3 or more injections, decreasing levels of alcohol consumption using the alcohol improvement score, and white race–predicted maximal VS (<50 copies/mL). Additional multivariate analyses (not shown) compared (1) those in the XR-NTX group who received 3 or more injections compared with (2) the XR-NTX group who received 2 or fewer injections plus all placebo participants. A second multivariate model was created placing (1) all the placebo participants who had received 3 or more injections against (2) participants who received placebo with 2 injections and fewer and all XR-NTX participants. In the first model, the XR-NTX with 3 or more injections was significantly related to VS (<50 copies/mL level; $P \leq 0.05$), whereas the second model was not significantly different for high injection placebo participants. Of note, as shown in Table 2, concurrent opioid use disorder diagnosis was not found to be associated with explaining the difference in VS at either the <200 copies per milliliter ($P = 0.241$) or <50 copies per milliliter outcomes (0.645).

DISCUSSION

To the best of our knowledge, this is the first double-blind, placebo-controlled prospective randomized trial that examines whether an evidence-based pharmacotherapy to treat AUDs, XR-NTX, influences HIV viral suppression in PLH with AUDs who are transitioning to the community from prison or jail. The key findings from this trial, using an ITT analysis with the most conservative assessments for missing data, support that both VS (<200 copies/mL) and maximal VS (<50 copies/mL) are more likely to be achieved in PLH receiving XR-NTX than in those receiving placebo. These findings support the use of XR-NTX in PLH with AUDs who are transitioning through prisons and jails, an intervention that may improve linkage to HIV care and promote VS. This is especially important given that as few as 21% and 34% of PLH in Connecticut prisons and jails are linked to HIV care within 14 and 30 days after release to the community, respectively,[4] the minimal time needed to get their ART prescriptions refilled.

To support the ITT findings, multiple logistic regression analyses provide further support for XR-NTX, and provide additional insights and interpretation of the data. Key among them is that receiving more XR-NTX injections results in improved HIV VS levels. This suggests that better retention on the intervention (ie, monthly injections) was highly correlated with better engagement in HIV treatment and adherence to ART. This is consistent with findings that patients consistently engaged in care have higher levels of VS.[37,38] For maximal VS (<50 copies/mL), 2 additional factors contributed to the outcome—reductions in alcohol consumption and white race. Although considerable health disparities by race/ethnicity persist in the United States, especially among prisoners and PLH,[39–43] recent studies have not found that race/ethnicity predicts linkage to HIV care after release.[4] Reductions in alcohol consumption were significantly predictive of maximal VS (<50 copies/mL) and approached significance ($P = 0.068$) for the primary VS outcome (<200 copies/mL). One explanation for these findings may be that previous data suggest that the number

TABLE 2. Multivariate Models for VS at <200 and <50 copies/mL

VS at <200 copies/mL			VS at <50 copies/mL		
Variables	**aOR (95% CI)**	***P***	**Variables**	**aOR (95% CI)**	***P***
Intercept	0.21 (0.04 to 1.2)	0.075	Intercept	0.12 (0.02 to 0.84)	0.032
Placebo	Referent		**Placebo**	Referent	
XR-NTX	**2.68 (1.01 to 7.09)**	**0.047**	**XR-NTX**	**4.54 (1.43 to 14.43)**	**0.009**
Sex			Sex		
Female	Referent		Female	Referent	
Male	1.17 (0.37 to 3.71)	0.784	Male	0.47 (0.13 to 1.70)	0.250
Transgender	2.09 (0.073 to 52.71)	0.653	Transgender	0.00 (0.000 to inf)	0.990
Homelessness	0.97 (0.37 to 2.52)	0.953	Homelessness	0.45 (0.15 to 1.32)	0.148
Number of injections			**Number of injections**		
2 or less	Referent		2 or less	Referent	
3 or more	**3.26 (1.26 to 8.47)**	**0.010**	**3 or more**	**6.34 (2.08 to 19.29)**	**0.001**
Major depression	0.94 (0.24 to 3.59)	0.924	Major depression	0.77 (0.17 to 3.52)	0.735
Cocaine use disorder	0.91 (0.74 to 1.12)	0.378	Cocaine use disorder	0.83 (0.66 to 1.04)	0.112
Opioid use disorder	0.90 (0.76 to 1.07)	0.241	Opioid use disorder	0.96 (0.79 to 1.15)	0.645
Race/ethnicity			Race/ethnicity		
Black	Referent		Black	Referent	
Hispanic	0.87 (0.25 to 2.99)	0.821	Hispanic	3.65 (0.84 to 15.94)	0.085
White	1.56 (0.41 to 5.92)	0.514	**White**	**5.37 (1.08 to 26.72)**	**0.040**
Alcohol improvement score	1.32 (0.98 to 1.78)	0.068	**Alcohol improvement score**	**1.43 (1.03 to 1.98)**	**0.033**
AIC: 137			AIC: 121		

Bold represents statistically significant.

of days of alcohol consumption is associated with missing ART doses, not only on drinking days but also for 2 days after consumption.[44] Thus, maximal VS (<50 copies/mL) may have been better achieved because of better reductions in alcohol consumption, which in turn, reduced the number of days that patients missed taking their ART. Of note, most participants, almost 90%, were already receiving ART at the time of randomization (baseline or time of release), and there were no significant differences between the groups in those receiving ART. In addition, at 6 months, we found that no participants in the placebo group who were not on ART at baseline achieved VS at the <50 copies per milliliter level, whereas 14.3% of those in the XR-NTX who were not on ART at baseline group did achieve VS at that level at the 6-month time point, suggesting that possibly XR-NTX through reductions in alcohol use also may have assisted in initiating ART. Thus the combination of ART with reductions in alcohol use through the use of a medication (XR-NTX) to reduce alcohol relapse can improve the likelihood of maintaining or achieving HIV VS. Although the effect of XR-NTX on VS is likely moderated by reductions in alcohol consumption thereby improving adherence to ART, further research is needed to determine whether these beneficial effects are either fully or partially mediated by antiviral or anti-inflammatory mechanisms.[45–47]

Findings from this study have important implications for both individual and public health. Given the magnitude of PLH and AUDs who cycle through US prisons and jails annually the and paucity of associated prescribed medications to reduce alcohol relapse before, during, or after incarceration,[11] these findings suggest that XR-NTX may help PLH with AUDs remain in HIV care and achieve VS after release. XR-NTX, if implemented properly, may markedly improve postrelease HIV treatment outcomes. Whether or not these findings can be extended to others in confined settings such as hospitals or addiction treatment programs must be further examined. These findings do, however, have important implications for HIV treatment guidelines. Presently, the International Association of Physicians in AIDS Care (IAPAC) ART adherence guidelines[48] for criminal justice populations transitioning to the community recommend (1) directly administered antiretroviral treatment (DAART) for released prisoners at high risk of ART nonadherence and for people who inject drugs and (2) treatment of opioid use disorders with opioid agonist therapies such as methadone or buprenorphine.[48] Findings here should extend these recommendations to include the use of XR-NTX for treatment of AUDs in eligible PLH transitioning from incarceration. Improved adherence with XR-NTX will likely reduce the need for DAART in this population.

The 90-90-90 Joint United Nations Programme on HIV/AIDS (UNAIDS) strategy[49] in the United States has nearly achieved its first step—HIV diagnosis. Engagement in care and VS, however, fall considerably short. Because XR-NTX seems to exert its influence both on better treatment engagement/retention, but also on VS levels, it can potentially

improve both individual health and "treatment as prevention" ideals through higher VS levels. This is especially true in incarcerated PLH with AUDs who engage in high-risk HIV behaviors after release and in whom higher VS levels may be translated into reduced transmission.

One of the major impediments of adoption and implementation of an evidence-based treatment for prisoners involves cost. The strongest evidence to improve VS levels for transitioning incarcerated individuals is DAART,[50] yet it is rarely implemented because of limited community resources and elevated costs.[48] Although pharmacotherapy using methadone or buprenorphine for transitioning incarcerated individuals with HIV and opioid use disorder is recommended and is associated with low cost;[27] XR-NTX, however, remains costly. A recently published randomized placebo-controlled trial found that XR-NTX also led to improved VS for incarcerated individuals released to the community with HIV and opioid use disorders.[51] Findings from this trial provide the highest level of support for treating AUDs in transitioning incarcerated individuals with HIV and pending cost-effectiveness analyses; it should be adopted as voluntary treatment of AUDs as part of the US response to controlling the HIV pandemic.

Despite the many new and important findings presented here, some limitations remain, including the sample size and lack of generalizability to other communities. Poor retention in clinical care, including missing follow-up data from research studies after release from criminal justice settings, is common.[6,10] In this study, missing follow-up data were low (13%), but the MCAR analysis allowed us to use the most conservative assumption for comparing VS with missing observations for HIV-1 RNA levels being treated as not achieving VS. This limitation, however, is typically what is considered in real-world treatment settings of PLH where the association between poor retention, particularly missed visits, and poorer biological outcomes evidenced by virological failure and mortality is well established in the literature.[37,38] Using a missing value as "failure" to achieve VS is the most conservative strategy for not achieving or maintaining VS. Despite some missingness of viral load data and the relatively small sample size, the findings remain robust even controlling for other factors. Moreover, although including persons with mental illness and polysubstance use likely contributed to elevated attrition levels as seen in this study,[16,18] these results are more reflective of the real-world effectiveness of XR-NTX as a community-based treatment.

CONCLUSIONS

Monthly administered XR-NTX is an effective strategy to reduce alcohol consumption in PLH with AUDs transitioning to the community from prisons and jails. This study extends the benefits of XR-NTX as a treatment for AUDs and supports the additional benefit it has on improving HIV treatment outcomes in combination with ART in this population, specifically the achievement and maintenance of VS and maximal VS, the cornerstone of individual and public health for PLH. This study is the first to demonstrate the multifaceted benefits of XR-NTX in this vulnerable population of incarcerated persons with HIV and AUDs and adds to the important recent findings of XR-NTX improving VS among incarcerated persons with HIV and opioid use disorder.[51] Newer longer-acting naltrexone preparations, including implantable naltrexone that lasts for 3–6 months, might overcome challenges with returning for monthly injections. Also, although the cost of XR-NTX remains high, one must balance the costs with the societal benefits. Real-world implementation studies are needed to examine its effectiveness. Future work should evaluate cost-effectiveness of XR-NTX in incarcerated individuals transitioning to the community as well as in other community settings where HIV and AUDs are highly prevalent to assess the generalizability of this strategy to improve VS and further, to examine its impact on treatment as prevention efforts.

REFERENCES

1. Dolan K, Wirtz AL, Moazen B, et al. Global burden of HIV, viral hepatitis, and tuberculosis in prisoners and detainees. *Lancet.* 2016;388:1089–1102.
2. Spaulding AC, Seals RM, Page MJ, et al. HIV/AIDS among inmates of and releases from US correctional facilities, 2006: declining share of epidemic but persistent public health opportunity. *PLoS One.* 2009;4:e7558.
3. Meyer JP, Cepeda J, Wu J, et al. Optimization of human immunodeficiency virus treatment during incarceration: viral suppression at the prison gate. *JAMA Intern Med.* 2014;174:721–729.
4. Loeliger KB, Altice FL, Desai MM, et al. Predictors of linkage to HIV care and viral suppression after release from jails and prisons: a retrospective cohort study. *Lancet HIV.* 2018;5:e96–e106.
5. Krishnan A, Wickersham JA, Chitsaz E, et al. Post-release substance abuse outcomes among HIV-infected jail detainees: results from a multisite study. *AIDS Behav.* 2013;17(suppl 2):S171–S180.
6. Zelenev A, Marcus R, Kopelev A, et al. Patterns of homelessness and implications for HIV health after release from jail. *AIDS Behav.* 2013;17(suppl 2):S181–S194.
7. Merrall EL, Kariminia A, Binswanger IA, et al. Meta-analysis of drug-related deaths soon after release from prison. *Addiction.* 2010;105:1545–1554.
8. Meyer JP, Cepeda J, Springer SA, et al. HIV in people reincarcerated in Connecticut prisons and jails: an observational cohort study. *Lancet HIV.* 2014;1:e77–e84.
9. Springer SA, Spaulding AC, Meyer JP, et al. Public health implications for adequate transitional care for HIV-infected prisoners: five essential components. *Clin Infect Dis.* 2011;53:469–479.
10. Springer SA, Pesanti E, Hodges J, et al. Effectiveness of antiretroviral therapy among HIV-infected prisoners: reincarceration and the lack of sustained benefit after release to the community. *Clin Infect Dis.* 2004;38:1754–1760.
11. Springer SA, Azar MM, Altice FL. HIV, alcohol dependence, and the criminal justice system: a review and call for evidence-based treatment for released prisoners. *Am J Drug Alcohol Abuse.* 2011;37:12–21.
12. Fazel S, Yoon IA, Hayes AJ. Substance use disorders in prisoners: an updated systematic review and meta-regression analysis in recently incarcerated men and women. *Addiction.* 2017;112:1725–1739.
13. Azar MM, Springer SA, Meyer JP, et al. A systematic review of the impact of alcohol use disorders on HIV treatment outcomes, adherence to antiretroviral therapy and health care utilization. *Drug Alcohol Depend.* 2010;112:178–193.
14. Oser CB, Knudsen HK, Staton-Tindall M, et al. Organizational-level correlates of the provision of detoxification services and medication-based treatments for substance abuse in correctional institutions. *Drug Alcohol Depend.* 2009;103(suppl 1):S73–S81.
15. Garbutt JC, Kranzler HR, O'Malley SS, et al. Efficacy and tolerability of long-acting injectable naltrexone for alcohol dependence: a randomized controlled trial. *JAMA.* 2005;293:1617–1625.
16. Springer SA, Di Paola A, Azar MM, et al. Extended-release naltrexone reduces alcohol consumption among released prisoners with HIV disease

as they transition to the community. *Drug Alcohol Depend.* 2017;174: 158–170.
17. Springer SA, Altice FL, Herme M, et al. Design and methods of a double blind randomized placebo-controlled trial of extended-release naltrexone for alcohol dependent and hazardous drinking prisoners with HIV who are transitioning to the community. *Contemp Clin Trials.* 2014;37:209–218.
18. Springer SA, Brown SE, Di Paola A, et al. Correlates of retention on extended-release naltrexone among persons living with HIV infection transitioning to the community from the criminal justice system. *Drug Alcohol Depend.* 2015;157:158–165.
19. Vagenas P, Di Paola A, Herme M, et al. An evaluation of hepatic enzyme elevations among HIV-infected released prisoners enrolled in two randomized placebo-controlled trials of extended release naltrexone. *J Subst Abuse Treat.* 2014;47:35–40.
20. Babor TF, Higgins-Biddle JC, Saunders JB, et al. *The Alcohol Use Disorders Identification Test (AUDIT)*. Geneva, Switzerland: World Health Organization; 2001.
21. Sheehan D, Lecrubier Y, Harnett-Sheehan K, et al. Reliability and validity of the MINI International Neuropsychiatric Interview (M.I.N.I.): according to the SCID-P. *Eur Psychiatry.* 1997;12:232–241.
22. Saunders JB, Aasland OG, Babor TF, et al. Development of the Alcohol Use Disorders Identification Test (AUDIT): WHO collaborative project on early detection of persons with harmful alcohol consumption–II. *Addiction.* 1993;88:791–804.
23. Derogatis LR. *Brief Symptom Inventory*. Baltimore, MD; Clinical Psychometric Research; 1975.
24. Sobell LC, Sobell MB. *Alcohol Timeline Followback (TLFB). Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Association; 2000:477–479.
25. Sobell L, Sobell M. Timeline follow-back. In: Litten R, Allen J, eds. *Measuring Alcohol Consumption: Psychosocial and Biological Methods*: Humana Press; 1992:41–72.
26. Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1- Infected Adults and Adolescents*. Washington, DC: Services DoHaH; 2015.
27. Springer SA, Qiu J, Saber-Tehrani AS, et al. Retention on buprenorphine is associated with high levels of maximal viral suppression among HIV-infected opioid dependent released prisoners. *PLoS One.* 2012;7:e38335.
28. Altice FL, Bruce RD, Lucas GM, et al. HIV treatment outcomes among HIV-infected, opioid-dependent patients receiving buprenorphine/naloxone treatment within HIV clinical care settings: results from a multisite study. *J Acquir Immune Defic Syndr.* 2011;56(suppl 1):S22–S32.
29. Saber-Tehrani AS, Springer SA, Qiu J, et al. Rationale, study design and sample characteristics of a randomized controlled trial of directly administered antiretroviral therapy for HIV-infected prisoners transitioning to the community—a potential conduit to improved HIV treatment outcomes. *Contemp Clin Trials.* 2012;33:436–444.
30. Dumville JC, Hahn S, Miles JN, et al. The use of unequal randomisation ratios in clinical trials: a review. *Contemp Clin Trials.* 2006;27:1–12.
31. Altice F, Tehrani A, Qiu J, et al. Directly administered antiretroviral therapy (DAART) is superior to self-administered therapy (SAT) among released HIV+ prisoners: results from a randomized controlled trial. 18th Conference on Retroviruses and Opportunistic Infections; 2011; Boston, MA. Abstract K-131.
32. Little RJA. A test of missing completely at random for multivariate data with missing values. *J Am Stat Assoc.* 1988;83:1198–1202.
33. *R Package for Baylor University Educational Psychology Quantitative Courses. R Package Version 0.5 [Computer Program]*. Waco, TX: Baylor University; 2012.
34. Smuk M, Carpenter JR, Morris TP. Erratum to: what impact do assumptions about missing data have on conclusions? a practical sensitivity analysis for a cancer survival registry. *BMC Med Res Methodol.* 2017;17:51.
35. Smuk M, Carpenter JR, Morris TP. What impact do assumptions about missing data have on conclusions? A practical sensitivity analysis for a cancer survival registry. *BMC Med Res Methodol.* 2017;17:21.
36. The AVANTI Steering Committee. Analysis of HIV-1 clinical trials: statistical magic? The AVANTI Steering Committee. *Lancet.* 1999;353: 2061–2064.
37. Zinski A, Westfall AO, Gardner LI, et al. The contribution of missed clinic visits to disparities in HIV viral load outcomes. *Am J Public Health.* 2015;105:2068–2075.
38. Horberg MA, Hurley LB, Silverberg MJ, et al. Missed office visits and risk of mortality among HIV-infected subjects in a large healthcare system in the United States. *AIDS Patient Care STDS.* 2013;27:442–449.
39. Stein MS, Spaulding AC, Cunningham M, et al. HIV-positive and in jail: race, risk factors, and prior access to care. *AIDS Behav.* 2013;17(suppl 2): S108–S117.
40. Barskey AE, Babu AS, Hernandez A, et al. Patterns and trends of newly diagnosed HIV infections among adults and adolescents in correctional and noncorrectional facilities, United States, 2008–2011. *Am J Public Health.* 2016;106:103–109.
41. Shrage L. African Americans, HIV, and mass incarceration. *Lancet.* 2016;388:e2–e3.
42. Abram KM, Stokes ML, Welty LJ, et al. Disparities in HIV/AIDS risk behaviors after youth leave detention: a 14-year longitudinal study. *Pediatrics.* 2017;139.
43. Vagenas P, Zelenev A, Altice FL, et al. HIV-infected men who have sex with men, before and after release from jail: the impact of age and race, results from a multi-site study. *AIDS Care.* 2016;28:22–31.
44. Braithwaite RS, McGinnis KA, Conigliaro J, et al. A temporal and dose-response association between alcohol consumption and medication adherence among veterans in care. *Alcohol Clin Exp Res.* 2005;29: 1190–1197.
45. Gekker G, Lokensgard JR, Peterson PK. Naltrexone potentiates anti-HIV-1 activity of antiretroviral drugs in CD4+ lymphocyte cultures. *Drug Alcohol Depend.* 2001;64:257–263.
46. Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol.* 2014;33:451–459.
47. Lie M, van der Giessen J, Fuhler GM, et al. Low dose naltrexone for induction of remission in inflammatory bowel disease patients. *J Transl Med.* 2018;16:55.
48. Thompson MA, Mugavero MJ, Amico KR, et al. Guidelines for improving entry into and retention in care and antiretroviral adherence for persons with HIV: evidence-based recommendations from an International Association of Physicians in AIDS Care panel. *Ann Intern Med.* 2012;156:817–833, W-284, W-285, W-286, W-287, W-288, W-289, W-290, W-291, W-292, W-293, W-294.
49. Joint United Nations Program on HIV/AIDS. *90-90-90: An Ambitious Treatment Target to Help End the AIDS Epidemic*. Geneva, Switzerland: United Nations; 2014. Available at: http://www.unaids.org/en/resources/documents/2017/90-90-90.
50. Altice FL, Maru DS, Bruce RD, et al. Superiority of directly administered antiretroviral therapy over self-administered therapy among HIV-infected drug users: a prospective, randomized, controlled trial. *Clin Infect Dis.* 2007;45:770–778.
51. Springer SA, Di Paola A, Azar M, et al. 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. *J Acquir Immune Defic Syndr.* 2018;78:43–53.