Anti-inflammatory therapy in well controlled HIV infection

In The Lancet HIV, the ADVICE study group1 report the results of the ADVICE study, which aimed to study the effect of vorapaxar in reducing deleterious pro-inflammatory and pro-coagulatory mechanisms in patients with well controlled HIV infection. Vorapaxar is an anticoagulatory drug that inhibits thrombin-induced platelet aggregation, and has not previously been studied in HIV.2 Vorapaxar is an antagonist of proteinase-activated receptor 1 (PAR-1), and findings from previous studies suggest that PAR-1 is upregulated by CD4 and CD8 cells, even in well suppressed HIV infection. In the setting of a multicentre, double-blind, placebo-controlled trial, the investigators randomly assigned 65 patients with suppressed HIV viraemia, who were taking antiretroviral therapy (ART) containing an integrase inhibitor or rilpivirine, and who had D-dimer concentrations greater than 200 ng/mL, to receive placebo (n=31) or vorapaxar (n=34). Merck provided vorapaxar and placebo but, according to the authors, was not involved in planning or conduct of the study, or in analysis of the results.

Vorapaxar was well tolerated and had a safety profile comparable with placebo; most notably, and by contrast with previous trials, the number of bleeding events was similar between groups (n=13 in the placebo group vs n=12 in the vorapaxar group). However, after 8–12 weeks, vorapaxar did not reduce serum concentrations of biomarkers that have well recorded associations with cardiovascular endpoints in HIV, including D-dimer (the primary endpoint), interleukin 6 (IL-6), high sensitivity C-reactive protein, soluble CD14, or soluble CD163. Biomarker concentrations did not decrease with vorapaxar during the 12-week treatment phase, nor did biomarkers rebound during the 18 weeks thereafter. For example, D-dimer concentrations decreased to a similar, modest degree with both placebo (mean percent change –8.5%, 95% CI –18.4 to 2.5) and vorapaxar (–10.8%, –23.1 to 3.4). The authors speculate that a different dose or a loading dose of vorapaxar might have shown favourable effects. However, on the basis of these biomarker results, the authors conclude that vorapaxar is not worth pursuing in an expensive large clinical endpoint trial.

How solid is the link between HIV infection, inflammation, and cardiovascular events? Concentrations of pro-inflammatory and pro-coagulatory biomarkers are increased in HIV infection before the start of antiretroviral therapy or when antiretroviral therapy is interrupted; IL-6 and D-dimer are associated with AIDS and non-AIDS (eg, cardiovascular) events; biomarker concentrations decrease along with suppression of HIV viraemia during effective antiretroviral therapy; and biomarkers remain increased thereafter, compared with HIV-negative controls.3,4 However, although HIV infection was associated with a several-times increase in cardiovascular event rate in early reports,5 in a large North American analysis6 HIV was associated with only a 21% increase in incidence of cardiovascular events (95% CI 2.45). In some studies, HIV-positive people had no increased cardiovascular risk. For example, Swiss HIV-positive people had neither more clinical cardiovascular events,7 nor more subclinical atherosclerosis on coronary CT angiography8 than did HIV-negative controls. Indeed, coronary atherosclerosis involvement and severity scores were lower than in HIV-negative people who had similar Framingham risk scores.

Are trials of anti-inflammatory drugs in HIV addressing the right question? In many HIV-positive people with regular follow-up, successful modern antiretroviral therapy regimens, and decreasing smoking rates in recent years,9 cardiovascular risk probably is not increased, amounts of deleterious systemic inflammation are presumably low, and anti-inflammatory therapy is unlikely to be worthwhile pursuing. Additionally, although the link between inflammation and cardiovascular disease in HIV is robust, an effective drug that successfully lowers residual inflammation or cardiovascular events in HIV remains elusive: chloroquine,10,11 aspirin,12 and most recently, low-dose weekly methotrexate,13 neither reduced inflammatory biomarkers nor improved endothelial function in HIV-positive people in the USA. Even pitavastatin, the statin being used in an ongoing primary cardiovascular prevention trial in HIV (REPRIEVE, NCT02344290), reduced only certain inflammatory biomarkers after 52 weeks of treatment compared with pravastatin, and to only a modest degree.14 Therefore, any putative cardiovascular benefit of pitavastatin in REPRIEVE should probably be expected more from its lipid-lowering activity15 than from any anti-inflammatory action.

For now, in people with well suppressed HIV, the hypothesis remains unproven that either inflammation.
or cardiovascular events can be further reduced with anti-inflammatory therapy. Meanwhile, the negative results of the ADVICE study remind us of the interventions already at hand to reduce non-AIDS comorbidities: early diagnosis, an early start of antiretroviral therapy, and management of cardiovascular risks, including a healthy, non-smoking lifestyle.

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PET reports grants from Gilead Sciences and ViiV Healthcare. AC reports grants from Gilead Sciences, ViiV Healthcare, AbbVie, Merck Sharpe & Dohme, and Bristol-Myers Squibb outside the submitted work.