EDITORIAL COMMENTARY

# Myocardial Infarction in HIV-Infected Persons: Time to Focus on the Silent Elephant in the Room?

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**(See the HIV/AIDS Major Article by Rasmussen et al on pages 1415–23.)**

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The landscape of human immunodeficiency virus (HIV) care shifted dramatically in 1996 with the arrival of new drugs and antiretroviral combinations. Many patients, while living their lives without the risk of AIDS-defining opportunistic infections or cancers, are now starting to experience medical conditions commonly associated with aging. The focus of much of their medical care has now shifted toward comorbidity management and treating the common conditions associated with aging. One area that has attracted intense attention is the high incidence of cardiovascular disease (CVD) being seen in individuals with HIV. HIV cohort studies now are consistently reporting an increased risk for experiencing a myocardial infarction (MI) of 1.5- to 2-fold [1]. Recent articles studying the causes of death in developed-country HIV cohorts have reinforced this concern by reporting that about 10% of deaths in their HIV patients are due to CVD and MI [2, 3]. The pathophysiology of the underlying processes explaining this figure is hotly debated and widely discussed [4]. There is evidence to suggest that HIV infection directly causes both chronic inflammation and lipid disturbances, which may act as an accelerant for incident CVD [4, 5]. A role for individual antiretroviral agents as well as classes of agents, either directly or indirectly through lipid perturbation or inflammation, has also been proposed as a contributing factor [6]. An unfavorable genetic background (in the context of traditional CVD risk factors) and poorly controlled hypertension have also both recently been proposed as contributors to the increased incidence of MI in HIV-infected populations [7, 8]. Intense basic science research and pharmaceutical company attention have been spent on explaining and offering strategies to clinicians for mitigating these risks. One confounding factor in many of the cohort observational studies is the well-known very high rate of tobacco smoking in the HIV-infected population [9]. Due to smoking's strong association with CVD, it has been the proverbial "silent elephant in the room" in any observational study exploring CVD in HIV infection.

In this issue of *Clinical Infectious Diseases*, Rasmussen et al explored the link between HIV infection, smoking, and the risk of MI in Denmark. They used for their study 3251 individuals from the Danish HIV cohort and 13 004 individuals matched for age and sex from the Copenhagen General Population Study. Data on MI were determined by registration in the hospital system as having had an *International Classification of Diseases, Eighth Revision* MI code and from the Danish National Registry of Causes of Death. Individuals with other risks for incident MI, such as a previous MI or injection drug use for their HIV risk, were excluded. The authors report that when compared to the Copenhagen population, HIV-infected never smokers had no increased risk for MI. Past and current smokers had a substantially increased risk for MI: relative risk, 1.78 (95% confidence interval [CI], .75–4.24) and 2.83 (95% CI, 1.71–4.70), respectively. The population-attributable fraction (PAF) of ever smoking (past or present) was 72% (95% CI, 55%–82%) for the HIV population and 24% (95% CI, 3%–40%) for the general Copenhagen population. The authors conclude that smoking cessation could help avoid a substantial proportion of MIs in the HIV population.

How can these results be interpreted? Excluding HIV-infected individuals with missing data on smoking (14.2%) may have introduced some selection bias

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complicating the interpretation of the study. The comparison population was the Copenhagen cohort study, whereas HIV-infected individuals were selected from the 8 clinical centers throughout Denmark. The risk in Copenhagen may be different from that in other parts of the country, and one may suspect that it is higher than in the rest of the country. This would lead to an underestimation of the differences in the risk of MI between HIV-infected individuals and the general population in the study. It is also unclear how results in the current article can be reconciled with previous works from the same group showing a higher risk of MI in those exposed to some antiretroviral drugs or classes of drugs [10, 11]. One previous study looking at this area has reported a 1.75 RR in HIV-infected never smokers [1]. Overall, the complete absence of excess risk in HIV-infected never smokers found in this study needs to be explained as it seems contrary to other research findings. In smokers, differences in rates of hepatitis C virus infection, cytomegalovirus infection [11], illicit drug use (not necessarily injection drugs), socioeconomic status, and ethnicity could also help to explain the difference in PAF between HIV-infected individuals and the Copenhagen general population. Smoking might be acting in the analysis as a surrogate for many of these conditions. Obviously, as acknowledged by the authors, the multivariate analysis cannot correct for all these differences.

Although it seems unlikely that the PAF of smoking is quite as high as estimated in the article by Rasmussen et al, this work should intensify clinicians' focus on addressing the dominant cause of MI in HIV populations—namely, smoking. Although lipid abnormalities, chronic inflammation, and antiretroviral drug selection still may play some role in MI pathogenesis, innovative approaches are desperately needed to reduce smoking and thereby the largest risk for MI in HIV patients. Patients being treated for HIV are already fully engaged into regular medical care, so smoking cessation should be the next logical step for many in optimizing their future health. Certainly the benefits of smoking cessation will extend well beyond decreasing the incidence of MI and CVD [12]. The PAF due to smoking in several other diseases, such as the malignancies commonly seen in HIV, is increasingly being investigated.

In summary, Rasmussen et al's useful analysis reminds us of the very high PAF of smoking in MI pathogenesis in HIV. Seizing every opportunity during HIV care delivery to focus our efforts to reduce the high rate of tobacco smoking offers the greatest potential for reducing MI rates. It is long overdue for us to recognize the elephant in the room of CVD in HIV infection. Encouragement and support for our patients in their efforts to stop smoking will offer immense health benefits [12].

## Note

***Potential conflict of interest.*** Both authors: No reported conflicts.

Both 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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