Reply to Tattevin et al

To the Editor—We appreciate Tattevin and colleagues’ interest in our article that examined the incidence of renal stones in patients on ritonavir-boosted atazanavir (ATV/r)—containing and other protease inhibitor (PI)—containing anti-retroviral therapy (ART) [1]. Tattevin et al [2] highlighted 3 limitations in our study and implied that the estimated risk of renal stones associated with ATV/r use was probably overestimated. However, these 3 limitations do not significantly undermine our results; the incidence of renal stones in patients on ATV/r was as high as 10 times that noted in patients on other PIs.

First, they argued that the risk of renal stones in the ATV/r group may have been overestimated because the median observation period was longer in the
ATV/r group (31 months; interquartile range [IQR], 15.0–48.7) than in the other PIs group (23 months; IQR, 10.3–42.4), whereas the median time period from the commencement of ART to the diagnosis of renal stones was 24.5 months (IQR, 14.7–34.6). However, it is unknown whether longer exposure to ATV/r increases the risk of renal stones. Furthermore, when we exclude the subjects with <12 months of observation and perform the same analysis, the median observation periods of the 2 groups were almost the same (ATV/r: 35.5 months vs other PIs: 33.4 months), and ATV/r was still significantly associated with a substantially high incidence of renal stones (hazard ratio [HR], 11.85; 95% confidence interval [CI], 3.60–39.07; \( P < .001 \)). Thus, it is incorrect to assume that the longer median observation period in the ATV/r group contributed to the higher incidence of renal stones. Second, they argued that the inclusion of unboosted PIs in the other PIs group while excluding unboosted ATV in the ATV/r group could have overestimated the effect of ATV/r use on renal stone formation. However, the number of patients on unboosted PIs, which was unboosted fosamprenavir in all subjects, was very small (45 of 775 subjects in the other PIs group [5.8%]). Furthermore, the inclusion of patients receiving only boosted PIs in the other PIs group did not change the hazard ratio of renal stones in the ATV/r group, compared to the other PIs group (HR, 13.44; 95% CI, 4.103–43.92; \( P < .001 \)).

Last, as Tattevin et al [2] pointed out, our conclusion that “the incidence of renal stones is substantially higher among patients of the ATV/r group compared with patients of the other PIs group” is probably not applicable to individual PIs, because the sample size in our study did not allow direct comparison of the incidence of renal stones in ATV/r group and in patients on each individual PIs. Larger studies are needed to address this issue.

We agree that our study has several limitations related to the sample size and retrospective study design. Nevertheless, as asserted by Tattevin et al [2], our conclusion is robust. The high incidence of ATV/r-related renal stones estimated in our study cannot be ignored. Clinicians should pay attention to this adverse event of ATV/r when selecting ART, because renal stone formation adds risk to the development of renal dysfunction and chronic kidney disease, which could result in serious outcomes [3–5].

Note

Potential conflicts of interest. S. O. has received honoraria and research grants from MSD KK, Abbott Japan, Janssen Pharmaceutical KK, Pfizer, and Roche Diagnostics KK; has received honoraria from Astellas Pharmaceutical KK, Bristol-Myers KK, Daiichisankyo, Dainippon Sumitomo Pharma, GlaxoSmithKline KK, Taisho Toyama Pharmaceutical, Torii Pharmaceutical, and ViiV Healthcare. H. G. has received honoraria from MSD KK, Abbott Japan, Janssen Pharmaceutical KK, Torii Pharmaceutical, and ViiV Healthcare. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References


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