POPULATIONS AT RISK

The Impact of Cigarette Smoking on Mortality, Quality of Life, and Comorbid Illness Among HIV-Positive Veterans

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BACKGROUND: The impact of smoking on outcomes among those with HIV infection has not been determined in the era of highly active antiretroviral therapy (HAART).

STUDY OBJECTIVE: Determine the impact of smoking on morbidity and mortality in HIV-positive patients post-HAART.

DESIGN: Prospective observational study.

PARTICIPANTS: Eight hundred and sixty-seven HIV-positive veterans enrolled in the Veterans Aging Cohort 3 Site Study.

MEASUREMENTS: Clinical data were collected through patient questionnaire, International Classification of Diseases—9th edition codes, and standardized chart extraction, and laboratory and mortality data through the national VA database. Quality of life was assessed with the physical component summary (PCS) of the Short-Form 12.

RESULTS: Current smokers had increased respiratory symptoms, chronic obstructive pulmonary disease (COPD), and bacterial pneumonia. In analyses adjusted for age, race/ethnicity, CD4 cell count, HIV RNA level, hemoglobin, illegal drug and alcohol use, quality of life was substantially decreased ($\beta = -3.3$, 95% confidence interval [CI] -5.3 to -1.4) and mortality was significantly increased (hazard ratio 1.99, 95% CI 1.03 to 3.86) in current smokers compared with never smokers.

CONCLUSIONS: HIV-positive patients who currently smoke have increased mortality and decreased quality of life, as well as increased respiratory symptoms, COPD, and bacterial pneumonia. These findings suggest that smoking cessation should be emphasized for HIV-infected patients.

KEY WORDS: HIV; AIDS; smoking; mortality; health-related quality of life.
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C igarette smoking is a leading cause of morbidity and mortality in HIV-negative persons[1] and is highly prevalent in HIV-positive populations. Approximately 40% to 70% of HIV-infected people smoke.[2–7] Yet, the impact of cigarette smoking on the course of HIV and the overall health of HIV-positive persons in the era of highly active antiretroviral therapy (HAART) is unclear. Studies examining the impact of smoking on mortality in HIV-positive patients pre-HAART have had contradictory results,[2–4] likely because of the competing risk of mortality from HIV. Studies pre-HAART have demonstrated increased HIV-related infectious complications such as oral candidiasis, acute bronchitis, bacterial pneumonia, and *Pneumocystis* pneumonia (PCP) in smokers,[2,8–11] as well as increased respiratory symptoms[7] and decreased quality of life.[6]

The impact of cigarette smoking on outcome in HIV-infected patients has not been examined post-HAART. As the mortality related to opportunistic infections and HIV-associated conditions has decreased, HIV-positive patients on HAART are living longer.[12,13] We hypothesized that cigarette smoking will emerge as an important determinant of morbidity and mortality in HIV-positive patients post-HAART and that quality of life would be negatively influenced by smoking. To address these issues, we examined the impact of cigarette smoking on symptoms, quality of life, infectious and noninfectious smoking-related comorbid illnesses and mortality in subjects enrolled in the Veterans Aging Cohort 3 Site Study.

METHODS

Veterans Aging Cohort 3 Site Study is a previously described ongoing prospective observational study of 881 HIV-infected veterans enrolled between June 1999 and July 2000 from 3 Veterans Affairs (VA) Medical Centers[14] (www.vacohort.org).

Smoking status was based on self-report to a written survey at study entry and standardized chart extraction. The survey included the question, "Do you smoke cigarettes?" Patients could answer "past," "present," or "never." We also identified patients as current, former, or never smokers from chart extraction. We then combined these 2 sources to improve our ability to detect behaviors such as smoking, drug use, or alcohol use. Thus, current smokers self-reported current use on survey or were current smokers according to chart extraction. Former smokers either self-reported past use on survey or were former smokers according to chart extraction, as long as either source did not indicate current smoking. Never smokers had no history of smoking according to either source. Patients with missing data regarding smoking were excluded ($n=3$). We also categorized patients into current, former, and never users of illegal drugs and alcohol using similar methods. We excluded an additional 10 patients with missing data regarding illegal drug and/or alcohol use; excluding these subjects had no significant effects on our multivariate analyses.

Data on respiratory symptoms and quality of life were obtained from the survey. Patients were asked if they had "cough or trouble catching your breath," and how burdensome the symptom was on a 4-point Likert scale ranging from "it doesn't bother me" to "it bothers me a lot." Patients were considered to have bothersome cough/dyspnea if they scored ≥ 2 on the Likert scale. Quality of life was measured using the physical component summary (PCS) of the Short Form-12 (SF-12).[15,16] Scored on a scale of 1 to 100, the mean score in the U.S. population was designed to be 50, and lower scores reflect poorer quality of life.

Comorbid conditions were diagnosed using International Classification of Diseases—9th edition codes from hospitalizations and outpatient visits using methods previously described.[17] We focused on general medical illnesses and HIV-associated conditions that have been related to cigarette smoking.[1,2,8–11] Birth date and laboratory data were from the electronic medical record. Mortality data were obtained from inpatient files and the VA Beneficiary Identification Records Locator System Death File, which records 95% of all veteran deaths.[14]

Analysis

Our primary end point was all-cause mortality. Our secondary end points were quality of life, as assessed by the SF-12 PCS, comorbid illnesses associated with smoking, and respiratory symptoms. All analyses were performed using Stata (version 7.0; StataCorp, College Station, Tex, USA). P values of $\leq .05$ were considered statistically significant.

Study subjects were categorized according to smoking status. Characteristics were compared between groups of smokers using parametric and nonparametric methods. Analysis of the association of smoking with our secondary outcomes was cross-sectional, using data obtained at study entry. In survival analysis, individuals were followed from study entry to their last encounter or death. The last follow-up date was September 2003. We calculated mortality rates per 100 person-years.

All multivariate models were adjusted for CD4 cell count, HIV RNA level, hemoglobin, age, race/ethnicity, as well as alcohol and illegal drug use. Age was expressed in 10-year increments. The square root of the CD4 cell count and the $\log_{10}$

HIV RNA level were used to approximate normally distributed variables. We entered smoking status as both an indicator variable as well as a continuous variable in order to examine differences in current versus former smoking. A multivariate linear regression model assessed the impact of smoking status on quality of life. A multivariate Cox proportional hazards model examined the strength of the association between smoking status and mortality.

RESULTS

Three patients with no smoking status and 1 patient who was lost to follow-up were excluded, and an additional 10 patients in whom alcohol and drug use data were missing were excluded. Thus, 867/881 or 98.4% of the enrolled sample was in the analytic sample.

Clinical Characteristics According to Smoking Status

Cigarette smoking was highly prevalent. Overall, 63% were current smokers and 22% were former smokers. Former smokers were significantly older than current and never smokers ($P<.001$) (Table 1). Current smoking was significantly associated with current illegal drug and alcohol use ($P<.001$ for both). Current smokers had the highest $\log_{10}$ HIV RNA levels when compared with never smokers ($P=.02$) and to former smokers ($P<.001$).

Association of Smoking Status with Respiratory Symptoms and Comorbid Illness

Cigarette smoking was strongly associated with increased respiratory symptoms, noninfectious pulmonary disease, and bacterial pneumonia (Table 1). Forty percent of current smokers reported symptoms of cough or dyspnea compared with 32% of former smokers and 25% of those who never smoked ($P=.003$). Noninfectious pulmonary diseases were substantially increased in both current smokers (odds ratio [OR] 3.92, 95% confidence interval [CI] 1.55 to 9.91) and in former smokers (OR 3.61, 95% CI 1.34 to 9.72) compared with never smokers. Of the 104 patients with noninfectious pulmonary diseases, all had a chronic obstructive lung disease, either chronic obstructive pulmonary disease (COPD) (82%) and/or asthma (24%). Chronic obstructive pulmonary disease was much more likely in current smokers (OR 5.25, 95% CI 1.62 to 17.01) and in former smokers (OR 5.25, 95% CI 1.53 to 17.99) than in never smokers. Current smokers were also substantially more likely to have bacterial pneumonia (OR 2.84, 95% CI 1.48 to 5.45) compared with never smokers. Former smokers had a nonsignificantly increased risk of bacterial pneumonia compared with never smokers (OR 1.94, 95% CI 0.93 to 4.05).

Association of Smoking with Decreased Quality of Life

Cigarette smoking was associated with a substantially decreased quality of life. Current smokers scored the lowest on the SF-12 PCS followed by former smokers and never smokers (Table 1). On linear regression, after adjusting for race/ethnicity, age, hemoglobin, CD4 cell count, HIV RNA level, illegal drug and alcohol use, current smoking was associated with a

Table 1. Characteristics, Comorbid Conditions, and Mortality Rates of Patients According to Smoking Status

Characteristic or Comorbid Condition	Current Smoker (n=549)	Former Smoker (n=189)	Never Smoker (n=129)	*P* Value
Baseline characteristics				
Age, mean (SD)	49 (8)	53 (10)	49 (11)	<.001
Gender, male (%)	98	99	99	.4
Race				.8
African American (%)	55	55	50	
White (%)	33	33	39	
Hispanic and other (%)	12	13	11	
Current illegal drug use (%)	47	17	22	<.001
Current alcohol use (%)	71	53	69	<.001
CD4 cells, median (range)	339 (3 to 1880)	319 (2 to 1450)	377 (4 to 1570)	.4
Log_{10} HIV RNA, median (range)	3.1 (1.6 to 5.9)	2.3 (1.6 to 5.7)	2.4 (1.6 to 5.8)	.001
Hemoglobin, g/dL, median (range)	13.9 (7 to 17.9)	13.6 (7.7 to 17.9)	14.1 (8 to 17.6)	.05
On HAART (%)	81	84	78	.4
Respiratory symptoms				
Cough/dyspnea (%)	40	32	25	.003
Comorbid conditions				
Noninfectious pulmonary disease (%)*	14	13	4	.008
MI/CAD (%)	5	8	4	.1
CHF (%)	3	3	1	.4
Non-AIDS related cancer (%)	6	10	8	.3
Lung cancer (%)	1	2	2	.5
Bacterial pneumonia (%)	21	15	9	.002
Thrush/esophageal candidiasis (%)	13	11	7	.2
PCP (%)	8	11	7	.4
Quality of life				
SF-12 physical component summary score, median	39	41	45	<.001
Mortality				
Unadjusted mortality rate per 100 person-years	5.4[†]	4.6[‡]	2.5	.05

Reported P values reflect the overall comparison of current, former, and never smokers.
*All patients with a noninfectious pulmonary disease had a diagnosis of either COPD and/or asthma.
[†]P value for comparison of current vs never smokers =.02.
[‡]P value for comparison of former vs never smokers =.10.
SD, standard deviation; HAART, highly active antiretroviral therapy; MI/CAD, myocardial infarction/coronary artery disease; CHF, congestive heart failure; PCP, Pneumocystis pneumonia; SF-12, short form-12.

significantly lower quality of life ($\beta = -3.3$, 95% CI -5.2 to -1.4). Although former smoking was also associated with a lower quality of life, this decrease was not statistically significant ($\beta = -2.0$, 95% CI -4.2 to -0.2).

Association of Smoking with Mortality

Veterans were followed for a median of 3.7 years, during which time there were 139 deaths. The unadjusted mortality rate was significantly different according to smoking status (Table 1) ($P=.05$ for the overall comparison of current, former, and never smokers). The attributable risk for smoking was 2.1 deaths per 100 person-years for former smoking and 2.9 deaths per 100-person years for current smoking.

Adjusting for age, race/ethnicity, baseline CD4 cell count, HIV RNA level, hemoglobin, illegal drug and alcohol use, mortality was significantly increased in current smokers compared with those who never smoked (hazard ratio [HR] 1.99, 95% CI 1.03 to 3.86) (Table 2). Mortality in former smokers was also increased, but was not significantly different from never smokers (HR 1.60, 95% CI 0.78 to 3.27).

DISCUSSION

To our knowledge, this is the first study to examine the impact of cigarette smoking on morbidity and mortality in HIV-positive patients in the HAART era. We found that current cigarette smoking was independently associated with increased mortal-

ity in HIV-positive veterans. Previous studies conducted pre-HAART have not consistently demonstrated increased mortality associated with cigarette smoking in HIV-positive patients.[2–4] Prior to the availability of HAART, mortality in HIV-positive patients has been primarily related to opportunistic infections and HIV-associated conditions. However, in

Table 2. Association of Cigarette Smoking with Increased Mortality

	Hazard Ratio	95% Confidence Interval	*P* Value
Smoking			
Current smoking	1.99	1.03 to 3.86	.04
Former smoking	1.60	0.78 to 3.27	.2
Race/ethnicity			
African American	0.96	0.63 to 1.45	.8
Hispanic and other	1.24	0.70 to 2.19	.5
Age (10 y increments)	1.56	1.27 to 1.90	<.001
CD4 cell count (square root)	0.96	0.93 to 0.99	.009
HIV RNA level (log_{10})	1.35	1.15 to 1.57	<.001
Hemoglobin (g/dL)	0.78	0.71 to 0.86	<.001
Illegal drug use			
Current drug use	0.88	0.54 to 1.44	.6
Former drug use	0.96	0.60 to 1.54	.9
Alcohol use			
Current alcohol use	1.03	0.43 to 2.46	.9
Former alcohol use	0.93	0.38 to 2.27	.9

Multivariate Cox proportional hazards models of the association of cigarette smoking and mortality. The multivariate model included 854 subjects and excluded those who did not have baseline measures of 1 or more of the following tests: CD4 cell count, viral load, or hemoglobin.

the current HAART era, our results demonstrate that current cigarette smoking is an important factor that contributes to the mortality of HIV-positive veterans.

We also found that smoking was associated with significant morbidity in HIV-positive veterans. Current smokers had substantially increased respiratory symptoms, noninfectious pulmonary diseases (particularly COPD), and bacterial pneumonia. Studies pre-HAART have demonstrated increased bacterial pneumonia in HIV-positive smokers.[2,10] Some studies pre-HAART have also demonstrated increased PCP in smokers, although others have not.[2,4,8,10,18] We did not find significantly increased PCP in smokers. We also observed that the HIV RNA levels were highest among current smokers compared with former and never smokers. Median CD4 cell counts or the proportion of patients on HAART did not differ according to smoking status. Differences in HIV RNA levels may relate to factors affecting adherence to antiretrovirals, particularly given the increased illegal drug and alcohol use among current smokers.

Our findings suggest that smoking cessation could result in improved outcomes. These findings may serve as an impetus to increase provider and patient efforts at smoking cessation. Despite the extremely high prevalence of smoking among HIV-infected patients in our study and in prior studies,[2,5] smoking cessation has not received significant attention.[5] For example, smoking cessation is not addressed in the recent guidelines published by the Infectious Diseases Society of America for the primary care of persons infected with HIV.[19]

Our study has limitations. We could not assess the impact of pack-years of smoking on morbidity and mortality. In addition, we may have misclassified some subjects who had quit recently as former smokers when they were more representative of current smokers. However, this potential misclassification would likely have biased us away from finding an association between current smoking and increased mortality.

In conclusion, respiratory symptoms and pulmonary diseases, especially COPD and bacterial pneumonia, are substantially increased in HIV-positive patients who currently smoke. Furthermore, current smokers have increased mortality and decreased quality of life. These findings suggest that smoking cessation should be emphasized for HIV-infected patients.

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