

Smoking and HIV: Prevalence, Health Risks, and Cessation Strategies

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Abstract Health hazards due to smoking may undermine benefits of HIV treatment on morbidity and mortality. Over 40 % of persons with HIV are current smokers. Health risks of smoking include increases in some HIV-associated infections, cardiovascular disease, some cancers, bacterial pneumonia and other lung disease, and overall mortality. Proven strategies for smoking cessation include various counseling approaches, nicotine replacement therapy and other pharmacotherapy; approaches may need to be individualized to address specific client needs and comorbidities. HIV clinicians and other service providers can have an influential role in screening their patients for smoking and promoting cessation programs to improve health.

Keywords HIV · Smoking · Nicotine · Cardiovascular disease · Cancer

Introduction

As life expectancy in HIV-infected patients continues to improve due to advances in HIV treatment, including highly active antiretroviral therapy (HAART), greater attention is focusing on modifiable risk factors that may further reduce morbidity and mortality in persons living with HIV (PLWH). One of the most important of these risk factors is tobacco smoking. Causes of illness in PLWH include AIDS-

related and serious non-AIDS illnesses, and smoking may increase the occurrence of both of these, as well as impact overall survival. To help current smokers quit, a variety of behavioral and pharmacological strategies have been evaluated and proven beneficial.

This review discusses the prevalence of smoking in PLWH, and the multiple diseases and health complications that smoking can cause in this population. Given the significant rates of smoking in this population, we then discuss strategies for smoking cessation that clinicians and other health professionals can use or promote for their patient population.

Prevalence of Smoking in Persons with HIV

Although approximately 19 % of U.S. adults are current cigarette smokers [1], the prevalence of current smoking among HIV-infected persons is considerably higher, with many recent studies reporting rates of over 40 % [2, 3, 4]. High rates of smoking are also reported among PLWH in Europe and Australia [5, 6, 7]. HIV-infected smokers have been reported as using an average of 16–23 cigarettes per day [5, 8], indicating high levels of nicotine dependence. In one study of low-income women on HIV therapy, 56 % reported current smoking, with estimates that a typical participant had smoked more than a pack a day for 50 % of her life since adolescence [9].

Data are much more limited on smoking among PLWH in resource-limited settings. The World Health Organization estimates that nearly 80 % of the more than one billion smokers worldwide live in low-income and middle-income countries, where the burden of tobacco-related illness and death is heaviest [10]; these are also many countries in which the HIV epidemic is most intense [11]. For example, in India with over

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two million people living with HIV, studies report almost a third of males in the general population are smokers [12]. Among PLWH in the Kathmandu Valley of Nepal, 47 % were current smokers [13]. In a survey of HIV patients in Nigeria, the prevalence of current cigarette smoking was 22 % [14]. Among adolescents age 13–15 years from two countries with significant HIV epidemics, 17 % of Ugandan and 13 % of Kenyan youth were currently using tobacco [15].

Health Risks of Smoking

Smoking and HIV-Associated Infections

Cigarette smoking has been associated with a variety of HIV-associated infections. In the oropharynx, smoking is associated with an increased risk of oral candidiasis [16–18]. Possible pathogenic mechanisms for this association include mucosal injury and epithelial alterations from smoke that facilitate *Candida* colonization, factors in cigarette smoke that directly promote candida growth, suppression of local or systemic immunologic defenses against *Candida*, or other mechanisms [18]. In another study, current smokers were 2.5 times more likely than non-smokers to develop esophageal candidiasis [2•].

The lungs of HIV-infected persons may be especially susceptible to the deleterious effects of cigarette smoke [19]. HIV infection may increase susceptibility to chronic obstructive pulmonary disease [20] (compromising underlying lung function), and smoking is associated with a variety of pulmonary infections. HIV-infected patients are more likely to develop recurrent bacterial pneumonia, and studies of PLWH have identified a clear association between bacterial pneumonia and smoking [2•, 21, 22]. Among HIV-infected patients enrolled in the Strategies for Management of Antiretroviral Therapy (SMART) study, compared to non-smokers, current smoking was associated with an over two-fold risk of bacterial pneumonia [2•]. Some studies of HIV-infected patients have also identified smoking as a risk factor for *Pneumocystis* pneumonia, an AIDS-defining pulmonary infection [21].

Globally, a major cause of morbidity and mortality in PLWH is pulmonary tuberculosis (TB). The risk of developing TB is over 20 times greater in PLWH than among those who do not have HIV infection, and TB is responsible for more than a quarter of deaths in people living with HIV, especially in developing countries [23]. Smoking has been demonstrated to be significant risk factor for TB [24–26]. In one meta-analysis, smoking was associated with a 1.7 increased risk for TB infection, and a 2.3–2.7 increased risk for developing TB disease [25]. Therefore, tobacco smoking, HIV and TB can synergistically interact in a very detrimental fashion [26].

Smoking and Cardiovascular Disease

In addition to AIDS-defining conditions, a number of studies indicate that HIV-infected patients, especially those with untreated HIV infection, may be at increased risk for development of non-AIDS-defining diseases including cardiovascular disease (CVD) and malignancy [27]. Smoking is a well-recognized risk factor in the general population for CVD complications, including coronary artery disease, myocardial infarction and stroke [28], and studies of PLWH also support this risk [2•, 7•, 29, 30]. Among HIV-positive patients in the SMART study, current smokers had a two-fold risk of major CVD events compared to non-smokers [2•]. In another HIV cohort study, among participants who had no previous CVD prior to enrollment, the risk of CVD in those who stopped smoking during follow-up (compared to never smokers) decreased from 2.3 within the first year of stopping to 1.5 after >3 years [7•]. In another study evaluating carotid artery intima medial thickness, in multivariate analysis HIV and smoking were both independent risk factors for greater thickness [31], indicating that these two risk factors may both independently contribute to pre-clinical atherosclerosis and subsequent CVD events.

Smoking and Malignancies

In the general population, smoking increases the risk for many types of cancer, including cancers of the oral cavity, pharynx, esophagus, stomach, pancreas, larynx, lung, cervix, urinary bladder, and kidney [28]. A number of malignancies have also been associated with HIV infection. For example, HIV-infected patients are at increased risk for a variety of cancers associated with human papillomavirus (HPV), including cancer of the cervix, anus, vulva, vagina, penis, oral cavity, and pharynx [32, 33]. As a reflection of the negative impact of smoking on development of HPV-associated disease, among both HIV-infected women and men, smoking has been shown to be an independent risk factor for anal cytological abnormality [34, 35].

PLWH are also at risk for a variety of other malignancies. For example, although HIV-infected persons are at increased risk for lung cancer independent of smoking status [36, 37], smoking additionally increases lung cancer risk. In one analysis with both HIV infection and smoking as lung cancer risk factors, there was a multivariate hazard ratio = 1.8 for each pack/day increase in cigarettes smoked [37]. For HIV patients in the SMART study, current smoking was associated with an adjusted hazard ratio compared to non-smokers for lung cancer of 9.4 [2•].

Smoking and Bone Disease

PLWH may be at greater risk for metabolic bone disease, including osteopenia and osteoporosis [38]. Several studies

of HIV-infected populations have shown that smoking is an independent risk factor for fractures [39, 40]. For example, in one study of HIV-infected persons who have received HAART, smoking was associated with a two-fold increased risk of developing a low-energy fracture, defined as fractures possibly due to osteoporosis, typically associated with low-energy trauma [39].

Smoking and Immunity

Smoking has a number of adverse effects on the immune system, including alterations in cellular and humoral immune system function, which may compromise the host's ability to mount an appropriate immune and inflammatory response to infectious agents [41]. Smoking may also have an effect on immune reconstitution in response to HIV treatment. In one study, HIV-infected women on HAART who smoked had poorer viral and immunologic responses, a greater risk of virologic rebound, and more frequent immunologic failure [9], indicating that some beneficial effects of HAART may be negated by cigarette smoking. It has been suggested that smoking may cause a heightened state of chronic immune activation in PLWH, potentially resulting in suboptimal immune reconstitution in response to HAART [42].

Immunologic abnormalities that persist despite effective suppression of HIV replication have been described as being consistent with changes to the adaptive immune system that are seen in the elderly; this immunosenescence is believed related in part to persistent inflammation [43]. It has been suggested that one mechanism associated with the cellular aging process is shortening of telomeres, DNA sequences that protect the ends of chromosomes; in one preliminary analysis, an HIV-smoking interaction was associated with shorter telomere length [44].

Smoking and Overall Mortality

Given the multiple morbidities associated with smoking, it is not surprising that a number of studies have found that PLWH who smoke have decreased survival compared to nonsmokers [2, 4, 9]. One study of U.S. veterans reported mortality rates per 100 person-years of 1.76 for HIV-negative never smokers, 2.45 for HIV-positive never smokers, and 5.48 for HIV-positive current smokers, indicating that both HIV-positive status and smoking contribute to increased mortality compared to never smokers [4]. Among HIV-infected patients in the SMART study, current smokers had a 2.4 greater risk of overall mortality; in this population, it was calculated that 24 % of all deaths were attributable to current smoking [2], highlighting the serious health risks that smoking represented in HIV patients.

Smoking Cessation Strategies

Benefits of Smoking Cessation for PLWH

Screening HIV-infected patients for smoking, and enrollment of current smokers in smoking cessation programs should be included as part of care of PLWH [45, 46]. Smoking cessation has a number of benefits. One study of PLWH showed that stopping smoking reduces the risk of CVD complications such as coronary heart disease and myocardial infarction [7]. Another analysis of HIV-infected patients showed that former smokers (compared to current smokers) had a decreased risk of AIDS-related diseases, CVD, non-AIDS cancers, and bacterial pneumonia [2]. Increasing time of smoking abstinence among PLWH has also been associated with lower levels of HIV symptom burden [47].

Studies indicate that many PLWH who are current smokers are thinking about or interested in quitting. In one survey of PLWH, 63 % reported that they were currently thinking about quitting [48]. In another study of PLWH that utilized the Transtheoretical Model of Behavior Change [49], 40 % of smokers were in the contemplation stage and 18 % were in the preparation stage to quit smoking [50]; a survey from Nepal of HIV-infected smokers found 34 % in the contemplation or preparation stage [13].

Despite the interest in smoking cessation, the actual ability of smokers to quit may be challenging and require a number of attempts. Many smokers who try to quit initially do not succeed [3, 50, 51, 52]. One group of current smokers reported having made an average of 2.8 quit attempts since their HIV diagnosis [50], and another group of HIV-positive smokers reported an average of 4.2 previous quit attempts [51].

Comorbidities in HIV-Positive Smokers

PLWH who are smokers may have a number of additional comorbidities that make smoking cessation especially challenging. Smokers are more likely to also be abusers of alcohol or drugs, and tobacco use may increase when persons are under the influence of these other substances; substance abuse can also be a risk factor for smoking cessation failure [5, 51, 52, 53].

PLWH may also have a number of psychological stresses and mental health challenges which contribute to smoking and make cessation more difficult [5, 51, 52, 53]. In one survey of PLWH, 62 % of regular smokers suffered from depressive symptoms [5], and in another, 38 % met criteria for a major depressive disorder [51]. Some PLWH may perceive smoking as one way to help cope with the stress of living with a difficult illness [52]. If PLWH also have other stresses due to economic and social disadvantage, smoking may represent a perceived outlet to help deal with

these pressures [52]. If so, these psychological and social sources of greater emotional distress may adversely impact readiness to quit smoking [50].

In addition to psychological factors that may contribute to smoking, some PLWH may believe that smoking helps relieve certain physical symptoms associated with their HIV disease, such as bodily pain [50]. In one study, respondents reported smoking as one way to help manage symptoms associated with peripheral neuropathy [54]. The ability of nicotine to actually decrease sensitivity to pain is unclear [55]. However, whether medically correct or not, the impression that smoking has such beneficial effects may make it more difficult for PLWH to embrace and adhere to smoking cessation efforts.

Role of Clinicians in Smoking Cessation

The health care setting offers a unique opportunity to screen patients for smoking and to counsel them about smoking cessation [56, 57]. Because PLWH frequently interact with the health care system as part of their monitoring and HIV care, there are multiple opportunities for providers to deliver smoking cessation interventions [45]. One study from Nepal reported that physicians can play a key role to encouraging smoking cessation among PLWH, including asking patients about their smoking status and their readiness to quit [13]. Counseling can also be provided by other health care professionals in a clinic setting such as nurses [58].

The U.S. Clinical Practice Guideline on Treating Tobacco Use and Dependence [56] concludes that even brief counseling by clinicians can improve abstinence outcomes, and recommends the following five major steps (the “5 A’s”) to intervention in the clinical setting: “ask” about tobacco use (identify and document tobacco use status for every patient at each visit); “advise” to quit (in a clear, strong and personalized manner urge every tobacco user to quit); “assess” willingness to make a quit attempt (Is the tobacco user willing to make a quit attempt at this time?); “assist” in quit attempt (for the patient willing to make a quit attempt, use counseling and pharmacotherapy to help him or her quit); and “arrange follow-up” (schedule follow-up contact, preferably within the first week after the quit date) [56]. For patients who smoke and who are not yet ready to quit, clinicians can still provide motivation to quit, and continue to address tobacco dependence and willingness to quit at follow-up clinic visits.

Despite these recommendations, many HIV clinicians and service providers are not assessing smoking status in their patients. In one study, HIV providers were more likely than other providers to miss current smoking status among their patients [59]; in another study, less than half of HIV service providers reported always assessing smoking status or interest in quitting at intake [3]. Some clinicians may feel

that they lack familiarity and skills with smoking cessation treatments, or that they have limited time for this health promotion activity in the setting of a busy clinic and the need to address in their patients the many other demands and complexities of HIV care. To address the situation of busy clinicians who view the 5 “A”s as burdensome, a streamlined approach of “ask,” “advise,” and “refer” to a smoking cessation program has been recommended [60, 61]. For example, physicians can use readily available referral resources such as the National Cancer Institute’s Smoking Quitline to assist patients in smoking cessation [62]. Telephone quitlines are a major referral resource for smokers who are interested in quitting and are available in all 50 states in the U.S. and in a number of other countries [63].

Counseling HIV-Positive Smokers

Various individual and group counseling approaches have been utilized to help promote smoking cessation among PLWH [53]. Many of these counseling approaches with PLWH have been used in conjunction with nicotine replacement therapy (NRT) [64–66]. Interestingly, in two studies of HIV-positive smokers, NRT plus motivational counseling sessions was no more effective than NRT plus brief meetings with a health educator and receipt of self-help quitting materials [64] or NRT plus receipt of self-guided reading about how to quit smoking [65].

In addition to in-person counseling, several investigators have used various technology-based strategies to help smokers in the cessation efforts. One approach is the use of cell phone counseling to provide health education, as well as assistance with development of coping and problem solving skills [67]. When used in conjunction with NRT, HIV-infected smokers were 3.6 more times more likely to quit than those who received usual care (physician advice, written materials and NRT). Given the widespread availability of cell phones throughout the world, delivery of interventions through cell phones may be feasible in many resource-limited settings. For example, in studies of PLWH in sub-Saharan Africa, cell phone technology has been shown to be beneficial in improving adherence to antiretroviral therapy [68], suggesting that it may be useful for other health promotion interventions for PLWH. In the general population, various web-based and online programs have been utilized to help support smoking cessation [69], and these may also be beneficial for PLWH.

Importantly, a positive association has been documented between social support received by smokers and their successes at smoking cessation [56]. Support can be effectively provided by individual or group counseling or by telephone quitline counselors. Social support can also be provided by family, co-workers or friends, who can be trained in various

ways as “helpers” to assist the smoker in quitting [70]. Such support may be especially important for PLWH who have other psychological or social stressors, who feel isolated or depressed, or who have additional comorbidities, as described above.

Nicotine Replacement Therapy

Many of the approaches to smoking cessation utilize nicotine replacement therapy [56, 71•, 72], which is intended to reduce the motivation to smoke and withdrawal symptoms experienced by those who attempt to quit. NRT is available in a variety of formats intended for absorption through the oral mucosa or skin, including gums, spray, inhaler, lozenges, sublingual tablet, and transdermal patches. One comprehensive meta analysis of over a hundred trials of NRT evaluated smoking abstinence rates at approximately 4 weeks post-target quit date; the pooled odds ratio for NRT (vs. inert controls) was 2.05 [71•]. When evaluating NRT vs. controls at 6 months, there was still a highly significant difference in efficacy, with a pooled odds ratio=1.92 [71•]. Another large meta analysis also reported significant benefits for NRT vs. controls, with a relative risk of 1.6; significant differences were also found when looking at specific types of formats, including nicotine gum, patches, inhalers, oral tablets/lozenges, and nasal spray [72]. As noted above, many studies, including those in PLWH, have combined NRT with some sort of counseling approach [64–67]. This supports the approach of integrating multiple strategies, including both behavioral and pharmacotherapy approaches as part of a smoking cessation program.

Other Pharmacotherapies

In addition to NRT, several other drugs have been used for smokers who wish to quit. Bupropion (a drug also used as an antidepressant) has been used in a number of studies to assist with smoking cessation [53, 56, 71•, 73]. When evaluating smoking abstinence rates at approximately 4 weeks post-target quit date, one meta-analysis of 31 clinical trials of bupropion (vs. placebo or education alone as controls) reported a statistically significant pooled odds ratio of 2.25 [71•]. Bupropion continued to show an approximately two-fold benefit (OR=1.94) in trials evaluating continuous abstinence over a 6-month period [71•].

Another drug which has been used in smoking cessation is varenicline, a nicotine receptor partial agonist that is reported to reduce the pleasurable effects of nicotine and urge to smoke [53•, 56, 71•, 74, 75]. When evaluating smoking abstinence rates at approximately 4 weeks post-target quit date, one meta-analysis of 9 clinical trials of varenicline vs. placebo controls reported a statistically significant pooled odds ratio of 3.16 [71•]. Varenicline continued to show a significant benefit

(OR=2.17) in trials evaluating continuous abstinence over 6 months [71•]. Finally, two trials evaluated varenicline compared to bupropion using abstinence rates at both 4 weeks and 6 months; both studies reported higher success rates with varenicline [71•, 74, 75].

Although both drugs have demonstrated efficacy, they must be used with caution in PLWH. Bupropion can have cytochrome interactions with antiretroviral drugs (such as non-nucleoside reverse transcriptase inhibitors and protease inhibitors) that may require dose adjustment [19, 53•, 76]. Varenicline has a number of side effects including insomnia, abnormal dreams, depressed mood, agitation, changes in behavior, suicidal ideation, and suicide [53•, 56]. This may be a challenge for HIV patients with a history of psychological problems, or who are on antiretroviral drugs such as efavirenz that also have central nervous system effects. Because of the potential for drug-drug interactions with HIV medications [76], as well as exacerbation of certain side effects, providers considering use of drugs for smoking cessation should first consult knowledgeable pharmacists and other current and authoritative sources of information.

Tobacco Control Measures

Although the focus of this review has been on measures to work with individual patients to help them quit smoking, it should be noted that there are a number of tobacco control measures that can and should be implemented to help protect the health of society in general, including PLWH. These include but are not limited to: advertising campaigns to warn people about the dangers of smoking, health warnings on cigarette packages, bans on tobacco advertising or promotion, taxes on tobacco products, promotion of smoke-free environments, and laws to ban smoking in public places [15, 77, 78].

Conclusions

Despite the multiple and well documented health hazards of smoking, the prevalence of smoking among PLWH remains high. HIV-infected smokers need to be provided with relevant knowledge about the impact of smoking on their disease and its treatment, as well as access to cessation services [45, 46, 52•, 53•, 79]. Smoking cessation efforts may need to be targeted and tailored to best meet the specific needs and circumstances of individual clients. Multiple strategies will likely need to be combined, such as both counseling and pharmacologic approaches. If the client has other comorbidities, such as mental health or substance abuse problems, addressing these issues may be needed as part of a comprehensive health promotion package. Some clients may have particular difficulty adhering to prescribed medical regimens, and may need adherence support, just as it is

provided for antiretroviral treatments. Discussions with clients should include what benefits they derive from smoking, and other ways these benefits might be realized. Support from health care providers, as well as from family, friends, and others may be very beneficial in helping the client avoid relapse. Since some smokers may need to make multiple quit attempts, continued encouragement is important.

In summary, the high prevalence of smoking among this population, the multiple health risks that can result from it, and the demonstrated success of cessation efforts in PLWH should encourage clinicians and other HIV service providers to make smoking cessation for their patients and clients a high priority.

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