Application for Review of Human Research: IRB Protocol Summary
Biomedical Research
Section II

Version 19: February 13, 2018

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PROTOCOL TITLE

1. Full Title

A Placebo Controlled Trial of Varenicline for Smoking among those with HIV/AIDS

2. Brief Title

Varenicline for Nicotine Dependence among those with HIV/AIDS

STUDY SPONSORSHIP

1. Funding Sponsor

National Institutes of Health

2. Primary Sponsor

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PROTOCOL ABSTRACT

Among people diagnosed with HIV/AIDS, the widespread use of highly active antiretroviral therapy (HAART) has greatly improved survival rates (Palella et al., 1998) and changed the leading causes of death, from AIDS-related diseases (e.g., non-Hodgkin's lymphoma, Kaposi sarcoma*)*, to cardiovascular disease and lung cancer (Palella et al., 2006). As such, addressing modifiable risk factors for disease mortality among those with HIV/AIDS, including tobacco use, has become a critical priority (Nahvi & Cooperman, 2009). To date, only three smoking cessation clinical trials have been conducted with those with HIV/AIDS (Lloyd-Richardson et al., 2009; Vidrine et al., 2006; Ingersoll et al., 2007) none of which investigated the efficacy of FDA-approved medications for nicotine dependence. Varenicline is an α4β2 nicotinic acetylcholine receptor partial agonist with greater efficacy for treating nicotine dependence than bupropion (Gonzales et al., 2006; Jorenby et al., 2006) or nicotine patch (Aubin et al., 2008; Biazzo et al., 2010; Stapleton et al., 2008). Varenicline may be particularly efficacious for treating nicotine dependence among individuals with HIV/AIDS given that depression symptoms (Cruess et al., 2003) and cognitive impairment (Lindl et al., 2010) are common in this population, increase during smoking abstinence and predict smoking relapse (Zvolensky et al., 2009; Evans & Drobes, 2009), and are significantly reduced by varenicline (Patterson et al., 2009; Smith et al., 2009; Philip et al., 2009; Rollema et al., 2009). Therefore, we will conduct a randomized, double-blind, placebo-controlled trial of varenicline with smokers with HIV/AIDS. Specifically, 310 smokers with HIV/AIDS will be randomized to varenicline plus 9 weeks of smoking cessation counseling or placebo plus 9 weeks of smoking cessation counseling. The primary outcome variable for this study will be 7-day biochemically confirmed tobacco

abstinence at weeks 12 and 24. Secondary outcomes include: prolonged abstinence to week 12, 18, and 24 (relapse defined as 7 consecutive days of self-reported smoking, after a 2-week grace period), continuous abstinence at weeks 12 and 24 (e.g., no smoking between quit day and follow-up), time to 7-day relapse (no grace period), and lapse and recovery events. The trial results may support the use of varenicline for the treatment of nicotine dependence among those with HIV/AIDS, thereby reducing tobacco-related morbidity and mortality in this population.

OBJECTIVES

1. Overall Objectives

Aim 1: Compare 12-weeks of varenicline treatment and behavioral counseling to 12-weeks of placebo treatment and behavioral counseling for treating nicotine dependence among individuals with HIV/AIDS. Hypothesis: Varenicline and counseling will significantly increase end-of-treatment (week 12) and 24-week biochemically-confirmed 7-day point prevalence abstinence, vs. placebo and counseling.

Aim 2: Assess effects of varenicline therapy on quality of life (QOL) and varenicline-associated side effects. Hypothesis: QOL will be rated higher in the varenicline and counseling group vs. the placebo and counseling group, and there will be no significant differences between treatment arms in terms of the frequency of severe varenicline-related side effects.

Aim 3: Assess changes in affect and cognitive performance as mediators of varenicline therapy's effect on quit rates. Hypothesis: Improved affect and reduced cognitive impairment will mediate the effect of varenicline therapy on quit rates.

Exploratory Aim: Explore participant-related variables as moderators of varenicline therapy's effect on quit rates. To generate new hypotheses, we will explore participant-related variables as moderators of varenicline therapy's effect on quit rates, including socio-demographic (e.g., gender, race), psychiatric (e.g., depression), and medical (e.g., HIV/AIDS symptoms, method of HIV transmission) variables. Variables were selected for this analysis based on their relationship with smoking behavior (e.g., Webb et al., 2007).

BACKGROUND

HAART and the Changing Causes of Death among Individuals with HIV/AIDS

The advent of HAART has greatly improved survival rates for those diagnosed with HIV/AIDS (Palella et al., 1998). In 1994-1995, prior to the advent of HAART, the mortality rate among HIV/AIDS patients was 20.2-29.4/100 person years, but was reduced to 8.4-8.8 deaths/100 person years in 1997-1998, after HAART (Palella et al., 1998; Moore & Chaisson, 1999). Recent data show the mortality rate among individuals with HIV/AIDS has dropped even further to 1.3 deaths per 100 person years (Palella et al., 2006). This medical advance has increased the number of Americans living with HIV/AIDS to about one million, with about 40,000 new cases each year (CDC, 2004). Improved medical treatment, however, has also changed the leading causes of death among those with HIV/AIDS. Prior to HAART, individuals with HIV/AIDS primarily died from AIDS-related diseases (e.g., Kaposi sarcoma), but post-HAART, the leading causes of death in this population are cardiovascular disease and lung cancer (Palella et al., 2006). As such, addressing modifiable risk factors for disease mortality among those with HIV/AIDS, including tobacco use, has become a critical priority (Niaura et al., 1998; Benard et al., 2006).

Rates of Smoking among Individuals with HIV/AIDS

Despite substantial achievements in lowering the rate of smoking in the general population from >50% in 1965 to ~20% today, recent data show that the rates of smoking in the US have remained constant over the past 5 years (CDC, 2009; 2011). One reason for this stalled decline in US smoking rates is that certain sub-groups of smokers, including those with HIV/AIDS, who show very high rates of tobacco use, have been almost uniformly excluded from tobacco cessation research (Niaura et al., 2000; Nahvi & Cooperman, 2009). As a result, rates of tobacco use among individuals with HIV/AIDS are very high. Studies show that 50-74% of individuals with HIV/AIDS are regular smokers (Burkhalter et al., 2005; Collins et al., 2001; Crothers et al., 2005; Feldman et

al., 2006; Miguez-Burbano et al., 2005; Webb et al., 2007). This rate greatly exceeds the 20% prevalence rate of smoking in the general population (CDC, 2009) and exceeds rates reported for other notable clinical populations, such as cancer (Schnoll et al., 2003), cardiovascular (Rigotti et al., 2006), and depressed (Grant et al., 2004) patients. As such, the targeting of HIV/AIDS patients for tobacco cessation treatment is a critical priority and may help to reignite the steady decline in tobacco use rates that has been witnessed over the past half-century.

Tobacco-Related Health Consequences for Individuals with HIV/AIDS

Continued smoking among those with HIV/AIDS can result in serious adverse health effects. Importantly, smoking by individuals with HIV/AIDS can reduce the effectiveness of HAART. Controlling for medication adherence and comorbid illicit drug use, Feldman et al. (2006) found that smokers with HIV on HAART had a significantly lower likelihood of achieving a viral or immunologic response and had a greater chance of developing a viral or immunologic failure, vs. non-smokers with HIV on HAART. Persistent smoking among individuals who are HIV+ may also increase the likelihood for progression to AIDS (Neiman et al., 1993). Further, smoking by HIV+ patients increases risk for cardiovascular disease and cancer (Bozkurt et al., 2004; Bonnet et al., 2004; Singh et al., 1996; Tirelli et al., 2000). There is also evidence that smoking among pregnant women with HIV/AIDS can increase the risk for transmission of HIV to infants (Ahmad, 1996; Burns et al., 1994; Loutfy & Walmsley, 2004; Sprauve, 1996; Turner et al., 1997). Lastly, smoking among individuals with HIV/AIDS can exacerbate HIV-related symptoms (e.g., respiratory problems, pulmonary pneumonia) and worsen overall QOL (Cui et al., 2010; Crothers et al., 2005; Turner et al., 2001; Webb et al., 2007), and increase the likelihood of death (Pines et al., 2011). Overall, as Nahvi & Cooperman (2009) note, the achievements associated with the advent and widespread use of HAART in terms of reduced mortality rates and improved QOL among those with HIV/AIDS are being jeopardized by the cardiovascular and neoplastic diseases attributable to tobacco use.

Nicotine Dependence Treatments for Individuals with HIV/AIDS

Given the data reviewed above, it is remarkable that very few smoking cessation trials have been conducted with this population (Gritz et al., 2007; Harris, 2010; Nahvi & Cooperman, 2009). One randomized trial with 95 patients (Vidrine et al., 2006) compared standard smoking cessation treatment (behavioral counseling and nicotine replacement therapy; NRT) to standard smoking cessation treatment plus proactive cell-phone counseling. Though this study found higher quit rates with the addition of the cell-phone counseling, the findings require replication with a larger sample and relying on cell phones to provide treatment may be a barrier to translating these results broadly across HIV/AIDS clinics. The second trial compared self-help smoking cessation plus NRT to motivational interviewing plus NRT (Ingersoll et al., 2007). This trial included only 40 smokers and found no difference in quit rates across groups. A third, larger trial (n = 444), compared NRT and standard behavioral counseling to NRT and counseling to enhance quit motivation (Lloyd-Richardson et al., 2009); no significant differences in quit rates between the arms were detected.

As such, as of yet, there is no demonstrated efficacious treatment model for addressing tobacco use among those with HIV/AIDS and no basis on which to disseminate recommendations for the use of pharmacotherapy to treat nicotine dependence in this sub-group of smokers. Importantly, no clinical trial has formally evaluated any of the US FDA-approved medications for nicotine dependence among those with HIV/AIDS using a controlled design, including varenicline, the most efficacious treatment available for nicotine dependence (Fiore et al., 2008; Schnoll & Lerman, 2006). It is essential that controlled clinical trials investigate interventions that have proven efficacy in the general population in smokers with HIV/AIDS since: 1) smokers with HIV/AIDS have been almost uniformly excluded from these trials (e.g., Gonzales et al., 2006); 2) differences between smokers with HIV/AIDS and the general population of smokers in terms of psychiatric and substance abuse history/comorbidity - factors that influence smoking cessation response rates (Humfleet et al., 1999; Zvolensky et al., 2009) - diminishes the generalizability of results from clinical trials with the general population; and 3) the safety of using these medications among individuals with HIV/AIDS is currently unknown and must be explicated before broad use in HIV/AIDS clinics (Nahvi & Cooperman, 2009).

Barriers to Quitting Smoking Among Those with HIV/AIDS

While there are limited data on specific barriers to quitting smoking that are unique to individuals with HIV/AIDS compared to the general population, two factors may be important. First, smoking cessation interventions for individuals with HIV/AIDS may need to address psychiatric history/comorbidity, most commonly depression and dysthymia (Nahvi & Cooperman, 2009). A large epidemiological study using a nationally representative sample found that more than a third of HIV+ patients exhibited major depression and another quarter had dysthymia (Bing et al., 2001). A meta-analysis of studies has shown that the risk for depression is 2-times greater if one is diagnosed with HIV/AIDS, compared to unaffected individuals (Ciesla & Roberts, 2001) which may be an under-estimate of risk (Asch et al., 2003). Symptoms of psychological distress, including depression symptoms, have been shown to be a strong risk factor for relapse following successful smoking cessation in the general population (Zvolensky et al., 2009) and have been associated with lower levels of motivation to quit smoking (Burkhalter et al., 2005) and higher risk of smoking (Webb et al., 2007) among those with HIV/AIDS. Second, smoking cessation interventions for individuals with HIV/AIDS may need to address cognitive impairment, which typically includes difficulties with memory, attention/concentration, and executive function (Heaton et al., 2011). While the advent of HAART has reduced the rate of cognitive impairment among those with HIV/AIDS, several recent surveys indicate that 39%-69% of individuals with HIV/AIDS show cognitive impairment (Robertson et al., 2007; Simioni et al., 2010). In the general population, smokers use nicotine to enhance cognitive function, nicotine withdrawal increases cognitive impairment which predicts relapse, and resuming smoking ameliorates abstinence-induced cognitive impairment (Heishman, 1999; Evans & Drobes, 2009; Rukstalis et al., 2005). Consequently, nicotine dependence treatments for individuals with HIV/AIDS may show greater efficacy if they adequately address the patient's relatively high level of psychological distress and cognitive impairment.

Varenicline for Nicotine Dependence

Varenicline, approved by the US FDA in 2006, is the most efficacious FDA-approved medication for nicotine dependence, yielding quit rates that significantly exceed those produced by bupropion (Gonzales et al., 2006; Jorenby et al., 2006) and nicotine patch (Aubin et al., 2008; Biazzo et al., 2010; Stapleton et al., 2008). Randomized clinical trials and meta-analyses indicate that 6-month quit rates for varenicline are ~30% (Gonzales et al., 2006; Jorenby et al., 2006; Cahill et al., 2011). Varenicline is an α4β2 nicotinic acetylcholine receptor (nAChR) partial agonist. As such, varenicline binds to the α4β2 nAChRs, preventing nicotine from binding and stimulating nAChRs and dopamine release. These processes reduce the rewarding effects of smoking and reduce abstinence induced withdrawal symptoms (Rollema et al., 2009). Varenicline's efficacy is also thought to be due to the drug's effects on abstinence-induced psychological distress and cognitive impairment. Several studies show that varenicline mitigates adverse psychological effects and cognitive impairment associated with quitting smoking (Patterson et al., 2009; Smith et al., 2009; Philip et al., 2009; Rollema et al., 2009; Sofuoglu et al., 2009). The anti-depressant-like (Rollema et al., 2009) and cognitive enhancing (Loughead et al., 2010) effects of varenicline is consistent with what we know about how this medication works. Preclinical studies indicate that α4β2 nAChRs subtypes are critical for cognition (Levin et al., 2009) and varenicline's stimulation of these receptors improves cognitive function (Loughead et al., 2010). Likewise, animal studies indicate that the simultaneous activation and desensitization of nAChRs produced by nicotinic partial agonists like varenicline can yield antidepressant-like effects (Mineur & Picciotto, 2010), which underlies current evaluations of varenicline as a treatment for major depression. Lastly, there are efficacy and safety data for varenicline among various clinical populations, including: cardiovascular disease patients (Rigotti et al., 2010), COPD patients (Tashkin et al., 2010), smokers with comorbid alcohol (Hays et al., 2010) and cocaine (Poling et al., 2010) dependence, and smokers with comorbid affective or psychotic disorders (McClure et al., 2010; Smith et al., 2009; Philip et al., 2009). It has been shown to be safe when used for 52 weeks (Williams et al., 2007). Although there have been reports of adverse psychiatric events following varenicline use, leading the FDA to mandate a boxed warning for varenicline, and a recent meta-analysis indicated a small yet statistically significant increased risk for cardiovascular side effects (Singh et al., 2011), pooled data from efficacy trials (Cahill et al., 2009; Tonstad et al., 2010), effectiveness trials (McClure et al., 2010), and large cohort studies (Gunnell et al., 2009; Kasliwal et al., 2009) show that varenicline is safe for treating nicotine dependence, even among smokers with psychiatric comorbidity, including depression

(Stapleton et al., 2008; McClure et al., 2010; Steinberg et al., 2010). A recent meta-analysis of varenicline trials concluded that there was insufficient evidence to associate varenicline use with serious adverse neuro-psychiatric events such as depression or suicidal thoughts/behavior but that additional trials testing varenicline with smokers with a range of comorbidities is needed (Cahill et al., 2011). Following a large-scale trial supporting the safety of varenicline for smoking cessation among those with and without a current psychiatric disorder (Anthenelli et al., 2016), the FDA removed the boxed warning on varenicline in December 2016.

CHARACTERISTICS OF THE STUDY POPULATION

1. Target Population

Three hundred ten adult male and female smokers 18 years of age or older who have been diagnosed with HIV/AIDS (identified through the UPENN CFAR Clinical Core, UPHS PennChart reviews and community-based HIV/AIDS organizations and events) and smoke at least 5 cigarettes per day will complete the study.

At PENN, a previous nicotine patch trial recruited a sample comprised of 45% women and 16% racial/ethnic minorities (Schnoll et al., 2010b). A separate PENN smoking cessation trial that used targeted efforts to recruit minority smokers had a sample comprised of 55% women and 52% racial/ethnic minorities (Schnoll et al., 2011). The UPENN CFAR Clinical Core population is 78% African American and 4% Hispanic American.

2. Accrual

For this trial, we project that we will screen ~1000 HIV/AIDS patients over 54 months (allowing six months to complete follow-up), 77% of whom will be current smokers (n = 770). Additional data indicate that upwards of three-quarters of these patients will want to quit smoking and will want to use a medication in their quit attempt (Drach et al., 2010), yielding a sample of ~575 patients to recruit. Based on past varenicline trials (Schnoll et al., 2011; Patterson et al., 2009) and the present inclusion/exclusion criteria, we expect ~two-thirds of these patients to be eligible for the trial (n = ~345). To be conservative, given the possible health problems evident in this population of smokers, we will project $\leq$ 20% of participants will withdraw from the trial and $\geq$80% of subjects will complete follow-ups. As is advised in smoking cessation trials (Hughes et al., 2003), intent-to-treat will be used for primary analyses, with missing outcome data coded as smokers.

3. Key Inclusion Criteria

Eligible subjects will be males and females:

1. 18 years of age or older who self-report smoking at least 1 cigarette (menthol and non-menthol) per day, on average.
2. Diagnosed with HIV infection and exhibiting viral load of ≤ 1000 copies/mL within the last 6 months.
3. Exhibiting CD4+ count of $\geq$ 200 cells/mm^3 within the last 6 months.
    1. If the participant has not had a CD4+ count test completed in the last 6 months, an older result ($\geq$ 200 cells/mm^3) may be used if evidence is provided that all subsequent viral loads results are ≤ 1000 copies/mL.
4. Able to use varenicline safely, based on a medical evaluation including medical history and psychiatric evaluation.
5. Residing in the geographic area for at least 7 months.
6. Women of childbearing potential (based on medical history) must consent to use a medically accepted method of birth control (e.g., condoms and spermicide, oral contraceptive, Depo-Provera injection, contraceptive patch, tubal ligation) or abstain from sexual intercourse during the time they are taking study medication and for at least one month after the medication period ends.
7. If current or past diagnosis of bipolar disorder (I, II, or NOS), eligible if:
    a. No psychotic features
    b. MADRS: total score $\leq$ 8 (past 4 weeks), suicidal item score $\leq$ 1 (past 4 weeks)
    c. Y-MRS: total score $\leq$ 8 (past 4 weeks), irritability, speech content, disruptive, or aggressive behavior items score $\leq$ 3 (past 4 weeks)
    d. No psychiatric hospitalization or Emergency Room visits for psychiatric issues in the past 6 months

e. No aggressive or violent acts or behavior in the past 6 months

8. Able to communicate fluently in English.
9. Capable of giving written informed consent, which includes compliance with the requirements and restrictions listed in the combined consent/HIPAA form.

4. Key Exclusion Criteria

Subjects who present with and/or self-report the following criteria will not be eligible to participate in the study.

Smoking Behavior

1. Current enrollment or plans to enroll in another smoking cessation program in the next 7 months.
2. Regular (daily) use of chewing tobacco, snuff, snus, cigars, cigarillos, or pipes.
3. Current use or plans to use nicotine substitutes (gum, patch, lozenge, e-cigarette) or smoking cessation treatments in the next 7 months.
    a. Note: Once participants are found eligible for the study, they are told they should refrain from using any nicotine replacement therapy (NRT) for the duration of the study. If a subject reports NRT use during the study, s/he may be permitted to continue pending approval from the study physician and PI.

Alcohol/Drug Exclusion Criteria

1. Current untreated and unstable diagnosis of substance dependence. Current untreated and unstable diagnosis of substance abuse requires Study Physician approval.
    a. Note: The participant is eligible if dependence was in the past (greater than 1 year ago) or if the participant is currently receiving treatment (eg. medication, group therapy, support groups and/or intensive outpatient programs) and has been stable for ≥30 days.
2. Breath Alcohol Concentration (BrAC) assessment greater than or equal to 0.01 at the Intake Session.

Medication Exclusion Criteria

Current use or recent discontinuation (within last 14 days) of the following medications:

1. Other smoking cessation medications (e.g. Zyban, Wellbutrin, Wellbutrin SR, Chantix)
    a. Note: Once participants are found eligible for the study, they are instructed to only use the smoking cessation medication provided to them by the study staff. If a subject reports using a non-study smoking cessation medication, the study physician and PI will evaluate the situation and determine if it is safe for the subject to continue participation.
2. Anti-psychotic medications (if used to treat psychotic symptoms. Other uses may be eligible pending physician approval).

Medical Exclusion Criteria

1. Women who are pregnant, planning a pregnancy within the next 7 months, or lactating.
2. Current diagnosis of unstable and untreated major depression, as determined by self-report & MINI.
    a. Note: The participant is eligible if stable for ≥30 days (stability is defined by the use of mood regulating medication and/or by receiving regular mental health care evaluations or therapy).
3. Current or past diagnosis of psychotic disorder, as determined by self-report or MINI.
4. History of unstable heart disease, stroke, myocardial infarction, angina, or tachycardia (if stable, requires Study Physician approval).
5. Uncontrolled hypertension (SBP >160 or DBP >100).
    a. Note: If a participant presents with blood pressure greater than 160/100 at sessions occurring on Week 0 (Pre-Quit) or at any other point during the treatment period, they will not be provided with/able to continue on medication unless the study physician grants approval.
6. History of seizures or current seizure disorder that is unstable and untreated. (If seizures are stable and treated, requires Study Physician approval.)
7. History of decompensated cirrhosis (i.e., a diagnosis of hepatic decompensation, decompensated cirrhosis, end-stage liver disease, ascites, variceal hemorrhage, spontaneous bacterial peritonitis,

hepatic encephalopathy) as determined by medical history review is subject to study physician approval.
8. Evidence of severe renal impairment including current dialysis treatment, estimated creatinine clearance <30 mL/min (within 6 months of enrollment) or eGFR <60 mL/min/1.73m^2 (within 6 months of enrollment).
9. Previous allergic reaction to varenicline.

Suicide Hx Exclusion Criteria
1. Any suicide attempt or suicidal behavior within 2 years of enrollment
    a. Note: Any participant that reports a suicide attempt or episode of suicidal behavior more than 2 years before enrollment will be evaluated by senior clinical staff (Dr. Hole or Dr. Thase) to assess final eligibility based on the complete psychological profile ascertained at the intake session.
2. Current suicidal ideation (within the last 30 days of enrollment)
3. Two or more lifetime suicide attempts or episodes of suicidal behavior
4. If the participant has a history of bipolar disorder, any suicide risk score on the MINI or self-reported lifetime suicide attempt or suicidal behavior

General Exclusion Criteria
1. Any medical condition or concomitant medication that could compromise subject safety or treatment, as determined by the Principal Investigator and/or Study Physician.
2. Inability to provide informed consent or complete any of the study tasks as determined by the Principal Investigator and/or Study Physician.

5. Vulnerable Populations
Children, pregnant women, fetuses, neonates, or prisoners are not included in this research study.

6. Populations vulnerable to undue influence or coercion
Educationally or economically disadvantaged persons are included but not solely targeted for recruitment. Cognitively impaired persons are not included in the current study. Because of our recruitment efforts for this study, it is possible that University of Pennsylvania employees and students may be invited to participate. Status of participation in the study will be independent of the subject's work or school activities.

7. Subject Recruitment
Participants will be recruited from the Infectious Disease practices at the Hospital of the UPENN, Presbyterian Hospital, and Pennsylvania Hospital. Dr. Frank will oversee the integration of this study into the clinics, ensuring access to participants, collection of medical data (through UPHS PennChart medical record reviews and laboratory result requests), and access to private consulting rooms for screening at the CFAR clinics. These practices see over 500 patients monthly and more than 200 new patients each year.

After obtaining the necessary training and clinic clearances to access PennChart for participating UPHS clinics, Research Assistants (RAs) will review the electronic medical records to identify potential subjects on a weekly basis (each site has patient smoking status indicated on the record). Individual medical records will be evaluated for eligibility based on the inclusion and exclusion criteria for this study. Daily clinic schedules will be ascertained and RAs will approach patients prior to or after consultation or treatment at the clinic. In addition to in-clinic recruitment, RAs will contact potentially eligible patients (after EMR review) by telephone based on their clinic provider's specified research contact preference. Providers may choose one of the following contact options: 1) all patients identified as initially eligible may be contacted 2) all patient records identified as initially eligible will be sent to the provider via PennChart for review and approval prior to contact 3) all patient records identified as initially eligible may be sent to the provider, who assumes full responsibility and discretion regarding the research contact (no contact may be made by the research staff). Those patients deemed eligible for contact will be contacted by telephone. RAs will introduce the research study and the collaboration

between the researchers, infectious disease clinic, and the patient's provider. After assessing the patient's interest, HIV status, and smoking status, the patient will then be provided with additional study information and an opportunity to assess his/her intake eligibility based on a screening questionnaire.

Research Recruitment Best Practice Advisories (BPAs) will also be integrated into electronic medical record recruitment. BPAs are designed to fire passive alerts within PennChart at the point of care, notifying providers that a patient may be eligible for a specific study. This specific BPA will evaluate if a patient meets specific criteria associated with the trial and will present the provider with the option to indicate if a patient is interested in participating in the study or not. This BPA will only present if the patient meets the initial screening criteria based on smoking status and problem list diagnoses and will only present in specified departments. This indication of interest only serves to trigger a notification to study staff that a patient has met initial screen criteria and further follow-up is requested to determine eligibility of the patient. This alert is a passive alert and will not interrupt the provider's workflow, but will be listed in the same section as other clinically warranted BPAs.

If our accrual rate is lower than anticipated based on our feasibility data, Dr. Metzger and the CFAR CAB will use their connections with community-based HIV/AIDS organizations in the Delaware Valley region to promote the trial and enhance accrual rates. The CFAR CAB, comprised of people with HIV/AIDS or professionals in the treatment of substance use among those with HIV, has numerous linkages to community-based organizations that can be used to enhance participant recruitment should that be necessary. We will also advertise the study using poster, newspaper, and internet based advertisements (this includes in-app advertising, Craigslist, and Twitter). Information about the study will be available on the CIRNA and iConnect websites. In addition, research staff will attend HIV/AIDS community events and community clinic intake hours to provide information about the study, distribute recruitment materials, and collect participant contact information via a secure, web-based data collection service. Additionally, we will place recruitment data requests with electronic research data warehouses such as Penn Data Store and Pennomics to obtain lists of pre-consented potential participants. ResearchMatch, a national health volunteer registry that was created by several academic institutions and supported by the U.S. National Institutes of Health as part of the Clinical Translational Science Award (CTSA) program, will also be utilized. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible.

RAs and UPHS medical personnel will screen patients from UPENN and community based HIV/AIDS clinics to identify potentially eligible and interested participants by phone or in person. Participants recruited through other methods will also be screened by phone or in person. Participants who are eligible and interested in the study will be scheduled for an Intake session (Week -1) with research staff. At the Intake session the participant will sign an informed consent and HIPAA form, complete eligibility and baseline assessments, and be scheduled for Week 0. The participant's eligibility will be confirmed by Drs. Leone, Thase and Hole.

To ensure a high level of retention and adherence in this trial we will: 1) educate subjects about the benefits of protocol compliance; 2) schedule in-person sessions at convenient times (e.g., evenings); 3) use a medication adherence component in the counseling protocol (Gariti et al., 2009; Schnoll et al., 2008), and 4) as is standard practice in smoking cessation trials (Schnoll et al., 2010b; Niaura et al., 2005), provide modest financial compensation for session completion and transportation costs.

STUDY DESIGN

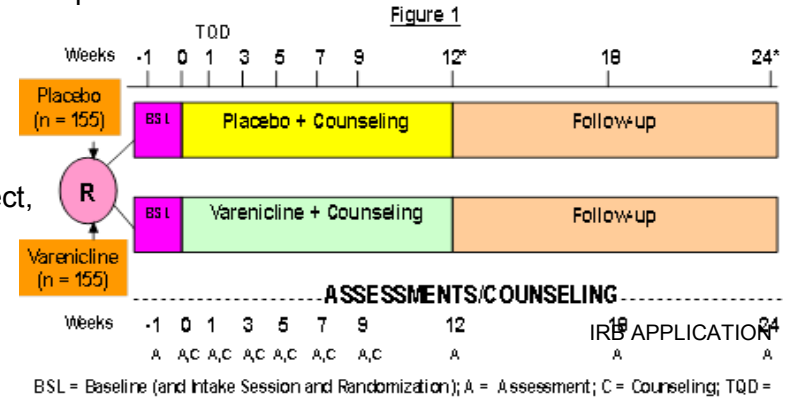
1. Phase

This study is a Phase III clinical trial.

2. Design

This is a randomized, between-subject, double-blind, placebo-controlled study.

Figure 1



BSL = Baseline (and Intake Session and Randomization); A = Assessment; C = Counseling; TQD = Target Quit Day; * Corresponds to End-of-Treatment and 6-months post-TQD and primary outcomes.

Figure 1. Study Overview

3. Study Duration

Length of Subject's Participation in Study

Subjects will participate in study related activities for approximately 7 months from initial eligibility assessment in the clinic through follow-up. A subject's length of participation may be affected by center or subject scheduling conflicts.

Projected date of completion of the proposed study

We expect to complete accrual in approximately 54 months, completing the trial in December 2016. We expect to obtain our numbers in this timeframe by enrolling approximately 6 subjects per month.

Table 1. Study Timeline

Tasks/Months	1 3	12	24	36	48	60
Refine and test DMS and Train Staff (1-3)	X-----X					
Recruitment/baselines (3-54)	X----------X					
Treatment (3-57)	X----------X					
Outcome assessments (15-60)	X----------X					
Analysis/manuscripts (48-60)	X----------X					

DRUGS OR DEVICES

Study Medication

Dosing

Varenicline will be used in accordance with FDA approved labeling: Day 1-Day 3 (0.5mg once daily); Day 4-Day 7 (0.5mg twice daily); and Day 8-Day 84 (1.0mg twice daily).

Supply, Preparation, Storage, Packaging and Dispensing of Study Medication

Varenicline and matching placebo, provided at no-cost by Pfizer, will be packaged and stored at the University of Pennsylvania Investigational Drug Service. Varenicline and matching placebo will be packaged into blister packs in 1-2 week supplies. Medication will be distributed to participants in increments at Weeks 0, 3, and 7.

IDS will oversee the randomization and labeling of all study medication, and will assign each kit, which contains 12 weeks of medication for one subject, and a unique Pharmacy Randomization Number (PRN). Once a new subject is enrolled and eligible, IDS will assign the subject the next available PRN. The research staff will then label the blister packs with the subject's study ID number. The PRN and study ID number must match for each blister pack a subject receives. Medication kits will be stored in a locked cabinet at our center until they are dispensed at participant medication pick-up visits.

Regular study drug reconciliation will be performed to document drug assigned, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed by the research staff member who completed the reconciliation.

At the completion of the study, there will be a final reconciliation of drug shipped, drug consumed, and drug remaining. This reconciliation will be logged on the drug reconciliation form, signed and dated by the research staff. Any discrepancies noted will be investigated, resolved, and documented prior to return or destruction of unused study drug. Drug destroyed on site will be documented in the study files.

STUDY PROCEDURES

1. Procedures

Subjects

Subjects will be 310 smokers who have been diagnosed with HIV/AIDS, meet study eligibility criteria, and provide written consent to participate in this between-subject trial.

Study Procedures

Initial Eligibility Screening.

Recruited subjects will complete an initial eligibility assessment in the HIV/AIDS clinic or over the telephone. This assessment reduces the likelihood that participants attend an Intake Session only to learn that they are ineligible or to allow us to ascertain physician's clearance should the participants have a medical condition that requires approval. Subjects who pass this pre-screening will be invited to attend an Intake Session.

Intake Session (Week -1): Consent, Eligibility Determination, Baseline Measures.

Subjects who pass the pre-screening will be invited to attend a 2.5-hour Intake Session where the following activities will occur:

1. Subjects will hear a study description where all study procedures, risks, and information about the study medication will be reviewed. Subject questions will be answered. Following this presentation, the combined informed consent and HIPAA form will be completed.

2. A urine pregnancy test (all female subjects) will be administered.

3. A breath alcohol concentration assessment (BrAC) to control for alcohol consumption. The handheld device uses a disposable mouthpiece, reports the concentration of alcohol in breath and takes about 2 minutes.

4. A carbon monoxide (CO) breath assessment to control for prior tobacco exposure. The handheld device uses a disposable mouthpiece, reports CO in parts per million (ppm), and takes about 3 minutes.

5. Mental status examinations (Mini International Neuropsychiatric Interview, HADS, C-SSRS, and MADRS, YMRS, Bipolar Disorder Additional Screener, if necessary) with a trained research staff member.

6. Complete routine medical history, including blood pressure assessment.

7. A concomitant medication review.

8. Complete baseline paper and pencil measures to assess 1) background variables that may serve as covariates and will allow for the assessment of the study's external validity (e.g., smoking history, demographics), 2) mediators (e.g., affect, cognition), 3) moderators (e.g., disease-related information, and 4) baseline smoking behavior.

9. Provide one 10ml blood sample (2 teaspoons) to assess nicotine metabolite ratio (cotinine and 3-hydroxycotinine).

10. Provide one 10ml blood sample (2 teaspoons) for DNA collection and genotyping.

Initially eligible participants who have not had kidney function tests within the last 6 months (as ascertained by medical record review or provision of results from the participant's health care provider) will provide one 10ml blood sample (2 teaspoons) to complete these tests following the Intake Session. Test results that are outside of normal ranges will be reviewed for final eligibility by the Study Physician prior to enrollment.

If eligible at this point, subjects will be scheduled for the first treatment session (Week 0).

Behavioral Counseling (Week 0-Week 9).

All subjects will receive manual-based counseling from a counselor trained and supervised by Dr. Hole. The counseling protocol is based on PHS guidelines for smoking cessation treatment (Fiore et al., 2008), used in our studies with cancer patients (Schnoll et al., 2010a) and the general population of smokers (Schnoll et al., 2010b; R01 DA025078). Counseling is included given its efficacy at helping smokers quit (Fiore et al., 2008),

to ensure that participants in the placebo arm receive active treatment to quit smoking and to increase study retention. Counseling is provided to both treatment arms until Week 9 to equate for time and attention across arms since this method was used in past varenicline trials (e.g., Gonzales et al., 2006). Counseling will be provided in-person at the CIRNA. Sessions can be arranged at convenient times for the participants, including evenings.

Pre-Quit Session (Week 0): The counseling program begins at Week 0 with a 1-hour in-person "pre-quit" counseling session to prepare for the target quit day. This session focuses on reviewing the participant's history and experience with quitting as well as beliefs about smoking, quitting and perceived barriers to cessation. A quitting plan is initiated and involves identifying smoking triggers and strategies to increase the chance for success, including relying on social support to quit smoking and altering behaviors associated with smoking. The first 3 weeks of medication is dispensed at this session and will begin at the session or immediately following the session.

Quit Day Session (Week 1): At Week 1, participants will receive a 30-minute in-person "quit-day" session to review the initial quit attempt, identify potential reasons for relapse, and review a plan for avoiding tempting situations.

Relapse Prevention Sessions (Weeks 3, 5, 7, and 9): Participants will then receive 4 additional 20-minute in-person booster sessions at Weeks 3, 5, 7, and 9 which focus on either reinforcing success and reviewing the quit plan or reestablishing a quit date and restarting the cessation process. The counseling sessions are designed to enhance awareness of the harmful effects of smoking, assist the person in developing skills to quit and avoid relapse, and instruct the smoker on varenicline use. Lastly, all counseling sessions may be audio-taped and a random 15% of sessions assessed for protocol adherence. The counselor is blind to randomization.

Varenicline or Placebo Treatment (Weeks 0-12).
The dosing regimen used in past varenicline trials and consistent with FDA guidelines will be used: Day 1-Day 3 (0.5mg once daily); Day 4-Day 7 (0.5mg twice daily); and Day 8-Day 84 (1.0mg twice daily). Medication and matching placebo will be packaged into blister packs in 1-2 week supplies. Medication will be distributed in increments at Weeks 0, 3, and 7. Day 1 of study medication will be scheduled no more than 60 days following the Intake Session. If Day 1 is scheduled more than 60 days following the Intake Session, the participant will be required to attend another Intake Session in order to reaffirm eligibility. Participants who discontinue the study medication for 14 or more consecutive days will require approval from the Principal Investigator and Study Physician before restarting the study medication.

Varenicline Adherence.
At each session after Pre-Quit until end of treatment, participants are evaluated in terms of their adherence by self-report and pill count. At Weeks 3 (steady-state) and 12 (end of treatment), participants will be asked to provide blood samples to evaluate varenicline levels as a measure of adherence. Specific strategies to address non-adherence will be used if necessary. The varenicline adherence approach formally assesses participant reasons for non-adherence using scenarios and uses specific strategies to enhance compliance. If the participant discontinues study medication for any reason for 14 or more consecutive days prior to an adherence blood draw, the blood draw will not be conducted.

Mid-treatment Assessments.
Assessments will be conducted at Weeks 0, 1, 3, 5, 7, and 9 by trained RAs to assess mediating variables and monitor safety. These assessments will take ~30 minutes to complete and will be done in-person prior to counseling. Assessments include measures of mediating variables (e.g., affect), HAART adherence, varenicline adherence (pill count and collection of blister packs), concomitant medication review, QOL, carbon monoxide assessment, and smoking behavior.

Cognitive Function.
We will assess cognitive function using validated computerized tasks as in our past varenicline study (Patterson et al., 2009). We will use the Visual/Spatial-N-Back task of working memory (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008; Green et al., 2005; Owen, et al., 2005) and the PENN Continuous Performance

Task (P-CPT) of sustained attention (Kurtz et al., 2001). These tasks will be administered on a computer during Pre-Quit, Target Quit Day, and Weeks 3, 7, and 12.

Side Effect Monitoring.
The research team has a clinical psychologist and physician to review initial eligibility and to monitor and address side effects during the trial. To reduce risk for adverse events, we will carefully assess eligibility to ensure that individuals with pre-existing conditions that can increase adverse event risk are excluded.

We will also frequently assess participant treatment reactions with established symptom checklists and validated suicidality and depression/anxiety scales. These assessments, as well as blood pressure assessments, are conducted at each visit before, during, and after the 12 week treatment phase by a research staff member.

We will use an established coding and reporting system for side effects also used in our ongoing varenicline trial (DA020830). In this system, personnel are trained to administer side effects measures, including validated scales of suicidality. If a side effect report or a score on an established scale indicates a safety concern, Drs. Schnoll, Hole, Leone, and Thase will be notified per the Safety Monitoring and Reporting Protocol and will assume responsibility for the determination of a course of action (e.g., continue to monitor, stop medication). Participants are given contact information so that, if an adverse event occurs, they can contact study staff 24-hours a day. These side effects are also coded and managed by Drs. Schnoll, Hole, Leone and Thase. Serious adverse events are reported to the IRB, Pfizer, NIDA, and FDA in accordance with DSMP reporting procedures and participants may be referred to a PENN out-patient department or to the ER.

There are no known HAART/varenicline drug interactions (Drach et al., 2010). Varenicline is renally cleared, while the non-nucleoside reverse transcriptase inhibitors, protease inhibitors, raltegravir, and maraviroc are hepatically cleared. The nucleoside reverse transcriptase inhibitors (NRTIs) are metabolized by the kidney and, among the NRTIs, tenofovir is the only one related to risk for nephrotoxicity. HAART use will be assessed throughout the trial and patients on tenofovir will be closely monitored. We will examine the relationship between tenofovir use and varenicline side effects, including the assessment of varenicline plasma levels as a possible mediator of this relationship.

Outcome Assessments.
The primary outcome variable for Aims 1 and 3 is 7-day point prevalence abstinence at Weeks 12 and 24, biochemically-confirmed with urine cotinine (Hughes et al., 2003). Secondary outcomes for Aim 1 include: biochemically-confirmed 7-day point prevalence abstinence at Week 18, smoking rate at Weeks 12, 18, and 24 for non-abstainers, prolonged abstinence to Weeks 12, 18, and 24, continuous abstinence at Weeks 12, 18, and 24, time to 7-day relapse (no grace period), and lapse and recovery events. For Aim 2, since individuals with HIV/AIDS who smoke report a lower QOL (Webb et al., 2007), we will closely monitor QOL, as measured by a commonly-used self-report scale for this population, and administer a checklist of varenicline-related side-effects.

Based on enrollment date, subjects will complete social impact assessments as part of a sub-study in collaboration with the Treatment Research Institute. Two assessments administered at Weeks 3, 7, and 12, include the self-administered, computer based ACASI-SHQ and the staff administered HVTN Social Impact Assessment. An additional client evaluation form is completed by participants at Week 12. Participants who miss administration sessions may complete the assessments at their subsequent study session.

Participants who are unable to quit smoking may be given referrals for smoking cessation treatment following the Week 24 assessment.

Note: If a participant is unable to complete a session in-person, assessments and counseling may be completed over the telephone. Participants will receive compensation for their time at the following in-person session.

Table 2: Study Measures/Events

Study Week Session Name	-1 Intake	0 Pre-Quit	1 TQD	3 W3	5 W5	7 W7	9 W9	12 W12	18 W18	24 W24
TREATMENT										
Varenicline/Placebo		X	X	X	X	X	X	X		
Counseling		X	X	X	X	X	X			
SCREENING/COVARIATES										
Urine Pregnancy Screen	X									
Breath Alcohol Concentration	X									
Blood Pressure	X	X	X	X	X	X	X	X	X	X
Depression/Anxiety (HADS)	X	X	X	X	X	X	X	X	X	X
Demographics	X									
Smoking History/FTND	X									
ETOH History	X									
Medical History	X									
Psychiatric History (MINI)	X		X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]	X[g]
Adherence to Antiretrovirals Instrument		X			X		X	X	X	X
Pharmacy Refill Data		X[d]			X[d]			X[c]		X[c]
Concomitant Medications	X	X	X	X	X	X	X	X	X	X
Creatinine Clearance	X[a]									
Viral Load Assessment								X[e]		
Nicotine Metabolite Ratio	X									
Genetic Polymorphisms	X									
Bipolar Disorder Symptoms (MADRS[f], YMRS, Additional Screener, MINI)[g]	X		X	X	X	X	X	X	X	X
MEDIATING VARIABLES										
Affect (PANAS)		X	X	X		X		X		
Cognitive Function (N-back, CPT)		X	X	X				X		
Nicotine Withdrawal (MNWS-W)		X	X	X		X		X		
Smoking Urges (QSU-B)		X	X	X		X		X		
TREATMENT VARIABLES										
Adherence (Pill Count)			X	X	X	X	X	X		
Adherence (Blood)				X[i]				X[i]		
Side Effects Checklist (SEC)		X	X	X	X	X	X	X	X	X
Side Effects (Open-Ended)			X	X	X	X	X	X	X	X
Suicidality (C-SSRS)	X	X	X	X	X	X	X	X	X	X
OUTCOMES										
Carbon Monoxide (CO) Test	X	X	X	X	X	X	X	X	X	X
Smoking Rate (TLFB)		X	X	X	X	X	X	X	X	X
Urine Cotinine								X[b]	X[b]	X[b]
Quality of Life (HAT-QoL)		X	X	X	X	X	X	X	X	X
ACASI-SHQ[h]				X		X		X		
HVTN Social Impact Assessment[h]				X		X		X		
Client Evaluation Form[h]								X		

*TQD = Target Quit Day

*W= Week

*Note: Target Quit Day visit may occur +3 days from target date; Week 3, 5, 7, 9, 12, 18, and 24 visits may occur +/- 1 week from target date.

[a] Will only be completed on initially eligible participants who have not had this test within last 6 months.

[b] Will only be completed on participants who self-report abstinence for ≥ 7 days prior to the assessment.

[c] Participant's pharmacy will be contacted to collect pharmacy refill data.
[d] Collection of pharmacy contact information only.
[e] A viral load assessment, conducted as part of routine clinical care any time between Week 6 and Week 18, will be ascertained through medical record review or contact with health clinic and recorded.
[f] MADRS administered at Intake only.
[g] Abbreviated MINI (Major Depressive Episode-Current & Psychotic Disorder modules) only administered if a diagnosis of bipolar disorder is self-reported at Initial Eligibility Screen or Intake, or revealed via the MINI at Intake.
[h] Participants whose Week 3 sessions fall after the approval date for these measures will not complete them. After 50 participants have completed the questionnaire sequence, the measures will no longer be administered. If a participant misses a session, he/she will be eligible to complete the questionnaires and receive compensation at the subsequent session. All participants who complete the assessments will receive compensation.
[l] Blood draw will not be completed if participant has not taken study medication for 14+ days

Screening/Covariate Measures.

Urine Pregnancy Screen
The urine pregnancy screen will assess for current pregnancy in all women and will be administered at the Intake Session.

Breath Alcohol Concentration/ETOH History
The breath alcohol concentration (BrAC) assessment will be administered at the Intake Session. The breath alcohol monitor assesses expired breath for alcohol content. Any reading >0.000 indicates alcohol consumption within the last 14 hours. The ETOH history form will be administered at the Intake Session visit and will ask subjects about their alcohol consumption over the past seven days.

Blood Pressure
Participants presenting at intake with a blood pressure reading above 160 mmHg systolic and/or 100 mmHg diastolic will be ineligible for the study. Participants presenting with an elevated blood pressure reading between 150-160 mmHg systolic and/or 90-100 mmHg diastolic at intake will have a second blood pressure reading taken after a ten minute period in which the participants will be instructed to sit comfortably. If, after the second reading:

- A participant has a blood pressure between 150-160 mmHg systolic and/or between 90-100 mmHg diastolic, the medical staff will evaluate the situation and the participant may be deemed ineligible for the study.
- A participant has a blood pressure reading above 160 mmHg systolic and/or 100 mmHg diastolic, s/he will be ineligible for the study.

Blood pressure will be measured at each study visit. If participants present with elevated blood pressure (above 160 mmHg systolic and/or 100 mmHg diastolic) at any visit following the Intake Session, the study physician will be notified to determine how to proceed. If the elevated blood pressure reading occurs during a medication distribution visit (Pre-Quit, Week 3 or Week 7), no medication may be distributed until the study physician is contacted to evaluate the situation. A record of this evaluation will be recorded and sent to the study physician by email and will be stored in the participant's chart.

Demographic and Smoking History
We will collect demographic (e.g., age, gender, race) and smoking history (e.g., age at initiation, past use of nicotine treatments, current rate, menthol vs. regular tobacco) data. The Fagerstrom Test for Nicotine Dependence, a validated 6-item measure of nicotine dependence, will be administered (Heatherton et al., 1991).

Medical History
A medical history will be conducted at the Intake Session to review for any contraindications listed previously. The medical history will be completed by a research staff member. Duration since HIV/AIDS diagnosis, mode

of transmission, and viral load and CD4+ counts will be assessed. Current medication usage will be tracked at each time-point.

Psychiatric History
Current and lifetime prevalence of major depression, suicidality, bipolar disorder, substance abuse or dependence, psychosis, and generalized anxiety disorder will be determined using the Mini International Neuropsychiatric Interview (MINI). The MINI (Sheehan, Lecrubier et al. 1998) is a 10-15 minute structured interview developed by the World Health Organization to assess major DSM-IV Axis 1 psychiatric diagnoses. This instrument, completed by a research staff member at the Intake Session, permits both current (past 30 days) and lifetime assessments of psychiatric illness and data support its reliability and validity (Sheehan, Lecrubier et al. 1998). Suicidality will be further assessed at each visit through the Columbia Suicide Severity Rating Scale (**www.cssrs.columbia.edu**).

Creatinine Clearance and Liver Function
Initially eligible participants who have not had tests of creatinine clearance within the past 6 months (as determined by medical record review or provision of lab results to study staff) will have this test completed during the Intake Visit.

Estimated Creatinine Clearance (or eCrCL) will be calculated through the Cockcroft-Gault formula, a commonly used surrogate marker for estimate of creatinine clearance (Cockcroft & Gault, 1976).

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$

Viral Load Assessment
A viral load assessment, conducted as part of routine clinical care any time between Week 6 and Week 18, will be ascertained through medical record review and recorded.

Depression and Anxiety
The Hospital Anxiety and Depression Scale (Zigmond & Snaith, 1983), a 14-item self-report measure, will assess depression and anxiety symptoms at each visit. This scale correlates with clinical ratings of depression and anxiety (Zigmond & Snaith, 1983) and is used with individuals with HIV/AIDS (Savard et al., 1998). This measure may be used as a mediator and a covariate.

HAART Adherence
HAART adherence will be assessed with a self-report measure, the Adult AIDS Clinical Trials Group Adherence to Antiretrovirals Instrument (Chesney et al., 2000) (Pre-Quit, Weeks 5, 9, 12, 18, 24) and pharmacy refill data (Weeks 12 & 24), as we have done successfully with CFAR patients (Grossberg, Zhang, & Gross, 2004). In order to collect pharmacy refill data, the research staff will call the participant's pharmacy to obtain prescription refill dates for a specified antiretroviral medication (see Index Drug determination procedures). The refill date, number dispensed, dosage, and frequency will be collected. We will compute an adherence variable that consists of the percentage of doses taken over doses prescribed according to medical refill records (Gross et al., 2006).These data will consider all information on HAART use (e.g., type, dose).

> *Index Drug*: The protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) will be the index drug of interest. For participants taking both a PI and NNRTI, the PI will be the index drug because studies to date that have assessed viral load change in relation to adherence have focused primarily on PIs. For participants taking two PIs including ritonavir, ritonavir will be the index drug. Ritonavir is rarely used as a single PI and is therefore indicative of dual PI therapy. Dual PI regimens are used primarily in patients who have experienced treatment failures with other PIs. Therefore, participants on ritonavir plus a second PI (e.g., saquinavir or indinavir) are more alike than individuals on the second PI (e.g., saquinavir or indinavir) alone. Thus, assessing the ritonavir will be more relevant in this subgroup. If the participant is not on NNRTI or PI, the integrase strand transfer inhibitor (ISTI) will be the index drug. If the participant is not on NNRTI, PI or ISTI, the CCR5 antagonist (maraviroc) will be the index drug. In participants taking an abacavir-containing triple nucleoside

regimen, abacavir will be the index drug because it has the most antiviral activity of the nucleoside analogue reverse transcriptase inhibitors and is used in the place of a PI or NNRTI in this setting.

Nicotine Metabolic Rate (3-HC/cotinine ratio) and Genes related to Nicotine Dependence
Two baseline blood samples will be collected at Intake and analyzed for nicotine metabolites to determine rate of nicotine metabolism. Nicotine is metabolized to cotinine and then to 3-HC by the P450 (CYP) 2A6 enzyme (Nakajima et al., 1996). The 3-HC/cotinine ratio is a stable measure of the rate of nicotine metabolism, which influences response to nicotine dependence treatments (Lerman et al., 2006; Patterson, Schnoll et al., 2008). Variation in 3-HC/cotinine and other genetic polymorphisms in nicotine metabolizing enzymes (CYP2A6) and in drug targets (CHRNA4, CHRNB2, etc.) will also be explored for associations with therapeutic response to treatment. The biosamples of individuals who complete the Pre-Quit visit will be sent to the laboratory of Dr. Rachel Tyndale at the University of Toronto for analysis. These analyses will be exploratory.

Bipolar Disorder Symptoms
If a diagnosis of bipolar disorder is self-reported at Initial Eligibility Screen or Intake, or revealed via the MINI at Intake, the Montgomery-Asberg Depression Rating Scale (MADRS), Young Mania Rating Scale (YMRS), and a Bipolar Disorder Additional Screener will be completed to evaluate and monitor the presence and severity of bipolar disorder symptoms.

Mediating Variables.

Mood: Positive and Negative Affect
The Positive and Negative Affect Schedule (PANAS; Watson et al., 1988), a 20-item self-report measure, assesses positive (PA; 10 items, e.g., enthusiastic) and negative (NA; 10 items, e.g., distressed) affect. The inclusion of PA is a strength since it is less frequently examined as a mediator of smoking cessation. The PANAS subscales are internally consistent (α = .84-.91) and exhibit good validity (Watson et al., 1988). The depression and anxiety scales described above will be mediators as well. The PANAS will be administered at Pre-Quit, Target Quit Day, and Weeks 3, 7, and 12.

Cognitive Function
Neuropsychological tests will be administered in a quiet laboratory testing room on a Dell® desktop computer running on Windows XP® at the CIRNA. Unless otherwise noted, all tasks will be administered via E-Prime 2.0 (Psychology Software Tools, Inc.). The computerized battery is administered in a random order using clickable icons. Total administration time is ~ 30 minutes. The tasks are:

- Visual/Spatial-N-Back: 3-back version (VSNB3). The n-back is one of the most commonly used paradigms in neuroimaging studies investigating the neurological underpinnings associated with maintenance and retrieval of information in working memory (Owen, McMillan, Laird, & Bullmore, 2005). The current study employs a visuo-spatial working memory task that is based on the visuo-spatial n-back paradigms used in prior research (Ehlis, Bahne, Jacob, Herrmann, & Fallgatter, 2008; Green et al., 2005; Owen, et al., 2005). During the n-back, participants are instructed to remember the location of a stimulus, a grey circle that is approximately 5 cm in diameter, as it appears randomly in 8 possible locations around the perimeter of a computer screen. The stimulus will appear for 200 ms, followed by an interstimulus interval (ISI) of 2800 ms. A cross hair will remain visible during the stimulus presentation to cue participants to look at the center of the screen so that all stimuli appearing around the perimeter of the screen can be seen clearly. The n-back task includes 4 conditions of varying difficulty levels: the 0-back, 1-back, 2-back, and 3-back. Participants respond only to targets (30% of stimuli) by pressing the SPACEBAR. They are instructed to do nothing on other trials.

  Each of the task conditions (0-, 1-, 2- & 3-back) will be administered in a pseudorandomized counterbalanced order. Each difficulty level will consist of 1 block of 50 trials, preceded by a practice block

of 20 trials. During the 0-back, participants are instructed to press the SPACEBAR if the stimulus appears in a predetermined location (designated as the upper left corner of the computer screen. The 0-back serves as a baseline condition of the n-back, during which participants are engaged in a task that does not require storage or manipulation of information in working memory, but is otherwise analogous to the other n-back conditions. During the 1-back, participants are instructed to press the SPACEBAR whenever the stimulus appears in the same location as the stimulus that immediately preceded it and to do nothing if it the stimulus appears in any other location. During the 2- and 3-back conditions, participants are instructed to press the SPACEBAR whenever the stimulus appears in the same location as the stimulus that preceded it by 2 or 3 trials, respectively. The primary dependent variables for this task are total number of correct responses and reaction time. Time: approximately 16 min.

- Penn Continuous Performance Test - Number/Letter Version (PCPT-nl). The PCPT-nl is a measure of visual attention and vigilance based on the Penn CPT (Kurtz et al., 2001). In this task, a series of red vertical and horizontal lines (7-segment displays) flash in a digital numeric frame (resembling a digital clock). The participant must press the spacebar whenever these lines form complete numbers or complete letters. The task is divided in two parts, each lasting three minutes: in the first part the participant is requested to respond to numbers and in the second part the response is to letters. The participant practices both sets of trials before the task begins. Time: approximately 10 min with practice.

For both measures, median reaction time for correct responses measures cognitive performance. These tasks will be administered at Pre-Quit, Target Quit Day, and Weeks 3 and 12.

Withdrawal Symptoms and Cravings
Minnesota Nicotine Withdrawal Scale (MNWS-W) (with a one-week frame of reference) will measure withdrawal symptoms associated with quitting smoking. The Likert-style scale assesses 7 DSM-IV items of nicotine withdrawal (e.g., restlessness, irritability).

Craving will be assessed by the well-validated Questionnaire of Smoking Urges (QSU-B). The QSU contains 10 items forming 2 subscales (anticipation of reward, relief from negative affect) with established reliability. Cravings to smoke following a quit attempt have been related to cessation.

These measures will be administered at Pre-Quit, Target Quit Day, and Weeks 3, 7, and 12.

Treatment Measures.

Varenicline Adherence
Varenicline adherence will be assessed by self-report using a time-line follow-back procedure and by pill count and the collection of used blister packs at each visit during the treatment period as done in past varenicline trials (e.g., Gonzales et al., 2006; Jorenby et al., 2006; Ebbert et al., 2009). We will also collect blood samples (10 mL) at Weeks 3 and 12 to assess varenicline levels as an additional measure of adherence and to examine the validity of self-report and pill count data. An adherence covariate will represent the proportion of total dose taken. These biosamples will be shipped to the laboratory of Dr. Neal Benowitz at the University of California San Francisco for analysis. These blood samples will not be collected if the participant has not taken the study medication for 14+ days.

Side Effects
As in our past varenicline trials (Patterson et al., 2009; Schnoll et al., 2011), a checklist and open-ended questions will assess the frequency and severity of varenicline-related side effects at all time-points after the Intake Session over the course of the 24-week study, before and after medication initiation. These assessments monitor participant safety and dose reductions or suspension can occur. Side effects will be a study outcome and can be a covariate in the analysis as the overall frequency and/or as the presence (ever) of specific side effects. This measure includes psychiatric events (e.g., depressed mood, suicidal ideation; Kuehn, 2008) and cardiovascular side effects.

Outcomes Variables.

Abstinence (primary)
Smoking status will be assessed using the timeline follow-back method (Brown et al., 1998) as done previously (Lerman et al., 2004; Schnoll et al., 2010b) and by using urinary cotinine to biochemically verify the self-report. Participants will be considered to be abstinent if they self-report abstinence (not even a puff of a cigarette) for ≥7 days prior to the assessment at Weeks 12 and 24 and have a urine cotinine <100ng/ml at the time-point (SRNT, 2002; Hughes et al., 2003). As per convention, participants are assumed to be smoking if they self-report to be smoking at the time-point, cannot be reached to provide data at the time-point, fail to provide a urine sample at the time-point, or provide a urine sample at the time-point that is >100ng/ml (SRNT, 2002).

Other Smoking Measures (secondary)
As per recommendations (Hughes et al., 2003), secondary smoking outcomes include: prolonged abstinence to Weeks 12 and 24 (relapse is 7 consecutive days of self-reported smoking, after a 2-week grace period), continuous abstinence at Weeks 12 and 24 (no smoking between the quit day and the follow-up; no smoking during weeks 9-12 as measured in previous varenicline trials with the general population of smokers; Gonzales et al., 2006), time to 7-day relapse (no grace period), smoking rate, and lapse (smoking episodes not lasting 7 days) and recovery (return to 24-hour abstinence) events (see Schnoll et al., 2010b). Abstinence and smoking rate outcome will also be available for Week 18.

Cessation/Smoking Rate: Daily smoking (presence and rate) will be assessed at each visit after Intake Session with the well validated timeline followback method (TLFB). These data can be used to assess the timing and rates of lapses (smoking episodes not lasting 7 days), recovery events (return to abstinence), and relapse events, as well as to monitor changes in smoking rates (i.e., # cigarettes/day). These data will also be used to compute and assess secondary measures of smoking cessation (e.g., continuous and prolonged abstinence).

Carbon Monoxide (CO) Test: Carbon monoxide will be measured at Intake and all subsequent visits to confirm smoking status.

NicAlert™ Urine Dipstick (cotinine assessment): Smoking status will be assessed with NicAlert™ urine dipsticks from Nymox Pharmaceutical Corporation (http://www.nymox.com/products/nicalert/product_insert_for_urine.html). A midstream urine sample of approximately 25mL will be used to test for the presence of cotinine. Results will appear in one of seven category levels of usage. Level 0 indicates no detectable tobacco use; levels 1-2 indicate presence of cotinine, but as a non-user, and levels 3-6 indicate cotinine consistent with tobacco use. Participants with results in levels 3-6 will be considered smokers. The NicAlert™ urine cotinine assessment will be used to verify smoking status at Weeks 12, 18, and 24.

Quality of Life (QOL)
The HIV/AIDS-Targeted Quality of Life scale (HAT-QoL; Holmes & Shea, 1998; 1999) measures overall functioning, which will be the primary measure of QOL for this study, but several subscales of QOL are also included such as life satisfaction, health worries, HIV mastery, financial worries, and disclosure worries which will be explored in Aim 2 analyses. This measure will be administered at each visit after the Intake Session.

Social Impact Assessments
Several National Institute of Allergy and Infectious Diseases (NIAID)-sponsored groups have incorporated general assessments to measure the social impact of research participation in HIV vaccine trials (e.g. Social Impact Assessment used by the HIV Vaccine Trial Network HVTN; Allen, 2008). The Client Evaluation Form is a modified version of the well-validated Client Satisfaction Questionnaire (CSQ; Larsen et al., 1979; Sabourin et al., 1988) that contains 12 likert-scale type items assessing overall acceptability and satisfaction with the content and format of the ACASI-SHQ. The audio computer assisted self-administered interview social harm questionnaire (ACASI-SHQ) was designed to allow researchers to more easily identify and monitor social

harms experienced by substance abusers participating in HIV trials. It is hypothesized that the ACASI-SHQ will (1) reduce the likelihood of socially desirable responding by using the ACASI medium, (2) increase the likelihood of identifying social harms (construct validity) by including items with greater levels of specificity, and (3) increase the likelihood of its adoption by HIV researchers by utilizing a self-interview format. These assessments constitute a sub-study by co-collaborators Dr. David Festinger and Dr. Karen Dugosh of the Treatment Research Institute.

2. Statistical Analysis

Power

Power is provided for the primary aims since the exploratory aim is hypothesis generating. Power calculations were all approximated as t- or z-tests (2-sided, α = .05), and conducted using PASS Software (Power and Sample Size, NCSS Software, Kaysville, UT).

Aim 1: The primary analysis is a comparison in week 12 and 24 cotinine-confirmed 7-day point prevalence quit rates between placebo and varenicline. For the week 12 comparison, we based our sample size selection on the expectation that quit rates in the placebo and varenicline arms would approximate those reported in past varenicline trials with the general population of smokers (i.e., placebo = 21.2%; varenicline = 50.3%; Gonzales et al., 2006). With a sample of 310, we have >90% power to detect a significant effect between our treatment arm. Notably, we have 80% to detect a difference in week 12 quit rates if the difference between treatment arms is as small as 15%, not 29% as found in Gonzales et al. (2006), since the effect for varenicline may be smaller in this sub-group of smokers. For the week 24 comparison, we based our sample size on the expectation that the quit rate in the placebo arm would be 14.5%, vs. 33.5% for varenicline (Gonzales et al., 2006). In this case, we have 85% power to detect a significant difference between treatment arms. However, we have 80% power to detect a difference between treatment arms if the treatment arm difference is only 15%, not the 19% reported in Gonzales et al. (2006), since the effect for varenicline may be smaller in this sub-group of smokers. Even though it may appear that we are over-powered for Aim 1, we require the proposed sample to conduct the non-inferiority analyses for Aim 2.

Aim 2**:** The analyses are a comparison in week 12 and 24 differences in QOL and severe side effects. For QOL, the overall scale mean among HIV/AIDS patients is 58.3 (SD = 24.5, Range 14-100; Holmes & Shea, 1998). We have 80% power to detect a mean difference of 7.8 at any time-point between the treatment arms with the proposed sample of 310. For side effects, the analyses will involve a test of non-inferiority since we cannot use standard statistical tests and conclude that a non-significant comparison shows that the drug is safe (i.e., "the absence of evidence is not evidence of absence"). In our past study with varenicline, 61% of participants on varenicline reported no severe side effects, vs. 76% of participants on placebo, a 15% difference (Patterson et al., 2009). With the present sample size, we will have 80% power to detect similar equivalence between treatment arms in terms of the frequency of severe side effects over the course of the 12-week treatment, given that side effects are actually non-significantly different across the treatment arms.

Aim 3: The analyses will assess changes in affect and cognitive function as mediators of treatment arm effects at week 12 and 24. These measures are continuous difference scores. Our sample of 310 is well above the minimum sample of 200 recommended for models of this size (Haduk, 1987; Boosma & Gabrielli, 1985). The mediation hypothesis will examine the proportion of treatment effect explained (Lin et al., 1997; Vittinghoff et al., 2009), and will test each mediation hypothesis with a z-score generated using the delta method. Our sample of 310 gives us 80% power to observe small effects in a 1-sample test (δ=0.20) when testing at α=0.05. There are four proposed mediating pathways (2 measures of affect and cognition, respectively) between treatment and outcome, so our type-1 error will be corrected to 0.0125. Our sample of 310 gives us 80% power to detect small to medium effects (δ=0.19) for changes in the proposed mediators, which we have seen in previous trials (Patterson et al., 2009; Schnoll et al., 2010a).

Data Analysis

Dr. Wileyto will oversee analyses which will be conducted using Stata, SAS, or R-Language software. Preliminary analyses will assess sample characteristics by treatment with chi-square or logistic regression (e.g., gender, dependence, depression). These variables will also be examined for their relationship to completion of outcome assessments. Variables related to treatment arm or completion of follow-ups will be included as covariates in analyses of study aims. Compliance measures will be evaluated across treatment arms, and controlled for in primary analyses. We will examine the correlation between self-report and pill count data and week 3 and 12 varenicline levels. Although we will use intent-to-treat as the primary method for

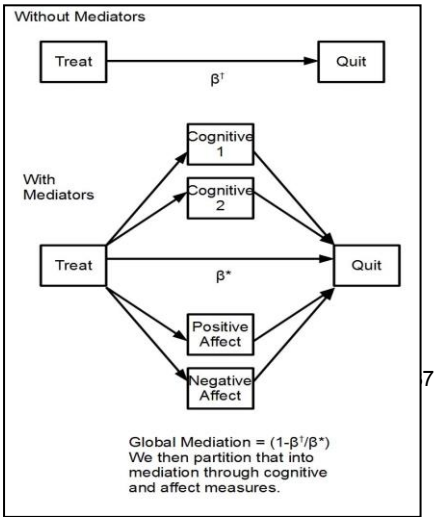
evaluating study aims, we will conduct a completers only analysis of study aims and examine study aims with participants lost to follow-up due to death excluded as done previously (Schnoll et al., 2003).

Missing Data: We will examine if the rate of missing data, primarily our smoking cessation outcome data, is related to a range of potential variables, including treatment arm allocation and HIV/AIDS-related, demographic, and smoking-related variables. Standard statistical methods will be used to identify possible correlates of missing data such as chi-square and regression. Variables found to be associated with the rate of missing data ($p < .05$) will be included as covariates in the analyses of aims. In the event of items missing at random on measures, items will be imputed prior to calculating final scores using conditional means, estimated with an iterated version of Buck's method (Gleason & Staelin, 1975). Dropout and missed sessions present a more serious issue. The best way to deal with this is to avoid the problem in the first place by keeping subjects connected to the trial and motivated to complete measures. In our clinical trials, compliance and retention rates were >80% thanks to our close monitoring of participants and use of incentives to offset travel costs (Schnoll et al., 2008). Primary analyses will assume that all subjects for whom smoking outcome data are unavailable are smokers (intent-to-treat). This assumption, which is conventional in smoking cessation research, can attenuate the differences between study groups in quit rates. Thus, we will also conduct a "completers-only" analysis.

Aim 1: Compare 12-weeks of varenicline treatment and behavioral counseling to 12-weeks of placebo treatment and behavioral counseling for treating nicotine dependence among individuals with HIV/AIDS. We will analyze quit rates using mixed effects logistic regression. The model will include a term for time-point and, possibly, *a small number of covariates as needed*. The hypothesized effect of treatment arm (placebo vs. varenicline) will be tested by including a dichotomous term for treatment arm; we will also test for an interaction between time-point and treatment. Outcomes of the logistic regression analyses will be characterized by odds ratios (e.g., odds of quitting smoking) and 95% confidence intervals. Although quit-rates at the end of 12 and 24 weeks will represent our primary outcome variables, similar logistic regression analyses will be performed for other measures of quit rates, including prolonged and continuous abstinence. In addition, many participants will fail to become completely abstinent, but may show a reduction in smoking. A secondary analysis will examine the effect of treatment arm on daily cigarette counts using mixed effects negative-binomial regression. Likewise, time to (recurrent) event models will be fitted using Cox regression, stratified by event sequence, as in Schnoll et al. (2010b), to assess lapse and recovery events over 24 weeks.

Aim 2: Assess effects of varenicline therapy on QOL and side effects. Repeated-measures MANOVA will examine differences across treatment arms in QOL (total scale score and subscale scores) over the trial. Participant covariates will be included, such as medical treatment history. In addition, we will compare treatment arms in terms of the frequency of severe side effects (*individual, including cardiovascular side effects*, and total). Using logistic regression, we will test against the lower boundary on percent reporting only mild-moderate (i.e., < severe) side effects. The hypothesis test for equivalence is a test of whether the OR is out of the prescribed range for the difference between the treatment arms. This approach provides a more valid test of the potential safety of varenicline for individuals with HIV/AIDS vs. a simple comparison of mean responses on a side effects measure. *We will also examine if participants on tenofovir (vs. other HAART) experience a greater frequency or more severe varenicline side effects by including type of HAART as a covariate in these analyses and, if so, we can explore if this relationship is mediated by varenicline plasma levels using a regression-based path model. Lastly, we will also examine if the frequency of cardiovascular side effects is different between treatment arms while considering if participants are currently taking HAART or not by including a covariate for current HAART use in the logistic regression models of side effects.*

Aim 3: Assess changes in affect and cognitive impairment as mediators of varenicline therapy's effect on quit rates. We will use a regression-based path model approach to examine mediation of treatment effects based on MacKinnon et al. (2007). All variables will be standardized for the analyses. Candidate mediators include positive and negative affect and two cognitive performance task measures. Suspected mediators will be entered as standardized pre-post differences, continuously distributed and treated as normal in linear regression. The effects of treatment arm on mediators, and of mediators on outcome, will be assessed using linear regression and standardized variables. We will focus on changes in



mediators from baseline to week 3, since abstinence-induced withdrawal effects typically peak within the first 3 weeks of cessation (Hughes, 2007) but we can examine delayed changes to weeks 5, 7, and 9 as well. We will then assemble the path model using "seemingly unrelated estimation" methods (Beasley, 2008; Zellner, 1962). The path model partitions the effect of treatment on outcome into direct (and unexplained) effects vs. mediated effects. We will then test the overall mediation hypothesis using the proportion of treatment effect explained (Lin et al., 1997; Vittinghoff & McCulloch, 2009), and the strength of each mediating pathway as follows. We will estimate the model for standardized treatment predicting abstinence without mediators to estimate the direct effect of treatment in the unadjusted model ($\hat{\beta}^{\dagger}$). We will then test whether treatment predicts each of the suspected mediators and, in turn, test whether mediators predict abstinence in an adjusted treatment model and estimate the effect of treatment in the mediator adjusted model $\hat{\beta}^{*}$. Finally, we will calculate the proportion of treatment effect explained, which is calculated as $\left(\hat{\beta}^{\dagger}/\hat{\beta}^{*}\right)$; the standard error for this quantity is calculated using the delta method, and the mediation hypothesis will be tested using a z-test. Individual pathways will be tested using products of the coefficients along each path using a delta-method based z-test.

Exploratory Aim: Explore participant-related variables as moderators of varenicline therapy's effect on quit rates. These analyses will be hypothesis-generating. Variables will be chosen for this analysis based on their association with smoking behavior among those with HIV/AIDS (e.g., Webb et al., 2007). The significance of participant-related variables (e.g., mode of transmission, level of nicotine dependence, use of menthol tobacco) as moderators of varenicline's effect on quit rates can be evaluated by fitting logistic regression models relating quit rates to treatment arm and covariates. The likelihood ratio test can determine whether including such variables in the model contributes significantly to model fit. Evaluating the effect of treatment arm on quit rates by history of IV drug use, for example, is essentially doing a subgroup analysis of the interaction effect separately by such variables. To test the significance of a moderating influence of these variables, 2-way interaction terms can be added sequentially in steps of a hierarchical logistic regression model. A range of participant-related characteristics, such as socio-demographic (e.g., gender, race), psychiatric (e.g., depression), and medical (e.g., HIV/AIDS symptoms, method of HIV transmission) variables can be explored for potential interactions with treatment arm to influence quit rates at weeks 12 and 24.

Additional Exploratory Analyses: This trial will allow us to explore additional secondary hypotheses. One such analysis will focus on the assessment of whether HAART adherence is related to smoking cessation outcomes. Dr. Gross, an expert in the assessment and evaluation of HAART adherence, will work with Dr. Wileyto to explore if response to varenicline, for example, affects HAART adherence or if HAART adherence is related to varenicline adherence. Prediction models of cessation outcomes (or varenicline adherence) using treatment arm and HAART adherence can be examined with logistic regression. We will also examine the relationship between 3-HC/cotinine and other variants in genes responsible for nicotine metabolism and drug target and response to varenicline for exploratory purposes.

3. Confidentiality

All subject information will be kept in a secure filing cabinet that is accessible only to authorized study personnel. All databases containing subject information will be password protected, and again, accessible only to authorized study personnel. Each subject will have a unique study ID number for all data collected. In all data sets we will use ID numbers, only. A separate data set linking names with ID numbers will be accessible only by the senior project staff. All communications about subjects will use the ID number only and never include names or other personal information. All data will be stored until all analyses are completed. No data will be shared with any unauthorized party (i.e., aside from study personnel and regulatory officials). Any publication of data will not identify subjects by name or with an identifier that could be used to reveal identity.

Data will be accessible the study Principal Investigator, Co-Investigators, the Study Physician, other study staff and the UPenn IRB and Office of Human Research.

How will confidentiality of data be maintained? Check all that apply.

☒ Paper-based records will be kept in a secure location and only be accessible to personnel involved in the study.

☒ Computer-based files will only be made available to personnel involved in the study through the use of access privileges and passwords.

☒ Prior to access to any study-related information, personnel will be required to sign statements agreeing to protect the security and confidentiality of identifiable information.
☒ Whenever feasible, identifiers will be removed from study-related information.
☐ A Certificate of Confidentiality will be obtained, because the research could place the subject at risk of criminal or civil liability or cause damage to the subject's financial standing, employability, or liability.
☐ A waiver of documentation of consent is being requested, because the only link between the subject and the study would be the consent document and the primary risk is a breach of confidentiality. (This is not an option for FDA-regulated research.)
☐ Precautions are in place to ensure the data is secure by using passwords and encryption, because the research involves web-based surveys.
☒ Audio and/or video recordings will be transcribed and then destroyed to eliminate audible identification of subjects.
☐ Other (specify):

4. Subject Privacy/Protected Health Information

The following personal health information will be collected as part of this study:

- Name, address, telephone number
- Date of birth
- Social security number (W-9 form)
- Some personal information that may be considered sensitive, such as medical history, psychological history, alcohol use history, etc.
- Results from physical examinations, tests or procedures
- Genetic information from the blood samples provided at the Intake Session
- Information on tobacco related biomarkers from the blood samples provided at the Intake Session and the follow-up the urine samples
- Information on medication adherence from the blood samples at Week 3 and Week 12 visits
- Medical Record Number
- Prescription Refill Information

Every possible precaution, as described above, will be taken to ensure that the privacy of subjects' personal health information will be maintained.

5. Tissue Specimens

Blood.

Because, on average, the quality of DNA that is extracted from blood is superior to the quality of DNA that is extracted from saliva, we are asking participants to provide 2 tubes of blood (up to 20mL or 1.5 tablespoons) at the Intake Session for genetic analysis (NMR & other genetic polymorphisms). Given that the complete predictive validity of the genotypes under study are not fully known at this time, participants will not be informed of the test results. All specimens are to be collected solely for research purposes.

One 10mL sample of blood will be drawn at two sessions (Weeks 3 and 12) to evaluate varenicline adherence, unless the participant has not taken the study medication for 14+ days.

An 8.5mL blood sample may also be collected following Intake to assess creatinine clearance in participants who have not had these assessments within the past 6 months.

Urine. A urine sample will be required from females at the Intake Session for pregnancy screening. Subjects who have a positive pregnancy test will be deemed ineligible. Urine samples will also be collected at Weeks 12, 18, and 24 to assess urine cotinine levels.

6. Genetic Testing

As described throughout the protocol, this study involves testing blood samples to identify NMR for participants and examination of DNA from blood samples to evaluate additional genetic variation related to smoking behavior and treatment outcomes. All biospecimens will be numerically coded and any information linking this

numeric code to the participant's protected health information will be kept separate and secure as described above. No information concerning the results of this testing will be shared with the study participants.

RISK/BENEFIT ASSESSMENT

1. Potential Study Risks

A detailed description of the study will be given to all subjects, which will include the risks of participation, assurance of full confidentiality, and the knowledge that their freedom to refuse participation or withdraw from the project will not affect the availability of treatment at the University of Pennsylvania. Informed consent procedures will comply with current standards of the IRB at the University of Pennsylvania. Subjects can choose, as an alternative, to not enroll in this study. Adverse reactions will be assessed and reported as required by Federal law and the regulations of PENN.

Blood Draw. Blood draws may result in bruising and/or slight bleeding at the needle site. This is rare and happens infrequently. Occasionally, blood drawing results in a feeling of faintness. This too is rare. A trained professional will draw blood, so the chances of these discomforts are minimal. Procedures are in place to ensure that PHI is not linked with the results of this research.

Assessments. Subjects may experience emotional distress during assessments from discussing feelings and attitudes about smoking or from learning about the risks from smoking. These events happen very rarely and in almost all cases are short-lived and of low intensity, lasting for 1-2 weeks. Study personnel will be alerted to expect this from a small number of subjects and will be trained to make referrals for mental health services as needed. Personnel will be trained to query for adverse emotional reactions during assessments and will be trained to deal with such reactions and to provide additional referrals if needed. In addition, if assessments indicate psychiatric concerns, referrals to appropriate psychological services will be provided.

Study Medication: Members of the study team have completed numerous clinical trials which tested medications for nicotine dependence (including varenicline). In order to ensure safety for all participants, the Principal Investigator will work closely with the study physician to determine participant eligibility and to continue to assess safety once a participant is enrolled. They will determine if any serious adverse event requires additional care. Such events may be referred to the out-patient department or to the emergency department of the clinical site. Information specific to each study medication is included below.

Varenicline. Some people who take varenicline may experience nausea, sleep disturbance, constipation, flatulence, and vomiting; however, these symptoms are usually mild and temporary. There have also been rare reports of erratic behavior, aggressive behavior, depressed mood, and suicidal thoughts/behavior. To minimize the likelihood of participants experiencing these side effects we will:

- Employ a stringent list of exclusionary criteria
- Administer the standard and recommended dose run-up to the 1mg B.I.D. dose
- Monitor self-reported side effects at each assessment time-point.
- Open-ended evaluation of any potential adverse events.

Study Physicians will be alerted to any severe side effects or any reported adverse events. The Study MD will review the information provided by the research staff and if applicable, will contact the study participant to gather more information and determine the appropriate course of action for the subject. Ultimately, the Study Physician will decide if the AE is related to study medication and whether the subject should discontinue taking study medication. Dose reductions, which will be tracked, may also be employed to minimize any side effect.

Varenicline may be associated with an increased risk of certain cardiac and vascular side effects, including chest pain, heart attack, and stroke. These risks are rare and are still being studied to determine how real they are. However, our study staff follows strict procedures to monitor for the presence of these side effects,

including monitoring blood pressure at each in person visit and asking specific side effect questions related to cardiovascular events (e.g. chest pain, weakness on one side, etc) during each session.

Varenicline may also be associated with new or worsening seizures during the first month of treatment. Some patients had no history of seizures, whereas others had a history of seizure disorder that was remote or well-controlled. Participants will be advised not to take Chantix if they have an unstable, untreated history of seizures.

Participants will also be told that varenicline may impair their ability to perform tasks requiring judgment or motor and cognitive skills and that they should proceed with caution in this regard until they are certain that varenicline does not affect their performance. Participants will be told that varenicline may be associated with somnambulism (sleep walking) that may result in harmful behavior to self, others, or property, and if they notice such behaviors that they should discontinue varenicline and notify the study staff after seeing their medical provider. Participants will also be advised that Chantix may affect their response to alcohol including lower alcohol tolerance, aggressive behavior, or impaired memory following consumption of alcohol. Participants will be instructed to minimize alcohol intake (no more than 3 drinks per occasion or within a 24-hour time period) while taking varenicline. Participants will be advised to inform the study staff if they are taking or plan to take any prescription or over-the-counter drugs. Women will be advised to notify the study staff if they become or intend to become pregnant during the study period. The research team has extensive prior experience conducting smoking cessation trials with varenicline.

Reproductive Risks. Because varenicline safety for an unborn baby is unknown, participants will be told that they should not become pregnant while on this study. Women taking study medication should not nurse a baby. If the woman is of childbearing potential, she must use an adequate form of contraception while study medication is being taken and for at least one month after the medication period. If the woman is pregnant or breast feeding, she may not participate in this study, and if she becomes pregnant during the study, study medication will be immediately discontinued and the woman will be permitted to continue with counseling and assessments only. Women will be asked to take a pregnancy test before starting the study.

Withdrawal Syndrome. Many individuals who quit smoking exhibit a pattern of symptoms related to withdrawal from tobacco use. These symptoms include: sadness and anxiety, irritability, anger, difficulty concentrating, appetite change and weight gain, insomnia, and decreased heart rate. Eliminating the risk for these would not be possible, although in most cases these events are short-lived and have low intensity, lasting for 1-2 weeks. The study personnel will be trained to recognize these symptoms and educate the participants about them (e.g., their duration, methods for reducing them).

Potential Loss of Confidentiality: Every attempt will be made by the investigators to maintain all information collected in this study strictly confidential. We will store subject information in a secure room with limited access. Only people working on this research project can work with subject information. We will control access to the computer files that hold this information. This information will not be released to anyone. When the results of the study are published, no names or identifying information will be used.

2. Potential Study Benefits

All participants who enroll in this study will receive behavioral counseling to aid them in their effort to quit smoking. They may also benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve cessation treatment for smokers.

3. Alternatives to Participation

As an alternative to enrolling in this study, participants may choose to continue to smoke or to seek assistance with quitting smoking through other treatment programs located in their area, including contacting the national quit-line. At any point in this trial, subjects may decide not to continue in their participation.

4. Data and Safety Monitoring

Who will monitor this study? Check all that apply.

☒ Principal Investigator
☐ Sponsor or contract research organization
☐ NCI sponsored cooperative group
☐ Cancer Center (if mandated by CTSMRC)
☐ Medical monitor
☒ Data and safety monitoring board

The PI will be responsible for the overall data and safety monitoring of the study. During the course of the study, data and safety monitoring will be performed on an ongoing basis by the DSM Board and by project staff and the site IRB. The Project Staff are responsible for collecting and recording all clinical data. This includes ensuring that all source documents exist for the data on the case report forms, ensuring all fields are completed appropriately, and all corrections are done according to Good Clinical Practice (GCP's). Any inconsistencies/deviations will be documented. The Study Coordinator will perform regular chart review to verify data integrity. The study medical personnel will be available to review assessments for each participant on an ongoing basis. Project Staff will meet on a regular basis to reconcile data queries and safety concerns. The site IRB will review the trial, including AEs and SAEs, on an annual basis. The DSMB will review the trial data as described below.

Frequency of DSM Reviews

Data will be reviewed on a regular basis. Specifically:

a. At data capture, the research staff will review data for completeness and integrity.
b. At data entry, the data management system will include multiple internal validity checks which will prompt the staff if an entry was made that is out of range or in an unacceptable format.
c. Eligibility data will be reviewed in real-time, such that the Site Coordinator will review the data in each participant's chart before eligibility decision is made. This will include verifying that all data has been collected and signed off on by the appropriate medical staff.
d. The study physician or medical personnel will review all data collected during the eligibility intake session to verify participant eligibility.
e. On a bi-weekly basis, the Site Coordinator will review data through a chart review procedure supported by the data management system.
f. The study statistician will review data prior to analysis to ensure integrity and validity.

Content of DSM Report

The following information will be included in the DSM report:

- brief description of the trial
- baseline socio-demographic characteristics
- retention and disposition of study participants
- quality control issues
- regulatory issues
- side effect data
- adverse events
- serious adverse events
- efficacy (when sample has been collected)
- recruitment, randomization, retention, compliance, form completion, gender and minority inclusion, intervention effects, and safety.

This report will be compiled following DSM Board meetings and then updated at the trial's conclusion. In addition, adverse events experienced by participants will be reported together with participants' antiretoviral regimen to the DSMB in order for the DSMB to adjudicate safety concerns with respect to overlapping toxicities with antiretrovirals and interactions between varenicline and HAART regimen.

DSM Board Plan

A protocol-specific Data Safety Monitoring Board will be used for this trial since this is considered a Phase III trial. The operation of this board will adhere to the guidelines for DSMBs outlined by the NIH. The specific aspects of the DSMB for this study are as follows:

a. The DSMB will consist of 3 members: 1) Vincent Lo Re, M.D., an Assistant Professor in the Division of Infectious Diseases and Department of Biostatistics and Epidemiology, a Senior Scholar in the Center for Clinical Epidemiology and Biostatistics, and an attending physician in the Viral Hepatitis Clinic and Infectious Diseases Consultation Service at the Penn Presbyterian Medical Center, an affiliate hospital in the University of Pennsylvania Health System; 2) Frank Leone, M.D., a pulmonologist at PENN and an expert in tobacco-related illness, and 3) Janet Audrain-McGovern, Ph.D., an Associate Professor in the Department of Psychiatry at PENN and an expert in nicotine dependence treatment.
b. The DSMB will meet twice per year in Year 1 and annually in Years 2-5 to review study data concerning recruitment, randomization, retention, compliance, form completion, gender and minority inclusion, intervention effects, and safety. In addition, the DSMB will: 1) identify specific safety concerns for participants and communicate these to the study PI; 2) consider the need for additional data concerning participant safety; 3) consider the rationale for the continuation of the study; and 4) provide a written report concerning the protocol to the IRB and to the study PI.
c. Each meeting will consist of 3 parts. First, an open session will occur in which Dr. Schnoll will review the conduct of the trial (e.g., accrual, protocol compliance, general toxicity). Next, to maintain the blind of the study, a closed session involving only the DSMB and Dr. Paul Wileyto, the study biostatistician, will be held wherein Dr. Wileyto can present outcome and safety results (unblinded) to the DSMB as requested. Lastly, an executive session involving only DSMB members will be held to allow the DSMB the opportunity to discuss the conduct of the trial and outcomes, including toxicities and adverse events, develop recommendations, and take votes as needed.
d. DSMB written recommendations will be provided to Dr. Schnoll and to the IRB. The DSMB may summarize adverse event reports for the study PI and the IRB Chair, and the PI must implement any DSMB recommendations expeditiously. All DSMB recommendations will also be forwarded to the NIDA Program Officer and the FDA (if necessary).

5. Management of Information for Multi-center Research where a Penn Investigator is the Lead Investigator of a multi- center study, or Penn is the lead site in a multi-site study.

This is a single-site study.

6. Risk/Benefit Assessment

There is minimal risk for serious adverse events. The treatments and procedures used in this study have been shown to be relatively safe. Varenicline has also been studied in several clinical trials and shown to be safe and efficacious. Nevertheless, there are risks in participating in this trial, which are described above.

However, the risks of participating in this trial are offset by the potential benefits for participants and society. Participants who enroll in this trial will benefit from the knowledge that they are contributing in an important way to potentially furthering scientific knowledge concerning ways to improve treatment for smokers with HIV/AIDS. All smokers will receive behavioral counseling for smoking cessation. Half of the sample will receive varenicline. The trial results may support the use of varenicline for the treatment of nicotine dependence among those with HIV/AIDS, thereby reducing tobacco-related morbidity and mortality in this population.

SUBJECT COMPENSATION

Subjects will be compensated for their time up to $160 (Table 3). Subjects will also be reimbursed for transportation expenses related to their participation in the study with $20 for each in-person visit. Participants will be asked to complete social impact assessments based on enrollment and approval date. Participants

whose Week 3 sessions fall after the approval date for these measures will not complete them. After 50 participants have completed the questionnaire sequence, the measures will no longer be administered. If a participant misses a session, he/she will be eligible to complete the questionnaires and receive compensation at the subsequent session. All participants who complete the assessments will receive compensation (Table 4).

Table 3. Subject Compensation

Study Session	Session Compensation	Travel Compensation
Intake Session (Week -1)	$15	$20
Pre-Quit (Week 0)	$15	$20
Target Quit Day (Week 1)	$15	$20
Week 3	$20	$20
Week 5	$15	$20
Week 7	$15	$20
Week 9	$15	$20
Week 12	$20	$20
Week 18	$15	$20
Week 24	$15	$20
	Up to $160	$200
	Total: $360	

Table 4. Social Impact Assessment Compensation

Study Session	Session Compensation
Week 3	$10
Week 7	$10
Week 12	$10
Total: $30	

INFORMED CONSENT

1. Consent Process

A fully trained study staff member will obtain informed consent using the combined consent and HIPAA form approved by the PENN IRB. The process will take place before study data are collected and prior to any treatment. The consenting process will occur in person during the Intake Session and will involve a discussion of the study requirements and procedures and an opportunity for subjects to ask questions and express concerns. The subjects will receive a copy of the combined consent and HIPAA form for their records. In addition, the subjects will be given the PI and Study Physician's contact information should they wish to speak to either of them during the course of the study regarding their consent or the study procedures. The consent process will take place in English, there will be no waiting period, no coercion to participate, and all subjects will be considered competent to provide informed consent (i.e., they will be asked if they understand what they are consenting for).

2. Waiver of Authorization

No waiver of informed consent is requested.

RESOURCES NECESSARY FOR HUMAN RESEARCH PROTECTION

Qualifications of Investigators. Brief highlights are presented below for key investigators.

Robert Schnoll, Ph.D. (Principal Investigator): Dr. Schnoll's research focuses on the evaluation of cessation interventions with clinical populations including cancer patients (Schnoll et al., 2005; Martinez et al., 2008), the identification of empirical methods to tailor smoking cessation interventions to improve treatment efficacy (Patterson, Schnoll et al., 2008; Lerman, Schnoll et al., 2007), and the integration of smoking cessation interventions into medical practice (Schnoll et al., 2006a; 2006b; Schnoll & Engstrom, 2004; Schnoll et al., 2003). Dr. Schnoll's smoking cessation clinical trials with cancer patients (Schnoll et al., 2005; 2010) demonstrates the ability to complete smoking cessation clinical trials with smokers with medical and psychiatric comorbidities. Dr. Schnoll has also conducted smoking cessation clinical trials using varenicline (Schnoll et al., 2011) and serves as PI and site-PI, respectively, for two ongoing varenicline clinical trials (R21 DA026404; U01 DA020830). These trials have afforded Dr. Schnoll the opportunity to develop the skills needed to coordinate a varenicline randomized clinical trial for nicotine dependence.

Ian Frank, M.D. (Co-Investigator, Study Physician): Dr. Frank, director of the UPENN CFAR Clinical Core, has close to 2 decades of experience coordinating HIV/AIDS clinical trials (e.g., Bisson et al., 2008; Reynolds et al., 2006).

Robert Gross, M.D. (Co-Investigator): Dr. Robert Gross, co-director of the Clinical Core, has spearheaded the validation of pharmacy refill data as a measure of HAART adherence (e.g., Grossberg et al., 2004; Gross et al., 2006) and he will oversee the assessment and analysis of data regarding HAART adherence in this trial.

David Metzger, Ph.D. (Co-Investigator): Dr. Metzger, director of the Behavioral and Social Sciences Core (BSSC), has more than 10 years of experience coordinating behavioral HIV/AIDS prevention and treatment research. These efforts have yielded publications on interventions for substance abuse to reduce HIV risk (Sullivan, Metzger et al., 2005; Metzger & Navaline, 2003; Metzger et al., 1998), the effects of substance abuse on HIV risk (Zhang et al., 2005), and methods to recruit and retain participants in HIV/AIDS trials (Kegeles et al., 2006; Halpern et al., 2001).

Caryn Lerman, Ph.D. (Co-Investigator): Dr. Lerman led the first study to assess potential mediators of varenicline efficacy, finding that varenicline improves affect, reduces withdrawal, and enhances cognitive performance during abstinence, relative to placebo (Patterson et al., 2009; see also Perkins et al., 2010). She recently published data demonstrating that varenicline increases working memory-related brain activity and cognitive performance (Loughead et al., 2010) and reduces amygdale activity and improves the speed of emotional processing (Loughead et al., in press). Affect and cognitive function will be examined as potential mediators of treatment effects in the proposed study and Dr. Lerman will assist in addressing this study aim.

Research Staff

The following research staff will be directly involved with the implementation and execution of the current study.

Frank Leone, M.D., Study Physician, Oversee staff training for eligibility screening, adverse event assessment and reporting
Anita (Annie) Hole, Ph.D., Oversees MINI and Counseling Training/Implementation
Michael Thase, M.D., Senior Clinical Staff
Susan Ware, B.S. Database Manager
Paul Sanborn, M.S. Samples Manager
Rebecca Ashare, Ph.D., Cognitive Testing Coordinator
David Festinger, Ph.D., Research Collaborator
Karen Leggett Dugosh, Ph.D., Research Collaborator
Dominique Spence (Vaughn), Research Staff

Jessica Weisbrot, M.S.W., Study Coordinator
Alex Flitter, M.A., Research Staff
Su Fen Lubitz, B.A., Research Staff
Joseph Bastian, B.A., Research Staff
Grace Crawford, B.A., Research Staff
Andrew Miele, B.A., Research Staff
Jonnie Handschin, B.A., Research Staff
Katrina Serrano, B.A., Research Staff
Nathaniel Stevens, Research Staff
Morgan Thompson, B.A., Research Staff
Cheyenne Allenby, B.A., Research Staff
Victoria McLaughlin, B.A., Research Staff
Chan To, B.A., Research Staff

Training and Quality Assurance

Given past (Schnoll et al., 2010b) and ongoing smoking cessation trials (DA020830), systems for training and QA are established to ensure accurate eligibility screening and recruitment, accurate data collection, entry, and management, and optimal delivery of the study protocol. A new Manual of Operations (MOP) will be devised for this study, given unique procedures and measures. Dr. Metzger, who coordinates behavioral research within the PENN CFAR, will assist with staff training to ensure that unique issues related to the population are integrated into the MOP. Training sessions will occur over the first 3 months and annually. Monthly team meetings will review progress, assess adherence, and determine the need for protocol changes or additional training/QA. A study-specific Data and Safety Monitoring Board (DSMB) will provide oversight. The MOP will ensure that the trial is conducted in a uniform manner over time and across staff. The MOP will describe roles and responsibilities for personnel and provide a detailed description of procedures for each point of contact with participants. For each visit/week, a checklist of events (e.g., measures, counseling) will be created that will be completed by study personnel. CRFs will be created for each measure at each week, and every participant will have a study binder, with sections for every visit/week. Every visit will be “milestoned” (e.g., attended, missed, scheduled) to ensure proper tracking of participants through the trial. A treatment manual for counseling is developed and will be provided to the counselors. Drs. Schnoll, Hole, and the project manager or coordinator will train the counselors using mock participants and didactic instruction. Lastly, a manual for data collection and entry is developed for the RAs and Dr. Schnoll, Hole and the project manager or coordinator will train the RAs and provide supervision. Ms. Ware, who oversees this DMS, has already developed this DMS for use in other smoking cessation trials. All training will involve didactic instruction in the MOP and mock sessions for all assessments, counseling, and the DMS by Drs. Schnoll, Hole and the project manager or coordinator. QA focuses on protocol adherence and data validity. We conduct 100% QA checks on study data. This involves comparison of all hard copy CRFs to computer data. In addition, we may audio-tape all counseling sessions and assess protocol adherence by selecting a random 15% of sessions for review.

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