

Smoking-Related Health Risks Among Persons With HIV in the Strategies for Management of Antiretroviral Therapy Clinical Trial

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Highly active antiretroviral therapy (HAART) for HIV has led to a decrease in AIDS-related events and deaths.^{1–3} However, HIV-infected persons are also at risk for a variety of serious non–AIDS-defining diseases, including cardiovascular, renal, and hepatic disease, as well as certain cancers and infections not included in the AIDS case definition.^{1,3–5} Studies conducted in the general population demonstrate that cigarette smoking increases the likelihood of many of these serious clinical conditions, including cardiovascular, pulmonary, and neoplastic diseases.^{6,7} For example, smoking is a major risk factor for peripheral vascular and coronary artery disease, increasing the risk for cardiovascular disease (CVD) complications, including myocardial infarction and stroke.^{6–8} Respiratory complications of smoking include chronic obstructive pulmonary disease and respiratory infections such as bacterial pneumonia or pulmonary tuberculosis.^{6,7,9} 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.^{6,7,10}

Studying smoking-related morbidity and mortality among persons with HIV is especially important because their smoking prevalence is higher than that of the general population. Twenty-one percent of US adults are current cigarette smokers,¹¹ but many recent studies have reported rates 2 or 3 times as high (46%–76%) among HIV-positive persons.^{12–18} HIV-infected current smokers are reported to smoke an average of 6 to 23 cigarettes daily and to have smoked for an average of 23 to 24 years.^{15,16,18,19}

Many smoking-related illnesses significantly affect HIV-infected persons. Lung cancer and other malignancies are important causes of death among persons with HIV.^{20,21} HIV infection or use of antiretroviral drugs may contribute to CVD risk,^{22,23} and use of effective HAART has resulted in increasing numbers of aging HIV-infected patients, who may develop

Objectives. We sought to determine smoking-related hazard ratios (HRs) and population-attributable risk percentage (PAR%) for serious clinical events and death among HIV-positive persons, whose smoking prevalence is higher than in the general population.

Methods. For 5472 HIV-infected persons enrolled from 33 countries in the Strategies for Management of Antiretroviral Therapy clinical trial, we evaluated the relationship between baseline smoking status and development of AIDS-related or serious non-AIDS events and overall mortality.

Results. Among all participants, 40.5% were current smokers and 24.8% were former smokers. Adjusted HRs were higher for current than for never smokers for overall mortality (2.4; $P < .001$), major cardiovascular disease (2.0; $P = .002$), non-AIDS cancer (1.8; $P = .008$), and bacterial pneumonia (2.3; $P < .001$). Adjusted HRs also were significantly higher for these outcomes among current than among former smokers. The PAR% for current versus former and never smokers combined was 24.3% for overall mortality, 25.3% for major cardiovascular disease, 30.6% for non-AIDS cancer, and 25.4% for bacterial pneumonia.

Conclusions. Smoking contributes to substantial morbidity and mortality in this HIV-infected population. Providers should routinely integrate smoking cessation programs into HIV health care. (*Am J Public Health.* 2010;100:1896–1903. doi:10.2105/AJPH.2009.188664)

metabolic syndrome, obesity, and other CVD risk factors.^{24,25} HIV-infected patients may develop a variety of pulmonary diseases, including bacterial pneumonia^{26,27}; recurrent pneumonia is considered an AIDS-defining condition.²⁸

Because persons with HIV are at risk for these serious and life-threatening clinical syndromes, critical prevention questions are whether and to what extent smoking further increases the risk of developing these diseases, especially in the era of HAART. Because smoking is a modifiable risk factor, it is important to define the magnitude of smoking's effect on overall mortality among HIV-infected patients and its effect on development of specific adverse clinical conditions, including those that are not AIDS defining. It is also important to identify the proportion of disease among an HIV-infected population that is attributable to smoking. This information can be used to help estimate the effect of smoking cessation on reducing disease and improving survival for HIV-infected persons

and to counsel individual patients about ways to optimize their health.

We evaluated data from a large multisite international study of 2 HAART treatment strategies. We determined the relative risks associated with smoking for development of different serious clinical events and on all-cause mortality, with adjustment for a variety of important potential confounders. We also calculated the population-attributable risk percentage (PAR%) associated with smoking for these clinical syndromes and all-cause mortality.

METHODS

The Strategies for Management of Antiretroviral Therapy (SMART) clinical trial compared continuous HAART use to episodic use on the basis of CD4+ lymphocyte count criteria among 5472 HIV-infected persons enrolled during 2002 to 2006 from 318 sites in 33 countries.²⁹

Health Conditions and Variables

In our analysis of data from this trial, we defined AIDS-related events as clinical diseases meeting the revised Centers for Disease Control and Prevention AIDS case definition,²⁸ plus other conditions considered to be attributable to HIV-related immunodeficiency; a full list of these conditions is available elsewhere.²⁹ Serious non-AIDS events included major CVD events, any CVD event (according to an expanded definition), non-AIDS cancer, major hepatic disease, major renal disease, and initial episodes of bacterial pneumonia. Major CVD events included nonfatal myocardial infarction requiring hospitalization or diagnosed by serial Q-wave change on an electrocardiogram, nonfatal stroke, coronary artery disease requiring surgery or invasive procedures, or death from CVD. The expanded CVD definition consisted of major CVD events, congestive heart failure, coronary artery disease requiring drug treatment, or peripheral vascular disease. Major renal disease was defined as nonfatal or fatal kidney failure; major hepatic disease was nonfatal or fatal cirrhosis.

We considered only the first event of a given type in an individual if more than 1 was reported. Specific criteria and standard definitions were developed for all AIDS-related and serious non-AIDS clinical events in SMART. An independent endpoint review committee blinded to treatment status reviewed and adjudicated all clinical events and reviewed all death reports to assign underlying cause of death.²⁰

The baseline data collection form identified whether participants were current, former, or never smokers. Current smoking status was reascertained at each annual follow-up visit. Although our analysis focused on baseline smoking status as the primary exposure of interest, we also evaluated data on annual smoking status to determine whether the proportion of current smokers significantly changed over the course of follow-up. Other baseline variables in our analysis included history of injection drug use (IDU), history of alcohol abuse, diabetes, and use of lipid- or blood pressure-lowering drugs. Body mass index was calculated from height and weight. Baseline laboratory measurements included CD4+ count; high- and low-density lipoprotein

cholesterol, triglyceride, and HIV RNA levels; and evidence of hepatitis B (HBV) and C (HCV) virus. HCV infection was defined as presence of HCV antibody, and HBV infection as persistence of HBV surface antigen for 6 months or longer.

Analyses

We compared characteristics across baseline smoking categories (never, former, current) with the Kruskal-Wallis nonparametric test for continuous variables and the χ^2 test for categorical variables. Baseline smoking status was included as a fixed covariate. We constructed Kaplan–Meier curves by baseline smoking categories and used the log-rank test to compare cumulative event proportions. We estimated hazard ratios (HRs) for comparison of smoking categories for clinical events from Cox proportional hazards models. We then calculated adjusted HRs (AHRs) with additional variables entered into the final model.

All adjusted models contained the following baseline covariates: age, gender, race/ethnicity (Black, Hispanic, other), SMART treatment arm, baseline HIV RNA, baseline CD4+ count, and nadir CD4+ count. For different clinical events, we added variables to the final adjusted model that we considered relevant to that endpoint. For all-cause mortality and AIDS-related events, these additional variables were history of alcohol abuse or IDU and previous AIDS events. For CVD events, additional variables were body mass index, diabetes, use of lipid-lowering and blood pressure-lowering drugs, low-density lipoprotein cholesterol level, and triglyceride level. For cancer events and liver events, additional variables were history of alcohol abuse or IDU and HBV or HCV infection.

We calculated the PAR% of a clinical endpoint attributable to smoking as $Pe(HR-1)/[Pe(HR-1)+1]$, where Pe was the proportion of the population with the exposure (e.g., proportion who reported current smoking at baseline), and HR represented the relative risk estimate.^{30,31} In PAR% calculations that compared only 2 smoking subgroups (e.g., current versus former smokers), we adjusted the population at risk to incorporate only participants belonging to those 2 subgroups. We used AHRs in the final calculations of PAR%. We calculated 95% confidence intervals (CIs) for rates, HRs, and PAR%.

RESULTS

Baseline characteristics for the 5472 participants are shown in Table 1. Mean follow-up time was 33 months; the total follow-up time was 15 095 person-years. At baseline, 2215 HIV-infected persons (40.5%) were current smokers, 1358 (24.8%) were former smokers, and 1899 (34.7%) reported never smoking. Comparison of the 3 smoking groups by demographic and other baseline characteristics revealed significant differences for many variables, although baseline smoking status was similar between SMART treatment arms.

Smoking status did not change greatly during the follow-up period. The proportion of current smokers was 38% at 12 months, 39% at 36 months, and 36% at 60 months. Among baseline current smokers, 89% reported current smoking on at least 1 follow-up visit; 89% of baseline former or never smokers reported not currently smoking at each follow-up visit.

Baseline Smoking Status and Risk

All-cause mortality. Three percent (167) of participants died from any cause. We calculated death rates by baseline smoking status, with the highest rate (1.5 per 100 person-years) for current smokers (Table 2). The estimated percentage of participants who died by 24 and 48 months was, respectively, 1.0% and 2.1% among never smokers, 2.3% and 4.9% among former smokers, and 2.3% and 6.6% among current smokers ($P<.001$; Figure 1). The AHR for all-cause mortality was significantly higher for current than for never smokers (2.4; $P<.001$; Table 3). The AHR for all-cause mortality was also significantly higher for current smokers than for former ones (1.5; $P=.04$).

AIDS-related events. Three percent (163) of participants experienced an AIDS-related event. The AIDS-related event rate was highest among current smokers (1.4 cases per 100 person-years; Table 2). The AHR for all AIDS-related events for current versus never smokers was 1.3 ($P=.18$) and for current versus former smokers was 1.6 ($P=.03$; Table 3). We conducted a subanalysis for esophageal candidiasis, the most common AIDS-related disease, with 36 (68%) of 53 cases among current smokers. The AHR for current versus

TABLE 1—Baseline Participant Characteristics by Baseline Smoking Status: Strategies for Management of Antiretroviral Therapy Clinical Trial, 2002–2006

	Never Smokers (n = 1899)	Former Smokers (n = 1358)	Current Smokers (n = 2215)	P
Treatment arm, episodic ART, %	48.9	49.3	50.7	.47
Age, y, median	42	46	43	<.001
Female, %	36.1	21.4	23.0	<.001
Race/ethnicity, %				<.001
Latino	26.1	24.0	19.5	
Black	26.7	25.9	28.7	
White	36.1	46.3	48.3	
Other	11.1	3.8	3.5	
Region, %				<.001
North America	48.6	63.0	59.3	
South America	13.2	10.0	7.3	
Europe	25.7	21.3	28.2	
Australia/New Zealand	3.0	3.5	3.2	
Asia/Africa	9.5	2.2	2.0	
History of injection drug use, %	2.5	9.7	15.9	<.001
History of alcohol abuse, %	3.2	12.6	17.0	<.001
Body mass index, kg/m ² , median	25.4	25.5	24.2	<.001
HIV RNA ≤ 400, %	76.9	73.3	66.2	<.001
CD4+ cells/mm ³ , median	589	594	606	.005
CD4+ nadir cells/mm ³ , median	246	245	260	.002
Previous AIDS disease, %	21.9	25.3	25.5	.02
Diabetes, %	6.9	9.1	5.9	.001
Lipid-lowering drugs, %	14.1	22.2	13.4	<.001
Blood pressure-lowering drugs, %	16.6	24.2	17.1	<.001
Hepatitis B, %	2.1	2.1	2.9	.17
Hepatitis C, %	6.1	15.1	22.2	<.001
LDL cholesterol, mg/dL, median	112	113	110	.02
HDL cholesterol, mg/dL, median	42	40	40	.004
Triglycerides, mg/dL, median	155	179	159	<.001

Note. ART = antiretroviral therapy; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

never smokers was 2.5 (95% CI=1.2, 5.4; $P=.02$); the AHR for current versus former smokers was 2.6 (95% CI=1.2, 5.7; $P=.02$).

Cardiovascular disease. Three percent (146) of participants experienced a major CVD event, and 4% (238) had any (expanded definition) CVD event. The event rate for both major and expanded CVD events was highest for current smokers (1.2 and 2.0 per 100 person-years, respectively; Table 2). The AHR for major CVD events for current versus never smokers was 2.0 ($P=.002$) and for current versus former smokers was 1.6 ($P=.02$; Table 3). The estimated percentage with at least 1 expanded definition CVD event by 24 and 48 months was, respectively, 2.2% and

4.1% among never smokers, 2.7% and 8.0% among former smokers, and 3.8% and 8.0% among current smokers ($P<.001$). The AHR for expanded CVD events for current versus never smokers was 1.9 ($P<.001$), and for current versus former smokers was 1.5 ($P=.009$; Table 3).

Non-AIDS cancer. Two percent (136) of participants developed a non-AIDS cancer. Current smokers had the highest event rate (1.2 per 100 person-years; Table 2). The cumulative estimated percentage with a non-AIDS cancer at 24 and 48 months was, respectively, 1.2% and 3.2% among never smokers, 1.4% and 2.7% among former smokers, and 2.0% and 4.6% among current smokers ($P=.02$).

The AHR for non-AIDS cancer for current versus never smokers was 1.8 ($P=.008$) and for current versus former smokers was 2.3 ($P<.001$; Table 3).

In our subanalysis for the 2 most common cancers, 15 (41%) of 37 nonmelanoma skin cancers and 13 (72%) of 18 lung cancers occurred in current smokers. The AHR for nonmelanoma skin cancer for current versus never smokers was 0.9 (95% CI=0.4, 1.9; $P=.82$); the AHR for current versus former smokers was 2.5 (95% CI=0.9, 6.7; $P=.06$). The AHR for lung cancer for current versus never smokers was 9.4 (95% CI=1.1, 76.3; $P=.04$); the AHR for current versus former smokers was 3.0 (95% CI=0.9, 9.6; $P=.07$).

Bacterial pneumonia. Four percent (204) of participants developed bacterial pneumonia at least once. The highest rate for pneumonia (1.9 per 100 person-years) was among current smokers (Table 2). The cumulative estimated percentage at 24 and 48 months with bacterial pneumonia was, respectively, 1.5% and 3.2% among never smokers, 2.6% and 5.8% among former smokers, and 3.2% and 8.1% among current smokers ($P<.001$). The AHR for bacterial pneumonia for current versus never smokers was 2.3 ($P<.001$) and for current versus former smokers was 1.5 ($P=.01$; Table 3).

Renal or hepatic disease. Eighteen participants experienced a major renal event, and 25 had a major hepatic event. The overall numbers and rates for renal and hepatic disease were relatively small, with limited power to detect differences (Table 2); none of the AHRs were statistically significant (Table 3).

Additional analyses. We recalculated AHRs with CD4+ count and HIV RNA level as time-dependent covariates. We also recalculated AHRs by confining our analysis to the continuous HAART group. In both cases, although some numerical estimates changed (usually slightly), we detected little change in overall significant results or the magnitude of association. For example, in the continuous HAART group, the AHR for current versus never smokers was 2.2 (95% CI=1.1, 4.3) for all-cause mortality. An additional sensitivity analyses was performed adding as a covariate years of education (≤ 12 years vs > 12 years) as one reflection of socioeconomic status; AHRs remained almost exactly the same.

TABLE 2—All-Cause Mortality and Specific Clinical Events by Smoking Status at Baseline: Strategies for Management of Antiretroviral Therapy Clinical Trial, 2002–2006

Clinical Event	Never Smokers		Former Smokers		Current Smokers	
	No.	Rate ^a (95% CI)	No.	Rate ^a (95% CI)	No.	Rate ^a (95% CI)
All-cause mortality	25	0.5 (0.3, 0.7)	47	1.2 (0.9, 1.5)	95	1.5 (1.2, 1.8)
AIDS-related disease	43	0.9 (0.6, 1.1)	34	0.9 (0.6, 1.2)	86	1.4 (1.1, 1.7)
Major CVD	33	0.7 (0.4, 0.9)	39	1.0 (0.7, 1.3)	74	1.2 (0.9, 1.5)
Expanded CVD ^b	53	1.1 (0.8, 1.4)	65	1.7 (1.3, 2.1)	120	2.0 (1.7, 2.4)
Non-AIDS cancer	35	0.7 (0.5, 0.9)	29	0.8 (0.5, 1.0)	72	1.2 (0.9, 1.5)
Major Renal disease	1	0.0 (0.0, 0.1)	9	0.2 (0.1, 0.4)	8	0.1 (0.0, 0.2)
Major Hepatic disease	5	0.1 (0.0, 0.2)	8	0.2 (0.1, 0.3)	12	0.2 (0.1, 0.3)
Bacterial pneumonia ^c	38	0.8 (0.5, 1.0)	51	1.3 (1.0, 1.7)	115	1.9 (1.6, 2.3)

Note. CI = confidence interval; CVD = cardiovascular disease.

^aPer 100 person-years.

^bMajor CVD events, as well as congestive heart failure, coronary artery disease requiring drug treatment, or peripheral vascular disease.

^cInitial occurrence.

Population-Attributable Risk Percentage

The PAR% was calculated for overall mortality and selected clinical endpoints. We first compared current smokers to nonsmokers (i.e., both former and never smokers) to help estimate what percentage of disease was attributable to current smoking. We used the AHRs and a current smoking prevalence of 40.5% to calculate a PAR% estimate of 24.3% (95% CI=10.6%, 37.6%) for all cause-mortality,

25.3% (95% CI=10.9%, 39.1%) for major CVD events, 22.9% (95% CI=11.6%, 33.9%) for any CVD event, 30.6% (95% CI=15.7%, 44.6%) for non-AIDS cancer, and 25.4% (95% CI=13.6%, 36.8%) for bacterial pneumonia.

We limited the second analysis to current and former smokers, to help estimate the reduction in incidence that would be observed among current smokers if they all became former smokers. Within this subpopulation, the

PAR% estimate was 15.6% (95% CI=0.5%, 30.8%) for all-cause mortality, 20.1% (95% CI=3.3%, 36.6%) for major CVD events, 17.4% (95% CI=4.3%, 30.5%) for any CVD event, 34.3% (95% CI=15.8%, 51.1%) for non-AIDS cancer, and 17.8% (95% CI=3.8%, 31.7%) for bacterial pneumonia.

DISCUSSION

A significant proportion (40.5%) of HIV-infected participants in this large, multinational clinical trial reported current smoking at enrollment; more than one third also reported smoking at 1-, 3-, and 5-year follow-up visits. Our results show that smoking contributed to substantial morbidity and mortality in this population. Current smokers had significantly higher rates of non-AIDS cancers, CVD, bacterial pneumonia, and all-cause mortality than did nonsmokers. These findings remained robust: significantly higher risk persisted after adjustment for multiple potential confounders, CD4+ count, and HIV RNA level. The association between current smoking and adverse clinical outcomes also persisted after we controlled for SMART treatment arm and in analyses restricted to the continuous HAART group.

Smoking in HIV-infected persons is of great concern for many reasons. Smoking

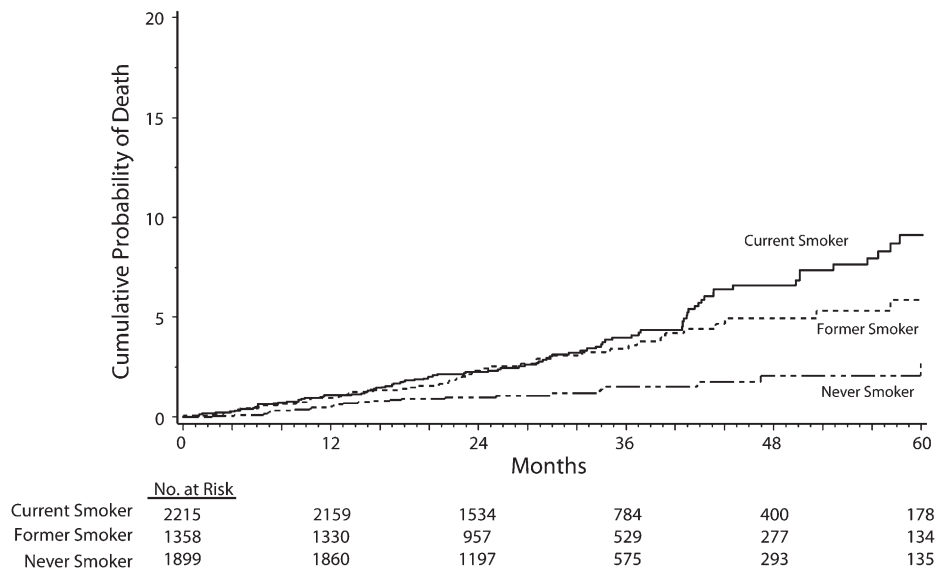


FIGURE 1—Cumulative probability of death (all-cause mortality) by months of follow-up, among current, former, and never smokers: Strategies for Management of Antiretroviral Therapy clinical trial, 2002–2006.

TABLE 3—Unadjusted and Adjusted Hazard Ratios for All-Cause Mortality and Specific Clinical Events by Baseline Smoking Status: Strategies for Management of Antiretroviral Therapy Clinical Trial, 2002–2006

Clinical Event	Current Versus Never Smokers		Current Versus Former Smokers	
	HR (95% CI)	P	HR (95% CI)	P
All-cause mortality				
Unadjusted	3.0 (1.9, 4.7)	<.001	1.3 (0.9, 1.8)	.15
Adjusted	2.4 (1.5, 3.8)	<.001	1.5 (1.0, 2.1)	.04
AIDS-related disease				
Unadjusted	1.6 (1.1, 2.3)	.01	1.6 (1.1, 2.4)	.02
Adjusted	1.3 (0.9, 1.9)	.18	1.6 (1.0, 2.3)	.03
Major CVD				
Unadjusted	1.8 (1.2, 2.8)	.004	1.2 (0.8, 1.8)	.31
Adjusted	2.0 (1.3, 3.1)	.002	1.6 (1.1, 2.4)	.02
Expanded CVD ^a				
Unadjusted	1.9 (1.3, 2.6)	<.001	1.2 (0.9, 1.6)	.25
Adjusted	1.9 (1.4, 2.7)	<.001	1.5 (1.1, 2.1)	.009
Non-AIDS cancer				
Unadjusted	1.7 (1.1, 2.5)	.01	1.6 (1.0, 2.5)	.03
Adjusted	1.8 (1.2, 2.8)	.008	2.3 (1.5, 3.6)	<.001
Major Renal disease				
Unadjusted	6.6 (0.8, 52.4)	.08	0.6 (0.2, 1.5)	.24
Adjusted	6.6 (0.8, 53.9)	.08	0.7 (0.2, 1.7)	.4
Major Hepatic disease				
Unadjusted	1.9 (0.7, 5.5)	.22	0.9 (0.4, 2.3)	.91
Adjusted	0.6 (0.2, 1.8)	.32	0.8 (0.3, 2.1)	.69
Bacterial pneumonia ^b				
Unadjusted	2.5 (1.7, 3.6)	<.001	1.5 (1.0, 2.0)	.03
Adjusted	2.3 (1.6, 3.3)	<.001	1.5 (1.1, 2.1)	.01

Note. CI = confidence interval; CVD = cardiovascular disease; HR = hazard ratio. All models adjusted for treatment group, age, gender, race/ethnicity (Black, Hispanic, other), baseline HIV RNA, and baseline and nadir CD4+ counts. Death and AIDS endpoints additionally adjusted for alcohol abuse, injection drug use, and previous AIDS disease. CVD endpoints additionally adjusted for body mass index, diabetes, blood pressure-lowering drugs, lipid-lowering drugs, low-density lipoprotein cholesterol, and triglycerides. Cancer and liver endpoints additionally adjusted for alcohol abuse, injection drug use, and hepatitis B or C.

^aMajor CVD events, as well as congestive heart failure, coronary artery disease requiring drug treatment, or peripheral vascular disease.

^bInitial occurrence.

prevalence is higher among persons with HIV than among the general population.^{12–18} Many diseases that occur more often among smokers than among nonsmokers are more common in HIV-infected persons, and smoking may even further increase risk among this population. For example, HIV-infected persons are at increased risk for lung cancer, independent of smoking status^{32–34}; however, smoking even further raises lung cancer risk. An analysis that considered both HIV infection and smoking as lung cancer risk factors found a multivariate HR of 1.8 for

each additional pack of cigarettes smoked per day.³³

Smoking may negate many positive benefits of HIV treatment, including HAART. Recent HIV treatment guidelines recommend earlier HAART initiation in part because data (from SMART and other studies) show that untreated HIV infection may be associated with development of certain non-AIDS-defining diseases, such as CVD and malignancy.^{35,36} In the SMART data, episodic HAART was also associated with higher rates

of bacterial pneumonia.³⁷ If smoking promotes development of these serious non-AIDS events, it may counteract many of the benefits of earlier HAART.

Although the AHR in our analysis for current versus never smokers was not statistically significant for the combined category of AIDS-related events, smoking may still increase the risk of specific AIDS-defining clinical diseases among HIV-infected persons, again weakening HIV treatment benefits. Studies of HIV-infected patients have identified smoking as a risk factor for AIDS-defining pulmonary infections, including *Pneumocystis jirovecii* pneumonia and tuberculosis.^{38,39} We also identified a significant association between current smoking and esophageal candidiasis, consistent with reports of an association between smoking and oral candidiasis.^{40–42} Among the possible pathogenic mechanisms for this association are mucosal injury and epithelial alterations from smoke that facilitate candida colonization, factors in cigarette smoke that directly promote candida growth, and suppression of local or systemic immunologic defenses against candida.⁴² Smokers' use of inhaled or systemic steroids for smoking-related diseases may further promote candidiasis.

The association of smoking and many adverse effects, supported by our findings, strongly suggests that smoking may further increase morbidity and mortality associated with HIV infection. One study of US veterans reported mortality rates per 100 person-years of 1.76 for HIV-negative never smokers, 2.35 for HIV-negative current smokers, 2.45 for HIV-positive never smokers, and 5.48 for HIV-positive current smokers.¹⁷

Our analysis had several strengths. Participants in SMART were enrolled from 33 countries and represented a variety of demographic populations and HIV risk groups.²⁹ Our findings are therefore applicable to a diverse population of HIV-infected persons. All clinical endpoints in SMART were reviewed according to standardized criteria by an independent endpoint review committee blinded to treatment status. SMART collected data on, and our analysis adjusted for, multiple risk factors and confounders, including CD4+ count, HIV RNA level, alcohol abuse and IDU, HBV and HCV infection, body mass index, diabetes, lipid levels, and hypertension treatment.

We analyzed and reported the relationship between smoking and adverse clinical events in several ways. HRs reflected the magnitude of association, expressing the hazard of developing death or disease among exposed versus unexposed groups. Attributable risk estimates reflected excess risk of disease among exposed compared with unexposed groups. PAR% expressed the proportion of disease among a population that was attributable to an exposure; this proportion helped to estimate the proportion of disease that would be reduced if the exposure were eliminated.³⁰ Our findings that 24% of deaths and 23% to 31% of certain serious clinical events were attributable to current smoking highlight the serious health risk that smoking represents among this HIV-infected population.

Our findings strongly support recommendations that for HIV-infected persons who smoke, smoking cessation should be a central health promotion strategy and should be routinely integrated with other HIV health care services.^{18,43} Proven benefits of smoking cessation include reducing the risk of clinical diseases such as lung cancer, CVD, and stroke.^{44–47} Clinical practice guidelines for treating tobacco use and dependence recommend that providers systematically and regularly assess their patients for tobacco use and strongly urge tobacco users to quit.⁴⁸ In practice, however, many HIV providers are unaware that their patients are currently smoking or do not assess the interest of their smoking patients in quitting.^{14,49}

For patients who indicate that they are willing to make a quit attempt, multiple strategies are available and have been used in HIV-infected patients.^{18,43,50–52} Behavioral interventions include telephone quit lines, motivational interviewing, cognitive behavioral interventions, and other individual or group counseling approaches.^{18,43,48,50–53} Nicotine replacement therapy is available in multiple forms, including gum, lozenges, transdermal patches, inhalers, and sprays.^{18,43,48,51–54} Other pharmacological agents used for smoking cessation include bupropion and varenicline^{18,43,48,54}; because of the potential for drug–drug interactions, including with HAART medications,^{18,55,56} providers considering these drugs should first consult knowledgeable

pharmacists and other current and authoritative sources of information.³⁵ Because it is common for smokers to make multiple quit attempts before successful cessation, continued support is important.^{15,16,18,47} Approaches must be individualized; multiple strategies (such as behavior interventions and nicotine replacement therapy) have been employed simultaneously for some persons with HIV.^{18,51–53} Other underlying comorbidities, such as depression or substance abuse, may also need to be addressed.^{16,18}

Limitations

We had no specific information on date of smoking cessation for former smokers in our study. However, consistent with other studies,^{17,45,46} former smokers in our analysis had risks intermediate between current smokers and never smokers for both overall mortality and several specific clinical events. The risk difference between current and former smokers would be expected to increase with increasing duration of cessation.^{44–47}

We also had no information on amount and duration of smoking (e.g., pack-years) for current or former smokers. Although heavy or prolonged smoking has greater adverse health consequences, even light smoking (1–4 cigarettes/day) has been associated with an increased risk (compared with that of nonsmokers) of dying from ischemic heart disease and of all-cause mortality.⁵⁷ Current smoking at any level therefore represents a health risk among HIV-infected populations and highlights the importance of smoking cessation.

Many clinical outcomes in our analysis, including cancer and CVD, have multiple risk factors, and we cannot rule out additional potential confounders, such as other health-related behaviors (e.g., those related to diet or exercise) or other health conditions. However, our results concerning the relationship of smoking with all-cause mortality and development of serious adverse clinical events were robust in multiple analyses and were consistent with many other studies in varied populations.

Conclusions

Among HIV-infected participants in this clinical trial of 2 HAART treatment strategies, current smoking represented a significant risk factor for

both all-cause mortality and several serious clinical disease outcomes, such as CVD, non-AIDS cancers, and bacterial pneumonia. Significant reductions in morbidity and mortality among HIV-infected patients achieved by advances in HIV therapy may be undercut by increases in adverse clinical outcomes attributable to smoking. The high prevalence of smoking among this population and other HIV-infected populations should cause encouraging smoking cessation to become a high priority for clinicians and other HIV service providers to promote health and reduce morbidity and mortality in their patients. ■

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Contributors

A. R. Lifson developed the overall analysis plan for this paper and led interpretation of the results and writing and revising of the article. J. Neuhaus helped design the study, analyze data, interpret results, and draft and revise the article. J. R. Arribas, M. van den Berg-Wolf, A. M. Labriola, and T. R. H. Read helped interpret data and draft and revise the manuscript.

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The SMART Protocol Team cochairs were Wafaa El-Sadr and James Neaton. A full listing of study investigators and other contributors to SMART is available in the appendix to the SMART Study Group article in the *New England Journal of Medicine*.²⁹

Human Participant Protection

Each of the participating sites in the SMART study was required to obtain the approval of the local institutional review board or ethics committee.

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