High Incidence of Renal Stones Among HIV-Infected Patients on Ritonavir-Boosted Atazanavir Than in Those Receiving Other Protease Inhibitor–Containing Antiretroviral Therapy

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(See the Brief Report by Rakotondravelo et al on pages 1270–2.)

Background. Little information is available on the incidence of renal stones with ritonavir-boosted atazanavir (ATV/r) use.

Methods. In a single-center study, the incidence of renal stones was compared between human immunodeficiency virus (HIV)–infected patients who commenced ritonavir-boosted atazanavir (ATV/r)–containing antiretroviral (ARV) therapy (the ATV/r group) and those who were receiving other protease inhibitors (the other PIs group). The effects of ATV/r were estimated by univariate and multivariate Cox proportional hazards regression models. Other possible risk factors were evaluated by univariate analysis, and those found to be significant were entered into multivariate analysis.

Results. Renal stones were diagnosed in 31 patients (23.7 cases per 1000 person-years) in the ATV/r group (n = 465) and 4 in patients (2.2 cases per 1000 person-years) in the other PIs group (n = 775). ATV/r use was significantly associated with renal stones, by univariate and multivariate analyses (adjusted hazard ratio, 10.44; 95% confidence interval [CI], 3.685–29.59; $P < .001$). ATV/r remained a significant risk factor for renal stones in all subgroups stratified by the median values of baseline variables. In the 31 patients receiving ATV/r who developed renal stones, the median time from commencement of ATV/r to diagnosis was 24.5 months (interquartile range, 14.7–34.6 months). Of the 18 patients who continued ATV/r despite the diagnosis of renal stones, 6 (33.3%) experienced recurrence. No patient who discontinued ATV/r experienced recurrence during the observation period (250.6 person-months).

Conclusions. The incidence of renal stones was substantially higher among patients in the ATV/r group, compared with patients in the other PIs group. Continuation of ATV/r after diagnosis of renal stones was associated with a high rate of recurrence. Switching ATV/r to other ARVs is warranted in patients who develop renal stones.

Ritonavir-boosted atazanavir (ATV/r) is a widely used protease inhibitor (PI) in combination with other antiretroviral drugs for patients infected with human immunodeficiency virus type 1 (HIV). According to the present guidelines, ATV/r is one of the key first-line drugs because of its high efficacy, tolerability, favorable lipid profile, and once-daily dosing [1–4]. However, renal stone formation has been reported in patients receiving ATV/r-containing antiretroviral therapy (ART) [5, 6].

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Urolithiasis is a well-known side effect of indinavir (IDV), and its etiology is considered to be drug crystallization in the urine [7]. Previous studies identified ATV-containing urolithiasis, suggesting a similar etiology [5, 6, 8, 9]. However, there is virtually no information on the incidence of ATV/r-induced renal stones, although ATV/r is one of the most frequently prescribed PIs. It is important to elucidate the incidence of ATV/r-associated renal stones, since renal stones are risk factors for chronic kidney diseases (CKD), an important comorbidity associated with AIDS and death [10–12].

On the basis of this background, we conducted a retrospective study to compare the incidence of renal stones among patients receiving an ATV/r-containing regimen with the incidence among patients receiving one of the following commonly used PIs: unboosted fosamprenavir (FPV), ritonavir-boosted fosamprenavir (FPV/r), lopinavir/ritonavir (LPV/r), and ritonavir-boosted darunavir (DRV/r).

METHODS

Ethics Statement

This study was approved by the Human Research Ethics Committee of our hospital, the National Center for Global Health and Medicine, Tokyo. Each participant provided a written informed consent. The study was conducted according to the principles expressed in the Declaration of Helsinki.

Study Subjects

We performed a retrospective, single-center cohort study of HIV-infected patients using the medical records at our hospital. Our facility is one of the largest clinics for patients with HIV infection in Japan, with >2700 registered patients. The study population was HIV-infected patients aged >17 years who commenced treatment with ART containing ATV/r, FPV/r, FPV, LPV/r, or DRV/r between 1 January 2004 and 30 June 2010. Both treatment-naive and treatment-experienced patients were included. The follow-up period started at the time of commencement of ART that contained the above-mentioned drug for the first time during the study period, and patients were followed until 30 June 2011. Patients were excluded if (1) they had started the above-mentioned ART during the study period at other facilities, (2) they were prescribed unboosted ATV, or (3) they were receiving treatment for urolithiasis at the time they commenced the above-mentioned ART. Patients with previous exposure to one of the above-mentioned drugs before the present study and commenced the same drug in this study were also excluded from the analysis.

The attending physician selected ATV/r, FPV, FPV/r, LPV/r, or DRV/r at baseline. The use of these drugs was based on the Japanese guidelines, which placed all of the above-mentioned drugs as the preferred choice, at least for 3 years during the study period [13]. The attending physician also selected the concurrent drugs, including nucleoside reverse-transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), integrase inhibitors, and CCR5 inhibitors. None of the patients received 2 PIs during the study period.

Measurements

The primary investigator (Y. H.) reviewed the medical records of all study patients who started new key drugs during the study period, to identify renal stone cases. Then 2 experienced HIV physicians (T. N. and K. W.) reviewed the set of medical records of each renal stone case to determine whether the cases fit into the following predefined criteria for renal stones: cases with a clinical diagnosis by the attending physician based on new onset of acute flank pain, plus one of the following: (1) new-onset hematuria confirmed by urine dipstick test; (2) documented presence of stones or radiological findings suggestive of renal stones, such as hydronephrosis or obstruction or dilatation of the ureter, by either abdominal ultrasonography or computed tomography; or (3) stone passage confirmed by either the patient or the attending physician. Patients with acute flank pain due to etiologies other than renal stones were excluded. In case of disagreement between the 2 reviewers, a third independent reviewer (H. K.) evaluated the deidentified document set by the same criteria to make the final determination. At the time of diagnosis of renal stones, the attending physician selected either continuation or modification of ART. In our clinic, it is customary for the patient to visit the clinic every month before the initiation of ART and until suppression of HIV load, but the visit interval is extended up to every 3 months after viral load suppression.

In this study, the primary exposure variable was ATV/r use over other PIs (FPV, FPV/r, LPV/r, and DRV/r). The potential risk factors for renal stones were determined according to previous studies and were collected from the medical records, together with the basic demographic characteristics [8, 9, 14]. They included age, sex, body weight, body mass index (BMI; defined as the weight in kilograms divided by the square of the height in meters), baseline laboratory data (CD4 cell count, HIV load, estimated glomerular filtration rate [eGFR], serum uric acid, and urine pH), and presence or absence of other medical conditions (ie, concurrent use of tenofovir [TDF]; past history of renal stones; previous exposure to IDV; coinfection with hepatitis B virus [HBV], defined by detection of HBV surface antigen; and coinfection with hepatitis C virus [HCV], defined by detection of HCV load). eGFR was calculated using the equation from the 4-variable Modification of Diet in Renal Diseases study [15]. Among patients receiving ATV/r-containing ART, the total serum bilirubin level measured on the day of stone diagnosis (for patients with renal stones) or 2 years after ATV/r initiation (for patients without

renal stones) was used. For patients who discontinued ATV/r within 2 years, the value closest to the day of discontinuation was used. At our clinic, weight was measured on every visit, whereas other variables were measured in the first visit and at least once annually. We used the data on or closest to and preceding the day of starting ART by ≤180 days.

Statistical Analysis

Baseline characteristics were compared using the unpaired Student *t* test or the χ^2 test (ie, the Fisher exact test) for quantitative or qualitative variables, respectively. The time to the diagnosis of urolithiasis was calculated from the date of commencement of predefined PI-containing ART to the date of diagnosis for urolithiasis. Censored cases represented those who discontinued the PIs, dropped out, were referred to other facilities, or at the end of the follow-up period. The time from the start of ART to the diagnosis of renal stones was analyzed by the Kaplan-Meier method for patients who started ATV/r (the ATV/r group) and those who started other PIs (the other PIs group), and the log-rank test was used to determine the statistical significance. The Cox proportional hazards regression analysis was used to estimate the impact of ATV/r use, compared with other PIs, on the incidence of renal stones. The impact of basic demographic characteristics, baseline laboratory data, and other medical conditions listed above was also estimated with univariate Cox proportional hazards regression. To estimate the unbiased prognostic impact of ATV/r use over other PIs for renal stones, we conducted 3 models using multivariate Cox proportional hazards regression analysis. Model 1 was the aforementioned univariate analysis for ATV/r use over other PIs. Model 2 included age, sex, and weight plus model 1 in order to adjust for basic characteristics. In model 3, we added variables with *P* values of < .05 in univariate analysis after adjustment (these included eGFR per 10 mL/min/1.73 m^2 and serum uric acid per 1 mg/dL). Possible risk factors for ATV/r-induced renal stones identified in previous studies were also added to model 3 (these included past history of renal stones and prior exposure to IDV) [8, 9].

To elucidate whether the impact of ATV/r on renal stones persist in subgroups, we divided patients into 2 groups on the basis of sex, age, baseline body weight, eGFR, and serum uric acid level, using the respective median value of each parameter. Then, the above-mentioned univariate analysis was conducted for each subgroup. In addition, to examine the association between total serum bilirubin level during ATV/r-containing ART and the incidence of renal stones, the median total serum bilirubin levels were compared between stone cases and nonstone cases, using the Mann-Whitney *U* test.

To explore the impact of urolithiasis on renal function, the change in eGFR was compared between stone cases (ie, the eGFR change between baseline and the diagnosis of renal stones) and nonstone cases (ie, the eGFR between baseline and 2 years after initiation of ATV/r) in patients receiving ATV/r, using the Student *t* test.

Statistical significance was defined as a 2-sided *P* value of < .05. We used hazard ratios (HRs) and 95% confidence intervals (CIs) to estimate the impact of each variable on renal stones. All statistical analyses were performed with SPSS, version 17.0 (SPSS, Chicago, IL).

RESULTS

A total of 1498 patients commenced or switched key drugs (PIs, NNRTIs, or an integrase inhibitor) between 1 January 2004 and 30 June 2010. Of the 1240 patients who were included in the analysis, 465 (37.5%) started ATV/r-containing ART, while 775 (62.5%) started other PI–containing ART (Figure 1). Table 1 shows the baseline characteristics of the study population. The majority of the study population was male, of East Asian origin, and comparatively young. The ATV/r group included significantly more patients of East Asian origin (*P* = .015) and had a significantly higher body weight (*P* < .001), higher CD4 cell count (*P* < .001), lower viral load (*P* < .001), higher baseline serum uric acid level (*P* = .034), and lower eGFR (*P* = .012). In contrast, patients in the other PIs group were significantly more likely to be treatment naive (*P* < .001) and significantly less likely to have had previous exposure to IDV (*P* = .036). However, all other major background parameters were similar in the 2 groups (Table 1).

The primary investigator (Y. H.) identified 37 renal stone cases, and 2 of these were excluded by the reviewers. Thirty-five patients fulfilled the predefined criteria for renal stones. Renal stones were identified in 31 patients (6.7%) from the ATV/r group and in 4 (0.52%) from the other PIs group, with an estimated incidence of 23.7 cases and 2.20 cases per 1000 person-years, respectively. The incidence of renal stones in the ATV/r group was approximately 10 times the incidence in the other PIs group. Of those renal stone cases, 4 and 14 patients were diagnosed on the basis of hematuria and stone passage, respectively, as defined above. Furthermore, 17 cases were diagnosed on the basis of radiological findings, of which renal calcification was identified in 4 cases. Figure 2 is a Kaplan-Meier curve of the time from initiation or switching of PIs defined above to the diagnosis of renal stones in the 2 groups. Patients in the ATV/r group were significantly more likely to develop renal stones, compared with those of the other PIs group (*P* < .001, by the log-rank test). The median time from the commencement of ART to the diagnosis of renal stones was 24.5 months (interquartile range [IQR], 14.7–34.6 months) for the ATV/r group and 21.9 months (IQR, 10.1–45.1 months) for the other PIs group. The total observation period was 1310.1 patient-years (median duration, 31.0 months; IQR, 15.0–48.7 months) for the

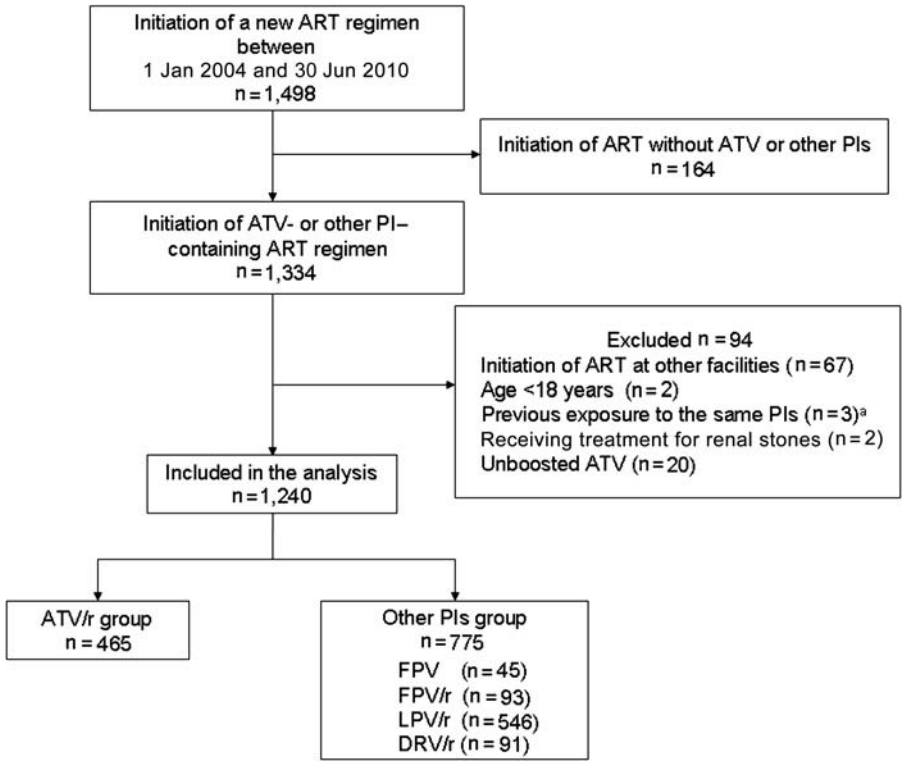

Figure 1. Flow diagram of patient selection. [a]Three patients were excluded for past lopinavir/ritonavir (LPV/r) exposure and commencement of LPV/r in the study. Abbreviations: ART, antiretroviral treatment; ATV, atazanavir; ATV/r, ritonavir-boosted atazanavir; DRV/r, ritonavir-boosted darunavir; FPV, fosamprenavir; FPV/r, ritonavir-boosted fosamprenavir; LPV/r, lopinavir/ritonavir; PIs, protease inhibitors.

Table 1. Baseline Demographic Characteristics and Laboratory Data for 1240 Patients Who Received Ritonavir-Boosted Atazanavir– or Other Protease Inhibitor–Containing Antiretroviral Therapy

Variable	ATV/r (n = 465)	Other PIs (n = 775)	*P*[a]
Age, years	39.0 ± 10.6	40.0 ± 11.5	.125
Male sex	433 (93.1)	712 (91.9)	.424
Race (East Asian origin)	448 (96.3)	721 (93.0)	.015
Body weight, kg	65.0 ± 10.5	62.1 ± 10.7	<.001
BMI, kg/m^2	22.7 ± 3.14	21.7 ± 3.25	<.001
CD4 cell count, cells/μL	303.9 ± 184.7	176.4 ± 170.9	<.001
HIV load, $\log_{10}$ copies/mL	3.58 ± 1.38	4.42 ± 1.40	<.001
Treatment naive	282 (60.6)	555 (71.6)	<.001
Tenofovir use	177 (38.1)	326 (42.1)	.165
eGFR, mL/min/1.73 m^2	117.4 ± 25.8	121.7 ± 33.6	.012
Serum uric acid level, mg/dL	5.90 ± 1.31	5.71 ± 1.64	.034
Urine pH	6.30 ± 0.67	6.32 ± 0.62	.759
HBV or HCV coinfection	57 (12.3)	111 (14.3)	.304
Past history of urinary stone	35 (7.5)	41 (5.3)	.114
Previous exposure to IDV	43 (9.2)	47 (6.1)	.036

Data are No. (%) of patients or mean ± standard deviation.

Abbreviations: ATV/r, ritonavir-boosted atazanavir; BMI, body mass index; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDV, indinavir; PI, protease inhibitor.

[a] The χ^2 test or Fisher exact test was used for categorical data, and the Student *t* test was used for continuous variables.

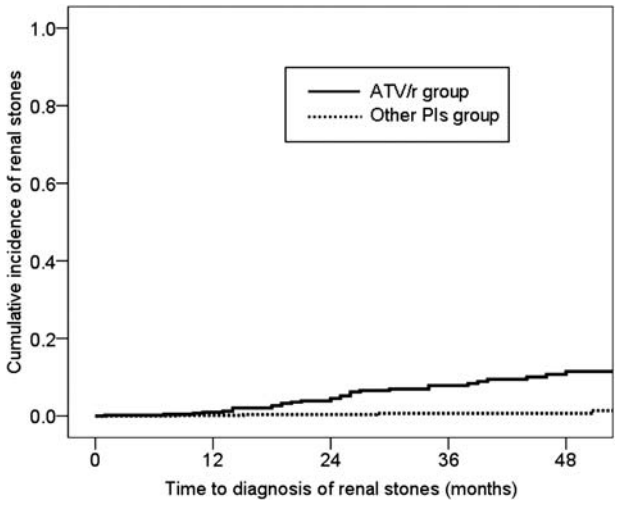

Figure 2. Kaplan-Meier curve showing time to diagnosis of renal stones. Abbreviations: ATV/r, ritonavir-boosted atazanavir; PIs, protease inhibitors.

ATV/r group and 1821.3 patient-years (median duration, 23.0 months; IQR, 10.3–42.4 months) for the other PIs group.

Univariate analysis showed a significant relationship between ATV/r use and renal stones (HR, 10.44; 95% CI, 3.685–29.59; $P < .001$; Table 2). Lower baseline eGFR (HR, 1.180; 95% CI, 1.042–1.336; $P = .009$) and higher serum uric acid level (HR, 1.334; 95% CI, 1.085–1.640; $P = .006$) were also significantly associated with the development of renal stones. On the other hand, body weight, BMI, history of IDV use, and past history of renal stones were not associated with renal stones (Table 2). Multivariate analysis identified ATV/r use as a significant risk for renal stones after adjustment for age, sex, and weight (adjusted HR, 9.339; 95% CI, 3.254–26.80; $P < .001$; Table 3, model 2) and also after adjustment for other risk factors (adjusted HR, 10.08; 95% CI, 3.487–29.17; $P < .001$; Table 3, model 3).

Figure 3 shows subgroup analysis of the patients stratified by sex and the median of the above-mentioned baseline variables. In all the subgroups, ATV/r remained an independent risk for renal stones. The median total bilirubin values in stone cases and nonstone cases were not significantly different (2.4 mg/dL [IQR, 1.8–3.4 mg/dL] and 2.3 mg/dL [IQR, 1.6–3.1 mg/dL], respectively; $P = .376$).

Of the 31 patients who developed renal stones in the ATV/r group, 13 discontinued ATV/r. Of the 18 patients who continued ATV/r despite the diagnosis of renal stones, 6 (33.3%) experienced recurrence of renal stones. The median time from the first episode of renal stones to recurrence was 4.9 months (IQR, 1.5–12.2 months). No patient required invasive procedures, such as lithotripsy. None of the 13 patients who discontinued ATV/r experienced recurrence during the observation period (total observation period, 250.6 person-months).

Table 2. Univariate Analysis to Estimate the Risk of Various Factors on Renal Stone Formation

	Hazard Ratio	95% CI	*P*
ATV/r use	10.44	3.685–29.59	<.001
Age, per 1 year increase	1.012	.981–1.043	.456
Male sex	1.380	.331–5.754	.659
Race (East Asian origin)	1.927	.264–14.08	.518
Body weight, per 1 kg increase	0.994	.962–1.028	.740
BMI per 1 kg/m^2 increase	0.997	.900–1.105	.954
CD4 cell count, per 10 cells/μL increase	1.013	.998–1.028	.096
HIV load, per $\log_{10}$/mL increase	0.909	.729–1.133	.395
Treatment naive	0.565	.291–1.099	.092
Tenofovir use	0.623	.299–1.299	.207
Baseline eGFR, per 10 mL/min/1.73 m^2 decrease	1.180	1.042–1.336	.009
Baseline serum uric acid level, per 1 mg/dL increase	1.334	1.085–1.640	.006
Baseline urine pH, per 1 increase	0.385	.133–1.119	.080
HBV or HCV coinfection	1.629	.712–3.729	.248
Past history of renal stone	2.109	.818–5.438	.122
Previous exposure to IDV	2.072	.860–4.996	.105

Abbreviations: BMI, body mass index; CI, confidence interval; eGFR, estimated glomerular filtration rate; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IDV, indinavir.

The mean eGFR decreased more significantly in the stone cases than in nonstone cases (30.7 vs 8.1 mL/min/1.73 m^2; $P < .001$). In the 13 patients who discontinued ATV/r after the first episode, the mean eGFR recovery was 20.1 mL/min/1.73 m^2 in 6 months after ATV/r discontinuation.

DISCUSSION

In the present study, the incidence of renal stones among patients receiving ATV/r was approximately 10 times the incidence among those receiving other PIs. Univariate and multivariate analyses identified ATV/r use as an independent risk factor for renal stones, with a high HR.

This study estimates the incidence of ATV/r-induced renal stones, using clinically feasible criteria: acute flank pain with clinical diagnosis of renal stones by the attending physician, confirmed by radiological findings, new-onset hematuria, or confirmation of stone passage. A single previous report compared the incidence of renal stones among patients receiving ATV/r and those receiving other antiretrovirals [16]. However, the diagnosis of renal stones in that study was based only on

Table 3. Multivariate Analysis to Estimate the Risk of Ritonavir-Boosted Atazanavir– or Other Protease Inhibitor–Containing Antiretroviral Therapy on Renal Stone Formation

	Model 1, Crude (n = 1240)		Model 2, Adjusted (n = 1115)		Model 3, Adjusted (n = 1115)	
	HR	95% CI	HR	95% CI	HR	95% CI
ATV/r use	10.44	3.685–29.59	9.339	3.254–26.80	10.08	3.487–29.12
Age, per 1 year increase	…	…	1.012	.980–1.046	1.002	.965–1.040
Male sex	…	…	1.731	.378–7.932	1.222	.257–5.799
Body weight, per 1 kg increase	…	…	0.980	.944–1.018	0.965	.927–1.004
Baseline eGFR, per 10 mL/min/1.73 m^2 decrease	…	…	…	…	1.157	.968–1.382
Baseline serum uric acid level, per 1 mg/dL increase	…	…	…	…	1.423	1.091–1.856
Past history of renal stone	…	…	…	…	1.182	.310–4.501
Past exposure to IDV	…	…	…	…	1.265	.415–3.859

Abbreviations: ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IDV, indinavir.

radiological findings. It is likely that the incidence of ATV/r-induced renal stones was underestimated in that study, because radiological studies were not necessarily performed on all patients suspected of renal stones. Accordingly, the reported incidence of ATV/r-induced renal stones was much lower (7.3 cases per 1000 person-years), compared with 23.7 cases per 1000 person-years in our study. Thus, our results more likely reflect the true incidence of ATV/r-induced renal stones.

The development of renal stones is a risk factor for CKD [10, 11]. Many studies have also demonstrated that ATV/r use is a risk factor for renal dysfunction or CKD [17–19]. The high incidence of renal stones with ATV/r use may in part contribute to ATV/r being a risk factor for CKD. Thus, ATV/r should be carefully introduced to patients with concomitant predisposing factors for CKD.

Six of the 18 patients who continued ATV/r despite the diagnosis of renal stones experienced recurrence. In contrast,

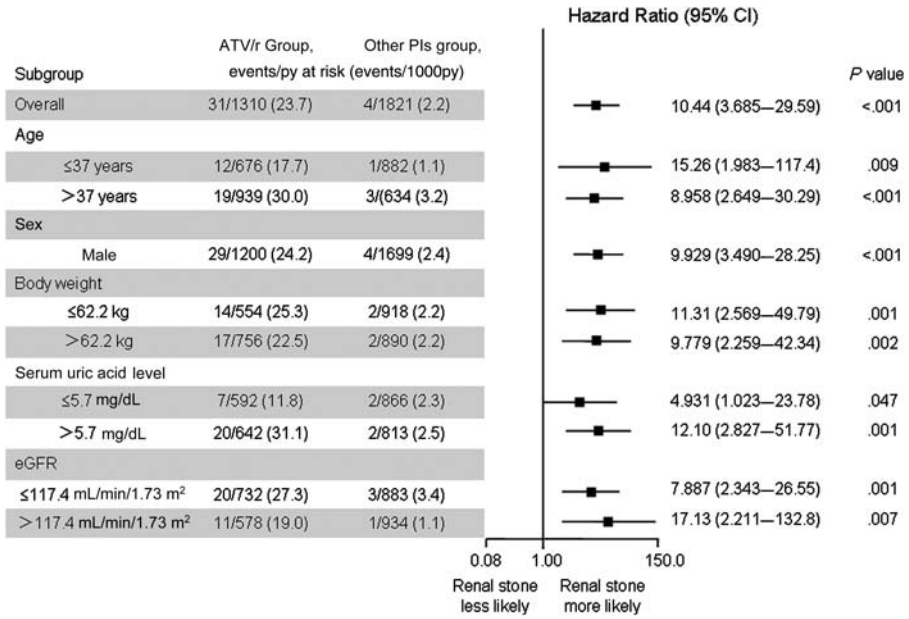

Figure 3. Estimated effect of ritonavir-boosted atazanavir, compared with other protease inhibitors on the hazard of renal stone formation, according to baseline characteristics. Abbreviations: ATV/r, ritonavir-boosted atazanavir; CI, confidence interval; eGFR, estimated glomerular filtration rate; PI, protease inhibitor; py, person-years.

none who discontinued ATV/r experienced recurrence. Thus, replacement of ATV/r with other drugs should be considered for patients who receive a diagnosis of renal stones, to prevent further deterioration in renal function.

Subgroup analysis showed that ATV/r was a risk factor for renal stones in all subgroups. Thus, we could not find any alleviating or aggravating factors for ATV/r-induced renal stones. Previous reports suggested several risk factors for ATV-induced renal stones, such as chronic renal impairment, coinfection with hepatitis virus, and past history of renal stones [9, 16]. However, the statistical methods used in those studies were inadequate to elucidate risks for ATV/r-induced renal stones. Our study did not add new findings to the risk for ATV/r-induced stones because of the small number of patients, leading to a low statistical power in subgroup analysis.

The mechanism of ATV/r-induced renal stone formation is not fully understood. However, like IDV stones, the precipitation of pure ATV is suggested as a possible etiology [9]. About 7% of ATV and 20% of IDV is excreted unchanged in the urine, which may contribute to the stone formation [24, 25]. In contrast, urolithiasis associated with other PIs, such as LPV/r, nelfinavir, and amprenavir, is rare, and this could be due to the minimal (<3%) excretion of these PIs [20–23]. Rockwood et al [16] found a close association between hyperbilirubinemia and the development of renal stones. This may be explained by the previously reported data that plasma ATV concentrations correlate with serum bilirubin level [26]. However, our data showed no relation between serum bilirubin level and the occurrence of renal stones. The concomitant use of TDF lowers plasma concentrations of ATV [1], and it is of interest whether the incidence of ATV/r-stones is lower among patients with concomitant use of TDF than among those without concomitant TDF use. Nevertheless, the present study did not find concomitant TDF to be a protective factor against ATV-renal stones.

There are several limitations to our study. First, because of the retrospective nature of the study, the baseline characteristics of the enrolled patients were not controlled. Thus, it is possible that more patients with potential risks for renal stones were included in the ATV/r group. Patients in the ATV/r group had hyperuricemia, which is a known risk factor for renal stones. However, ATV/r use remained a strong risk factor by multivariate analysis, even after adjustment for possible risk factors, including hyperuricemia. Second, the definition of renal stones in our study did not necessarily require radiological confirmation in all cases. However, the definition used in our study is well suited to cover clinically significant renal stone cases, especially considering that many ATV-induced renal stones are radiolucent [9]. Third, none of the patients with renal stones had stone composition analysis performed. Therefore, it is possible that renal stones with other etiologies were included. Fourth, because the number of individuals receiving efavirenz or raltegravir was small in our cohort, they were not included in the analysis, and we thus could not compare the effect of ATV/r to effect of these widely used antiretroviral drugs on the development of renal stones (Figure 1). Last, since most of the patients were of East Asian origin, our results may not be applicable to other populations.

In conclusion, the present study demonstrated a high incidence of renal stones among patients receiving ATV/r-containing ART, compared with those receiving other PI–containing ART. ATV/r use was an independent risk for renal stones in a robust statistical model that included ATV/r use as a primary exposure. ATV/r should be carefully prescribed to patients with predisposing factors for renal stone formation or those with CKD. For those who develop ATV/r-induced renal stones, discontinuation of ATV/r is warranted because of the high risk of recurrence.

Notes

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Potential conflicts of interest. S. O. has received honoraria and research grants from MSD, Abbott Japan, Janssen Pharmaceutical, Pfizer, and Roche Diagnostics and has received honoraria from Astellas Pharmaceutical, Bristol-Myers, Daiichisankyo, Dainippon Sumitomo Pharma, GlaxoSmithKline, Taisho Toyama Pharmaceutical, Torii Pharmaceutical, and ViiV Healthcare. H. G. has received honoraria from MSD, Abbott Japan, Janssen Pharmaceutical, 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.

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