Time to change cardiovascular prevention in people with HIV

Today, people with HIV live longer because of antiretroviral therapy (ART) but experience a higher risk of comorbidities, including atherosclerotic cardiovascular disease.\(^1\) Increased risk of cardiovascular disease might be due to not only classic risk factors, which are over-represented in the HIV-positive population, but also additional factors not present in the general population. These factors include chronic inflammation associated with HIV infection (even if successfully treated) and the use of some antiretroviral drugs, through mechanisms that are poorly understood.\(^1\) Because cardiovascular events are rare, assessment of subclinical atherosclerosis measured by carotid artery intima-media thickness (cIMT) has been used as a surrogate marker of cardiovascular disease. cIMT reliably predicts cardiovascular events in the general population.\(^1\) However, the prognostic value of cIMT in people with HIV is not proven and comparisons of cIMT between HIV-positive and HIV-negative adults have shown discordant data.\(^4,5\)

In *The Lancet HIV*, Haijiang Lin and colleagues\(^6\) evaluated cIMT in HIV-positive adults across different ages and compared it with age-matched and gender-matched HIV-negative adults in Taizhou, China. The authors investigated to what extent the association of HIV infection with subclinical atherosclerosis could be due to a greater prevalence of classic cardiovascular risk factors in people with HIV or if HIV infection is associated with subclinical atherosclerosis, independent of the risk factors. They found that HIV-positive individuals had fewer classic cardiovascular risk factors and lower Framingham risk scores than did HIV-negative individuals. Despite these findings, HIV-positive individuals had a greater prevalence of subclinical atherosclerosis and a higher cIMT than did HIV-negative individuals after adjustment for age, gender, and Framingham risk score. Differences between HIV-positive and HIV-negative individuals were greater at younger ages and decreased gradually with increasing age until no difference was observed. This study provides a common explanation for previous discordant data and confirms that HIV infection alone, even when successfully controlled with suppressive therapy and after adjustment for age, gender, and other known cardiovascular factors, increases the risk of subclinical cardiovascular disease. The influence of HIV infection was better observed at younger ages because it was not overshadowed by the classic risk factors. It is particularly worrisome that 16% of HIV-positive individuals aged between 18 and 29 years had subclinical atherosclerosis.

Lin and colleagues’\(^6\) study has two important practical implications. First, the Framingham risk score and other similar scores used in the general population as predictors of cardiovascular disease, can underestimate subclinical atherosclerosis in people with HIV, limiting their clinical usefulness. Second, people with HIV, even those who are virologically suppressed, have an increased risk of subclinical atherosclerosis; and if they do develop the disease, they might need treatment options other than those offered by the current guidelines, which are the same as the recommendations for the general population.

The Pooled Cohorts Equation for Atherosclerotic Cardiovascular Disease did better than the Framingham risk score to assess subclinical atherosclerosis in a study of sub-Saharan HIV-positive adults;\(^7\) however, it underestimated cardiovascular risk in HIV-positive individuals in the USA and Europe.\(^8,9\) Tailored risk prediction scores, incorporating cardiovascular risk factors and specific factors related to HIV infection and ART, might result in more accurate risk estimation to guide cardiovascular prevention, but this could be a difficult task requiring large populations of HIV-positive people with a long-follow-up and no guarantee of success. The efforts of the D:A:D group to propose a cardiovascular risk score specifically developed for HIV-positive individuals are laudable,\(^10\) but it has the same problems of inaccuracy as other general scores and has not become popular. A more pragmatic approach is the direct measurement of cIMT to construct cIMT-based monitoring and prevention guidelines for HIV-positive people.

In any case, HIV infection itself renders a higher than expected cardiovascular risk. Large studies with hard clinical endpoints of common preventive therapies have not been done on people with HIV. Recommending standard preventive measures for people with HIV, which are outlined in major guidelines and recommended for the general population, intuitively makes sense, but it seems necessary that people with HIV should have earlier and more aggressive interventions to reduce HIV-related cardiovascular disease risk beyond suppressive ART. The well-powered REPRIEVE study (NCT02344290),
the largest clinical trial ever done in HIV-positive patients, will test whether administration of a statin (pitavastatin) to people with HIV with a low cardiovascular risk will have an effect on major cardiovascular events, subclinical atherosclerosis, inflammatory biomarkers, non-AIDS comorbidities other than cardiovascular disease, and death. If the results of the REPRIEVE study are favourable, they will dramatically affect the prevention of cardiovascular disease in people with HIV and establish a new standard in the clinical care of this population.

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