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Tobacco use and cessation in HIV-infected individuals

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Synopsis

The smoking prevalence estimates among HIV-infected individuals range from 40%-84%; much higher than the overall adult prevalence in the United States. Characteristics that are associated with smokers who are HIV-positive include drug and alcohol abuse, psychiatric comorbidities, and lower education and socioeconomic status. There are important health implications for HIV-infected smokers, including bacterial and *Pneumocystis* pneumonia, tuberculosis, COPD, lung cancer and coronary artery disease. To date, there have been few tobacco dependence treatment trials conducted among HIV-infected smokers. Most have used nicotine replacement therapy but abstinence rates were low. A recent preliminary study found the use of varenicline to be well tolerated and it may increase abstinence rates with HIV-infected individuals. Recommendations for future research include examining underlying factors that contribute to persistent smoking and barriers to abstinence, identifying ways to increase motivation for quit attempts, increasing the number of multi-centered, two-arm tobacco dependence treatment trials, and using highly efficacious first-line pharmacotherapy in tobacco dependence treatment intervention studies. Addressing the above-mentioned research gaps will help to reduce the tobacco-related disease burden of HIV-infected individuals in the future.

Keywords

HIV; tobacco dependence treatment; smoking cessation; tobacco dependence treatment trials

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The prevalence of current smoking among HIV-infected individuals ranges between 40% and 84% across various studies [1-6]. These estimates for the HIV-infected population are several-fold higher than the current 20% overall adult prevalence in the United States [7]. With the aging of the HIV-infected population, such a high smoking prevalence has profound health implications for this group of individuals. In this review we will: 1) identify clinical and sociodemographic characteristics associated with tobacco use in this population; 2) discuss the health risks and consequences (pulmonary and non-pulmonary) of tobacco use that are associated with HIV infection; 3) summarize results of tobacco dependence treatment studies among HIV-infected smokers; 4) discuss strategies for smoking cessation, highlighting key components of the United States Public Health Service (USPHS) *Treating Tobacco Use and Dependence* Guideline; and 5) provide recommendations for future directions of research.

Characteristics of HIV-Infected Smokers

Several studies have examined the characteristics of HIV-infected smokers in the United States. Gritz and colleagues examined 348 low-income HIV-infected individuals who received care at an HIV/AIDS care facility [2] where the smoking prevalence was 47%. In a multivariable model they found that age, white race (versus Hispanic ethnicity), and heavy alcohol drinking were positively associated with current smoking. In another low-income sample of HIV-infected individuals receiving Medicaid benefits, the current smoking prevalence was 66% and smoking was positively related to age, low education, heavy drinking, and illicit substance use [3]. Shuter and colleagues found that almost 50% of HIV-infected smokers reported both current cocaine and marijuana use and 33% reported current heroin use and almost 40% of participants exhibited depressive symptoms and symptoms of anxiety [8].

Webb and colleagues examined predictors of various levels of smoking (light smoking, 1-10 cigarettes per day (CPD); moderate smoking, 11-19 CPD; and heavy smoking, 20 or more CPD) in a sample of 221 HIV-infected individuals recruited from an infectious disease clinic [4]. The prevalence estimates of light, moderate and heavy smoking were 25%, 22%, and 27%, respectively. Heavy drinking was the only consistent variable related to smoking status; however, age, education, income, race, marijuana use, and social support were significantly related to smoking in one or more of the models. In a large (n=1,094) representative sample of HIV-infected individuals in New York state, Tesoriero et al. (2010) reported a smoking prevalence of 59%. Similar to other studies, smoking was positively associated with younger age and a low level of education. In addition, those who self-reported as "other" race/ethnicity, which did not include African American, or Hispanic, were significantly less likely than whites to be current smokers.

At least four studies have examined characteristics related to smoking cessation. Burkhalter and colleagues found that about one-third of smokers had not made a quit attempt since diagnosis and that only 82% of smokers were in either the precontemplation (not interested in trying to quit in the next 6 months) or contemplation (interested in quitting in the next 6 months but not the next 30 days) stage of quitting [3]. Furthermore, only 38% of smokers reported trying any cessation treatment, and less than half reported interest in using a cessation program if available. However, Shuter and colleagues report that 66% of participants were in the preparation (ready to quit in the next 30 days) or action stages of quitting [8].

Tesoriero and colleagues reported that nearly half of the smokers in their sample did not change their level of smoking after receiving their HIV diagnosis, whereas a similar percentage reported smoking more (23%) or smoking less (29%) after diagnosis [1]. Almost

two-thirds (64%) reported a serious quit attempt, defined as not smoking for 24 hours or more in the past year, and 75% indicated that they wanted to quit smoking [1]. And, in another study, 40% of HIV-infected smokers were motivated to quit smoking and 70% reported at least one serious quit attempt in the past [9].

In summary, studies reporting the interest or motivation to quit among HIV-infected smokers are mixed. Furthermore, it is likely that characteristics associated with increased smoking prevalence in the general population play a role in the high smoking rates among HIV-infected individuals [10]. These characteristics may represent important barriers to smoking cessation for HIV-infected smokers and include lower education and socioeconomic status [10], alcohol and drug abuse [2, 3, 8, 11], and psychiatric comorbidities [11].

Cigarette Smoking and Health Implications for the HIV-infected Population Smoking and Pulmonary Complications

Since details of pulmonary complications and their relationship to cigarette smoking are elucidated in chapters reviewing specific complications, we will only briefly summarize the pulmonary effects of smoking in the HIV-infected population. In the current antiretroviral therapy (ART) era, bacterial pneumonia has become the most important pulmonary infectious complication in the HIV-infected population [12]. Bacterial pneumonia is closely linked to cigarette smoking and studies in both the pre-ART and ART eras have demonstrated a greatly increased risk of bacterial pneumonia in HIV-infected smokers [6, 13-15]. Furthermore, evidence now exists that cigarette smoking has become the single most important clinical risk factor for bacterial pneumonia in the HIV-infected population [14, 15]. Smoking effects on lung host defense, including adverse effects on alveolar macrophage function and chemotactic properties, may be an important contributing mechanism [16-18]. Importantly, evidence exists that the risk of bacterial pneumonia in the HIV-infected population is much greater in current than former smokers, underscoring the importance of smoking cessation in this population [19].

Cigarette smoking may also be an important risk factor for other lower respiratory tract infections in the HIV-infected population. For example, Miguez-Burbano and colleagues have demonstrated that smoking may be an important risk factor for *Pneumocystis* pneumonia (PCP) among hospitalized individuals with HIV [20]. Furthermore, in a murine model of PCP, cigarette smoke greatly increases the organism load in the lung [21]. In addition, smoking increases the risk for developing tuberculosis (TB) [22-24] and it has been suggested that HIV combined with high smoking rates will be critical determinants of the global burden of TB in the coming years [25].

Numerous studies have demonstrated that HIV-infected individuals are at increased risk for lung cancer [26-29]. Given the high prevalence of cigarette smoking in this population, it has been difficult to determine whether this risk is primarily related to a higher smoking prevalence [28]. However, recent data suggest that HIV-infection may represent an independent risk factor for lung cancer development [26, 29]. Similarly, data from the pre-ART and ART eras are consistent in demonstrating that HIV is an independent risk factor for COPD [30, 31]. This may involve an interaction of HIV with smoking to increase the susceptibility of COPD in this population [30].

In summary evidence indicates that the lungs of persons infected with HIV are unusually susceptible to the adverse effects of cigarette smoking. These adverse effects include a heightened risk for lower respiratory tract infections, lung cancer and COPD. As such, it can be argued that the single most important issue relevant to the natural history of HIV-related

pulmonary complications today is the exceedingly high prevalence of cigarette smoking in this population.

Smoking and Non-pulmonary Complications

Numerous other complications in the HIV-infected population have been linked to cigarette smoking. These include an increase in perinatal mortality among infants born to HIV infected women [32], periodontal disease [33], accelerated bone loss [34] and a significantly poorer health-related quality of life [35]. Crothers and colleagues in the Veterans Aging cohort study compared HIV infected and non-infected veterans and found that smoking was associated with increased comorbid conditions and mortality in the HIV-infected group [36]. Lifson and colleagues utilizing data from the Strategies for Management of Anti-Retroviral Therapy (SMART) study demonstrated that compared to non-smokers, smokers had a significantly greater risk of all-cause mortality and an increased adjusted hazard ratio for bacterial pneumonia, non-AIDS malignancies and major cardiovascular disease [6].

Comorbid conditions of increasing relevance to the HIV-infected population include the increased risk of atherosclerosis and coronary artery disease [37-43]. Numerous reports have documented that the HIV-infected population has an increased disease burden of atherosclerotic vascular disease including increased coronary calcium scores [37], progression of carotid and coronary artery disease documented by imaging studies [38], and an increased risk of cardiovascular (CV) complications, including acute myocardial infarction [39-41], hospitalization for cardiac ischemia [42], and sudden cardiac death [43].

Notably, studies have demonstrated that even when accounting for demographics and traditional risk factors, HIV-infected individuals have a significantly greater risk for the development of CV disease, suggesting that a number of HIV-specific factors may be involved in the pathogenesis, including adverse effects of certain antiretroviral medications, heightened inflammation and immune dysfunction [44-50].

Given that HIV-infection may independently raise cardiovascular risk, it is imperative that adequate attention to traditional risk factor modification is given [51, 52]. Indeed cigarette smoking has been shown to be a far greater risk factor for cardiovascular morbidity than antiretroviral therapy [53] and smoking has been shown to be the most common traditional cardiovascular risk factor in a cohort of HIV-infected individuals [54]. Furthermore, smoking cessation has been shown to decrease the risk of acute myocardial infarction rates in an HIV-infected population [54]. In fact, Triant has suggested that smoking cessation is the most important specific management principle in modifying cardiovascular risk in the HIV-infected population [55].

Tobacco Dependence Treatment Studies

In the decade after the HIV epidemic emerged in the United States, *JAMA* published a commentary in 1994 noting that stopping smoking may provide short-term health benefits to patients with HIV infection who continue to smoke [56]. Further, the article emphasized to clinicians that tobacco dependence treatment was warranted to reduce the incidence of complications related to smoking in HIV-infected smokers. Shortly afterward, investigators started to design and test tobacco dependence treatment approaches for HIV-infected smokers. To date, only a small number of tobacco dependence treatment trials have been conducted. The first feasibility trial was conducted in 2000 [57]; more recently, findings from larger trials have been published [58-60]. Table 1 provides a chronological listing and summary of published studies that have included a two-group design to examine the feasibility and efficacy of treatment approaches [57-64].

All studies summarized in Table 1 included treatment that consisted of behavioral counseling and pharmacotherapy; all investigations were grounded in evidence-based treatment strategies recommended by the USPHS *Treating Tobacco Use and Dependence* Clinical Practice Guideline [65, 66]. With the exception of the Swiss HIV Cohort investigation [61], all studies included cognitive-behavioral strategies tailored for smokers with HIV infection.

The pharmacotherapeutic agent of choice in all but one of the above studies was nicotine replacement. Concern about drug interactions for HIV-infected smokers receiving antiretroviral therapy may have contributed to the paucity of studies examining the efficacy of other agents. However, Pedrol-Clotet and others [67] conducted a single-arm trial testing the use of bupropion with 21 HIV-positive patients and reported a 38% success rate for more than one year post-treatment. In this trial, no clinically significant drug interactions were noted.

Ferketich and colleagues have recently reported the largest experience of varenicline in HIV-infected smokers, comparing the success rate of NRT and varenicline among 228 HIV-infected smokers involved in a smoking cessation study [60]. Both groups also received a weekly telephone smoking cessation counseling from a nurse specialist. The rates of biochemically confirmed abstinence at 3 months were higher in the varenicline group compared to the NRT group (25.6% versus 11.8%, respectively). Although the design was non-randomized, inverse probability of treatment weighted logistic regression modeling was used to compare the two groups and the odds ratio of successful abstinence was significantly greater with varenicline (adjusted odds ratio = 2.72; 95% CI = 1.50-4.94).

Importantly, varenicline was reasonably well tolerated in the HIV population with the most common side effects being nausea (32.2%), abnormal dreams (22.9%), and difficulty sleeping (17.8%). Fourteen percent had to discontinue therapy because of adverse effects. Of note, no coronary events were observed. One patient reported suicidal ideation but the symptoms resolved after stopping varenicline. There were no differences in the side effect profile among those on antiretroviral therapy (ART) compared to those not on ART [60].

Recommendations for smoking cessation for the HIV-infected smoker

In general, the approach for smoking cessation with an HIV-infected population should follow the USPHS *Treating Tobacco Use and Dependence* Guideline. The guideline, now in its third update, is comprised of the systematic review of approximately 8,700 research articles that address the assessment and treatment recommendations for tobacco dependence. Clinicians can make a difference when providing tobacco dependence treatment even when it is minimal (e.g., less than 3 minutes). When patients are not willing to make a quit attempt, clinician-delivered brief interventions can increase motivation and the likelihood of future quit attempts. Furthermore, there is evidence that smokers who receive advice and assistance on quitting from their clinician have greater satisfaction with their health care [68-70]. The guideline also provides key strategies and recommendations that are designed to assist the clinician in delivering evidence-based tobacco dependence treatment. Table 2 summarizes key recommendations.

The USPHS guideline recommendations are based upon research that included a wide-range of populations. Clearly, the HIV-infected population is a special population with substantial barriers to smoking abstinence. Nevertheless, the potential benefits to smoking cessation are considerable given the increased risk of numerous complications, including bacterial pneumonia, PCP, TB, COPD, lung cancer and coronary artery disease. Clinicians should be aggressive in using available resources, including pharmacologic management and counseling to address tobacco dependence in this population. As noted above, preliminary

evidence suggests that varenicline has an acceptable safety profile and may be more effective than NRT for this population.

Recommendations for Future Directions of Research

Smoking prevalence remains high among HIV-infected individuals, despite important disease-related consequences of continued smoking. The success of ART has resulted in increased survival for individuals living with HIV [71]. Thus, careful examination and efficacy testing of successful tobacco dependence treatment strategies in the general population are important in this special population of smokers. Recommendations for future research among HIV-infected smokers include: 1) examining the underlying factors that contribute to persistent smoking as well as barriers to abstinence; 2) identifying ways to increase motivation for quit attempts; 3) increasing the number of two-arm tobacco dependence treatment trials that are multicentered; and 4) using highly efficacious first-line pharmacotherapy in tobacco dependence treatment intervention studies. While continued implementation of clinician and system-level tobacco dependence treatment interventions for HIV-infected individuals is warranted, addressing the above-mentioned research gaps could help to substantially reduce smoking-related comorbidities in the future.

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Key points

- Smoking prevalence among HIV-infected individuals remains much higher than the U.S. adult smoking prevalence.
- HIV-infected smokers have an increased risk for developing numerous health-related complications such as bacterial pneumonia, pneumocystis pneumonia, tuberculosis, lung cancer, COPD, and cardiovascular disease.
- To date, a small number of tobacco dependence treatment trials among HIV-infected smokers have been conducted, most have used nicotine replacement therapy with cognitive-behavioral therapy; abstinence rates were low.
- A recent preliminary study found the use of varenicline to be well tolerated and it may increase abstinence rates with HIV-infected individuals.
- Clinicians should be aggressive in using available resources (i.e., USPHS Treating Tobacco Use and Dependence Guideline), including pharmacologic management and counseling to address tobacco dependence in this population.
- Recommendations for future research include examining underlying factors that contribute to persistent smoking and barriers to abstinence, identifying ways to increase motivation for quit attempts and increasing the number of multi-centered, two-arm tobacco dependence treatment trials.

Table 1

Published Controlled Studies of Tobacco Dependence Treatment Trials in HIV-infected Smokers.

Study	Sample	Intervention	Abstinence Outcomes	Comments
Wewers et al. 2000	AIDS Clinical Trials Unit patients Intervention n=8 100% male Mean age=42 CPD=27 Control n=7 100% male Mean age=37 CPD=28	Intervention: Eight weeks of weekly peer support telephone counseling + NRT Control: Written self-help materials	Intervention: 62.5% at 8 wk 50% at 8 mo Control: 0% at 8 wk 0% at 8 mo	Intent-to-treat analysis with randomization; biochemical confirmation of abstinence; small sample size
Elzi et al. 2006	Swiss HIV Cohort Study Intervention n=34 82% male Median age=43 CPD=28 Control n=383 67% male Median age=40 CPD=21	Intervention: Twelve months of counseling + NRT Control: No treatment	Intervention: 38% at 12 mo Control: 7% at 12 mo	Intent-to-treat analysis without randomization; self-reported abstinence; pilot study
Lloyd-Richardson et al. 2009	Immunology Clinic patients Intervention n=232 67.7% male Mean age=41.2 CPD=18.3 Control n=212 58.5% male Mean age=42.9 CPD=18.2	Intervention: Four sessions of tailored motivational counseling + quit day counseling call + NRT for those willing to quit Control: Two counseling sessions with health educator + NRT for those willing to quit	Intervention: 12% at 2 mo 9% at 4 mo 9% at 6 mo Control: 13% at 2 mo 10% at 4 mo 10% at 6 mo	Intent-to-treat analysis with randomization; biochemical confirmation of abstinence; only those ready to quit were offered NRT
Ingersoll et al. 2009	Infectious Disease Clinic patients Whole sample n=40 Mean age=42 CPD=17.3	Intervention: Single motivational interviewing session + NRT (n=22) Control: Written materials + NRT (n=18)	No differences between groups; 22.5% of whole sample abstinent at 3 mo	Intent-to-treat analysis with randomization; biochemical confirmation of abstinence; small sample size
Vidrine et al. 2012	Primary Care/HIV-Care Clinic Intervention n=236 71.9% male Mean age=43.9 CPD=18.6 Control n=238 68.9% male Mean age=45.7 CPD=19.7	Intervention: Physician advice to quit + setting a quit date+ NRT + personalized quit plan and written materials + 2 month proactive cell phone counseling + hotline access Control: Physician advice to quit + setting a quit date + personalized quit plan and written materials + NRT	Intervention: 11.9% 7 day point prevalence at 3 mo 8.9% continuous at 3 mo Control: 3.4% 7 day point prevalence at 3 mo 2.1% continuous at 3 mo	Intent-to-treat analysis with randomization; biochemical confirmation of abstinence; continuation of Vidrine et al. 2006 pilot study with updated results at 3 months postintervention
Moadel et al. 2012	Infectious Disease Clinic Intervention n=73 49.3% male Mean age=49.2 CPD=12.8	Intervention: Eight session group intervention; offer of 3 month supply of NRT	Intervention: 19.2% at 3 mo	Intent-to-treat analysis with biochemical confirmation of abstinence; small sample size

Study	Sample	Intervention	Abstinence Outcomes	Comments
Ferketich et al. 2012	Infectious Disease Clinic Control n=72 48.6% male Mean age=47.9 CPD=11.1 Intervention n=228 85.1% male Mean age=42.7 CPD=19.8	Control: Physician advice to quit; written materials; offer of 3 month supply of NRT Intervention: Twelve weeks of nurse counseling + varenicline or NRT	Control: 9.7% at 3 mo Varenicline: 25.6% at 3 mo NRT: 11.8% at 3 mo	Intent-to-treat analysis without biochemical confirmation of abstinence

CPD= cigarettes per day; NRT=nicotine replacement therapy

Table 2USPHS Recommendations for Treating Tobacco Use and Dependence ^{*}.

USPHS Components	Recommendation
Tobacco dependence is a chronic disease	<ul style="list-style-type: none"> • Requires repeated intervention • Often multiple quit attempts
The 5 A's model (ask, advise, assess, assist, arrange)	<ul style="list-style-type: none"> • Clinicians should offer 5 A's to <i>every</i> patient at <i>each</i> visit • Systematically, ask tobacco use status: <ul style="list-style-type: none"> – identify all users at each visit – document on each user at each visit – encourage every willing patient to quit • In a clear, strong, personalized message, advise all tobacco users to quit • For current tobacco users, assess willingness to make a quit attempt <ul style="list-style-type: none"> – For patients willing to make a quit attempt, – assist with a quit plan o For patients unwilling to quit, provide – interventions to increase quit attempts in the future – For recent quitters, provide relapse prevention • All patients receiving previous A's, arrange for follow up
Individual, group, and telephone counseling are effective	<ul style="list-style-type: none"> • Effectiveness increases with treatment intensity • Most effective components: <ul style="list-style-type: none"> – problem solving and skills training – social support
7 first-line medications that increase long-term smoking abstinence rates	<ul style="list-style-type: none"> • bupropion (Zyban) • nicotine gum • nicotine inhaler • nicotine lozenge • nicotine nasal spray • nicotine patch • varenicline (Chantix)
Counseling and medication	<ul style="list-style-type: none"> • Effective when used alone, more effective when used together • Clinically and highly cost effective
Telephone quitline counseling	<ul style="list-style-type: none"> • Effective, particularly with diverse populations

^{*} Information in this table from the USPHS *Treating Tobacco Use and Dependence* Guideline [65]