

Should everyone ageing with HIV take a statin?

Wherever antiretroviral therapy (ART) is available, people are ageing with HIV infection. But ageing with HIV is not the same as ageing without it. People with HIV have high incidences of ageing-associated disorders including cardiovascular, renal, liver, and lung diseases and cancers. HIV-1 RNA suppression and high CD4 cell counts decrease, but do not eliminate, these differences, and this situation shows our limited understanding of the long-term implications of chronic HIV infection.

Furthermore, the ageing experience depends on individual susceptibilities. For example, patients with HIV on ART co-infected with hepatitis C have a substantially higher risk of liver decompensation than do those with hepatitis C alone. Achieving HIV viral suppression does not eliminate excess risk.¹ Furthermore, people with HIV who drink alcohol at any level have a higher risk of advanced hepatic fibrosis than do those without HIV who drink. Those with HIV, viral hepatitis, and harmful alcohol use have very high risks of adverse liver outcomes.² Similarly, patients with HIV have a high risk of acute myocardial infarction after adjusting for known risk factors. This risk is diminished but not eliminated after patients achieve viral suppression.³

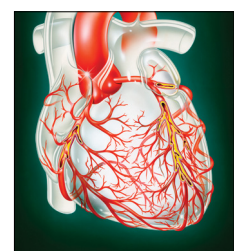
Observational studies can take us only so far. We do not know the extent to which we can further modify HIV-associated cardiovascular risk through expanded use of statins. Janet Lo and colleagues' study in *The Lancet HIV*⁴ is a welcome contribution. This randomised, double-blind, single-site, 12 month, placebo-controlled trial of statin administration included 40 people with HIV achieving and largely maintaining viral suppression who did not have an established indication for statin therapy but did have preclinical cardiovascular disease. The study has several key findings: preclinical cardiovascular disease is common in people with HIV on ART; patients on ART can tolerate statin therapy for 12 months without major toxic effects of treatment; and, comparing their results with previous research, statin therapy seems to have similar effects in those with HIV as in those without it. Although only a single-site study with modest power and without hard clinical endpoints, this study provided preliminary data in support of a multisite trial. The AIDS Clinical Trials Group A5332 Randomized Trial to Prevent Vascular Events in HIV (REPREIVE) has a targeted enrolment of 6500 participants and is just getting underway.

Unfortunately, even large randomised trials may not adequately explore untoward effects of statin treatment.⁵ Although biomarkers such as C-reactive protein or coronary plaque characteristics can help to understand the effects of statins on a well identified mechanism of cardiovascular disease, they do not reflect toxic effects that might affect other organs including the liver. Standard thresholds used for hepatotoxicity (aminotransferase abnormalities) are often insensitive indicators of substantial liver injury, and indicators of liver synthetic function (eg, albumin, total bilirubin, international normalised ratio) might be more clinically relevant.⁶ Progression of fibrosis, as determined by non-invasive modalities, might also be an important outcome.⁷ The effect of chronic drug therapies, such as a statin use, on progression of fibrosis is poorly understood but important in the setting of long-term use, particularly given the high prevalence of liver disease in people with HIV.⁸ Of note, about 20% of patients in the statin group were co-infected with hepatitis C virus, and whether chronic viral hepatitis increases the risk of statin hepatotoxicity is unknown.

Furthermore, although haemoglobin is closely associated with markers of inflammation (interleukin 6, D-dimer, and sCD14),⁹ there was no improvement in haemoglobin concentrations in either group. This finding might be because this group was, overall, quite healthy on the basis of the Veterans Aging Cohort Study Index with high haemoglobin measures at baseline.

An additional non-ART drug might adversely affect ART adherence:^{10,11} adherence rates were lower in statin users than in the placebo group. The investigators are to be recognised for doing a 12 month study, but longer observation periods are needed to understand the effect of adding lifelong statin use to ART. People with HIV begin to be exposed to chronic polypharmacy (typically defined as five or more drugs) at least a decade earlier than the general population.¹² Whereas ART is essential, the degree to which additional medication helps rather than causes harm remains to be seen. Harm from additional medication may depend upon total number of drugs in use and pre-existing organ system injury (which increase with age).

Lo and colleagues' study is informative, but is neither definitive nor generalisable. Before we expand the



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indication for statin use in people ageing with HIV we must carefully consider its effectiveness and safety over more extended periods and in the larger context of growing polypharmacy in ageing patients—particularly those with underlying chronic liver disease. We will inevitably need to prioritise treatments if we are to do more good than harm.

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