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Table 1. Characteristics of all patients who underwent anti-Eh testing (n=1303).

	Anti-Eh negatives (n=1026)	Anti-Eh positives (n=277)	*P* value
age (years) (range)	36 (18-77)	37 (19-74)	0.06
Japanese nationality (%)	921 (89.8%)	250 (90.3%)	0.81
male sex (%)	960 (93.6%)	272 (98.2%)	0.003
MSM (%)	789 (76.9%)	245 (88.4%)	<0.001
TPHA test positive (%)	366/1012 (36.2%)	151/275 (54.9%)	<0.001
HBV exposure* (%)	524/1017 (51.5%)	187/272 (68.8%)	<0.001
HCV Ab positive (%)	40/1011 (4.0%)	5/273 (1.8%)	0.09
Past history of IA (%)	13 (1.3%)	60 (21.7%)	<0.001
Diagnosis of IA at first visit	1 (0.1%)	7 (2.5%)	<0.001

*HBV exposure: HBsAg-positive or HBsAb-positive, and/or HBc-Ab positive

Anti-Eh, anti *E. histolytica* antibody; MSM, Men who have sex with men; IA, invasive amebiasis; TPHA, *Treponema pallidum* hemagglutination; HBV, hepatitis B virus; HCV, hepatitis C virus; Ab, antibody.

Table 2. Comparison of clinical characteristics of patients with and without invasive amebiasis.

	amebic colitis (n=11)	extraintestinal IA* (n=7)	Non-IA (n=1189)	*P* value IA vs. non-IA
age (years), average (SD)	35.9 (12.3)	38.2 (11.0)	37.5 (10.8)	0.81
Japanese nationality (%)	10 (90.9)	6 (85.7)	1068 (89.8)	0.71
male sex (%)	11 (100)	7 (100)	1119 (94.1)	0.62
MSM (%)	11 (100)	6 (85.7)	929 (78.1)	0.15
TPHA test-positive (%)	5 (45.5)	2 (28.6)	451/1175 (38.4)	0.91
HBV exposure* (%)	6 (54.5)	5 (71.4)	630/1178 (53.5)	0.15
HCV Ab-positive (%)	0/11 (0)	0/7 (0)	42/1172 (3.6)	1.00
Anti-Eh at baseline, median (IQR)	x100 (<x100-x800)	x400 (x100-x400)	<x100 (<x100-<x100)	< 0.001
Anti-Eh at the onset of IA, median (IQR)	x800 (x200-x800)	x400 (x100-x800)	-	
Follow up period, median months (IQR)	7.8 (3.3-25.1)	10.5 (4.9-17.9)	25.5 (7.0-47.3)	

*Extraintestinal cases include one case of appendicitis and 6 cases of liver abscess.

Data were compared using chi-square test, Student t-test or Mann-Whitney U test for qualitative or quantitative variables, respectively.

IQR, interquartile range; IA, invasive amebiasis; other abbreviations as in Table 1.

Table 3. Risk analysis for development of invasive amebiasis by Cox proportional hazard regression model.

	univariate analysis		multivariate analysis	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
older age (by 1 year)	0.989 (0.947-1.033)	0.624		
Japanese nationality	1.334 (0.305-5.840)	0.702		
male sex	21.884 (0.002-241297.39)	0.516		
MSM	4.318 (0.573-32.518)	0.156	4.048 (0.488-33.584)	0.195
TPHA test-positive	0.901 (0.348-2.335)	0.831		
HBV exposure-positive	2.183 (0.778-6.124)	0.138	1.839 (0.644-5.249)	0.255
HCV Ab-positive	0.047 (0.000-2697.344)	0.584		
Anti-Eh titer ≥ x400	20.985 (8.085-54.467)	<0.001	22.079 (7.964-61.215)	<0.001

The Cox proportional-hazards regression analysis was used to estimate the impact of anti-Eh titer at baseline on the incidence of invasive amebiasis. The impact of basic clinical characteristics, such as sexuality and serology status of other STIs, was estimated with univariate Cox proportional hazards regression. Multivariate Cox hazards regression analysis using variables identified in univariate analysis with *P* values of <0.20. In all analyses, statistical significance was defined as *P* value of <0.05.

Abbreviations as in Table 1.

Figure Legends

Figure 1. Flow diagram of patient recruitment process.

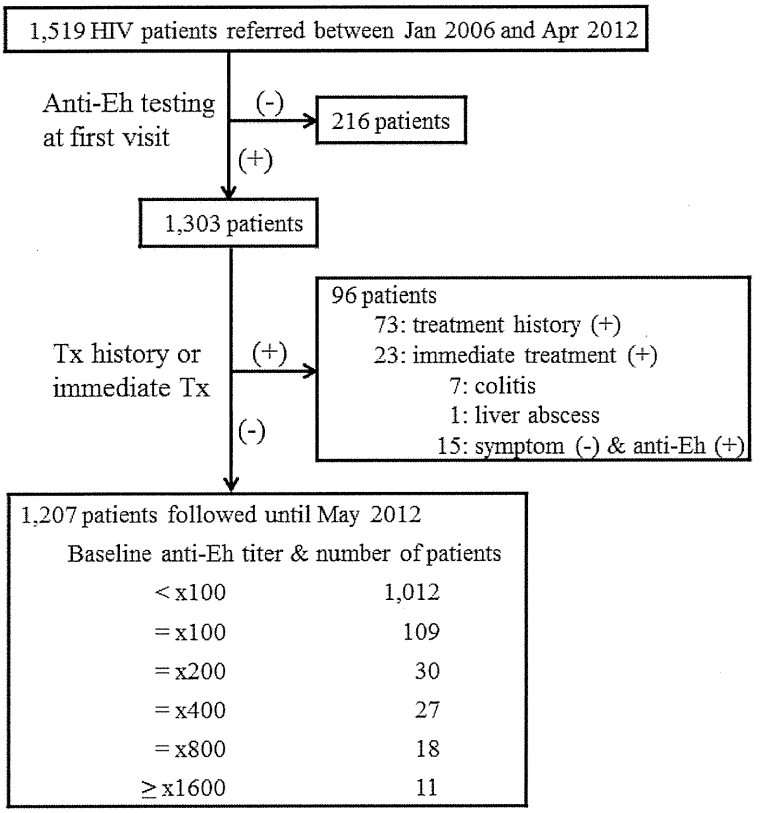
Anti-Eh, anti-*Entamoeba histolytica* antibody; IA, invasive amebiasis

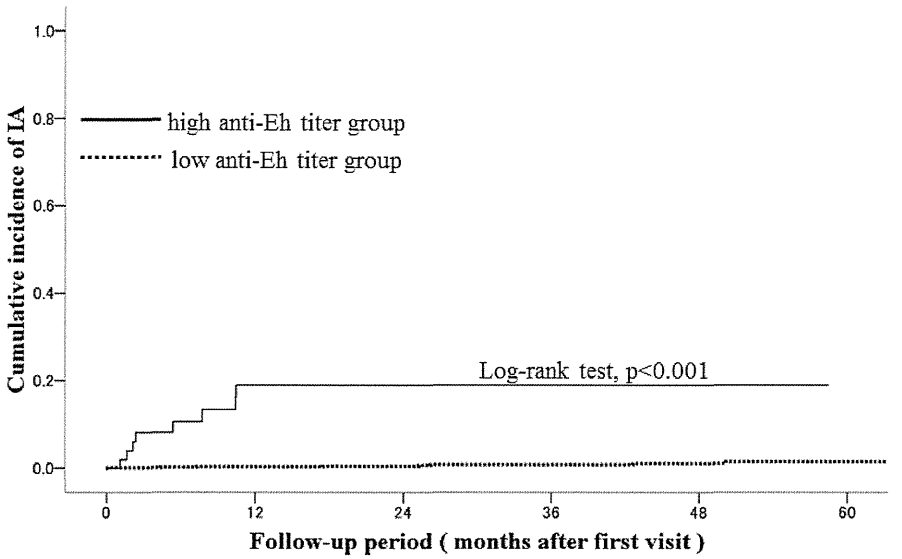
Figure 2. Incidence of invasive amebiasis in low and high anti-Eh titer groups.

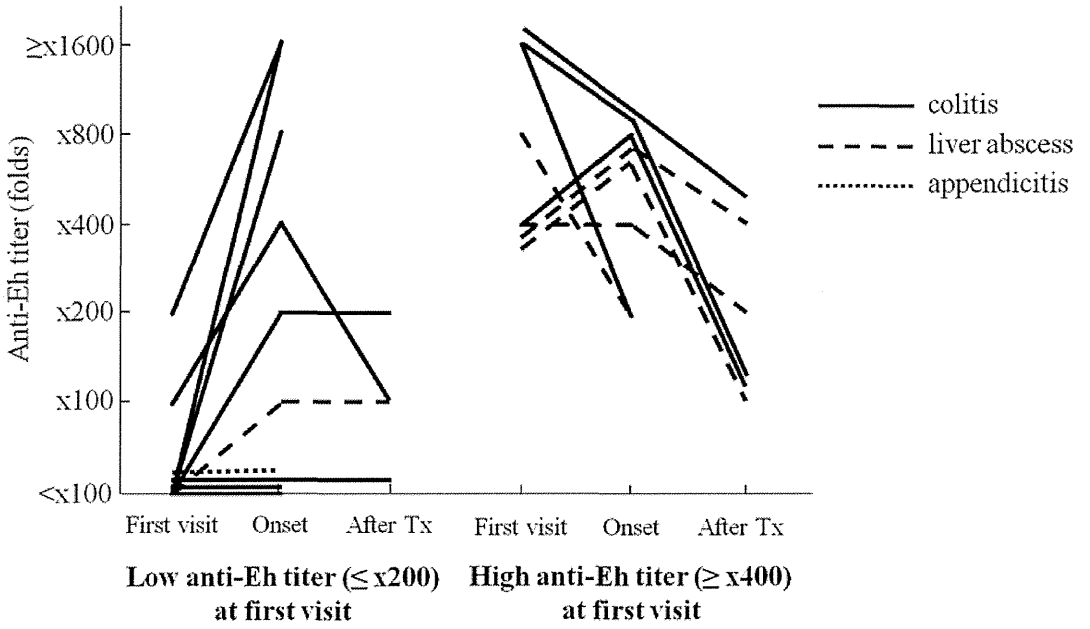
Differences in the time from first visit to the diagnosis of invasive amebiasis (IA) between the low anti-Eh titer group (≤ x200 at baseline) and high anti-Eh titer group (≥ x400 at baseline) were analyzed by Kaplan-Meier method. Log-rank test was used to determine the statistical significance.

Anti-Eh, anti-*Entamoeba histolytica* antibody; IA, invasive amebiasis

Figure 3. Anti-Eh titer before and after diagnosis of invasive amebiasis. Anti-Eh titer at the onset of invasive amebiasis (IA) was compared to that at baseline (first visit to the clinic) by Wilcoxon signed-rank test. Anti-Eh titers after treatment were measured at 219 days [range: 174-252] and 367 days [272-841] after the completion of treatment of patients with low and high anti-Eh titer at first visit, respectively.


1,519 HIV patients referred between Jan 2006 and Apr 2012
Anti-Eh testing at first visit
(-)
216 patients
(+)
1,303 patients
Tx history or immediate Tx
(+)
96 patients
73: treatment history (+)
23: immediate treatment (+)
7: colitis
1: liver abscess
15: symptom (-) & anti-Eh (+)
(-)
1,207 patients followed until May 2012
Baseline anti-Eh titer & number of patients
< x100 1,012
= x100 109
= x200 30
= x400 27
= x800 18
≥ x1600 11


1.0
0.8
0.6
0.4
0.2
0.0
Cumulative incidence of IA
high anti-Eh titer group
low anti-Eh titer group
Log-rank test, p<0.001
0
12
24
36
48
60
Follow-up period (months after first visit)


≥x1600
x800
x400
x200
x100
<x100
Anti-Eh titer (folds)
First visit
Onset
After Tx
First visit
Onset
After Tx
colitis
liver abscess
appendicitis
Low anti-Eh titer (≤ x200) at first visit
High anti-Eh titer (≥ x400) at first visit

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Cumulative exposure to ritonavir-boosted atazanavir is associated with cholelithiasis in patients with HIV-1 infection

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Objectives: This study aimed to examine the effect of long-term treatment with ritonavir-boosted atazanavir (atazanavir/ritonavir) on cholelithiasis.

Methods: A single-centre, cross-sectional study was conducted to elucidate the prevalence of cholelithiasis in patients with HIV-1 infection who underwent abdominal ultrasonography between January 2004 and March 2013. Univariate and multivariate logistic regression analyses were applied to estimate the effects of >2 years of atazanavir/ritonavir exposure on cholelithiasis as the primary exposure.

Results: Of the 890 study patients, 84 (9.4%) had >2 years of atazanavir/ritonavir exposure. Cholelithiasis was twice as frequent in those treated for >2 years with atazanavir/ritonavir [15 (18%) of 84 patients] compared with those treated for <2 years [72 (8.9%) of 806 patients] ($P=0.018$). Univariate analysis showed a significant association between >2 years of atazanavir/ritonavir exposure and cholelithiasis (OR=2.216; 95% CI=1.206–4.073; $P=0.010$) and the association almost persisted in multivariate analysis (adjusted OR=1.806; 95% CI=0.922–3.537; $P=0.085$). Long-term treatment (>2 years) with other commonly used protease inhibitors, such as ritonavir-boosted lopinavir and ritonavir-boosted darunavir, was not associated with cholelithiasis in univariate and multivariate analysis. Additional analysis showed that >1 year of exposure to atazanavir/ritonavir was significantly associated with cholelithiasis (OR=1.857; 95% CI=1.073–3.214; $P=0.027$), whereas >1 year of exposure to ritonavir-boosted lopinavir and ritonavir-boosted darunavir was not.

Conclusions: Long-term treatment of patients with HIV-1 infection for >2 years with atazanavir/ritonavir was associated with an increased risk of cholelithiasis compared with patients with shorter exposure. Long-term exposure to atazanavir/ritonavir appears to increase the risk of cholelithiasis in patients with HIV-1 infection.

Keywords: protease inhibitors, antiretroviral therapy, gallstones

Introduction

Ritonavir-boosted atazanavir (atazanavir/ritonavir) is a widely used protease inhibitor in the treatment of patients infected with HIV-1.[1–3] Cholelithiasis was not reported in atazanavir/ritonavir Phase 3 clinical trials;[4] however, recent post-marketing studies have suggested potential association between cumulative atazanavir/ritonavir exposure and cholelithiasis.[5–7] Only a couple of studies have so far reported the incidence of complicated cholelithiasis, such as cholecystitis, cholangitis and pancreatitis, in patients treated with atazanavir/ritonavir.[5,8] However, the effects of prolonged exposure to atazanavir/ritonavir on the incidence of cholelithiasis, including asymptomatic cholelithiasis, is unknown at this stage. This is of importance because ~20% of patients with cholelithiasis develop symptoms in the long term.[9]

The aim of this study was to elucidate the effects of atazanavir/ritonavir exposure on cholelithiasis, including asymptomatic cholelithiasis, in patients with HIV-1 infection.

Patients and methods

Study design

We performed a cross-sectional study of HIV-1-infected patients using the abdominal ultrasonography data and the medical records at the National Center for Global Health and Medicine, Tokyo, Japan.[10] The study

population was HIV-1-infected patients, aged >17 years, who underwent abdominal ultrasonography at the Physiological Examination Unit of the hospital between 1 January 2004 and 31 March 2013 as part of clinical practice. Atazanavir/ritonavir became available in Japan in January 2004. Exclusion criteria were: (i) patients with cholecystectomy performed before the study period; and (ii) patients with missing data on antiretroviral therapy (ART). At the Physiological Examination Unit, ultrasonography was conducted by certified medical technologists and the images and diagnosis were double-checked and confirmed by radiologists, hepatologists or gastroenterologists. If abdominal ultrasonography was conducted more than once during the study period, the latest ultrasonography data were used for the study. This study was approved by the Human Research Ethics Committee of the hospital. Each participant provided a written informed consent for the clinical and laboratory data to be used and published for research purposes.

Measurements

The primary exposure variable was a history of atazanavir/ritonavir use for >2 years, regardless of continuation of atazanavir/ritonavir at the time of abdominal ultrasonography. A 2 years threshold for atazanavir/ritonavir exposure was selected because cholelithiasis was not reported in atazanavir/ritonavir Phase 3 clinical trials with the primary endpoint set at week 48[4] and prolonged excretion of atazanavir in the bile appears necessary for gallstone formation.[5] The potential risk factors for cholelithiasis were collected from the medical records, together with the basic demographics.[9,11–13] They included age, sex, ethnicity, body mass index (BMI), cirrhosis, diabetes mellitus, CD4 count, HIV viral load, ART experienced or naive, duration of ART, length of exposure to atazanavir/ritonavir, ritonavir-boosted lopinavir (lopinavir/ritonavir) and ritonavir-boosted darunavir (darunavir/ritonavir), history of AIDS and hepatitis B or C coinfection. We used data collected within 3 months of the day ultrasonography was conducted.

Statistical analysis

Univariate and multivariate logistic regression analysis was used to estimate the effects of atazanavir/ritonavir exposure of >2 years, relative to <2 years or no atazanavir/ritonavir exposure, on cholelithiasis as the primary exposure. Basic demographics (age and sex), possible risk factors for cholelithiasis (BMI, cirrhosis and diabetes mellitus)[11–13] and variables with P values <0.05 in univariate analysis (HIV load and duration of ART) were added to the multivariate model. The variable 'treatment naive' was not added because of its multicollinearity with HIV load.

Statistical significance was defined as two-sided P values <0.05. We used ORs and 95% CIs to estimate the effects of each variable on cholelithiasis. All statistical analyses were performed with the Statistical Package for Social Sciences ver. 20.0 (SPSS, Chicago, IL, USA).

Results

Of the 890 study patients, cholelithiasis was diagnosed by abdominal ultrasonography in 87 patients, with a prevalence of 9.8% (see Figure S1, available as Supplementary data at *JAC* Online). Patients with cholelithiasis were significantly older, more likely to be females, have lower HIV-1 viral load, be diabetic, have cirrhosis and have longer exposure to ART (Table 1). On the other hand, patients without cholelithiasis were more likely to be treatment naive.

Of the 890 study patients, 186 (21%) were treated with atazanavir for a median duration of 1.79 years (IQR 0.68–3.78 years) and 84 (9.4%) patients were treated with atazanavir for >2 years. Of the 186 patients treated with atazanavir, 173 (93%) patients were on atazanavir/ritonavir, whereas only 13 (7%) were on non-boosted atazanavir. Cholelithiasis was twice as frequent in patients treated for >2 years with atazanavir [15 (18%) of

Table 1. Basic demographics of total study patients, patients with cholelithiasis and no cholelithiasis

	Total (n=890)	Cholelithiasis (n=87)	No cholelithiasis (n=803)	P^a
Age, years[b]	41 (35–50)	45 (38–55)	40 (34–49)	<0.001
Female sex, n (%)	49 (5.5)	9 (10)	40 (5)	0.047
Race (Asian), n (%)	869 (98)	87 (100)	782 (97)	0.253
BMI, kg/m^2[b]	21.9 (20.1–24.6)	22.5 (20.1–25.7)	21.8 (20–24.4)	0.665
CD4 cell count, cells/μL[b]	365 (207–525)	370 (226–572)	365 (206–523)	0.206
HIV load, $\log_{10}$ copies/mL[b]	1.70 (1.07–4.04)	1.70 (1.70–1.90)	1.70 (1.70–4.20)	0.002
HIV load <50 copies/mL, n (%)	510 (57)	64 (74)	446 (56)	0.001
Diabetes mellitus, n (%)	53 (6)	10 (12)	43 (5)	0.030
Hepatitis B or C coinfection, n (%)	242 (27)	23 (26)	219 (27)	1.000
History of AIDS, n (%)	298 (34)	31 (36)	267 (33)	0.720
Cirrhosis, n (%)	14 (1.6)	6 (7)	8 (1)	0.001
Treatment naive, n (%)	267 (30)	14 (16)	253 (32)	0.003
History of atazanavir/ritonavir exposure, n (%)	186 (21)	25 (29)	161 (20)	0.070
History of lopinavir/ritonavir exposure, n (%)	294 (33)	32 (37)	262 (33)	0.472
History of darunavir/ritonavir exposure, n (%)	100 (11)	13 (15)	87 (11)	0.281
Duration of ART (years)[b]	2.7 (0–7.9)	4.8 (0.9–12)	2.2 (0–7.4)	<0.001

Cirrhosis was diagnosed by abdominal ultrasonography, diabetes mellitus was defined by use of antidiabetic agents or fasting plasma glucose >126 mg/dL or plasma glucose >200 mg/dL on two different days, hepatitis B infection was defined by positive hepatitis B surface antigen and hepatitis C infection was defined by positive hepatitis C virus viral load.

[a]The χ^2 test or Fisher's exact test was used for comparison of categorical data and Student's t-test was used for comparison of continuous variables.

[b]Median (IQR).

Table 2. Univariate and multivariate analysis to estimate the risk for cholelithiasis posed by long-term (>2 years) treatment with ritonavir-boosted atazanavir

	Model 1, crude (n=890)			Model 2, adjusted (n=890)			Model 3, adjusted (n=851)		
	OR	95% CI	P	OR	95% CI	P	OR	95% CI	P
>2 years of atazanavir/ritonavir exposure	2.216	1.206–4.073	0.010	2.096	1.131–3.883	0.019	1.806	0.922–3.537	0.085
Age per 1 year increment	1.034	1.016–1.053	<0.001	1.009	0.980–1.039	0.001	1.028	1.008–1.049	0.005
Female sex	2.201	1.030–4.705	0.042	2.005	0.921–4.368	0.080	2.183	0.986–4.834	0.054
BMI per 1 kg/m^2 increment	1.004	0.985–1.024	0.673				1.001	0.983–1.020	0.881
Cirrhosis	7.361	2.493–21.74	<0.001				6.947	2.133–22.63	0.001
Diabetes mellitus	2.295	1.110–4.748	0.025				1.017	0.417–2.481	0.971
CD4 count per 1 cell/μL increment	1.001	1.000–1.001	0.206						
HIV viral load per $\log_{10}$/mL increment	0.748	0.618–0.906	0.003				0.900	0.717–1.129	0.363
History of AIDS	1.111	0.700–1.765	0.655						
Treatment naive	0.417	0.231–0.753	0.004						
Hepatitis B or hepatitis C coinfection	0.958	0.581–1.582	0.868						
Duration of ART per 1 year increment	1.077	1.040–1.115	<0.001				1.030	0.983–1.080	0.216

Model 1 was the univariate analysis to estimate the risk of various factors for cholelithiasis for atazanavir/ritonavir exposure of >2 years, relative to <2 years or no atazanavir/ritonavir exposure. In Model 2, atazanavir/ritonavir exposure of >2 years, relative to <2 years or no atazanavir/ritonavir exposure, was adjusted by adding age and sex. In Model 3, possible risk factors for cholelithiasis (BMI, cirrhosis and diabetes mellitus) and variables with P values <0.05 in Model 1 (HIV load and duration of ART) were added. The variable 'treatment naive' was not added because of its multicollinearity with HIV load.

84 patients] compared with patients with no or <2 years of atazanavir [72 (8.9%) of 806 patients] (P=0.018).

Univariate analysis showed a significant association between >2 years of atazanavir/ritonavir exposure and cholelithiasis (OR=2.216; 95% CI=1.206–4.073; P=0.010) (Table 2, Model 1). Older age, female sex, cirrhosis, diabetes mellitus, low HIV viral load and duration of ART per 1 year increment were also significantly associated with cholelithiasis.

Multivariate analysis identified >2 years of atazanavir/ritonavir exposure as an independent risk factor for cholelithiasis after adjustment for age and female sex (adjusted OR=2.096; 95% CI=1.131–3.883; P=0.019) (Table 2, Model 2). The association was marginally significant after adjustment for other variables (adjusted OR=1.806; 95% CI=0.922–3.537; P=0.085) (Table 2, Model 3). Older age and cirrhosis also persisted in being significantly associated with cholelithiasis in multivariate analysis (age per 1 year increment, adjusted OR=1.028; 95% CI=1.008–1.049; P=0.005) (cirrhosis, adjusted OR=6.947; 95% CI=2.133–22.63; P=0.001).

Additional analyses focusing on the impact of other commonly used protease inhibitors demonstrated that 148 (16.6%) patients were treated with lopinavir/ritonavir for >2 years, while 29 (3.3%) were treated with darunavir/ritonavir for >2 years. Treatment for >2 years with lopinavir/ritonavir and darunavir/ritonavir was not associated with cholelithiasis in univariate and multivariate analysis adjusted with the same variables in Table 2, Model 3 (lopinavir/ritonavir: OR=1.246; 95% CI=0.710–2.185; P=0.443/adjusted OR=1.221; 95% CI=0.674–2.214; P=0.510) (darunavir/ritonavir: OR=1.067; 95% CI=0.316–3.601; P=0.916/adjusted OR=0.641; 95% CI=0.173–2.377; P=0.506). In univariate analysis, treatment for >1 year with atazanavir/ritonavir [n=124 (13.9%)] was also significantly associated with cholelithiasis (OR=1.857; 95% CI=1.073–3.214; P=0.027), whereas >1 year exposure to lopinavir/ritonavir [n=199 (22.4%)] and darunavir/ritonavir [n=53 (6%)] did not correlate with cholelithiasis (lopinavir/ritonavir: OR=1.367; 95% CI=0.830–2.252; P=0.220) (darunavir/ritonavir: OR=0.961; 95% CI=0.375–2.464; P=0.934).

Discussion

To our knowledge, this is the first study to investigate the effects of atazanavir/ritonavir exposure on cholelithiasis, including asymptomatic cholelithiasis. Patients treated for >2 years with atazanavir/ritonavir were twice as likely to develop cholelithiasis compared with patients with no or <2 years of atazanavir/ritonavir exposure. Univariate analysis demonstrated a significant association between >2 years of atazanavir/ritonavir exposure and cholelithiasis (OR=2.216; 95% CI=1.206–4.073; P=0.010) and the association almost persisted in multivariate analysis (adjusted OR=1.806; 95% CI=0.922–3.537; P=0.085) (Table 2). Thus, long-term treatment with atazanavir/ritonavir was associated with cholelithiasis in this cohort. On the other hand, exposure to lopinavir/ritonavir or darunavir/ritonavir, other widely prescribed protease inhibitors, was not associated with cholelithiasis.

Two mechanisms are suggested for the observed atazanavir-induced cholelithiasis. First, precipitation of atazanavir in the bile might enhance the formation of calculi composed of atazanavir and other biliary components. This hypothesis is supported by the documentation of atazanavir as a component of gallstones in several case reports.[5–7] Strong acidity (e.g. pH of 1.9) is required to achieve optimal dissolution of atazanavir, whereas biliary pH is usually >6.5.[4] This feature of atazanavir might result in precipitation of atazanavir and consequent cholelithiasis.[4] It is well known that atazanavir/ritonavir is a risk factor for nephrolithiasis[14,15] and, recently, a case of atazanavir-containing sialolithiasis in a patient treated with atazanavir/ritonavir was also reported.[16] These data further support the likelihood of atazanavir involvement in lithiasis. Second, because atazanavir is a competitive

inhibitor of uridine diphosphate glucuronyl transferase 1A1 (UGT1A1), a bilirubin-conjugating enzyme, atazanavir is known to cause hyperbilirubinaemia.[17] This might result in a rise in the bilirubin level in the bile, which could facilitate the formation of gallstones because bilirubin is also a component of such stones. This hypothesis is supported by a case report that showed the presence of indinavir, another protease inhibitor, in the gallstones of a patient on indinavir-containing ART.[18] Indinavir has similar characteristics to atazanavir: optimal solubility at low pH and being an inhibitor of UGT1A1.[18,19]

There are several limitations to our study. First, because stone composition analysis was not conducted in this study, one cannot rule out other causes of cholelithiasis in addition to atazanavir/ritonavir. Second, the prevalence of gallstones is generally lower in Asians than in Europeans and since most of the patients in this study were Asian, the effect of atazanavir/ritonavir might be different in other populations.[20] Third, because the study population included patients who had undergone abdominal ultrasonography in clinical practice with various indications, the prevalence of cholelithiasis might be overestimated.

In conclusion, the present study demonstrated that patients on long-term treatment (>2 years) with atazanavir/ritonavir were twice as likely to develop cholelithiasis compared with those treated for <2 years. A similar effect was not demonstrated in patients treated with lopinavir/ritonavir or darunavir/ritonavir. Long-term, large prospective studies are warranted to elucidate the incidence and risk factors for complicated cholelithiasis in patients exposed to atazanavir/ritonavir-containing ART.

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Transparency declarations

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Supplementary data

Figure S1 is available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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