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Tobacco Use, Use Disorders, and Smoking Cessation Interventions in Persons Living with HIV

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Abstract

Cigarette smoking remains highly prevalent among persons living with HIV, estimated to be 40–75%, and is significantly higher than what is observed among the general population. Health risks of smoking in this population include cardiovascular disease; bacterial pneumonia, chronic obstructive pulmonary disease, and other respiratory conditions; lung cancer and other malignancies; adverse cognitive and neurological outcomes; low birth weight, preterm birth, and small for gestational age infants; and overall mortality. Smokers with HIV now lose more life years to smoking than they do to the HIV virus itself. A majority of smokers living with HIV report being interested in cessation and a significant proportion have made recent quit attempts. There is a general paucity of large randomized controlled trials of smoking cessation interventions among smokers living with HIV, and among the existing research, cessation rates are suboptimal. Greater resources and effort should be allocated to developing and evaluating cessation treatment modalities for smokers living with HIV. Efforts to individualize and tailor treatments to address specific client needs and comorbidities are warranted. HIV care providers and other health professionals can play a key role in improving health among this population by regularly screening for smoking and promoting cessation.

Keywords

HIV; nicotine; smoking; dependence; cessation

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Compliance with Ethics Guidelines

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Introduction

Until recently, little research focused on issues related to cigarette smoking among persons living with human immunodeficiency virus (HIV; PLWH). However, with the development and utilization of highly effective medical treatments for HIV infection, PLWH are experiencing increased life expectancies. According to a recent review, individuals with newly-diagnosed HIV, when diagnosed early and engaged in care, have similar life expectancies as their uninfected counterparts [1]. Importantly, numerous studies have demonstrated that cigarette smoking in PLWH increases the incidence of not only AIDS-related and non-AIDS-related illnesses, and also decreases overall survival [2–4]. An increased focus on modifiable risk factors, such as cigarette smoking, will potentially improve quality of life and reduce morbidity and mortality among PLWH.

The purpose of this review is to bring readers up to date on issues concerning the intersection of HIV and cigarette smoking. Thus, this review presents the most recent available research findings, with a focus on findings from the past five years. We discuss the prevalence of smoking and nicotine dependence among PLWH, smoking-related morbidity and mortality, and existing smoking cessation research among this group. Lastly, we explore future directions for research.

Prevalence of Smoking and Nicotine Dependence

Despite public health successes in reducing the prevalence of cigarette smoking in general population in the United States from approximately 42.4% to 17.8% since 1965 [5,6], the prevalence of smoking remains disproportionately high among certain subgroups of the population. For instance, among PLWH, the prevalence of smoking is estimated to be 40–75% in most studies [7–13]. Additionally, though largely understudied to date, polytobacco use is common among smokers living with HIV; in fact, one study [14] found that approximately 21.6% of current smokers living with HIV used other tobacco products concurrently with cigarettes, most commonly cigars. Furthermore, the majority (54.8%–65.3%) of smokers living with HIV have been found to have moderate to high levels of nicotine dependence [9, 10, 13, 15] according to the Fagerström Test for Nicotine Dependence [16] and Heaviness of Smoking Index [17].

Morbidity and mortality among smokers living with HIV

Smoking and Cardiovascular Disease

Cigarette smoking has been consistently identified as a risk factor for cardiovascular disease (CVD), both among the general population and among PLWH [18]. Freiberg and colleagues [19] found that, among veterans living with HIV, current smoking was significantly associated with CVD. Additionally, when comparing veterans with and without HIV, the authors identified a significant interaction between HIV status and smoking status such that prevalent CVD was more pronounced among HIV-infected individuals who were current smokers. Conversely, research has also shown that smoking cessation is associated with improved cardiovascular health: among participants in the Data Collection on Adverse

Events of Anti-HIV Drugs (D:A:D) study, the risk of CVD events in patients with HIV declined over time in those who stopped smoking [20].

Smoking and Respiratory Conditions

The literature demonstrates that cigarette smoking among PLWH is a risk factor for bacterial pneumonia, but not the AIDS-defining *Pneumocystis pneumonia* (PCP) [21]. Cui and colleagues [22] found that the greater proportion of chronic obstructive pulmonary disease (COPD) cases among PLWH compared with uninfected controls was likely due to the increased prevalence of cigarette smoking among the population. Additionally, in an investigation of COPD among PLWH, current cigarette smoking was a significant predictor of both increased respiratory symptoms and COPD [23]. Moreover, smoking cessation appears to reduce the risk of bacterial pneumonia [21].

Smoking and Malignancies

Among the general population, smoking increases the risk for many types of cancers, including cancers of the lung, esophagus, larynx, mouth, throat, bladder, and cervix [24]. Among PLWH, the risk for cancer and malignancies is also elevated and research indicates that the risk of cancer is increased approximately two-fold among PLWH who are engaged in long-term care as compared to population controls [8]. Additionally, smoking-related cancers have been found to be three times more likely among PLWH, when compared with general population controls [8]. In the absence of smoking, this increased risk has been shown to be confined to cancers related to viral infections (e.g., Kaposi sarcoma, cervical cancer), whereas the risk of non-viral-infection-related cancers (e.g., lung cancer, bone cancer) is not elevated and does not seem to be associated with immune deficiency [8]. In the United States, the number of AIDS-related cancers decreased greater than three-fold between 1991–2005, while non-AIDS-related cancers increased approximately threefold. Specifically, significant increases in the number of lung cancer cases were noted in this period [25]. Data collected during the years 2000, 2005, and 2010 in France revealed strikingly similar findings [26]. These findings appear to indicate that cigarette smoking may be an especially pertinent risk factor for certain types of cancers among PLWH.

Lung cancer is among the most common of the non-AIDS-related cancers that occur among PLWH, and in the Swiss HIV Cohort Study the risk for lung cancer was three times higher than what was observed in the general population [27]. Clifford and colleagues [28] also showed that lung cancer risk was strongly associated with current smoking, and that former smokers were at significantly lower risk than current smokers. In the Swiss HIV Cohort Study, between 1995 and 2011, cancers related to smoking accounted for 23% of all cancers among PLWH [8]. Though some research has shown a strong relationship between declining CD4+ cell counts and the risk for lung cancer [29], others [28] have found no evidence of associations between lung cancer and immunodeficiency, adding further impetus to the need for effective smoking cessation strategies in PLWH.

Smoking and Cognitive/Neurological Outcomes

Bryant and colleagues [30] found that, among PLWH, current smoking status was negatively associated with a variety of neurocognitive measures: learning and memory, as

measured by the Hopkins Verbal Learning Test-Revised [31] and Brief Visuospatial Memory Test-Revised global scores [32]; as well as global cognitive functioning, which was measured as a composite score of all included neurocognitive measures. Additionally, some evidence from this work seemed to indicate that these deficits were more pronounced among men, as compared to women. Maria Jose and colleagues [33] observed that smokers living with HIV had elevated plasma levels of brain-derived neurotrophic factor (BDNF), which plays a prominent role in protecting the brain from insults. The alterations in BDNF levels were most prominent among individuals who smoked menthol cigarettes and had higher nicotine dependence scores. The authors hypothesized that these increased levels of BDNF, rather than indicating a beneficial effect, were the central nervous system's way of compensating for the chronic neuronal damage that was induced by exposure to nicotine via cigarette smoking. Additionally, recent research conducted in vitro showed that nicotine and HIV appear to work synergistically to regulate synaptic plasticity gene expression and spine density of neuronal cells, which may contribute to the increased risk of HIV-associated neurocognitive disorder (HAND) that is seen in some smokers living with HIV [34].

Smoking and Pregnancy/Birth Outcomes

Data in PLWH that examines the effect of smoking on pregnancy and birth outcomes is scarce. However, one recent study [35] showed that maternal HIV status and cigarette smoking were independent predictors of low birth weight, preterm birth, and small for gestational age infants. Additionally, they observed an interaction between maternal HIV and smoking, such that mothers who were HIV positive and smoked during pregnancy experienced the greatest risks for their babies being small for gestational age, preterm birth, and having low birth weight.

Smoking and Death

Smoking is directly related to approximately 480,000 deaths in the United States annually in the general population [6]. Not surprisingly, among PLWH, research has indicated that cigarette smoking is associated with an increased likelihood of death, and several studies have found that PWLH smokers have nearly double the risk of all-cause mortality compared to non-smokers with HIV [3, 11]. Smokers with HIV had higher mortality risk ratios from CVD (6.28) and non-AIDS malignancies (2.67) compared with non-smokers with HIV [3]. Futhermore, in a Danish population-based HIV cohort study, Helleberg and colleagues [2] concluded that smokers living with HIV lost more life-years to smoking than to HIV itself. Among 35-year-old men living with HIV, it was estimated that 5.9 years of life were lost due to HIV infection while 7.9 years were estimated to be lost from cigarette smoking [3]. Moreover, it is estimated that currently 24% of deaths among PLWH on highly active antiretroviral therapy (HAART) are attributable to tobacco use [12].

Smoking Cessation

Interest in cessation

Recent studies indicate that many smokers living with HIV are interested in smoking cessation. In one study among HIV-infected smokers [36], the majority of participants (97%) indicated interest in quitting, though 42% indicated that they planned to quit within

the next year, while 55% intended to quit but had no plan to do so. Among two samples of urban HIV-infected smokers living in the United States, approximately three-quarters of participants reported interest in quitting [13, 38], and this intention was associated with both older age and lifetime use of nicotine replacement therapy (NRT) or other medications for smoking cessation.

In addition to general interest in cessation, interest in specific cessation modalities has been explored among smokers living with HIV. Among current and former persons who inject drugs (PWID), the majority (>70%) of smokers interested in quitting reported interest in cessation modalities that included a social component, such as group cessation therapy, or cessation therapy with a friend, family member, or significant other [38]. However, interest in pharmacological cessation therapy among this sample was low: 39.7% reported interest in using NRT, while only 32.4% reported interest in using oral medications for cessation (i.e., varenicline or bupropion). Similarly, interest in oral medications for smoking cessation was low (40.7%) among smokers living with HIV in another study [39]; however, interest in using NRT in this sample was somewhat higher (64.4%). Approximately half of participants in the study conducted by Shuter and colleagues [38] also indicated interest in individual counseling (64.4%), group counseling (55.9%), telephone quitlines (52.5%), and couples smoking cessation therapy (49.2%). The relatively low reported interest in NRT or oral medications for cessation may be explained, at least in part, by the cost of these cessation therapies. Shapiro and colleagues [36] found that, when counseled about NRT and cessation medications that smokers could receive at no cost, 91% of study participants reported interest. Conversely, when asked about NRT and medications that smokers would have to pay for, only 28% and 26% reported interest in NRT and cessation medications, respectively. Interest in talking with a doctor or nurse about cessation (83%), participating in a support group (85%), or participating in a support group restricted to PLWH (87%) were highly endorsed [36].

Quit attempts

Among smokers living with HIV, research has indicated that approximately 45–64% have made a quit attempt within the past year [13, 15, 37]. McQueen and colleagues [15] found that 21.9% of participants recruited from a university-based outpatient HIV clinic reported lifetime use of counseling methods (e.g., individual counseling, support groups, quitlines). Lifetime use of any oral medications for cessation was reported by 43.8% of the sample [15]. Among a sample of current and former injection drug users living with HIV, 59% reported lifetime use of pharmacotherapies [38], and closer examination revealed that 57.6% of smokers had utilized NRT in their lifetime, while only 8.6% had utilized oral medications (e.g., varenicline or bupropion).

Cessation interventions among PLWH

Despite the fact that cigarette smoking is highly prevalent among PLWH, contributes significantly to morbidity and mortality in this population, and that a large proportion of smokers report interest in quitting, relatively little research has been conducted to evaluate smoking cessation interventions among this group. A summary of the 10 studies published during the past 5 years is presented in Table 1. Studies of interventions were gathered from

PubMed and Google Scholar using combinations of the search terms “HIV”, “AIDS”, “smoking”, and “smoking cessation”.

Non-pharmacological interventions—In recent years, several trials have been published to explore the use of non-pharmacological interventions for smoking cessation among PLWH. While all have been randomized controlled trials, two trials have focused specifically on the use of technology to promote smoking cessation. Vidrine and colleagues [40] evaluated the efficacy of a cell phone counseling intervention, and compared with standard care, there was a significant difference in 7-day point prevalence abstinence. At 3-months, 8.9% of participants in the treatment condition were abstinent compared with 2.9% in the control condition. Shuter and colleagues [41] investigated the use of a web-based treatment tailored to PLWH compared to standard care; though group differences were not significant, the overall prevalence of abstinence at 3-months was 7.2%.

Among the non-technology-based smoking cessation interventions, Moadel and colleagues [42] found no significant differences in 7-day point prevalence abstinence at 3-months when comparing a tailored group intervention to standard care (14.5% overall). Manuel and colleagues [43] used a motivational interviewing-based intervention, compared to prescribed advice (i.e., literature about cessation and brief discussion with therapist). Though no significant differences in abstinence were found between groups at 1-month, individuals in the motivational interviewing group reported a significant decrease in cigarettes smoked per day compared to the prescribed advice group.

Pharmacological interventions—Some smoking cessation trials for smokers living with HIV have utilized pharmacological methods. These studies have yielded mixed findings. Much of this work is limited in that many of the trials have been non-randomized studies, have had small sample sizes, or have not utilized a control group. One notable exception is a study conducted by Humfleet and colleagues [44] in which they conducted a three-arm randomized trial evaluating the efficacy of: 1) six sessions of individual counseling plus NRT, 2) computer-based internet treatment (i.e., website based intervention modeled on the counseling intervention content) plus NRT, and, 3) self-help (i.e., brief meeting with research staff during which they received a quick reference guide on cessation) plus NRT. At 12-months of follow up, 7-day point prevalence abstinence was estimated to be 15%–29%, though differences between the treatment groups were not significant. Conversely, the self-reported number of cigarettes smoked during the past 24 hours prior to study visits declined significantly over time across all conditions.

Among the non-randomized pharmacological smoking cessation interventions, Matthews and colleagues [45] published preliminary findings from a tailored treatment for HIV-infected African American smokers in which participants were enrolled in a group-based treatment combined with the nicotine patch. Abstinence rates at 3 months were low (10%) among those who had completed at least 3 sessions, and the investigators speculated that abstinence might have been impacted by low adherence to nicotine patch treatment and low group therapy attendance rates. Two additional studies focused on the use of varenicline as a smoking cessation aid for smokers living with HIV. In 2011, Cui and colleagues [46] published an open-label pilot study in which 36 participants were given varenicline and

evaluated for 3 months; at follow-up, the serum cotinine-verified 4-week continuous abstinence rate for weeks 9–12 was 42%. Additional endpoints of interest indicated that varenicline was safe, with no adverse effects noted. Furthermore, Ferketich and colleagues [47] reported preliminary findings from a trial examining the efficacy of a 12-week telephone counseling (TC) intervention plus either varenicline or NRT. At 3 months, 7-day point prevalence abstinence was assessed and individuals in the TC plus varenicline group reported greater abstinence than those in the TC plus NRT group (25.6% vs. 11.8%). Moreover, similar to Cui and colleagues [46], the safety profile of varenicline among smokers living with HIV was evaluated, and appeared to be similar to that of smokers without HIV [47].

Interventions with non-abstinence-related smoking outcomes

Two recent trials by Cropsey and colleagues [48, 49] examined non-abstinence-related smoking primary endpoints following an intervention. In a pilot study [48], smokers with HIV were randomized to receive 8-weeks of combination NRT (i.e., 14 mg nicotine patches and 2 mg nicotine lozenges) plus brief counseling (i.e., Screening, Brief Intervention, and Referral for Treatment [SBIRT]), or NRT plus usual care. After 8 weeks of follow up, participants in the NRT plus SBIRT group reported significantly decreased CPD, nicotine dependence as measured by the Fagerström Test for Nicotine Dependence, smoking urge, and smoking withdrawal symptoms, even among smokers who reported not being ready to quit within the next 6 months. Most recently, Cropsey and colleagues [49] tested an algorithm-based model of smoking cessation, in which participants were randomized to receive 12-weeks of pharmacotherapy for cessation (i.e., varenicline, bupropion, nicotine patch, nicotine lozenge, or combination NRT) as determined by an algorithm, as compared to those receiving treatment as usual. Outcomes of the algorithm were based on a variety of factors including: 1) current interest in quitting; 2) willingness/ability to take medications; 3) contraindications for cessation treatments (i.e., suicidal ideation, pregnancy, other medications); 4) prior history with various cessation treatments. Outcomes of participants randomized to the algorithm condition were compared to outcomes of those receiving usual care. At the end of follow-up, smokers prescribed medications via the algorithm reported more quit attempts and greater reduction in smoking, indicating a potential utility of algorithm-based proactive models of smoking cessation in clinical settings.

Conclusion

Cigarette smoking and nicotine dependence are highly prevalent among PLWH, and are often reported as two- to three times higher when compared with the general population. Importantly, cigarette smoking is related to increased morbidity and mortality in PLWH, with approximately one-quarter of the deaths among PLWH in the HAART era attributed to tobacco use. Recent research has shown, however, that developing effective smoking cessation strategies for PLWH is imperative, as they have the potential to decrease the risk of many smoking-related health conditions that are common among PLWH.

The majority of smokers living with HIV report being interested in cessation, though often they are not interested in quitting in the next 30-day period. In recent years, smoking

cessation interventions studies among PLWH have begun to flourish. Many of these trials are pilot or feasibility studies and, as such, often do not utilize random assignment, and have small sample sizes. Nevertheless, these studies demonstrate that a variety of cessation modalities targeted at smokers living with HIV, including pharmacologic and non-pharmacologic interventions, have yielded disappointing outcomes with low abstinence rates. Some studies have shown promise by identifying treatment modalities that aid in reductions in other non-cessation smoking-related endpoints, including CPD, nicotine dependence levels, and nicotine withdrawal symptoms.

Given the relative paucity of large, randomized controlled trials, as well as the suboptimal cessation rates that have been thus far observed in the extant research among smokers living with HIV, additional research is needed to identify effective cessation strategies that lead to sustained abstinence in this population of cigarette smokers. Greater resources and effort need to be allocated to developing and evaluating behavioral, pharmacologic, and combined cessation treatment modalities for smokers living with HIV. For instance, contingency management has been found to increase smoking cessation among other vulnerable populations [50, 51], and may serve as an effective intervention alone or as an adjunct to pharmacological interventions among PLWH. Additionally, efforts to individualize and tailor treatments to address specific client needs and comorbidities are warranted. Moreover, clinical investigations that examine whether smoking cessation improves HIV biomarkers (i.e., viral load) and related comorbid health conditions (i.e., lung function, respiratory conditions), or risk for the development of comorbid conditions, should be considered. Such evidence has the potential to increase the perceived benefit of smoking cessation among this population. Given that a large proportion of this population is in regular contact with the medical system during the course of treatment for HIV, HIV clinicians and other healthcare providers have the potential to play a pivotal role in increasing cessation among this population by regularly screening for tobacco use and promoting smoking cessation programs.

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Table 1

Summary of studies investigating smoking cessation among samples of persons living with HIV

Study	R/NR[a]	Intervention(s)	*n*	Follow-up	Outcome	Findings
Cropsey, 2015	R	Algorithm-assigned 12-week pharmacotherapy (patch (38%), varenicline (36%), patch + lozenge (12%), bupropion (10%), lozenge (4%))-based algorithm; TAU[b]	100; 356	12 weeks	CPD[c] reduction Number of 24-hour quit attempts	Algorithm group had greater reduction in CPD vs. TAU (10 vs. 6; p=0.021) Greater proportion of algorithm group made 24-hour quit attempts vs. TAU (50% vs. 38%; p=0.006)
Shuter, 2014	R	Positively Smoke Free on the Web (PSFW; 8-session, 7-week targeted tobacco treatment program for persons living with HIV); Standard care (brief advice to quit and self-help brochure)	69; 69	3 months	7-day point prevalence abstinence (BCV[d])	7.2% overall; ns group differences
Cropsey, 2013	R	NRT[e] + SBIRT; NRT + usual care	23; 17	8 weeks	CPD reduction Nicotine dependence Smoking urge Withdrawal symptoms	SBIRT group had greater decrease in CPD (p=0.13), dependence (p=0.01), smoking urge (p=0.01), and withdrawal scores (p=0.13)
Ferketich, 2013	NR	Varenicline + telephone counseling + 1 session behavioral intervention; NRT (21 mg patch plus 4 mg ad lib gum) + telephone counseling + 1 session behavioral intervention	118; 110	3 months	7-day point prevalence abstinence (BCV) Safety	25.6% vs. 11.8% (p<0.05) Safety profile of varenicline among HIV-positive smokers looks similar to that of HIV-negative smokers
Humfleet, 2013	R	Counseling + NRT; computer-based Internet treatment + NRT; self-help + NRT	69; 58; 82	12 months	7-day abstinence (BCV) Cigarettes smoked in past 24 hours	15%–29%; ns[f] group differences Number of cigarettes smoked in past 24 hours declined significantly over time (p<0.001); ns group differences
Manuel, 2013	R	MI[g]; Prescribed advice	15; 15	1 month	7-day point prevalence abstinence (BCV) CPD	ns group difference for abstinence MI group had significant decrease in CPD (p<0.05)
Matthews, 2013	NR	Group-based treatment + patch	23	3 months	7-day point prevalence abstinence (BCV)	10% when at least 3 sessions completed
Moadel, 2012	R	Group treatment; standard care	73; 72	3 months	7-day point prevalence abstinence (BCV)	14.5% overall; ns group difference
Vidrine, 2012	R	Cell phone counseling; standard care	236; 238	3 months	7-day point prevalence abstinence (BCV)	8.9% vs. 2.9% (p=0.005)
Cui, 2011	NR	Varenicline	36	3 months	4-week continuous abstinence (BCV)	42%

[a] R=randomized; NR=non-randomized

[b] TAU=treatment as usual

[c] CPD=cigarettes per day

[d] BCV=biochemically verified

[e] NRT=nicotine replacement therapy

[f] ns=non significant

[g] MI=motivational interviewing