

# Myocardial Infarction Among Danish HIV-Infected Individuals: Population-Attributable Fractions Associated With Smoking

Line D. Rasmussen,<sup>1</sup> Marie Helleberg,<sup>2</sup> Margaret T. May,<sup>3</sup> Shoaib Afzal,<sup>4,5</sup> Gitte Kronborg,<sup>6</sup> Carsten S. Larsen,<sup>7</sup> Court Pedersen,<sup>1</sup> Jan Gerstoft,<sup>2</sup> Børge G. Nordestgaard,<sup>4,5</sup> and Niels Obel<sup>2</sup>

<sup>1</sup>Department of Infectious Diseases, Odense University Hospital, and <sup>2</sup>Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Denmark; <sup>3</sup>School of Social and Community Medicine, University of Bristol, United Kingdom; <sup>4</sup>The Copenhagen General Population Study, and <sup>5</sup>Department of Clinical Biochemistry, Copenhagen University Hospital, Herlev Hospital, <sup>6</sup>Department of Infectious Diseases, Copenhagen University Hospital, Hvidovre Hospital, and <sup>7</sup>Department of Infectious Diseases, Aarhus University Hospital, Skejby, Denmark

(See the Editorial Commentary by Gill and Costagliola on pages 1424–5.)

**Background.** Human immunodeficiency virus-infected individuals have increased risk of myocardial infarction (MI); however, the contribution from smoking and potentiating effects of HIV are controversial.

**Methods.** From the Danish HIV Cohort Study and the Copenhagen General Population Study, we identified 3251 HIV-infected individuals and 13 004 population controls matched on age and gender. Data on MI were obtained from the National Hospital Registry and the National Registry of Causes of Death. We calculated adjusted incidence rate ratios (aIRR) for risk of MI and population-attributable fractions (PAF) of MI associated with smoking.

**Results.** In never smokers, HIV was not associated with an increased risk of MI (aIRR, 1.01; 95% confidence interval [CI], .41–2.54). In previous and current smokers, HIV was associated with a substantially increased risk of MI (aIRR, 1.78; 95% CI, .75–4.24 and aIRR, 2.83; 95% CI, 1.71–4.70). The PAF associated with ever smoking (previous or current) was 72% (95% CI, 55%–82%) for HIV-infected individuals and 24% (95% CI, 3%–40%) for population controls. If all current smokers stopped smoking, 42% (95% CI, 21%–57%) and 21% (95% CI, 12%–28%) of all MIs could potentially be avoided in these 2 populations.

**Conclusions.** Smoking is associated with a higher risk of MI in the HIV-infected population than in the general population. Approximately 3 of 4 MIs among HIV-infected individuals are associated with ever smoking compared with only 1 of 4 MIs among population controls. Smoking cessation could potentially prevent more than 40% of MIs among HIV-infected individuals, and smoking cessation should be a primary focus in modern HIV care.

**Keywords.** HIV; smoking; cardiovascular disease; population attributable risk.

The risk of cardiovascular disease in human immunodeficiency virus (HIV)-infected individuals has been extensively debated over the last decade. In several observational studies, a 1.5- to 2-fold increased risk of myocardial infarction (MI) among HIV-infected

individuals was seen [1–4]. Although prior observational studies have indicated that the higher risk of MI in HIV-infected individuals is due to drug toxicities associated with some antiretroviral drugs [1, 4–7], results from the Strategies for Management of Antiretroviral Therapy trial [8] in 2006 indicate that continuous exposure to highly active antiretroviral therapy (HAART) as opposed to drug-sparing regimens (CD4 count-guided HAART) not only reduced the risk of death but also the risk of MI. As such, the mechanisms that drive the association between HIV and risk of MI seem to rely on complex associations of known and unknown factors. In recent years, there has been an ongoing debate about the potential effects of chronic immune activation, persistent

Received 22 October 2014; accepted 18 November 2014; electronically published 16 February 2015.

Correspondence: Line D. Rasmussen, MD, PhD, Department of Infectious Diseases, Odense University Hospital, Sdr. Boulevard 29, 5000 Odense C, Denmark (linedahlerup@hotmail.com).

**Clinical Infectious Diseases**® 2015;60(9):1415–23

© The Author 2015. Published by Oxford University Press on behalf of the Infectious Diseases Society of America. All rights reserved. For Permissions, please e-mail: journals.permissions@oup.com.

DOI: 10.1093/cid/civ013

inflammation, and accelerated aging on risk of MI [9]. However, it is important to emphasize the effect of factors associated with an HIV-positive status, including ethnicity, socioeconomic factors, and behavioral and lifestyle-associated factors including a high prevalence of conventional cardiovascular disease risk factors.

Smoking is one of the largest contributors to MI worldwide [10] and possibly one of the predominant risk factors for MI among HIV-infected individuals [11]. As smoking is highly prevalent in the HIV-infected population (40%–70%), with rates 2- to 3-fold higher than in the general population and with a high average number of pack-years [12–14], smoking has profound health implications for the HIV-infected population [15–19]. In a recent study by our group [18], smoking was found to be associated with a 4.4-fold risk of all-cause mortality and a 5.3-fold risk of non-AIDS death. Furthermore, the number of life-years lost due to smoking in the HIV-infected population exceeded the number of life-years lost due to HIV itself [18]. It is therefore important to determine whether smoking has a higher impact on risk of MI among those who are HIV positive than HIV-negative smokers and to estimate to what extent smoking can explain the increased risk of MI in the HIV-infected population. We therefore estimated the risk of MI associated with smoking in HIV-infected individuals compared with that of the background population. In order to estimate the fraction of the risk of MI that could be prevented if the potential risk factors were eliminated, we calculated the population-attributable fraction (PAF) of MI associated with smoking in the Danish HIV-infected population and a matched population control cohort.

## METHODS

### Setting

As of 1 January 2013 Denmark had a population of 5.6 million, with an estimated HIV prevalence of 0.1% among adults. Treatment of HIV is restricted to 8 specialized centers where patients are seen on an outpatient basis at established intervals of 12–24 weeks. The healthcare in Denmark is universal tax-funded, and antiretroviral treatment is provided free of charge. HAART is prescribed according to national guidelines [20].

### Data Sources

We used the unique 10-digit personal identification number assigned to all individuals in Denmark at birth or upon immigration to track individuals in the national healthcare registries described below.

### Danish HIV Cohort Study

The Danish HIV Cohort Study (DHCS) is a nationwide, prospective, population-based cohort study of all Danish HIV-infected individuals treated at Danish hospitals since 1 January

1995; the study has been described in detail elsewhere [21]. DHCS is consecutively enrolling patients newly diagnosed with HIV and immigrants with HIV infection. Data on smoking have been collected prospectively since 2004 and were obtained retrospectively from medical files for patients who died or emigrated prior to 2004. DHCS included data on 6228 individuals diagnosed with HIV before 1 April 2013.

### Copenhagen General Population Study

The Copenhagen General Population Study (CGPS) is a prospective cohort study initiated in 2003 and still recruiting individuals randomly selected from greater Copenhagen [22, 23]. Study participants are interviewed about lifestyle and health-related factors.

### Danish Civil Registration System

The Danish Civil Registration System, established in 1968, is a national registry that stores information on vital status, residency, and migration for all Danish residents [24].

### Danish National Hospital Registry

The Danish National Hospital Registry (DNHR), established in 1977, records data on all patients discharged from nonpsychiatric hospitals and, since 1995, data on all visits to outpatient departments and emergency clinics in Denmark. Diagnoses were coded by the attending physician according to the *International Classification of Diseases*, 8th revision (ICD-8), until 31 December 1993 and according to the 10th revision (ICD-10) thereafter [25].

### Danish National Registry of Causes of Death

The Danish National Registry of Causes of Death (DNRC) contains information from all Danish death certificates since 1970, specifying up to 4 diagnoses according to ICD codes [26].

### Study Population

#### HIV Cohort

From DHCS we identified all HIV-infected individuals who were alive and living in Denmark at index date, were followed for HIV in Denmark between 1 January 1995 and 1 April 2013, had not reported injection drug use as the route of HIV infection, and had no diagnosis of MI prior to the index date.

#### General Population Comparison Cohort

The comparison cohort consisted of population controls from the Copenhagen General Population Study that were frequency matched according to gender and 5-year age intervals, with 4 controls per gender-specific age interval ([Supplementary Material](#)). The same criteria for inclusion as for the HIV-infected cohort had to be fulfilled.

### Outcome

The study outcome was time to incident MI, defined as the first date an individual was registered in the DNHR with 1 of the

**Table 1. Characteristics of the Study Population**

Characteristic	HIV-Infected Individuals			Population Controls		
	Never (34.3)	Previous (18.7)	Current (47.0)	Never (46.0)	Previous (34.4)	Current (19.5)
No. of individuals <sup>a</sup>	3233			12 932		
Male <sup>a</sup>	2548 (78.8)			10 192 (78.8)		
Age at baseline (years) <sup>b</sup>	44.6 (40.0–52.5)			44.8 (41.9–52.6)		
Total observation time (person-years)	18 263			63 128		
Myocardial infarctions <sup>a</sup>	95 (2.9)			125 (1.0)		
Incidence rate <sup>c</sup>	5.20 (4.25–6.36)			1.99 (1.66–2.36)		
	Smoking Status			Smoking Status		
	Never (34.3)	Previous (18.7)	Current (47.0)	Never (46.0)	Previous (34.4)	Current (19.5)
No. of individuals <sup>a</sup>	1108	604	1521	5955	4451	2526
Male <sup>a</sup>	737 (66.5)	495 (82.0)	1316 (86.5)	4685 (78.7)	3508 (78.8)	1999 (79.1)
Age at baseline (years) <sup>b</sup>	43.8 (40.0–52.1)	46.7 (40.5–55.3)	44.3 (40.0–51.6)	44.1 (41.4–49.7)	46.9 (42.5–55.6)	45.6 (42.3–53.7)
Origin						
Danish born <sup>a</sup>	680 (61.4)	448 (74.2)	1195 (78.6)	5955 (100)	4451 (100)	2526 (100)
Body mass index <sup>b,d</sup>	21.5 (19.5–23.9)	21.2 (19.3–23.4)	20.4 (18.3–22.4)	25.6 (23.5–28.11)	26.1 (24.0–28.8)	25.6 (23.4–28.4)
Total cholesterol <sup>b,d</sup>	5.3 (4.5–6.0)	5.2 (4.5–6.2)	5.3 (4.4–6.1)	5.4 (4.7–6.0)	5.5 (4.8–6.2)	5.6 (4.9–6.4)
Hypertension <sup>a</sup>	53 (4.8)	21 (3.5)	39 (2.6)	129 (2.2)	185 (4.2)	77 (3.0)
Diabetes <sup>a</sup>	40 (3.6)	15 (2.5)	40 (2.6)	50 (0.8)	82 (1.8)	36 (1.4)
Route of transmission						
Men who have sex with men <sup>a</sup>	469 (42.3)	329 (54.5)	847 (55.7)			
Heterosexual <sup>a</sup>	575 (51.9)	233 (38.6)	584 (38.4)			
Other <sup>a</sup>	64 (5.8)	42 (7.0)	90 (5.9)			
Hepatitis C <sup>a</sup>	61 (5.5)	34 (5.6)	149 (9.8)			
HIV before year 1995 <sup>a</sup>	287 (25.9)	221 (36.6)	513 (33.7)			
Years since HIV diagnosis <sup>b</sup>	7.2 (2.9–12.2)	7.5 (1.8–13.8)	7.7 (2.7–13.3)			
AIDS at baseline <sup>a</sup>	237 (21.4)	139 (23.0)	325 (21.4)			
CD4 cell count at baseline (cells/μL) <sup>b,d</sup>	470 (320–635)	440 (263–654)	503 (322–702)			
Viral load <400 copies/mL at baseline	839 (75.8)	419 (69.5)	1038 (68.7)			
HAART at baseline <sup>a</sup>	878 (79.2)	462 (76.5)	1157 (76.1)			
Years on HAART at baseline <sup>b</sup>	5.8 (3.1–8.6)	4.9 (2.8–8.3)	5.1 (2.6–8.4)			
Total observation time (person-years)	6301	3554	8407	27 987	21 413	13 728
Observation time (years) <sup>b</sup>	6.0 (3.3–7.3)	5.9 (3.3–7.3)	5.7 (3.1–7.3)	4.7 (2.7–6.4)	4.8 (2.7–6.7)	5.5 (3.4–7.7)
Death <sup>a</sup>	43 (3.9)	50 (8.3)	195 (12.8)	47 (0.8)	89 (2.0)	90 (3.6)
Emigration <sup>a</sup>	25 (2.3)	18 (3.0)	28 (1.8)	40 (0.7)	19 (0.4)	12 (0.5)
Loss to follow-up <sup>a</sup>	0 (0.0)	2 (0.3)	1 (0.1)	0 (0)	0 (0)	0 (0)
Myocardial infarctions <sup>a</sup>	9 (0.8)	16 (2.6)	70 (4.6)	36 (0.6)	40 (0.9)	49 (1.9)
Incidence Rate <sup>c</sup>	1.43 (0.74–2.75)	4.50 (2.76–7.35)	8.32 (6.59–10.52)	1.29 (0.93–1.78)	1.87 (1.37–2.55)	3.57 (2.70–4.72)

For conversion from the SI unit mmol/L to mg/dL: mg/dL cholesterol = mmol/L \* 38.6 [27].

Abbreviations: HAART, highly active antiretroviral therapy; HIV, human immunodeficiency virus; SI, International System of Units; VL, viral load.

<sup>a</sup> Number (%).

<sup>b</sup> Median (interquartile range).

<sup>c</sup> 95% confidence interval.

<sup>d</sup> Missing values: body mass index = 636; cholesterol = 112; CD4 cell count = 10, VL = 13.

following codes: ICD-8: 410.9, 410.99 and ICD-10: I21.0–22.9, or date of death caused by MI as registered in the DNRCD (Supplementary Material).

### Exposure

Individuals were classified as smokers if they reported to have smoked any kind of tobacco at least once per week. Individuals were categorized as current, previous, or never smokers on the basis of information on smoking status at time of study inclusion and did not change category during the observation period. In some analyses, smoking status was dichotomized into never smoker and ever smoker (current or previous).

### Covariates

Data on the following covariates were recorded: age (time-updated variable in 5-year intervals), gender, calendar year (before or after 2005), Danish origin, total cholesterol level and body mass index at date of study inclusion, and a diagnosis of diabetes mellitus or hypertension at or before study inclusion. In analyses comparing only HIV-infected individuals, we further adjusted for hepatitis C status, baseline CD4 cell count, and AIDS-defining diseases. Definitions and diagnostic codes of the covariates are included in Supplementary Material.

### Statistical Analysis

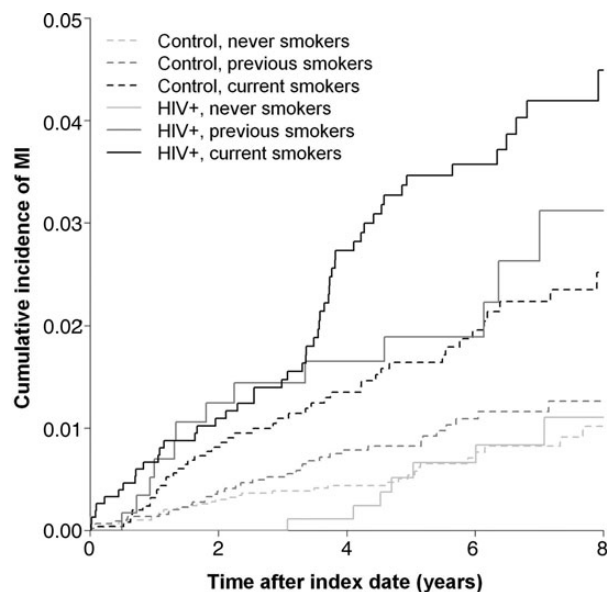
The index date was defined as 1 January 1999, HIV diagnosis, first available data on smoking status, age 40 years, or date of immigration, whichever was more recent. We computed time from index date until date of first MI, death, emigration, loss to follow-up, or 1 April 2013, whichever occurred first. Cumulative incidence functions were used to illustrate time to first diagnosis of MI, recognizing death from causes other than MI as a competing risk. We estimated the incidence rates and the excess incidence rates, and used Poisson regression analysis to compute incidence rate ratios (IRR) and 95% confidence intervals (CI) as a measure of the relative risk. Analyses were adjusted for potential confounders as described above. Interactions of clinical significance were examined using the likelihood ratio test. The PAF (and associated 95% CIs) of MI associated with smoking, which is the fraction of the incidence of MI in the population (exposed vs unexposed) that is associated with the exposure (smoking), was further computed based on the adjusted regression analyses [28].

In a sensitivity analysis, the estimated adjusted IRR (aIRR) and PAF were performed for men only.

SPSS statistical software, version 15.0 (SPSS Inc., Chicago, Illinois), STATA software, version 13.0 (StataCorp, College Station, Texas), and R version 2.11.1 were used for data analysis.

### Ethical Approval

Data from DNHR, DNRCD, and DNPR were obtained with approval from the Danish National Board of Health. The study was approved by the Danish Data Protection Agency (journal



**Figure 1.** Cumulative incidence of myocardial infarction (MI) among human immunodeficiency virus (HIV)-infected individuals compared with population controls, stratified by smoking status. Index date: 1 January 1999, HIV diagnosis, date of first available data on smoking status, age 40 years, or date of immigration, whichever was more recent.

2008-41-1781). Ethics approval and individual consent are not required by Danish legislation governing this type of research on HIV-infected individuals; however, the CGPS was approved by a Danish ethical committee (H-KF-01-144/01), and all individuals from the CGPS provided written informed consent.

## RESULTS

A total of 3765 individuals fulfilled the inclusion criteria, of whom 532 (14.2%) were excluded due to missing data on smoking status, leaving 3233 HIV-infected individuals and 12 932 matched population controls in the study. At baseline, 34.3%, 18.7%, and 47% of the HIV-infected individuals were never, previous, and current smokers compared with 46.0%, 34.4%, and 19.5% of the population controls, respectively. Additional characteristics are provided in Table 1.

The study gave rise to a total of 18 263 person-years of follow-up and 95 (2.9%) incident MIs for the HIV cohort and 63 128 person-years of follow-up and 125 (1.0%) incident MIs for the comparison cohort (Table 1).

The cumulative incidences of MI stratified on HIV status and smoking status are presented in Figure 1. The relative risk of MI among HIV-infected individuals was more than 2-fold that for the population controls (aIRR, 2.13; 95% CI, 1.47–3.09; Table 2). Due to an interaction term between HIV status and smoking status ( $P$  value, .02), we further stratified the analyses by smoking

**Table 2. Risk of Myocardial Infarction Among Human Immunodeficiency Virus-Infected Individuals and Population Controls**

Exposure	Events (n)	Person-Years of Follow-up	IR/1000 PY (95% CI)	Excess IR/1000 PY (95% CI)	Unadjusted IRR (95% CI)	Adjusted <sup>a</sup> IRR (95% CI)
Controls, all	125	63 128	1.98 (1.66–2.36)	Ref.	Ref.	Ref. <sup>a</sup>
HIV+, all	95	18 263	5.20 (4.25–6.36)	3.22 (2.11–4.32)	2.63 (2.01–3.43)	2.13 (1.47–3.09)
<b>Impact of HIV status stratified on smoking status</b>						
Controls, never smokers	36	27 986	1.29 (.93–1.78)	Ref.	Ref.	Ref. <sup>b</sup>
HIV+, never smokers	9	6301	1.43 (.74–2.75)	0.14 (–.88–1.17)	1.11 (.53–2.31)	1.01 (.41–2.54)
Controls, previous smokers	40	21 414	1.87 (1.37–2.55)	Ref.	Ref.	Ref. <sup>b</sup>
HIV+, previous smokers	16	3555	4.50 (2.76–7.35)	2.63 (.35–4.91)	2.41 (1.35–4.30)	1.78 (.75–4.24)
Controls, current smokers	49	13 728	3.57 (2.70–4.72)	Ref.	Ref.	Ref. <sup>b</sup>
HIV+, current smokers	70	8407	8.33 (6.59–10.52)	4.76 (2.57–6.95)	2.33 (1.62–3.36)	2.83 (1.71–4.70)
<b>Impact of smoking status stratified on HIV status</b>						
HIV+, never smokers	9	6301	1.43 (.74–2.75)	Ref.	Ref.	Ref. <sup>c</sup>
HIV+, previous smokers	16	3555	4.50 (2.76–7.35)	3.07 (.68–5.47)	3.15 (1.39–7.13)	2.64 (1.16–6.01)
HIV+, current smokers	70	8407	8.33 (6.59–10.52)	3.83 (.88–6.77)	5.82 (2.91–11.67)	6.06 (2.99–12.25)
Controls, never smokers	36	27 986	1.29 (.93–1.78)	Ref.	Ref.	Ref. <sup>b</sup>
Controls, previous smokers	40	21 414	1.87 (1.37–2.55)	0.58 (–.13–1.30)	1.45 (.93–2.28)	1.06 (.67–1.67)
Controls, current smokers	49	13 728	3.57 (2.70–4.72)	1.70 (.55–2.86)	2.77 (1.80–4.27)	2.22 (1.44–3.44)

Abbreviations: CI, confidence interval; HIV+, HIV-infected individuals; IR, incidence rate; IRR, incidence rate ratio; PY, person-year; Ref., reference.

<sup>a</sup> Adjusted for gender, age (time updated, 5-years interval–categorical) and calendar year (time updates, split at 2005–binary), Danish origin (binary), smoking status (fixed–categorical), body mass index (fixed–categorical), total cholesterol (fixed–categorical), diabetes mellitus (fixed–binary), and hypertension (fixed–binary) at baseline (see [Supplementary Materials](#) for further definition of the variables).

<sup>b</sup> Due to interaction between smoking status and HIV status, further analyses were stratified according to smoking status and adjusted as footnote a.

<sup>c</sup> Analyses comparing HIV-infected individuals were adjusted for baseline CD4 cell count (fixed–categorical), hepatitis C virus status (fixed–binary), and AIDS at baseline (fixed–binary).

status. These analyses showed that HIV infection was associated with increased risk of MI among individuals who reported current or previous smoking (aIRR, 2.83; 95% CI, 1.71–4.70 and aIRR, 1.78; 95% CI, .75–4.24), whereas no such association was found among never smokers (aIRR, 1.01; 95% CI, .41–2.54). When stratifying the analyses by HIV status, the excess and relative risk of MI associated with being a previous or current smoker compared with a never smoker was markedly higher in the HIV-infected population than in the population controls (Table 2).

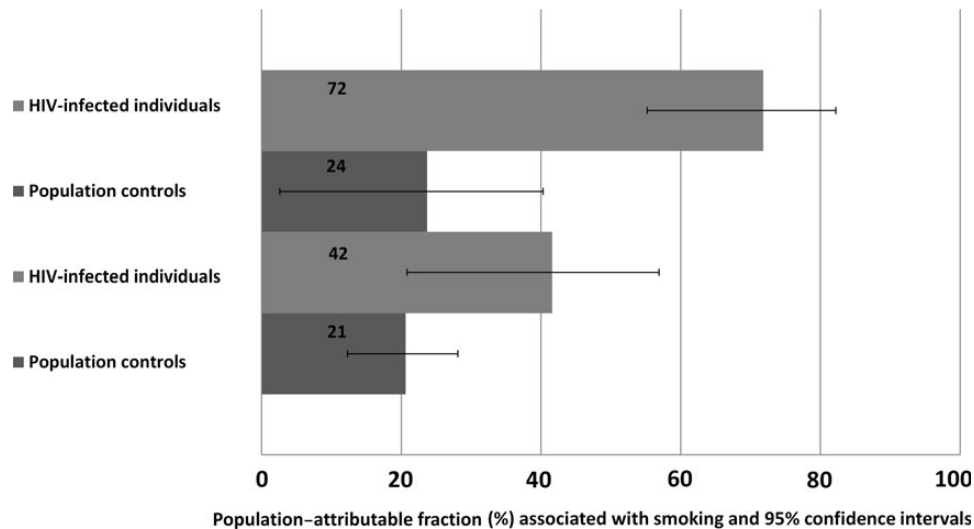
In the HIV-infected cohort, exposure to ever smoking (current and previous smoking) was associated with a PAF of 72% (95% CI, 55%–82%) of all MIs in this population (Figure 2). In contrast, a much lower PAF associated with ever smoking was found for an age- and gender-matched population control cohort (PAF, 24%; 95% CI, 3%–40%; Figure 2). If current smokers could obtain a risk equivalent to that of previous smokers, the

number of MIs in the HIV population could be reduced by 42% (95% CI, 21%–57%) and by 21% (95% CI, 12%–28%) in the population of matched population controls (Figure 2).

Including only men did not change the estimated aIRR or PAFs considerably ([Supplementary Material, Tables 1 and 2](#)).

## DISCUSSION

We found the prevalence of current smoking in the HIV-infected population to be more than 2-fold higher and the increased risk of MI among current smoking HIV-infected individuals to be almost 3-fold compared with current smoking population controls. However, no difference in risk was found between never-smoking individuals (HIV vs controls). The excess risk associated with previous and current smoking was much higher for HIV-infected individuals than for population controls. Ever



**Figure 2.** Population attributable fraction of myocardial infarction (MI) associated with smoking in the Danish human immunodeficiency virus (HIV)-infected population and an age- and gender-matched population control cohort. The upper 2 bars demonstrate the fraction of MIs that could be prevented if all individuals had the same risk as never smokers. The lower 2 bars demonstrate the fraction of MIs that could be prevented if current smokers obtained the same risk as previous smokers.

smoking was associated with more than 70% of all MIs diagnosed in the HIV-infected population but only approximately 25% of all MIs of an age- and gender-matched population cohort. If HIV-infected individuals who currently smoke stopped smoking, more than 40% of all MIs in the HIV population could potentially be prevented.

The strengths of our study include the use of a population-based, nationwide cohort of HIV-infected individuals and a well-matched population-based control cohort, both with a long observation period, almost complete follow-up, and access to data on smoking status. High-quality Danish registries provided full access to data on all individuals in the study concerning vital status, hospital contacts, and deaths. As almost all HIV-infected individuals with a history of injection drug use were smokers and differed considerably according to risk-taking behavior and prevalence of comorbidities, these individuals were excluded in order to avoid confounding [29]. Furthermore, IRRs were adjusted for confounders of importance. We estimated the PAF, which has a value in identifying potential priority areas in terms of public health burden. As the distribution of smoking status by sex differed in the 2 cohorts, we performed a sensitivity analysis that included men only. However, this did not have any major impact on the estimates.

The study has some limitations. We had to rely on hospital registry-based discharge diagnoses in order to identify MI, which may have led to misclassification. However, importantly we used the same source of data to ascertain MI diagnosis for both cohorts and included death of presumed ischemic etiology.

Using discharge diagnosis to identify MIs has previously been shown to be valid [30]. However, as we identified our population cohort among voluntary participants in a health study of Danish individuals living in Copenhagen and the DHCS is a population-based nationwide cohort, the 2 cohorts may differ according to ethnicity, socioeconomic status, educational level, sexual orientation, abuse, and health-seeking behavior. We excluded individuals with missing data on smoking status (14%), which may have introduced bias. However, as individuals with no data on smoking were mainly individuals who died before 2004 and individuals in whom death occurred shortly after the HIV diagnosis, our study mainly represents the HIV-infected population and setting as of today. As a clear dose-effect relationship of smoking and MI exists [10], the intensity, duration, and time since quitting may better predict the risk of MI; however, only categorical baseline measures (current/previous/never smoker) were available. Of note, the PAF assumes causality between the exposure and the outcome. Although our results may rely on the detrimental effects of tobacco, it may also in part reflect differences in behavior and social disparities (low socioeconomic and educational levels) associated with smoking status [17]. As such, we are aware that the results associated with smoking in our study may represent an underlying prevalence of other risk factors associated with being a smoker and do not apply a strict causal association.

A recent study by Freiburg et al [4], who identified their population controls from a broadly similar demographic, geographic, and behavioral background, found a relative risk of 1.48 of

MI in association with HIV, independent of cardiovascular risk factors. This is in agreement with our results of a 2-fold increased risk of MI and the results of previous studies [1, 5, 6, 31]. However, whereas Freiberg et al [4] found a relative risk of 1.75 when their samples were restricted to never smokers, we observed no such difference (aIRR, 1.01; 95% CI, .41–2.54). It cannot be ruled out that this may rely on lack of power. Yet, as we analyzed risk of MI in never-smoking HIV-infected individuals, using data from a nationwide cohort and detecting only a few events, it is crucial to consider that these results might actually illustrate the lack of excess risk associated with being HIV positive among never-smoking individuals.

The present study illustrated a 6-fold increased risk associated with current smoking among HIV-infected individuals. The excess and relative risks were markedly higher than those for other HIV cohorts [4–6, 13, 32] and higher than that associated with current smoking among population controls (aIRR, 2.22; 95% CI, 1.44–3.44). In addition, HIV-infected current smokers had a 2.83 times higher risk of MI than the current smoking population cohort. The magnitude of the MI risk has been shown to be linearly related to the number of cigarettes smoked [10]. Therefore, a high prevalence of heavy smokers among Danish HIV-infected individuals may be a plausible explanation for the observed effect modification. However, we cannot exclude an effect of smoking-associated risk behavior such as high alcohol intake or cocaine abuse, which may be higher among HIV-infected individuals. Furthermore, some of the antiretroviral drugs that have previously been found to be associated with risk of MI in several observational studies [1, 4–7, 33] might potentiate the effect of smoking. Finally, HIV-induced chronic inflammation may exacerbate the detrimental effect of smoking [34].

In our study, almost three quarters (PAF, 72%; 95% CI, 55%–82%) of all MIs among Danish HIV-infected individuals were attributable to factors associated with ever smoking and could potentially have been prevented if this population had never started smoking. This estimated PAF was much larger than that observed for the population controls of the same age and gender (PAF, 24%; 95% CI, 3%–40%). Yet, the latter result may rely on a lower prevalence of smoking as well as a lower relative risk associated with smoking for the population controls. As the estimated PAF depends on the prevalence and impact of the estimated risk factor in the population, and thus also the composition of the population, the PAF cannot be extrapolated directly between populations, cohorts, and countries. Given the lower prevalence of smoking among women, smoking confers a lower PAF for women than men [10, 12]. As women were underrepresented in our study, we could not generate valid estimates for females, and therefore the results cannot be generalized to women.

Lastly, smoking is associated with a loss of at least 10 years of life expectancy [35] in the general population compared with 12.3 years in the HIV-infected population [18]. Cessation of

smoking before age 40 years avoids about 90% of the excess hazards among continued smokers in the general population [35–37] and more than 97% of the excess mortality if stopping before age 30. In addition, the risk of MI among smokers aged <55 years has been shown to decrease within a few years of quitting to a level similar to that of men who have never smoked [38]. Although, a recent study could not illustrate similar reductions in mortality in association with smoking cessation among HIV-infected individuals, the aIRR of MI for current smokers compared with never smokers decreased from 3.73 to 2.07 among those who had stopped for more than 3 years [39]. Furthermore, the estimated benefit of smoking cessation in the HIV-infected population (PAF, 42%; 95% CI, 21%–57%) was double that found for the comparison cohort (PAF, 21%; 95% CI, 12%–28%). As a high consumption of alcohol, illicit drug use, and collateral psychiatric disorders as well as a lower socioeconomic status are highly associated with smoking in the HIV-infected population and their risk perception moreover might be inaccurate, smoking cessation programs may face numerous barriers prior to success [16, 40, 41]. Considering these results, specific designed interventions to reduce the prevalence of smoking should be highly prioritized, actively pursued, and integrated into modern HIV care.

## Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). 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

**Acknowledgments.** We are grateful to the staff of our clinical departments for their continuous support and enthusiasm.

**Financial support.** This work was supported by Preben og Anna Simonsens Fond, NOVO Nordisk Foundation, University of Copenhagen and University of Southern Denmark.

**Disclaimer.** The study was investigator driven and thus independent of any pharmaceutical company. The funding sources were not involved in study design, data collection, analyses, report writing, or decision to submit the paper. The authors had full access to all data in the study, and the responsibility for the decision to submit for publication was shared between all authors.

**Centers in the Danish HIV Cohort Study.** Departments of Infectious Diseases at Copenhagen University Hospitals, Rigshospitalet (J. G., N. O.) and Hvidovre (G. K.); Odense University Hospital (C. P.); Aarhus University Hospitals, Skejby (C. S. L.) and Aalborg (G. P.); Herning Hospital (A. L. L.); Hillerød Hospital (L. N.); and Kolding Hospital (J. J.).

**Author Contributions.** *Conception and design:* L. D. R., M. H., S. A., C. S. L., C. P., J. G., G. K., B. G. N., and N. O. *Analysis of the data:* L. D. R., M. H. *Statistical expertise:* L. D. R., M. H., M. T. M., N. O. *Interpretation of the data:* L. D. R., M. H., N. O. *Drafting of the article:* L. D. R. *Critical revision of the article for important intellectual content:* L. D. R., M. H., M. T. M., S. A., C. S. L., C. P., J. G., G. K., B. G. N., N. O. *Final approval of the article:* L. D. R., M. H., M. T. M., S. A., C. S. L., G. K., C. P., J. G., B. G. N., N. O. *Provision of study materials or patients:* S. A., C. S. L., C. P., G. K., J. G., B. G. N., N. O. *Obtaining of funding:* N. O., C. S. L., C. P., G. K., J. G., B. G. N. *Administrative, technical, and*

logistic support: L. D. R., M. H., N. O. Collection and assembly of data: S. A., C. S. L., C. P., G. K., J. G., B. G. N., N. O.

**Potential conflicts of interest.** N. O. has received research funding from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, GlaxoSmithKline, Abbott, Boehringer Ingelheim, Janssen-Cilag and Swedish Orphan Drugs. C. P. has received funding from Abbott and Merck Sharp & Dohme. J. G. has received research funding from Abbott, Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Pharmasia, GlaxoSmithKline, Swedish Orphan Drugs and Boehringer Ingelheim. M. T. M. is funded by the UK Medical Research Council and the Department for International Development (grant no. MR/J002380/1). All other authors report no potential conflicts.

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.

## References

1. Obel N, Thomsen HF, Kronborg G, et al. Ischemic heart disease in HIV-infected and HIV-uninfected individuals: a population-based cohort study. *Clin Infect Dis* **2007**; 44:1625–31.
2. Lang S, Mary-Krause M, Cotte L, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. *AIDS* **2010**; 24:1228–30.
3. Durand M, Sheehy O, Baril JG, Leloir J, Tremblay CL. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infarction: a cohort and nested case-control study using Quebec's public health insurance database. *J Acquir Immune Defic Syndr* **2011**; 57:245–53.
4. Freiberg MS, Chang CC, Kuller LH, et al. HIV infection and the risk of acute myocardial infarction. *JAMA Intern Med* **2013**; 173:614–22.
5. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* **2003**; 349:1993–2003.
6. Friis-Moller N, Reiss P, Sabin CA, et al. Class of antiretroviral drugs and the risk of myocardial infarction. *N Engl J Med* **2007**; 356:1723–35.
7. Obel N, Farkas DK, Kronborg G, et al. Abacavir and risk of myocardial infarction in HIV-infected patients on highly active antiretroviral therapy: a population-based nationwide cohort study. *HIV Med* **2010**; 11:130–6.
8. El-Sadr WM, Lundgren J, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med* **2006**; 355:2283–96.
9. Deeks SG. HIV infection, inflammation, immunosenescence, and aging. *Annu Rev Med* **2011**; 62:141–55.
10. Teo KK, Ounpuu S, Hawken S, et al. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* **2006**; 368:647–58.
11. Boccara F, Mary-Krause M, Teiger E, et al. Acute coronary syndrome in human immunodeficiency virus-infected patients: characteristics and 1 year prognosis. *Eur Heart J* **2011**; 32:41–50.
12. Saves M, Chene G, Ducimetiere P, et al. Risk factors for coronary heart disease in patients treated for human immunodeficiency virus infection compared with the general population. *Clin Infect Dis* **2003**; 37:292–8.
13. Calvo-Sanchez M, Perello R, Perez I, et al. Differences between HIV-infected and uninfected adults in the contributions of smoking, diabetes and hypertension to acute coronary syndrome: two parallel case-control studies. *HIV Med* **2013**; 14:40–8.
14. Tron L, Lert F, Spire B, Dray-Spira R. Tobacco smoking in HIV-infected versus general population in France: heterogeneity across the various groups of people living with HIV. *PLoS One* **2014**; 9:e107451.
15. Crothers K, Griffith TA, McGinnis KA, et al. The impact of cigarette smoking on mortality, quality of life, and comorbid illness among HIV-positive veterans. *J Gen Intern Med* **2005**; 20:1142–5.
16. Rahmanian S, Wewers ME, Koletar S, Reynolds N, Ferketich A, Diaz P. Cigarette smoking in the HIV-infected population. *Proc Am Thorac Soc* **2011**; 8:313–9.
17. Shirley DK, Kaner RJ, Glesby MJ. Effects of smoking on non-AIDS-related morbidity in HIV-infected patients. *Clin Infect Dis* **2013**; 57:275–82.
18. Helleberg M, Afzal S, Kronborg G, et al. Mortality attributable to smoking among HIV-1-infected individuals: a nationwide, population-based cohort study. *Clin Infect Dis* **2013**; 56:727–34.
19. Helleberg M, Gerstoft J, Afzal S, et al. Risk of cancer among HIV-infected individuals compared to the background population: impact of smoking and HIV. *AIDS* **2014**; 28:1499–508.
20. Petersen TS, Andersen SE, Gerstoft J, et al. Adherence to national guidelines for initiation of antiretroviral regimens in HIV patients: a Danish nationwide study. *Br J Clin Pharmacol* **2011**; 72:116–24.
21. Omland LH, Ahlstrom MG, Obel N. Cohort profile update: the Danish HIV Cohort Study (DHCS). *Int J Epidemiol* **2014**; 43:1769–1769e.
22. Nordestgaard BG, Palmer TM, Benn M, et al. The effect of elevated body mass index on ischemic heart disease risk: causal estimates from a Mendelian randomisation approach. *PLoS Med* **2012**; 9:e1001212.
23. Thomsen M, Nordestgaard BG. Myocardial infarction and ischemic heart disease in overweight and obesity with and without metabolic syndrome. *JAMA Intern Med* **2014**; 174:15–22.
24. Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* **2011**; 39(suppl 7):22–5.
25. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* **2011**; 39(suppl 7):30–3.
26. Juel K, Helweg-Larsen K. The Danish registers of causes of death. *Dan Med Bull* **1999**; 46:354–7.
27. European Association for Cardiovascular Prevention & Rehabilitation; Reiner Z, Catapano AL, De Backer G, et al; ESC Committee for Practice Guidelines (CPG) 2008–2010 and 2010–2012 Committees. ESC/EAS Guidelines for the management of dyslipidemia: the Task Force for the management of dyslipidemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). *Eur Heart J* **2011**; 32:1769–1818.
28. RB N. Attributable and unattributable risks and fractions and other scenario comparisons. *Stata J* **2013**; 13:672–98.
29. Larsen MV, Omland LH, Gerstoft J, et al. Impact of injecting drug use on mortality in Danish HIV-infected patients: a nation-wide population-based cohort study. *Addiction* **2010**; 105:529–35.
30. Madsen M, Davidsen M, Rasmussen S, Abildstrom SZ, Osler M. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol* **2003**; 56:124–30.
31. Holmberg SD, Moorman AC, Williamson JM, et al. Protease inhibitors and cardiovascular outcomes in patients with HIV-1. *Lancet* **2002**; 360:1747–8.
32. Lifson AR, Neuhaus J, Arribas JR, van den Berg-Wolf M, Labriola AM, Read TR. Smoking-related health risks among persons with HIV in the Strategies for Management of Antiretroviral Therapy clinical trial. *Am J Public Health* **2010**; 100:1896–903.
33. Sabin CA, Worm SW, Weber R, et al. Use of nucleoside reverse transcriptase inhibitors and risk of myocardial infarction in HIV-infected patients enrolled in the D:A:D study: a multi-cohort collaboration. *Lancet* **2008**; 371:1417–26.
34. Valiathan R, Miguez MJ, Patel B, Arheart KL, Asthana D. Tobacco smoking increases immune activation and impairs T-cell function in HIV infected patients on antiretrovirals: a cross-sectional pilot study. *PLoS One* **2014**; 9:e97698.
35. Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet* **2013**; 381:133–41.
36. Jha P, Ramasundarahettige C, Landsman V, et al. 21st-century hazards of smoking and benefits of cessation in the United States. *N Engl J Med* **2013**; 368:341–50.
37. Thun MJ, Carter BD, Feskanich D, et al. 50-year trends in smoking-related mortality in the United States. *N Engl J Med* **2013**; 368:351–64.
38. Rosenberg L, Kaufman DW, Helmrich SP, Shapiro S. The risk of myocardial infarction after quitting smoking in men under 55 years of age. *N Engl J Med* **1985**; 313:1511–4.



39. Petoumenos K, Worm S, Reiss P, et al. Rates of cardiovascular disease following smoking cessation in patients with HIV infection: results from the D:A:D study(\*). *HIV Med* **2011**; 12:412–21.
40. O’Cleirigh C, Valentine SE, Pinkston M, et al. The unique challenges facing HIV-positive patients who smoke cigarettes: HIV viremia, ART adherence, engagement in HIV care, and concurrent substance use. *AIDS Behav* **2015**; 19:178–85.
41. Schafer J, Young J, Bernasconi E, et al. Predicting smoking cessation and its relapse in HIV-infected patients: the Swiss HIV Cohort Study. *HIV Med* **2015**; 16:3–14.