TITLE: Preloading with Nicotine Replacement Therapy in Smokers with HIV to Improve Self-Efficacy and Quit Attempts

NCT04994444

V.2. 08/12/2021

Project Title: Preloading with Nicotine Replacement Therapy in People with HIV who Smoke to Improve Self-Efficacy and Quit Attempts

Principal Investigator: **Patricia A. Cioe, PhD**
Co-Investigator: **Christopher Kahler, PhD**

Description and Purpose of the Project

Cigarette smoking is more prevalent in persons with HIV (PWH) in the U.S. when compared with the general population and is linked to increased morbidity and mortality in this population. Furthermore, PWH whoPWH who smoke have increased rates of lung and other smoking-related cancers. PWH who smoke are a particularly challenging group, often reporting high severity of nicotine dependence and low rates of self-efficacy for quitting, both factors related to poor smoking cessation outcomes. Establishing more effective smoking cessation approaches for people with HIV who smoke, particularly those that address low self-efficacy and severe dependence, is a public health priority.

The overall goal of this research project is to examine the feasibility, acceptability, and preliminary efficacy of nicotine replacement therapy preloading (NRT-P) in PWH who smoke, who are struggling with cigarette dependence, urge to smoke (craving) and low self-efficacy as barriers to successful smoking cessation. Sixty participants will be recruited into a 16-week randomized pilot study. Thirty participants (control condition) will receive standard smoking cessation counseling (NRT-S) and will initiate an 8-week course of combination nicotine patch and lozenge (or gum, based on preference) on quit date (week 4), consistent with recommended guidelines based on smoking rate. Thirty participants (active condition) will start NRT patch 3 weeks prior to quit date, followed by an 8-week course of combination nicotine patch and lozenge (or gum, based on preference), initiated on quit date. We will examine dependence, urge to smoke and self-efficacy for quitting prior to and following quit date. We will also examine differences in quit attempts and biochemically validated smoking abstinence between the control and active conditions at weeks 8, 12, and 16.

This study will be the first to examine the feasibility and initial efficacy of a novel intervention using NRT preloading to improve smoking cessation outcomes in PWH. Given the high prevalence of smoking and the significant morbidity associated with it in PWH, the development of effective strategies to reduce the risks related to smoking in this group is critical. If determined to be effective, this intervention could be readily disseminated in HIV clinics. Our study will provide key information on the potential benefit of NRT preloading in a population that is highly dependent on nicotine and highly vulnerable to smoking-related morbidity and mortality. The results from this project will provide the foundation for a future R01 application to the National Cancer Institute to conduct a full-scale randomized clinical trial.

Aims

The **specific aims** of this randomized pilot study are:

Aim 1: To examine the feasibility and acceptability of NRT preloading in smokers with HIV. We will examine adherence (percent of days using the patch) to NRT prior to quit date in the preloading condition, and compare adherence after quit date across the standard (NRT-S) and preloading (NRT-P) conditions.

Aim 2: To examine differences in quit attempts and biochemically validated smoking abstinence between the

control and active conditions. We hypothesize that participants in NRT-P, compared to NRT-S, will have higher rates of CO-verified abstinence from smoking at weeks 8, 12 and 16. Cotinine verified abstinence at week 16.

Aim 3: To examine nicotine dependence, self-efficacy for cessation, and urge to smoke (craving) as mediators of abstinence. We hypothesize that participants in NRT-P, compared to NRT-S, will show greater reductions in dependence and urge to smoke, and greater increase in self-efficacy from baseline through quit date, and that these mediators will account for the effect of NRT-P on smoking abstinence at weeks 8 and 12 and 16.

Investigative Team. Patricia Cioe, PhD (PI) is Associate Professor of Behavioral & Social Sciences at the Brown University School of Public Health and a board-certified nurse practitioner. She has been an HIV provider and has been conducting research related to substance use and smoking cessation with PWH since 2001. She has expertise in the assessment and management of smoking cessation behavioral interventions in both the general population and PWH who smoke. Christopher Kahler, PhD (Co-I) is Professor and Associate Director at CAAS, and Chair of the Department of Behavioral and Social Sciences in the Brown University School of Public Health. He has been conducting NIH-funded research on behavioral treatments for smoking cessation since 2002 including studies using positive psychology, behavioral activation therapy, and Acceptance and Commitment Therapy (ACT). He also has conducted laboratory-based studies to examine cognitive and affective factors impacting smoking behavior. Megan E. Piper, PhD (Consultant) is Associate Professor of Medicine at the University of Wisconsin and Associate Director of Research at the University of Wisconsin Center for Tobacco Research and Intervention. Dr. Piper's research focuses on understanding and treating tobacco dependence, with an additional interest in different populations of smokers who have more difficulty quitting, such as women and smokers with mental illness. In 2020, she was elected president of the Society for Research on Nicotine & Tobacco. In 2019, she was named the recipient of the UW Faculty Excellence in Research Award.

Study Timeline

We estimate 3 months for startup, staff training, and finalizing the protocol/study manuals. Starting in the second quarter of the grant period, **we will recruit 4 participants per month. Participants will be recruited for 15 months,** and follow-ups will be completed through the second year. Data cleaning and analysis will begin upon completion of recruitment. We will also prepare manuscripts in the final 6 months of the project with the primary outcomes paper submitted before the end of the 24-month project period.

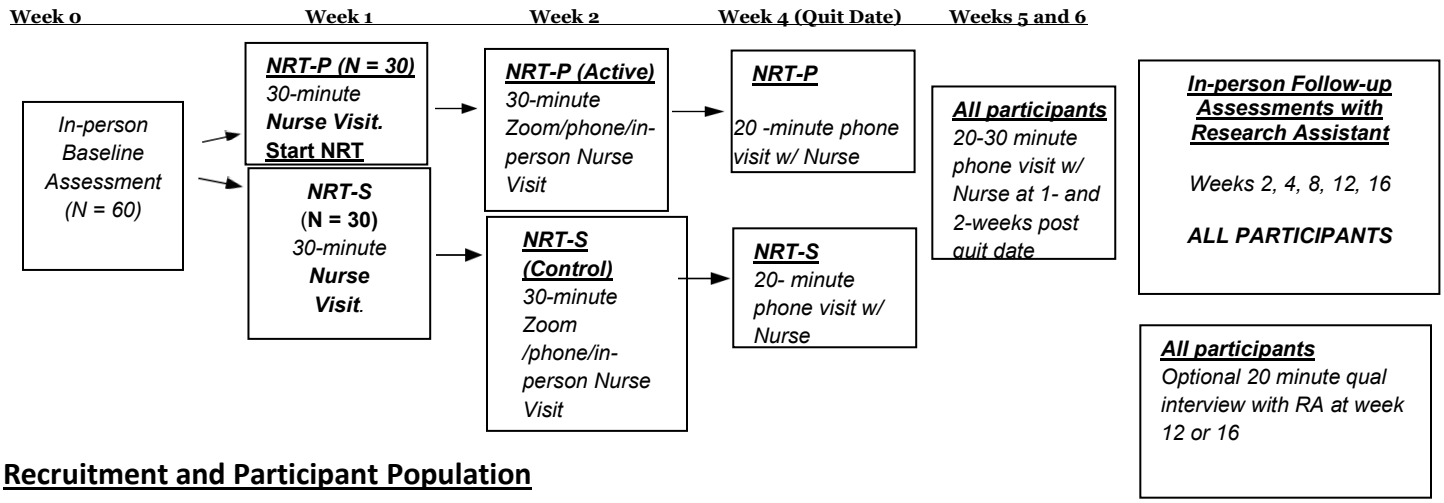
Study Methods

The primary objective of this project is to pilot test NRT preloading for smoking cessation in smokers with HIV. This pilot randomized clinical trial uses a 2-group between subjects' design with repeated measures over 16 weeks to test the feasibility, acceptability, and initial efficacy of NRT preloading (NRT-P) versus standard NRT (NRT-S).

We will randomize 60 smokers with HIV to either NRT-P or NRT-S using urn randomization[17] to ensure balance on gender and level of cigarette dependence (Fagerström Test of Cigarette Dependence (FTCD) score)[18]. Both

conditions will receive the same behavioral counseling support, which will be delivered in 5 sessions over 5 weeks, with the target quit date (TQD) scheduled at week 4. We will include 8 weeks of TNP for those in the ST condition (starting at TQD and continuing for 8 weeks) or 11 weeks of TNP for those in the NRT-P condition (starting 3 weeks prior to TQD). Dosage of TNP in each condition will be based on smoking rate and level of nicotine dependence at baseline (BL). All participants will also be provided with 8 weeks of nicotine lozenge or gum (started on TQD) and will be encouraged to use them every 1-2 hours to manage cravings and urge to smoke, with a goal of using at least 5 lozenges or gum daily. This instruction has been used in previous studies of this type and been shown to be beneficial[19,20]. Smoking outcomes (7-day CO-verified point prevalence abstinence) will be assessed at 4, 8-, and 12-weeks after the TQD (Weeks 8, 12, and 16). Cigarettes per day, FTCD, urge to smoke, and self-efficacy for quitting will be collected at Baseline, and at 2- weeks after Baseline. We will compare NRT-P and NRT-S on adherence to pharmacotherapy (percent days using patch), smoking cessation rates, study retention and study satisfaction. We will calculate a preliminary effect size estimate of NRT-P on smoking and other secondary outcomes, and mechanisms of change. See Study Flow Diagram below.

Figure 1. Study Flow Diagram.



Recruitment and Participant Population

We will recruit participants (N=60) from the Providence community, the Miriam Immunology Center (MIC) in Providence, RI, and on social media (such as Facebook, Craigslist, Today@ Brown, Share lab website). Study information will be posted on the Share lab website at Brown. Study flyers will be posted on MIC bulletin boards, in the Providence community, and at AIDS-service organizations.

When patients call in response to the ad, the RA will describe the study and ask questions pertinent to inclusion and exclusion criteria. The phone screen will allow us to determine preliminary eligibility for this study. Those who are eligible based on the initial phone screen will be invited to schedule an in-person Baseline interview. All study sessions will be conducted at the Center for Alcohol & Addition Studies (CAAS). The telephone screen forms will be destroyed once eligibility is determined (upon completion of the baseline session).

The RA may also call patients from the list of patients that indicated they were willing to be screened for future studies. That list is found in the H drive Screening and Tracking folder for the Preload study.

Participants will be invited to the Center for Alcohol and Addiction Studies research lab where they will complete written, informed consent and a Baseline interview to confirm eligibility. Once the Baseline interview is complete, the data manager (or the PI) who is not involved in data collection activities, will randomize eligible participants to one of two study conditions (NRT-P or NRT-S). Urn randomization[17] will be used to ensure the groups are balanced on gender and FTCD[18] score. All participants will be scheduled for a week 1 in-person session with a study nurse within one week of the Baseline appointment. The nurse will use a detailed counseling manual to ensure standardization of treatment delivery. Quit date will be scheduled for 3 weeks following the first nurse appointment for all participants (Week 4). Participants will be assessed on a variety of self-report and biochemical measures at BL, and at 2, 4, 8, 12 and 16 weeks after the BL interview. The RA conducting follow-ups will not be aware of participants' treatment condition assignment.

Inclusion Criteria: 1) diagnosed with HIV; 2) at least 18 years of age; 3) smoking at least 5 cigarettes/day and a CO level greater than 5 at BL; 4) willing to use transdermal nicotine patch (TNP); (4) ready to quit in the next 30 days (score of 7 or greater on the Contemplation Ladder[21]).

Exclusion criteria: 1) currently using pharmacotherapy for smoking cessation; 2) medically or psychiatrically unstable (defined as: uncontrolled hypertension, unstable angina, or a medical or psychiatric hospitalization in the 30 days prior to enrollment); 3) experiencing psychotic symptoms; 4) endorsing suicidal ideation upon screening or past-year suicide attempt; 5) pregnant or nursing.

Only one person per household can enroll.

A blood pressure reading will be taken to exclude subjects who have very high blood pressure that may require medical treatment (greater than 160/100). Because some smoking cessation therapies are contraindicated for nursing or pregnant women, women will be administered a pregnancy test to ensure non-pregnancy status.
Participants who do not meet screening criteria will be provided resources to local and state smoking cessation programs and will be compensated $10 (money order or cash) for their time.

Recruitment Procedures

Prospective participants will be screened by telephone by the study RA according to the inclusion criteria. At the Baseline appointment, participants will be asked to read and then sign an informed consent form. Potential participants will be given oral descriptions of the project including procedures, potential risks and benefits, and confidentiality.

Informed Consent

All participants will be fully informed of the purposes and procedures of the study. An RA will describe the screening and the study to potential participants, including that if they are eligible and then agree to

participate, they are paid for completing the follow-up interviews at weeks 2, 4, 8, 12, and 16, that the information they provide is kept confidential, and that they may withdraw at any time without penalty. Time will be allowed for participants to ask all questions. If any individual wishes to participate, he/she will be asked to sign an informed consent form prior to completing the baseline assessment. Participants will be provided with a printed copy of the consent form.
A Consent Addendum will be completed by any participant who is willing to participate in the Brief Qualitative Interview at week 12 or week 16 (see description below)

Baseline Assessment
Eligible participants will complete a baseline interview to confirm eligibility and, if eligible, will complete all Baseline measures via Qualtrics or paper surveys. Participants will be assessed on a variety of interview and self-report measures at each study session.

The following information will be gathered in the baseline assessment: demographic information, smoking history, level of nicotine dependence, current smoking pattern, current alcohol and other drug use, and psychiatric disorder history. We will assess intention/readiness to quit, using the Contemplation Ladder, perceived risks of smoking using the Perceived Health Risks scale; and self-efficacy for smoking cessation, using the Confidence Inventory from the Smoking Cessation Self-Efficacy scale.

Participants will complete a brief medical screen. Participants will provide a breath sample for exhaled Carbon Monoxide (CO) monitoring. The RA will obtain a blood pressure reading using an Omron Automatic blood pressure cuff. The RA will obtain an oxygen saturation reading using a pulse oximeter. We will assess for potential contraindications to nicotine replacement therapy (NRT) use (such as unstable angina, uncontrolled high blood pressure (>160/100). Because NRT is not recommended for use during pregnancy, women of childbearing age will complete a urine pregnancy test to ensure non-pregnancy status. Participants will be asked to provide a copy of their most recent T-cell count and HIV viral load. Medical screens will be reviewed by the study PI (Cioe) who is a licensed and certified nurse practitioner. If the medical screen precludes participation, Dr. Cioe will explain to the individual why they cannot participate. The baseline assessment will take approximately 60 minutes.

All participants will be offered the Participant Resource pamphlet at the Baseline visit. This provides a list of RI-based and MA-based community resources for mental health and other services.

Follow-up Interviews.
Participants will be seen by the RA for follow-up assessments at weeks 2, 4, 8, 12, and 16. At each of these sessions, participants will provide a breath sample for exhaled Carbon Monoxide (CO) monitoring. The RA will obtain a blood pressure reading using an Omron Automatic blood pressure cuff. Participants will complete questionnaires (see Study Schedule and Schedule of Assessments below).

STUDY SCHEDULE:

VISIT:	MEET WITH:	TIME INVOLVED:	ACTIVITY:	PAYMENT:
Baseline (in-person)	Research Assistant	60 minutes	Surveys, blood pressure, breath test, pregnancy test (for females)	$40
Week 1	Nurse (in-person)	30 minutes	Counseling	$20
Week 2	Research Assistant	20 minutes	surveys	$20
Week 2	Nurse (In-person, phone call or Zoom)	30 minutes	Counseling	None
Week 4	Research Assistant	20 minutes	Surveys, blood pressure, breath test	$20
Week 5	Nurse (phone call)	20-30 minutes	Counseling	None
Week 6	Nurse (phone call)	20-30 minutes	Counseling	None
Week 8	Research Assistant	20 minutes	Surveys, blood pressure, breath test	$25
Week 12	Research Assistant	20 minutes	Surveys, blood pressure, breath test	$25
Week 16	Research Assistant	20 minutes	Surveys, blood pressure, breath test	$50
Week 12 OR Week 16	Research Assistant	20 minutes	Brief Qualitative Interview	$10

Brief Qualitative Interview.

An open-ended interview will be completed at the Week 12 or Week 16 study visit, or as an additional, optional session for participants who have already completed their final study session. The qualitative interview will ask about participants' perspectives and opinions on using psychedelics, specifically Psilocybin, for smoking cessation.

Pharmacotherapy.

Nicotine Patch, Lozenge & Gum.

All participants in the NRT-S condition will receive an 8-week course of transdermal nicotine patch (TNP) and nicotine lozenge or gum. Participants will be provided with an initial 4-week supply of patch and lozenge or gum at their Week 1 session with the nurse in anticipation of their TQD, and will be instructed to start using the TNP on the morning of their quit date.

NRT Dosing.

Participants will use a 21 mg patch for 4 weeks, followed by 2 weeks of 14 mg and 2 weeks of 7 mg; those participants smoking 5-10 cigarettes a day will start with the 14 mg patch.

Participants will be instructed to use lozenges (2mg each) or gum consistent with the package insert labeling: one every 1-2 hours and up to 12 daily. They will be advised to use at least 5 lozenges or gum daily.

At the week 8 visit, participants will receive instructions for patch tapering and be provided the needed 14 mg and 7 mg patches.

Possible side effects, which are typically mild, will be explained and participants will be urged to contact study staff if they have questions. Participants who discontinue the patch or lozenge early will be retained in the study.

In addition to the pharmacotherapy procedure described above, participants in the NRT-P condition will be provided with a 21mg TNP for 3 weeks prior to the QD (started during the first session with the nurse). This course of pre-loading will be followed by the same 8-week course of TNP/lozenge started on the target quit date as described above.

Study Safety Monitoring

Adverse effects of NRT are infrequent and tend to be minor. The most common discomfort from NRT is skin irritation. Participants will be advised to rotate the site of the NRT patch each day when it is changed. A Nicotine Patch Information Sheet will be provided to each participant. Participants will be asked to contact study staff in the event of any unexpected reaction. The RA will contact the study medical provider (Cioe, PI) regarding any adverse events within 24 hours. In these cases, participants will be contacted by Dr. Cioe and may be advised to stop using the NRT.

Compensation. Total possible compensation $210: $40 for the baseline assessment; $20 for the nurse visit at week 1, $20 for the week 2 assessment, $20 for the week 4 assessment, $25 for the week 8 assessment, and $25 at week 12, and $50 at week 16.

Ten dollars ($10) compensation will be given for completion of the qualitative interview. Participants can now receive up to $210 compensation for completing the entire study.

Participants will receive compensation only for the sessions they complete. Compensation will not be contingent upon smoking status.

ClinCard. Payment for participating in this study will be made using the ClinCard, a pre-paid card that works like a bank debit card. Each participant will be issued one card for the duration of their participation. They will be given the ClinCard information sheet about how to use this card and who to call if they have any questions. Money will be added to their card according to the study's payment schedule. They may use this card at any store that accepts Mastercard. They may also use an ATM with the Mastercard logo to withdraw cash. If they use the card to withdraw cash, or if the card is not used within any six (6) month period, they will be charged a fee that will reduce the total amount of money left on the card. Please ask them to read the FAQ information sheet that the RA will give them at the Baseline appointment for full details about fees.

The ClinCard is administered by an outside company called Greenphire. If they lose the card or if it is stolen, they should call the Research Assistant and ask for a replacement card. They may be charged a fee if they request a replacement card from Greenphire directly.

Participant Locator

Contact information (home address, contact phone number, and email address) will be recorded at baseline for all participants for the purposes of collecting follow-up data. In addition, participants will be asked to provide the name of one friend or relative who can act as a locator in the event that the participant moves.

Measures

Screening Measures for Inclusion/Exclusion Criteria

Phone Screen –The initial phone screen will include questions about age, current smoking history and pattern (using standard indices), intentions to quit smoking (the Smoking Stage of Change questionnaire), current use of pharmacotherapy for cessation, current EC use, and unstable medical conditions (opportunistic infection, hospitalization). Women will be asked if they are pregnant, intend to become pregnant in the next 3 months, are using a reliable means of birth control, or are nursing. These data will be used for initial eligibility determination.

Mini International Neuropsychiatric Interview (MINI) will be used to evaluate suicide risk. The MINI will be administered by a trained RA and will be supervised by Dr. Cioe. Participants will be asked whether they have had thoughts of death or about hurting themselves. Participants answering positively to this question will be evaluated by Drs. Cioe or Kahler. The clinician will assess intent to injure self and provide appropriate intervention, including calling for emergency transportation for those who are at risk. A clinician will be available at the CAAS whenever a research interview is being conducted.

Medical Screening and Vital Signs – Subjects will complete a medical screening questionnaire to assess medical and psychiatric histories, current use of antiretroviral therapy (ART), contraindications for using NRT (unstable angina, recent hospitalization). Participants will be asked at the screening call to get a copy of their HIV viral load and T-cell count so that they can show them to the RA at Baseline. If they forget to get them in time for BL, the RA can collect that information after the BL. Women will be asked if they are pregnant, or are nursing, and all women of childbearing potential will complete a urine pregnancy test. Results of the pregnancy test will be recorded by the RA during the Baseline interview session. Medical resources will be offered to any participant who is found to be pregnant. Smoking will be confirmed via exhaled carbon monoxide breath sample of greater than or equal to 5 on the Smokerlyzer monitor- the RA will confirm a positive smoking status.

Baseline Measures of Individual Differences

Demographics will be collected such as age, sex at birth, gender identity, race, ethnicity, marital status, employment status, income level, education level, and number of years living with HIV.

Smoking History/Dependence. Smoking history and pattern will be assessed at baseline using standard smoking history and current status indices. These include but are not limited to: current smoking rate, number of years of regular smoking, previous quit attempts and duration, etc. The Fagerstrom Test for

Cigarette Dependence will be used as a continuous measure of cigarette dependence. Depressive symptoms will be assessed with the Center for Epidemiologic Studies – Depression scale (CES-D). Alcohol and drug use disorders will be assessed using the AUDIT-C and the DUDIT.

Feasibility and Acceptability Measures

To examine the feasibility and acceptability of NRT preloading in smokers with HIV, we will examine adherence (percent of days using the patch) to NRT prior to quit date in the preloading condition, and compare adherence after quit date across the standard (NRT-S) and preloading (NRT-P) conditions.

Timeline Followback (TLFB) is a calendar-assisted structured interview designed to cue memory so that accurate recall is enhanced. The TLFB has established reliability and validity for smoking. The TLFB will be used to assess adherence to nicotine patch, all forms of tobacco use, marijuana use, and self-reported smoking for 7 days prior to baseline and week 2 visit, and for 7 days prior to each follow-up session at weeks 8, 12, and 16.

The Self-efficacy for Smoking Cessation Scale, which has shown good psychometric properties and excellent predictive validity, will be assessed at baseline, weeks 2, 4, 8, 12, and week 16.

Urge to smoke will be assessed at baseline and at weeks 2, 4, 8, 12, and 16 follow-up assessments using the Brief Questionnaire of Smoking Urges (B-QSU). This well-validated measure includes 10 items which assess urges to smoke for either positive reinforcement or negative reinforcement.

Biochemical Verification. All participants will provide breath samples for exhaled CO testing at baseline and at follow up sessions with the RA, at weeks 2, 4, 8, 12, and 16.

Other Measures

1. session attendance after baseline (continuous variable, range 1-6 study sessions);
2. retention (dichotomous variable, participants who complete the 16-week session with the RA will be characterized as completers, those not attending the final session as non-completers);
3. Smoking Situations Confidence scale, to measure self-efficacy for smoking cessation;
4. Readiness to Quit, using the Contemplation Ladder;
5. Treatment Satisfaction scale (CSQ-8).
6. Minnesota Nicotine Withdrawal Scale, to measure nicotine withdrawal symptoms. To be administered at weeks 4, 8, 12, and 16.
7. Commitment (to Quit) Scale, to be administered at baseline and week 4.
8. Quit Attempts (1-item) questionnaire, to measure quit attempts at weeks 4, 8, 12, and 16;
9. Anhedonia scale (3-item scale) at baseline, weeks 2, 4, 8, 12, and 16.
10. Medication Adherence Calendar, at weeks 4 (in active condition only), weeks 8 and 12.
11. Brief Qualitative Interview. An interview agenda will be utilized to explore perceptions of using psilocybin for smoking cessation in a future study. This is an opt-in procedure for current (at week 12 or week 16) and past study participants.

Analytic Plan.

Assessments will be designed as Qualtrics surveys and paper surveys. Qualtrics will be used for all data collection. If Qualtrics is unavailable, the RA may use paper surveys for data collection. The data will then be transferred into Qualtrics. Data will be verified, checked, and uploaded to an SPSS file to conduct analyses. Initial data analysis will include distribution properties of baseline variables, and correlations among outcome measures.

Data Analysis. Initial data analysis will include examination of BL characteristics by condition, distribution properties of dependent and other variables, patterns of missing data by condition and correlations among outcome measures. Sample Size and Power Considerations. Our primary objective will be to examine preliminary effect sizes for NRT-P, rather than to determine statistical significance between groups at certain *p* values. At the same time, we are well aware of the dangers of relying exclusively on small-scale pilots to determine the promise of novel treatment approaches[101]. These effect size estimates have a large standard error, and we primarily will be hoping to find a pattern of results that is supportive of the experimental treatment. Effect size estimates will include odds ratios for smoking abstinence. We believe a sample size of 60 should allow adequate examination of NRT-P intervention effect sizes while staying within the scope of a developmental project. We recognize that only large effect sizes will be likely to attain statistical significance with a sample of this size, and large effect size are not anticipated. Our data also will allow us to obtain stability estimates for point-prevalence abstinence (i.e., intercorrelations among outcomes at 4 and 12 weeks). Using a program that allows us to specify proportions at each time point and the correlations between time points[102], we will be able to get a good estimate of the sample size needed to find a significant main effect of treatment in a repeated measures analysis using generalized estimating equations[103,104]. All analyses will include sex as a covariate, and follow-up analyses will test the Sex x Condition interaction to determine whether sex moderates the effects.

Treatment Feasibility, Acceptability, & Efficacy (Aims 1 and 2). We will first examine percent adherence to NRT prior to quit date in the NRT-P condition. We will then use *t*-tests to compare conditions on percent days adherent to NRT after TQD, and number of counseling sessions attended, and client satisfaction scores. We will compare side effects and NRT discontinuation rates between the active and control conditions. For treatment retention rate (dichotomous), a chi-square analysis will be used. Analyses of Aim 2 will test the hypothesis that NRT-P improves point prevalence abstinence relative to NRT-S. Tests of the effect of treatment condition on 7-day point-prevalence abstinence across the 8-, and 12-week assessments will be conducted using GEE, which provides appropriate modeling of covariance structures when observations are correlated across time[82]. The primary, between groups, independent variable in the GEE analysis is treatment condition assignment, which will be dummy-coded using NRT-S as the reference group. Following the intention-to-treat principle, all participants who have been randomized will be included in the analyses.

Potential Mechanisms of NRT-P Effects. Sample size in this pilot trial precludes formal mediation analysis with adequate power. The analyses are designed to test the plausibility of potential mechanisms of the NRT-P treatment effect. We will first run regression analyses predicting the putative mediators (nicotine dependence, self-efficacy for cessation, and urge to smoke) at both week 2 (1 week after those in NRT-P have initiated preloading) and week 4 (TQD) with treatment assignment and the BL value of the respective outcome as predictors. We will then enter change in the mediators from BL to week 2 and week 4 in the GEE models of smoking abstinence. Due to limited sample size, each mediator will be examined separately. We will examine

whether the effect of treatment is reduced when the mediator is added to the model and can test for significance (not expected given the sample size) using the products of coefficients method[105].

Missing Data. Following an intent-to-treat principle, all participants randomized to treatment will be included in analyses with those lost to follow-up counted as smoking. We will explore patterns of missing data to determine possible mechanisms of missingness and will explore different techniques to impute missing data values in different analyses[106]. For smoking abstinence, we will use the missing = smoking assumption for the primary approach.

Confidentiality

Confidentiality will be maintained as follows: Data files are recorded with an identification number, are stored at the Center for Alcohol and Addiction Studies, and are accessed only by project staff. All project staff are knowledgeable about confidentiality and human subjects' protection. Follow-up contact forms that require identifying information are stored separately from data files and are accessed only by those staff conducting follow-up interviews. During follow-up telephone calls to the participants' homes, no information is provided to others in the household.

Potential Research Risks

Potential risks in the study are considered minimal and include: 1) potential discomfort related to completing questionnaires about sensitive information such as psychological and alcohol/drug problems, 2) potential breach of confidentiality and/or privacy, 3) risk of adverse effects of NRT.

Alternative treatments. There are no alternative treatments. Participants may choose to contact their health care provider for smoking cessation treatment.

Protection Against Risk

Potential risks of the study are considered minimal. For the possibility of subjective discomfort from answering questions, any distress will be minimized by assurance that participants can refuse to answer any question that they do not feel comfortable addressing and may withdraw at any time without penalty. RAs are skilled in talking about sensitive information with subjects, and subjects may decide to end an interview at any time.

Breach of confidentiality is highly unlikely because all information will be identified with a numeric code only and stored in a Brown University secure fil. An enrollment database linking names and study identification numbers will be kept in a secure file separate from other subject data sources and will be used to facilitate the collection of follow-up data. Only grant staff will have access to this database. All staff are fully trained in relevant ethical principles and procedures, including confidentiality. All assessment and procedures will be closely supervised by the PI.

Regarding the potential discomfort using NRT: we will ask subjects about nicotine withdrawal symptoms and adverse effects of the NRT at each study visit, and the study staff will provide advice on minimizing these

symptoms. Study staff will be available to answer questions and concerns regarding the NRT. Participants will be advised to contact the study staff with any questions related to NRT, adverse effects, or general concerns. During the study, we will notify officials, as mandated by law, if a participant reports intention to harm him/herself or others, or reports child abuse or abuse of an elder.

Participant Safety Plan

During the MINI at baseline, we ask about recent (past month) suicidal ideation. If participants provide a positive response on that item, the RA will immediately contact a study clinician (Drs. Cioe or Kahler), who will speak with the participant by phone. The RA will explain to the participant that we will be asking the participant to speak with a licensed health professional given that he/she has reported some thoughts about self-harm. Clinicians are licensed clinical psychologists or licensed medical providers and can be reached by text message or cell phone during the hours that the RA will interview participants. Drs. Cioe and Kahler are licensed clinicians in RI and meet these qualifications. In the unlikely event that neither of the investigators are available during a study session, we will coordinate with other clinical psychologists at CAAS to ensure that there is always clinical coverage available. The MINI will only be conducted when clinical coverage is confirmed to be available. The clinician will evaluate the participant by phone to determine whether there is current active suicidal ideation and risk. The clinician will then provide appropriate referrals, or in the event of immediate risk, will call 911. RAs will be fully trained in these procedures and have clinician phone numbers with them during online sessions.

Potential Benefits of the Proposed Research to the Subjects and Others

As part of their participation in the study, subjects will receive smoking cessation counseling at no cost. Participants will make a quit attempt while in the study (at week 4) and will be provided with an 8-week supply of NRT. Furthermore, subjects will be provided with smoking cessation information and resources that they may choose to access. Given that the risks to subjects are considered to be minimal, the risk-benefit ratio is deemed favorable.

REFERENCES

1. Hajek P, Lewis S, Munafo M, Lindson N, Coleman T, Aveyard P. Mediators of the effect of nicotine pre-treatment on quitting smoking. Addiction 2018;113:2280-9.
2. Lindson N, Chepkin SC, Ye W, Fanshawe TR, Bullen C, Hartmann-Boyce J. Different doses, durations and modes of delivery of nicotine replacement therapy for smoking cessation. The Cochrane database of systematic reviews 2019;4:CD013308.
3. Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2006;8:89-101.
4. Rose JE, Herskovic JE, Behm FM, Westman EC. Precessation treatment with nicotine patch significantly increases abstinence rates relative to conventional treatment. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2009;11:1067-75.
5. Fagerström KO, Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: a review. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco 2002;4 Suppl 2:S73-9.
6. Lindson N, Aveyard P. An updated meta-analysis of nicotine preloading for smoking cessation: investigating mediators of the effect. Psychopharmacology 2011;214:579-92.
7. Etter JF, Huguelet P, Perneger TV, Cornuz J. Nicotine gum treatment before smoking cessation: a randomized trial. Archives of internal medicine 2009;169:1028-34.
8. Przulj D, Wehbe L, McRobbie H, Hajek P. Progressive nicotine patch dosing prior to quitting smoking: feasibility, safety and effects during the pre-quit and post-quit periods. Addiction 2019;114:515-22.
9. West R, Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. Psychopharmacology 2001;155:115-22.
10. Shiffman S, Shadel WG, Niaura R, et al. Efficacy of acute administration of nicotine gum in relief of cue-provoked cigarette craving. Psychopharmacology 2003;166:343-50.
11. Lindson-Hawley N, Coleman T, Docherty G, et al. Nicotine patch preloading for smoking cessation (the preloading trial): study protocol for a randomized controlled trial. Trials 2014;15:296.
12. Kim N, McCarthy DE, Loh WY, et al. Predictors of adherence to nicotine replacement therapy: Machine learning evidence that perceived need predicts medication use. Drug Alcohol Depend 2019;205:107668.
13. Gwaltney CJ, Metrik J, Kahler CW, Shiffman S. Self-efficacy and smoking cessation: a meta-analysis. Psychol Addict Behav 2009;23:56-66.
14. Cioe PA, Gordon REF, Guthrie KM, Freiberg MS, Kahler CW. Perceived barriers to smoking cessation and perceptions of electronic cigarettes among persons living with HIV. AIDS Care 2018;30:1469-75.
15. Pacek LR, Latkin C, Crum RM, Stuart EA, Knowlton AR. Current cigarette smoking among HIV-positive current and former drug users: associations with individual and social characteristics. AIDS and behavior 2014;18:1368-77.
16. Pacek LR, Cioe PA. Tobacco Use, Use Disorders, and Smoking Cessation Interventions in Persons Living With HIV. Current HIV/AIDS reports 2015;12:413-20.
17. Wei I. Application of an urn model to the design of sequential controlled clinical trials. Journal of the American Statistical Association 1978;73:559-63.
18. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom test for nicotine dependence: A revision of the Fagerstrom Tolerance Questionnaire. British Journal of Addiction 1991;86:1119-27.
19. Piper ME, Smith SS, Schlam TR, et al. A randomized placebo-controlled clinical trial of 5 smoking cessation pharmacotherapies. Arch Gen Psychiatry 2009;66:1253-62.
20. Piper ME, Cook JW, Schlam TR, et al. A Randomized Controlled Trial of an Optimized Smoking Treatment Delivered in Primary Care. Ann Behav Med 2018;52:854-64.
21. DiClemente CC, Prochaska JO, Fairhurst SK, Velicer WF, Velasquez MM, Rossi JS. The process of smoking cessation: an analysis of precontemplation, contemplation, and preparation stages of change. J Consult Clin Psychol 1991;59:295-304.