Lipid-lowering effect of tenofovir in HIV-infected patients

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Keywords: cholesterol, simplification, antiretroviral therapy, cardiovascular risk

Sir,

A recent study by Tungsiripat et al.1 showed a decrease in cholesterol plasma levels in HIV-infected patients after adding tenofovir to a stable antiretroviral regimen, thus suggesting a lipid-lowering effect of this drug. We analysed the modification of lipid parameters after tenofovir discontinuation in a group of patients prospectively enrolled in a pilot trial of treatment simplification to a dual therapy with atazanavir/ritonavir plus lamivudine (Atazanavir/ritonavir and Lamivudine for treatment Simplification, AtLaS study).2 The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards, was approved by the local Ethics Committee and signed informed consent was collected from all participants.

Of the 40 patients enrolled, 39 subjects were treated with atazanavir/ritonavir plus tenofovir with lamivudine or

Table 1. Evolution of fasting lipid parameters throughout the study visits

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Mean (95% CI)</th>
<th>Week 4 Mean (95% CI)</th>
<th>Week 12 Mean (95% CI)</th>
<th>Week 24 Mean (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>187 (153–231)</td>
<td>221 (176–267)</td>
<td>219 (171–267)</td>
<td>207 (152–236)</td>
<td>-0.001</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>49 (39–61)</td>
<td>43 (33–56)</td>
<td>41 (31–52)</td>
<td>39 (29–50)</td>
<td>-0.001</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>110 (80–160)</td>
<td>125 (95–165)</td>
<td>120 (90–160)</td>
<td>118 (80–160)</td>
<td>0.001</td>
</tr>
<tr>
<td>Non-HDL cholesterol, mg/dL</td>
<td>142 (100–190)</td>
<td>147 (105–200)</td>
<td>145 (100–200)</td>
<td>143 (90–200)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total cholesterol:HDL ratio</td>
<td>4.34 (2.60–6.50)</td>
<td>4.40 (2.72–6.79)</td>
<td>4.47 (2.58–7.42)</td>
<td>4.53 (2.58–7.42)</td>
<td>0.001</td>
</tr>
<tr>
<td>HDL:LDL ratio</td>
<td>0.44 (0.20–0.80)</td>
<td>0.44 (0.20–0.83)</td>
<td>0.45 (0.20–0.83)</td>
<td>0.46 (0.20–0.83)</td>
<td>0.001</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>179 (125–234)</td>
<td>196 (151–241)</td>
<td>184 (139–234)</td>
<td>176 (125–234)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

CI, confidence interval. Bold type indicates significant P values (<0.05).

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emtricitabine and discontinued tenofovir at baseline according to study design. Participants were 56% males, their median age was 45 years [interquartile range (IQR) 41–52], 23.1% had a history of previous AIDS-defining events, their median CD4 count was 590 cells/mm³ (IQR 480–776) and all had HIV-RNA <50 copies/mL. None of the patients taking lipid-lowering agents at baseline (six statins, one fibrate, five omega-3 fatty acids) underwent dosage modifications during follow-up. All subjects completed week 4, 37/39 subjects completed week 12 and 35/39 subjects completed the week 24 visit.

The evolution of fasting lipid parameters throughout the study visits is shown in Table 1. During the study, we observed a small but significant increase in total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and non-HDL cholesterol, without significant modification of the total cholesterol/HDL and HDL/LDL ratios. Triglycerides did not show significant changes during follow-up. At baseline, no patient showed any grade 3–4 elevation of total cholesterol, LDL cholesterol or triglycerides; during the first 24 weeks after tenofovir discontinuation, we observed grade 3 elevations of total cholesterol, LDL cholesterol and triglycerides in three patients, four patients and one patient, respectively.

Our data seem to confirm the observation by Tungsiripat et al., if a lipid-lowering effect of tenofovir, involving mainly total cholesterol, LDL cholesterol and non-HDL cholesterol. Triglycerides did not seem to be influenced by tenofovir administration in either study. However, in contrast to Tungsiripat et al., we also observed an effect on HDL levels; HDL (measured by a colorimetric enzymatic method [Roche Diagnostics] on plasma samples) seemed to increase after tenofovir discontinuation, preventing the significant modification of the total cholesterol/ HDL and HDL/LDL ratios. A possible reason for this discordance between the two studies could be the lower number of subjects (n=13) analysed by Tungsiripat et al., with a consequent lower statistical power in detecting small modifications of lipid parameters. Interestingly and in agreement with these observations, a recently published randomized study comparing a switch to darunavir/ritonavir monotherapy versus darunavir/ritonavir plus two nucleos(t)ide reverse transcriptase inhibitors in virologically suppressed individuals showed an increase in total cholesterol in patients who stopped taking tenofovir.4 Further evidence supporting an independent lipid-lowering effect of tenofovir is represented by similar results observed in HIV-negative subjects treated with this drug.5 Clinical implications of these findings remain to be determined. Tenofovir-containing regimens could be preferred in HIV-infected patients with dyslipidaemia. However, it should be clarified whether the potential concomitant effect on lowering HDL could mitigate the benefit demonstrated on the other cholesterol parameters. Since exposure to other antiretroviral drugs (lopinavir, indinavir and possibly abacavir) is associated with an increased risk of myocardial infarction,6 we can hypothesize that the neutral effect of tenofovir on cardiovascular risk could be partially due to its lipid-lowering effect. Meanwhile, this effect could be taken into account when considering treatment switches in patients on suppressive antiretroviral therapy. Further studies are needed to understand the mechanisms at the basis of these observations.

Acknowledgements
Preliminary data were presented at the Eighteenth International AIDS Conference, Vienna, Austria, 2010 [Abstract THLB207; De Luca A, Bracciale L, Doino M et al. Safety and efficacy of treatment simplification to atazanavir/ritonavir plus lamivudine in patients on two NRTIs plus atazanavir/ritonavir with optimal virologic control: 24 weeks results from a pilot study (atazanavir and lamivudine simplification study, ATLAS.).].

Funding
No specific funding has been received for this work or for the AtLaS study.

Transparency declarations
R. C. and A. D. L. have received speaker's honoraria from or have been advisors for GlaxoSmithKline, Bristol-Myers Squibb, Gilead, Abbott Virology, Boehringer Ingelheim, Merck Sharp and Dohme, Pfizer, Janssen-Cilag and Bayer Diagnostics. S. D. G. has received speaker’s honoraria from GlaxoSmithKline, Bristol-Myers Squibb, Gilead, Merck Sharp and Dohme and Janssen-Cilag. All other authors: none to declare.

References