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Contingency management with stepped care for unhealthy alcohol use among individuals with HIV: Protocol for a randomized controlled trial

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HIGHLIGHTS

- People with HIV (PWH) often are ambivalent about engaging in treatment of unhealthy alcohol use.
- Contingency management holds promise for reducing unhealthy alcohol use among PWH.
- Stepped care strategies are important given lack of consistent response to alcohol treatments.

ABSTRACT

Background: Although unhealthy alcohol use is associated with increased morbidity and mortality among people with HIV (PWH), many are ambivalent about engaging in treatment and experience variable responses to treatment. We describe the rationale, aims, and study design for the **F**inancial **I**ncentives, **R**andomization, with **S**tepped **T**reatment (FIRST) Trial, a multi-site randomized controlled efficacy trial.

Methods: PWH in care recruited from clinics across the United States who reported unhealthy alcohol use, had a phosphatidylethanol (PEth) >20ng/mL, and were not engaged in formal alcohol treatment were randomized to integrated contingency management with stepped care versus treatment as usual. The intervention involved two steps; **Step 1**: Contingency management (n=5 sessions) with potential rewards based on 1) short-term abstinence; 2) longer-term abstinence; and 3) completion of healthy activities to promote progress in addressing alcohol consumption or conditions potentially impacted by alcohol; **Step 2**: Addiction physician management (n=6 sessions) plus motivational enhancement therapy (n=4 sessions). Participants' treatment was stepped up at week 12 if they lacked evidence of longer-term abstinence. Primary outcome was abstinence at week 24. Secondary outcomes included alcohol consumption (assessed by TLFB and PEth) and the Veterans Aging Cohort Study (VACS) Index 2.0 scores; exploratory outcomes included progress in addressing medical conditions potentially impacted by alcohol. Protocol adaptations due to the COVID-19 pandemic are described.

Conclusions: The *FIRST Trial* is anticipated to yield insights on the feasibility and preliminary efficacy of integrated contingency management with stepped care to address unhealthy alcohol use among PWH.

ClinicalTrials.gov identifier: NCT03089320

Key words: multicenter study; randomized controlled trial; algorithms; HIV; alcohol; contingency management; motivational enhancement therapy

1. Introduction

Unhealthy alcohol use, the spectrum of alcohol consumption typically defined as ranging from at-risk drinking to alcohol use disorder (AUD, **Table 1**)(1), is prevalent among people with HIV (PWH)(2-4) and a modifiable risk factor for morbidity and mortality(5, 6). Specifically, among PWH, consumption of alcohol exceeding an average of one drink per day is associated with a 30% increased risk of mortality with increasing risk observed with increasing levels of consumption(6). In addition, unhealthy alcohol use is associated with adverse effects on HIV-related outcomes and other medical conditions common among PWH (e.g., depression) and may interact with psychoactive medications frequently prescribed to PWH to cause harm (e.g., falls)(7, 8). Thus, in some patients, there is rationale to intervene even on lower levels of alcohol consumption (i.e., levels below the traditional "at-risk" threshold(9)).Clinical guidelines recommend behavioral treatments(10) and, for those with AUD, medication too(11). Informed by our research(12), guidelines also support integrated models of care that co-locate treatment for unhealthy alcohol use and HIV(11). PWH often are ambivalent about engaging in alcohol treatment and current treatments do not produce a consistent response (e.g., alcohol reduction)(12-16) even when co-located with HIV care.

Strategies that enhance patient motivation for treatment and that adapt to patients' treatment response are needed. Rooted in behavioral economics, contingency management (CM) provides individuals with rewards contingent upon achieving behaviors such as abstinence(17, 18). CM decreases substance use(19-23), including alcohol use(24, 25). It improves HIV treatment engagement, retention, and antiretroviral medication adherence among PWH(26, 27). To our knowledge, CM has not been used for unhealthy alcohol use in general medical settings(28) and specifically in HIV clinics nor been offered in the context of a stepped care model(29). Further, there is need for evaluation of the impact of alcohol interventions on clinically relevant health outcomes (e.g., depressive symptoms) that commonly occur among PWH and are impacted by alcohol use.

We conducted the ***F**inancial **I**ncentives, **R**andomization, with **S**tepped **T**reatment (FIRST) Trial* to examine the efficacy of CM with stepped care compared to treatment as usual (TAU) for unhealthy alcohol use on alcohol consumption and other health outcomes among PWH. We describe the rationale, aims, and study design of the *FIRST Trial* and modifications made in response to the COVID-19 pandemic(30, 31).

2. Methods

2.1. *Overall design*

The *FIRST Trial* enrolled PWH reporting unhealthy alcohol use with evidence of recent significant alcohol consumption, confirmed by phosphatidylethanol (PEth) >20ng/mL(32), who were not engaged in formal alcohol treatment. Upon completing consent for screening, potential participants were evaluated to determine whether they met eligibility criteria; those eligible, were invited to provide written informed consent. Enrolled participants were randomized 1:1 to integrated CM with stepped care versus TAU. Participants randomized to the intervention were invited to participate in a prize CM program(18) with three target behaviors (**Step 1**); if a participant did not have evidence of longer-term abstinence at week 12, their treatment was stepped up to Addiction Physician Management (APM) plus Motivational Enhancement Therapy (MET) (**Step 2**) (**Figure 1**). Participants randomized to TAU received a health handout and, if they met criteria for AUD, a referral to specialty care at the discretion of their HIV clinician. The primary outcome was abstinence at week 24. Secondary outcomes included alcohol consumption assessed (by self-report TLFB and PEth) and VACS Index 2.0 scores (a validated measure of morbidity and mortality based on routinely collected labs)(33); exploratory outcomes included progress by the patient in addressing medical conditions potentially impacted by alcohol. Modifications in response to COVID-19 pandemic are detailed below.

2.2. *Rationale for study design*

This study's design was based on several factors. First, CM is an evidence-based intervention that may enhance motivation among PWH to engage in treatment to reduce alcohol use and its consequences. Second, we have found that integrated and stepped care models to address unhealthy alcohol use in the context of HIV clinics are feasible and effective at promoting delivery of evidence-based treatment; this model is responsive to individuals' needs while minimizing demands on patients and maximizing resources(12-14). Third, PWH may be more sensitive to the effects of alcohol (34) and consumption of more than one drink per day increases mortality risk among PWH(6) making alcohol abstinence an appropriate goal. Fourth, PEth has features that make it a useful marker upon which to determine both entry criteria and contingent reinforcement(35). With good sensitivity and specificity for detecting abstinence, this biomarker reflects alcohol consumption over the prior ~21 days, a window that is potentially suitable for CM rewards schedule offered in HIV clinics where patient visits are infrequent(36, 37). Lastly, VACS Index 2.0 is a validated measure of morbidity and mortality based on routinely collected labs (including age, CD4 cell count, HIV RNA viral load, hemoglobin, FIB-4, estimated glomerular filtration rate, Hepatitis C virus, albumin, white blood cell count, and body mass index) that is responsive to changes in alcohol use(38, 39) and addiction treatment(40). Each 5-point increment is associated with a ~20% increase in 5-year mortality risk(41).

2.3. *Study aims and hypotheses*

The original primary aim of the *FIRST Trial* was to compare the efficacy of CM with stepped care (intervention condition) versus TAU (control condition) on alcohol abstinence measured by PEth (primary outcome) and self-report using TLFB. We hypothesized that the intervention would lead to a greater proportion of individuals with PEth-verified abstinence and fewer self-reported drinks per week by TLFB. The secondary aim was to compare the efficacy of the intervention versus TAU on the VACS Index 2.0; we hypothesized that the intervention would lead to a greater proportion of individuals who

experienced a 5-point decrease. The third exploratory aim was to examine the efficacy of the intervention versus TAU on measures including HIV viral suppression, tobacco abstinence, liver fibrosis (by FIB-4), undetectable hepatitis C virus, depressive symptoms, and receipt of psychoactive medications that may interact with alcohol among individuals with medical conditions impacted by alcohol.

2.4. *Study context, coordinating center, and institutional review*

Conducted in follow-up to the *STEP Trials*(12-14, 29, 42), the *FIRST Trial* was funded as part of the National Institute on Alcohol Abuse and Alcoholism (NIAAA) Consortiums for HIV/AIDS and Alcohol Research Translation (CHAART). The coordinating center for the *FIRST Trial* is located at Yale University, New Haven, CT and VA Connecticut Healthcare System, West Haven, CT. Yale Center for Analytic Sciences oversees data management, randomization procedures, monitoring, and analyses. Participant recruitment and enrollment was originally launched at Veterans Health Administration (VA)-based HIV clinics in Atlanta, GA; Bronx, NY; Manhattan/Brooklyn, NY; Dallas, TX; Houston, TX; Los Angeles, CA; and Washington, DC. In response to recruitment challenges, activities were expanded to the HIV Outpatient Program (HOP), an HIV clinic based in the Louisiana State University Health Sciences Center-affiliated University Medical Center New Orleans in New Orleans, LA. The study is registered at www.clinicaltrials.gov (Identifier: NCT03089320).

2.5. *Inclusion and exclusion criteria*

To be eligible, individuals had to meet each of the following criteria: 1) had a HIV diagnosis; 2) met criteria for unhealthy alcohol use (**Table 1**); 3) had evidence of recent significant alcohol consumption by PEth >20ng/mL, likely consistent with drinking on average at least one to four drinks per day(32, 43); and 4) were able to provide informed consent. Individuals were excluded if they met any of the following criteria: 1) expressed suicidal ideation or had an active psychiatric condition that affected their ability to provide informed consent or participate in counseling interventions; 2) were enrolled in formal

treatment for alcohol (i.e., excluding mutual help, e.g. Alcoholics Anonymous); 3) had a medical condition that would preclude completing or be of harm during the course of the study; 4) were a pregnant or nursing woman or woman who did not agree to use a reliable form of birth control; or 5) had a current diagnosis of or were in remission for a gambling disorder based on a positive screen to the item "Have you ever tried to stop or reduce gambling because it was causing you problems?" followed by >4 positive criteria on the modified National Opinion Research Center DSM Screening for Gambling Problems (NODS) given prize CM's use of probabilistic rewards(18).

2.6. *Recruitment and randomization*

Individuals were recruited for study participation with a multi-pronged approach, including: 1) direct recruitment with a pro-active, opt-out approach involving mailing of letters upon clinic director permission to individuals identified as potentially eligible and appropriate for study participation through electronic health record review and a follow-up phone call (unless the individual opted-out); 2) referral of patients by clinicians and/or health care provider staff to the study team directly and/or upon guidance by research staff; 3) Alcohol Use Disorder Identification Test-Consumption (AUDIT-C) screen(44) administered by research coordinators; and 4) self-referral based on recruitment flyers. Individuals who met entry criteria after electronic health record review and self-report were consented for PEth testing; individuals with a PEth >20ng/mL were asked to provide written informed consent and were invited to enroll in the trial.

Enrolled participants were randomized using a randomization procedure with stratification by site and unhealthy alcohol use category in a 1:1 fashion to CM with stepped care or TAU. Randomization schemes were implemented in the Research Electronic Data Capture (REDCap) web-based platform(45, 46) and treatment assignment was allocated by the system.

Randomized participants were reimbursed with $50 equivalent upon completing the baseline assessment and each of the follow-up assessments for a total possible compensation of $250. Participants randomized to CM with stepped care also had the potential to earn an average maximum of approximately $469 in prizes and $15 to off-set travel costs for each completed intervention visit. Completion of informed consent and enrollment in the trial was documented in the electronic health record to inform clinicians of their patients' study participation.

2.7. *Data collection protocol*

Assessments were collected by trained research coordinators (**Table 2**) at baseline, week 12, week 24, month 9, and month 12 to ascertain baseline characteristics, outcomes, and potentially moderating and mediating factors of the impact of the intervention on outcomes.

2.8. *Intervention overview*

2.8.1. Intervention overview

The intervention, CM with stepped care, began with CM (**Step 1**) over 12 weeks. Participants who did not have evidence of abstinence at week 12 had their treatment stepped up to receive APM plus MET (**Step 2**). The intervention strategy was designed to begin with lower intensity services and be intensified based on response at *a priori* criteria. Treatment duration of each step was informed by the existing literature and guided by our own experiences(29, 47). Intervention sessions were intended to be delivered in the context of the HIV clinic when possible. Participants could be referred for additional services as deemed indicated by their clinicians, study team interventionists, and other research staff. Interventionists were advised to document notes consistent with their usual practice in the electronic health record per local standards. Intervention materials, including the intervention manual, are available online(48).

2.8.2. Step 1: Contingency management (CM)

Consistent with standards in the field (18) and informed by prior work (24), CM included: 1) use of agreements between clinicians and participants to document target behaviors (e.g., alcohol abstinence) and how they would be verified; 2) objectively quantified behavioral outcomes (e.g., breathalyzer testing and PEth); 3) valued rewards; 4) escalating rewards consistent with progress toward goals; and 5) withholding rewards when target behaviors were not completed. Delivered by trained Social Workers and manual-guided, CM visits were designed to occur every 3 weeks over 12 weeks to correspond to the timeframe of abstinence detected by PEth and include a schedule that would be feasible for patients and clinicians in HIV clinics. Rewards were obtained using the prize CM model(18) in which participants make draws from a fishbowl containing prize slips of various values. In this application of prize CM, the fishbowl contained 100 prize slips with the following descriptors and values: 20 “Good Job” ($0); 64 “Medium” ($5), 15 “Large" ($25), and one “Jumbo” “$100.” For the VA sites, rewards were coupons that could be used to purchase items at retail stores, cafeterias, and coffee shops operated by the VA’s Canteen Service, while for the non-VA site, rewards were provided added to a debit card (i.e., Clincard).

This multi-target CM prize program was designed to reward 1) short-term abstinence (past 6 to 12 hours) verified by breath or saliva testing, 2) longer-term abstinence (past 21 days) verified by PEth, and 3) completion of activities (e.g., attendance at mutual help meeting; HCV treatment initiation) consistent with achieving progress in addressing alcohol use or medical conditions potentially impacted by alcohol use that were verified by objective evidence agreed upon in advance by the participant and interventionist (**Table 3**). The reward schedule was designed to reflect the effort required to complete the target behaviors (e.g., evidence of longer-term abstinence earned the highest number of draws while short-term abstinence earned the lowest number of draws). Adapted from prior protocols(49) and available online, the *FIRST Contingency Management Manual for Unhealthy Alcohol Use in HIV* provides additional details regarding intervention procedures, including the needs assessments to guide selection

of activities, a list of potential activities, suggested counseling scripts, and guidance for handling unexcused absences(48).

2.8.3. Step 2: Addiction Physician Management (APM) with Motivational Enhancement Therapy (MET)

Participants stepped up to Step 2 were offered additional support to achieve abstinence with Addiction Psychiatrist-delivered APM and Social Worker-delivered MET that were designed to be mutually reinforcing. Our intervention model included Addiction Physician management because: 1) the intervention was focused on patients with likely harm associated with unhealthy alcohol use (such as alcohol use with cirrhosis)(6); 2) HIV clinicians are less prepared to address unhealthy alcohol use(50); 3) our prior experiences support use a stepped care model involving Addiction Physician Management to address a range of alcohol use to promote delivery of evidence-based care to improve clinical outcomes,(12-14) and 4) Addiction Physicians can also address factors that might be contributing to unhealthy alcohol use (e.g., untreated depression) based on their clinical discretion. After an initial 45-minute evaluation session, the physicians followed participants weekly for 2 weeks, every 2 weeks for 4 weeks and then monthly; goals of these sessions are outlined in **Table 4**.

Medications are useful adjuncts to counseling in initiating abstinence and preventing return to alcohol use among participants with AUD. Physicians were advised to prioritize prescribing of a Food and Drug Administration (FDA)-approved medication for alcohol use disorder (MAUD; i.e., oral or injectable naltrexone, disulfiram, or acamprosate) over non-FDA approved medications with data to support their use for this indication (e.g., topiramate, gabapentin, baclofen); however, the ultimate decision to prescribe and the medication choice, dose, and duration were at the discretion of the addiction psychiatrist and participant. MAUD were provided through usual means via the VA or community-based pharmacy.

MET was provided over four sessions to coincide with the initial Addiction Psychiatrist visit. Informed by the ELM Brief Intervention Study(51) and previously adapted for PWH(29, 52). Social Workers employed motivational interviewing strategies and provided participants with a *Personal Feedback Report* and associated brochure(48) to evoke participants' motivation to remain in treatment and change their drinking behavior.

2.8.4. Criteria for stepping up

Consistent with tenets of stepped care designs, the intervention package included *a priori* intervals and criteria (drinking targets) that dictated the decision to increase the intensity of treatment (i.e., stepping up)(53) based on research and standards in the field. Participants who lacked evidence of abstinence were stepped up to Step 2.

2.8.5. Interventionists, training, and monitoring

CM and MET were designed to be delivered by front-line Social Workers, or Psychologists depending on staff availability, while APM was designed to be delivered by Addiction Psychiatrists. Training included an overall orientation to the trial, its goals, and study materials including study manuals. Prior to trial launch, interventionists were invited to an in-person full day training held at the coordinating center that included didactics and case-based materials. All interventionists were provided relevant study manuals and structured encounter forms to guide each visit. Digital recordings of the CM sessions and associated tracking forms that documented provision of the reward schedule, as well as digital recordings of the motivational enhancement therapy sessions, were reviewed for fidelity and discussed on monthly to bimonthly calls with interventionists and study investigators. A separate monthly to bimonthly call reviewed Addiction Psychiatrist experiences and prescribing of MAUD with study investigators.

2.9. *Treatment as Usual (TAU)*

In addition to standard care, which at the VA sites included mandatory routine screening for unhealthy alcohol use and electronic clinical reminder prompts for brief intervention, participants randomized to TAU received a health handout with information about alcohol treatment services embedded with general health information. Among participants who met criteria for AUD, HIV clinicians and/or site-PIs were informed of the AUD diagnosis, and referrals were made at the discretion of the clinician and participant to facilitate appropriate treatment services with medications for AUD and otherwise. Given that unhealthy alcohol use is inconsistently addressed outside of the research context in these settings(54), this control was selected to provide a "real world" comparison.

2.10. *Statistical Consideration*

2.10.1. Sample size calculations

The primary aim of the *FIRST Trial* was to determine if CM with stepped care for unhealthy alcohol use, compared to TAU, leads to a greater proportion of participants with alcohol abstinence. The primary outcome as originally designed was the proportion of participants with PEth <8ng/mL at 24 weeks (**Aim 1**). Data from *STEP Trials* participants randomized to TAU who had a PEth >20ng/mL, demonstrated 11% spontaneous abstinence as assessed using PEth <8ng/mL at 24 weeks(12-14). To detect an increase in abstinence of 15% difference (i.e., proportion demonstrating abstinence in CM with stepped care of 26%) with 80% power at a two-sided 0.05 significance level and two randomization stratification variables, a sample size of 139 per group was expected with a planned overall recruitment target of n=348 participants to account for up to 20% drop-out.

2.10.2. Statistical analyses

Descriptive statistics will be used to evaluate the balance in baseline characteristics by condition and the adequacy of the randomization procedures.

2.10.2.1. Primary and secondary alcohol consumption outcomes

A likelihood-based ignorable analysis using a generalized linear mixed model (GLMM) will be used to compare abstinence between groups (55, 56) given its flexibility in handling missing data. This analysis will make use of all available outcome data at each timepoint and assume that missing data occurs at random (i.e., not informative)(57). The inclusion of week 12, week 24, month 9, and month 12 outcome data in the model will assist in meeting this assumption. More specifically the mixed models will include fixed effects for intervention (CM with stepped care versus TAU, time (week 12, week 24, month 9, month 12), and the interaction of intervention with time. Additional fixed effects will be included for baseline covariates: unhealthy alcohol use category (at-risk drinking, medical condition impacted by alcohol, AUD), number of drinks per week, gender, VACS Index and study site. To account for heterogeneity in the participant groups, the interactions between intervention and stratification variables will be evaluated and included in the primary analysis at the $p<0.10$ significance level. Linear contrasts will be used to estimate intervention group differences and 95% confidence intervals at the primary 24-week outcome assessment. Similar contrasts will be performed at the other secondary follow-up times and supportive analyses examining the average and slope of change in abstinence rates across post-randomization time will be performed. Subgroup analyses will be performed to evaluate moderation of the intervention response by stratification variables. We will also use linear mixed effect models to compare continuous PEth and alcohol consumption using data from the TLFB as data allows. We will perform sensitivity analyses pattern-mixture models under missing not at random (MNAR) assumptions to examine the robustness of conclusions of the primary analysis to missing data.

2.10.2.2. Other secondary and exploratory outcomes

Secondary aims are to determine using if the VACS Index 2.0 score differs between participants randomized to receive CM with stepped care compared to those receiving TAU. The primary response will be defined as a 5-point improvement from baseline on the VACS index adjusting for baseline VACS Index Scores. As with the primary outcome, a GLMM will be used to compare this response. We will also

use a repeated measures mixed model analysis with continuous VACS index 2.0 as the outcome. As with the primary outcome, we will perform subgroup analyses to evaluate moderators as possible.

In exploratory analyses, we will evaluate the impact of the intervention among those with medical conditions on condition-specific outcomes such as HIV viral load, exhaled carbon monoxide or urine cotinine (for smoking cessation), FIB-4, detectable HCV virus, and depressive symptoms. In addition, we will assess whether use of psychoactive medications that interact with alcohol decrease given the underlying hypothesis that participants may experience improvements in symptoms (e.g., anxiety) with reductions in alcohol use(58). These analyses will focus on estimation rather than hypothesis testing and will be performed only in those identified with the specific medical condition at baseline. GLMMs will be used to describe these outcomes by treatment group and time. Treatment differences for continuous outcomes, odds ratios for dichotomous outcomes and rate ratios for count outcomes along with 95% CIs will be estimated.

2.10.3. Protection of participants

The *FIRST Trial* was approved by the Human Investigation Committees/Institutional Review Boards and the coordinating centers and each participating site. The study is HIPAAA compliant, and a Certificate of Confidentiality was automatically issued by NIAAA. The Data Safety and Monitoring Board reviewed study progress at approximately 6-month intervals to review study progress and implementation.

2.10.4. COVID-19 related modifications and current status of the FIRST Trial

The *FIRST Trial* opened to enrollment on January 5, 2018 and enrolled the last participant on March 1, 2022. Due to recruitment challenges, one site was closed prematurely on January 22, 2019 without enrolling any participants. Study implementation was then significantly disrupted due to the COVID-19 pandemic with complete pause of study activities during lock-down periods and need for subsequent modifications to minimize COVID-19 transmission and adaptation to evolving clinic flow and safety procedures (**Table 5**). A total of n=120 participants were recruited, 34% of the original target. For these

reasons, ultimate reporting of study findings will focus on feasibility, acceptability, and preliminary efficacy of CM with stepped care. To gain a deeper understanding of participant, interventionist, and research staff experiences with CM in the context of the *FIRST Trial*, we conducted a qualitative sub-study. Its findings will be reported separately.

3. Discussion

The *FIRST Trial* findings will generate new data on the potential for integrated CM with stepped care to reduce unhealthy alcohol use among PWH. Several innovative aspects of this protocol deserve mention. First, it adds to prior work employing a multi-targeted CM program addressing substance use among hospitalized PWH(59) focusing on reducing unhealthy alcohol use among PWH in outpatient HIV clinics. Second, to our knowledge, this is the first protocol to incorporate CM into a stepped care model to address unhealthy alcohol use. Third, given evidence that low levels of alcohol use adversely affect medical conditions common among PWH, the study protocol expanded the definition of unhealthy alcohol use to thresholds of alcohol use below traditional *at-risk* levels. Lastly, we focused on promoting alcohol abstinence given that observational data demonstrates that exceeding an average of one drink per day among PWH increases risk of morbidity and mortality(6).

Our study has limitations. First, due to recruitment challenges and the COVID-19 pandemic we did not reach recruitment targets and will be underpowered to make definitive conclusions regarding the efficacy of our intervention package. Second, most participants were recruited in VA HIV clinics and thus data from this study may not be generalize to populations with different characteristics (e.g., those with a larger proportion of women) or receiving care in non-VA settings. Third, due to practical considerations, the research coordinators were not blinded to participant study condition. Fourth, the delays associated with using PEth and the >72 hours from sample collection to availability of results are not consistent with the behavioral principle of immediacy in the provision or withholding of rewards. In addition, to increase expected feasibility and acceptability for the HIV clinical setting, the reward

schedule was less frequent than is typical for CM protocols and may impact its efficacy. However, it is possible that the delay discounting that would be anticipated to occur among FIRST participants might be offset by the higher magnitude of reinforcement available to them in this trial. The magnitude of reinforcement available to FIRST participants over 12 weeks was greater than that typically available in Prize CM reinforcing abstinence over 12 weeks(60). Regardless, future studies involving CM may consider including more consistent monitoring as available with transdermal biosensors(61-63). Fifth, by basing rewards or consequences on alcohol abstinence, rather than decreases in drinking, we missed the opportunity to shape abstinence behavior by reinforcing decreases in drinking. Sixth, the COVID-19 pandemic effectively shut down in-person visits at the clinical sites; this resulted in an inability to conduct objective assessments (e.g., PEth, breathalyzer) and eliminated opportunities for patients to access some services particularly during the first wave of COVID-19 (e.g., HCV treatment, A.A. meetings) that would have led to rewards. Lastly, biomarkers such as PEth do not distinguish between various drinking patterns which might engender different therapeutic responses. Specifically, an elevated PEth can be seen in an individual with either continuous heavy drinking or prolonged abstinence interrupted by a recent day of heavy drinking. However, patient report may provide complementary insights.

These limitations notwithstanding, the *FIRST Trial* experiences will generate new data on the feasibility, acceptability, and preliminary efficacy of a novel intervention package designed to enhance PWH motivation to reduce unhealthy alcohol use for delivery in HIV clinics. As enthusiasm and financial reimbursement for CM expand(64), the *FIRST Trial* experiences will be critical for informing future models of care to reduce unhealthy alcohol use among individuals accessing HIV care and beyond.

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Data sharing: With written request and after review and approval by the Principal Investigator (DAF and ACJ) and Veteran Aging Cohort Study team, a data dictionary defining each field in the analytic data set and de-identified individual participant data will be made available after findings of the main analyses have been published.

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Table 1. Criteria for unhealthy alcohol use by category of alcohol use

Unhealthy alcohol use category	Definition
Moderate alcohol use in presence of a medical condition potentially impacted by alcohol	• Report alcohol use in the past 21 days, but do not meet criteria for at-risk alcohol use or alcohol use disorder AND have presence of at least one of the following: o Detectable HIV viral load [>200 copies/mL]; o Tobacco use disorder and smoking > 5 cigarettes per day; o Detectable HCV viral load; o Liver fibrosis with a FIB-4 >1.45; o Depressive symptoms with Patient Health Questionnaire-9 score >9; o Current prescription of a psychoactive medication that may interact with alcohol, including benzodiazepines, opioids, antipsychotics, antidepressants, sleeping medications and muscle relaxants.
At-risk alcohol use	• Men ≤65 years old: alcohol consumption >14 drinks per week or >4 drinks per occasion; • Women and those >65 years old: >7 drinks per week or >3 drinks per occasion; • Do not meet criteria for alcohol use disorder.
Alcohol use disorder	• Meet Diagnostic and Statistical Manual Criteria-5 for alcohol use disorder, not in remission, based on presence of 2 or more of the following criteria: o Alcohol is often taken in larger amounts or over a longer period of time than was intended; o There is persistent desire or unsuccessful efforts to cut down or control use; o A great deal of time is spent in activities necessary to obtain alcohol, use alcohol, or recover from its effects; o Craving, or a strong desire to urge to use alcohol; o Recurrent alcohol use resulting in a failure to fulfill role or obligations at work, school, or home; o Continued alcohol use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of alcohol; o Important social, occupational, or recreational activities are given up or reduced because of alcohol use; o Recurrent alcohol use in situations in which it is physically hazardous; o Alcohol use is continued despite knowledge of having persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by alcohol; o Tolerance as defined by either of the following: ▪ A need for markedly increased amounts of alcohol to achieve intoxication or desired effect ▪ A markedly diminished effect with continued use of the same amount of alcohol; o Withdrawal as manifested by either of the following: ▪ Characteristic withdrawal syndrome for alcohol ▪ Alcohol (or a closely related substance, such as benzodiazepine) is taken to relieve or avoid withdrawal symptoms.

Table 2. FIRST Trial: Summary of study assessments and schedule

Assessments	Baseline	Week 12	Week 24	Month 9	Month 12
Sociodemographic characteristics	X				
Gambling disorder screener	X				
National Opinion Research Center Diagnostic Screen for Gambling Problems	X				
Alcohol and other substance use-related measures					
AUDIT-C(44)	X				
NIAAA single item screen for alcohol use(65)	X				
Mini-SCID alcohol (only if AUDIT-C >4)	X				
Alcohol Timeline Followback(66)	X	X	X	X	X
Breathalyzer test (BAC) or alcohol saliva test	X	X	X	X	X
PEth(67)	X	X	X	X	X
Readiness to change ruler	X				
Family history	X				
ASSIST-Lite(68)	X	X	X	X	X
Addiction Severity Index-Lite(69)	X		X		X
Smoking assessment with Fagerstrom Test for Nicotine Dependence(70), e-cigarette use	X	X	X	X	X
Exhaled carbon monoxide or urine cotinine test[a]	X	X	X	X	X
HIV and other health and behavior measures					
HIV history	X				
VACS Index(33)[b]	X	X	X	X	X
HIV risk-taking behavior scale (HRBS)(71)	X	X	X	X	X
Patient Health Questionnaire (PQH)-9(72)	X	X	X	X	X
Neurocognitive assessment (TRAILS A, TRAILS B)	X	X	X	X	X
PROMIS Sleep related impairment (Short Form 8a) and sleep disturbance (Short Form 4a) scales	X	X	X	X	X
Urine pregnancy test (as clinically indicated)	X				
Medication receipt					
Antiretroviral medication adherence by pharmacy fill/refill data(73)[b]	X	X	X	X	X
Medications for alcohol and tobacco addiction treatment[b]	X	X	X	X	X
Medications for depression[b]	X	X	X	X	X
Medications for hepatitis C virus infection[b]	X	X	X	X	X
Psychoactive medications that may potentially interaction with alcohol (benzodiazepines, opioids, antipsychotics, antidepressants, sleeping medications, muscle relaxants) [b]	X	X	X	X	X
Treatment services					
Treatment services review(74), modified to assess VA and non-VA services, web-based services and legal history	X	X	X	X	X
Healthcare utilization[b]	X	X	X	X	X
Process measures					
Intervention visit adherence and duration[c]	**Intervention sessions**				
Contingency management rewards[c]	**Intervention sessions**				
Patient satisfaction survey		X	X	X	X

a. Only among participants who smoke tobacco.

b. Extracted via electronic health record

c. Only among participants randomized to contingency management with stepped care

Table 3. FIRST Trial Reinforcement Schedule Overview

	Target		
Purpose	**Short-term abstinence**	**Longer-term abstinence**	**Progress in addressing alcohol use or medical condition impacted by alcohol[a]**
Verification	Breathalyzer test <0.003g/dL	PEth < 8ng/mL	Verification of completed activity
Visits potentially rewarded	Week 0, 3, 6, 9, 12	Week 3, 6, 9, 12	Week 3, 6, 9, 12
Initial reward	1 draw	5 draws	3 draws
Potential increase in between visits	1 draw	1 draw	1 draw
Maximum associated draws at week 12	5 draws	8 draws	6 draws

a. Targeted conditions included unhealthy alcohol use, HIV, tobacco use disorder, untreated hepatitis C virus infection, depressive symptoms

Table 4. Overview of Goals Addiction Physician Management Sessions

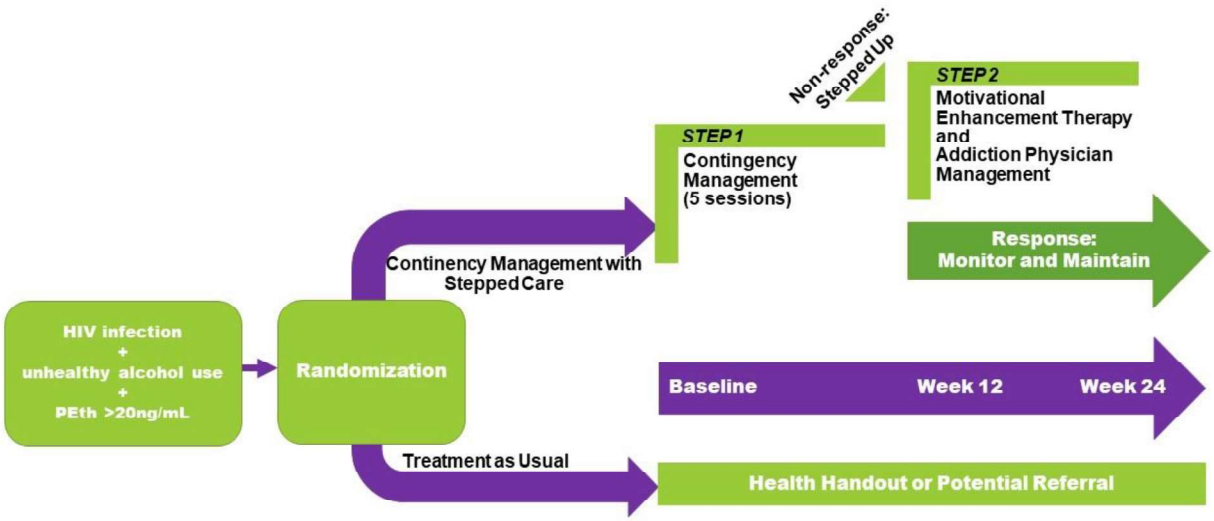
1) Assessed the impact of alcohol use on participants' medical, psychiatric, social, employment, and legal functioning
2) Educated participants about alcohol
3) Prescribed medication, if indicated, to help participants' manage alcohol cravings and/or reduce alcohol reinforcement
4) Encouraged abstinence and adherence to medication (as appropriate)
5) Encouraged lifestyle changes, avoidance of triggers and attendance at mutual-help groups
6) Identified and addressed medical complications of alcohol use
7) Referred participants to indicated treatment services (e.g., vocational, housing or social service

Table 5. FIRST Trial Protocol Modifications due to the COVID-19 pandemic

Protocol Domain	Original Protocol	Modification
Assessments	• In-person	• In-person or telephone-based
Contingency management reward targets and processes	• Potential rewards for short-term abstinence by breathalyzer testing; longer-term abstinence by PEth testing; and verified progress in addressing alcohol use or medical condition potentially impacted by alcohol; • Breathalyzer testing for short-term abstinence; • Exhaled carbon monoxide testing or urinary cotinine to confirm tobacco abstinence; • Participant would draw directly from fishbowl for earnings.	• During lock-down, potential rewards only for verified progress in addressing alcohol use or medical condition potentially impacted by alcohol; • Breathalyzer testing or alcohol saliva test for short-term alcohol abstinence; • Exhaled carbon monoxide testing or urinary cotinine to confirm tobacco abstinence; • Interventionist would complete fishbowl draws for earnings.
Criteria for being stepped up	• Lack of biomarker confirmed abstinence by PEth.	• Lack of self-reported abstinence by Timeline Followback when PEth could not be obtained.
Addiction Physician Management and Motivational Enhancement Therapy visits	• In-person	• In-person, videoconference, or telephone based
Primary outcome	• Biomarker confirmed abstinence by PEth.	• Self-reported abstinence by Timeline Followback due to challenges in collecting PEth.

Note: PEth=phosphatidylethanol

Figure 1. FIRST Trial: Protocol overview



Participants are considered to have non-response to contingency management if lack PEth <8ng/mL at week 12 visit and "stepped up."

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