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Extended-release naltrexone reduces alcohol consumption among released prisoners with HIV disease as they transition to the community

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ABSTRACT

Background: Alcohol use disorders (AUDs) are highly prevalent among persons living with HIV (PLH) within the criminal justice system (CJS). Extended-release naltrexone (XR-NTX) has not been previously evaluated among CJS-involved PLH with AUDs.
Methods: A randomized, double-blind, placebo-controlled trial was conducted among 100 HIV+ prisoners with AUDs. Participants were randomized 2:1 to receive 6 monthly injections of XR-NTX or placebo starting one week prior to release. Using multiple imputation strategies for data missing completely at random, data were analyzed for the 6-month post-incarceration period. Main outcomes included: time to first heavy drinking day; number of standardized drinks/drinking day; percent of heavy drinking days; pre- to post-incarceration change in average drinks/day; total number of drinking days; and a composite alcohol improvement score comprised of all 5 parameters.
Results: There was no statistically significant difference overall between treatment arms for time-to-heavy-drinking day. However, participants aged 20–29 years who received XR-NTX had a longer time to first heavy drinking day compared to the placebo group (24.1 vs. 9.5 days; $p < 0.001$). There were no statistically significant differences between groups for other individual drinking outcomes. A sub-analysis, however, found participants who received ≥4 XR-NTX were more likely ($p < 0.005$) to have improved composite alcohol scores than the placebo group. Post-hoc power analysis revealed that despite the study being powered for HIV outcomes, sufficient power (0.94) was available to distinguish the observed differences.
Conclusions: Among CJS-involved PLH with AUDs transitioning to the community, XR-NTX lengthens the time to heavy drinking day for younger persons; reduces alcohol consumption when using a composite alcohol consumption score; and is not associated with any serious adverse events.
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1. Introduction

Globally, the U.S. has the highest incarceration rate with over 700 people incarcerated per 100,000 population (Walmsley, 2014). People living with HIV (PLH) and substance use disorders, especially alcohol use disorders (AUDs), are concentrated in criminal justice settings (CJS). HIV seroprevalence in prisoners is 1.5%, 3-fold greater than among the general U.S. population (Maruschak, 2012), while 40%–60% of prisoners have AUDs, or 8-fold greater than the general population (Mumola, 1999).

In community settings, alcohol use negatively impacts HIV treatment outcomes for PLH (Vagenas et al., 2015; Azar et al., 2010) at all alcohol consumption levels, especially heavy drinking which is associated with HIV medication treatment interrup-

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tions (Conen et al., 2013), and increases mortality from direct liver injury or disruptions along the HIV continuum of care including suboptimal antiretroviral therapy (ART) adherence, ultimately leading to loss of HIV viral suppression (Azar et al., 2010; Justice et al., 2016; Palepu et al., 2004; Palepu et al., 2003; Springer et al., 2011a). While studies demonstrate that effectively treating other substance use disorders avoids such outcomes, the impact of treating AUDs on HIV treatment outcomes is unknown.

Naltrexone (NTX), an FDA-approved and evidence-based pharmacotherapy used to treat AUDs, acts as a competitive antagonist at the *mu* opioid receptor (Anton et al., 2006; Garbutt et al., 2005; Littleton and Zieglgansberger, 2003; O'Malley et al., 2007) and is commercially available in both oral and injectable extended-release (XR-NTX) formulations (Anton et al., 2006; Garbutt et al., 2005). While both preparations effectively lengthen the time to first heavy drinking day among individuals with AUDs in community settings, once-monthly XR-NTX has been proposed to have an adherence advantage over the daily oral formulation (Anton et al., 2006; Kranzler et al., 2008; O'Malley et al., 2007). The extent to which XR-NTX reduces alcohol consumption in PLH, however, is unknown and it is crucial to understand how such pharmacotherapies may improve HIV treatment outcomes.

To date, no randomized controlled trials of XR-NTX have specifically included PLH or prisoners with AUDs. For PLH, particularly those being released from incarceration, XR-NTX has the potential to lengthen the time to first heavy drinking day after release to the community and, therefore, potentially lead to increased stability, linkage to and retention in care, greater ART adherence and long-term HIV viral suppression (Springer et al., 2011a), the ultimate goal of the HIV treatment cascade (Vagenas et al., 2015). It is important to establish whether XR-NTX will have an impact on alcohol relapse in this population and further examine if this has an influence on HIV treatment outcomes given that the U.S. CJS does not routinely provide pharmacotherapies to prevent relapse to AUDs after release to the community (Chandler et al., 2009; Springer et al., 2011b; Taxman et al., 2007).

This current study employs a randomized placebo-controlled design of XR-NTX among incarcerated PLH with AUDs as they transition to the community to evaluate the effect on alcohol consumption post-release with the overall goal of assessing impact on HIV viral suppression. Here, we present results of the alcohol-related analyses.

2. Methods

The study protocol and methods have previously been described extensively (Springer et al., 2014), along with preliminary safety (Vagenas et al., 2014) and early post-release retention data (Springer et al., 2015). Briefly, Project INSPIRE is a prospective, double-blinded randomized, placebo-controlled trial of XR-NTX among incarcerated PLH with AUDs who were transitioning to the community from September 2010 and February 2015. The study hypothesis for the parent study is whether XR-NTX effectively reduces alcohol consumption sufficiently to further influence HIV treatment outcomes proximally on the HIV continuum of care including ART adherence and distally as HIV viral suppression (Springer et al., 2014). Therefore, the primary outcome for this study is whether HIV viral suppression rates are higher in PLH treated with XR-NTX compared to placebo at 6 months post-release. In this analysis, we aimed to determine if XR-NTX improved alcohol consumption parameters (our secondary outcomes) among PLH as compared to placebo upon release to the community.

2.1. Recruitment

Recruitment of participants was conducted within the Connecticut Department of Correction (CTDOC) and from a community-based organization that initiates transitional case management 90 days prior to release. Due to uncertainty in release date, PLH either within 90 days of release from CJS or 30 days post-release were screened for hazardous drinking. Screening tools included NIAAA's single AUD screening question (≥4 drinks daily for women or ≥5 drinks daily for men) (National Institute on Alcohol Abuse and Alcoholism, 2005) or having met criteria for having an AUD using the Alcohol Use Disorders Identification Test (AUDIT) (Babor et al., 2001). Individuals who screened positive were further referred for study inclusion and exclusion assessments. Inclusion criteria included: 1) documented HIV-infection; 2) transitioning to greater New Haven or Hartford metropolitan areas in Connecticut; 3) met criteria for alcohol abuse or dependence using the Mini International Neuropsychiatric Interview (M.I.N.I.) (Amorim et al., 1998; Lecrubier et al., 1997; Sheehan et al., 1997) or hazardous drinking using AUDIT (score ≥4 for women and ≥8 for men) (Barbor, 2001; National Institute on Alcohol Abuse and Alcoholism, 2005; Saunders et al., 1993); 4) able to provide informed consent; 5) speak English or Spanish; and 6) being ≥18 years. Exclusion criteria included: 1) concurrent prescription of opioid pain medications or expressing a medical indication for them; 2) having grade 3 or higher aspartate aminotransferase (AST) or alanine aminotransferase (ALT) elevations (>5 x upper limit of normal); 3) evidence of Child's Pugh Class C cirrhosis; 4) enrolled in another pharmacological or ART adherence research study; or 5) breastfeeding, pregnant or unwilling to use contraception for women. Prisoners who were deemed eligible and who expressed interest in the study underwent verbal and written consent. The consent process was repeated after release from prison to prevent real or perceived coercion.

2.2. Ethical oversight

All study procedures were reviewed and approved by the Institutional Review Board at Yale University and the CTDOC Research Advisory Committee and registered at www.clinicaltrials.gov (NCT01077310). This trial involved prisoners with alcohol and substance use disorders, thus additional protections were afforded by the Office of Human Research Protections at the Department of Health and Human Services and a Certificate of Confidentiality was obtained from the National Institutes of Health.

2.3. Randomization

Participants were randomly assigned receiving, identically packaged, 380 mg of XR-NTX (Vivitrol®) or placebo (provided by Alkermes, Inc), administered intramuscularly every 28 days for six months in a 2:1 ratio of XR-NTX: placebo. XR-NTX patients were oversampled to measure potential adverse side effects. A covariate-adapted randomization was performed using stratified randomization blocks and included the following covariates: city of return (Greater Hartford vs. Greater New Haven) and being prescribed ART.

2.4. Study measures

Alcohol consumption variables used in this analysis were primarily derived from the Timeline Followback (TLFB) (Sobell and Sobell, 1992, 2000) and assessed self-reported daily totals of standard units of drink 90 days prior to incarceration, the last 30 days of incarceration, and monthly throughout the study period. Alcohol craving was assessed using a monthly-administered 10-point