PHARMACOTHERAPY FOR ALCOHOL CONSUMPTION IN HIV-INFECTED WOMEN: A RANDOMIZED CLINICAL TRIAL

RESEARCH OBJECTIVES

HIV infection represents the 3rd leading cause of death among African American women, aged 25-44 years, in the United States (CDC 2008). In the United States, HIV infection is most prevalent in large urban areas and in rural areas across the Southeastern US (CDC, 2008a). The state of Florida currently ranks 3rd in terms of total HIV/AIDS cases in the United States, and in Miami-Dade County, 22,873 people are estimated to be living with HIV (CDC 2008, Florida DOH 2008). Further, approximately 10% to 20% of U.S. women with HIV infection consume alcohol at levels associated with non-adherence to medications, risky sexual behavior, and increased disease progression (Cook 2009). However, there are no data on the effectiveness of pharmacologic treatment for hazardous drinking in women seen in HIV clinic settings.

The University of Florida’s research team would like to analyze the de-identified data collected from a clinical trial study in Miami, to evaluate whether an intervention that involves the medication naltrexone will reduce drinking and improve health outcomes in women with HIV infection and hazardous drinking patterns. Our central hypotheses are that, compared to women who receive placebo, women who receive naltrexone will have decreased rates of hazardous drinking, improved HIV medication adherence, less rapid disease progression, and reduced sexual risk behavior. The study design is a double-blind, placebo-controlled randomized trial involving 240 HIV-infected women with hazardous drinking. Women will be recruited from HIV clinics, neighborhoods and referrals in Miami, Florida. Eligible women will be randomized to receive a daily pill containing naltrexone (50mg) or identical-appearing placebo for four months. All participants will receive encouragement and feedback related to their drinking regardless of medication assignment. The study endpoints will be assessed at two, four and seven months after enrollment. The proposed work is innovative because pharmacologic treatment for alcohol has not been evaluated in HIV-infected women. If our hypotheses are confirmed, the study findings would transform the approach to hazardous drinking within clinics serving HIV-infected women.

This study protocol was designed as part of a pilot study funded by NIH in 2009 to assess the acceptability and feasibility of conducting this clinical trial. As an NIH-funded study, the protocol received careful scrutiny from three IRBs (University of Florida, Rush University in Chicago, IL, and Georgetown University in Washington DC), an NIH scientific advisory committee, and a medical monitor at the National Institute of Allergy and Infectious Diseases. In preliminary work to date, we have recruited 17 women with HIV infection and hazardous drinking in Chicago, IL, Washington DC, and Jacksonville Florida. The preliminary findings showed that women seemed interested in participating in the study, that they could reduce their drinking after enrollment, and that no serious adverse events have occurred that are related to study participation.

With this current protocol, UF received a new NIH award to extend the study and recruit up to 240 women with HIV infection from clinics in South Florida.
The principal investigator of this study is Robert L. Cook, MD, MPH, who is in the Department of Epidemiology in the College of Public Health and Health Professions, and the College of Medicine at the University of Florida [UF], Gainesville. The majority of the participants will be recruited and enrolled at clinical facilities managed by the University of Miami [UM] and the neighboring communities. We will use informed consent templates based on the UM format. We will seek approval at the Jackson Memorial Hospital IRB regarding the review of patient records and the appropriate consent and procedures for participants receiving care in their clinics. Additional investigators are involved from Florida International University [FIU]. Therefore, the protocol will also be reviewed at FIU and UF as well as Jackson Memorial Hospital.

We will recruit women with HIV infection who drink alcohol in an "at-risk" range (but are not necessarily alcohol dependent). Women will be recruited using brochures, word of mouth, and referrals from both clinical and community-based settings in Dade County. Women in Miami/Dade will present to the University of Miami Clinical Research Center for informed consent, baseline data collection, and follow-up visits. The study data include blood samples, urine/drug samples, and questionnaires. We will ask women for permission to examine their clinical records through the UM computer system. Women will be randomized to receive naltrexone or placebo and take one pill daily for 4 months. Naltrexone has an indication for this purpose, so it is not an "experimental drug". Women will be followed for 7 months; the primary outcomes are the amount of alcohol consumption and several HIV-related health outcomes. A Data Safety and Monitoring Board will oversee the trial.

**DATA ANALYSIS**

Data analysis will be conducted at UF in Gainesville, FL. The study database will include information from study questionnaires and blood test results. Data will be linked by subject ID numbers. The 4-month assessment will represent the primary study outcome assessment point, and our primary analyses are based on comparisons at this time point. A 2-month and a 7-month comparison is also planned. This will allow us to determine whether the benefits of alcohol treatment (if any) occur early or if they persist after the treatment program is stopped.

We will conduct descriptive analyses to compare demographic and clinical characteristics of women according to their randomized group.

The primary statistical outcome for the trial is alcohol consumption (weekly quantity/frequency, number of binge episodes per month, number of alcohol-related problems). Additional outcome measures will include medication adherence (continuous measure), risky sexual behaviors (number of unprotected sexual events with a partner who is sero-discordant or unknown HIV serostatus), and HIV clinical status (CD-4 count, HIV-viral-load). We will also assess the impact of the intervention on symptoms of depression and anxiety, other drug use, cognitive function, and health services use. Our primary analysis will simply compare outcomes based on whether the participant is in the naltrexone or the placebo group. We will also conduct sensitivity analyses that adjust for any factors that are unbalanced between the two treatment groups at baseline, to determine if such factors may be influencing the conclusions.
We will use the intent-to-treat (ITT) approach for the primary analysis, wherein participants will be analyzed as randomized, regardless of subsequent discontinuation of treatment or study dropout. We will also conduct a secondary, adherence-adjusted analysis after categorizing according to their adherence to the pharmacologic treatment. Finally, we will conduct additional subgroup analyses to evaluate the impact of the intervention among women who meet criteria for alcohol abuse or dependence at enrollment (based on baseline assessment).

**Additional analyses**

We will conduct an additional, secondary analysis to examine factors associated with adherence to naltrexone (and placebo) during the four months for which treatment is offered. For these analyses, we will measure adherence as the proportion of medications taken over the entire four-month follow-up period. Previous literature suggests an adherence rate of approximately 50% to 70%. We will use logistic regression to predict who is adherent versus who is not.

Predictor variables will include demographic characteristics (age, race), geographic setting, severity of alcohol consumption, use of other drugs, baseline mental health conditions, attitudes and beliefs about alcohol treatment, presence of liver disease, and severity of HIV infection. For each variable, we will report an unadjusted odds ratio as well as an adjusted (for the other variables) odds ratio to characterize its association with acceptance of treatment. Missing covariate data will be handled using multiple imputation, and in a sensitivity analysis we will instead use inverse weighting.