March 24 2016

Protocol

Title: Biobehavioral Intervention for Smokers Living With HIV (Human Immunodeficiency Virus)

Phase 4 Clinical Trial of the FDA approved Nicotine Replacement Therapy with over the counter medications (Nicorette gums and Nicotine Patch 1 and 2

NCT: 02982772

APPROACH

OBJECTIVES

To address the scarcity of effective tailored cessation treatments for PLWH. [11, 30-41] Our hypothesis-driven grant proposes to develop an evidence-based, tailored smoking cessation strategy to address the specific needs of this population. This goal will be attained by:

1. ***Using a Grounded Theory Model****:* The use of cognitive behavioral theory [53-54] is the blueprint for implementing a scientifically sound behavioral intervention

TARGET POPULATION AND SETTING:

The target population will be PLWH (> 18 years old) daily smokers, fluent in English or Spanish, who have received care in our partner networks of HIV primary care clinics. Since quitting tobacco benefits everyone, smokers will be eligible regardless of the number of cigarettes smoked per day. Only those who express interest in quitting will be eligible, and the individual's current readiness will be confirmed using the **Readiness to Quit Ladder** score >6 (previous research has found an average mean value ranging between 5.3 and 5.6). [56-57]

- *Inclusion/Exclusion Criteria*:
- One of the team members (either a physician, a nurse, a case manager, or a public health specialist all trained in HIV and tobacco) will assess eligibility which later will be confirmed by one of the medical doctors after reviewing a medical record (Drs. Vargas, Miguez, or Espinoza). Consistent with a practical clinical trial model emphasized by NIH, the study is designed to minimize exclusion for safety concerns, and to be more representative of real world scenarios. Accordingly, we will only exclude subjects involved in other smoking and/or drug cessation or weight control programs, and those with comorbid conditions that may limit their safe participation, such as presence of psychotic or disabling psychiatric disorders, or those having contraindications for nicotine replacement (i.e., 6 months post-myocardial infarction or stroke, diabetes requiring insulin, treatment for vascular problems, non-treated hypertension, severe liver or kidney disease or history of allergies to the nicotine patches, severe eczema or psoriasis, or temporo-mandibular joint disease, dental appliances, etc.). These broad inclusion criteria will assure high participation rates, maximize external validity, and enhance our capacity to define the study outcomes across different age, gender and ethnic groups.

- *Expected Population*: Based on our design, we project that our sample will comprise 40% females and 60% males, 50% Black, 25% White, and 25% Hispanic, with 40% of the population being >50 years old. Thus, gender, race and age distribution will be balanced.

- **Setting:** The study procedures will be administered at the Clinical Research Center, which is staffed by bilingual professionals who have experience in clinical trials involving PLWH. In addition, the CRC possess its own clinical trial pharmacy that strictly follow the regulatory process. Our two clinical trials are currently taking place in this facility.

PRETREATMENT ASSESSMENT

Procedures will take place at the UM Clinical Research Center, and will follow a study protocol manual. The initial visit will require 90 minutes and will involve completing a baseline survey, available in English and Spanish. All the questionnaires included have established reliability/validity >0.70, and can be completed via computer assistant programs. After collecting demographic, behavioral and clinical data we will focus on smoking assessments. This session will summarize the "5

A's": Ask, Advise, Assess, Assist, and Arrange. The visit will begin by surveying the participant about smoking history, using

a) **Tobacco Use questionnaire**
b) **Motives for Smoking Scale**
c) **Smoking Motives**
d) **Smoking Self-Efficacy** questionnaire
e) **Reasons for Quitting Scale**
f) **Pack Tracks**
g) **Carbon monoxide**
h) **Cotinine**.

CLINICAL TRIAL

To test our intervention we designed a single site, randomized 2-arms clinical trial which is the gold standard for establishing the efficacy of investigational interventions. The trial has 3 formal time assessment points, and one visit to monitor/adjust the treatment response. This design will allow us to not only test high and low levels of nicotine doses, but also to examine interactions.

Randomization: Based on the information on the pre-trial visit, the statistician will generate the randomization sequence in each stratum using randomly permuted blocks. A block randomization has been selected to ensure that the groups are balanced, to facilitate appointment scheduling, and to reduce loss of follow-ups. In addition, the statistician will closely examine the distribution across the trial to eliminate any source of bias in treatment assignment, and ensure that groups are balanced with respect to important participant characteristics (i.e., stage of change, risk group, depression history, number of cigarettes/day, nicotine dependence, CD4, sociodemographics).

The 500 HIV+ smokers will be allocated on a 1:1 ratio in one of the two treatment conditions.

MAIN STUDY OUTCOMES

Clinical trial endpoints include point prevalence abstinence (prior 7 and prior 30 days), and verified continuous abstinence **3-, 6-, and 12-months** post scheduled quit day.

Abstinence: Consistent with national goals to reduce tobacco related morbidity and mortality, we will focus on abstinence from all forms of tobacco as the endpoint**.** Self-Reported 7-Day Point Prevalence**,** defined by self-reported cigarette abstinence that will be biochemically verified, will be assessed at the 3, 6 and 12 month follow-ups. This definition of point-prevalence abstinence is consistent with consensus statements from the Society for Research on Nicotine and Tobacco. [11, 68-70]

The Society also endorsed the use of both the point-prevalence and continuous abstinence rates, as outcomes of tobacco cessation interventions. [11, 68-70] Thus, other smoking outcomes of interest include 24-hr abstinence, 30-day abstinence, and continuous abstinence. Self-reported quit attempt (yes/no—defined as quitting for at least a 24-hr period) will also be assessed. Since quitting can be followed by either relapse or maintenance of abstinence, the length of abstinence will also be considered (number of consecutive days the subject will be able to go without smoking).

Abstinence will be verified by CO < 10ppm and cotinine <15 ng/mL.[87] However, ad libitum use of NRTs, particularly users of 4-mg nicotine gum, may reach 20-25 ng/mL. As per SRNT convention, [69-70] if abstinence cannot be verified with the biological sample or the subject is lost to follow-up, they will be considered non-abstinent.

EFFECT OF INTERVENTION ON SECONDARY OUTCOMES

In order to be consistent with clinical goals of smoking cessation, though they are not the main goal of the proposed study, we will examine intervention effects on HIV and therapy by directly measuring CD4, viral load (LabCorp). We will analyze as well, changes in vital signs obtained during each visit (i.e. blood pressure, pulse), anthropometrics (body mass index, waist and hip circumference) and the health-related quality of life (HRQOL).

• Standard Care Brief Behavioral Intervention

Based on the assumption that the higher the knowledge and perception of risk, the higher the interest in modifying a risky behavior(s) we will start with a behavioral intervention. Since time is a significant barrier in HIV clinics and community centers, we have selected a single session (45 minutes). Sessions will be led by the trained health care professional, with ongoing monitoring of treatment fidelity by site supervisors, and will be focused on completing the last 2 As (Assist - with counseling and pharmacotherapy to help him or her quit; and Arrange – follow-up contact within the first week after the quit date); and strengthening smoker motivation to quit using the five "**R"s:** Relevance, Risks, Rewards, Roadblocks, and Repetition. Throughout treatment, each participant will be seen by a single smoking treatment counselor. The team member will start by introducing the concepts of smoking habits and addiction. The session will proceed with an overview of the consequences of smoking, risk of hospitalizations, survival, and quality of life (**risks**). These facts will be contrasted with the health, social and economic benefits of cessation (**rewards**) by focusing on cognitive processes (i.e., cognitive dissonance, costs/benefits) that supports and encourages patients to change behaviors in a nonthreatening and non-punitive way. Subjects in both conditions will learn that the NRP will help with the nicotine withdrawal symptoms, as well as to minimize the stress and mood disorders associated with quitting (**roadblocks**). **Repetition**: We will provide positive reinforcement with those successful and encourage quitting attempts in those who have slips. Yet, in order to keep the supportive role to the minimum standard, team members will be trained on how to answer any study related questions, encourage, but not to provide any additional advice. This brief approach reflects the minimum standard of care recommended by the Agency for Health Research and Quality panel regarding smoking cessation treatment**.**

PHARMCOLOGICAL INTERVENTION

Standard Pharmacotherapy ARM 1: Per current recommendations, NRT will be initiated at the start of a quit attempt, and will follow the company's suggested dosing, which is based on the participant phenotype (type 1 or type 2 NRT based on number of packs). **The patch will be used for up to 10 weeks**, after which the smoker should taper and discontinue treatment. NRT will be discontinued if there is a relapse. Subjects will be instructed on how to use the patches and about the importance of adherence. Subjects in this arm will be encouraged to start reducing smoking before the pre-quit visit. During that visit smokers will be provided with a supply of NRT until the next visit, and with a pocket diary to record NRT use, craving time(s) and triggers.

Tailored Pharmacotherapy ARM 2:

To address the specific problems of PLWH we propose to tailor nicotine replacement based on:

1) Pre-trial plasma nicotine levels: Participants will be informed that the selected dose of NRT is based on their plasma nicotine levels. "*Your extra NRT is based on the results of a laboratory test. People have different levels of tobacco metabolites in the blood depending on age, body weight and medications they are taking*.

2) Characterizing smoking behaviors: Then, participants will be informed that the use of NRT

should help to control craving and other withdrawal symptoms, including weight and negative mood issues.

3) Past quitting attempts.

As depicted in Figure 4, smoking profiles will be used to develop a unique algorithm to determine the desirable dose of NRT or the need of combined therapy. Smokers in the tailored arm will be categorized into low or high risk groups, allowing us to avoid over-prescribing or under-prescribing due to dosage miscalculations. Individuals will receive a + or a – point for each risk factor (cut off score of 7 on the Fagerström Test, 250 of plasma cotinine levels prior SC fails). Those scoring 2 or below of the possible 4 points will be considered at low risk. On the other hand, high nicotine levels, high Fagerström scores, and/or past history of a failed attempt at correct use of NRT monotherapy are all indicators of high risk and that more intensive therapy is needed. Thus, all smokers in the high risk group will begin with combination pharmacotherapy to facilitate increased success. Based on these analyses, participants will be provided with either type 1 or type 2 NRT, and will be instructed to chew a 2-mg piece of gum every 2 hours during weeks 1–6; chew a 2-mg piece every 2–4 hours during weeks 7–9, and chew a 2-mg piece every 4–8 hours during weeks 10–12 of therapy.

They will also be asked to chew a 2-mg piece of gum whenever the urge to smoke occurs, not exceeding 2 pieces (4 mg) per hour, which leads to about 2 mg absorption. Gums will provide acute nicotine delivery to address situation-induced cravings to smoke.
Although standard NRT is normally used for 10 weeks and suspended if a relapse occurs, emerging studies suggest that extended use could be beneficial. [67-75] Hence, the tailored arm will use it 2 weeks before the quit attempt to progressively wean smokers from the smoking habit. They will also be advised to keep using the NRT during the relapse and try again.

INITIAL ASSESSMENTS

Subjects in arm 2 will be provided at baseline with a supply of NRT for one week (type 1 or type 2 based on phenotype), and will be instructed to start use and to return one week later to check if the doses need to be adjusted based on the laboratory results and to give them additional patches. During this visit the participant will be provided with the tailored feedback, and participants in this arm will be instructed to set the goal of smoking no more than 5 cigarettes for the seven days prior to the quit day, and preferably to achieve that goal by the pre-quit assessment day. Participants in the standard care will receive the standard advice and 2 weeks of NRT supplies. A call will be placed to confirm that the quitting took place, or to encourage to set a new one. The call will serve as reminder for the next visit, to maintain motivation and answer questions about the study.

ONE MONTH VISIT
1) Biologically confirm smoking self-reports.

2) Closely monitor withdrawal symptoms, which are more prevalent during the initial weeks and impact success rates.

- Using the **Minnesota Nicotine Withdrawal Scale,** [85-86] subjects will be queried about hunger, irritability, anxiety, difficulty concentrating, restlessness, and dysphoria.

- **Cravings:** The short-form of the Questionnaire of Smoking Urges will be used to assess cravings. [87]

- **Appetite and body weight:** Participants' height, weight, hip and waist circumferences which are routinely take it in our studies will be documented at each visit, to determine if adequate

doses of NRT help reduce weight gain. [72, 73, 88-89]
This information will be complemented with a **24-hour dietary intake and analyzed using the Food Processor software,** [92] **We will also apply the Stanford 7-day Activity Recall** assessments. [94]

- **Adherence:** Three strategies will be used to ensure accurate documentation of NRT adherence:
- **D**irect observation that participants are wearing their patches at each visit.
- Self-reports using an adapted ACTG form, and
- The interviewer will calculate the proportion of NRT used/dispensed.

3) **Document Side Effects:** SAFTEE (Systematic Assessment for Treatment Emergent Events) will be used to categorize adverse events in terms of severity, frequency, and relationship to NRT. [95]

PREVENTING SLIPS AND RELAPSES

A slip is when a smoker who has quit smokes one or two cigarettes. A relapse is when a smoker who has quit returns to regular smoking. We will record the number of days and the number of cigarettes smoke during these episodes. This measure cannot be verified by cotinine or carbon monoxide, because daily monitoring of cotinine or carbon monoxide throughout the study is not feasible. [96]
Subjects in the tailored arm will be advised to keep using NRT in the event these situations occur. Such advice will not be given to ARM1 participants.

These subjects will receive a "rescue" treatment by having their NRT treatment increased to the next available level or to be changed to other pharmacological treatment. Dr. Espinoza and Dr. Stanton will discussed the best alternative. If the medical team decides to maintain NRT and if participant is under standard care he/she will receive type 2 patches. For those in the enhanced intervention arm, and if subject was classified as low risk, she/he will be moved to medium risk and treated accordingly. If the subject is a high risk smoker, 2 mg gum will be replaced with a 4-mg gum every 2 hours during weeks 1–6; a 4-mg piece every 2–4 hours during weeks 7–9; and a 4-mg piece every 4–8 hours during weeks 10–12 of therapy. To address breakthrough craving, subjects may also chew a 4-mg piece whenever the urge to smoke occurs without exceeding 2 pieces (8 mg) per hour, or 24 pieces/day.

Intervention Assessment and Compliance

To achieve consistency and adherence across the arms of the trial, both interventions will be implemented under the same conditions, and will be guided by a written manual. We do not expect that the selected frequency of assessments will affect the validity of the surveys. In addition, since the duration and nature of each participant's contact has been matched their effects will be controlled during statistical analyses. Importantly, side effects, number of patches and pieces of gum provided and unused before, during, and through quit attempts and relapses, will be tracked**.** Several control procedures will be followed to maximize the integrity/fidelity of the interventions, such as using a fidelity checklist, and unobtrusively monitoring levels of adherence of the study members to the protocol. At the end of the trial, participants will be asked to complete a Likert-scale to rate the content, clarity, and responsiveness to the participants' expressed needs. In addition, at each visit compliance with treatment recommendations (such as reading material, nicotine replacement, and the calculation of an overall percentage of doses taken over the course of treatment) will be checked.

AIM 2 Measurement issues are very important, and therefore we have carefully selected short, reliable, and valid measures of the key constructs.

NeuroPsychological Status

- Quantification of pro-BDNF/BDNF will be achieved using commercially available enzyme-linked immune sorbent assay, and following the manufacturer's instructions (R&D System).

- The Profile of Mood States, a 40-item tool that assesses six affective subscales and one overall index of distress.[97]

- We will also apply the HIV neurocognitive screening examination (Trail Making Test Part A,[98] Grooved Pegboard Non-dominant Hand, [99-100] and PASAT50 [101]). Evidence of at least ANI will be determined for a participant if his/her Global Deficit Score (GDS) is greater than or equal to 0.5, based on these tests using established methods.

- THE IOWA GAMBLING TASK (IGT). Risky DM will be investigated with the IGT, which is also considered a reliable probe of emotional decision-making and believed to reflect orbitofrontal cortex (OFC) function. [102-103]

Body Image

While it is well recognized that body image is highly relevant for PLWH, and key in tobacco quitting, [5, 89] to our knowledge these issues have been largely neglected. To correct this gap in knowledge, we will use

- The Appearance Evaluation Subscale (AES), [104-105] a tool used in several national studies because of its' excellent psychometric qualities, with an internal consistency of Cronbach's alpha = 0.88 among adult women.
- The Body Image Satisfaction (BIS) Score**:** [106-107] This test presents images of nine figures, ranging from very thin to very heavy. The discrepancy between the figure selected as ideal and the current body size will be utilized as the BIS score.
- Other Information: To have a more complete profile of body weight history and concerns, we will inquire about obesity during the periods of childhood, adolescence, post-partum and menopause/andropause and history of diets or taking medications to lose weight.

Perceptions

To assess the perceived pros and cons of smoking we will use the six-item Smoking Decisional Balance Scale. [108]

To measure the degree of self-efficacy in resisting temptations to smoke in various situations, we will use the 9-item Smoking Self-Efficacy Scale (higher scores indicate higher self-efficacy). [109]

The Perceived Vulnerability and Response Efficacy, [110] with subscales assessing perceptions of the probability of acquiring a smoking-related illness if continued smoking versus if quit smoking.

Sociodemographics

Participant's characteristics that may be associated with improved outcomes will be assessed, and will include:

- Demographics (age, gender, ethnicity, education, and marital status). As in the prior grant we will collect gynecological history and time of the cycle when the participant attempts to quit.
- Five indicators of socioeconomic status (housing and employment status, annual income and neighborhood deprivation);
- Social support (spouse/partner, family, or friend to support their quit attempt); and
- Network (proportion of smokers in his/her family and social network).

STUDY TIMELINES

Start-up: The initial two months will be used to complete administrative paperwork, and to train the study personnel.

Recruitment: As depicted in Figure 3 recruitment will start at the third month and expect enrollment to be completed before the end of the third year.

Potential Pitfalls and Solutions: We are confident in the expected recruitment attainment, given that we are following two cohorts in the same clinics. However, in the unlikely event that recruitment runs behind, there is also a community pool of 4,000 PLWH, who are not enrolled in the clinics. Since we have used this pool before with recruitment responses above 90%, we can assure our success.

Follow-up: Follow-up visits will take approximately 1.5 hours, and will mirror baseline procedures.

Covariates: As described below, each analysis will be performed with and without these variables, to assess possible confounding effects.

HIV Disease: Current and past HIV and non-HIV related conditions will be documented at each visit using our clinical questionnaire.

Pharmacotherapy: We will document all medications received, along with the dates for starting and discontinuing, which will be confirmed with medical records. Particularly attention will be devoted to antidepressant, ART and certain medications capable of modifying CYP2B6, CYP2A6 enzymes (inducers: rifampicin, dexamethasone, and phenobarbital; Inhibitors: methoxsalen, tranylcypromine, tryptamine and coumarin). We will record **adherence,** using the ACTG questionnaires and pharmacy records.

Drug Abuse -10 minutes: The Alcohol Dependence Scale and the Addiction Severity Index [111-112] questionnaire for drug abuse will be used to calculate lifetime exposure, and will be complemented with a urine toxicology screening for all commonly used drugs (Roche OnTrak(R)).