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Mortality Attributable to Smoking Among HIV-1–Infected Individuals: A Nationwide, Population-Based Cohort Study

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Background. We assessed mortality attributable to smoking among patients with human immunodeficiency virus (HIV).

Methods. We estimated mortality rates (MRs), mortality rate ratios (MRRs), life expectancies, life-years lost, and population-attributable risk of death associated with smoking and with HIV among current and nonsmoking individuals from a population-based, nationwide HIV cohort and a cohort of matched HIV-negative individuals.

Results. A total of 2921 HIV patients and 10 642 controls were followed for 14 281 and 45 122 person-years, respectively. All-cause and non-AIDS-related mortality was substantially increased among smoking compared to nonsmoking HIV patients (MRR, 4.4 [95% confidence interval {CI}, 3.0–6.7] and 5.3 [95% CI, 3.2–8.8], respectively). Excess MR per 1000 person-years among current vs nonsmokers was 17.6 (95% CI, 13.3–21.9) for HIV patients and 4.8 (95% CI, 3.2–6.4) for controls. A 35-year-old HIV patient had a median life expectancy of 62.6 years (95% CI, 59.9–64.6) for smokers and 78.4 years (95% CI, 70.8–84.0) for nonsmokers; the numbers of life-years lost in association with smoking and HIV were 12.3 (95% CI, 8.1–16.4) and 5.1 (95% CI, 1.6–8.5). The population-attributable risk of death associated with smoking was 61.5% among HIV patients and 34.2% among controls.

Conclusions. In a setting where HIV care is well organized and antiretroviral therapy is free of charge, HIV-infected smokers lose more life-years to smoking than to HIV. The excess mortality of smokers is tripled and the population-attributable risk of death associated with smoking is doubled among HIV patients compared to the background population.

Keywords. HIV; smoking; mortality; population attributable risk; non-AIDS related mortality.

Human immunodeficiency virus (HIV)–induced immune suppression and risk of AIDS-related death can be reversed or prevented in the majority of HIV-infected individuals by highly active antiretroviral therapy (HAART) [1, 2]. In the post-HAART era, lifestyle-related factors may pose a greater threat to long-term survival of HIV-infected individuals than those related to the HIV infection [3]. In the general population, smoking is one of the most important causes of reduced life expectancy [4]. It has been estimated that smoking results in 24% of all deaths in the general population in Denmark and is the preventable factor that accounts for the highest number of life-years lost [5]. In the present study, we aimed to evaluate the effect of smoking on all-cause mortality and death due to cardiovascular diseases and cancer among HIV patients. Furthermore, we compared the risk of death and loss of life-years associated with smoking to that associated with HIV-related factors among HIV-1–infected patients treated in Denmark in the period 1995–2010.

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METHODS

In a nationwide, population-based cohort study of HIV patients, followed in the period 1995–2010, we estimated the effect of smoking on all-cause mortality and on risk of death caused by cardiovascular disease and cancer. Mortality associated with smoking was compared between HIV patients and the background population. We also estimated life expectancies, number of life-years lost, and population-attributable risks of death associated with smoking and HIV.

Setting

Denmark had a population of 5.5 million as of 31 December 2010, with an estimated HIV prevalence of approximately 0.09% among adults. Individuals with HIV infection are treated in one of the country's 8 specialized medical centers, where they are seen at intended intervals of 12 weeks. Antiretroviral treatment is provided free of charge. HIV care is well organized, and treatment failures and loss to follow-up are rare [6, 7].

Data Sources

The Danish HIV Cohort Study [8] is a population-based nationwide cohort study of all HIV-infected individuals treated at Danish HIV centers after 1 January 1995. Individuals are consecutively enrolled. Data are updated yearly and include demographics, date and route of HIV transmission, AIDS-defining events, and antiretroviral treatment. Since 2004, patients have systematically been interviewed annually about use of tobacco and alcohol. CD4 cell counts and HIV RNA measurements are extracted electronically from laboratory data files.

The Copenhagen General Population Study is a prospective study of a cohort of individuals randomly selected from greater Copenhagen [9–11]. Study participants are interviewed about lifestyle and health-related factors.

Data on migration and vital status were obtained from the Danish Civil Registration System [12], which is a national register established in 1967 that contains demographic data and vital status of all Danish citizens. Data on causes of death among HIV patients were obtained from the Danish National Registry of Causes of Death, which contains information from all Danish death certificates [13] specifying up to 4 diagnoses, according to the *International Classification of Diseases, 10th Revision* (*ICD-10*) [14].

Study Population

We included all HIV-1–infected individuals who were >16 years at HIV diagnosis, treated in Danish HIV centers in the period between 1 January 1995 and 1 August 2010 and for whom data on smoking status were available. We excluded injection drug users, of whom only 7 were nonsmokers, as risk-taking behavior, mortality, and causes of death in this group differ significantly from the rest of the HIV-infected population.

A population control cohort of up to 4 subjects for each HIV patient, individually matched on sex and year of birth, was identified from the Copenhagen General Population Study (2317 patients were matched with 4 controls, 245 with 3 controls, 221 with 2 controls, and 138 with 1 control).

Definitions

Data on smoking were obtained by interview. Individuals smoking any type of tobacco at least once per week were categorized as smokers. Individuals were categorized as current, previous, or never smokers on the basis of information on smoking status at time of enrollment, and did not change category during the observation period. Deaths were categorized as AIDS related if the last CD4 count (within 6 months of death) was <200 cells/μL or an AIDS-related illness had been diagnosed within 1 year of death. Deaths caused by injury, accident, suicide, or intoxication were categorized as violent. All other deaths were categorized as non-AIDS-related deaths.

Statistics

Time was calculated from the date of first available data on smoking status, age 35 years or, for HIV patients, 1 year after the date of HIV diagnosis, whichever came last, until the first of death, emigration, or 1 September 2010. Mortality rates (MRs) were calculated as number of deaths per 1000 person-years (PY). Excess MRs were estimated using the formula: $MR_{exposed} - MR_{unexposed}$. Mortality rate ratios (MRRs) of smoking vs never-smoking HIV patients were estimated using Poisson regression analyses adjusted for the following confounders: sex, origin (Danish, African, Asian, or other), route of transmission (men who have sex with men, heterosexual, or other), year of HIV diagnosis (before or after 1997), body mass index (BMI; <18.5, 18.5–25, 25–30, or >30 kg/m^2), excess consumption of alcohol (>180 g/week for women and >275 g/week for men, yes/no), CD4 count (<200, 200–350, 350–500, or >500 cells/μL), and viral load <400 copies/mL (yes/no) at baseline. Age was included as a time-updated variable. In primary analyses there were no significant interactions between smoking status and variables mentioned above; thus, no interaction terms were included in the final model. Data on CD4 counts, BMI, and alcohol abuse were not complete, so categories of "missing data" were included. In analyses of MRR among population controls, only sex and age were included in the model. MRRs among HIV patients vs population controls were analyzed by conditional Poisson regression.

Kaplan-Meier methods were used to construct survival curves, stratified by smoking and HIV status, and to estimate life expectancies from age 35 years. We estimated life-years from age 35 to 80 years among 4 groups of study subjects by

calculating the area under the Kaplan-Meier survival curve (group 1: never-smoking controls, group 2: currently smoking controls, group 3: never-smoking HIV patients, and group 4: currently smoking HIV patients). Life-years lost to smoking (among controls and HIV patients) and to HIV were calculated by subtracting the estimated life-years of group 1 – group 2, group 3 – group 4, and group 1 – group 3, respectively.

Population-attributable risks (PARs) were calculated using the formula $[PAR = P_e^*(RR_e-1)/1+P_e^*(RR_e-1)]$, where P_e is the proportion of population with exposure and RR_e is the relative risk of death among exposed compared to unexposed.

We conducted 3 sensitivity analyses including only (1) HIV patients of Danish origin and their controls, (2) males, and (3) HIV patients from centers in Copenhagen and their controls.

The study was approved by the Danish Data Protection Agency. Ethics approval and individual consent are not required by Danish legislation governing this type of research on HIV-infected individuals; however, studies on controls were approved by a Danish ethical committee (H-KF-01-144/01) and all controls provided written consent.

SPSS statistical software, version 15.0 (SPSS Inc, Chicago, Illinois) and Stata software, version 8.0 (StataCorp, College Station, Texas), were used for data analysis.

RESULTS

From the Danish HIV Cohort Study, we identified 5348 potential study subjects; 2427 were excluded because of injection drug use (n = 567), missing data on smoking status (n = 1497), or age <35 years at the end of the study period or at censoring (n = 363), leaving 2921 HIV patients in the study. Only 4 patients were lost to follow-up. A matched cohort of 10 642 individuals was extracted from the Copenhagen General Population Study (Table 1). The 2 study populations were followed for 14 281 and 45 122 PY, respectively. The median follow-up time was 4.2 years (interquartile range [IQR], 3.1–5.5) for HIV patients and 4.1 years (IQR, 2.9–5.8) for population controls. Among HIV patients, 47.4%, 17.7%, and 34.9% were current, previous, and never smokers, respectively, whereas the corresponding numbers for population controls were 20.6%, 32.8%, and 46.6%, respectively.

All-Cause Mortality

Current smokers had higher mortality than never smokers (Table 2). The excess mortality associated with smoking was markedly higher among HIV patients compared to population controls, whereas the relative risk of death associated with smoking did not differ. The mortality of never-smoking HIV patients did not differ from that of currently smoking population controls (MRR, 1.1 [95% confidence interval {CI}, .7–1.7]).

Among HIV patients, heavy smokers had higher mortality than those who smoked less (MRR, 4.2 [95% CI, 2.6–6.9] for ≥30 vs <30 cigarettes per day, and MRR, 7.5 [95% CI, 4.0–14.2] for heavy vs never smokers), and previous smokers had decreased mortality compared with current smokers (MRR, 0.6 [95% CI, .4–.9]).

In analyses including injection drug users, the MR per 1000 PY was 28.2 (95% CI, 24.8–32.1), 15.1 (95% CI, 11.4–20.2), and 7.8 (95% CI, 5.7–10.4) among current, previous, and nonsmokers, respectively.

AIDS-Related and Non-AIDS-Related Deaths

The risk of non-AIDS-related death was >5-fold higher among currently smoking compared to never-smoking HIV patients (Table 2). The risk of AIDS-related death was also increased. There was a tendency toward higher risk of violent death among current smokers compared to never smokers, although the difference was not statistically significant. Previous smokers had increased risk of AIDS-related death, but not of non-AIDS-related or violent death compared with never smokers.

Deaths Caused by Cardiovascular Disease and Cancer

The risk of death due to cardiovascular disease and cancer was markedly higher among current smokers compared to never smokers, whereas mortality in previous smokers was increased due to cancer but not cardiovascular disease (Table 2).

Life Expectancies and Life-Years Lost

The life expectancy of 35-year-old HIV patients differed markedly according to smoking status (62.6 years [95% CI, 60.9–64.9] for current smokers, 69.1 years [95% CI, 67.5–71.2] for previous smokers, and 78.4 years [95% CI, 71.9–84.9] for never smokers; Figure 1). The loss of life-years associated with smoking was twice as high as that associated with HIV (Table 3).

Population-Attributable Risks of Death

The population-attributable risk of death associated with smoking was considerably higher among HIV patients than among population controls owing to the larger proportion of smokers among HIV patients (Table 3).

Factors Associated With Risk of Death

In multivariable analysis including age, year of HIV diagnosis, excess consumption of alcohol, body mass index, CD4 cell count, and viral load at baseline, smoking was the factor associated with the highest risk of death (Supplementary Table 4). There were no interactions detected between smoking and age or other variables included in the model (Supplementary Table 5).

Table 1. Characteristics of the Study Population

	HIV Patients			Population Controls		
	Smoking Status			Smoking Status		
	Current	Previous	Never	Current	Previous	Never
No. of individuals	1384	518	1019	2194	3487	4961
Total observation time, y	6511	2829	4941	10 196	14 496	20 429
Deaths	156	37	30	63	41	28
Observation time, y[a]	4.3 (3.1–5.6)	4.2 (3.1–9.3)	4.5 (3.3–5.5)	4.5 (3.3–6.2)	4.0 (2.7–5.7)	4.0 (2.8–5.6)
Male	1186 (85.7)	415 (80.1)	680 (66.7)	1730 (78.9)	2647 (75.9)	3782 (76.2)
Age at baseline, y[a]	43 (38–51)	45 (39–54)	42 (37–52)	45 (39–53)	46 (39–55)	42 (37–49)
Origin						
Danish	1095 (79.3)	395 (76.3)	649 (63.8)	2194 (100)	3487 (100)	4961 (100)
African	86 (6.2)	52 (10.0)	236 (23.2)	0	0	0
Asian	46 (3.3)	19 (3.7)	75 (7.4)	0	0	0
Other	154 (11.2)	52 (10.0)	58 (5.7)	0	0	0
Body mass index, kg/m^2[b]						
<18.5	75 (7.8)	23 (6.3)	49 (6.9)	18 (0.8)	8 (0.2)	27 (0.6)
18.5–25	682 (70.8)	248 (67.4)	441 (61.9)	924 (42.3)	1203 (34.5)	2051 (42.5)
25–30	180 (18.7)	84 (22.8)	181 (25.4)	916 (42.0)	1687 (48.4)	2038 (42.2)
>30	26 (2.7)	13 (3.5)	41 (5.8)	322 (14.8)	585 (16.8)	710 (14.7)
No. of cigarettes per day[a]	20 (10–20)			15 (10–20)		
Excess alcohol consumption[b]	155 (17.6)	28 (9.5)	41 (5.8)	546 (24.9)	634 (18.2)	479 (9.9)
Route of transmission						
MSM	799 (57.7)	291 (56.2)	456 (44.8)			
Heterosexual	513 (37.1)	192 (37.1)	502 (49.2)			
Other	72 (5.2)	35 (6.8)	61 (6.0)			
Years since HIV diagnosis[a]	7.0 (2.5–12.4)	7.5 (3.0–13.6)	6.5 (2.9–10.7)			
CD4 count at baseline[a,b], cells/μL	480 (310–700)	425 (290–612)	444 (309–630)			
Viral load <400 cells/μL at baseline	875 (65.4)	355 (70.3)	748 (74.4)			
AIDS at baseline	309 (22.3)	115 (22.2)	223 (21.9)			
HAART at baseline	1027 (74.2)	412 (79.5)	800 (78.5)			
Years on HAART at baseline[a]	4.5 (2.7–7.7)	3.7 (2.8–6.9)	4.9 (2.9–7.7)			
Hepatitis C antibody positive	136 (9.8)	28 (5.4)	49 (4.8)			

Data are No. (%) unless otherwise specified.

Abbreviations: HAART, highly active antiretroviral therapy, HIV, human immunodeficiency virus; MSM, men who have sex with men.

[a] Median (interquartile range).

[b] No. of HIV patients with missing data for CD4: 54, alcohol consumption: 1031, BMI: 878; No. of controls with missing data: alcohol consumption: 4, BMI: 34.

Table 2. Mortality Rates and Adjusted Mortality Rate Ratios Stratified by HIV and Smoking Status

	Events, No.	Smoking Status			Excess Mortality Current vs Never Smoker, MR (95% CI)	Excess Mortality Previous vs Never Smoker, MR (95% CI)	Relative Mortality Current vs Never Smoker, MRR (95% CI)	Relative Mortality Previous vs Never Smoker, MRR (95% CI)
		Current, MR (95% CI)	Previous, MR (95% CI)	Never, MR (95% CI)				
HIV patients								
All-cause mortality	221	23.7 (20.2–27.7)	13.1 (9.4–18.1)	6.1 (4.2–8.7)	17.6 (13.3–21.9)	7.0 (2.3–11.7)	4.4 (3.0–6.7)	1.7 (1.0–2.8)
Non-AIDS related	142	16.3 (13.5–19.7)	6.0 (3.7–9.7)	3.8 (2.5–6.0)	12.4 (8.9–16.0)	2.2 (−1.2 to 5.1)	5.3 (3.2–8.8)	1.3 (.7–2.6)
AIDS related	58	5.2 (3.7–7.3)	6.0 (4.0–10.0)	1.4 (0.7–3.0)	3.8 (1.6–9.9)	4.6 (1.5–7.6)	4.0 (1.7–9.4)	3.1 (1.3–7.6)
Violent	21	2.2 (1.3–3.6)	1.1 (.3–3.3)	0.8 (0.3–2.2)	1.3 (.0–2.7)	0.3 (−1.2 to 1.7)	2.1 (.7–6.5)	0.9 (.2–4.1)
Cardiovascular disease	23	2.7 (1.7–4.3)	0.7 (.2–2.9)	0.8 (.3–2.2)	1.9 (.4–3.4)	−0.1 (−1.4 to 1.2)	4.3 (1.4–13.1)	0.8 (.2–4.4)
Cancer	54	5.1 (3.6–7.2)	5.1 (3.0–8.6)	1.7 (.8–3.3)	3.4 (1.3–5.5)	3.4 (.5–6.3)	3.5 (1.6–7.8)	2.7 (1.1–6.3)
Population controls								
All-cause mortality	132	6.2 (4.8–7.9)	2.8 (2.1–3.8)	1.4 (.9–2.0)	4.8 (3.2–6.4)	1.5 (.5–2.5)	3.5 (2.2–5.5)	1.3 (.8–2.1)

Poisson regression analyses adjusted for sex and age and, for HIV patients, for origin, route of transmission, year of HIV diagnosis, body mass index, excess alcohol consumption, CD4 count, and viral load at baseline.

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; MR, mortality rate per 1000 person-years; MRR, mortality rate ratio.

Sensitivity Analyses

Results of sensitivity analyses did not differ significantly from results of main analyses (1: HIV patients of Danish origin; 2: males; and 3: HIV patients from Copenhagen and their respective controls; Figures 1*B–D* and Supplementary Tables 2*B–D* and 3*B–D*).

DISCUSSION

We found that among HIV infected smokers the rate of non-AIDS-related deaths was raised >5-fold with markedly increased risk of death caused by cardiovascular disease and cancer. The loss of life-years associated with smoking was larger than that associated with HIV. Mortality was almost halved in previous smokers compared to current smokers. The relative risk of death associated with smoking did not differ between HIV patients and population controls, but HIV patients had considerably higher excess mortality associated with smoking. In addition, the proportion of current smokers was more than twice as high among HIV patients compared to the background population, and >60% of deaths in the HIV cohort were attributable to factors associated with smoking.

The prevalence of comorbidities and rates of death due to cardiovascular disease and cancer are higher among HIV patients than among individuals of the same age in the background population [17, 18]. It is debated whether the relative increase in morbidity and mortality is caused by continuous inflammation due to HIV and thereby accelerated aging in spite of HAART, or if it is caused by social factors, lifestyle, and risk-taking behavior [19, 20]. The present study illustrates that a larger part of the increased mortality among well-treated HIV patients is associated with smoking rather than HIV-related factors. Smoking has a number of toxic effects, one of which is induction of inflammation and thereby increased risk of morbidity (eg, cardiovascular disease). One might speculate that smoking could have a synergistic rather than additive effect on inflammation in HIV-infected individuals, but we found no interaction between HIV and smoking in the associated risk of death. Previous smoker HIV patients had increased risk of death due to cancer but not of death caused by cardiovascular disease. It is well known that the detrimental effects of smoking on cardiovascular disease diminish relatively shortly after smoking cessation, whereas the risk of cancer is increased for several years.

Previous studies of HIV patients in the post-HAART era have, in agreement with our findings, concluded that smoking is associated with increased mortality [21–23], as well as with increased risk of loss of bone density, pulmonary and cardiac disease, and malignancy [23–26]. Studies from the pre-HAART era did not find association between smoking and mortality [27–29], presumably because HIV-infected individuals died

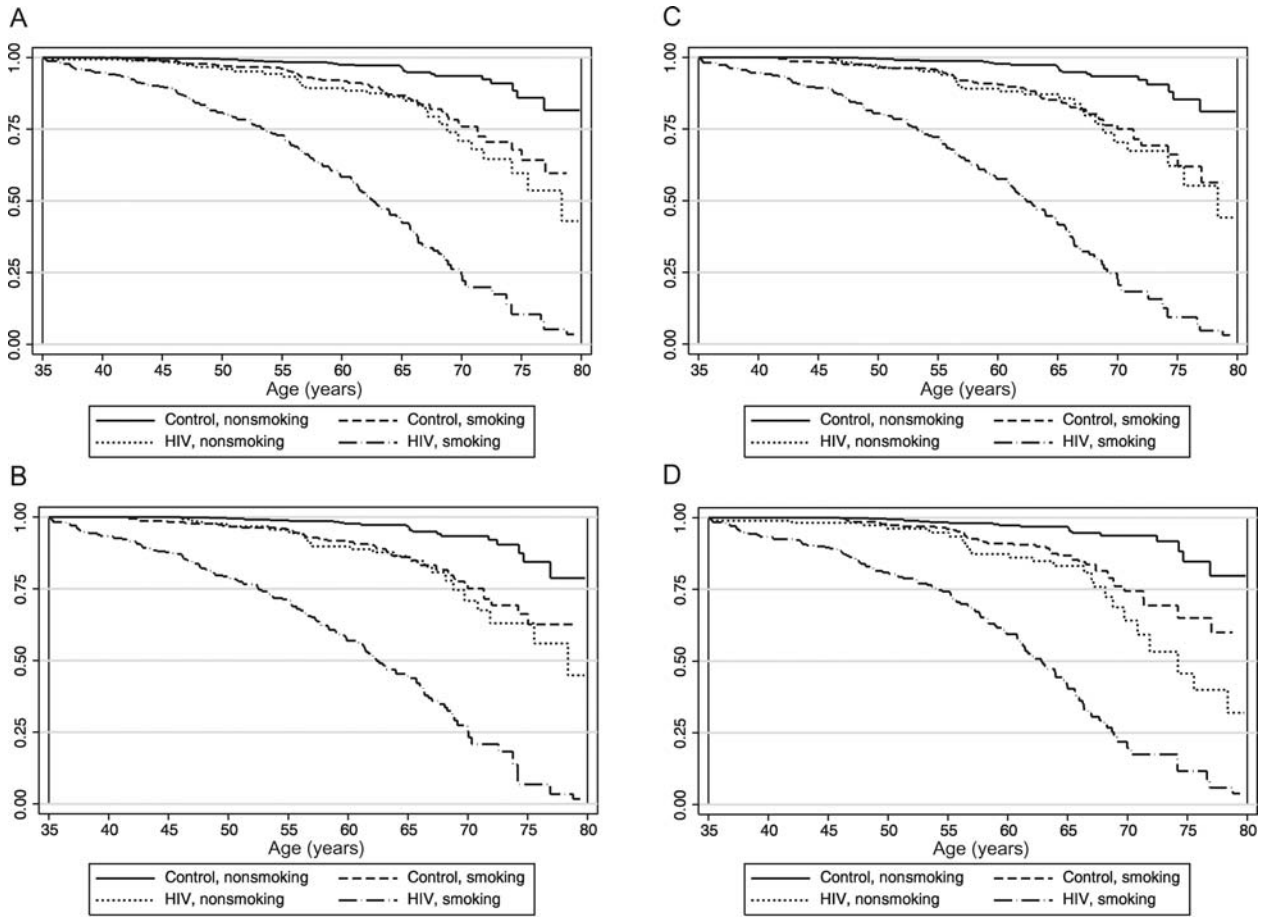

Figure 1. Kaplan-Meier curve showing survival by age, stratified by human immunodeficiency virus and smoking status for all study subjects (*A*), only males (*B*), only study subjects of Danish origin (*C*), and only study subjects from Copenhagen (*D*). Abbreviation: HIV, human immunodeficiency virus.

from AIDS at a young age and did not live long enough to develop severe morbidity related to smoking. We believe the present study is the first to estimate life expectancies of smoking vs nonsmoking HIV patients and life-years lost to smoking vs years lost to HIV and to estimate the attributable risk of death associated with smoking.

Our finding of lower mortality among previous compared to current smokers emphasizes the importance of counseling HIV patients on smoking cessation, as smoking may impact their life expectancy considerably more than the HIV infection itself. Owing to the high proportion of smokers among HIV patients, the population-attributable risk of death associated with smoking was large, which underscores the importance of prioritizing interventions for smoking cessation in the care of HIV patients as well as in the general population.

Injection drug users were excluded, as they differ markedly from the rest of the HIV-infected population regarding proportion of smokers, risk-taking behavior, mortality, and causes of death [30]. Observation time was left truncated at age 35 years owing to limited observation time and events in younger age groups. We excluded the first year after HIV diagnosis from the analyses as we aimed to evaluate risk factors for long-term mortality rather than the period shortly after diagnosis where the prognosis is closely associated with the immune status at the time of presentation [31, 32]. Time at risk was calculated from the date when the smoking status for the HIV patients was registered, which was a median of 6 years after HIV diagnosis, and therefore results can only be generalized to individuals aged >35 years who are not injection drug users and are rather stably engaged in HIV care in a well-organized healthcare system with free access to treatment.

A major strength of the study is the nationwide population-based design. The civil registration system, which assigns a unique registration number to each individual resident in Denmark, enabled linkage between different registries and long-term follow-up, and provided valid information on vital status of individuals under study with almost no loss to

Table 3. Number of Life-Years Lost and Population-Attributable Risk of Death Associated With Smoking and With HIV Among Individuals in the Danish HIV Cohort and the Copenhagen General Population Study (Controls)

Factor	Lost Life-Years (Age 35–80 y) Years (95% CI)	PAR, %
HIV among never smokers		
(never smoking HIV patients vs never smoking controls)	5.1 (4.4–5.8)	0.3
Smoking among controls		
(smoking controls vs never smoking controls)	3.6 (3.1–4.0)	34.4
Smoking among HIV patients		
(smoking HIV patients vs never smoking HIV patients)	12.3 (11.5–13.0)	61.5

Abbreviations: CI, confidence interval; HIV, human immunodeficiency virus; PAR, population-attributable risk.

follow-up. Inclusion of a large population control group allowed us to compare the effect sizes of smoking in HIV infected vs noninfected individuals as well as the effect size of smoking vs that of HIV on mortality among HIV patients.

The study has some limitations. We may have underestimated mortality of the background population by identifying the population control cohort among individuals participating in a general population health study of persons of Danish descent living in Copenhagen. This would bias our results toward overestimating the mortality associated with HIV. We did not have information about duration of smoking among the HIV patients and were not able to adjust analyses for this factor. However the majority of HIV patients start smoking at a young age (>50% of HIV patients in the cohort aged <25 years are current smokers), and thus we do not believe that the lack of data made us underestimate the effect of smoking in HIV patients compared to population controls and thereby fail to detect an interaction between smoking and HIV. Although the analyses were adjusted for a number of both HIV-related and non-HIV-related variables associated with mortality, residual confounding is likely. Smoking may be a marker of socioeconomic status and it is likely that the prominent risk associated with smoking in part reflects the social disparities between smokers and never smokers. In order to reduce bias, we excluded injection drug users, since almost all are smokers and generally have a low socioeconomic status, high risk-taking behavior, and markedly increased mortality from factors not related to HIV or smoking. The proportion of smokers is higher among individuals with low income or limited education [15, 16] and the relative increase in risk of death associated with smoking is similar between groups of individuals with different educational level [16]; thus, not being able to include social factors in the analyses may affect our estimates of the effect of smoking on mortality toward a higher risk. Smokers may have more risk-taking behavior than never smokers. Indeed the proportion of individuals with excess alcohol consumption was higher among smokers compared to previous and never smokers, which we adjusted for in analyses of MRRs. We also found a higher rate of violent deaths among smokers compared to never-smoking HIV patients, although this difference was not statistically significant. Previous smokers had lower mortality than current smokers. Individuals who manage to quit smoking may have a healthier lifestyle, which may explain part of the observed difference in survival.

We conclude that in a setting where HIV care is well organized and HAART is available free of charge, HIV-infected smokers with long-term engagement in care lose more life-years to smoking than to HIV. The excess mortality of smokers is tripled and the population-attributable risk of death associated with smoking is doubled among HIV patients in Denmark compared to the background population.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (http://www.oxfordjournals.org/our_journals/cid/). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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