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Placebo-controlled randomized clinical trial testing the efficacy and safety of varenicline for smokers with HIV

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Abstract

Background: People living with HIV/AIDS (PLWH) smoke tobacco at higher rates and have more difficulty quitting than the general population, which contributes to significant life-years lost. The effectiveness of varenicline, one of the most effective tobacco dependence treatments, is understudied in HIV. We evaluated the safety and efficacy of varenicline for smoking cessation among PLWH.

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Contributors

Rebecca Ashare co-drafted the manuscript with Dr. Schnoll and handled aspects of the statistical analyses. Morgan Thompson and Katrina Serrano oversaw data collection. David Metzger helped with sample recruitment. Karam Mounzer, Ian Frank, Robert Gross, and Anita Hole ensured participant safety and helped with participant recruitment. Ronald Collman facilitated access to participants and helped draft the manuscript. Paul Wileyto assisted with randomization and data analysis. Robert Schnoll is the overall study Principal Investigator, conceptualized the present study, handled some of the analyses, and co-drafted the manuscript. All authors reviewed the manuscript for content and have approved the final version.

Conflicts of Interest

Dr. Schnoll received medication and placebo free of charge from Pfizer for clinical trials and has provided consultation to Pfizer, GlaxoSmithKline, and Curaleaf. Dr. Gross serves on a Pfizer Data and Safety Monitoring Board for a drug unrelated to smoking or HIV. Dr. Ashare has an investigator-initiated grant from Novo Nordisk for a drug unrelated to the current study.

Methods: This was a single-site randomized, double-blind, placebo-controlled, phase 3 clinical trial (NCT01710137). PLWH on antiretroviral therapy (ART) who were treatment-seeking daily smokers were randomized (1:1) to 12 weeks of varenicline (n=89) or placebo (n=90). All participants were offered six smoking cessation behavioral counseling sessions. The primary outcome was 7-day point prevalence abstinence, confirmed with breath carbon monoxide, at Weeks 12 and 24. Continuous abstinence and time to relapse were secondary outcomes. Safety measures were treatment-related side effects, adverse events, blood pressure, viral load, and ART adherence.

Results: Of the 179 smokers, 81% were African American, and 68% were male. Varenicline increased cessation at Week 12 (28.1% vs. 12.1%; OR=4.54, 95% CI:1.83–11.25, *P*=.001). Continuous abstinence from Week 9 to 12 was higher for varenicline vs. placebo (23.6% vs. 10%; OR=4.65, 95% CI:1.71–12.67, *P*=.003); at Week 24, there was no effect of varenicline for point prevalence (14.6% vs. 10%), continuous abstinence (10.1% vs. 6.7%), or time to relapse (*P*s>.05). There were no differences between varenicline and placebo on safety measures (*P*s>.05).

Conclusions: Varenicline is safe and efficacious for short-term smoking cessation among PLWH and should be used to reduce tobacco-related life-years lost in this population.

Keywords

HIV; AIDS; Tobacco Use; Smoking Cessation; Varenicline; Nicotine Dependence

1. Introduction

Antiretroviral therapy (ART) for people living with HIV/AIDS (PLWH) substantially improved life expectancy (Wandeler et al., 2016) but has led to the need to address modifiable risk factors associated with the leading causes of death among PLWH, including cardiovascular disease and cancer, such as tobacco smoking (Althoff, 2016; Petoumenos and Law, 2016). HIV-infected smokers lose more life-years due to tobacco use than to HIV (Helleberg et al., 2013) and exhibit greater immune activation versus HIV-infected non-smokers (Valiathan et al., 2014). Tobacco cessation among PLWH could save 265,000 life-years, would yield greater life-years saved than hepatitis C treatment or ART for those with higher CD4+ T-cell counts, and can yield health benefits up to 10 years after diagnosis (Reddy et al., 2016).

Unfortunately, the prevalence of tobacco use among PLWH greatly exceeds that found in the general population (Raposeiras-Roubin et al., 2017). Current smoking among PLWH in the US surpasses 40% (Mdodo et al., 2015) [vs. 14% in the general population (Norris et al., 2017)] and exceeds 30% in low- and middle- income countries (Akhtar-Khaleel et al., 2016; Mdege et al., 2017). PLWH may also experience unique barriers to smoking cessation. For instance, depression and deficits in cognitive function are risk factors for relapse (Hitsman et al., 2013; Loughead et al., 2015) and are more prevalent among PLWH than HIV-uninfected individuals (Heaton et al., 2015; Nanni et al., 2015). Moreover, PLWH report that nicotine dependence, concerns about cravings, weight gain, and the ability to manage stress, as well as having a social network of smokers are barriers to smoking cessation (Cioe et al., 2018;

Weinberger et al., 2018). Thus, there is a clear need to evaluate the efficacy of nicotine dependence treatments in this population.

Varenicline, a nicotine acetylcholine α4β2 receptor partial agonist, when paired with counseling, is one of the most efficacious medications for tobacco dependence (Cahill et al., 2016). Clinicians who care for PLWH are uniquely positioned to provide evidence-based treatment for tobacco dependence, including varenicline. Although ~10% of smokers in the general population report using varenicline (Shah et al., 2017), less than 4% of PLWH report using varenicline, and 1 in 5 clinicians caring for PLWH recommend varenicline to their patients who smoke (Pacek et al., 2017). The paucity of evidence from rigorous studies establishing the efficacy of varenicline for PLWH, coupled with concerns about the psychiatric (Wu et al., 2016) and cardiovascular (Sterling et al., 2016) side effects of varenicline, may limit patient and physician use of this evidence-based treatment.

There have been remarkably few tobacco dependence treatment studies for PLWH relative to the general population, and three reviews show that there are insufficient data to conclude that tobacco dependence interventions that are efficacious in the general population are efficacious for PLWH (Ledgerwood and Yskes, 2016; Pacek and Cioe, 2015; Pool et al., 2016). Further, many studies have methodological weaknesses, including the lack of randomization and a control group, infrequent use of biological verification of tobacco abstinence, and lack of post-treatment follow-up (Ferketich et al., 2013; Ledgerwood and Yskes, 2016). The safety and efficacy of varenicline in PLWH has been evaluated in only one randomized, placebo-controlled trial (Mercie et al., 2018). While this trial, conducted in France, showed that varenicline was safe and efficacious for HIV- infected smokers, additional studies are needed to generalize these results and to facilitate the pooling of data for meta-analytic evaluations. The current study tested the efficacy and safety of varenicline among smokers with HIV. We expected higher abstinence rates among the varenicline group, compared to placebo, but did not expect differences in safety measures between treatment arms.

2. Methods

2.1 Study Design

This was a randomized, placebo-controlled, phase 3 clinical trial evaluating the safety and efficacy of 12 weeks of varenicline vs. 12 weeks of placebo for HIV-infected smokers. The trial was implemented at the University of Pennsylvania and recruited smokers through the university's Infectious Diseases Division, a community-based HIV medical clinic, and advertisements. The trial was registered with ClinicalTrials.gov (NCT01710137), approved by the University of Pennsylvania IRB, and conformed to US Federal Policy for the Protection of Human Subjects. Written informed consent was obtained from participants.

2.2 Participants

Prospective participants were screened by telephone and, if initially eligible, were scheduled for an in-person visit. To be eligible, individuals had to be age >18, have a confirmed HIV diagnosis, be treated with ART with HIV viral loads <1000 copies/ml and CD4+ counts

>200 cells/mm^3, report daily smoking, ALT and AST <2 times upper limit of normal, and creatinine clearance >50 mL/min. Exclusion criteria included: self-reported history of psychosis or a suicide attempt, self-reported current or planned pregnancy, self-reported current use of smoking cessation medications, unstable or untreated alcohol/substance abuse [those with current alcohol/substance use disorder were considered stable if they were currently receiving treatment (e.g., medication, group therapy, etc.) and had beenin treatment and/or not using for more than 30 days], and uncontrolled hypertension (systolic>160 or diastolic>100).

2.3 Randomization and Masking

Eligible participants were randomized 1:1 by a computer-generated protocol provided by the study statistician to the University of Pennsylvania's Investigational Drug Service (IDS), who maintained the supply of varenicline and placebo. As part of this investigator-initiated project, Pfizer provided varenicline and placebo directly to IDS who repackaged the pills into blister packs. All participants and study personnel, aside from IDS, were blinded from treatment arm allocation throughout the trial. The study statistician was permitted to be unblinded if a Serious Adverse Event (SAE) occurred.

2.4 Procedures

During the eligibility visit, trained personnel administered self-report questionnaires, ascertained laboratory results, and completed a medical history, the Mini International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) to assess for DSM-IV psychiatric disorders, and the Columbia Suicide Severity Rating Scale (CSSRS) (Posner et al., 2011). Study physicians and a clinical psychologist confirmed eligibility. Eligible participants were randomized to treatment arm and scheduled for a pre-quit session (Week 0). Subjects were considered ITT once the pre-quit session was completed and medication was assigned. Varenicline was provided at Week 0 based on U.S. Food and Drug Administration labeling: Day 1-Day 3 (0.5 mg once daily), Day 4–7 (0.5 mg twice daily), and Day 8-Day 84 (1.0 mg twice daily). Placebo pills were identical in appearance and dosing regimen.

All participants were offered six standardized, PHS guideline-based smoking cessation counseling sessions at Weeks 0, 1, 3, 5, 7, and 9, in-person or by telephone (Fiore et al., 2008). All sessions were one-on-one and delivered by trained counselors who were supervised by a clinical psychologist. Sessions were designed to help participants understand the risks associated with smoking, prepare for a target quit-date at Week 1, and develop skills to manage nicotine withdrawal and avoid relapse (Lerman et al., 2015; Schnoll et al., 2010; Schnoll et al., 2015). One HIV-specific module was included to educate participants about the unique health risks associated with smoking among PLWH. Thirty percent of sessions were recorded and assessed for fidelity by senior study personnel.

At the eligibility visit, demographic information (e.g., age, race), mode of HIV acquisition and current ART medications and adherence were ascertained from self-report. Disease-related characteristics, including HIV viral load and CD4+ count (within the past 6 months), were collected from medical records. Smoking-related data included current smoking rate, number of previous quit attempts, years smoked, measures of nicotine dependence including

time-to-first- cigarette (TTFC) (Transdisciplinary Tobacco Use Research Center Tobacco Dependence et al., 2007) and the heaviness of smoking index (HSI) (Kozlowski et al., 1994), and a breath carbon monoxide (CO) assessment.

Safety assessments occurred at Weeks 0, 1, 3, 5, 7, 9, and 12. Varenicline-related side effects (e.g., nausea, sleep problems, and hostility) (Lerman et al., 2015; Price et al., 2017) were rated from 0 (*none*) to 3 (*severe*), and ratings were summed to create a side-effects index (these are referred to as "side effects"). Participants were instructed to contact study personnel if they experienced any problems between assessments. Using a previously developed algorithm that considered severity and expectedness (Lerman et al., 2015), side effects were classified as Code 1–4, with Code 3 reports possibly representing adverse events (AEs) and Code 4 events representing Serious Adverse Events (SAEs) based on whether the event was considered by the participant to be debilitating or if they required hospitalization. The study physicians and psychologist were consulted to determine if an event was an AE and an SAE and what, if any, treatment or follow-up was required. Blood pressure and self-reported ART adherence were assessed at each time-point (Holmes et al., 2007). Viral load was reassessed via chart review at Week 12.

Pill and counseling adherence were assessed at Weeks 0, 1, 3, 5, 7, 9, and 12 (Crawford et al., 2018; Lerman et al., 2015). Counseling adherence was defined as completing at least 5/6 sessions. Pill adherence was tracked using the timeline follow-back method (Brown et al., 1998) and blister-pack collection. The total pills taken out of the total pills prescribed (i.e., 165) was computed for an overall proportion of medication adherence. Pill adherence was defined by taking >80% of prescribed medication (Pacek et al., 2018).

Smoking behavior was assessed at Weeks 0, 1, 3, 5, 7, 9, 12, 18 and 24 using the timeline follow-back procedure (Lerman et al., 2015; Schnoll et al., 2015). The primary smoking cessation outcomes for this trial were 7-day point-prevalence abstinence at Weeks 12 and 24, based on no self-reported tobacco use (not even a puff) during the 7 days preceding the assessment and a CO ≤8ppm (Benowitz et al., 2002; Hughes et al., 2003). Secondary outcomes included point-prevalence abstinence at Week 18, continuous abstinence rates (with CO) from Weeks 9–12, 9–18, and 9–24, defined as no self-reported tobacco use for the duration of the timeframe (based on previous varenicline trials (Gonzales et al., 2006; Mercie et al., 2018)), and time to relapse across the 24-week trial. An ITT approach was taken such that participants who completed the pre-quit session (Week 0) and were randomized to treatment arm but were lost to follow-up or failed to provide the CO measure were considered not abstinent.

2.5 Data Analysis

The sample size was based on our expectation of a 14–16% difference in quit rates between the varenicline and placebo groups at Week 12 (Gonzales et al., 2006) (80% power, α=.05). Specifically, the sample size of 179 provided 80% power to detect an OR of 2.2 given a 12% quit rate in the placebo group at Week 12. For Week 24, we had 80% power to detect an OR of 2.3 given a 10% quit rate in the placebo group. Sample characteristics were examined for clinically meaningful baseline differences between groups. Variables associated with treatment arm (P<.10) were included as covariates in subsequent models. Varenicline and

counseling adherence and Weeks 12, 18, and 24 assessment completion rates were characterized as proportions, and differences between treatment arms were determined using chi-square. Lastly, we (Schnoll et al., 2018) and others (Tanner and Tyndale, 2017) have found the antiretroviral treatment efavirenz to be positively associated with nicotine metabolism rate, which is a strong predictor of smoking abstinence and response to varenicline (Lerman et al., 2015). Because 18% of the current sample reported taking efavirenz, efavirenz use was a covariate in all models.

The primary analyses utilized multiple logistic regression models to test the relationship between treatment arm and 7-day point-prevalence abstinence, CO-confirmed. Separate models were conducted for point-prevalence abstinence outcomes at Weeks 12 and 24. A secondary outcome was 7-day point-prevalence abstinence at Week 18. The results were characterized by odds ratios and 95% confidence intervals. We then used longitudinal logistic regression (General Estimating Equations, GEE) to account for within-subject correlations among repeated measures at each follow-up time-point. The GEE models included a variable for time-point as a fixed effect and subject as a random effect. An interaction term between time-point and treatment arm was included to determine whether the treatment effect varied across time. This approach was also used for continuous abstinence. For all models, missing outcomes were considered non-abstinent. Lastly, we evaluated time to relapse through Week 24 using a Cox regression model excluding individuals who failed to quit for at least 24 hours. All models included covariates (see below).

Safety was assessed by examining treatment arm effects on mean (average of severity rating for all side effects at a given time point) and total count (number of symptoms with responses of 1, 2, or 3) on the side effects checklist from Weeks 0–12. Because nausea is a common side effect of varenicline (Cahill et al., 2016), we also examined this item separately. Repeated-measures ANOVA was used with mean or count side effects from Weeks 0, 3, 7, and 12 across treatment arms. Chi-square compared the cumulative frequencies of AEs and SAEs from Weeks 0–12 across treatment arms and high blood pressure rates at Weeks 0, 3, 7, and 12. Mean changes in viral load and ART adherence from Weeks 0–12 across treatment arms were assessed using ANOVA. No adjustments were made for multiple comparisons. Analyses were conducted using SPSS (IBM Corporation, Armonk, NY) or STATA (StataCorp, College Station, TX).

3. Results

The study was conducted from October 2012 to June 2018. As shown in the CONSORT diagram (Figure 1), 748 individuals were screened, of which 305 (40.7%) were eligible and attended the in-person eligibility evaluation; 179 individuals were eligible, willing to enroll, completed the pre-quit session, and randomized to varenicline (n=89) or placebo (n=90). Overall, only 7/179 participants (3.9%) withdrew from the trial. Visit completion rates in the varenicline arm were 81%, 75%, and 73% at Weeks 12, 18, and 24, respectively, and were 87%, 80%, and 84% at Weeks 12, 18, and 24 for placebo participants, respectively (P's>. 05).

3.1 Sample Characteristics

Demographic, smoking-related, and HIV-related characteristics are shown in Table 1. The placebo arm had more very low-income participants than the varenicline arm. Study medication adherence was greater in the placebo arm [138.0 pills (SD=40.3)] than varenicline arm [124.0 pills (SD=51.5), *P*=.05]; 75.6% of placebo participants reported taking >80% of pills, compared to 58.4% of varenicline participants (*P*=.02). The average number of counseling sessions completed was 5.4 out of 6 (SD=1.3); 90% of placebo participants completed >5 counseling sessions, compared to 82% of varenicline participants (χ^2[1]=2.40, *P*=.14). Lastly, the prevalence of any past or current diagnosis of alcohol or substance use disorder was similar between the placebo (n=16, 18%) and varenicline groups (n=21, 24%). Income, TTFC, varenicline adherence (number of pills), and efavirenz use were included as covariates in all models (Supplementary Table 1* contains all ARTs reported).

3.2 Varenicline Efficacy

The 7-day point prevalence abstinence rates are shown in Figure 2. As shown in Table 2, at Week 12, varenicline participants reported significantly higher point prevalence abstinence rates (OR=4.5 [95% CI: 1.83–11.2], *P*=.001), but this effect was no longer significant at Week 24 (OR=1.9 [95% CI: 0.71–5.1], *P*=.20). Point prevalence abstinence at Week 18 was evaluated as a secondary outcome. Similar to Week 12, those in the varenicline group were more likely to be abstinent than those in the placebo group (*P*=.02). The overall GEE model for point prevalence abstinence, including all three time-points, indicated a significant effect of varenicline (OR=3.2 [95% CI: 1.4–7.3], *P*=.006). The effect of time-point (OR=0.72 [95% CI: 0.60–0.88], *P*=.001) and the treatment arm by time-point interaction (OR=0.67 [95% CI: 0.45–1.0], *P*=.05) indicated that varenicline's efficacy declined over time. Varenicline participants reported significantly higher continuous abstinence rates between Weeks 9–12 (OR=4.65 [95% CI: 1.71–12.67], *P*=.003), but this effect was no longer significant between Weeks 9–24 (OR=1.92 [95% CI: .57–6.47, *P*=.29], see Figure 2 and Table 2). Similar to point prevalence abstinence, those in the varenicline group reported higher continuous abstinence rates between Weeks 9–18 than the placebo group (*P*=.05). The overall GEE model for continuous abstinence, including all three time-points, revealed a significant effect of varenicline (OR=2.3 [95% CI: 1.1–4.6], *P*=.02), although neither the time-point or treatment arm by time-point interaction was significant (*P*'s>.05). The effect of varenicline was not significant in the survival analysis (HR=0.75, [95% CI: 0.38–1.5], *P*=.40).

3.3 Varenicline Safety

There was no significant time by treatment arm effects on mean side effect severity or side effect counts from Week 0 through Weeks 3, 7, and 12 (*P*s>0.05; Supplementary Table 2*). As shown in Figure 3, when nausea was evaluated separately, the varenicline group reported a greater increase from Week 0 to Week 3 vs. the placebo group (*P*=.002), but there were no treatment arm effects at any other timepoint (*P*s>.1). There were no ratings of severe nausea,

*Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:…

and across all visits there were 11 counts of moderate nausea (4 placebo, 7 varenicline). There were no significant differences between treatment arms in the number of participants with AEs or SAEs coded as either Code 3 or Code 4 (*P*s>0.05; see Table 3) or in the rate of hypertension at any time-point (*P*'s>.05). Examination of changes in ART adherence or the proportion of subjects with detectable viral load from Week 0 to Week 12 indicated no time × treatment arm interaction (*P*s>.05).

4. Discussion

Tobacco use is a major health concern among PLWH, with prevalence rates that far exceed those seen in the general population and substantial adverse health consequences. Yet, there have been remarkably few studies rigorously testing smoking cessation interventions in this population and only one randomized, placebo-controlled trial of varenicline among PLWH, one of the most efficacious treatments available for tobacco dependence. The present study demonstrates that varenicline is safe and effective in the short-term and should be widely considered for treating tobacco dependence among PLWH.

The efficacy data showed that varenicline-treated participants showed a significant increase in smoking cessation, measured as CO-confirmed 7-day point prevalence or continuous abstinence, at the end of treatment, and this effect was maintained for 6 weeks following treatment cessation. While the quit rates are lower than in the general population (Gonzales et al., 2006) and when compared to an open-label study of varenicline with PLWH (Cui et al., 2012), varenicline more than doubled abstinence rates at Week 12. Although this effect decreased over time, with only about a 10% difference between the placebo and varenicline groups at Week 18, even small increases in abstinence can have meaningful effects. A recent US study estimated that a 10% reduction in smoking prevalence in each state could yield a $63 billion reduction in healthcare costs the following year (Lightwood and Glantz, 2016). However, there is limited support for the long-term effects of tobacco cessation interventions for PLWH (Pool et al., 2016). Indeed, although the treatment effect was no longer significant at Week 24, there was a ~5% difference in abstinence rates between the varenicline and placebo groups. The present results are also remarkably similar to the only other randomized placebo-controlled varenicline trial for smokers with HIV that was conducted in France (Mercie et al., 2018). Taken together, varenicline is efficacious for promoting tobacco cessation among PLWH in the short-term.

In contrast to studies with the general population (Gonzales et al., 2006), we found that the efficacy of varenicline decreased over time, and quit rates at Week 24 did not differ between groups. Thus, to maintain the benefits of varenicline, future studies should pair effective relapse prevention interventions with varenicline. One option could be the continued use of varenicline after 12 weeks. In the general population, 12 additional weeks of varenicline after confirmed abstinence following an initial 12 weeks of treatment increased the abstinence rate at 24 weeks (Tonstad et al., 2006), and retreatment after failure from 12 weeks of treatment increased cessation in the long-term (Gonzales et al., 2014). The FDA labeling allows for extended duration use, which may be particularly important for smokers with HIV. Importantly, recent evidence suggests that the effectiveness of varenicline, including extended duration use, is highly dependent upon adherence to the treatment

regimen (Pacek et al., 2018; Schnoll et al., 2019). Thus, future studies should examine the added benefit of maintenance treatment, perhaps combined with approaches to improve medication adherence, as a strategy for improving quit rates in this population.

Analyses of the safety data showed no indication that varenicline use among PLWH is associated with adverse outcomes. While we were not powered to detect small differences, the varenicline- and placebo-treated participants did not differ in terms of the severity or total number of side effects, the total number of AEs or SAEs, or the number of participants who reported an AE or SAE. Neither psychiatric events, such as depression or suicidality, nor the rate of hypertension were significantly different across treatment arms, indicating that varenicline is not associated with adverse events that may underlie the reluctance to use and prescribe varenicline. Furthermore, varenicline was not associated with adverse HIV-related outcomes, including change in viral load or ART adherence. These results are similar to previous varenicline trials with HIV-infected smokers (Mercie et al., 2018) and smokers with serious mental illness (Anthenelli et al., 2016).

Thus, in most cases, concerns about side effects or AEs associated with varenicline should not serve as a barrier to use among PLWH.

These results should be interpreted within the context of study limitations. First, when recruitment began in 2012, safety concerns regarding varenicline required implementation of strict inclusion/exclusion criteria which reduced interest in the study and the number of eligible subjects. Despite the removal of several restrictions in 2016, we did not meet our proposed target sample of 310, and the final sample represented 24% of the overall screened sample, with 47% of those screened considered ineligible and 29% of those screened refusing to enroll. Nevertheless, our final sample of 179 was adequately powered for our primary outcome. Future studies should collect data regarding decisions not to enroll in clinical trials. Given the inclusion/exclusion criteria to control for confounding variables and increase safety, and the need for participants to be motivated to quit smoking, the present study may be generalizable to a smaller proportion of PLWH who is relatively healthy and motivated to quit smoking. Second, the rate of varenicline adherence was 58%. While this proportion compares to the general population (Peng et al., 2017) and another study with HIV-infected smokers (Shelley et al., 2015), the strong association between adherence and cessation (Catz et al., 2011) indicates the need to evaluate novel behavioral approaches to increase medication adherence to maximize the benefits of varenicline (Tseng et al., 2016). Moreover, low adherence may have resulted in underestimating the potential efficacy of varenicline and may have contributed to the lack of a statistically significant effect at Week 24. Lastly, while the sample was representative of the population of PLWH and smokers in Philadelphia, findings may not be generalizable to the broader U.S. population.

4.1 Conclusions

Nevertheless, there are several notable strengths to this trial. Most noteworthily, this is only the second placebo-controlled randomized clinical trial of varenicline for HIV-infected smokers and the first conducted in the US. Methodological strengths include follow-up of smoking cessation outcomes until 24 weeks, biochemical verification of self-reported abstinence, inclusion of standard behavioral smoking cessation counseling, examination of a

broad range of potential adverse outcomes, and excellent retention across the 24 weeks. The overall findings indicate that use of varenicline combined with behavioral counseling is safe and effective in the short-term for HIV-infected smokers compared with behavioral counseling alone. Varenicline was not associated with adverse outcomes, including cardiovascular and psychiatric events, and significantly increased quit rates at the end-of-treatment and through 6 weeks following end-of-treatment. These results provide important information for patients and clinicians as they engage in efforts to address smoking among PLWH and improve their quality of life.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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De-identified data and the full study protocol are available upon request from the corresponding author.

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Highlights

- Varenicline is safe for smokers with HIV to use as a smoking cessation aid
- Varenicline improved smoking cessation in the short-term among smokers with HIV
- At 6 months, there was no difference between varenicline and placebo in quit rates

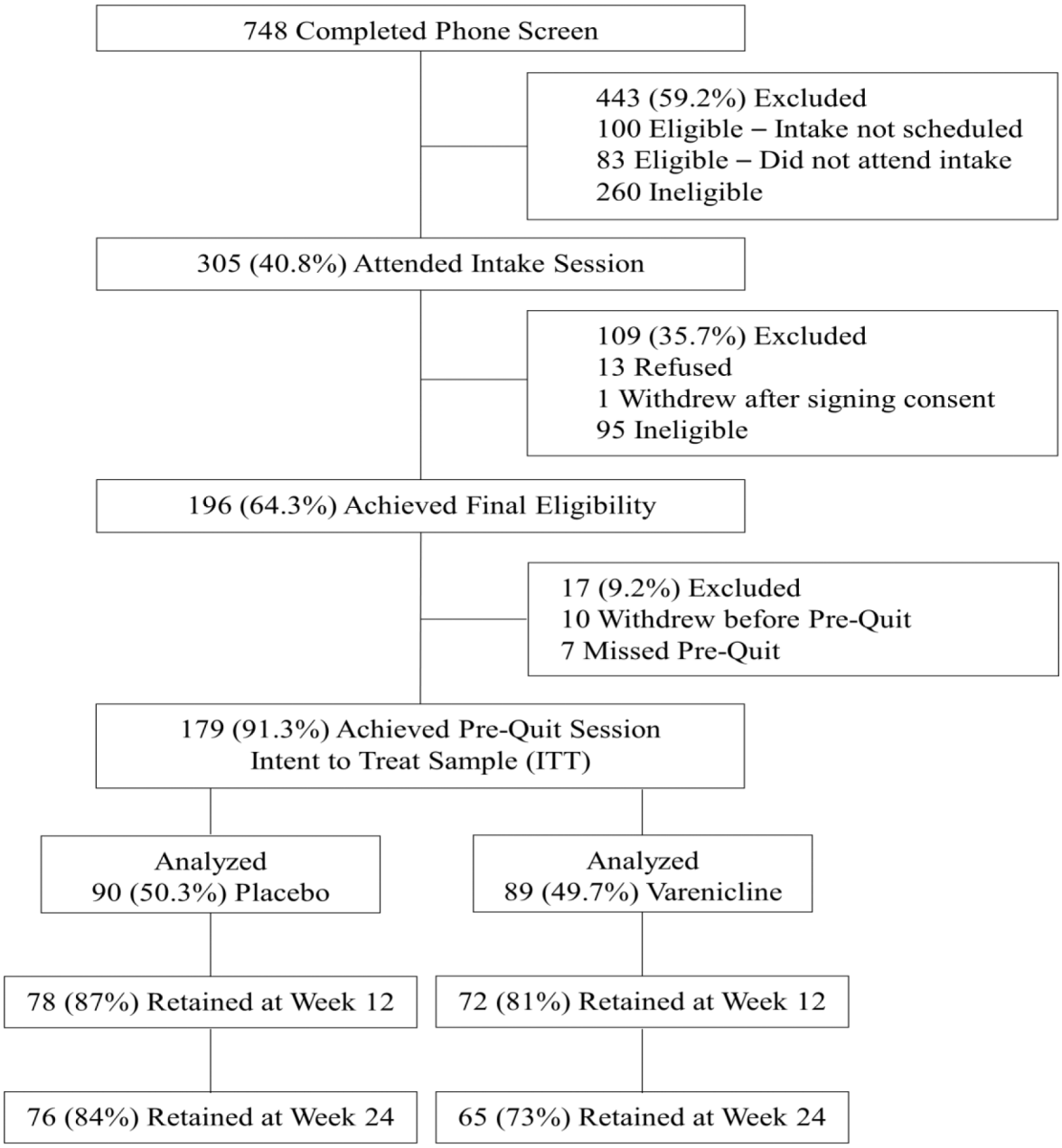

Figure 1.
CONSORT Diagram.

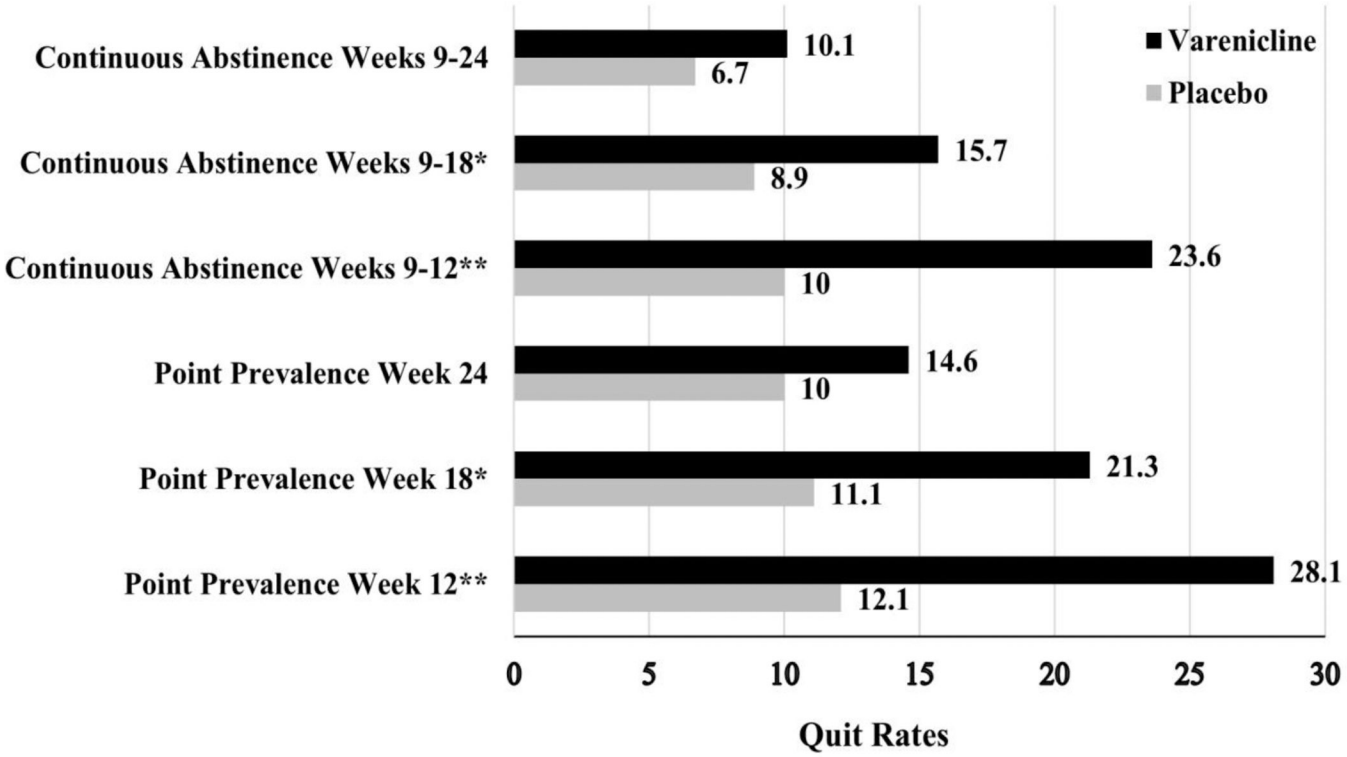

Figure 2.

Rates of 7-day point prevalence and continuous abstinence at weeks 12, 18, and 24 across treatment arm.

Intent to treat sample (N=179); point prevalence quit rates are 7-day self-reported, carbon monoxide confirmed; continuous abstinence are self-reported cessation from week 9 to the follow-up time-point, confirmed with carbon monoxide at the follow-up assessment time-point. All values are % abstinent. Weeks 12 and 24 were primary outcomes and Week 18 was a secondary end point. ** $P<0.001$; * $P<0.05$

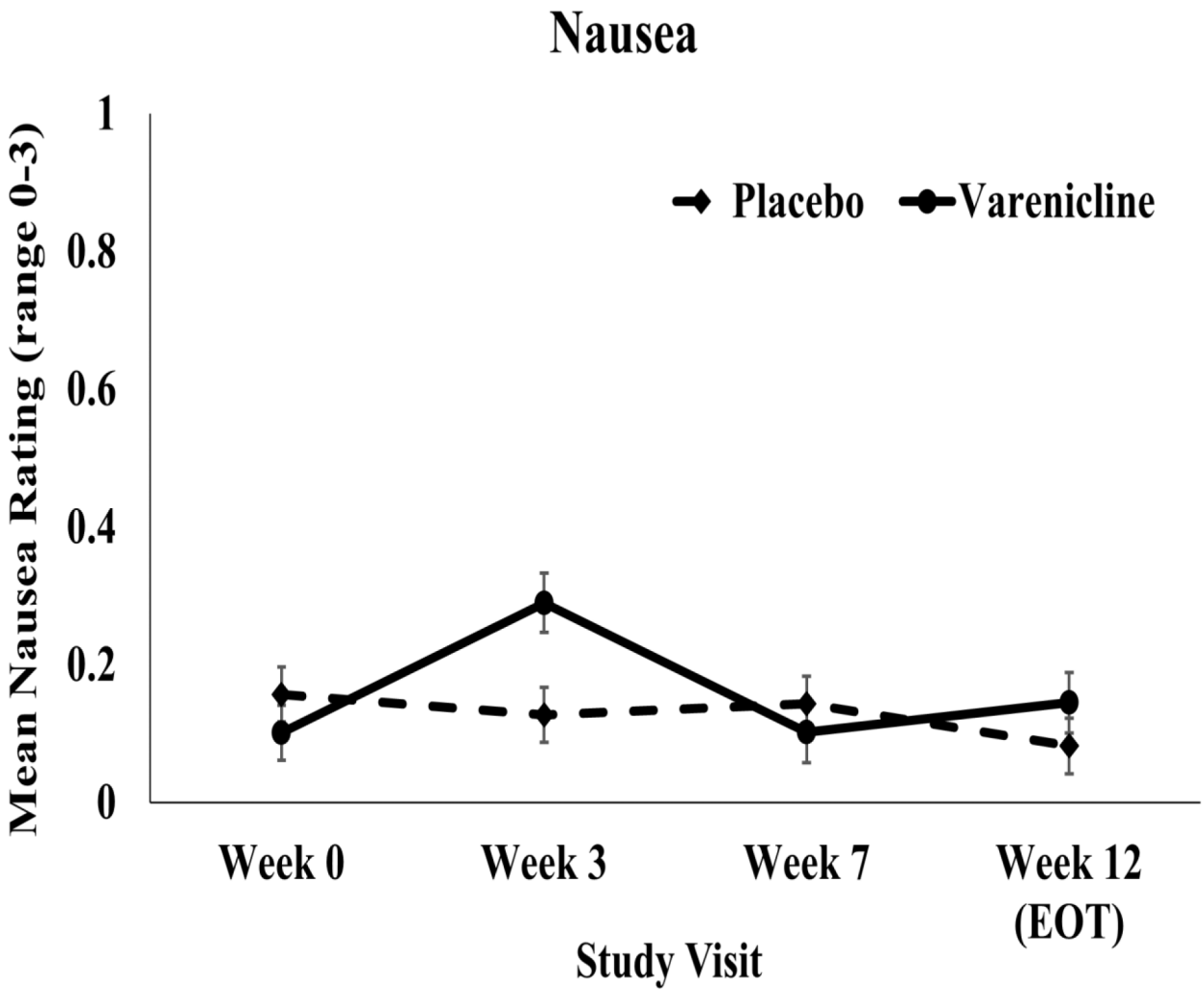

Figure 3.

Nausea severity by treatment arm at Weeks 0, 3, 7, and 12.

Mean ratings of nausea severity (range: 0=none at all to 3=severe) throughout the trial. Except for a greater increase in nausea between Weeks 0 and 3 in the varenicline group, there were no treatment arm effects at any other timepoint.

Table 1.

Baseline demographic, smoking-related, and disease-related characteristics across treatment arms for the ITT sample

	Placebo (N=90)	**Varenicline (N=89)**	**Total (N=179)**
Variable	**N (%) or M (SD)**	**N (%) or M (SD)**	**N (%) or M (SD)**
Demographic variables			
Race (% African American)	72 (83.7)	69 (79.3)	141 (81.5)
Sex (% Male)	58 (64.4)	64 (71.9)	122 (68.2)
Education (% High School Grad or less)	55 (61.1)	46 (51.7)	101 (56.4)
Annual Household Income (<20K)	71 (79.8)	55 (61.8)	126 (70.8)
Age (Range: 21–70)	48.5 (9.7)	48.7 (10.1)	48.6 (9.9)
BMI (Range: 15.3–58.2)	27.1 (6.3)	27.5 (7.2)	27.3 (6.7)
Smoking-related variables			
HSI (% High HSI)	60 (66.7)	60 (67.4)	120 (67.0)
TTFC			
Within 5 minutes	3 (3.3)	11 (12.4)	14 (7.8)
6–30 minutes	12 (13.3)	3 (3.4)	15 (8.4)
31–60 minutes	38 (42.2)	38 (42.7)	76 (42.5)
More than 60 minutes	37 (41.1)	37 (41.6)	74 (41.3)
Cigarettes/Day in Past 7 Days (Range: 1–60)	11.8 (9.0)	11.2 (6.6)	11.5 (7.9)
Breath CO, ppm (Range: 1–60)	13.1 (7.9)	15.0 (10.4)	14.1 (9.2)
Number of Years Smoking (Range: 4–56)	31.1 (11.0)	31.8 (10.8)	31.5 (10.9)
Number of Times Quit Smoking for>24 Hours (Range: 0–500)	4.9 (12.3)	8.8 (52.9)	6.9 (38.2)
Disease-related characteristics			
% of ART Prescribed in Past 2 Weeks Taken (Range: 79–100)	98 (1.0)	99 (3.0)	98 (4.0)
% Undetectable Viral Load (<50 copies/ml)	69 (77)	75 (84)	144 (80)
CD4+ cells/mm^3 (Range: 214–1932)	688.8 (322.7)	737.2 (329.5)	712.8 (326.1)
% Acquired HIV via Sex	71 (78.9)	73 (82.0)	144 (80.4)
% ART regimen containing efavirenz	18 (20.9)	14 (15.9)	32 (18.4)
Estimated creatinine clearance (mL/min)	107.7 (39.2)	103.5 (38.9)	105.6(39.0)
Drug and Alcohol Use History			
# Alcohol Drinks in Past 7 Days (Range: 0–27)	4.9 (4.2)	5.1 (6.3)	5.0 (5.2)
DSM-IV Alcohol Abuse (Current)	3 (3)	2 (2)	5 (3)
DSM-IV Alcohol Abuse (Past)	1 (1)	4 (4)	5 (3)
DSM-IV Substance Abuse (Current)[a]	3 (3)	6 (7)	9 (5)
DSM-IV Substance Abuse (Past)[a]	11 (12)	12 (13)	23 (13)
History Injection Drug Use	4 (4)	3 (3)	7 (4)

	Placebo (N=90)	**Varenicline (N=89)**	**Total (N=179)**
Variable	**N (%) or M (SD)**	**N (%) or M (SD)**	**N (%) or M (SD)**
History/Current Alcohol or Substance Abuse	16 (18)	21 (24)	37 (21)

Note. BMI=Body Mass Index; CO=Carbon Monoxide; HSI=Heaviness of Smoking Index; TTFC=Time to First Cigarette.

[a]Other than nicotine

Table 2.

Multiple logistic regression models predicting 7-day point prevalence and continuous abstinence at Weeks 12, 18, and 24

Dependent Variable: Point Prevalence Abstinence Week 12	**OR**	**95% CI**	**P**
Income (Reference=20K or less)	1.23	0.78, 1.93	0.37
Medication Adherence	1.01	1.00, 1.02	0.12
Efavirenz Use (Reference=Yes)	2.83	1.04, 7.73	0.04
TTFC (Reference=Within 30 minutes)	0.59	0.22, 1.57	0.29
Treatment Arm (Reference=Placebo)	**4.54**	**1.83, 11.25**	**0.001**
Dependent Variable: Point Prevalence Abstinence Week 18	OR	95% CI	p
Income (Reference=20K or less)	1.16	0.75, 1.86	0.56
Medication Adherence	1.01	0.99, 1.02	0.31
Efavirenz Use (Reference=Yes)	1.84	0.62, 5.42	0.27
TTFC (Reference=Within 30 minutes)	0.52	0.18, 1.39	0.19
Treatment Arm (Reference=Placebo)	**3.12**	**1.22, 7.97**	**0.02**
Dependent Variable: Point Prevalence Abstinence Week 24	OR	95% CI	p
Income (Reference=20K or less)	1.10	0.64, 1.89	0.72
Medication Adherence	1.01	0.99, 1.02	0.30
Efavirenz Use (Reference=Yes)	1.84	0.58, 5.77	0.30
TTFC (ReferencêWithin 30 minutes)	0.60	0.19, 1.85	0.37
Treatment Arm (Reference=Placebo)	**1.90**	**0.71, 5.10**	**0.20**
Dependent Variable: Continuous Abstinence Weeks 9–12	OR	95% CI	p
Income (Reference=20K or less)	1.37	0.86, 2.18	0.19
Medication Adherence	1.01	1.00, 1.02	0.18
Efavirenz Use (Reference=Yes)	3.16	1.1, 9.1	0.03
TTFC (Reference=Within 30 minutes)	0.54	0.19, 1.52	0.24
Treatment Arm (Reference=Placebo)	**4.65**	**1.71, 12.67**	**0.003**
Dependent Variable: Continuous Abstinence Weeks 9–18	OR	95% CI	p
Income (Reference=20K or less)	1.28	0.76, 2.16	0.36
Medication Adherence	1.01	0.99, 1.02	0.27
Efavirenz Use (Reference=Yes)	2.11	0.65, 6.83	0.21
TTFC (Reference=Within 30 minutes)	0.56	0.18, 1.78	0.33
Treatment Arm (Reference=Placebo)	**2.90**	**1.00, 8.43**	**0.05**
Dependent Variable: Continuous Abstinence Weeks 9–24	OR	95% CI	p
Income (Reference=20K or less)	1.36	0.76, 2.43	0.31
Medication Adherence	1.01	0.99, 1.02	0.51
Efavirenz Use (Reference=Yes)	2.43	0.66, 8.94	0.18
TTFC (Reference=Within 30 minutes)	0.72	0.18, 2.88	0.64
Treatment Arm (Reference=Placebo)	**1.92**	**0.57, 6.47**	**0.29**

Note. Medication adherence was continuous measure of number of pills taken

Table 3.

Side effects, adverse events, and serious adverse events across treatment arm

Variable	Placebo (N=90)	Varenicline (N=89)	Total (N=179)
Participants with an Adverse Event	28 (31.1%)	19 (21.3%)	47 (26.3%)
Participants with a Serious Adverse Event	3 (3.3%)	5 (5.6%)	8 (4.5%)
Total Number of Adverse Events	70	43	113
Skin swelling	28	19	47
Depression	16	7	23
Agitation	16	8	24
Weakness	0	1	1
Hostility	5	2	7
Irritability	2	0	2
Skin redness	1	1	2
Dizziness	0	1	1
Headache	1	3	4
Abdominal pain	1	1	2
ER visit	2	0	2
Total Number of Serious Adverse Events	8	8	16
Suicidality	1	1	2
Cancer diagnosis	1	1	2
Cancer metastasis	0	1	1
Hospitalization	3	5	8
Death	1	0	1
Number of High Blood Pressure Recordings[a]	30	17	47

Note. Adverse events and serious adverse events were determined by study physicians to be coded either Code 3 or Code 4.

[a]A total of 10 recordings documented at baseline (5 per treatment arm).