Another statin option in HIV

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In *The Lancet HIV*, Judith Aberg and colleagues present results of the INTREPID study.[1] This study was a multicentre, double-blind, double-dummy, randomised clinical trial comparing the safety and lipid lowering effects of pitavastatin (4 mg daily) and pravastatin (40 mg daily) in 252 people with HIV and dyslipidaemia. Study participants were on suppressive antiretroviral therapy (ART), more than 80% were white men, and those with glucose intolerance, established diabetes, or coronary artery disease were not eligible to participate.

At 12 weeks, LDL cholesterol decreased more with pitavastatin than with pravastatin and these effects were sustained at 52 weeks. The proportion of adverse events were similar between the two treatment groups and no effect on fasting glucose, insulin, or glycosylated haemoglobin was recorded. This finding is important given the increased risk of diabetes with statins, particularly with high-dose statin therapy[2] and with rosuvastatin.[3] HIV clinicians will welcome the results of the INTREPID trial because they establish pitavastatin as an additional appropriate option to treat dyslipidemia also in HIV.

Because pitavastatin is considered to be a weaker LDL-lowering drug than atorvastatin and rosuvastatin,[4] we are reassured by the efficacy of pitavastatin in INTREPID (median LDL cholesterol decrease of 31·1%). However, pitavastatin fared better in a randomised, placebo-controlled trial[5] that the authors previously did in people without HIV (median LDL cholesterol concentration decrease of 38·1%). Statins are believed to be less effective at lowering LDL cholesterol concentrations in people with HIV than in the general population because of drug interactions or concurrent use of antiretroviral drugs that promote dyslipidaemia. This notion was confirmed in a large retrospective analysis[6] of 550 people with HIV and 5170 seronegative patients starting statin therapy but the difference was relatively small (–25·6% adjusted LDL cholesterol change in people with HIV versus –28·3% in seronegative people).

Among statins, pitavastatin and pravastatin have the advantage of few drug interactions with ART because they are minimally metabolised by hepatic cytochrome P450 enzymes. More than 20% of INTREPID participants were treated with protease inhibitors that are no longer among preferred drugs because of their association with atherogenic dyslipidaemia, according to European and US ART guidelines. In some of these patients, changing the protease inhibitor to a drug that causes fewer metabolic disturbances could have made a statin unnecessary. Moreover, ritonavir-boosted protease inhibitors have a high interaction potential with statins. With the increasing use of integrase inhibitors with few drug interactions in recent years, such as dolutegravir and raltegravir, the clinical need for statins with low drug interaction potential has become less urgent. Nonetheless, pitavastatin might be a valuable, alternative statin choice in patients with dyslipidaemia treated with integrase inhibitors who are unable to tolerate other statins.

Is it a problem that the INTREPID study was fully funded, implemented, and analysed by the manufacturers of pitavastatin? We believe not; the authors appropriately disclose this information and the study was well conducted. However, the funders are likely to explain why pravastatin was selected as comparator. Pravastatin is a relatively weak statin,[4] and, of particular interest to HIV, pravastatin might not[5] (but atorvastatin might[7,8]) reduce markers of chronic T-cell activation in people with HIV.

What is next? The effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in INTREPID have now been published.[9] At week 52 and compared with pravastatin, pitavastatin led to somewhat larger reductions in some biomarkers (soluble CD14, oxidised LDL, and lipoprotein-associated phospholipase A2 [Lp-PLA2]) but no differences in other biomarkers that are also of interest to researchers in the field (soluble CD163, interleukin 6, monocyte chemoattractant protein-1). Also, in a study[10] done in HIV-negative people, pitavastatin showed no effect (at a 2 mg daily dose) on Lp-PLA2.

Importantly, we do not yet know whether statin treatment translates into meaningful clinical benefits in people with HIV. Statin therapy reduces atherosclerotic plaque in people with HIV[11] but conclusive data that statins reduce the cardiovascular event rate in this population are not yet available.[12,13] This finding is perhaps surprising given the substantial attention to the notion of accelerated atherosclerosis, or even accelerated aging, in people with HIV in the past few years.

Hopes are therefore high that the ongoing REPRIEVE trial (NCT02344290), sponsored by the manufacturer of pitavastatin and the US National Heart Lung and Blood Institute, will answer this question.[14] REPRIEVE investigators intend to randomise 6500 people with HIV aged 40–75 years without known cardiovascular disease to pitavastatin 4 mg per day versus placebo and assess the cardiovascular event rate during 6 years of follow-up. Meanwhile, that lipid-lowering treatment with statins is as relevant to people with HIV at increased cardiovascular risk as it is in the general population remains a reasonable but unproved assumption.

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1 Aberg JA, Sponseller CA, Ward DJ, Kryzhanovski VA, Campbell SE, Thompson MA. Pitavastatin versus pravastatin in adults with HIV-1 infection and dyslipidaemia (INTREPID): 12 week and 52 week results of a phase 4, multicentre, randomised, double-blind, superiority trial. *Lancet HIV* 2017; published online April 13. http://dx.doi.org/10.1016/S2352-3018(17)30075-9.

2 Preiss D, Seshasai SRK, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. *JAMA* 2011; **305:** 2556–64.

3 Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med* 2008; **359:** 2195–207.

4 Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation* 2014; **129:** S1–45.

5 Sponseller CA, Morgan RE, Kryzhanovski VA, Campbell SE, Davidson MH. Comparison of the lipid-lowering effects of pitavastatin 4 mg versus pravastatin 40 mg in adults with primary hyperlipidemia or mixed (combined) dyslipidemia: a phase IV, prospective, US, multicenter, randomized, double-blind, superiority trial. *Clin Ther* 2014; **36:** 1211–22.

6 Silverberg MJ, Leyden W, Hurley L, et al. Response to newly prescribed lipid-lowering therapy in patients with and without HIV infection. *Ann Intern Med* 2009; **150:** 301–13.

7 Ganesan A, Crum-Cianflone N, Higgins J, et al. High dose atorvastatin decreases cellular markers of immune activation without affecting HIV-1 RNA levels: results of a double-blind randomized placebo controlled clinical trial. *J Infect Dis* 2011; **203:** 756–64.

8 Overton ET, Sterrett S, Westfall AO, et al. Effects of atorvastatin and pravastatin on immune activation and T-cell function in antiretroviral therapy-suppressed HIV-1-infected patients. *AIDS* 2014; **28:** 2627–31.

9 Toribio M, Fitch KV, Sanchez L, et al. Effects of pitavastatin and pravastatin on markers of immune activation and arterial inflammation in HIV. *AIDS* 2017; **31:** 797–806.

10 Lee HS, Jung CH, Kim SR, et al. Effect of pitavastatin treatment on ApoB-48 and Lp-PLA2 in patients with metabolic syndrome: substudy of PROspective comparative clinical study evaluating the efficacy and safety of PITavastatin in patients with metabolic syndrome. *Endocrinol Metab (Seoul)* 2016; **31:** 120–26.

11 Lo J, Lu MT, Ihenachor EJ, et al. Effects of statin therapy on coronary artery plaque volume and high-risk plaque morphology in HIV-infected patients with subclinical atherosclerosis: a randomised, double-blind, placebo-controlled trial. *Lancet HIV* 2015; **2:** e52–63.

12 Moore RD, Bartlett JG, Gallant JE. Association between use of HMG CoA reductase inhibitors and mortality in HIV-infected patients. *PLoS One* 2011; **6:** e21843.

13 Rasmussen LD, Kronborg G, Larsen CS, Pedersen C, Gerstoft J, Obel N. Statin therapy and mortality in HIV-infected individuals; a Danish nationwide population-based cohort study. *PLoS One* 2013; **8:** e52828.

14 Gilbert JM, Fitch KV, Grinspoon SK. HIV-related cardiovascular disease, statins, and the REPRIEVE Trial. *Top Antivir Med* 2015; **23:** 146–49.