Rosuvastatin was not beneficial in reducing arterial stiffness and may be associated with cardiometabolic adverse events in men with HIV

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AIDS 2024, **38**:1720–1721

Statins, also known as hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, are a class of drugs widely prescribed to lower plasma low-density lipoprotein (LDL) cholesterol, thereby reducing the risk for development of atherosclerosis and cardiovascular disease (CVD) [1]. Statins inhibit HMG-CoA reductase enzyme which is key in the mevalonate pathway of cholesterol synthesis [2]. HMG-CoA reductase catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol production within the liver [3]. By inhibiting HMG-CoA reductase, statins block mevalonate synthesis, decreasing intracellular cholesterol levels [4]. The reduction in hepatic cholesterol levels triggers an upregulation of LDL receptors on hepatocyte surfaces, enhancing the clearance of LDL cholesterol from the bloodstream [5]. A consequential decrease of plasma LDL cholesterol levels is a desired outcome in reducing atherosclerosis and associated CVD [6]. Moreover, statins also exhibit pleiotropic effects, including improving endothelial function, stabilizing atherosclerotic plaques, and antithrombotic effects, reduction of oxidative stress, anti-inflammatory properties, immunomodulation, and optimizing bone metabolism [7]. These additional benefits further contribute to the cardio-protective effects of statins beyond their cholesterol-lowering capacity.

While their role in reducing CVD risk is well established in the general population, there is still limited evidence on the effectiveness of statins in specific populations such as people with HIV (PWH). Studying the effectiveness of drugs in particular populations is of utmost importance as some pathological conditions and medications may influence the efficacy of some drugs [8]. The findings of such studies could prove invaluable to healthcare providers when making decisions in patient management, thus increasing the prospects of positive health outcomes especially in PWH who are disproportionately at increased risk for development of CVD.

Pulse wave velocity (PWV) is the speed at which pressure waves generated by the systolic heart contraction travel through the arterial system [9]. It is a widely used indicator of arterial stiffness, with higher PWV values signifying increased arterial rigidity [10]. PWV is a reliable predictor of cardiovascular events and overall cardiovascular health, as increased arterial stiffness is associated with a higher risk of heart disease and other cardiovascular conditions [11]. Therefore, PWV is recognized as a strong predictor of cardiovascular events and all-cause mortality, with each 1 m/s increase in PWV correlating with a 12% rise in CVD risk [12]. Given its predictive value, PWV offers a noninvasive method to identify individuals who might benefit from interventions such as statin therapy [13].

Trevillyan *et al.* [14], in this issue of *AIDS*, conducted a study investigating whether rosuvastatin, a statin, reduces PWV in PWH, thus potentially lowering their cardiovascular risk. Their study was a single-center sub-study within a larger, multicenter double-blind, randomized, placebo-controlled trial. Their study included 55 male participants with HIV, stable on antiretroviral therapy, with controlled viral loads, and a moderate CVD risk as

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Received: 7 June 2024; accepted: 9 June 2024.

DOI:10.1097/QAD.0000000000003957

defined by a Framingham risk score of 10–15%. The study randomly assigned participants to receive either rosuvastatin (20 mg, or 10 mg for those on ritonavir or cobicistat) or a placebo for 96 weeks with PWV measurements being taken at baseline, 48 weeks, and 96 weeks using tonometry.

The study found no significant difference between the rosuvastatin and placebo groups for the change in PWV from baseline to 96 weeks. In fact, PWV increased moderately in both arms ($\geq$10 m/s) in nearly half of the participants, indicating a higher cardiovascular risk. However, there was a significant decrease in total and LDL cholesterol observed by week 24 and this was sustained throughout the 96 weeks' time course.

Interestingly, while rosuvastatin effectively lowered cholesterol levels, it was also associated with a higher incidence of cardiometabolic adverse events compared to placebo with seven out of eight serious adverse events occurring in the rosuvastatin arm. These included myocardial infarctions, heart failure, a fatal cerebrovascular event, new onset of diabetes mellitus, and an increase in creatinine kinase and liver enzymes. This highlights the importance of cautious use of rosuvastatin in PWH, considering the potential for severe adverse effects which may outweigh the benefits.

While Trevillyan *et al*. have interesting findings, the study is not without limitations. The limitations include a small sample size and homogeneous participant population, which limits the generalizability of the findings. Future research should therefore consider larger, more diverse populations and explore the effects of different statins or combinational therapies to identify more effective strategies for reducing arterial stiffness and cardiovascular risk in PWH.

Despite its limitations, the study by Trevillyan *et al*. underscores the increased risk for the development of cardiovascular adverse events that may be potentiated by the use of rosuvastatin in elderly PWH. Regardless of the treatment arms, a significant proportion of participants progressed from moderate to high-risk category for CVD, suggesting that additional mechanisms such as aging may likely be contributing to this progression. Thus, more investigations are required to elucidate and plan for successful interventional strategies in PWH.

Acknowledgements

Conflicts of interest

L.M. and S.K.M. have no conflicts to declare.

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