Methods (Study Design, Data Sources/Collection, Interventions, Measures, Limitations).

Study Design

The study used a factorial design to randomize participants into 4 conditions: (1) Varenicline (12 weeks) + Positively Smoke Free (8 weeks); (2) Varenicline (12 weeks) + Standard of Care (brief advice to quit); (3) Placebo (12 weeks) + Positively Smoke Free (8 weeks); and (4) Placebo (12 weeks) + Standard of Care. The factorial design is highly efficient method of assessing the efficacy of multiple treatments in a single trial as well as evaluating additive effects. The primary outcome was the 7-day point prevalence abstinence (PPA) (<10mm) at 36 weeks. The trial was IRB approved and registered with ClinicalTrials.gov (NCT02460900). The study was conducted from June 2016 to November 2020.

Participants

The study recruitment occurred at an urban HIV clinic. Eligibility screening occurred in person. Inclusion criteria were: (1) chart diagnosis of HIV; (2) current self-report of smoking ≥10 cigarettes per day or a score of ≥ 5 of expired carbon monoxide (CO) as measured by Covita micro smokrlyzer;(3) motivation to quit smoking within the next 6 months (score 6-8 on the Abrams and Briener Readiness to Quit Ladder), (4) and not meeting criteria for moderate or severe DSM 5 substance use disorder as established by the Mini International Neuropsychiatric Interview (MINI). Exclusion criteria were: (1) recent use of varenicline (past 3 months); (2) previous allergic reaction or hypersensitivity to varenicline; (3) current or planned pregnancy or nursing; (4) moderate to severe renal impairment; (5) unstable cardiovascular disease; (6) meeting criteria for possible dementia by scoring below 10 on the Hopkins HIV Dementia Scale; (7) current use of medication that would interfere with the protocol in the opinion of the Medically Accountable Physician including use of bupropion targeting nicotine dependence or (8) not medically stable enough to participate in the study based on the opinion of the Medically Accountable Physician.

Randomization and Masking

Study participants meeting eligibility criteria were randomized 1:1:1:1 to one of the four study conditions using permuted blocks, randomly varying in size. Each randomization consisted of two components, the drug (placebo vs Varenicline) and the behavioral intervention (PSF vs SOC) allocation. Participants and study personnel were masked to allocation of medication (i.e., varenicline versus placebo); however, because of the nature of psychological interventions, the intervention team and participants were not masked to the treatment condition. Participants randomized to PSF were asked not to reveal their treatment condition to the study staff. Study personnel completing assessments were masked to all study conditions.

Procedures

During the eligibility visit, trained study personnel administered self-report questionnaires and documented laboratory results. The medically accountable study clinician completed a medical history, reviewed eligibility criteria including laboratory results, the results of a physical assessment (i.e., vital signs--blood pressure, heart and respiratory rates, height and weight) and confirmed study eligibility.

Randomization

Eligible participants were randomized (i.e., 1:1:1:1) to four study conditions: (1) Varenicline + PSF; (2) Varenicline + SOC; (3) Placebo + PSF; (4) Placebo + SOC using permuted blocks that randomly varied in size assuring both approximately equal sample sizes in each cell and minimizing the prediction of future allocations. Randomization consisted of two components, the drug (placebo vs Varenicline) allocation which is double blind

and the behavioral intervention (PSF vs SOC) allocation. For drug assignment, all raters, investigators, other staff and participants were blind to drug treatment assignment except for the dispensing pharmacist. Separate emergency unmasking envelopes for each participant were kept in a locked cabinet at the dispensing pharmacy in the case of a medical emergency. No medical emergencies occurred during the trial that required the dispensing pharmacist to be unmasked.

Treatment allocation

For those randomized to Varenicline, participants received 0.5 mg/day (days 1-3), then 0.5 mg twice per day (days 4-7). After the 7th day, participants received 1 mg twice per day for weeks 2-12 of the study. This is in accordance with package labeling. Placebo pills were identical in appearance and dosing regimen. Per recommendations by Varenicline package insert, the quit date was established as day 8. As a part of this investigator-initiated project, Pfizer provided Varenicline and matching placebo directly to the research pharmacy.

For those randomized to Positively Smoke Free (PSF), participants received eight smoking cessation counseling sessions either in-person or by telephone by trained providers who received supervision by a study psychologist. PSF is an intensive, tailored, social cognitive theory-driven intervention that promotes cessation in PLWH smokers. The quit date was established as day 8 to be in accordance with the Varenicline quit date. Twenty-five percent of sessions were recorded and assessed by an independent reviewer completed a standardized checklist of topics covered. For those randomized to receive the standard of care condition, participants were given a quit smoking brochure and brief advice to quit (i.e. < five minutes) administered by a trained study staff.

Outcome Assessment

Trained research personnel assessed smoking behavior at baseline (week 0) and weeks 1, 2, 4, 8, 12, and 36. At baseline, current smoking and quitting history was assessed with questions drawn from the NHANES III. At all other time-points, trained research personnel assessed 7-day point-prevalence abstinence based on no self-reported tobacco use (not even a puff) during the 7 days preceding the assessment and a CO ≤10ppm as measured by Covita micro smokrlyzer.

Trained study personnel also collected participant's response to a variety of questionnaires specifically chosen to evaluate mediators of Varenicline's impact on smoking as well as PSF's impact on smoking. These assessments occurred at baseline, 12 and 36 weeks. Mediators associated with Varenicline impact on smoking included Tobacco Craving, Smoking Temptation Scale Questionnaire (TCQ-SF) and Shiffman/Jarvik Withdrawal Questionnaire (SWQ). Mediators associated with PSF impact on smoking included the UCLA Loneliness Scale, Stages of Change Algorithm, the Abstinence Self-Efficacy Scale, Smoking Decisional Balance Questionnaire , Center for Epidemiologic Studies Depression Scale, and the Addictions Severity Index Lite.

Pill and counseling adherence were assessed at Weeks 0, 1, 2, 4, 8, and 12. Pill adherence was tracked by the following question at each study visit: How many days in the last week did you take at least one of your study pills. Pill adherence was defined by participant self-report of taking 6 or 7 pills at week 8 which coincided with their last receipt of varenicline or placebo. Counseling adherence was tracked by the percent of participant attendance at study completion. The total number of sessions a participant could attend was 8.

Safety Monitoring

Safety assessments occurred at Weeks 0, 1, 2, 4, 8 and 12. Adverse events were monitored at each study contact and classified and graded using the Common Terminology Criteria for Adverse Events and Common Toxicity

Criteria provided by the National Cancer Institute. The study physicians were consulted to determine if an event was an adverse event (AE) and a serious adverse event (SAE) and what, if any, treatment or follow-up was required. Separate emergency unblinding envelopes for each participant were kept in a locked cabinet at the dispensing pharmacy in the case of a medical emergency. A Data Safety Monitoring Board assessed all adverse events and serious adverse events.

Power Calculation

All power analyses were conducted with a two tailed alpha of .05 and power set to .80. With 184 participants, the study's 2 main effects ((1) varenicline vs. placebo; (2) PSF versus Standard of Care were each powered to detect a Cohen's *h* of .41 (medium effect) based on a quit rate of 6% for the control condition.

Analysis

Primary Aims: We used separate logistic regression models (SAS, 9.4: Proc Logistic) at each post baseline time point (12 weeks, 36 weeks) to assess the main effects of varenicline vs. placebo and PSF vs. SOC on smoking cessation. To assess if the combination of varenicline and PSF is significantly more effective than either of the treatments alone, we created an indicator variable for these 3 conditions with the combined treatment as the reference. Participants who completed baseline assessment and were randomized to treatment arm but were lost to follow-up were considered not abstinent.