

Effects of Smoking on Non-AIDS-Related Morbidity in HIV-Infected Patients

Daniel K. Shirley,¹ Robert J. Kaner,^{2,3} and Marshall J. Glesby¹

¹Division of Infectious Diseases, ²Division of Pulmonary and Critical Care Medicine, and ³Department of Genetic Medicine, Weill Cornell Medical College, New York, New York

Tobacco smoking has many adverse health consequences. Patients with human immunodeficiency virus (HIV) infection smoke at very high rates, and many of the comorbidities associated with smoking in the general population are more prevalent in this population. It is likely that a combination of higher smoking rates along with an altered response to cigarette smoke throughout the body in persons with HIV infection leads to increased rates of the known conditions related to smoking. Several AIDS-defining conditions associated with smoking have been reviewed elsewhere. This review aims to summarize the data on non-AIDS-related health consequences of smoking in the HIV-infected population and explore evidence for the potential compounding effects on chronic systemic inflammation due to HIV infection and smoking.

Keywords. smoking; tobacco; HIV; comorbidity.

In the current era of treatment for human immunodeficiency virus (HIV), the incidence of non-AIDS-related morbidity and mortality has begun to surpass that of AIDS-related complications in resource-rich settings [1]. Smoking is very common in patients with HIV, putting them at risk for many of the known health consequences of smoking (Table 1). Although the effect of smoking on certain AIDS-defining illnesses has been well characterized—including increased risk for bacterial pneumonia, *Pneumocystis pneumonia* (PCP), invasive cervical cancer, and tuberculosis [2–7]—less attention has been paid to associations between smoking and non-AIDS-defining complications. While investigators have paid increasing attention to the roles of inflammation and immune activation in the pathogenesis of non-AIDS-related comorbidities, the potential additive or synergistic effects of smoking are important to consider and are the subject of this review.

PREVALENCE OF SMOKING

Rates of smoking in the HIV-infected population are generally thought to be 2–3 times that of the general population but vary between studies [8, 9]. The most accurate prevalence data likely come from outpatient HIV clinics with diverse populations, where the rate ranges from 39% to 59% [10–12]. In contrast, the rate of active smoking in the general US population in 2010 was 19.3% [13]. In addition, studies of HIV-infected patients generally show very high rates (>75%) of having ever smoked [8, 11, 14]. The reasons for the high prevalence of smoking in HIV-infected populations are likely multifactorial and include known associations between smoking and factors that are common in HIV populations, including low socioeconomic and educational levels, psychiatric comorbidity, concurrent illicit drug and alcohol use, and mental stress [15].

SMOKING-RELATED MORTALITY AND QUALITY OF LIFE

Smoking is associated with increased mortality in HIV-infected patients. In one study from 2010, current smokers had a significantly higher risk for all-cause mortality than former smokers and never smokers when controlling for age, race, sex, CD4 count, viral load at

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Correspondence: Marshall J. Glesby, MD, PhD, Division of Infectious Diseases, Weill Cornell Medical College, 525 E 68th St, Floor 24, New York, NY 10065 (mag2005@med.cornell.edu).

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Table 1. Known Health Effects of Smoking

Chronic diseases
Stroke ^a
Periodontitis ^a
Chronic obstructive pulmonary disease ^a
Asthma
Coronary artery disease ^a
Peripheral vascular disease ^a
Aortic aneurysm
Hip fracture ^a
Reproductive effects ^a
Cancers
Oropharynx ^a
Larynx ^a
Esophagus ^a
Lung ^a
Stomach
Pancreas
Kidney
Bladder
Cervix ^{a,b}
Acute myelogenous leukemia

^a Data also exist for detrimental health effects of smoking in the human immunodeficiency virus–infected population as reviewed in this article.

^b AIDS-defining illness.

Source: Surgeon General. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease. Rockville, MD: Public Health Service, Office of the Surgeon General, 2010.

baseline, alcohol and drug use, and past AIDS events [2]. Another recent cohort study confirmed this excess mortality in HIV-infected smokers, where current smoking led to an increase in all-cause mortality and non-AIDS-related mortality when compared to nonsmokers. In fact, the mortality rate and life-years lost were higher in current smokers than either former smokers or never smokers, reflecting the positive impact of smoking cessation. Although the relative risk for death was higher in the HIV-infected cohort vs population controls, this was not statistically significant. The number of life-years lost due to smoking was higher than the number of life-years lost due to HIV-infection [16].

In a large study of HIV-infected US veterans, current smokers scored significantly lower on the physical component of the SF-12 quality of life scale after controlling for age, race, CD4 count, viral load, and illegal drug use. Former smokers also showed decreased scores, but this did not reach statistical significance [17]. In another large cohort study of HIV-infected individuals, current smokers had significantly lower scores on another measure of quality of life, the Medical Outcomes Survey Scale adapted to HIV (MOS-HIV), specifically within

sections measuring general health perception, physical functioning, bodily pain, energy, role functioning, and cognitive functioning [18]. Other data, however, suggest that decreased quality of life in HIV-infected individuals may be attributable to chronic obstructive pulmonary disease (COPD) rather than smoking itself [19].

NON-AIDS-RELATED COMORBIDITIES

Chronic Obstructive Pulmonary Disease

The available data suggest that COPD is more common and emphysema is accelerated in HIV-infected patients, as reviewed elsewhere [8, 20–23]. Recent prospective studies measuring pulmonary function in HIV-infected persons confirmed that smoking was an independent risk factor for airway obstruction in this population [14, 24, 25]. As outlined earlier, HIV-infected patients are more likely to smoke, which expectedly predicts increased rates of smoking-related lung diseases such as COPD. However, this fact does not fully explain the increased rates of COPD seen in this population, which suggests an interaction between smoking and HIV-related factors. Studies have revealed potential HIV-related mechanisms in the pathogenesis of COPD in this population as summarized in Table 2 and reviewed elsewhere [21, 22].

Lung Cancer

Smoking is clearly the major risk factor for lung cancer in the general population. It has long been observed that rates of lung cancer were higher in the HIV-infected population, but it was unclear if this was due to direct effects of the virus itself, or related to increased smoking rates or susceptibility to pulmonary infection that could lead to chronic inflammation. Recent data show that HIV infection is an independent risk factor for lung cancer, even when controlling for smoking and bacterial pneumonia history [37]. Furthermore, diagnosis of lung cancer is made at a significantly younger age in HIV-infected patients, which may in part be a reflection of the younger age distribution of the HIV-infected population [38]. Recurrent bacterial pneumonia may also be a risk factor for lung cancer in the HIV-infected population, but no clear association has been found between lung cancer and PCP or tuberculosis [38, 39]. A study of HIV-infected patients with lung cancer, matched for age, sex, and HIV transmission risk, confirmed that smoking is a clear risk for lung cancer in this population, and nearly all of those with lung cancer had smoked [40]. Theories on the pathogenesis of lung cancer in HIV-infected individuals focus on 2 main mechanisms: the presence of increased inflammation in the lung at baseline in those with HIV infection, which is related to immune suppression and resulting infection; and the direct influence of the virus itself on carcinogenic pathways, resulting in greater susceptibility to aberrant cell replication [41].

Table 2. Pathogenesis of Chronic Obstructive Pulmonary Disease: Potential Opportunities for Interactions With HIV

Population	Proposed Mechanism of Lung Inflammation/Tissue Destruction
All COPD	<ul style="list-style-type: none"> • Inflammation is induced by tobacco smoke [26] <ul style="list-style-type: none"> ◦ Lung tissue destruction due to influx of: <ul style="list-style-type: none"> ■ Neutrophils ■ CD8⁺ lymphocytes ■ Macrophages • Remodeled lung increases the risk for bacterial colonization [27] <ul style="list-style-type: none"> ◦ Increased risk for repeated bacterial infection ◦ Increased chronic inflammatory state within lungs
HIV infection and COPD	<ul style="list-style-type: none"> • Independent influx of CD8⁺ lymphocytes [23, 28] • Increased number of activated macrophages [29, 30] <ul style="list-style-type: none"> ◦ Increased expression of matrix-metalloproteinase 9, a destructive enzyme [31] • Oxidant-antioxidant imbalance <ul style="list-style-type: none"> ◦ Increased oxidant stress from direct viral effects of HIV [32] ◦ Decreased levels of antioxidants in the lung, including glutathione [33] • HIV protein induction of apoptosis of lung endothelial cells [22, 34] • Antiretroviral effects [14, 21, 24] <ul style="list-style-type: none"> ◦ Direct effects ◦ IRIS-type response to organisms in the lung • Increased susceptibility to bacterial pulmonary infection [27] • Increased susceptibility to <i>Pneumocystis</i> colonization after <i>Pneumocystis</i> infection <ul style="list-style-type: none"> ◦ Primates with SHIV infection with <i>Pneumocystis</i> colonization develop airway obstruction over time [35] ◦ Humans with HIV infection with <i>Pneumocystis</i> colonization show increased rates of airway obstruction after controlling for smoking [36]

Abbreviations: COPD, chronic obstructive pulmonary disease; HIV, human immunodeficiency virus; IRIS, immune reconstitution inflammatory syndrome; SHIV, simian/human immunodeficiency virus.

Atherosclerotic Disease

Smoking is a classic risk factor for cardiovascular disease (CVD), and in the general population, incremental increases in tobacco smoke exposure predict incremental increases in CVD risk [42]. Recent data from the general population receiving optimal medical therapy for CVD including a statin (theorized to stabilize endothelial cell function and alter detrimental effects of smoking) show that the risk for CVD is significantly higher in current smokers compared to former or never smokers, suggesting that decreasing exposure to smoke decreases CVD risk [43]. Patients with HIV appear to be at increased risk for CVD, in part due to a higher prevalence of traditional risk factors, especially smoking and metabolic disturbances [44, 45]. However, studies controlling for classic risk factors suggest that HIV infection independently increases risk of CVD. Altered systemic inflammation and immune dysregulation, possibly related to macrophage activation in HIV infection, likely contribute to the increased risk [45, 46]. Exposure to antiretroviral medications and a general hypercoagulable state could influence risk, although these factors remain controversial [45, 47]. In a large study of HIV-infected subjects, those who were current smokers had a significantly higher risk for major and non-major CVD events than never smokers and former smokers [2]. Data also suggest that in HIV-infected individuals, the level of lifetime smoke exposure correlates with degree of atherosclerosis [48]. In a recent case-control study of

acute coronary syndrome, the population-attributable risk for smoking was higher in HIV-infected than uninfected patients (54% vs 31%) and exceeded that of diabetes and hypertension [49].

In addition to traditional CVD risk factors, HIV infection is an independent risk factor for ischemic stroke [50], and evidence suggests that HIV-infected smokers have higher risk than HIV-infected nonsmokers [51]. A study of peripheral artery disease in HIV-infected individuals showed rates much higher than expected, and smoking was an independent risk factor [52].

Taken together, the available data suggest that HIV-infected patients are at increased risk for atherosclerotic disease and special attention should be given to addressing modifiable risk factors, including smoking.

Decreased Bone Mineral Density and Fracture

Smoking is a significant independent risk factor for decreased bone mineral density (BMD) in the general population [53, 54]. The prevalence of osteopenia and osteoporosis is also higher in the HIV-infected population, where the classic risk factors of hypogonadism, smoking, and other substance abuse are all more common, and where the effects of each may be amplified [55]. Evidence suggests additional influence on bone from direct effects of HIV itself, chronic systemic inflammation secondary to HIV infection, and antiretroviral therapy.

A study of HIV-infected and uninfected women similar in age, race, and body mass index found smoking to be a risk factor for low BMD in the entire cohort as well as within the HIV-infected cohort. Smoking, however, was not associated with progression of bone loss over time [56]. In an analysis from the Women's Interagency HIV Study comparing HIV-infected and uninfected women, the majority of whom were premenopausal, HIV was not associated with increased fracture risk, but within the HIV-infected cohort, smoking increased the risk for fracture [57]. Another study showed that HIV infection was a risk factor for fracture, and within the antiretroviral therapy-treated subgroup, smoking increased the fracture risk further [58]. When HIV-infected and uninfected men ≥ 49 years of age were compared, HIV and heroin use were independent risk factors for low BMD, but smoking was not; however, 95% of enrolled subjects had significant smoking histories, making evaluation of smoking as an independent risk factor difficult [59]. In the Veteran's Administration Cohort Study of men, smoking was found to increase the risk for fragility fractures in both HIV-infected and uninfected subjects, and risk trended higher in HIV-infected smokers [60]. Thus, smoking is a modifiable risk factor for decreased BMD and fracture in HIV-infected patients.

Human Papillomavirus Infection and Related Cancers

In the general population, cigarette smoking is an independent risk factor for oral infection with human papillomavirus (HPV) [61]. Studies also show an association between smoking and cervical infection with HPV, as well as decreased immune response to HPV at the cervix leading to persistence of infection and increased risk for progression to precancerous cervical lesions and invasive cervical cancer [62, 63]. Smoking is also independently associated with anal HPV infection and persistence in men who have sex with men (MSM) [64]. HIV infection is associated with increased HPV infection and persistence in both women and men [65, 66]. In individuals with HIV infection, one large study found that smoking increased the rate of HPV infection but not persistence [67], and another study also failed to show an impact of smoking on clearance of cervical HPV [68]. Further research is needed to clarify the impact on HPV infection of coexisting smoking and HIV infection.

There is evidence that HIV infection is a risk factor for HPV-related cervical, vaginal, vulvar, oral, penile, and anal cancers, and this risk has some correlation with the level of immune suppression [69, 70]. Smoking is a known risk factor for invasive cervical cancer, an AIDS-defining illness that is beyond the scope of this review [71, 72].

Rates of anal cancer are elevated with HIV infection and are highest for HIV-infected MSM, where risk is at least 30 times higher than the general population, and where anal cancer may occur at an earlier age [38, 73]. Within the HIV-infected

population, studies suggest smoking increases the risk of anal cancer by an estimated 8 times [74]. In the Multicenter AIDS Cohort Study, increased anal cancer rates were associated with HIV infection and having ever smoked when compared to never smokers, although the study was not powered to detect differences in anal cancer risk based on the degree of lifetime cigarette smoke exposure [75]. In a study of anal cancer survival, a positive smoking history was associated with decreased survival, although HIV status was not [76].

Smoking appears to contribute to the rates of both HPV and non-HPV-related head and neck cancers in the general population, but whether the interaction between smoking and HPV increase these rates beyond an additive effect remains controversial [61, 77, 78]. There is also an association between HIV infection and increased rates of head and neck cancers, but mechanisms are likely multifactorial [79]. Further research is needed to determine how increased risk behavior and altered immune/inflammatory reaction to smoking and HPV each contribute to this increased risk.

Periodontal Disease

Smoking is a major risk factor for periodontal disease (gingivitis, periodontitis) in the general population, increasing the risk 2–3 times [80]. HIV infection has long been associated with serious oral infections and lesions, and is a significant risk factor for periodontal disease, especially severe forms (linear gingivitis erythema, necrotizing ulcerative gingivitis, and necrotizing ulcerative periodontitis). HIV infection is also associated with higher rates of tooth loss [81]. Within the HIV-infected population, cumulative smoking exposure is significantly associated with increased gingivitis, periodontitis, and tooth loss in a linear relationship [82]. In the general population, periodontitis is associated with significant morbidity and many medical conditions, although the causal relationships remain unclear and the effect on mortality is controversial [80, 83]. Poor oral health, including periodontitis, has been associated with avoidance of healthy food choices in older adults in the general population [84, 85]. Although no studies to our knowledge have focused on nutrition in HIV-infected individuals with periodontitis, increased rates of periodontitis could lead to poor nutrition and add to the general state of immunosuppression.

Reproductive Effects

In one large cohort study evaluating risk for low birth weight and preterm labor in all births in Florida from 1998 through 2007, both HIV infection and smoking were independent risk factors. In addition, HIV-infected mothers who smoked during pregnancy had 43%–79% higher risk of low birth weight and preterm labor than those with either HIV or who smoked alone. HIV-infected mothers who smoked also had about 2 times the risk for low birth weight and preterm birth than

HIV-uninfected nonsmokers [86]. Another study of HIV-infected mothers showed that smoking was an independent risk for fetal growth restriction, as was CD4 <200 cells/mm³ in the first trimester [87].

As HIV progresses, testosterone levels often decrease, rates of erectile dysfunction increase, and sperm counts may decrease, all likely due to multiple factors [88]. Although not specifically studied in those with HIV, in the general population, smoking decreases sperm counts and quality, and in women, smoking decreases the quality of follicular function in the ovary, uterine receptiveness, and in vitro fertilization pregnancy rates [89]. Further studies of these measures in HIV-infected patients are warranted. In one study of MSM, smoking was a significant risk factor for erectile dysfunction, but this risk was no longer significant when focusing on the HIV-infected cohort [90]. In a small study of HIV-infected men, 61% reported erectile dysfunction, and those subjects were more likely to be current smokers, although this was not statistically significant. Current smoking actually appeared protective with regard to hypogonadism in HIV-infected patients, as measured by testosterone levels [91].

SMOKING CESSATION IN HIV

Clearly, cigarette smoking causes widespread morbidity in the HIV-infected population, and it is therefore a high priority to focus on cessation. Many of the complications of smoking are related to chronic use, and the impact may be lessened or altogether avoided if patients are able to quit. Several studies of HIV-infected persons show decreased risk in former vs current smokers for incident CVD, non-AIDS cancers, bacterial pneumonia, and AIDS-related diseases [2]. Data from HIV-infected subjects in the D:A:D study showed that cessation of smoking decreases the risk for CVD, with suggestion of more benefit the sooner smoking is ceased [92]. Smoking cessation also results in improvements in quality of life, with effects seen after only 3 months [93]. In addition to obstacles to cessation known for the general population, substance abuse, psychiatric disorders, low socioeconomic status, poor access to care, and resulting low utilization of cessation programs are more prevalent with HIV and present significant risks for continued smoking and barriers to cessation [15, 94, 95]. Also, social groups of HIV-infected individuals are more likely to include other smokers [94]. Evidence from one healthcare system suggests that HIV providers are less likely to assess tobacco use than non-HIV providers [96]. This may be a result of decreased confidence by providers in treating tobacco dependence or the complexity of the patient population, but could change as electronic medical record use increases and smoking assessment is linked to reimbursement.

A group therapy program called Positively Smoke Free focused on HIV-infected individuals and resulted in twice the

quit rate at 3 months compared to standard nicotine replacement treatment [97]. Several studies compared group counseling and nicotine replacement therapy (NRT) vs self-guided material and NRT and showed mixed results [98]. Bupropion is an attractive option because of its utility in concomitant mental illness, and one small trial suggests some effect on cessation. There are concerns, however, about interactions between bupropion and protease inhibitors [99]. Recent data from 2 studies show that varenicline is safe and effective in the HIV-infected population with the same potential adverse effects as for the general population, where caution is advised in patients with prior psychiatric disorders. These studies suggest similar or even higher cessation rates than for the general population [100, 101]. One study evaluated the rates of smoking in the HIV-infected population as the cost of smoking increased and found that the impact was tied closely to socioeconomic factors, where those in the lower socioeconomic groups were less affected by increases in cigarette cost [102]. Some evidence suggests that implementing bans on smoking in certain settings can decrease smoking rates, but there has been no study focused on the HIV-infected population [103].

SUMMARY

HIV-infected patients clearly have increased morbidity and mortality related to smoking. For some time, it was presumed that the increased rates of the conditions outlined in this review were due solely to the increased prevalence of smoking in the HIV-infected population. However, evidence is beginning to suggest that in the setting of chronic inflammation due to HIV infection, smoking may elicit additional inflammatory responses beyond what would be expected in a smoker without HIV infection. As reviewed, the strongest evidence for an exaggerated response to cigarette smoke comes from studies of COPD that demonstrate residual increased risk associated with HIV infection after controlling for smoking exposure. These observations set the groundwork for more basic studies of proposed mechanisms, yielding evidence of multifaceted insults leading to lung destruction. Similarly, observational studies controlling for smoke exposure have shown that lung cancer is more common in those patients with HIV, leading to more basic pathogenesis studies showing viral and inflammatory influences on carcinogenesis. Risk for atherosclerotic disease, decreased BMD, HPV-related diseases, and periodontitis is elevated in all smokers and among HIV-infected nonsmokers. Further studies are needed, however, to define whether HIV-infected smokers are at higher risk than HIV-uninfected smokers and to understand potential mechanisms if this is indeed the case. Smoking also has notable negative effects in HIV-infected patients on reproduction and general quality of life, both of which influence long-term health. The increase in mortality associated with smoking is

significant, and it can now be said that years of life lost due to smoking is higher than years of life lost due to HIV. As the care of the HIV-infected patient shifts toward managing chronic disease, the importance of smoking-related conditions will increase. It is clear that smoking as a risk factor for disease is modifiable, and providers can make a huge impact on the long-term health of HIV-infected patients by assisting in cessation.

Notes

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