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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

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ABSTRACT

Background: HIV-infected prisoners have a high prevalence of alcohol use disorders and commonly relapse to alcohol soon after release to the community which is linked to high morbidity, poor antiretroviral therapy (ART) adherence and increased sexual risk-taking behaviors. Extended-release naltrexone (XR-NTX) effectively reduces relapse to alcohol in alcohol dependent persons, yet it remains unexamined among criminal justice system (CJS) populations transitioning to the community.

Methods: A randomized double-blind, placebo-controlled trial of XR-NTX to improve HIV treatment outcomes via reducing relapse to alcohol use after prison release for HIV-infected hazardous drinking and alcohol dependent prisoners is discussed.

Results: Acceptability of study participation is high with 86% of those referred who met eligibility criteria and 85% of those who were able to receive injections prior to release accepted injections, yet important implementation issues are identified and addressed during the study and are discussed in this paper.

Conclusion: Medication-assisted therapies for prevention of relapse to alcohol use for CJS populations transitioning to the community, especially for HIV-infected patients, are urgently needed in order to reduce alcohol relapse after release and improve HIV treatment outcomes and contribute to improved individual and public health.

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1. Introduction

Incarceration in the United States has become epidemic with 1 in every 100 Americans currently behind bars [1]. Compared to the general population, the U.S. criminal justice system (CJS) disproportionately houses individuals with significant medical and substance use disorders (SUDs); specifically, the prevalence for HIV/AIDS is 3-4-fold [2] and Hepatitis C (HCV) is 13-fold higher than that in surrounding communities [1]. Similarly, it is estimated that the prevalence of alcohol dependence and problematic drinking is 40–60% among prisoners [3]. Alcohol use negatively impacts the health outcomes for individuals infected with HIV, HCV or both [4,5].

Abbreviations: CJS, criminal justice system; SUDs, substance use disorders; NTX, naltrexone; XR-NTX, extended-release naltrexone; RCT, randomized controlled trial; PLWHA, people living with HIV/AIDS; CTDOC, Connecticut Department of Correction; IRB, Internal Review Board; IDCN, infectious disease control nurse; ROI, release of information; RA, Research Assistant; MINI, Mini International Neuropsychiatric Interview; AUDIT, Alcohol Use Disorders Identification Test; SAFTEE, Systemic Assessment for Treatment Emergent Effects Intervention; CASI, computer-assisted survey; YIDS, Yale Investigational Drug Service; PEth, phosphatidylethanol; CR, Clinician Researcher; MM, medical management; TLFB, timeline follow-back; CMHC, Correctional Managed Health Care.

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Similar to the case for infectious diseases, prisoners transitioning to the community are at high risk for negative consequences from SUDs, including overdose, death, relapse to alcohol and drug use, and discontinuity from chronic care — in particular, HIV care [5–10]. Naltrexone (NTX), an FDA-approved and evidence-based pharmacotherapy used to treat alcohol dependence, is available in both oral and the injectable extended-release-formulation (XR-NTX). In the most comprehensive, prospective, randomized controlled trial (RCT) of alcohol treatment pharmacotherapies, the COMBINE trial affirmed oral NTX as superior to acamprosate, including with or without adjunctive cognitive behavioral counseling [11,12]. XR-NTX also effectively prevents relapse and decreases heavy drinking in alcohol-dependent people without HIV [12–14]. Despite no head-to-head comparisons, monthly XR-NTX is perceived to have an adherence advantage over oral naltrexone [15]. Despite people living with HIV/AIDS (PLWHA) having a high prevalence of alcohol use disorders and that alcohol negatively impacts HIV treatment outcomes, no RCTs of available pharmacotherapies have focused on HIV-infected patients. Moreover, no trials directly examine the impact of alcohol treatment on HIV rather than on alcohol treatment outcomes with the hypothesis that reductions in alcohol use would improve HIV treatment outcomes — specifically retention in care, antiretroviral therapy (ART) adherence and HIV risk behaviors. Moreover, where HIV and alcohol are concentrated within the CJS, NTX in either formulation has not been empirically tested to assess its impact on HIV treatment and criminal justice outcomes. The current study specifically uses a placebo-controlled design to examine if XR-NTX administered before release reduces alcohol consumption and thereby improves ART adherence, viral suppression and reduction in HIV risk behaviors in HIV-infected patients — the only patients that can transmit HIV.

2. Methods

2.1. Study design

Project INSPIRE is a prospective, double-blind randomized, placebo-controlled trial of XR-NTX among HIV-infected prisoners with alcohol use disorders (alcohol dependence or hazardous drinking) who are transitioning to the community. The study design is depicted in Fig. 1.

2.2. Ethical oversight

All procedures were reviewed and approved by Institutional Review Boards (IRB) at Yale University and Connecticut Department of Correction (CTDOC) Research Advisory Committee and it was registered at www.clinicaltrials.gov (NCT10177310). Because the trial 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 a Certificate of Confidentiality was obtained from the National Institutes of Health (NIH).

2.3. Research goals

Because alcohol consumption, especially heavy drinking, negatively impacts numerous HIV treatment outcomes, including poor linkage and retention in care, ART adherence and viral suppression [16], the primary aim of this study is to examine if an evidence-based alcohol treatment pharmacotherapy (XR-NTX used here due to its adherence advantage and avoidance of pill burden) effectively improves HIV treatment outcomes. Thus for HIV-infected persons, we focused primarily on the most distal HIV treatment outcome, viral suppression (HIV-1 RNA < 400 copies/mL) 6-months post-release, since it is a surrogate for both retention in care and optimal ART adherence. Viral suppression, even in the absence of suboptimal condom use, also markedly reduces HIV transmission among heterosexual adults [17]. The secondary HIV treatment outcomes include maximal viral suppression (HIV-1 RNA < 50 copies/mL) and XR-NTX's effect on HIV risk behaviors. Other secondary outcomes include those related to alcohol relapse (time to alcohol relapse, percent days drinking or heavy drinking and alcohol craving), and XR-NTX toxicity when combined with ART, especially hepatotoxicity and injection site reactions.

2.4. Sample size and power calculations

We calculated the sample size needed to detect the difference in primary outcome with at least 80% power and a two-sided significance level of $p < 0.05$. We assumed 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

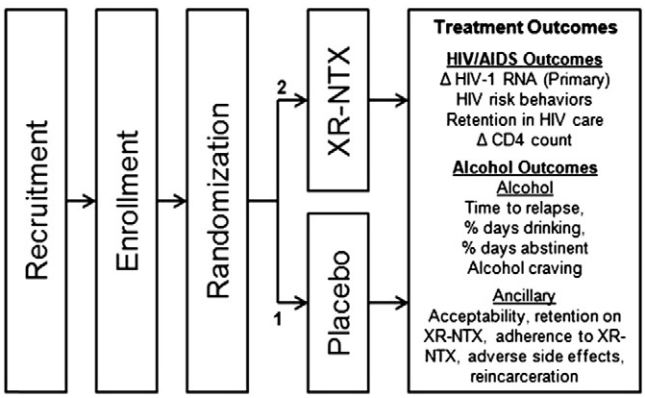

Fig. 1. Study design.