YALE UNIVERSITY SCHOOL OF MEDICINE
HUMAN INVESTIGATION COMMITTEE

Application to Involve Human Subjects in Research

Please refer to the HIC website for application instructions and information required to complete this application. The Instructions are available at http://info.med.yale.edu/hic/forms/index.html. Submit the original application and two (2) copies of all materials including relevant sections of the grant which funds this project (if applicable) to the HIC.	**HIC OFFICE USE ONLY**	
	DATE STAMPED-RECEIVED	PROTOCOL NUMBER 0909005730

SECTION I: ADMINISTRATIVE INFORMATION

Title of Research Project: ***Reducing Heavy Drinking to Optimize HIV/AIDS Treatment and Prevention***			
Principal Investigator: **Lynn E. Fiellin**		**Yale Academic Appointment:** **Associate Professor of Medicine**	
Campus Address: 367 Cedar Street, P.O. Box 208093, New Haven, CT 06520			
Campus Phone: 203-688-9105	**Fax:** 203-737-3306	**Pager: 203-766-2135**	**E-mail:** lynn.fiellin@yale.edu
Protocol Correspondent Name & Address (*if different than PI*): Lisa Nichols, 367 Cedar Street, Harkness A Suite 411, New Haven, CT 06510			
Campus Phone: 203-737-3347	**Fax:** 203-737-3306	**E-mail: lisa.nichols@yale.edu**	

Faculty Advisor:(required if PI is a student, resident, fellow or other trainee) ☒ **NA**		**Yale Academic Appointment:**	
Campus Address:			
Campus Phone:	**Fax:**	**Pager:**	**E-mail:**

SECTION II: GENERAL INFORMATION

1. **Performing Organizations:** Identify the hospital, in-patient or outpatient facility, school or other agency that will serve as the location of the research. Choose all that apply:

a. Internal Location[s] of the Study:

☐ Magnetic Resonance Research Center (MR-TAC)
☐ PET Center
☐ YCCI/Church Street Research Unit (CSRU)

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☐ Yale Cancer Center
☒ Yale-New Haven Hospital
☒ Specify Other Yale Location:
YNHH Nathan Smith Clinic
☐ YCCI/Hospital Research Unit (HRU)
☐ YCCI/Keck Laboratories
☐ Cancer Data Repository/Tumor Registry

b. External Location[s]:

☒ APT Foundation, Inc.
☐ Connecticut Mental Health Center
☒ Veterans Affairs Hospital, West Haven
YNHH-HSR Campus
☐ Haskins Laboratories
☐ John B. Pierce Laboratory, Inc.
☒ Other Locations, Specify: The Haelen Center,

c. Additional Required Documents *(check all that apply)*: ☒ N/A

☐ *YCCI-Scientific and Safety Committee (YCCI-SSC) Approval Date:
☐ *Pediatric Protocol Review Committee (PPRC) Approval Date:
☐ *YCC Protocol Review Committee (YRC-PRC) Approval Date:
☐ *Dept. of Veterans Affairs, West Haven VA HSS Approval Date:
☐ *Radioactive Drug Research Committee (RDRC) Approval Date:
☐ YNHH-Radiation Safety Committee (YNHH-RSC) Approval Date:
☐ Magnetic Resonance Research Center PRC (MRRC-PRC) Approval Date:
☐ YSM/YNHH Cancer Data Repository (CaDR) Approval Date:
☐ Dept. of Lab Medicine request for services or specimens form

Approval from these committees is required before final HIC approval is granted. See instructions for documents required for initial submission and approval of the protocol. Allow sufficient time for these requests. Check with the oversight body for their time requirements.

2. **Probable Duration of Project:** State the expected duration of the project, including all follow-up and data analysis activities. 5 years

3. **Targeted Enrollment:** What is the number of subjects

1. targeted for enrollment at Yale for this protocol? 50
2. what is the total number of subjects targeted across all sites? 154
3. expected to sign the consent form? 170
4. expected to complete some or all interventions for this protocol? 154

5. Research Type/Phase: (Check all that apply)

a. **Study Type**

☐ Single Center Study
☒ Multi-Center Study
Does the Yale PI serve as the PI of the multi-site study? Yes ☒ No ☐
☐ Coordinating Center/Data Management
☐ Other:

b. **Study Phase** ☐ **N/A**

☐ Pilot ☐ Phase I ☐ Phase II ☐ Phase III ☒ Phase IV
☐ Other (*Specify)*

c. **Area of Research: (Check all that apply)** Note that these are overlapping definitions and more than one category may apply to your research protocol. Definitions for the following can be found in the instructions section 4c:

☒ Clinical Research: Patient-Oriented
☒ Clinical Research: Outcomes and

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☒ Clinical Research: Epidemiologic and Behavioral
☐ Translational Research #1 ("Bench-to-Bedside")
☐ Translational Research #2 ("Bedside-to-Community")
Health Services
☒ Interdisciplinary Research
☐ Community-Based Research

5. Is this study required to be registered in a public database? Yes ☒ No ☐

If yes, where is it registered?

Clinical Trials.gov registry ☒

Other (*Specify*)

1. Will this research study utilize clinical care services at Yale New Haven Hospital or YMG?

Yes ☐ No ☒

If yes, might these be billable to the subject, the sponsor, grant or other third party payer?

Yes ☐ No ☐

If you answered "yes", please register this study in the IDX/GE system at http://www.yalemedicalgroup.org/pfs/forms/10000/NewStudyRequest.pdf

SECTION III: FUNDING, RESEARCH TEAM AND TRAINING

1. **Funding Source:** Indicate all of the funding source(s) for this study. Check all boxes that apply.

Provide information regarding the external funding source. This information should include identification of the agency/sponsor, the funding mechanism (grant or contract), and whether the award is pending or has been awarded. Provide the M/C# and Agency name (if grant-funded). If the funding source associated with a protocol is "pending" at the time of the protocol submission to the HIC (as is the case for most NIH submissions), the PI should note "Pending" in the appropriate section of the protocol application, provide the M/C# and Agency name (if grant-funded) and further note that University (departmental) funds support the research (until such time that an award is made).

PI	Title of Grant	Name of Funding Source	Funding	Funding Mechanism
Lynn E. Fiellin	**Reducing Heavy Drinking to Optimize HIV/AIDS Treatment and Prevention**	National Institute on Alcohol Abuse and Alcoholism	☐ Internal ☒ External	☒ Grant-M# 1 R01AA018923-01 ☐ Contract#
			☐ Internal ☐ External	☐ Grant-M# ☐ Contract#
			☐ Internal ☐ External	☐ Grant-M# ☐ Contract#

1. **Research Team:** List all members of the research team. Indicate under the affiliation column whether the investigators or study personnel are part of the Yale faculty or staff, or part of the faculty or staff from a collaborating institution, or are not formally affiliated with any institution. **ALL members of the research team MUST complete Human Subject Protection Training (HSPT) and Health Insurance Portability and Accountability Act (HIPAA) Training before they may be listed on the protocol. See NOTE below.**

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	Name	**Signature *****	Protocol-Related COI?	Affiliation
Principal Investigator	Lynn Fiellin		☐ Yes ☒ No	Yale University
[redacted]	[redacted]		☐ [redacted] ☒ [redacted]	[redacted]
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*****My signature here indicates that I have read, am in compliance with, and will continue to be in compliance with the HIC's Protocol-Specific Conflict of Interest policy and the University's policy on Conflict of Interest and Conflict of Commitment.**
NOTE: The HIC will remove from the protocol any personnel who have not signed the application and/or completed required training. A personnel protocol amendment will need to be submitted when training is complete or signature is provided.

SECTION IV: PRINCIPAL INVESTIGATOR/FACULTY ADVISOR/ DEPARTMENT CHAIR AGREEMENT

As the **principal investigator** of this research project, I certify that:

1. The information provided in this application is complete and accurate.
2. I assume full responsibility for the protection of human subjects and the proper conduct of the research.
3. Subject safety will be of paramount concern, and every effort will be made to protect subjects' rights and welfare.
4 The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
5 All members of the research team will be kept apprised of research goals.
6 I will obtain approval for this research study and any subsequent revisions prior to my initiating the study or any change and I will obtain continuing approval of this study prior to the expiration date of any approval period.
7 I will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
8 I am in compliance with the requirements set by the University and qualify to serve as the principal investigator of this project or have acquired the appropriate approval from the Dean's Office or Office of the Provost, or the Human Subject Protection Administrator at Yale-New Haven Hospital, or have a faculty advisor.
9 I will identify a qualified successor should I cease my role as principal investigator and facilitate a smooth transfer of investigator responsibilities.

Lynn E. Fiellin (Sullivan), M.D. _____
PI Name (PRINT) and Signature Date

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As the **faculty advisor** of this research project, I certify that:

1. The information provided in this application is complete and accurate.
2. This project has scientific value and merit and that the student or trainee investigator has the necessary resources to complete the project and achieve the aims.
3. I will train the student investigator in matters of appropriate research compliance, protection of human subjects and proper conduct of research.
4. The research will be performed according to ethical principles and in compliance with all federal, state and local laws, as well as institutional regulations and policies regarding the protection of human subjects.
5. The student investigator will obtain approval for this research study and any subsequent revisions Prior to initiating the study or revision and will obtain continuing approval prior to the e xpiration of any approval period.
1. The student investigator will report to the HIC any serious injuries and/or other unanticipated problems involving risk to participants.
1. I am in compliance with the requirements set forth by the University and qualify to serve as the faculty advisor of this project.

I assure the HIC that the principal investigator and all members of the research team are qualified by education, training, licensure and/or experience to assume participation in the conduct of this research trial. I also assure that the principal investigator has departmental support and sufficient resources to conduct this trial appropriately.

_____ _____

Chair Name (PRINT) and Signature Date

_____

Department

YNHH Human Subjects Protection Administrator Assurance Statement

Required when the study is conducted solely at YNHH by YNHH health care providers.

As Human Subject Protection Administrator (HSPA) for YNHH, I certify that:

1. I have read a copy of the protocol and approve it being conducted at YNHH.
2. I agree to submit a Protocol-Specific Conflict of Interest Disclosure Form if I am aware of any real or apparent institutional conflict of interest.
3. The principal investigator of this study is qualified to serve as P.I. and had the support of the hospital for this research project.

_____ _____

YNHH HSPA Name (PRINT) and Signature Date

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For HIC Use Only

Date Approved **Human Investigation Committee Signature**

SECTION V: RESEARCH PLAN

1. **Statement of Purpose:** State the scientific aim(s) of the study, or the hypotheses to be tested.

We plan to conduct a double-blind placebo-controlled study to evaluate the effect of naltrexone for extended release injectable suspension (VIVITROL®/XR-NTX) and counseling on highly active antiretroviral treatment (HAART) medication adherence in a cohort of HIV-infected patients who report heavy drinking, or meet criteria for alcohol abuse and/or dependence, and inadequate (< 95%) HAART adherence. All patients will receive a behavioral intervention, termed Medical Management/Medication Coaching or MM/MC. MM/MC incorporates the behavioral platform Medical Management (MM) from the **National** Institute on Alcohol Abuse and Alcoholism (NIAAA)-funded COMBINE Study to reduce heavy alcohol use with Medication Coaching (MC), a manualized treatment designed to improve HAART medication adherence in HIV-infected patients with substance use disorders.
The **specific aims** and **hypotheses** of the study are as follows:

Specific Aim 1: To compare the efficacy of VIVITROL +MM/MC versus placebo +MM/MC on adherence to HAART.
Hypothesis 1: VIVITROL +MM/MC will lead to improved adherence to HAART when compared to placebo + MM/MC.

Specific Aim 2: To compare the efficacy of VIVITROL +MM/MC versus placebo +MM/MC in reducing days of heavy drinking.
Hypothesis 2: VIVITROL +MM/MC will lead to greater reductions in the number of days of heavy drinking when compared to placebo + MM/MC.

Specific Aim 3 (Exploratory): To explore the effect of VIVITROL +MM/MC versus placebo +MM/MC on biologic and psychosocial outcomes including:
3a) HIV markers—viral mutations (using standard assays and ultra-deep sequencing), CD4 lymphocyte count and HIV RNA viral load; and
3b) Liver function tests
3c) Depression, anxiety, pain, and quality of life

2. **Background:** Describe the background information that led to the plan for this project. Provide references to support the expectation of obtaining useful scientific data.

Heavy drinking and alcohol use and dependence are common in HIV-infected individuals and are associated with poor HAART medication adherence and disease progression

The lifetime prevalence of alcohol use disorders in patients with HIV ranges from 22% to 60% [2, 12-14]. In a national sample of patients with HIV, 8% to12% were classified as heavy drinkers, a rate approximately twice that of the U.S. national average [3, 15]. The rates are

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even higher for a diagnosis of lifetime alcohol use disorders with estimates of 26% to 60% in people living with HIV/AIDS as compared with 14% to 24% in the general population [16-20].

The impact of alcohol use on HIV treatment outcomes is substantial. Patients with alcohol use disorders delay seeking treatment for HIV [21]. Alcohol problems in HIV-infected patients are associated with poor adherence to HAART medications [1-6]. While HAART adherence in the general HIV-infected population ranges from 60% to 70% [22, 23], estimates for adherence in HIV-infected at-risk drinkers is significantly lower at 42% [24]. The risk for non-adherence has been shown to increase with increasing levels of alcohol consumption with one study revealing a 1.7 times increase in non-adherence in heavy drinkers (OR, 1.7 (95% CI, 1.3-2.3)) and a 2.7 times increase in non-adherence in frequent heavy drinkers (OR, 2.7 (1.7-4.5)) [25]. A recent study using the Veteran's Aging Cohort (VACS) (a large NIAAA-funded national sample of HIV-infected and HIV-negative patients affiliated with the current proposal) examining the relationship between alcohol consumption and medication adherence found a strong temporal inverse dose response association between alcohol and adherence. Adherence was lower on days in which patients drank heavily, and on the following day. The effect of alcohol was most pronounced in HIV-infected individuals, with an odds ratio for non-adherence of 1.8 in non-binge drinkers and 4.3 in binge drinkers [26]. In this study, alcohol consumption was the most significant predictor of HAART medication adherence (p=0.0001) with the greatest adherence associated with recent abstinence from alcohol. These findings support the argument that any reduction in heavy drinking may have a positive effect on HAART adherence. Heavy drinking in HIV-infected patients is also associated with poor treatment response as evidenced by lower CD4 lymphocyte counts and higher HIV RNA [4, 5]. In turn, it has been shown that individuals who have stopped drinking have an improved response to HIV therapy [4].

HAART non-adherence is linked to heavy drinking and can lead to increased rates of viral mutations, including minor resistance variants

The advent of HAART has revolutionized outcomes in HIV treatment [27]. As discussed above, ongoing untreated heavy drinking is strongly associated with poor HAART adherence and in turn suboptimal HAART adherence not only leads to HIV progression but also to HIV drug resistance [28, 29]. This drug resistance diminishes the effectiveness of HAART treatment for individual patients and for individuals subsequently infected with these viral strains. HIV drug resistance is the consequence of mutations that arise in the viral proteins targeted by antiretroviral (ARV) medications [30, 31]. Resistance can occur as a result of incomplete adherence to HAART or through sexual or injection drug-related transmission events. The mutations that occur during ARV exposure can cause resistance to a single ARV or can cause cross-resistance within an entire class of ARVs. HIV drug resistance leads to virologic failure (inability to suppress HIV virus) and limits future therapeutic options. Additionally, from a public health perspective, the transmission of drug-resistant HIV is of growing concern. Ten to 15% of new HIV infections are with drug- resistant virus which can limit treatment options [32]. HIV infection in patients exists as viral quasi-species, a collection of genetically diverse viral strains. Not all the viral strains that make up the collection in a person are detected by the standard resistance assays routinely used by clinicians. Standard assays only detect drug-resistant HIV if it makes up at least 20% of the viral population. Recent data suggest that minor resistant variants, constituting as little as 1% of viral quasi-species or "swarm" in a patient, are clinically important and can proliferate after the introduction of a new antiretroviral medication, leading to treatment failure [33, 34].

Recent data from the Center for Disease Control and Prevention (CDC) [35] demonstrate that high-sensitivity genotyping methods can detect minor resistant variants in patients such that the prevalence of drug resistance in newly HIV-infected patients and in chronically HIV-

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infected patients receiving ARVs nearly doubles. The detection of these minor resistant variants in the CDC study was strongly associated with future virologic failure on ARVs [35]. These CDC investigators recommend screening for minor resistant variants in HIV-infected patients [36]. They had developed allele specific polymerase chain reaction (PCR) methods to detect 9 resistance mutations. However, there are ~200 mutations associated with HIV drug resistance. New technologies that enable screening for all the HIV resistance mutations that contribute to drug resistance are needed. One such technology is ultra-deep sequencing. This technology, which we plan to use in the current study, employs microfabricated high-density picoliter reactors and pyrosequencing methods to identify and quantify minor resistant variants present at very low (<1%) levels in patient samples [37, 38].

Liver injury is central to morbidity and mortality in HIV and is impacted by alcohol and HAART

Prior work from our group has demonstrated that even low levels of liver injury are associated with substantial increases in risk of mortality among patients with HIV infection [39]. We have also shown that these levels of injury are common among HIV-infected patients in care; due to multiple causes including alcohol, viral hepatitis, ARV treatment toxicity, and, likely, non-ARV medication (e.g. statins) toxicity. Morbidity and mortality associated with alcohol-induced liver injury is well described and is marked by progressive liver inflammation and fibrosis, leading to cirrhosis and its complications [1]. Among individuals with chronic hepatitis C (HCV) infection, regular alcohol abuse or dependence contributes to an increased risk of cirrhosis, liver decompensation, hepatocellular carcinoma, and death [5]. Although hepatocellular injury is increasingly recognized as a particularly important source of morbidity and mortality among HIV-infected individuals, it is largely ascribed to co-existing viral hepatitis and medication-associated hepatotoxicity (e.g., ARV medications). The additive impact of varying, and even low levels, of alcohol consumption on progression of this injury is not clear. Prior work from our group has revealed that liver injury and fibrosis increase across increasing levels of alcohol consumption ($p<0.0001$). Significant increases in advanced fibrosis or cirrhosis are found at all levels of alcohol exposure among individuals with HIV mono-infection (8.6%), HCV mono-infection (13.8%), and HCV-HIV co-infection (31.8%). In multivariate analysis, after controlling for HCV and HIV infections, alcohol abuse or dependence represented the strongest predictor of advanced fibrosis (OR 2.38, 95% CI 1.83-3.09) [40].

The gold standard diagnostic tool for assessing liver injury and fibrosis is a liver biopsy, although this is limited by intrinsic procedural risks, sampling error, and inter and intra-observer variability in histologic interpretation, and is not practical for large research studies. In this setting, non-invasive approaches to assessing liver fibrosis represent important and clinically useful surrogates for distinguishing mild versus advanced liver fibrosis, and have been validated across liver disease populations. One commonly used index marker is FIB-4 $\left(\frac{age * AST}{ALT * \sqrt{platelets}}\right)$ (calculated as [age x AST] / [ALT x $\sqrt{platelets}$], a validated surrogate serum fibrosis index marker used to distinguish no or minimal liver fibrosis (F0-F1) from advanced fibrosis (F3) and cirrhosis (F4). Based on pivotal validation studies in patients with chronic HCV and HCV-HIV co-infected patients [41, 42], scores of FIB-4>3.25 were used to designate advanced fibrosis or cirrhosis (F3-F4). Scores of FIB-4<1.45 were used to designate the absence of significant fibrosis (F0-F1). We plan to use FIB-4 in the proposed study as a non-invasive marker of liver fibrosis.

Therefore, based on evidence that even low levels of alcohol can act synergistically with HIV, HCV and HAART to cause hepatoxicity, strategies that can decrease the adverse impact

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of alcohol, such as effective treatments for alcohol consumption are likely to yield substantial benefits for this population.

Heavy drinking is associated with increased sexual risk behaviors in those who are HIV-infected

Sexual risk behaviors (e.g. sexual intercourse without condom use, multiple sexual partners) that accompany alcohol use in HIV-infected individuals have major public health implications given the predominant role that sexual transmission plays in the current HIV epidemic [43-46]. Alcohol use at any level is associated with increased sexual risk behaviors [43]. Work from our group indicates a close temporal relationship between alcohol consumption and sexual risk behavior among HIV-infected individuals [47]. Among sexually active HIV-infected men, intoxication before intercourse was significantly associated with having 5 or more sexual partners in the past year (odds ratio [OR] 1.8, 95% confidence interval [CI] 1.1-2.8), inconsistent condom use (OR 1.8, 95% CI 1.2-2.7), and the combined measure of 2 or more partners and inconsistent condom use (OR 1.8, 95% CI 1.1-3.0). The evidence for the impact of the treatment of alcohol use disorders on decreasing sexual risk behaviors is mixed. There is data that those entering treatment for alcohol problems have declines in risky behaviors with an increase in condom use and a decrease in the number of sexual partners and high-risk partners [46]. Patients who completely abstain from alcohol use for the year following treatment have the greatest reductions in these behaviors. In turn, other studies have shown no change in the prevalence of sexual risk behaviors among individuals entering treatment for alcohol use disorders [46, 48]. To our knowledge, there is no data on the impact of alcohol treatment on sexual risk in HIV-infected patients. Therefore there is a need to assess how suppressing alcohol use, especially when it is linked to risky sex, impacts on the rates of sexual risk behavior in heavy drinking HIV-infected individuals.

NTX is an effective treatment for alcohol problems but has not been systematically examined in HIV-infected individuals

Effective pharmacologic approaches to treating alcohol dependence are currently available yet no data exists on these treatments in HIV-infected individuals. NTX is an opioid antagonist that is FDA-approved for the treatment of alcohol dependence. Clinical trials have demonstrated success in preventing relapse among alcohol dependent patients treated with NTX [7, 8] and decreased drinking in those with heavy or problem drinking [49-52], however, these studies have almost universally excluded HIV-infected patients. A pooled analysis of two such studies conducted in alcohol dependent individuals concluded that treatment with NTX as compared to placebo resulted in a 36% reduction in non-abstinent drinking rates and a 50% reduction in rates of relapse to heavy drinking [53]. A Cochrane Collaborative Group systematic review of opioid antagonists for alcohol dependence reviewed 27 randomized controlled trials of NTX and found that short-term (up to 3 months) and medium-term (3 to 12 months) treatment lead to improved alcohol use outcomes [54]. While one trial concluded that NTX treatment for alcohol dependence offered no benefits over placebo, this trial enrolled only individuals with severe and chronic alcohol dependence and therefore these findings are not generalizable to a population that includes those with heavy drinking [55].

NTX has also been shown to decrease drinking behavior in studies conducted by our group in alcohol dependent patients treated using a primary care model [56] [57]. The COMBINE Study [10] also examined the efficacy of NTX alone, and in combination with acamprosate, and counseling interventions in a large multi-site trial in HIV-negative patients. In this study, participants were randomized to receive placebo, NTX, or acamprosate alone or in combination. Some participants received Medical Management (MM) provided by a health care practitioner with or without Combined Behavioral Intervention provided by a trained therapist. NTX reduced the risk of a heavy drinking day (hazard ratio, 0.72; 97.5% CI, 0.53-

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0.98; *P*=.02) over time, most evident in those receiving MM. The proposed study will use the same counseling platform, MM, as was used in the COMBINE Study.

Despite the known adverse effects of alcohol problems on HIV-infected individuals and the demonstrated benefit of NTX and counseling in HIV-negative heavy drinkers, there has not been a systematic evaluation of the impact of this treatment on HIV outcomes or of the efficacy and tolerability of NTX in HIV-infected patients. This lack of evidence means that HIV-infected patients who are heavy drinkers are unlikely to receive the potential benefits of NTX and counseling. The current trial will provide evidence on the efficacy of NTX in this important and vulnerable population.

Extended release naltrexone is well tolerated and addresses adherence

Patient adherence to oral NTX can predict treatment response [8, 58, 59]. To address this concern, an extended release formulation of naltrexone (XR-NTX; VIVITROL®Alkermes, Inc., Waltham MA, USA) has been developed. The extended release formulation is administered once every 4 weeks as an intramuscular injection and shows pharmacological properties consistent with oral naltrexone. The extended release formulation is generally well tolerated; and as with oral naltrexone, the most common side effects are nausea, headache and fatigue. In addition, given that many patients with HIV are taking a number of medications, the extended release formulation possesses the advantage of not adding to their pill burden. In terms of efficacy, in one clinical trial, the 380mg dosage of extended release intramuscular VIVITROL in combination with psychosocial therapy was shown to reduce the heavy drinking rate by 25% compared with placebo ($p = .03$). In a subgroup of patients who were abstinent for at least four days prior to treatment initiation [60], extended release naltrexone resulted in significant improvements in rate of abstinence, time to first drink, and decreased the number of heavy drinking days per month compared to placebo ($p<0.04$). Three early studies of oral NTX demonstrated that the effect of NTX on relapse to heavy drinking fades in the months following treatment, whereas extended release VIVITROL appears to improve drinking outcome over a period of 18 months [61]. Therefore, the current trial will provide evidence for the efficacy of naltrexone treatment using a paradigm designed to help assure adherence to alcohol pharmacotherapy and is consistent with care provided in an HIV primary care clinic.

Why NTX and not other alcohol pharmacotherapies?

Naltrexone has demonstrated efficacy in patients who meet criteria for alcohol abuse and dependence [54] and in those with heavy drinking [49-52, 62]. While NTX should be used with caution in patients with severe liver disease (see B.11 Medical concerns of NTX treatment in HIV-infected individuals below) we believe the hepatic safety profile of extended release VIVITROL [63] and the stepwise approach that we have outlined, with ongoing surveillance for side effects and hepatotoxicity, will provide important safety data in this patient population. One reason we have chosen NTX as the medication in this proposal is that it may be a better treatment option for heavy drinkers who do not identify themselves as alcohol dependent or who do not have abstinence as a treatment goal [64]. Disulfiram is more appropriate for patients who wish to abstain completely from alcohol, although its efficacy in this regard is suspect [65]. Unlike disulfiram, NTX does not have adverse interactions with alcohol so it can be initiated in patients who are not abstinent. NTX has a favorable side effect profile and has been shown to reduce the risk of heavy drinking in the majority of clinical trials [54, 66, 67]. Most of the studies evaluating the use of NTX have demonstrated reduced drinking [51, 52, 61, 62, 68]. NTX has demonstrated efficacy even in heavy drinkers who are not necessarily motivated to decrease their alcohol consumption. For instance, drinking data obtained from smokers enrolled in a trial of NTX for smoking cessation revealed reduced heavy drinking indicating that motivation to change drinking does not have

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to be high for NTX to be effective [69].

Naltrexone also appears to result in greater reductions in alcohol consumption than other pharmacotherapies approved for the treatment of alcohol dependence. The COMBINE study examined different combinations of NTX and acamprosate along with different behavioral therapies including MM [10]. This study showed that patients who received MM with NTX, or with a combined behavioral intervention (CBI), or with both, had greater reductions in heavy drinking compared to MM and placebo NTX, and that there was no benefit of acamprosate compared to placebo whether provided with MM only or MM plus CBI. Further, a recently completed study evaluating the efficacy of acamprosate for maintaining abstinence in alcohol dependent patients found in an intention-to-treat analysis the percentage of abstinent days did not differ from placebo [70]. Finally, topiramate has shown promise as a pharmacotherapy for alcohol dependence [71]. However, topiramate shares cytochrome P450 (CYO450) metabolism with many antiretroviral agents (although by a different isoform) and can be associated with significant side effects. In one recent study, approximately half of the subjects who discontinued topiramate had a limiting adverse event. In this placebo-controlled trial, subjects receiving topiramate were more likely to report paresthesias (51% of subjects), taste perversion (23%), anorexia (20%), difficulty with concentration (15%), nervousness (15%), dizziness (12%), and pruritis (10%). These side effects are likely to limit topiramate's utility in HIV-infected patients who are already exposed to an array of side effects from their HAART and other medications.

The rationale for focusing on HAART medication adherence in heavy drinkers

We have chosen HAART adherence as our primary HIV outcome because it is one of the most proximal steps in the pathway between alcohol consumption and poor HIV outcomes. The association between HAART adherence and HIV treatment outcomes is well- established [72, 73]. However, the optimal level of HAART adherence is not known. Nonetheless, it has been shown that the highest levels of adherence (>95%) are an appropriate goal [74] and if not attainable, incremental increases in adherence at levels < 95% should be considered worthwhile endpoints [75-77]. Therefore, in the current study we are evaluating HAART adherence in terms of the proportion of patients achieving 95% or greater HAART adherence. The threshold of 95% adherence is used because of its consistent association with improved clinical, virological, and immunological outcomes [74]. Although one could argue that lesser levels of adherence might produce a satisfactory viral load response, particularly with certain types of HAART regimens (e.g., non-nucleoside reverse transcriptase inhibitor-based regimens) [29], 95% remains a standard target for HAART adherence and is therefore the most compelling choice for a primary adherence measure. Furthermore, lower adherence levels (e.g. 80%), while potentially resulting in adequate viral load suppression, run the risk of increasing the danger of accumulating HIV resistance mutations and decreasing future treatment options. Indeed, studies have suggested that the maximum rate of accruing resistance mutations accrues in the range of 70-80% [78, 79]**.** This finding reinforces our rationale for choosing greater than 95% HAART adherence as the primary outcome measure.

In the context of alcohol use, one study found that in HIV-infected patients, there was no difference in biological markers between non-drinking and drinking patients receiving HAART [1]. A second study showed that in HIV-infected patients, there was no difference in biological markers in all drinking groups not on HAART, but drinkers on HAART had worse markers than drinkers not on HAART [5]. Possible explanations include the effect of alcohol on the immune system, alcohol-related liver toxicity, drug interactions between alcohol and HAART medications, and the behavioral effects of alcohol on HAART adherence. While there may be several pathways in which NTX may improve HIV outcomes (Figure 1) the other HIV outcome data we are collecting for each step of these pathways will inform the potential contribution of each step.

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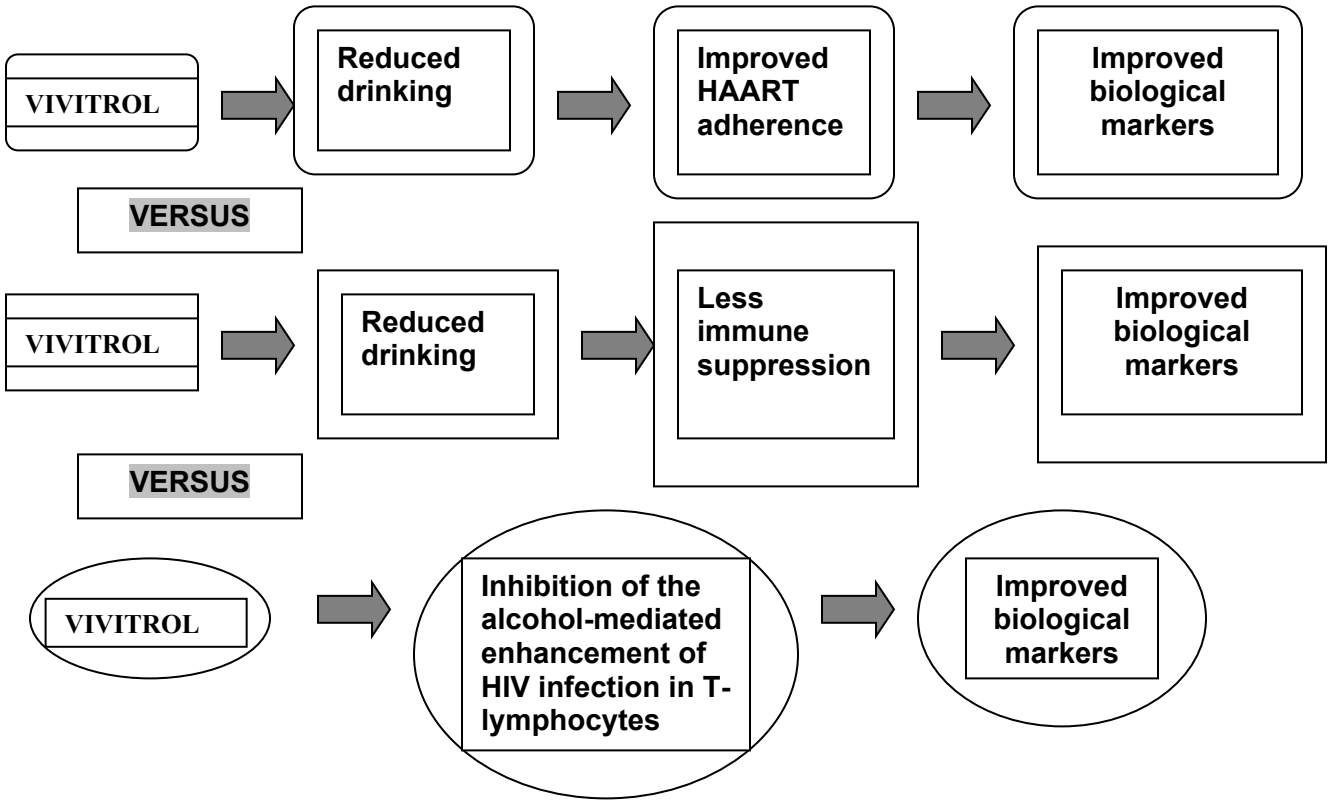
Figure 1. Pathways of how VIVITROL may lead to improved HIV outcomes



Pharmacy refill provides an accurate measure of HAART adherence and refill "persistence" is valid, reliable, and linked to clinical outcomes in HIV

Measuring HAART adherence can be challenging and can include self-report, pill count, and electronic monitoring. One additional assessment of adherence that is amenable to measurement, and will be used in the current trial, is "persistence". Persistence is defined as the continuous refill of prescribed medications using pharmacy data. Persistence can be conceptualized as necessary, though not sufficient, for adherence to occur. Without the filling and refilling of medications, patients can not adhere to their medications. Unlike other adherence measurements such as self-report, pill count, or electronic monitoring, persistence is an objective measure that does not rely on provider or patient action to obtain. It can also be updated easily so as to avoid the pitfall of defining an individual as adherent at a single point in time and miss their later non-adherence [75]. Persistence has been used to measure patients' adherence to HAART [80], to NTX for alcohol treatment [81] and to investigate refill behaviors with drug regimens such as statins and anti-hypertensive medications used for other chronic diseases [82, 83]. There are a number of ways that pharmacy refill data can be analyzed to create persistence measures of adherence. The medication possession ratio (MPR) is a commonly used metric that has been validated with virologic response [84-86]. It is calculated as the days' supply of medication divided by the number of days between the first fill and the last refill and represents the maximum possible adherence that a patient can attain over a defined refill period. The MPR has the capacity to detect inconsistent adherence patterns, is low-cost and has been validated [87]. Within HIV, pharmacy refill of HAART has been used to characterize the following associations: CD4 levels and HAART initiation [88], intermittent use of HAART and mortality [72], as well as HAART adherence and virologic response [89].

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The rationale for using Medical Management (MM) and HAART Medication Coaching (MC) counseling in conjunction with NTX

The role of counseling is well-established in the care of patients with alcohol problems. MM is a largely medical approach to counseling which is appealing because of its familiarity to practitioners and ease of implementation in a setting that does not routinely provide addiction treatment (e.g. HIV clinic). This type of approach is consistent with studies evaluating psychoeducational counseling in patients with diabetes, hypertension, asthma or congestive heart failure suggesting that intensive education about a patients medical condition and advice about disease management improves treatment effectiveness [90-98].
HIV primary care clinics often provide onsite care for comorbid medical conditions including psychiatric conditions, HCV, and most recently opioid dependence with buprenorphine [99]. Onsite treatment of alcohol use disorders in patients with HIV would allow for integrated care for both disorders. Our earlier work in primary care compared NTX combined with "primary care management" versus NTX combined with cognitive behavior therapy and found similar results between the two treatments during the initial 10 weeks of treatment [57]. The feasibility and efficacy of combining MM with NTX was also documented in the COMBINE Study [10]. For the proposed study we will provide MM along with counseling, termed Medication Coaching (MC) [11], designed to enhance HAART medication adherence in HIV-infected individuals with substance use disorders. We have used an earlier version of MC as an adjunct to drug counseling in HIV-infected opioid dependent patients receiving buprenorphine in an HIV clinic [100, 101].

Medical concerns of NTX treatment in HIV-infected individuals

Increased prevalence of hepatitis C (HCV)

Because of its potential for hepatotoxicity, NTX should be used with caution in individuals with impaired hepatic function. We plan to use low, but effective doses of NTX, and to assess hepatic safety using a standard self report form [102] and serial serum transaminases in the proposed study. Approximately 30% of HIV-infected individuals in the U.S. are co-infected with HCV [103]. HIV has a significant effect on the progression of HCV to severe liver disease [104-106]. After 15 years of infection with HCV, those co-infected with HIV have a 25% risk of cirrhosis, while those with HCV alone have only a 6.5% risk [105]. Co-infection may increase the risk but not the severity of hepatotoxicity from HAART medication, and therefore HAART should not be avoided in these individuals, but transaminases need careful monitoring [103, 107, 108]. VIVITROL can also have hepatotoxic effects, though at higher dosages than will be used in the proposed study. A recent large study of extended release VIVITROL found that mean liver enzymes did not change significantly over the course of treatment and there was no effect of medication on the proportion of patients in the different groups who had liver enzyme elevations higher than several times the upper limit of normal [61]. In addition, it has been found to be safe for use in patients with mild to moderate liver impairment [109] with evidence of a 15% greater reduction in liver enzyme levels in the VIVITROL group as compared with the placebo group [110]. VIVITROL is approved for use in patients who meet criteria for Child-Pugh classification A and B indicating tolerance in patients with impaired hepatic function. While these data are reassuring, monitoring of liver function, to assess for hepatotoxicity, will be important, especially in HIV/HCV co-infected patients.

Lower tolerance for medication interactions and side effects (NTX and HAART)

While there is little literature on interactions between NTX and HAART, based on previous studies outlining metabolism of NTX, these interactions appear to be minimal. The majority of HAART medications are metabolized via the CYP450 system. This metabolic pathway is known to lead to drug interactions with a number of medication classes. NTX,

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however, is not completely metabolized via CYP450 and therefore significant interactions are not expected [111, 112]. One study on the disposition of zidovudine (AZT) found that NTX had no significant effect on the area under the curve, maximal concentration or half-life of AZT [113]. In turn, another study suggested that NTX might potentiate the antiviral effects of AZT and a protease inhibitor, Indinavir, increasing their antiviral activity 2-3 fold [9]. A recent study suggests that NTX may inhibit the alcohol-mediated enhancement of HIV infection in T lymphocytes [114]. In addition, a large multi-center safety study of the use of NTX for alcoholism in 865 individuals, including patients with comorbid psychiatric illness and HIV, demonstrated that serious side effects in these populations were uncommon [115]. While this study was not randomized and was not intended to look at medication interactions, the findings are reassuring for patients with HIV disease. The proposed study will examine the question of clinically significant medication interactions through laboratory assessments and a systematic evaluation of adverse effects.

Addressing HIV provider's concern regarding provision of NTX for alcohol problems

Physicians cite a number of barriers to providing NTX for the treatment of alcohol use disorders including lack of knowledge of the medication's safety and efficacy, time for patient management, and overall lack of involvement in alcoholism treatment [116-119]. The model proposed in the current study, alcohol treatment that is integrated into the HIV care setting, has potential to address some of these concerns. Integrated treatment for HIV and substance abuse disorders has been shown to help ameliorate some of the problems with access to care and sub-optimal treatment for both conditions [12, 120]. While integration of these services can be implemented at various levels including at that of the provider, the clinic, or the system, any successful integration will require support of providers based on treatment efficacy. The goal of the proposed study is to provide clinicians with data on the efficacy of VIVITROL in HIV-infected patients in order to reassure them about its tolerability and utility.

3. **Research Plan:** Provide an orderly scientific description of the study design and research procedures as they directly affect the subjects.

Overview

The proposed study of HIV-infected patients with inadequate HAART adherence and heavy drinking, alcohol abuse and dependence will consist of a 24-week double-blind placebo-controlled randomized clinical trial, with an additional 6 months of follow-up, to evaluate the effect of treatment with VIVITROL versus placebo in conjunction with a counseling intervention on HIV outcomes. HIV outcomes will include: HAART medication adherence (specifically the proportion of patients achieving 95% or greater HAART adherence, viral mutations, HIV biologic markers, and alcohol-HAART hepatotoxicity. The counseling intervention is a "compound" therapy consisting of Medical Management (MM) counseling and Medication Coaching (MC). MM was developed for the NIAAA-funded COMBINE Study and consists of a series of brief interventions delivered by medically trained providers (physician or nurse) that has demonstrated efficacy when combined with NTX to reduce the frequency of heavy drinking [10]. MC is a counseling strategy which focuses on HAART medication adherence in substance abusing populations [11]. Of the total study population of 154 patients, 50 patients will be enrolled in the study at Yale and will be randomized to receive one of two treatment conditions: VIVITROL + MM/MC versus Placebo + MM/MC. MM/MC is intended to approximate the type of treatment that would be suitable for implementation by a trained individual (e.g. physician, nurse, nurse practitioner, physician assistant,) in a HIV primary care setting and approximates the counseling interventions that we have implemented in opioid dependent patients receiving buprenorphine treatment in primary care [122] and HIV primary care settings [100].

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Participants

Sample size estimation

A total of 154 participants will be enrolled at the three participating clinics. The following assumptions were used to derive this sample size:

Proportion of Placebo+MM/MC participants achieving >95% adherence = 20%
Proportion of Vivitrol+MM/MC participants achieving >95% adherence = 40%
Power=72%
Alpha level=0.05

Participants at the Nathan Smith Clinic will be 50 HIV-infected men and women who report heavy drinking, alcohol abuse or dependence. Referrals will come from within the Nathan Smith Clinic site, via local HIV care sites, website advertisements, local papers, community postings, community physicians, other patients, local mental health centers, local hospitals, and substance abuse treatment facilities.

Inclusion criteria: Each subject must:
1. Be HIV-infected.
2. Currently be prescribed HAART medication.
3. Report less than 95% adherence to their HAART medication.
4. Report heavy drinking 4 or more times in the past 4 weeks, or meet current criteria for alcohol abuse or dependence. Heavy drinking is defined as 4 or more drinks for women and 5 or more drinks for men on one occasion.
5. Be at least 18 years old.
6. Be able to understand English and provide informed consent.

Exclusion criteria: No subject may:
1. Be psychotic or severely psychiatrically disabled.
2. Be currently enrolled in formal treatment for alcohol (excluding self-help, e.g. Alcoholics Anonymous)
3. Have medical conditions that would preclude completing or be of harm during the course of the study.
4. Have laboratory or clinical evidence of significant liver dysfunction (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times the upper limit of the normal range) or cirrhosis with a Child-Pugh classification greater than A or B.
5. Have a known contraindication to NTX therapy (e.g. requiring opioid medication for pain).
6. Be pregnant, nursing or unable to use an effective method of birth control (women).
7. Patients with a positive urine opioid screen result
8. Known hypersensitivity to naltrexone, PLG (polylactide-co-glycolide, carboxymethylcellulose, or any other components of the diluent

Procedures and design

Pretreatment
Consent: Subjects who present requesting treatment and meet the above criteria will be asked to attend a baseline interview, at which time written informed consent will be obtained by a

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research assistant prior to further evaluation. Given that the study involves the potential use of naltrexone, a wallet card indicating the study number, contact information and the subject's study identification number will be prepared for subjects to carry in the event of an emergency.

Collection of Patient Locator Information: Retention and tracking strategies developed in the NIAAA Project Match and previously used by our group will help minimize participant attrition [122, 124]. Dr. Fiellin's connections with the clinics from which patients will be recruited will enhance the ability to follow patients and keep them engaged in the study. Locator information on up to 5 individuals will be obtained on all study subjects at enrollment. To set up and confirm appointments, research assistants will notify each subject by phone, including through electronic text messaging, and/or mail before subjects are expected to return for their next assessment. Approximately 1-2 weeks prior to the monthly and quarterly interviews a registered confirmation letter will be mailed to the patient. If after three attempts by telephone the patient is not contacted, contact with the other 4 locators will be initiated, and if unsuccessful a registered letter will be sent to the patient. If at this point the research assistant can not contact the patient, he/she will notify the project director who will try all the locators as well as investigate the support systems noted on the index visit. Subjects will also receive compensation for completing assessments during treatment and at the 9-month and 12-month follow-up.

Pretreatment Assessment: The baseline interview will include evaluations for alcohol, drug, and psychiatric disorders, a physical examination, blood work, urine sample and pregnancy test for women.

Randomization: Eligible participants will be randomly assigned to VIVITROL + MM/MC or placebo + MM/MC by the investigational pharmacist. All staff, other than this individual and the study biostatistician(s), will be blind to treatment allocation. Subjects will be assigned to one of the two conditions using stratified randomization. There will be 6 strata: (a) participating clinic (3) and (b) alcohol abuse/dependence (Yes/No; 2) in the randomization scheme.

Treatment

Medication: VIVITROL versus placebo:

Medication: VIVITROL versus placebo: Participants will receive either active VIVITROL or placebo throughout the 24-week treatment period; they will be told that they have a 50% chance of receiving the active drug. Those assigned to the VIVITROL arm will receive monthly extended release VIVITROL doses at 380mg (4 mL), administered as an intramuscular gluteal injection at 4-week intervals. Consistent with prior studies [60], we will encourage patients to be abstinent from alcohol use for four days or more prior to receiving the dose of extended release VIVITROL. We chose the 380mg dose because it was found in a recent randomized trial to be more efficacious than a 190mg dose with no significant differences in side effects or rates of hepatotoxicity. For the placebo arm of the study, patients will be dosed in a similar manner receiving 4 mL injections of placebo at 4-week intervals. All active and placebo doses will be administered by the study nurse.

Counseling Intervention: Our compound counseling intervention will consist of two efficacious, manualized behavioral treatments intended to augment VIVITROL's effects: Medical Management (MM) and Medication Coaching (MC). MM is a manual-guided supportive counseling therapy with demonstrated effectiveness (see the COMBINE Study [10] , Appendix B). This treatment incorporates the clinical skills and advice used by primary

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care practitioners supplemented with referrals for all patients to Alcoholics Anonymous. The initial MM visit will consist of: discussion of medical concerns, information on VIVITROL, assessment of medication compliance, provision of written educational materials on alcohol problems and treatment, and a question/answer period. The core elements covered at each follow-up MM visit are: 1) Medical status, medication safety, medication adherence, 2) Drinking status, and 3) Troubleshooting based on patients' drinking and medication adherence status. Each follow-up visit will include approximately 10-15 minutes of MM counseling.

Medication Coaching (MC) is a counseling strategy focusing on HAART medication adherence in substance abusing populations [11] (Appendix C), an early version of which we piloted in our recent study examining the use of buprenorphine for the treatment of opioid dependence in HIV-infected patients [100, 101]. This counseling uses ten strategies to increase medication adherence during the intervention and promote long-term maintenance: 1) assessing adherence, 2) designing an individual adherence management plan, 3) coordinating with medical care, 4) collaborating with other team members (e.g., substance abuse counseling), 5) developing a medication routine, 6) addressing barriers, 7) providing feedback on health outcomes, 8) maintaining adherence, 9) reducing HIV progression, and 10) promoting continued adherence and assessing goals. Each follow-up visit will include approximately 10-15 minutes of MC counseling.

Both treatments will be provided during 8 counseling sessions at week 0, 2, 4, 6, 8, 12, 16 and20. We have added two booster sessions at weeks 20 and 24 in order to target multiple risk behaviors simultaneously and also to provide an opportunity to provide health feedback at 6-months post-enrollment. Each of these visits will be guided by a structured initial visit or progress note.

The treatments will be delivered consecutively within each session by a trained primary care practitioner (e.g., nurse), with the exception of overlapping content that has been integrated to increase treatment efficiency. For example, we have selected the more detailed adherence assessment from the MM and adapted it to include antiretroviral medications, followed by the more comprehensive multimodal strategies for increasing medication adherence (e.g., cueing strategies, building social support for adherence) taken from the MC. We have also adapted the MM by tailoring the medical evaluation and medical feedback components to include medical comorbidities associated with HIV, further caveats about liver disease, and the adverse medical consequences of using alcohol when HIV-infected. Finally, we have incorporated brief strategies for addressing possible concerns about stigma when trying to engage clients in support groups for abstinence.

Adherence to the MM and MC manuals, as well as competence/performance of the practitioners, will be assessed throughout the study during weekly supervision and through ratings of audiotapes evaluated by blinded trained raters, using rating forms to assess time spent with the patient, content material reviewed, and proficiency of the provider at each session.

Study Period: The study period will be 24 weeks. This length was chosen because the largest study of extended release VIVITROL conducted to date followed outcomes over 24 weeks of active treatment [61]. In addition, this period will give adequate time for us to detect differences in adherence, biologic markers (e.g. CD4 lymphocyte counts, HIV RNA, and alcohol and HAART hepatotoxicity) that may emerge. Given that there is some evidence VIVITROL treatment effects do not persist at follow-up after treatment [10], we are planning to conduct follow-up assessments at 9 months and 12 months.

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Treatment setting

Yale-New Haven Hospital Nathan Smith Clinic (NSC)

The NSC is located within the Yale-New Haven Hospital Medical Center and provides care for over 775 patients with HIV/AIDS, 40% of whom are women. In a review of clinical data from the electronic medical record maintained on all patients at the NSC over the past two years, the prevalence of alcohol abuse and dependence in patients receiving their care in the NSC was 139/775 or 18%. We suspect that this is an under-estimation of the actual prevalence. Of note, Dr. Fiellin has been an HIV provider in the NSC for the past 12 years and has coordinated addiction treatment studies there for the past 7 years.

Assessments

Overview

We plan to assess a range of pretreatment measures at the baseline assessment to ensure that participants meet eligibility criteria and that important baseline and predictor variables are assessed (see Table 1 for Summary of Study Assessments). Using validated instruments during treatment and at end-of-treatment, we will be able to examine the differential impact of VIVITROL on a range of measures, including medication adherence and standard assessments of alcohol consumption used across NIAAA studies of alcohol treatment. The primary study outcome is adherence to HAART medications. Secondary study outcomes include: 1) Frequency of heavy drinking; 2) HIV viral mutations; 3) Change in biological markers (CD4 lymphocyte counts and HIV RNA); 4) Alcohol-HAART hepatotoxicity; and 5) Sexual risk behaviors.

Baseline and in-treatment assessments

Prior to entrance into the study each patient will undergo a medical history, physical and laboratory assessments (Complete blood count (CBC), chemistry panel, and viral hepatitis serologies). A urine pregnancy test will be performed at baseline and each month thereafter and must be negative throughout the study. The research assistant will collect demographic data including items such as marital status, highest level of education completed, employment, substance use history, duration of HIV disease, and a detailed HAART medication history. Charts will be extracted to collect information including medical co-morbidities, prior CD4 lymphocyte cell counts and HIV RNA levels, HAART medication history, historical genotypic information from prior HIV drug resistance testing, and patient satisfaction data.

HAART medication adherence, with the goal of determining the proportion of patients achieving 95% or greater HAART adherence, will be measured using pharmacy fill/refill data using the medication possession ratio defined as the total days supply/refill interval. Information needed to calculate the medication possession ratio is readily available in the patient's pharmacy data. With subject written consent, we will call the pharmacy designated by the subject to determine refill dates and days supply of medication. In addition, self-reported HAART adherence will be collected using the AIDS Clinical Trials Group (ACTG) assessment [128]. Patients will be asked how often they took each of their medications during the preceding month. We will also be conducting the Morisky 4-item adherence scale, a brief "persistence" measurement for medication persistence, and a single item visual analog scale for adherence. We will use a valid adjustment strategy [129] to resolve discrepancies between the various methods of assessing HAART adherence. The use of electronic drug monitoring in the form of medication event monitoring system (MEMS) caps for measuring HAART adherence was considered as it offers the best correlation with virologic outcomes [130]. However, several documented disadvantages such as expense, lack of feasibility for most

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clinical settings, and the likelihood of underestimation of adherence due to patients' "pocket dosing" their medication or removing more than one dose for each bottle opening, lead us to choose the other three methods in order to measure adherence [130].

We anticipate that a number of HIV-infected patients with heavy drinking may not be prescribed HAART medications due to their providers' concerns about poor medication adherence. While such patients do not meet the second eligibility criterion, we will encourage interested patients to discuss the possibility of resuming HAART with their HIV providers, such that they could be considered for enrollment at a later date. In addition, in an effort to include this target sub-population without mandating the usual 90 days of HAART-adherence data, we will determine their baseline adherence after 30 days; patients will be invited to present for an eligibility assessment one month after their first HAART prescription. We will use a simple 30-day pill count to calculate their baseline adherence.

The Morisky scale is a commonly used, validated, 4-item self-reported adherence measure that has been shown to be predictive of medication adherence. It includes two items that measure intentional medication non-adherence.

Alcohol Use will be assessed using the Time-Line Follow Back Interview (TLFB) [131] which will obtain the quantity/frequency of alcohol consumed for each day in the past month (baseline) and since the prior visit. TLFB has good test-retest reliability and good validity [131]. In addition, in order to better determine the "category" of drinking behavior of a subject at baseline, we will use the Alcohol Use Disorders Identification Test (AUDIT) [26], a valid instrument for categorizing alcohol consumption.

The Obsessive-Compulsive Drinking Scale (OCDS) is a 14-item, self-administered questionnaire for characterizing and quantifying the obsessive and compulsive cognitive aspects of craving and heavy (alcoholic) drinking, such as drinking-related thought, urges to drink, and the ability to resist those thoughts and urges.

Phosphatidyl ethanol (PEth), a phospholipid formed only in the presence of alcohol, has shown 95-100% sensitivity and 100% specificity to detect heavy drinking over a period of 2-3 weeks in several studies of dependent patients and abstainers in Europe.[1-7] The detection of PEth appears to be dose-dependent.[3, 6, 8, 9] The threshold for PEth is around 1000 grams over 2-3 weeks with a mean daily intake of 50 grams (4.2 standard drinks).[10] The identification of serum PEth will be performed by liquid chromatography-tandem mass spectrometry (LC-MS-MS) as previously described.[11, 12]

Rates of viral mutations, according to International AIDS Society guidelines [132], will be determined by collecting plasma and conducting standard HIV drug resistance testing. We will also collect historical genotypic information through chart review. Our team has extensive experience in DNA sequencing techniques and has used these methods in HIV transmission risk studies [34, 133, 134]. For patients with a detectable viral load (>400 HIV RNA copies/mL) we will conduct standard HIV drug resistance testing [34, 133, 134] at baseline and follow up. Standard DNA sequencing will be performed using a consensus population sequencing of the HIV-1 *pol* gene [135]. In addition, a sample from each monthly blood draw will be archived. Ultimately these samples will be processed in a batched fashion and a second aliquot of HIV RNA from the patient sample will be screened for high and low abundance resistant variants (to ~1% levels) by ultra-deep sequencing techniques [33, 38, 136].

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CD4 lymphocyte counts and HIV RNA levels will be checked at baseline and monthly.

Potential alcohol/HAART interactions resulting in hepatotoxicity will be evaluated with monthly liver function tests including AST, ALT and gamma-glutamyl transpeptidase (GGT). We will also collect monthly platelet counts to calculate an AST to platelet ratio index (APRI) and FIB-4. APRI and FIB-4 represent commonly utilized fibrosis indices which provide non-invasive assessments using readily available clinical markers. The AST-platelet ratio index (APRI) index $\left(\frac{AST * ULN * 100}{platelets}\right)$(calculated as [AST x ULN x 100]/[platelet count (10^9/L)]) and FIB-4 score $\left(\frac{age * AST}{ALT * \sqrt{platelets}}\right)$(calculated as [age x AST] / [ALT x $\sqrt{platelets}$] scores, represent validated surrogate fibrosis indices used to distinguish no or minimal liver fibrosis from advanced fibrosis and cirrhosis. Based on validation studies in a spectrum of cohorts with chronic HCV and HIV infection, scores of FIB-4>3.25 were used to designate advanced fibrosis or cirrhosis. Scores of FIB-4<1.45 were used to designate the absence of significant fibrosis. Monthly blood work will also include creatinine and hemoglobin levels to incorporate into the VACs Index, a scoring system that assesses both HIV-related and -unrelated morbidity/mortality.

Sexual risk behaviors will be measured using a modified assessment incorporating specific questions from the High Risk Behavior Survey (HRBS) [137], a validated instrument that measures sexual risk (non-condom use, multiple partners) behaviors that have been associated in previous studies with HIV serostatus and seroconversion.

Side effects/adverse experiences will be collected at each visit using the Systematic Assessment for Treatment Emergent Effects (SAFTEE) [102], a validated measure of side effects in clinical trials.

The alcohol and drug use disorders section of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I/P) [138] will assess for past or present alcohol use disorders [139] at baseline.

Lifetime and current DSM-IV-TR Axis I and II psychiatric disorders will be assessed using the Structured Clinical Interview for DSM-IV (SCID) [138].

Blood Alcohol Concentration (breathalyzer) will be obtained at baseline and at each visit. We will use this data to monitor patients and identify those in whom self-report would be suspect (e.g. BAC > 0.4).

The Addiction Severity Index 5th Edition Lite (ASI-Lite) will be used to assess the severity of alcohol and any drug dependence and associated psychosocial impairment. This instrument is a modified version of the ASI [140].

The Brief Symptom Inventory (BSI) is a multidimensional symptom inventory designed to reflect psychological symptom patterns of psychiatric and medical patients.

The Short Inventory of Problems (SIP) is an assessment that measures physical, social, intrapersonal, impulsive, and interpersonal consequences of alcohol and drug consumption.

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The Brief Pain Inventory is an assessment to measure pain symptoms.

The Treatment Services Review (TSR) is a brief, structured interview administered to collect information on the type and amount of services received by the patient outside of the study.

Urine toxicology testing will be performed at baseline to assess for THC, opioids, cocaine, and benzodiazepines. We will conduct rapid urine toxicology testing for opioids prior to each monthly VIVITROL injection.

SF-12: We will be collecting data on health and well-being using the SF-12 form.

Substance Use Survey: We will collect data on ongoing or new substance use, including cigarette use, using the Substance Use Survey.

Patient Satisfaction: A semi-structured interview, administered by a research assistant, will be used to assess overall satisfaction with the clinic setting, including specific components of treatment such as medication, nursing interactions, and physician visits.

Opioid receptor genotyping: A number of recent studies have identified specific genetic variants that predict responsiveness to naltrexone. In particular, a single nucleotide polymorphism in exon 1 (Asn40Asp) in the mu-opioid receptor gene (OPRM1) has been identified in numerous retrospective studies as highly correlated with clinical response (144-146). Subjects with one or two Asp40 alleles have a 74-87% response to naltrexone, as compared with a 49% response in those lacking this variant (146). In order to control for this important variable, and to further explore the interaction of this polymorphism with clinical response, we will perform targeted gene testing to identify the presence of the Asp40 allelic variant.

End-of-treatment assessments

The end-of-treatment assessments will include: Pharmacy fill/refill data, HAART medication adherence measures, HAART pill counts, TLFB for heavy drinking, OCDS, PEth, HIV drug resistance testing, HIV biological markers (CD4 lymphocyte count and HIV RNA levels), liver enzymes, platelet counts, hemoglobin, creatinine, sexual risk behavior assessment, SAFTEE, BAC, ASI, BSI, SIP, Brief Pain Inventory, TSR, SF-12, the Substance Use Survey, and patient satisfaction.

Follow-up assessments

Follow-up assessments at 9 months and 12 months will include: Pharmacy fill/refill data for HAART, HAART medication adherence measures, HAART pill counts, TLFB for heavy drinking, OCDS, PEth, HIV drug resistance testing, HIV biological markers (CD4 lymphocyte count and HIV RNA levels), liver enzymes, platelet counts, hemoglobin, creatinine, sexual risk behavior assessment, BAC, ASI, BSI, SIP, Brief Pain Inventory, TSR, SF-12, and Substance Use Survey.

[redacted]

Reasons for discontinuation/transfer

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If a patient develops significant psychiatric difficulties (suicidal or homicidal ideations, or psychosis) they will be referred to an independent psychiatrist for evaluation. The psychiatrist will determine whether patients can continue to safely receive care for their heavy drinking in the Nathan Smith Clinic or should be referred for alternate treatment.

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Table 1: Summary of Study Assessments

	Wk -1	Wk 0	Wk 2	Wk4	Wk 6	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Mn 9	Mn 12
History (demographic and clinical data) and physical exam	X											
Chart review for historical genotypic information	X											
SCID	X											
AUDIT	X											
OPRM1 genotyping	X											
Hepatitis B and C serologies	X											
Urine pregnancy test	X			X		X	X	X	X			
Liver enzymes (AST, ALT, GGT)	X			X		X	X	X	X	X	X	X
CBC, chemistries	X			X		X	X	X	X	X	X	X
CD4 count and HIV RNA	X			X		X	X	X	X	X	X	X
Standard HIV drug resistance testing and ultra-deep sequencing	X			X		X	X	X	X	X	X	X
Pharmacy fill/refill data for HAART adherence	X						X			X	X	X
Urine Drug Screen (for THC, opioids, coke, benzos at baseline; for opioids at other timepoints prior to VIVITROL injection)		X		X		X	X	X	X			
ACTG HAART medication adherence		X	X	X	X	X	X	X	X	X	X	X
HAART Persistence Questions		X	X	X	X	X	X	X	X	X	X	X
Visual Analog Scale (10cm): Adherence		X	X	X	X	X	X	X	X	X	X	X
Morisky 4-item Adherence Scale		X	X	X	X	X	X	X	X	X	X	X
Time-Line Follow Back (TLFB) for alcohol consumption	X		X	X	X	X	X	X	X	X	X	X
Alcohol Craving analog scale		X		X		X	X	X	X	X	X	X
OCDS		X		X		X	X	X	X	X	X	X
Substance Use Survey		X		X		X	X	X	X	X	X	X
PEth testing		X					X			X		X
Breathalyzer test (BAC)		X	X	X	X	X	X	X	X	X		
Sexual risk behaviors		X		X		X	X	X	X	X	X	X
SF-12		X		X		X	X	X	X	X	X	X
TSR				X		X	X	X	X	X	X	X
ASI-Lite		X								X		X
BSI		X								X		X
SIP		X								X		X
Brief Pain Inventory (+ Supplement)		X								X		X
SAFTEE		X	X	X	X	X	X	X	X	X		
VIVITROL injection		X		X		X	X	X	X			
Counseling Session		X	X	X	X	X	X	X	X			
Assessment compensation	X			X		X	X	X	X	X	X	X
Patient satisfaction survey							X			X		

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4. **Statistical Considerations:** Describe the statistical analyses that support the study design.

Data monitoring

Our Web-based computer system, TrialDB, for data collection is used by the research assistant to administer the research instruments from any computer with Internet access. TrialDB is a Web-accessible, multi-disciplinary database for study- or disease-specific clinical research data designed to store the focused data required for clinical trials and clinical research studies. TrialDB is "open-source" software developed [redacted] at the Yale Center for Medical Informatics (YCMI) and is being used at Yale and outside Yale to support clinical trials and clinical research. TrialDB has a large number of advanced features for data management and monitoring, including standard web reports and exports to SAS, SPSS, and SQL.

The core of this system will consist of a database hosted on a network of secure servers that are capable of collecting and storing data using Web-based applications that are accessed by remote users via standard Internet browsers such as Netscape or Microsoft's Internet Explorer. The system meets the highest security and reliability standards. All connections to the systems are secured and encrypted using 128-bit strong encryption protocols and only authorized users are able to access the system. The core of this system will consist of a SQL Server database and a Web server capable of collecting data and storing data using Web-based applications that are accessed by remote users via Microsoft's Internet Explorer. The system meets the highest security and reliability standards. All connections to the systems are secured and encrypted using 128-bit strong encryption protocols and only authorized users are able to access the system. All data is stored and backed up on servers located in a secured environment. Electronic files of all study data can be transferred securely to designated and authorized persons at any point during or after the study. At the request of the Principal Investigator, the host will erase all data from its systems and backed up data. This approach complies with security requirements and is consistent with other current projects that are being conducted.

Statistical analyses

General considerations: Statistical procedures and models for analyzing data have been selected according to the research hypotheses being investigated and the types of data available. In general, p-values <0.05 will be considered statistically significant. When necessary, however, we will use appropriate corrections of p-values to account for multiple statistical tests. Statistical analyses will be conducted on an intention-to-treat sample using SAS Release 8.1 (SAS Institute, Inc., Cary, NC) and SPSS 14.0 (SPSS Inc., Chicago IL) statistical packages. Where appropriate, hypotheses will be tested by independent statistical analyses using Mixed Models procedure to test for significant effect of group assignment (VIVITROL vs. placebo), time, and the interaction between group assignment and time. Loss to follow-up is of concern in longitudinal analyses, particularly if loss to follow-up is differential. We plan to use established strategies (> 90% follow-up) to reduce loss to follow-up [122, 124]. A benefit of the mixed effects models approach is that subjects who do not have complete information on the outcome variable can be included, provided that missing data is missing at random.

Specific Aim 1: To compare the efficacy of VIVITROL +MM/MC versus placebo +MM/MC on adherence to HAART.

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Hypothesis 1: VIVITROL +MM/MC will lead to improved adherence to HAART when compared to placebo + MM/MC.

HAART medication adherence, specifically focusing on the proportion of patients achieving 95% or greater HAART adherence (See justification for this threshold in Section B.7.), will be evaluated using pharmacy fill/refill data on a monthly basis and self-report. For each month of the 24-week treatment period, and the 9 and 12 month follow-up periods, we will calculate the number of days of HAART medication adherence. Because HAART, the simultaneous use of ≥ 3 antiretroviral medications, is considered the standard of care for HIV-infected individuals, patients will be classified as adherent when their regimen medication possession ratio (MPR) (calculated as the days' supply of medication divided by the number of days between the first fill and the last refill [84]) is > 0.95, signifying greater than 95% adherence. We will also capture the MPR of all anti-retroviral medications. In prior work, we have shown that over a one year study period in VACS, the HAART MPR was 70% compared to 77% of any anti-retroviral total (Kim et al, unpublished). For patients who are on HAART but less than 95% adherent, we will determine what proportion of this group achieved greater than 95% adherence.

For primary outcome analysis, both aggregate and stratified analyses will be carried out to compare the proportion of participants in each of the two groups who achieve ≥95% adherence during the last four months of observation.

The probability of achieving the primary outcome will be modeled using logistic regression analysis. An unadjusted model (treatment) and models that include covariate adjustment (treatment plus other predictor variables eg depression, race, opiate receptor genetics, CD4 level, viral load level) will be executed.

In addition and, as appropriate, linear mixed effects models will be used to assess changes in adherence over the six months of observation. Models will include a fixed effect for treatment status, time as a continuous variable representing the month of observation, and the interaction between treatment and time in order to assess difference in slopes of change by treatment status. Random effects will be included to account for intra-subject correlation of repeated measures. Additional factors that may impact rate of change in adherence include time-varying covariates such as CD4 and viral load. Model fit will be assessed with analysis of residuals and other standard methods for assessing goodness-of-fit [136].

There are multiple strategies to measure adherence (See Sections B.8. and B.9.). Based on strong evidence in support of this strategy [72, 88, 89], we have chosen to examine the percentage of patients, using pharmacy fill-refill data, who achieve 95% or better adherence to their HAART treatment as our primary outcome measure of adherence [60, 117]. We will also examine adherence using self-report data collected using AIDS Clinical Trials Group (ACTG) assessment. Patients will be classified as meeting the criteria for greater than 95% adherence if they are adherent 29-30 days out of the past 30 days. We will use the Chi-Square test to compare the proportion of patients in each randomization group meeting these criteria during each month of the study. The t-test will be used to compare HAART medication adherence between the two treatment conditions based on self-report.

Specific Aim 2: To compare the efficacy of VIVITROL +MM/MC versus placebo +MM/MC in reducing days of heavy drinking.

Hypothesis 2: VIVITROL +MM/MC counseling will lead to greater reductions in the number of days of heavy drinking when compared to placebo + MM/MC.

We plan to use a standard alcohol consumption outcome, the number of days of heavy drinking (4 or more drinks per drinking occasion for women and 5 or more drinks per drinking occasion for men) in the past 30 days. This measurement was one of the outcomes

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that differed between the control and VIVITROL group in the recent study of extended release VIVITROL [57]. The planned analyses for this outcome will include examining the number of days of heavy drinking over the 24-week treatment period and at the 9-month and 12-month follow-up periods. This measure will be based on self-reported alcohol use from the Time-Line Follow Back. Since individuals may choose to leave during treatment and a small proportion could be lost to follow-up we plan to use repeated measures analysis of variance with the MIXED Models procedure. The MIXED Models procedure was designed for unbalanced repeated measures with missing data, allowing for intra-participant serial correlation and unequal variance and covariance structure across time [137]. A repeated measures analysis of variance in the Mixed Models procedure takes into consideration differences that may emerge over time, and we will use this procedure to test for a significant treatment effect, time effects, and the interaction of these two on the primary outcome measure.

Specific Aim 3 (Exploratory): To explore the effect of VIVITROL +MM/MC versus placebo +MM/MC on biologic outcomes including:
3a) HIV markers—viral mutations (using standard assays and ultra-deep sequencing), CD4 lymphocyte count and HIV RNA level; and
3b) Liver function tests

Specific Aim 3a:

To compare differences between the two treatment conditions in the impact on viral mutations, we will use descriptive statistics to report the prevalence of current HIV drug resistance mutation patterns at baseline and at 24-weeks, 9 and 12 months. HIV resistance mutations, as defined by the International AIDS Society guidelines [138], will be evaluated. We will evaluate the association between heavy drinking and HIV viral mutations first in a dichotomous way. We will evaluate the bivariate association of heaving drinking and viral mutations and conduct a chi-square evaluation that contrasts the development of HIV viral mutations (positive vs. negative) with heavy drinking (yes vs. no). Subsequently we will conduct exploratory analyses using multinomial logistic regression to adjust for the potential effects of prior resistance mutations, antiretroviral medication class, duration of HIV disease, and duration of HAART. We will explore the effect of HAART adherence on the relationship between heavy drinking and the development of HIV drug resistance using sequential modeling to test for a potential mediating effect of HAART adherence. Finally, we will conduct an exploratory analysis to determine if the presence and quantity of minor variants affects virologic and HIV outcomes.

To compare differences between the treatment conditions, monthly CD4 lymphocyte counts and HIV RNA will be evaluated using the Mixed Models repeated-measures analysis controlling for baseline differences. To compare differences between the treatment conditions on their impact on liver function tests and Fib-4, we will use the Mixed Models repeated-measures analysis controlling for baseline differences.

We also plan to explore the effect of the treatment conditions on sexual risk behaviors (as measured by the HRBS on a monthly basis). A Mixed Models repeated-measures analysis will be used to evaluate treatment group, time, and interaction effects. We will also collect data on baseline hepatitis status, depressive symptoms at baseline and at the completion of the study, and any side effects reported by patients during the course of the study.

1. **Identification of Drug, Device or Biologic:** What is (are) the **name(s)** of the drug(s), device(s) or biologic(s) being used? Identify whether FDA approval has been granted and for what indication(s).

Extended release formulation of naltrexone (XR-NTX; Vivitrol ®).

All protocols which utilize a drug, device or biologic **not** approved by, but regulated by, the FDA must provide the following information: ☒ **Not applicable to this research project**

i. What is the Investigational New Drug (IND) or Investigational Device Exemption (IDE) **number** assigned by the FDA?

ii. For IDE's: Did the FDA approve this IDE as a Category A (experimental/investigational) or as a Category B (non-experimental/investigational)?

iii. Who holds the IND or IDE?

The clinical investigation of a drug product that is lawfully marketed in the United States may be exempt from the requirements for filing an IND. If there is no IND and an exemption is being sought, complete the following: NA

i. Is the intention of the investigation to report to the FDA as a well controlled study in support of a new indication for use or to be used to support any other significant change in the labeling for the drug? ☐ Yes ☐ No

1. If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, is the intention of the investigation to support a significant change in the advertising for the product? ☐ Yes ☐ No

iii. Does the investigation involve a route of administration or dosage level or use in populations or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product? ☐ Yes ☐ No

1. Will the investigation be conducted in compliance with the requirements for institutional (HIC) review and with the requirements for informed consent of the FDA regulations (21 CFR Part 50 and 21 CFR Part 56)? ☐ Yes ☐ No

v. Will the investigation be conducted in compliance with the requirements regarding promotion and charging for investigational drugs? ☐ Yes ☐ No

2. **Background Information:** Provide a description of previous human use, known risks, and data addressing dosage(s), interval(s), route(s) of administration, and any other factors that might influence risks. If this is the first time this drug is being administered to humans, include relevant data on animal models.

Numerous studies have found NTX to be safe and rarely associated with toxicity or severe side effects. These side effects appear to be dose-related and are less likely to occur at the dose proposed in this study. The most frequently reported side effects are gastrointestinal in nature, including epigastric pain, nausea and vomiting. Other, less frequent side effects include nervousness, headaches, low energy, sweating, joint and muscle pain, blurred vision and insomnia. Hepatotoxicity can occur but typically at much higher doses (e.g., 200-300 mg daily) and resolves when NTX is discontinued. Additionally, case reports have reported elevated liver enzyme tests in patients who were taking non-steroidal anti-inflammatory drugs in combination with high-dose NTX. NTX has been shown to have an effect on the embryo in the rat and the rabbit when given in doses approximately 140 times the human therapeutic dose.

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Thus, we will not enroll pregnant or nursing women or those who do not agree to use a reliable form of birth control. NTX, as an opioid antagonist, can block the effects of opioids and can precipitate opioid withdrawal in an opioids dependent individual. Thus, we will not enroll opiate dependent individuals, those requiring opioids for analgesia, and those who have a positive urine toxicology test for opioids.

Before FDA approval, extended release naltrexone was studied in more than 900 patients [63]. Extended release naltrexone appears to be generally well tolerated, and adverse effects tend to be mild [61, 110]. Patients using extended release naltrexone do not develop tolerance for or dependence on the medication.

The extended release formula has been shown to be safe, tolerable, and efficacious in the treatment of alcohol use disorders [61]. In this large 6-month multi-site study in the treatment of alcohol dependence the most common adverse events (AEs) were nausea, headache, and fatigue. Other less common AEs included insomnia, vomiting, decreased appetite, diarrhea, dizziness, injection site pain, nasopharyngitis, and upper respiratory tract infection. Nausea was mild or moderate in 95% of cases; however the large majority of these cases occurred only during the first month of treatment. The most common injection site reaction was tenderness. Seven patients (1%) discontinued injections due to site reactions. Study discontinuation secondary to AEs occurred in 29 (14.1%) of the 380mg naltrexone group, 14(6.7%) of the 190mg group, and 14 (6.7%) in the placebo group. Group differences were accounted for by a greater number of AEs of nausea, injection site reaction, and headache. The percentage of patients who experienced serious AEs (SAEs) was similar among groups (5.4% for 380mg, 4.8% for 190mg, and 7.2% for placebo). The most common SAE was hospitalization for alcohol intoxication. Two SAEs (eosinophilic pneumonia and interstitial pneumonia) were judged as possibly related to study medications. Mean AST and ALT levels did not change significantly over the course of treatment or with medication. A recent large study of extended release NTX found that mean liver enzymes did not change significantly over the course of treatment and there was no effect of medication on the proportion of patients in the different groups who had liver enzyme elevations higher than 3 times the upper limit of normal [61]. In addition, it has been found to be safe for use in patients with mild to moderate liver impairment [109] with evidence of a 15% greater reduction in liver enzyme levels in the NTX group as compared with the placebo group [110].

In a 3-month study of 315 alcohol dependent patients [110] who received monthly injections of NTX, there were no major differences between the NTX group and the placebo group in terms of serious adverse events, adverse events other than injection site reactions, or reactions at the injection site. Six subjects experienced serious adverse events. One subject in the NTX group experienced two such events (i.e., an orbital fracture and a human bite to the face). Five subjects in the placebo group experienced serious adverse events (three subjects were hospitalized due to alcoholic relapse, one of whom required detoxification and had suicidal depression; one subject required surgical repair of an ulnar fracture; and one subject was hospitalized for cellulitis at the injection site, which resolved within 2 weeks). There was no overall group difference in the percentage of patients reporting one or more adverse events. The most common adverse events were headache, nausea, and fatigue. Three adverse events differed significantly by treatment group: upper abdominal pain was more common in the NTX group, and irritability and chest pain occurred more commonly among placebo subjects. Injection site adverse events occurred at an overall frequency of 5% and this rate differed significantly by group. A significantly greater percentage of subjects in the NTX group reported one or more injection site reactions. The most common injection site reactions were pain, induration, and contusion, with a trend for pain to be more common in the NTX group.

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While the concern for NTX's hepatotoxicity appropriately warrants monitoring of liver function, theoretically and based on the minimal existing literature on interactions between NTX and HAART, these interactions should be clinically insignificant. Many of the medications used for the treatment of HIV are metabolized via the cytochrome P-450 system (CYP450) leading to issues surrounding drug interactions with a number of medication classes. The metabolism of NTX, however, is not entirely metabolized via CYP450 and therefore significant interactions with HAART medications would not be expected [111, 112]. The first step of NTX metabolism involves hydroxylation which likely involves the CYP450 system. The second step, glucuronidation, does not involve the CYP450 system. These findings would indicate that given the hydroxylation step being CYP450-dependent, it is important to monitor for interactions with the non-nucleoside reverse transcriptase class of HIV medications as well as being vigilant to the fact that patients with impaired hepatic function due to HCV or alcohol dependence. One study evaluating the effect of opioid medications on the disposition of the antiretroviral medication zidovudine (AZT) found that NTX had no significant effect on the area under the curve, maximal concentration or half-life of AZT [113]. In turn, another study suggested that NTX might potentiate the antiviral effects of AZT and one of the protease inhibitors Indinavir, increasing their antiviral activity 2-3 fold [9]. In addition, a large multi-center safety study of the use of NTX for alcoholism in 865 individuals, including patients with comorbid psychiatric illness, concomitant medications, polysubstance abuse, and HIV demonstrated that serious side effects in these populations were uncommon [115]. While this study was not randomized in design and was intended to look at medication interactions, the findings are reassuring for patients with HIV disease. Extended release naltrexone is approved for use in patients who meet criteria for Childs-Pugh A and B liver disease. While these data are reassuring, monitoring of liver function, to assess for hepatotoxicity, will be important, especially in HIV/HCV co-infected patients. The proposed study will systematically examine the question of medication interactions by closely following for adverse effects.

3. **Source:** a) Identify the source of the drug, device or biologic to be used.
   Extended release VIVITROL will be provided from Alkermes Inc., Waltham, MA. Injectable placebo will be donated by Alkermes.

   b) Is the drug or device provided free of charge? ☒ Yes ☐ No, the medication will be paid for with funding from the grant (NIAAA).
   If yes, by whom? VIVITROL will be donated by Alkermes.

4. **Preparation and Use:** Describe the method of preparation, storage, stability information, and for parenteral products, method of sterilization and method of testing sterility and pyrogenicity.

5. **Use of Placebo:** ☐ **Not applicable to this research project**
   Provide a justification which addresses the following:
   a. Describe the safety and efficacy of other available therapies (if any).

   Other medication options that have been approved for the treatment of alcohol problems by the Food and Drug Administration (FDA) are acamprosate (Campral), and disulfiram (Antabuse). As with NTX and with any other medication, acamprosate, disulfiram, and topiramate (currently not FDA-approved for treatment of alcohol problems) have side effects about which patients should be informed by their physicians. Other non-medication treatments include psychotherapy and referral to Alcoholics Anonymous or other support groups. All three medications and forms of psychotherapy such as cognitive behavioral therapy and

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motivational interviewing have been found to be efficacious in the treatment of alcohol problems.

b. State the maximum total length of time a participant may receive placebo while on the study.

24 weeks.

c. Address the greatest potential harm that may come to a participant as a result of not receiving effective therapy (immediate or delayed onset.)

Throughout the study both groups, the naltrexone and the placebo group, will receive psychosocial counseling focused on reducing their heavy drinking. This form of treatment, while not pharmacotherapy, has been shown to be effective therapy for heavy drinking and alcohol abuse and dependence.

d. Describe the procedures that are in place to safeguard participants receiving placebo.

All participants will be informed that there is a chance that they may receive placebo as part of this study. All participants will receive active therapy in the form of psychosocial counseling which will include Medical Management and Medication Coaching which focuses on helping patients take their antiretroviral medication. They will receive this combined counseling treatment during 8 sessions.

6. **Use of Controlled Substances:**
Will this research project involve the use of controlled substances in human subjects?
☐ Yes ☒ No See instructions to view controlled substance listings.

If yes, is the use of the controlled substance considered:
☐ Therapeutic: The use of the controlled substance, within the context of the research, has the potential to benefit the research participant.
☐ Non Therapeutic: Note, the use of a controlled substance in a non therapeutic research study involving human subjects may require that the investigator obtain a Laboratory Research License. Examples include controlled substances used for basic imaging, observation or biochemical studies or other non-therapeutic purposes. See Instructions for further information.

7. **Continuation of Drug Therapy After Study Closure** ☐ **Not applicable to this project**
Are subjects provided the opportunity to continue to receive the study drug(s) after the study has ended? ☐ Yes ☒ No
If yes, describe the conditions under which continued access to study drug(s) may apply as well as conditions for termination of such access.

SECTION VII: HUMAN SUBJECTS

1. **Recruitment Procedures:** How will potential subjects be identified, contacted and recruited? Attach copies of any recruitment materials that will be used.

☒ Flyers	☒ Internet/Web Postings	☐ Radio
☐ Posters	☐ Mass E-mail Solicitation	☐ Telephone
☐ Letter	☐ Departmental/Center Website	☐ Television
☐ Medical Record Review	☐ Departmental/Center Research Boards	☐ Newspaper

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☐ Departmental/Center Newsletters ☐ Web-Based Clinical Trial Registries
☒ Other (describe): ☒ Clinicaltrials.gov Registry (do not send materials to HIC)

Recruitment will occur by conducting AUDIT-C screenings at the study sites in coordination with the clinical teams. In addition to recruiting through clinics (NSC, West Haven VA, and the Haelen Center), we will recruit at sites that provide services to HIV-infected patients, including AIDS Project New Haven, Hill Health Center, Fair Haven Community Health Center, Hispanos Unidos, and Liberty Housing.

Recruitment via Respondent Driven Sampling (RDS):

In addition to the recruitment methods listed above, a sampling approach termed respondent driven sampling (RDS) will be employed. One of the goals of this approach is to gain more access to subjects that would not ordinarily present for routine medical care. In using RDS, we will attempt to engage our current study participants as active recruiters by way of the provision of incentives. Each study participant will be offered the opportunity to participate in recruitment of other subjects. If they choose not to participate, this in no way will affect their treatment in the study. Those subjects who agree to participate in RDS will each be given 5 coupons, [redacted] for each enrollee they recruit. To create waves of chain referral, participants are given these coupons to give to other out-of-treatment HIV positive patients with heavy drinking or alcohol abuse/dependence they seek to refer to the study. To protect the confidentiality of all respondents, each participant is assigned a series of unique coupon identification codes, and these codes will be placed on the coupons. These codes will be stored in a secure central database. [redacted]

1.a. **Assessment of Current Health Provider Relationship for HIPAA Consideration:**
Does the Investigator or any member of the research team have a direct existing clinical relationship with any potential subject?

☐ Yes, all subjects
☒ Yes, some of the subjects
☐ No
If yes, describe the nature of this relationship.

Some of the members of the research team may have a clinical relationship with patients who subsequently enroll as subjects in the study.

2. **Subject Population** Provide a detailed description of the targeted involvement of human subjects for this research project.

Participants will be 50 HIV-infected men and women who report heavy drinking, alcohol abuse or dependence. Referrals will come from within the Nathan Smith Clinic HIV clinic sites, via local HIV care sites, website advertisements, local papers, community postings, community physicians, other patients, local mental health centers, local hospitals, and substance abuse treatment facilities.

3. **Inclusion/Exclusion Criteria:** What are the criteria used to determine subject inclusion or exclusion? How will eligibility be determined, and by whom?

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Inclusion criteria: Each subject must:

1. 1.Be HIV-infected.
2. Be currently prescribed HAART medication.
3. Report less than 95% adherence to their HAART medication.
4. Report heavy drinking 4 or more times in the past 4 weeks, or meets current criteria for alcohol abuse or dependence. Heavy drinking is defined as 4 or more drinks for women and 5 or more drinks for men on an occasion.
5. Be at least 18 years old.
6. Be able to understand English and provide informed consent.

Exclusion criteria: No subject may:

1. Be psychotic or severely psychiatrically disabled.
2. Be currently enrolled in formal treatment for alcohol (excluding self-help, e.g. Alcoholics Anonymous)
3. Have medical conditions that would preclude completing or be of harm during the course of the study.
4. Have laboratory or clinical evidence of significant liver dysfunction (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 5 times the upper limit of the normal range) or cirrhosis with a Child-Pugh classification greater than A or B.
5. Have a known contraindication to NTX therapy (e.g. requiring opioid medication for pain).
6. Be pregnant, nursing or unable to use an effective method of birth control (women).
7. Patients with a positive urine opioid screen result
8. Known hypersensitivity to naltrexone, PLG (polylactide-co-glycolide, carboxymethylcellulose, or any other components of the diluent

Subjects will first be screened by the research assistant and final eligibility will be determined by the Investigators. Research participants will be interviewed by specially trained research assistants, using standardized psychological assessments. Participants will also complete self-report rating forms.

3.a. Will email or telephone correspondence be used to screen potential subjects for eligibility prior to the potential subject coming to the research office? ☒ Yes ☒ No

3.b. If yes, will identifiable health information be collected during this screening process and retained by the research team? ☐ Yes ☒ No

4. **Subject Classifications: Check off all classifications of subjects that will be invited to enroll in the research project.** Will subjects, who may require additional safeguards or other considerations, be enrolled in the study? If so, identify the population of subjects requiring special safeguards and provide a justification for their involvement.

☐ Children	☒ Healthy	☐ Fetal material, placenta, or dead fetus
☐ Non-English Speaking	☐ Prisoners	☐ Economically disadvantaged persons
☐ Decisionally Impaired	☐ Employees	☐ Pregnant women and/or fetuses
	☐ Students	☐ Females of childbearing potential

a. Is this research proposal designed to enroll children who are wards of the state as potential subjects? ☐ Yes ☒ No (If yes, see Instructions section VII #4 for further requirements)

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SECTION VIII: CONSENT/ ASSENT PROCEDURES

1. **Consent Personnel:** List all members of the research team who will be obtaining consent/assent.

   Stephen Holt (Project Director), [redacted] Jennifer Edelman, Lynn Fiellin, David Fiellin, and Patrick O'Connor (Investigators).

2. **Process of Consent/Assent:** Describe the setting and conditions under which consent/assent will be obtained, including parental permission or surrogate permission and the steps taken to ensure subjects' independent decision-making.

   Participants will be recruited through clinical sites, word of mouth, flyers, posters, websites, and advertisements. A phone number will be provided for potential participants to call to arrange an appointment to come speak to a Research Assistant about the study. During this meeting, the research assistant will describe the study in more detail, determine interest in participating, and assess potential eligibility. After fully informing participants about the study and answering any questions, the research assistant will obtain written informed consent from participants for participating in the study and allowing us to complete all baseline evaluations and to assess them throughout the study. Prior to admitting the participant to the treatment phase of the study, all participants will be evaluated by the study physician or nurse who will review all medical and assessment data, review the study protocol with the participant, and discuss the risks and benefits of treatment with VIVITROL. Individuals who do not meet eligibility criteria or who decline to take part in the study will be referred to an appropriate treatment program. Once the subject has signed the consent, they may withdraw consent at any time.

3. **Evaluation of Subject(s) Capacity to Provide Informed Consent/Assent:** Indicate how the personnel obtaining consent will assess the potential subject's ability and capacity to consent to the research being proposed.

   This research does not involve subjects with limited decision making capacity.

4. **Documentation of Consent/Assent:** Specify the documents that will be used during the consent/assent process. Copies of all documents should be appended to the protocol, in the same format that they will be given to subjects.

   Please see attached consent forms.

5. **Non-English Speaking Subjects:** Explain provisions in place to ensure comprehension for research involving non-English speaking subjects. Translated copies of all consent materials must be submitted for approval prior to use. NA

6. **Waiver of Consent:** Will you request either a waiver of consent, or a waiver of signed consent, for this study? If so, please address the following:
   ☒ **This section is not applicable to this research project**
   Waiver of consent: (No consent form from subjects will be obtained.)

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a. Does the research pose greater than minimal risk to subjects? ☐ Yes ☐ No
b. Will the waiver adversely affect subjects' rights and welfare? ☐ Yes ☐ No
c. Why would the research be impracticable to conduct without the waiver?
d. Where appropriate, how will pertinent information be returned to, or shared with subjects at a later date?

Waiver of **signed** consent: (Verbal consent from subjects will be obtained.)

☒ **This section is not applicable to this research project**

a. Would the signed consent form be the only record linking the subject and the research? ☐ Yes ☐ No
b. Does a breach of confidentiality constitute the principal risk to subjects? ☐ Yes ☐ No

OR

c. Does the research pose greater than minimal risk? ☐ Yes ☐ No **AND**
d. Does the research include any activities that would require signed consent in a non-research context? ☐ Yes ☐ No

7. **Required HIPAA Authorization:** If the research involves the creation, use or disclosure of protected health information (PHI), separate subject authorization is required under the HIPAA Privacy Rule. Indicate which of the following forms are being provided:

☐ Compound Consent and Authorization form
☒ HIPAA Research Authorization Form

1. **Request for waiver of HIPAA authorization:** (When requesting a waiver of HIPAA Authorization for either the entire study, or for recruitment purposes only)

Choose one: For entire study: _____ For recruitment purposes only: _____

1. Describe why it would be impracticable to obtain the subject's authorization for use/disclosure of this data;
2. If requesting a waiver of **signed** authorization, describe why it would be impracticable to obtain the subject's signed authorization for use/disclosure of this data;

By signing this protocol application, the investigator assures that the protected health information for which a Waiver of Authorization has been requested will not be reused or disclosed to any person or entity other than those listed in this application, except as required by law, for authorized oversight of this research study, or as specifically approved for use in another study by an IRB.

Researchers are reminded that unauthorized disclosures of PHI to individuals outside of the Yale HIPAA-Covered entity must be accounted for in the "accounting for disclosures log", by subject name, purpose, date, recipients, and a description of information provided. Logs are to be forwarded to the Deputy HIPAA Privacy Officer.

SECTION IX: PROTECTION OF RESEARCH SUBJECTS

1. **Risks:** Describe the reasonably foreseeable risks, including risks to subject privacy, discomforts, or inconveniences associated with subjects participating in the research.

Naltrexone (NTX): Numerous studies have found NTX to be safe and rarely associated with toxicity or severe side effects. These side effects appear to be dose-related and are less likely to occur at the dose proposed in this study. The most frequently reported side effects are gastrointestinal in nature, including epigastric pain, nausea and vomiting. Other, less frequent side effects include nervousness, headaches, low energy, sweating, joint and muscle pain, blurred vision and insomnia. Hepatotoxicity can occur but typically at much higher doses (e.g., 200-300 mg daily) and resolves when NTX is discontinued. Additionally, case reports have reported elevated liver enzyme tests in patients who were taking non-steroidal anti-inflammatory drugs in combination with high-dose NTX. NTX has been shown to have an effect on the embryo in the rat and the rabbit when given in doses approximately 140 times the human therapeutic dose. Thus, we will not enroll pregnant or nursing women or those who do not agree to use a reliable form of birth control. NTX, as an opioid antagonist, can block the effects of opioids and can precipitate opioid withdrawal in an opioids dependent individual. Thus, we will not enroll opiate dependent individuals, those requiring opioids for analgesia, and those who have a positive urine toxicology test for opioids.

Before FDA approval, extended release naltrexone was studied in more than 900 patients [63]. Extended release naltrexone appears to be generally well tolerated, and adverse effects tend to be mild [61, 110]. Patients using extended release naltrexone do not develop tolerance for or dependence on the medication.

The extended release formula has been shown to be safe, tolerable, and efficacious in the treatment of alcohol use disorders [61]. In this large 6-month multi-site study in the treatment of alcohol dependence the most common adverse events (AEs) were nausea, headache, and fatigue. Other less common AEs included insomnia, vomiting, decreased appetite, diarrhea, dizziness, injection site pain, nasopharyngitis, and upper respiratory tract infection. Nausea was mild or moderate in 95% of cases; however the large majority of these cases occurred only during the first month of treatment. The most common injection site reaction was tenderness. Seven patients (1%) discontinued injections due to site reactions. Study discontinuation secondary to AEs occurred in 29 (14.1%) of the 380mg naltrexone group, 14 (6.7%) of the 190mg group, and 14 (6.7%) in the placebo group. Group differences were accounted for by a greater number of AEs of nausea, injection site reaction, and headache. The percentage of patients who experienced serious AEs (SAEs) was similar among groups (5.4% for 380mg, 4.8% for 190mg, and 7.2% for placebo). The most common SAE was hospitalization for alcohol intoxication. Two SAEs (eosinophilic pneumonia and interstitial pneumonia) were judged as possibly related to study medications. Mean AST and ALT levels did not change significantly over the course of treatment or with medication. A recent large study of extended release NTX found that mean liver enzymes did not change significantly over the course of treatment and there was no effect of medication on the proportion of patients in the different groups who had liver enzyme elevations higher than 3 times the upper limit of normal [61]. In addition, it has been found to be safe for use in patients with mild to moderate liver impairment [109] with evidence of a 15% greater reduction in liver enzyme levels in the NTX group as compared with the placebo group [110].

In a 3-month study of 315 alcohol dependent patients [110] who received monthly injections of NTX, there were no major differences between the NTX group and the placebo group in terms of serious adverse events, adverse events other than injection site reactions, or reactions at the injection site. Six subjects experienced serious adverse events. One subject in the NTX group experienced two such events (i.e., an orbital fracture and a human bite to the face). Five subjects in the placebo group experienced serious adverse events (three subjects were

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hospitalized due to alcoholic relapse, one of whom required detoxification and had suicidal depression; one subject required surgical repair of an ulnar fracture; and one subject was hospitalized for cellulitis at the injection site, which resolved within 2 weeks). There was no overall group difference in the percentage of patients reporting one or more adverse events. The most common adverse events were headache, nausea, and fatigue. Three adverse events differed significantly by treatment group: upper abdominal pain was more common in the NTX group, and irritability and chest pain occurred more commonly among placebo subjects. Injection site adverse events occurred at an overall frequency of 5% and this rate differed significantly by group. A significantly greater percentage of subjects in the NTX group reported one or more injection site reactions. The most common injection site reactions were pain, induration, and contusion, with a trend for pain to be more common in the NTX group.

While there is an inherent risk of precipitating alcohol withdrawal in any patient with alcohol dependence who seeks medical treatment, VIVITROL does not itself increase the risk of alcohol withdrawals. Alcohol withdrawal syndromes are not listed as known adverse reactions to this medication, nor is there any physiologic mechanism by which VIVITROL should precipitate withdrawal, insofar as VIVITROL has no direct alcohol antagonistic effects. Moreover, the current proposal emphasizes *cutting back* on drinking, rather than abstinence, which further attenuates any theoretical risk of alcohol withdrawal. Thus, while each subject is followed closely by a physician or nurse practitioner throughout the course of the study, no additional monitoring for alcohol withdrawal is indicated. Nonetheless, patients will be cautioned regarding the signs and symptoms of alcohol withdrawal syndromes, and will be provided relevant emergency contact information in the event that they begin to experience such symptoms. Should they experience symptoms of alcohol withdrawal patients will be instructed to seek emergency medical care without delay and to contact the study team as soon as they are able.

While the concern for NTX's hepatotoxicity appropriately warrants monitoring of liver function, theoretically and based on the minimal existing literature on interactions between NTX and HAART, these interactions should be clinically insignificant. Many of the medications used for the treatment of HIV are metabolized via the cytochrome P-450 system (CYP450) leading to issues surrounding drug interactions with a number of medication classes. The metabolism of NTX, however, is not entirely metabolized via CYP450 and therefore significant interactions with HAART medications would not be expected [111, 112]. The first step of NTX metabolism involves hydroxylation which likely involves the CYP450 system. The second step, glucuronidation, does not involve the CYP450 system. These findings would indicate that given the hydroxylation step being CYP450-dependent, it is important to monitor for interactions with the non-nucleoside reverse transcriptase class of HIV medications as well as being vigilant to the fact that patients with impaired hepatic function due to HCV or alcohol dependence. One study evaluating the effect of opioid medications on the disposition of the antiretroviral medication zidovudine (AZT) found that NTX had no significant effect on the area under the curve, maximal concentration or half-life of AZT [113]. In turn, another study suggested that NTX might potentiate the antiviral effects of AZT and one of the protease inhibitors Indinavir, increasing their antiviral activity 2-3 fold [9]. In addition, a large multi-center safety study of the use of NTX for alcoholism in 865 individuals, including patients with comorbid psychiatric illness, concomitant medications, polysubstance abuse, and HIV demonstrated that serious side effects in these populations were uncommon [115]. While this study was not randomized in design and was intended to look at medication interactions, the findings are reassuring for patients with HIV disease. Extended release naltrexone is approved for use in patients who meet criteria for Childs-Pugh A and B liver disease. While these data are reassuring, monitoring of liver function, to assess for

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hepatotoxicity, will be important, especially in HIV/HCV co-infected patients. The proposed study will systematically examine the question of medication interactions by closely following for adverse effects.

To examine antiretroviral and hepatic safety in HIV-infected patients receiving naltrexone we conducted an analysis of the NIAAA-funded VACS Virtual Cohort. All patients were receiving antitretroviral medications. The median duration of naltrexone treatment for the cohort was 90 days. We compared CD4 cell count, HIV viral load (VL), AST and ALT during the period in which patients had received a prescription for naltrexone. We compared baseline and follow-up laboratory results using descriptive statistics and Wilcoxon signed-rank tests. The results are included in the table below.

First and last labs for HIV-infected patients receiving naltrexone and antiretroviral medications

Labs	N	Median At First date (IQR)	Median At Last Date (IQR)	P-Value*
CD4	58	323 (156-573)	441 (243-612)	.06
VL	54	1916 (399.7-35977)	879 (75-16582)	.3
AST	52	53 (41-80)	66 (40-139)	.2
ALT	63	36 (21-74)	48 (33-115)	.2

In addition, in a recent 6-month randomized clinical trial (unpublished) evaluating buprenorphine/naloxone versus naltrexone therapy for the treatment of opioid dependence, 12 HIV-infected patients received naltrexone at a dose of 50 mg per day (**Schottenfeld RS, Chawarski MC, Mazlan M.** Maintenance treatment with buprenorphine and naltrexone for heroin dependence in Malaysia: a randomised, double-blind, placebo-controlled trial. *Lancet*. 2008;371(9631):2192-200). All were infected with Hepatitis C. No patients experienced adverse events that required changing the dose or discontinuing the medication. One patient experienced an isolated elevation in their ALT level.

Summary: Naltrexone treatment is associated with no significant adverse alterations in CD4, viral load, AST and ALT in HIV-infected patients who are receiving antiretroviral medication. The stability of these biological markers during naltrexone treatment supports safety when provided along with antiretroviral medications.

Interaction of NTX and alcohol: NTX has been shown to reduce the number of drinks consumed in the laboratory and in the clinic. No safety concerns have been identified in these studies when alcohol is consumed in combination with NTX. There is no evidence that individuals attempt to over-ride the effects of NTX by drinking more. NTX does not block the aversive effects of alcohol consumption which serve to limit drinking.

Counseling: There are no significant adverse effects of participating in the counseling intervention (MM/MC) portion of this study provided by the study nurse and supervised by a Clinical Psychologist. Participation is likely to be of benefit.

Breath screening, blood/urine collections: Breath screening and blood and urine collections are performed primarily as safeguards and should add no risks other than those normally associated with these procedures.

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Rating scales and questionnaires: Rating scales, structured interviews, and questionnaires are all non-invasive, and should also add no risks to subjects, as our past experience indicates.

Audiotaped sessions: Participants will be made aware during the informed consent process that sessions with the study physician or nurse will be audiotaped and that the nature of these sessions will involve participants speaking about information regarding their health status, alcohol use, HIV status, medical history, and participation in the study. However, participant names will never be recorded on the tapes and the tapes will be coded by participant number rather than name in order to protect participant confidentiality. Participants will be given the option to decline to be taped during the study.

2. **Minimizing Risks:** Describe the manner in which the above-mentioned risks will be minimized.

Naltrexone (VIVITROL): Prospective participants with medical conditions that would contraindicate the use of VIVITROL will be screened out. We will exclude individuals with evidence of significant hepatocellular injury (AST, ALT > 5 times the upper limit of normal or a diagnosis of cirrhosis and Child-Pugh class greater than A or B). The dose of VIVITROL used is low and so the risk of hepatotoxicity is low. However, we will monitor liver enzyme tests prior to, during, and at end of treatment and a subject whose AST or ALT rises to > 5 times the upper limit of normal will have laboratory tests repeated in one week. If liver enzymes are persistently elevated or if the individual is symptomatic, study medication will be discontinued and the subject will be referred for GI evaluation.

As the safety of VIVITROL has not been established in pregnant and nursing women, they will be excluded from participation. Women of child-bearing capacity must agree to use a reliable form of birth control. A urine pregnancy test will be performed at baseline and monthly. Pregnant women will be referred for other alcohol treatment. Women who become pregnant during the study will be taken off study medications immediately. Individuals with urine tests positive for recent opioid use, who are taking opioid medication for the treatment of pain, or have a diagnosis of current opioid dependence will be excluded. In case of an emergency situation requiring opioids, subjects will be provided with a card showing that they are receiving VIVITROL. This card will provide detailed information to medical personnel describing the special precautions necessary in the event that the subject should require pain management. Specifically, the amount of opioids necessary for analgesia may be greater than usual, and the resulting respiratory depression may be deeper and more prolonged. As a result, a rapidly acting analgesic that minimizes respiratory depression is preferred and the amount of the analgesic administration titrated to the needs of the patient in a setting equipped and staffed for cardiopulmonary resuscitation. In addition, this card will have a code number on it that can be used to identify which medication the subject is on. A phone number of the pharmacy and for the physician on call for the study will be listed on the card in the event of an emergency in which it is necessary to determine whether the subject is on active VIVITROL.

Rating scales and questionnaires The major risk of the assessments is the potential loss of confidentiality which is discussed in the section related to confidentiality below. To minimize any discomfort associated with reporting on sensitive behaviors, participants will be informed that they may refuse to answer questions that they are not comfortable answering. Questions related to eligibility determination and monitoring of safety and treatment response are not optional. If a person declines to answer these questions, we will advise them that they will not be able to participate and we will make a referral to other treatment if they are interested.

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Audiotaped sessions: All appropriate actions will be taken by staff members in order to minimize the risks associated with loss of confidentiality. Tapes will be coded by number and will be erased

Confidentiality: Numerous steps will be taken to protect confidentiality as described under the section on Sources of Materials (E.1.b). In addition, a Certificate of Confidentiality will be obtained from NIAAA. This certificate will protect the confidentiality of all research records generated by this study. Individually identifiable health information will be protected in accordance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996. All research personnel will be trained on Institutional Review Board (IRB) and HIPAA procedures.

In Case of Injury: If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

All participants will be asked to carry a medication card that will, in case of emergency, alert the treating medical personnel that they are taking VIVITROL. Participants will be asked to carry this card at all times. The card will include appropriate drug information and precautions. If immediate information is needed about the study, participants will be instructed to contact either the study physician or nurse.

During the follow-up period, any patient requiring additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms will receive a referral to treatment.

3. **Data and Safety Monitoring Plan:** Include an appropriate Data and Safety Monitoring Plan (DSMP) based on the investigator's risk assessment stated below. (Note: the HIC will make the final determination of the risk to subjects.) For more information, see the Instructions, page 24.
    a. What is the investigator's assessment of the overall risk level for subjects participating in this study? Moderate
    b. If children are involved, what is the investigator's assessment of the overall risk level for the children participating in this study? NA
    c. Data and Safety Monitoring Plan:

The risks associated with participating in this study can be categorized as moderate (i.e., risks are recognized as being greater than everyday risks but not high, and there is adequate surveillance and protections to discover adverse events promptly and keep their effects minimal). Because of the risks associated with this medication, we have included in the protocol procedures to exclude participants who would be at the greatest risk (e.g. concomitant significant medical conditions or liver dysfunction) and to monitor potential adverse effects and transfer patients to alternative treatment if medical problems possibly related to either of the study medications develop. The medical transfer procedure along with the procedures for detecting and responding to adverse events are sufficient to ensure prompt discovery of any adverse events and to minimize their effects. Consistent with the Data and Safety Monitoring Plan (DSMP) template of the Yale University School of Medicine, the DSMP includes provisions for data review and performance of safety reviews, as described below.

Data and safety monitoring procedures in this study include computerized data collection and monitoring systems and an organizational structure of clearly defined tasks assigned to all

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research and clinical personnel involved in the conduct of this study. The computerized data collection and monitoring system consists of a data base system that records clinical and research activities, completion of scheduled assessments, and delivers computerized versions of most of research instruments used in this study. Research assistants use this database to monitor and schedule patients and activities and to administer study assessments. Data entry of non-computerized assessments is accomplished by using specialized data entry software (such as, SPSS Data Entry or Microsoft Access Data base) facilitating efficient data entry and allowing elimination of out-of-range values and double entry of data for detection of key punch errors.

The organizational structure used to ensure quality of data in this project include: 1) extensive training and close supervision of research assistants in data collection; 2) preliminary review of all data for completeness and coding errors by data manager/analyst; and 3) utilization of error-checking statistical procedures. Experienced data manager/analysts and the PI supervise data procedures. All error corrections are fully documented in the research records of the study. All research personnel are required to participate in and document training in protection of human subjects and the responsible conduct of scientific research.

The computerized data collection and monitoring system consists of a data base system that records clinical and research activities, completion of scheduled assessments, and delivers computerized versions of most of research instruments used in this study. Research assistants use this database to monitor and schedule patients and activities and to administer study assessments. Data entry of non-computerized assessments is accomplished by using specialized data entry software (such as, SPSS Data Entry or Microsoft Access Data base) facilitating efficient data entry and allowing elimination of out-of-range values and double entry of data for detection of key punch errors.

All reports generated from this study will not contain any identifying information about the participants. Research records will be coded only by a number, and will be stored in locked cabinets. Data are stored behind the Yale's firewall on password-protected computers.

Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Data will only be reported in aggregate. Data will be de-identified prior to formal data analysis, making individual subject identification impossible. Moveable devices will be encrypted to protect identifiable information, following University policy

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State law. Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Data will only be reported in aggregate. Data will be de-identified prior to formal data analysis, making individual subject identification impossible.

Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI, investigators and study personnel will have access. All paper files with subject information will remain in locked files in the study office of the PI, until they are destroyed, after all analyses are complete.

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All clinical aspects of the study, such as treatment delivery and monitoring of subjects' progress or the lack of thereof are also fully documented and supervised. The research team meets weekly to review the overall progress of the study, as well as to review videotaped sessions and/or discuss progress of each subject in the study. All members of the research team, both research assistants and clinicians, are familiar with procedures for identifying and reporting possible adverse reactions.

All adverse events meeting the criteria for expedited reporting are reported to the Yale Institutional Review Board (IRB) using Form 6A for reporting adverse events. The Principal Investigator (PI) reviews all adverse events, classifies the attribution of adverse events (e.g., definitely, probably, possibly related; unlikely or unrelated) and grades the severity of the event, on a 6-point scale (0=no adverse event or within normal limit; 1=mild; 2=moderate; 3=severe; 4=life-threatening; 5=fatal). Serious unanticipated or anticipated adverse events will be reported immediately to NIAAA. The summary will include the number of subjects enrolled and a summary of graded adverse events to date, using the chart format included in the Yale University DSMP template. All serious adverse events will be reported to the local IRB according to local IRB requirements and to the NIAAA project officer within 48 hours. In addition, an annual report will be submitted to the NIAAA Project Officer summarizing all adverse events documented. The PI will evaluate all adverse events and determine whether the event affects the Risk/Benefit ratio of the study and whether modifications to the protocol (e.g., Risks to Subjects) or consent form (e.g., Risks and Inconveniences) are required.

Definition of Adverse Event Terms

Adverse Event – Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). [NIH Guidelines, January 2001]

Serious Adverse Event (SAE) – Any adverse drug experience occurring at any dose that results in any of the following outcomes:

1. death,
2. a life-threatening adverse drug experience,
3. in patient hospitalization or prolongation of existing hospitalization,
4. any persistent or significant disability/incapacity,
5. or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. [21CFR312.32(a)]

Life-threatening Adverse Drug Experience – Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e. it does not include a reaction that, had it occurred in a more severe form, might have caused death. [21CFR312.32(a)]

Unexpected Adverse Drug Experience – Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator

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brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.[21CFR312.32(a)]

Attribution

Assessment of attribution is made by consideration of all clinically relevant data prior to, during, and after occurrence of the event, including diagnostic tests to assess the cause of the event. Clinically relevant data include, but are not limited to; underlying disease, past and present medical history (all concurrent non-malignant disease), concurrent medications, and timing between event and drug administration. The mechanism of action and prior toxicology of the study drug should be considered.

An adverse event is *associated with the use of the drug* when there is a reasonable possibility that the experience may have been caused by the drug. [21CFR312.32(a)]

Attribution Standards

Unrelated: The Adverse Event is *clearly not related* to the investigational agent (s)
Unlikely: The Adverse Event is *doubtfully related* to the investigational agent(s)
Possible: The Adverse Event *may be related* to the investigational agent(s)
Probable: The Adverse Event is *likely related* to the investigational agent(s)
Definite: The Adverse Event is *clearly related* to the investigational agent(s)

PRINCIPAL INVESTIGATOR SAE REPORTING REQUIREMENTS

Expedited Reporting of Unexpected SAEs

AEs classified as "serious" and "unexpected" that are possibly, probably, or definitely attributed to drug administration, or SAEs whose frequency exceeds expectations, require expeditious handling and reporting.

The PI will promptly investigate all safety information related to an adverse experience. If the results of the PI's investigation show an adverse drug experience not initially determined to be reportable (based on whether the event is serious, unexpected, and associated with drug administration) is so reportable, the PI will report such experience. Follow-up information to a safety report shall be submitted as soon as the relevant information is available.

Reporting to the Yale Human Investigation Committee

All SAEs, whether originating at Yale or a collaborating center, meeting the criteria for expedited reporting will be reported to the Yale University Human Investigation Committee (HIC) using HIC Form 6A within 48 hours of discovery.

The Yale University Human Investigation Committee expedited reporting criteria are:

a. Serious AND unanticipated AND possibly, probably or definitely related events;
and

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b. Anticipated Adverse Events occurring with a greater frequency than expected.

The HIC does not require reporting of any other Adverse Event type. A copy of the HIC Adverse Event Policy is available at: http://info.med.yale.edu/hic/policy/AdverseEventPolicy.pdf

Reporting to Alkermes

Serious Adverse Events, regardless of attribution, shall be reported to Alkermes on FDA Form 3500 within 1 business day of discovery via fax or email:

Alkermes, Inc.
Attention: Alkermes Drug Safety
Dedicated Safety Fax No.: 1-617-494-5202
Dedicated email: drsafety@alkermes.com

The written report must include the opinion of the study site's PI or designated sub-investigator as to whether the event is related to the study drug. If this relationship is determined to be possibly, probably, or definitely related to study drug, evidence to support this assessment must be provided.

The PI is responsible for monitoring the data and conducting performance and safety reviews, at the specified frequency. Either the PI or the IRB have the authority to stop or modify the study. The monitoring by the IRB will occur annually at the time of re-approval. The PI will conduct data and safety review at least quarterly and at any time a serious adverse event occurs. During the review process, the PI will evaluate whether the study should continue unchanged, requires modification or amendment to continue, or should be closed to enrollment.

During the follow-up period, any patient requiring additional intervention due to significantly increased alcohol consumption or serious psychiatric/medical symptoms will receive a referral to treatment. In addition, any and all adverse events during the follow-up period will be reported to the IRB and the Project Officer at NIAAA with serious adverse events being reported within 48 hours.

We plan to comprise the Data Safety and Monitoring Board (DSMB) with experts in antiretroviral medications and addiction pharmacotherapies. The DSMB will review the progress of the study, and also conduct an interim analysis. The DSMB will monitor the occurrence and frequency of serious adverse events on a quarterly basis and review the results of the interim analysis. The interim analysis will be conducted six months after 40 subjects have been randomized to either of the treatment groups or when all of the 40 subjects in each group have completed the treatment protocol, whichever comes first. The interim analysis will evaluate whether the proportion of subjects achieving >95% adherence differs significantly (at $p<.05$) by treatment condition. This interim analysis will determine whether one of the interventions is significantly inferior to the other on the primary outcome of improving HAART adherence.

4. **Confidentiality & Security of Data:**

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a. What protected health information about subjects will be collected and used for the research?

Baseline Assessments:

Prior to entrance into the study each patient will undergo a medical history, physical and laboratory assessments [Complete blood count (CBC), chemistry panel, and viral hepatitis serologies]. A urine pregnancy test will be performed on female subjects and must be negative prior to beginning the study medication and will be checked monthly. Demographic data to be will collected include age, gender, marital status, highest level education completed, employment, substance use history, duration of HIV disease, and a detailed HAART medication history. Charts will be extracted to collect information including medical co-morbidities, prior CD4 lymphocyte cell counts and HIV RNA levels, HAART medication history, and historical genotypic information from prior HIV drug resistance testing

Informed consent:

Subjects will be recruited for participation and provided with a written consent form requiring their witnessed signature (see attached). Only subjects capable of giving informed consent will be admitted into the study. Informed consent will be obtained by trained and highly qualified research personnel.

Confidentiality:

The computerized data collection and monitoring system consists of a data base system that records clinical and research activities, completion of scheduled assessments, and delivers computerized versions of most of research instruments used in this study. Research assistants use this database to monitor and schedule patients and activities and to administer study assessments. Data entry of non-computerized assessments is accomplished by using specialized data entry software (such as, SPSS Data Entry or Microsoft Access Data base) facilitating efficient data entry and allowing elimination of out-of-range values and double entry of data for detection of key punch errors.

All reports generated from this study will not contain any identifying information about the participants. Research records will be coded only by a number, and will be stored in locked cabinets. Data are stored behind the Yale's firewall on password-protected computers.

b. How will the research data be collected, recorded and stored?

c. How will the digital data be stored? ☒ CD ☒ DVD ☒ Flash Drive ☐ Portable Hard Drive ☒ Secured Server ☒ Laptop Computer ☒ Desktop Computer ☐ Other

d. What methods and procedures will be used to safeguard the confidentiality and security of the identifiable study data and the storage media indicated above during the subject participation in the study?

Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Data will only be reported in aggregate. Data will be deidentified prior to formal data analysis, making individual subject identification impossible. Moveable devices will be encrypted to protect identifiable information, following University policy

e. What mechanisms are in place to ensure the proper use and continued protection of these data after the subject participation in the study has ceased?

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with subject permission or as required by U.S. or State

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law. Once enrolled, subjects will be given a unique study number, to which only members of our research team will have access. Study data will be kept protected and treated as confidential at all times. Computerized subject data will be password protected. Data will only be reported in aggregate. Data will be deidentified prior to formal data analysis, making individual subject identification impossible.

f. What will be done with the data when the research is completed? Are there plans to destroy the identifiable data? If yes, describe how, by whom and when identifiers will be destroyed. If no, describe how the data and/or identifiers will be secured.

Upon completion of the study, all computerized subject datasets will be de-identified and stored in a password-protected study computer, to which only the PI, investigators and study personnel will have access. All paper files with subject information will remain in locked files in the study office of the PI, until they are destroyed, after all analyses are complete.

g. Who will have access to the protected health information? (such as the research sponsor, the investigator, the research staff, all research monitors, FDA, QUACS, SSC, etc.)

During an audit or program evaluation, representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data, but will strictly follow rules of confidentiality.

h. Which external or internal individuals or agencies (such as the study sponsor, FDA, QUACS, SSC, etc.) will have access to the study data?

Representatives from the Yale Human Investigation Committee and from the National Institutes of Health may have access to subject data, but will strictly follow rules of confidentiality.

i. If appropriate, has a Certificate of Confidentiality been obtained?

A Certificate of Confidentiality from the National Institute on Alcohol Abuse and Alcoholism will be obtained to insure the confidentiality of all records and data and to better protect subjects.

j Are there any mandatory reporting requirements? (Incidents of child abuse, elderly abuse, communicable diseases, etc.)

This protocol will include testing for hepatitis and therefore all positive test results will be reported to the State of CT Department of Public Health.

5. **Potential Benefits:** Identify any benefits that may be reasonably expected to result from the research, either to the subject(s) or to society at large. (Payment of subjects is not considered a benefit in this context of the risk benefit assessment.)

While there is no guaranteed benefit from participating in this study, participants in this study may benefit from active study medication and MM/MC which may lead to cessation or reduction in alcohol use and improvement in their HAART medication adherence, reduction in risk of viral mutations, improved HIV biological markers, and reduced HIV risk behaviors. In addition, participants will be compensated for their participation. They will also receive a comprehensive evaluation, close monitoring of their HIV disease, and possible referrals for

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any outside psychiatric and/or medical care if necessary.

SECTION X: RESEARCH ALTERNATIVES AND ECONOMIC CONSIDERATIONS

1. **Alternatives:** What other alternatives are available to the study subjects outside of the research?

Individuals who are not eligible to participate or decline to participate may still receive treatment and other services to which they are otherwise entitled. Other medication options that have been approved for the treatment of alcohol problems by the Food and Drug Administration (FDA) are acamprosate (Campral), and disulfiram (Antabuse) As with VIVITROL and with any other medication, acamprosate, disulfiram, and topiramate (currently not FDA-approved for treatment of alcohol problems) have side effects about which patients should be informed by their physicians. Other non-medication treatments include psychotherapy and referral to Alcoholics Anonymous or other support groups. All three medications and forms of psychotherapy such as cognitive behavioral therapy and motivational interviewing have been found to be efficacious in the treatment of alcohol problems.

2. **Payments for Participation (Economic Considerations):** Describe any payments that will be made to subjects and the conditions for receiving this compensation.

Participants will receive a [redacted] gift card for completing monthly assessments (6) and a [redacted] gift card for the baseline assessments and 9-month and 12-month assessments. The total possible compensation for the study per patient is [redacted] for completion of all assessments, including bloodwork.

3. **Costs for Participation (Economic Considerations):** Clearly describe the subject's costs associated with participation in the research, and the interventions or procedures of the study that will be provided at no cost to subjects.

There are no costs to the subjects to participate in this research. At no cost to them, they will receive a medical evaluation including ongoing monitoring of their HIV markers, potentially receive medication to treat their heavy drinking, and will receive comprehensive psychosocial counseling addressing their drinking.

4. **In Case of Injury:** This section is required for any research involving more than minimal risk.
   a. Will medical treatment be available if research-related injury occurs?
   b. Where and from whom may treatment be obtained?
   c. Are there any limits to the treatment being provided?
   d. Who will pay for this treatment?
   e. How will the medical treatment be accessed by subjects?

If a participant is injured as a direct result of participation in this study, treatment will be provided. The participant and/or his or her insurance carrier will be expected to pay the costs of this treatment. No additional financial compensation for injury or lost wages is available. Participants will not waive their legal rights by participating in this study.

All participants will be asked to carry a medication card that will, in case of emergency, alert the treating medical personnel that they may be taking VIVITROL. Participants will be asked

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to carry this card at all times. The card will include appropriate drug information and precautions. If immediate information is needed about the study, participants will be instructed to contact either the study physician or nurse.

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