ONLINE FIRST

Getting to the Heart of HIV and Myocardial Infarction

For people infected with the human immunodeficiency virus (HIV) with access to antiretroviral therapy (ART), the benefits, particularly for those with low CD4+ T-cell counts, have been clearly established.[1] Management strategies have shifted firmly toward earlier HIV diagnosis to reduce HIV-related morbidity alongside increased ART access to maximize its benefits with a view to mitigating the potential detrimental effects of HIV infection on overall lifelong survival.

As the current era in HIV management evolves, it is increasingly apparent that, despite effective ART, people living with HIV experience excess comorbidities that may increase mortality and limit overall survival. Not surprisingly, as in the general population, cardiovascular diseases, such as myocardial infarction (MI), rank among the most common causes of death in treated HIV-positive populations.

In determining the causes of excess comorbidities such as MI, 3 main issues arise:

1. Is there a truly increased incidence of MI as a result of HIV infection or do observed, elevated rates simply reflect background disease rates that would be expected in a group of people with the demographic characteristics and risk factor profiles present within a HIV-positive population?
2. If HIV infection is implicated, what are the mechanisms whereby HIV infection and/or immune dysfunction drive increased MI?
3. How do potential ART-related toxicities influence the incidence of MI?

Until recently, much of the estimation of MI risk in HIV relied on cross-study comparisons of MI rates in HIV-positive populations with either published population rates or those derived from separate cohort studies of uninfected populations. These comparisons were based on a presumption that the HIV-positive populations were broadly similar to the comparator populations, with most studies unable to consider the likely effect of differences in socioeconomic and lifestyle factors within HIV-positive populations on resulting MI rates. Indeed, the potential effects of socioeconomic factors on treatment outcomes in HIV were recently discussed in this journal, where a study of mortality rates within an HIV-positive population showed significantly different mortality depending on sex, educational status, and race/ethnicity.[2] To date, relatively few studies have attempted to correct for this potential bias.

In this issue of *JAMA Internal Medicine*, Freiberg and colleagues[3] attempt to do exactly this by drawing their control population from broadly similar demographic and geographic backgrounds, therefore attempting to limit potential bias. They followed up a large (82 459 participants and 33.2% HIV positive) prospective cohort, examining incident MI rates in participants with and without HIV drawn from the Veterans Aging Cohort Study Virtual Cohort. The cohort has several advantages: its large size, the ability to draw detailed data on both HIV and MI from a number of linked databases, the diverse population, and the ability to match HIV-positive participants and HIV-negative controls for a variety of potential confounders, providing the capacity to better estimate the effect of HIV infection itself on MI rates.

Although the cohort studied was almost exclusively male (>97%), the results demonstrate a clear and consistent excess risk of MI (approximately 50% increase) in HIV-positive people across a range of age groups, with the association between HIV status and MI remaining significant when controlled for a number of covariates including traditional cardiovascular risk factors, such as lipids, blood pressure, and smoking status. In addition, study findings suggest that use of the Framingham risk assessment likely underestimates the risk of MI in HIV-positive populations.

For HIV-positive men, this study goes a long way toward clearly addressing the first of the 3 fundamental issues previously mentioned: that HIV-positive populations carry an approximately 50% relative increased risk of incident MI. That this excess risk cannot be explained by correction for traditional risk factors implicates either HIV infection or exposure to ART among potential underlying drivers.

Human immunodeficiency virus is characterized by a particular dyslipidemia; in untreated HIV infection, decreased high-density lipoprotein (HDL) cholesterol is prevalent and inversely correlates with HIV RNA levels, likely reflecting HIV-mediated interruption of the reverse cholesterol transport pathway through which cholesterol is cleared from peripheral tissues.[4] Contemporary ART-treated populations exhibit persistently decreased HDL cholesterol accompanied by modest increases in triglycerides rather than elevated low-density lipoprotein cholesterol, a pattern of dyslipidemia reflected in the study population of Freiberg et al.[3] Despite its being second only to age as the largest contributor to estimated 10-year cardiovascular risk in a cohort study[5] of HIV-positive people, we have only a limited un-

derstanding of why HDL cholesterol remains low in ART-treated, HIV-positive patients, and interventions to increase HDL cholesterol have been shown to be relatively ineffective in altering cardiovascular risk.

The persistent immune dysfunction in ART-treated, HIV-positive people also raises concerns that potential associated systemic inflammation may contribute to increased MI. In a large, prospective study[6] of HIV-positive patients both receiving and not receiving ART, those with higher markers of systemic inflammation experienced more cardiovascular disease events. Other than ART, effective interventions to reduce inflammation or modify the immune response in chronic HIV infection that also result in reductions in MI rates are not currently available.

Although, as Freiberg et al[3] rightly point out, the overall benefit of ART on mortality in HIV-positive people is clear, their study has limited capacity to determine associations between ART and the risk of MI. However, the Data Collection on Adverse Events of Anti-HIV Drugs study, a large (>170 000 person-years of follow-up), multicenter, prospective study examining incident MI in HIV-positive people, has determined an association between cumulative exposure to some protease inhibitors and nucleoside reverse-transcriptase inhibitors and MI, an effect that is not fully explained by traditional cardiovascular risk factors, including dyslipidemia.[7] However, although nontraditional pathways, such as altered platelet reactivity, have been implicated,[8] our understanding of the pathogenesis of how specific antiretrovirals contribute to cardiovascular disease risk and our options for mitigating these effects are limited.

Together, these data point to a significant excess risk of MI in HIV-positive people, the pathogenesis of which we do not clearly understand and which cannot be explained by traditional cardiovascular risk factors or accurately estimated using conventional cardiovascular risk assessments. Taking this into account, presuming that interventions used in the general population to reduce the risk of MI will translate into similar reductions in MI incidence in HIV-positive populations is arguably naive. That the HIV-positive cohort in the study by Freiberg et al[3] experienced a 50% increased risk of MI highlights the need for further research in women, research into the underlying mechanisms of the increased risk, and the development of specific interventions to reduce the risk of MI in HIV-positive populations.

Advances are being made; in addition to the publication of well-designed, robust studies such as that by Freiberg et al,[3] HIV-specific assessment tools have been developed to estimate cardiovascular disease risk in people with HIV (see http://www.cphiv.dk/tools.aspx). Furthermore, prospective, controlled studies, such as the Pharmacokinetic and Clinical Observations in People Over Fifty Study (http://clinicaltrials.gov/ct2/show/NCT01737047), focused on clinical end points, including MI, in HIV-positive and HIV-negative cohorts older than 50 years, an age range in which the majority of MI events occur, will help to better define the relative contribution of specific socioeconomic and lifestyle factors as well as HIV infection and exposure to ART on clinical outcomes. The collection of linked clinical samples within such studies will enable interrogation of disease pathogenesis that may provide a platform for the development of HIV-specific interventions to reduce this excess MI risk and ensure that the benefits derived from safe, effective, long-term control of HIV replication by ART translate into reduced mortality for all people living with HIV.

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