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Original Investigation

Safety of Varenicline Among Smokers Enrolled in the Lung HIV Study

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Abstract

Introduction: The prevalence of smoking is high among the human immunodeficiency virus (HIV)-infected population, yet there are few studies of tobacco dependence treatment in this population. This paper reports the safety of varenicline versus nicotine replacement therapy (NRT) and describes preliminary results about the effectiveness of varenicline versus NRT in HIV-infected smokers.

Methods: Participants completed 12 weeks of telephone counseling and either varenicline or NRT. Varenicline was encouraged as the preferred intervention; NRT was used for those unable/unwilling to take varenicline. Adverse events (AEs), related to pharmacotherapy, were monitored. Biochemically confirmed abstinence at 3 months was examined. Inverse probability of treatment weighted logistic regression models was fit to compare participants on varenicline to those on NRT.

Results: Among participants on varenicline ($n = 118$), the most common AEs were nausea, sleep problems, and mood disturbances. One person reported suicidal ideation; there were no cardiovascular complications. There were no differences in the varenicline AE profile between participants on combination antiretroviral therapy (ART) and those not on ART. The percentages of confirmed abstainers were 11.8% in the NRT group and 25.6% in the varenicline group. The odds of being abstinent were 2.54 times as great in the varenicline group compared with the NRT group in the propensity weighted model (95% *CI* 1.43–4.49).

Conclusions: In this preliminary study, the safety profile of varenicline among HIV-infected smokers resembles findings among smokers without HIV. In addition, varenicline may be more effective at promoting abstinence in this population. Future randomized clinical trials are warranted.

Introduction

In the era of increasingly effective treatments for HIV, persons living with HIV have the potential to live longer (CASCADE Collaboration, 2006; Lohse et al., 2007; van Sighem et al., 2010). This, coupled with the fact that smoking continues to be a problem among HIV-infected individuals in the United States, suggests that smoking-related comorbidities could become more prevalent in this population of patients. Furthermore, there is evidence to suggest that serious non-AIDS events, such as cardiovascular disease and cancer, are now more prevalent than serious AIDS events in the HIV-infected population (Neuhaus et al., 2010).

The prevalence of current smoking among HIV-infected individuals ranges between 40% and 85% across various studies (Lifson et al., 2010; Marshall et al., 2011; Tesoriero, Gieryic, Carrascal, & Lavigne, 2010); these estimates for the HIV-infected population are several fold higher than the current 20% overall prevalence in the United States (Barnes, Ward, Freeman, & Schiller, 2011). Specifically, the United States as a whole has never witnessed a smoking prevalence as high as some of these estimates. The peak was in 1957, when the prevalence reached 46% (de Walque, 2004). Similar to the characteristics of smokers in the general population in the United States, HIV-infected smokers tend to be more socioeconomically disadvantaged and consume more alcohol and illicit drugs (Burkhalter, Springer, Chhabra, Ostroff, & Rapkin, 2005; Lifson et al., 2010).

Smokers with HIV infection are particularly susceptible to chronic obstructive pulmonary disease (COPD; Diaz, Clanton, & Pacht, 1992) and lung cancer (Clifford et al., 2005; Kirk et al., 2007). Notably, HIV-infected smokers have approximately twice the risk of developing bacterial pneumonia compared with their nonsmoking counterparts (Gordin et al., 2008; Heffernan et al., 2005; Kohli et al., 2006; Miguez-Burbano et al., 2005). Smokers with HIV infection are at a significantly increased risk for COPD and lung cancer compared with smokers without HIV infection (Diaz et al., 2000; Kirk et al., 2007).

In the general population, quitting smoking is beneficial for all smokers, regardless of age (Doll, Peto, Wheatley, Gray, & Sutherland, 1994; National Cancer Institute [NCI], 1997; Peto et al., 2000). Studies have reported benefits of cessation among HIV-infected smokers. Recent findings indicate that quitting

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smoking decreases the risk of cardiovascular disease among HIV-infected individuals (Petoumenos et al., 2011). Smoking cessation also appears to lower the risk for bacterial pneumonia (Benard et al., 2010).

To date, tobacco dependence treatment has not been a high priority among clinicians and researchers involved in HIV care. While approximately 80% of health care providers that treat HIV-infected patients believe that smoking is a major health issue affecting HIV-infected individuals, less than half report that they frequently prescribe nicotine replacement therapy (NRT), varenicline, or bupropion (Shuter, Salmo, Shuter, Nivasch, Fazzari, & Moadal, 2011). Also, there have been few studies that have examined the efficacy of tobacco dependence treatment pharmacotherapy in this population, and the studies that have been reported have used NRT and not other treatments such as varenicline (Lloyd-Richardson et al., 2009; Vidrine, Arduino, Lazev, & Gritz, 2006; Wewers, Neidig, & Kihm, 2000). Varenicline is an effective tobacco dependence treatment pharmacotherapy among healthy smokers (Cahill, Stead, & Lancaster, 2011; Fiore et al., 2008) and smokers with cardiovascular disease (Rigotti, Pipe, Benowitz, Arteaga, Garza, & Tonstad, 2010). However, a recent meta-analysis suggests that varenicline increases the risk of adverse cardiovascular events (Singh, Loke, Spangler, & Furberg, 2011). Further, a Food and Drug Administration (FDA) warning was issued in 2009, advising health care professionals about the risks of serious psychiatric symptoms in patients taking varenicline (FDA, 2009). Thus, the safety of this pharmacotherapy among HIV-infected smokers could be a concern given the increased risk of both cardiovascular disease and psychiatric problems in the HIV-infected population.

In this paper, we report the safety of varenicline and NRT among HIV-infected individuals enrolled in a tobacco dependence treatment protocol as part of a prospective study. Preliminary information regarding the effectiveness of varenicline in this population is also provided.

Methods

Participants

The participants were recruited from one site of the Lung HIV study, a multisite study funded by the National Heart, Lung, and Blood Institute (R01HL090313-01). The overall objective of the Lung HIV study is to characterize HIV-associated lung infections and complications in the era of combination antiretroviral therapy (ART). The eight sites conduct independent projects as well as collaborative projects (Crothers et al., 2011). Our site is focused on examining longitudinal changes in lung function among HIV-infected smokers who quit, as compared with those who continue to smoke. As such, study participants were exposed to intensive tobacco dependence treatment in order to obtain the maximum number of abstinent individuals. Randomization was not used to assign participants to treatment, since our goal was to deliver the most efficacious therapy available based on the Clinical Practice Guideline (Fiore et al., 2008).

To be eligible for this study, an individual had to be an adult infected with HIV, a daily smoker of five or more cigarettes, and interested in quitting smoking in the next 30 days. Participants at our site were recruited from infectious disease clinics and community agencies. All procedures were approved by The Ohio State University Institutional Review Board.

Intervention

The intervention consisted of 12 weeks of pharmacotherapy and telephone counseling provided by an advanced practice nurse who was experienced in delivering tobacco dependence treatment using the U.S. Public Health Service's clinical practice guideline (Fiore et al., 2008). The pharmacotherapy included NRT or varenicline. Participants were encouraged to select varenicline, if appropriate. However, if the participant had a history of schizophrenia, biopolar disorder, or if the current Beck Depression Inventory (BDI) score was greater than 20, then NRT was prescribed. For this study, NRT included a daily 21 mg patch plus 4 mg *ad lib* gum. Participants were informed that they could chew up to 24 pieces of gum per day. If a participant experienced side effects from the 21 mg patch that were believed to be related to the dose of NRT, then the patch dose was decreased to 7 or 14 mg. The varenicline dose was 0.5 mg per day on Days 1–3, 0.5 mg twice daily on Days 4–7, and 1 mg twice daily for the remainder of the study (11 weeks). Participants were instructed not to use tobacco or other NRT products while taking NRT or varenicline. A one-month supply of pharmacotherapy was given at the baseline visit, and the remaining two months were given either in-person at the clinic or mailed to the participants if they could not come in to the clinic.

The behavioral intervention consisted of one face-to-face session, followed by 11 weekly telephone sessions. A quit date was set at the face-to-face session, and the quit date occurred during Week 3 of the protocol. The nurse called the participant on the quit date. A tobacco dependence treatment protocol manual was followed; identical behavioral counseling topics were discussed with participants. The topics of discussion included self-monitoring of tobacco consumption behaviors; adherence to and side effects of pharmacotherapy; integration of tobacco cessation into daily living; coping with triggers; withdrawal symptomatology; seeking assistance with mood management; access to social support; and reinforcement of motivational messages about quitting tobacco use (e.g., relevance to disease status, risks to health, and rewards of quitting). Participants were given an opportunity to ask questions or seek clarifications and a toll-free telephone number to contact the nurses if questions or problems arose in between telephone calls.

Measures

Questionnaires were completed at baseline and 3 months post-treatment initiation. The baseline questionnaire included demographic, smoking-related, and mental health items. The smoking-related items included questions about age at initiation, smoking intensity, previous quit attempts, decisional balance, and nicotine dependence. Decisional balance consisted of two subscales (10 items each): the pros of smoking and the cons of smoking. This tool uses a scale with scores ranging from 1 (*not important*) to 5 (*extremely important*). The items for each scale are summed yielding a mean score with good internal consistency scores of 0.87 (pros) and 0.90 (cons) (Velicer, DiClemente, Prochaska, & Brandenburg, 1985). The cons scale score was subtracted from the pros scale score to yield the "decisional balance" score. Thus, a positive score implies that there are more pros than cons of using tobacco. Nicotine dependence was measured with the Fagerström Test for Nicotine Dependence (Heatherton, Kozlowski, Frecker, & Fagerström, 1991), a 6-item questionnaire that continues to be the gold standard measure utilized in all tobacco studies (Fiore et al., 2008). Mental health

items assessed past and current psychiatric comorbidities and included questions about self-reported history of a diagnosis of depression, bipolar disorder, and/or schizophrenia, the BDI (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961) and the SF-8 (Ware, Kosinski, Dewey, & Gandek, 2001). The SF-8 Health Survey is a short form survey of health status. The 8 items each relate to distinct domains of health. Physical and mental component scores were calculated. Norm-based scoring is used for these subscales, with a mean of 50 and *SD* of 10. Thus, scores above 50 reflect better mental or physical health, and scores below 50 represent worse mental or physical health than the norm. At 3 months posttreatment initiation, biochemically confirmed point prevalence abstinence was assessed. Participants completed a face-to-face interview, during which they were asked whether they had smoked a cigarette in the past 7 days. Those who reported zero cigarettes smoked in the past 7 days were next asked to provide a saliva or expired air sample to confirm nonsmoking. Those who self-reported no smoking in the past 7 days at 3 months and were no longer on NRT were confirmed as abstinent if their saliva cotinine concentration was <15 ng/ml (Society for Research on Nicotine and Tobacco [SRNT] Subcommittee on Biochemical Verification, 2002). If a participant indicated zero cigarettes smoked in the past 7 days at this visit, but was still taking NRT, an expired carbon monoxide sample was taken, and if the value was less than 10 ppm, the participant was considered to be abstinent.

The adverse events (AEs) that were monitored included all that are listed in Table 2. These are the standard AEs that are tracked for NRT and varenicline (Fiore et al., 2008).

Statistical Analysis

t tests and chi-square tests were used to compare the two treatment groups. AEs were summarized by ART status, and comparisons were made using Fisher's exact tests.

Three-month abstinence rates among participants who received NRT were compared with those who received varenicline. Even though some participants stopped taking the pharmacotherapy, or switched from varenicline to NRT, for the analysis, they were kept in their initial group. Because treatment assignment was not random, inverse probability of treatment weighting (IPTW) adjustment was performed (Robins, Hernan, & Brumback, 2000). IPTW is commonly used to estimate causal relationships in observational studies provided that all confounders are observed and included in the weights. This adjustment is different from the traditional regression analysis since it removes the confounding effect by adjusting the probability of selecting into treatment, which is the case in many nonrandomized studies. IPTW is also robust to misspecified function form in the response model. A propensity score was estimated as the probability of receiving varenicline, given all measured pretreatment covariates (the demographic, smoking, and mental health indicators listed in Table 1). A weight was calculated as the inverse of the propensity score. A weighted logistic regression model was used to compare the biochemically confirmed abstinence rates. Additionally, models were fit that controlled for all potential confounders (i.e., those that were significantly related to being in the varenicline vs. NRT group), as well as the variables that in fact were confounders (defined as altering the odds ratio for treatment by 10% or more).

To determine the stability of the results, a sensitivity analysis was performed. The data were limited to individuals with no history of depression or bipolar disease, to individuals with a BDI below 10 (the standard cut-point), and separately, a BDI below 20 (the cutpoint used in this study for determining whether a person could take varenicline). We could not include schizophrenia alone in the sensitivity analysis, given that there was no overlap in pharmacotherapy among participants with a history of schizophrenia. The logistic regression models were fit to these three subsamples.

Results

A total of 315 individuals inquired about the study: 21 were ineligible, 66 were eligible but refused to participate after learning the details of the study, and 228 enrolled in the tobacco dependence treatment protocol. There were similar numbers of participants in the NRT ($n = 110$) and varenicline ($n = 118$) groups. The reasons for assignment to NRT over varenicline were the following: psychiatric history (66%), patient preference that included a desire to not have to take another pill (28%), renal condition (4%), and other reasons (2%). Compliance with the intervention was similar between the two groups. Approximately 57% in the varenicline and 55% in the NRT group completed 80% or more of the weekly counseling calls, with no significant difference between groups. Among participants in the varenicline arm, 50.4% completed 8 or more weeks of therapy, as compared with 47.2% in the NRT arm. The characteristics of the groups are presented in Table 1. As seen in the table, the two groups differed with respect to employment status, income, nicotine dependence, decisional balance, all of the mental health indicators, and viral load.

AEs information, by treatment arm and ART status, is listed in Table 2. Among participants treated with varenicline, the most common AEs were nausea, abnormal dreams, sleep-related problems, agitation, constipation, flatulence, headache, fatigue, insomnia, and depression. Approximately 14% of participants on varenicline had to switch to NRT or stop taking varenicline because of AEs. Among participants in the NRT group, the most common AEs were rash around patch site, nausea, vivid dreams, and insomnia. Less than 2% of participants on NRT had to stop taking the product because of AEs. There were no differences in the varenicline AEs profile between participants on ART and those not on ART. One person on varenicline reported suicidal ideation during the study period. The symptoms resolved after the drug was stopped. One person receiving NRT developed chest pain and a myocardial infarction and ultimately required a stent placement. No subjects taking varenicline had cardiovascular complications during the course of the study.

The percentages of participants who were biochemically confirmed as abstinent at 3-month posttreatment initiation were 11.8% in the NRT group and 25.6% in the varenicline group (Table 1). Table 3 contains the results from the propensity weighted logistic regression models. The odds of being abstinent were 2.75 times as great in the varenicline group compared with the NRT group in the unadjusted weighted model (95% *CI* 1.57–4.84). In the fully adjusted model that controlled for all variables that were significant in Table 1, except schizophrenia because of the fact that there was no overlap between groups

Table 1. Comparison of Participants on NRT Versus Varenicline at Baseline (*n* = 228)

Characteristic	NRT (*n* = 110)		Varenicline (*n* = 118)	
	Percent	*M* ± *SD*	Percent	*M* ± *SD*
Demographics				
Age		42.7 ± 8.7		42.8 ± 9.1
Male	84.6		85.6	
White race	50.0		60.7	
Education level				
Less than HS	15.4		12.7	
HS or GED	28.2		20.3	
HS or more	56.4		67.0	
Current employment status**				
Employed full- or part-time	14.5		39.0	
Unemployed or disabled	70.0		45.8	
Other	7.3		9.3	
Refused to answer	8.2		5.9	
Marital status				
Married or member of couple	24.8		21.4	
Never married	55.0		50.4	
Divorced/separated/widowed	20.2		28.2	
Household income**				
≤$20,000	70.9		46.6	
>$20,000	23.6		43.2	
Don't know/refused	5.5		10.2	
Smoking-related variables				
Age at initiation		17.3 ± 5.3		17.8 ± 5.5
Current cigarettes per day		20.0 ± 11.5		19.7 ± 11.1
One or more quit attempts in past year	53.8		49.2	
Fagerström Scale score*		5.4 ± 2.3		4.9 ± 2.3
Baseline cotinine (ng/ml)		260 ± 192		247 ± 163
Decisional balance (pros minus the cons of using tobacco)*		1.49 ± 12.8		−1.61 ± 11.8
Mental health indicators				
Physical component (SF-8)**		44.1 ± 10.6		49.4 ± 8.7
Mental component (SF-8)**		41.3 ± 11.7		48.9 ± 8.7
Beck Depression Inventory**		15.7 ± 9.8		7.4 ± 5.5
History of depression**	73.4		33.9	
History of bipolar disorder**	36.1		6.0	
History of schizophrenia**	6.5		0	
Physical health indicators				
CD4 count (cells/mm^3)		480 ± 257		512 ± 302
On antiretroviral therapy	74.6		70.3	
HIV ribonucleic acid below detection**	44.3		63.6	
Abstinence at 3 months	11.8		25.6	

Note. GED = General Educational Development test; HS = High School; NRT = nicotine replacement therapy.
*$p < .10$. **$p < .01$ from *t* tests (continuous variables) or chi-square tests (categorical variables).

among patients with schizophrenia, the odds ratio were unchanged (*OR* 2.72, 95% *CI* 1.50–4.94). In the model that controlled for only the variables that confounded the relation between treatment and abstinence by 10% or more, the *OR* was slightly lower, 2.54 (95% *CI* 1.43–4.49). This implies that Model 1 adjusts the confounding effect very well, and further regression adjustment does not improve the estimation. The results changed little when the analysis was limited to individuals with no history of depression or bipolar disorder (*OR* 2.93, 95% *CI* 1.18–7.33), to individuals who scored below 10 on the BDI (*OR* 2.84, 95% *CI* 1.25–6.46), or to individuals who scored below 20 on the BDI (*OR* 1.82, 95% *CI* 0.99–3.34; Table 3).

Discussion

Persons infected with HIV are unusually susceptible to the adverse effects of cigarette smoking and have a heightened risk for lung cancer (Clifford et al., 2005; Kirk et al., 2007), bacterial pneumonia (Heffernan et al., 2005; Kohli et al, 2006), and emphysema (Diaz et al., 2000). With this in mind, it can be argued that the single most important issue relevant to the natural history of HIV-related pulmonary complications is the exceedingly high prevalence of cigarette smoking in this population. As such, there is an urgent need to examine potentially effective tobacco

Table 2. Adverse Events Associated With Pharmacotherapy, by Treatment Group (n = 228)

	NRT patch & gum		Varenicline	
Side effects	ART (n = 82)	No ART (n = 28)	ART (n = 83)	No ART (n = 35)
At least one AE	48 (58.5)	19 (67.9)	65 (78.3)	29 (82.9)
Stopped/switched drug due to AE	2 (2.4)	0	9 (10.8)	8 (22.9)
Varenicline & NRT AEs				
Nausea	9 (11.0)	4 (14.3)	27 (32.5)	11 (31.4)
Vomiting	1 (1.2)	2 (7.1)	2 (2.4)	2 (5.7)
Insomnia	7 (8.5)	2 (7.1)	5 (6.0)	3 (8.6)
Abnormal/vivid dreams	9 (11.0)	2 (7.1)	21 (25.3)	6 (17.1)
Dizziness	1 (1.2)	0	0	2 (5.7)
Fatigue/weakness	1 (1.2)	2 (7.1)	6 (7.2)	2 (5.7)
Varenicline-specific AEs				
Constipation			8 (9.6)	3 (8.6)
Flatulence			9 (10.8)	2 (5.7)
Dry mouth			3 (3.6)	0
Dyspepsia			3 (3.6)	1 (2.9)
Difficulty sleeping			15 (18.1)	6 (17.1)
Anxiety			5 (6.0)	1 (2.9)
Headache			6 (7.2)	3 (8.6)
Suicide ideation			0	1 (2.9)
Depressed mood			4 (4.8)	4 (11.4)
Agitation			9 (10.8)	3 (8.6)
Changes in behavior			4 (4.8)	2 (5.7)
NRT-specific AEs				
Skin rash	9 (11.0)	8 (28.6)*		
Skin redness around patch site	3 (3.7)	3 (10.7)		
Rapid heart rate or palpitations	1 (1.2)	0		
Gum, tooth, or jaw soreness	1 (1.2)	1 (3.6)		
Hiccups	0	2 (7.1)		

Note. All results are given as n (%). AE = adverse event; ART = antiretroviral therapy; NRT = nicotine replacement therapy.
*$p < .05$ by Fisher's exact test.

dependence treatment strategies in this population. While varenicline appears to be superior to other smoking cessation interventions in the general population, potential AEs could complicate its use in the HIV-infected population. Furthermore, negative publicity surrounding AEs could present a barrier to its use among providers and patients (Saul, 2008).

Our data suggest that varenicline is safe and reasonably well tolerated in HIV-infected individuals, including those on combination ART. Of note, only one person on varenicline reported suicidal ideation during the study period and after this person stopped varenicline, the symptoms resolved. Reports of suicidal ideation, although rare, have received extensive attention in the popular press (Saul, 2008) and may deter clinicians from prescribing this medication. Likewise, the recent meta-analysis that suggests varenicline increases the risk of adverse cardiovascular events (Singh et al., 2011) may also be a cause of concern for providers and patients. No participant in the varenicline group experienced an adverse cardiovascular event. The one person in the study who developed a myocardial infarction was receiving NRT. Anecdotally, many participants were aware of negative publicity about varenicline and specifically requested NRT. This heightened negative publicity could result in fewer smokers who might use varenicline, an effective medication (Fiore et al., 2008), during a quit attempt.

While our results suggest that varenicline is reasonably well tolerated, we did observe that 14.4% of participants on varenicline had to switch to NRT or stop taking varenicline due to AEs; 10 participants switched due to mood changes, four due to nausea or vomiting, and the remaining three due to headache or fatigue. This rate of discontinuation is only slightly higher than other reports of varenicline among individuals without HIV infection, where the range is 9%–11% (Nides et al., 2006; Rigotti et al., 2010). Only two studies to date have reported AEs among HIV-infected individuals on varenicline. In one study of 18 participants, nausea was reported by five individuals and sleep disturbances in six; none had to discontinue medication due to AEs (Tornero & Mafé, 2009). In another study of 36 participants, the most common AEs were nausea (33%) and abnormal dreams (31%); 17% had to discontinue varenicline due to an AE (Cui et al., 2012). Nausea and abnormal/vivid dreams were the most frequently reported side effects for all participants in our study. These side effects are also associated with many ART and non-ART medications that HIV-infected individuals regularly take (Kenedi & Goforth, 2011; Kumarasamy et al., 2011). Of note, there were only minor differences in the reporting of AEs between participants on ART and those not on ART.

The major limitation of this study is the nonrandomized design, limiting our ability to make firm conclusions regarding

Table 3. Inverse Probability of Treatment Weighted Adjusted Odds Ratios and 95% *CI*s for Biochemically Confirmed Abstinence at 3 Months

	OR	95% *CI*
Unadjusted		
NRT	1.0	
Varenicline	2.75	1.57–4.84
Fully adjusted[a]		
NRT	1.0	
Varenicline	2.72	1.50–4.94
Adjusted for confounders[b] only		
NRT	1.0	
Varenicline	2.54	1.43–4.49
Limited to participants without a history of depression or bipolar disorder		
NRT	1.0	
Varenicline	2.93	1.18–7.33
Limited to participants with a BDI < 10		
NRT	1.0	
Varenicline	2.84	1.25–6.46
Limited to participants with a BDI < 20		
NRT	1.0	
Varenicline	1.82	0.99–3.34

Note. BDI = Beck Depression Inventory; MCS = Mental Component Score; NRT = nicotine replacement therapy; PCS = Physical Component Score.

[a]Adjusted for significant variables in Table 1 (employment, income, MCS and PCS from the SF-8, history of depression, history of bipolar disorder, Fagerström Test for Nicotine Dependence score, and decisional balance score).

[b]Employment category and Mental Component Score from the SF-8.

the efficacy of varenicline versus NRT. Nevertheless, our analyses provide preliminary evidence that varenicline may be more effective than NRT as a tobacco dependence treatment aid in the HIV-infected population. We used IPTW as an attempt to account for self-selection bias and compare abstinence rates between the two groups. This IPTW approach removes the selection bias in treatment effect estimation provided all confounders are observed. Unmeasured confounding variables, however, could still introduce bias in the estimation. We attempted to identify and include all relevant pretreatment covariates in our propensity score model in order to minimize unobserved confounders. Also, in our analysis, we observed that the distributions of the estimated propensity score between the varenicline and NRT groups showed some discrepancies. We also examined different subpopulations in which the two groups were more comparable (i.e., no history of depression or bipolar disorder, BDI score less than 20, and a BDI score less than 10) in order to gauge the stability of the observed treatment effect. These analyses confirmed that the *OR*s were consistent. Also, IPTW adjustment may produce results with large variance when the treatment selection is rare for some subpopulation, and consequently, large weights are used in the analysis. We checked the estimated weights to make sure that they are in the reasonable range, and our regression analysis results do not suggest inflated variances.

The strengths of this study include a relatively large sample of HIV-infected individuals receiving varenicline, biochemical confirmation of self-reported abstinence with salivary cotinine and expired air carbon monoxide, and careful prospective tracking of symptoms and side effects related to the pharmacologic intervention.

In conclusion, varenicline, combined with counseling, is a promising approach to treat tobacco dependence in HIV-infected individuals who wish to quit smoking. Future rigorous randomized clinical trials should be conducted to determine the efficacy of varenicline in this at-risk group of smokers. Additionally, future studies should examine factors that are related to adherence to tobacco dependence treatment in this population.

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Declaration of Interests

The authors have no competing interests to report.

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