Can the Risk of Cardiovascular Disease in HIV-Infected Patients Be Estimated from Conventional Risk Prediction Tools?

Nina Friis-Møller1,2 and Signe Westring Worm1

1Copenhagen HIV Programme, Faculty of Health Sciences, University of Copenhagen, Panum Institute, Copenhagen, and 2Department of Infectious Diseases, Hvidovre University Hospital, Hvidovre, Denmark

(See the article by Kaplan et al. on pages 1074–81)

Although the striking benefits of combination antiretroviral therapy continue to prevail, a number of complications to treatment have been observed, including the increased risk of metabolic complications and the risk of cardiovascular disease associated with some antiretroviral drugs.

The preponderance of studies assessing clinical outcomes have identified a risk associated with protease inhibitor (PI) treatment [1–4]. In general, the incidence of cardiovascular disease is not high in most HIV-infected populations studied, which consist mainly of younger individuals (although, for all age groups, the incidence has been found to be higher among HIV-infected individuals than among matched HIV-uninfected control groups) [5–7]. For the individual, the absolute risk of cardiovascular disease results from the composite risk factor profile, comprising age, sex, diabetes status, family history of cardiovascular disease, and modifiable risks. With the aging of the HIV-infected population, brought about by improved survival among HIV-infected patients, it is likely that rates of cardiovascular disease in this population will increase in the future unless interventions to reduce risk factors are actively pursued. At present, cardiovascular disease is one of the most frequent causes of death in the HIV-infected population. Asymptomatic patients who are thought to be at high risk of cardiovascular disease need to be identified so that they can be offered advice about medical interventions and lifestyle changes.

Current guidelines recommend that the risk of cardiovascular disease be estimated from a conventional risk-prediction model, such as the Framingham score, which combines different risk factors into a numeric estimate of absolute risk. However, few studies have explored whether such models accurately predict the risk in HIV-infected patients. Such models may not accurately predict the risk in this population, because (1) these patients are generally younger than populations for whom risk-prediction tools were developed, (2) there may be an independent effect of the underlying HIV infection, (3) an independent effect of PI treatment has been observed, and (4) the effect of some of the conventional risk factors may differ from what has been observed in the background population, as outlined below.

In the Data Collection on Adverse Effects of Anti-HIV Drugs cohort collaboration, which includes HIV-infected persons from Europe, Australia, and the United States, an earlier prediction model from the Framingham Study [8] was found to slightly under-predict the risk of myocardial infarction, whereas the underestimation was even greater for a European prediction model [9].

The report by Kaplan et al. [10] in this issue of Clinical Infectious Diseases has applied a more recent Framingham risk prediction tool [11] to 2 large US cohorts of HIV-infected patients, the Women’s Interagency HIV Study (consisting of female patients) and the Multicenter AIDS Cohort Study (consisting of male patients), with HIV-uninfected comparison groups. Of note, the applied Framingham score does not incorporate diabetes, and in this study, the presence of diabetes was instead considered to be a “coronary heart disease (CHD) equivalent,” conferring a 10-year risk of CHD of ≥25% [12].

Overall, in the study by Kaplan et al. [10], 17% of HIV-infected men and 12%
of HIV-infected women were estimated to be at high (≥25%) 10-year risk of CHD. Much of this predicted risk was attributable to patients receiving a diagnosis of diabetes mellitus (diabetes prevalence was 11% and 18% in HIV-positive men aged <40 years and ≥40 years, respectively, and was 6% and 16% in HIV-positive women aged <40 years and ≥40 years, respectively).

However, it is currently unknown whether the CHD risk attributable to diabetes in patients with HIV infection is similar to what has been observed in the background population, in which diabetes is considered to confer a risk similar to that of established preexisting CHD [12, 13].

Diabetes is a known complication associated with several antiretroviral drugs, with current evidence suggesting acute effects from some PIs [14, 15], whereas long-term use of drugs from the nucleoside reverse-transcriptase drug class may induce diabetes [16]. The extent to which a predisposition to diabetes is being revealed by the effects of the drug, as opposed to diabetes occurring as the result of entirely novel mechanisms, is unclear. It is also not easy to disentangle the proportion of cases of new-onset diabetes observed in HIV-infected persons that are unrelated to the drug exposure. In the study by Kaplan et al. [10], a high diabetes prevalence was also observed in the HIV-uninfected comparison groups, and indeed, there are well-known major differences in background rates of diabetes in different populations.

Although there is evidence to support the belief that diabetes is an important risk factor for CHD in HIV-infected individuals [4], it will be important to establish whether antiretroviral therapy–induced diabetes constitutes a similar risk factor for the absolute risk of CHD as diabetes that occurs from other causes (e.g., hereditary, dietary, and sedentary lifestyle–related causes).

In the study by Kaplan et al. [10], as has also been reported elsewhere, many HIV-infected individuals had other conventional, modifiable risk factors for CHD. The prevalence of current smoking was high (35%–40%). High rates of smoking have often been observed in cohorts of HIV-infected individuals, as well as a high proportion of heavy smokers [4, 17, 18]. Of note, in the applied prediction model, smoking is fitted as a binary variable (as current smoking “yes” or “no”).

This does not take into account the well-known dose-response relationship of cigarette smoking and risk of CHD, nor does it take into account the increased risk observed in ex-smokers, which persists for years following smoking cessation [19]. For these reasons, the model may not accurately estimate the risk of CHD associated with smoking in this population.

Although data on smoking cessation programs suggest similar penetration in HIV-infected populations and HIV-uninfected populations [20], such support may not always be available. However, the beneficial effect of smoking cessation for this and other outcomes is irrefutable, and cessation should be encouraged.

The study confirms the observation from other studies of an increased CHD risk with exposure to PIs, estimating the 10-year CHD risk to be almost twice as high in PI-exposed individuals, compared with HAART-naive individuals, and 35% higher than the risk in those receiving non–PI-based HAART. Of note, these are predicted risks that are based on the observed risk factor profiles and do not take into account the potential independent effect of PI treatment over and above the effect of this drug class on lipid levels. Whether and how well predictions translate into actual observed differences in risk in the Women’s Interagency HIV Study and the Multicenter AIDS Cohort Study cohorts will require the study of clinical outcomes.

In the study by Kaplan et al. [10], obesity and low income were also found to be associated with increased likelihood of moderate-to-high CHD risk. This finding reflects more-severe risk factor profiles of the components included in the Framingham risk score (e.g., more-severe dyslipidemia and/or a higher prevalence of smoking) among patients with elevated body mass index and among those with low income, respectively. However, it does not address whether elevated body mass index or low-income status adds any independent predictive value. As such, this finding has local public health implications, because the identification of additional characteristics of HIV-infected men and HIV-infected women potentially in need of targeted intervention is valuable. Such characteristics may assist the daily clinical work, as an indicator for the need of intensive risk factor screening. However, the degree to which these findings can be extrapolated to other populations outside of the Women’s Interagency HIV Study and the Multicenter AIDS Cohort Study is questionable. There may well be inherent sociodemographic and CHD risk differences between low-income populations in different regions within and outside of the United States, hindering generalization of these data.

Current efforts are ongoing to develop standardized tools for more-precise CHD risk estimation tailored to HIV-infected individuals [21]. Such tools will facilitate the identification of at-risk individuals, further improving our ability to target interventions.

It would be desirable to have more studies assessing the validity of applying these tailored tools (when available), as well as the validity of conventional risk-prediction tools (such as the Framingham score), in HIV-infected populations (in particular, in different geographical regions and different ethnic groups). Until such data are available, the study of estimated risks, developed from models that have not been validated for HIV-infected patients, is an imprecise science. To better understand the risk factors for clinical disease, more prospective studies with long-term follow-up periods, data on HIV infection and antiretroviral-related exposures, complete cardiovascular disease risk factor screen-
ing, and thorough adjudication of CHD outcomes are required.

However, in daily clinical practice, even with the caveats and uncertainties outlined above, the risk-prediction tools at hand should be applied until a better alternative emerges. HIV-infected patients are generally followed up regularly (e.g., every 3–6 months) at the treating facility, which introduces the possibility of regular screening for cardiovascular disease risk factors. With many diverse issues to handle during short outpatient visits, the implementation of routine cardiovascular disease risk factor screening and risk prediction (e.g., on a yearly basis) to improve the means of identification of patients in need of interventions would be recommendable [22].

Acknowledgments


References