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

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Abstract

Background: The effect of long-term treatment with ritonavir-boosted atazanavir (ATV/r) on cholelithiasis formation is unknown.

Methods: A single-center, 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 2012. Uni- and multi-variate logistic regression analyses were applied to estimate the effects of >2 years of ATV/r exposure on cholelithiasis as the primary exposure.

Results: Of the 890 study patients, 84 (9.4%) had >2 years of ATV/r exposure. Cholelithiasis was twice more frequently diagnosed in those treated for >2 years with ATV/r [15 (18%) of 84 patients] than in those treated for <2 years [72 (8.9%) of 806 patients] (p=0.018). Univariate analysis showed a significant association between >2 years of ATV/r 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). Treatment for >2 years with ritonavir-boosted lopinavir (LPV/r) and ritonavir-boosted darunavir (DRV/r) was not associated with cholelithiasis in uni- and multi-variate analysis { >2 years exposure to LPV/r [n=148 (16.6%)]: 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} { >2 years exposure to DRV/r [n=29 (3.3%)]: 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}. Additional analysis showed that >1 year exposure to ATV/r [n=124 (13.9 %)] was significantly associated with cholelithiasis (OR 1.857, 95%CI 1.073-3.214, p=0.027), whereas >1 year exposure to LPV/r and DRV/r was not.

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

Background

✓It is well-known that ritonavir-boosted atazanavir (ATV/r) use is a risk for nephrolithiasis.[1)]

✓Several case series also suggested potential association between ATV/r exposure and cholelithiasis.[2-4)]

✓However, the effects of prolonged exposure to ATV/r on the incidence of cholelithiasis is unknown.[5)]

✓This is important because approximately 20% of patients with gallstones develop symptoms in the long-term.[6)]

✓The aim of this study is to elucidate the effects of ATV/r exposure on cholelithiasis formation, including asymptomatic cholelithiasis, in patients with HIV-1 infection.

Methods

A single-center cross sectional study

Major entry criteria: Patients aged >17 years, who underwent abdominal ultrasonography at the Physiological Examination Unit of the hospital between Jan 2004 and Mar 2013 as part of clinical practice.

Exclusion criteria: *1)* the patient with cholecystectomy performed before the study period, and *2)* patient with missing data on ART.

Ultrasonography was conducted by certified medical technologists, and the images and diagnosis were double-checked and confirmed by radiologists, hepatologists, or gastroenterologists.

Measurements

✓**Patient characteristics:** *age, sex, ethnicity, BMI, presence or absence of cirrhosis, diabetes mellitus, hepatitis B or C infection*

✓**HIV-related variables:** *CD4 count, HIV load, ART-experienced or -naïve, duration of ART, darunavir (DRV/r), and history of AIDS*

We used data collected within three months of the day ultrasonography was conducted.

Cirrhosis was diagnosed by abdominal ultrasonography, diabetes mellitus defined by using anti-diabetic agents or fasting plasma glucose >126 mg/dl or plasma glucose >200 mg/dl on two different days, hepatitis B infection defined by positive hepatitis B surface antigen and hepatitis C infection defined by positive HCV viral load.

Statistical analysis

The primary exposure variable was a history of ATV/r use for >2 years, regardless of continuation of ATV/r at the time of sonography. Two years threshold for ATV/r exposure was selected because cholelithiasis was not reported in ATV/r phase 3 clinical trials with the primary endpoint set at week 48, and prolonged excretion of ATV in the bile appears necessary for gall stone formation.[2)]

Logistic regression was used to estimate the effects of ATV/r exposure of >2 years, relative to <2 years or no ATV/r exposure, on cholelithiasis.

Multivariate analysis adjusted by basic demographics (*age and sex*), possible risk factors for cholelithiasis (*BMI, cirrhosis, diabetes mellitus*), and variables with *P* values <0.05 in univariate analysis (*HIV load and duration of ART*) were conducted. The variable "*treatment-naïve*" was not added to the model because of its multicollinearity with HIV load.

In order to elucidate the impact of other commonly used protease inhibitors, additional analysis was conducted to examine the effects of LPV/r and DRV/r exposure for >2 years, respectively.

Results

Summary of the Results

✓Of 890 study patients, 87 (9.8%) had cholelithiasis.

✓186 (21 %) were treated with ATV/r for a median duration of 1.79 years (IQR 0.68-3.78 years), and 84 (9.4 %) patients were treated with ATV/r for >2 years.

✓**Cholelithiasis was twice more frequently diagnosed in patients treated for >2 years with ATV/r [15 (18 %) of 84 patients] than in patients with no or <2 years of ATV/r [72 (8.9 %) of 806 patients] (p=0.02).**

✓Univariate analysis showed **a significant association between >2 years of ATV/r exposure and cholelithiasis (OR=2.22; 95%CI, 1.21–4.07; p=0.01)** (Table 2).

✓Multivariate analysis identified **>2 years of ATV/r exposure as an independent risk for cholelithiasis after adjustment for age and female sex (OR=2.10 95%CI, 1.13–3.88; p=0.02),** and **the association was marginally significant after adjustment for other variables (OR= 1.81; 95%CI, 0.92-3.54; p=0.09)** (Table 3).

✓Additional analyses demonstrated that treatment for >2 years with LPV/r and DRV/r was not associated with cholelithiasis in multivariate analysis adjusted with the same variables in Table 3 (LPV/r: OR 1.22, 95% CI 0.67-2.21, p=0.51) (DRV/r: OR 0.64, 95%CI 0.17-2.38, p=0.51).

✓Univariate analysis also showed that treatment for >1 year with ATV/r was significantly associated with cholelithiasis (OR 1.86, 95%CI 1.07-3.21, p=0.03), whereas >1 year exposure to LPV/r and DRV/r did not correlate with cholelithiasis (LPV/r: OR 1.37, 95%CI 0.83-2.25, p=0.22) (DRV/r: OR 0.96, 95%CI 0.38-2.46, p=0.93), respectively.

Figure 1. Patient enrollment process

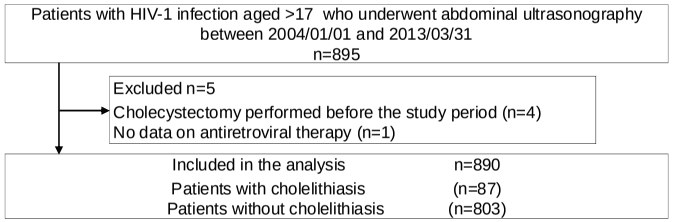


Table 1. Basic demographics of the study patients

	Gallstone (n=87)	No gallstones (n=803)	P[a]
ATV/r exposure, n (%)	**25 (29)**	**161 (20)**	**0.07**
LPV/r exposure, n (%)	32 (37)	262 (33)	0.47
DRV/r exposure, n (%)	13 (15)	87 (11)	0.28
Age, years[¶]	**45 (38-55)**	**40 (34-49)**	**<0.01**
Female sex, n (%)	**9 (10)**	**40 (5)**	**0.05**
Race (Asian), n (%)	87 (100)	782 (97)	0.25
BMI, kg/m^2[¶]	22.5 (20.1-25.7)	21.8 (20-24.4)	0.67
CD4 count, cells/μL[¶]	370 (226-572)	365 (206-523)	0.21
HIV load, $\log_{10}$ copies/mL[¶]	**1.70 (1.70-1.90)**	**1.70 (1.70-4.20)**	**<0.01**
HIV load <50 copies/mL, n (%)	**64 (74)**	**446 (56)**	**<0.01**
Diabetes mellitus, n (%)	**10 (12)**	**43 (5)**	**0.03**
Hepatitis B or C infection, n (%)	23 (26)	219 (27)	1.00
History of AIDS, n (%)	31 (36)	267 (33)	0.72
Cirrhosis, n (%)	**6 (7)**	**8 (1)**	**<0.01**
Treatment naïve, n (%)	**14 (16)**	**253 (32)**	**<0.01**
Duration of ART (years)[¶]	**4.8 (0.9-12)**	**2.2 (0-7.4)**	**<0.01**

[¶]median (interquartile range) [a]The χ^2 test or Fisher's exact test was used for comparison of categorical data, and the Student's *t* test was used for comparison of continuous variables.

Table 2. Univariate analysis to estimate the risk of various factors for cholelithiasis

	Odds ratio	95% CI	P value
>2 years of ATV/r exposure	**2.22**	**1.21-4.07**	**0.01**
Age per 1 year increment	**1.03**	**1.02-1.05**	**<0.01**
Female sex	**2.20**	**1.03-4.71**	**0.04**
BMI per 1 kg/m^2 increment	1.00	0.99-1.02	0.67
Cirrhosis	**7.36**	**2.49-21.7**	**<0.01**
Diabetes mellitus	**2.30**	**1.11-4.75**	**0.03**
CD4 count per 1 /μl increment	1.00	1.00-1.00	0.21
HIV load per $\log_{10}$/ml increment	**0.75**	**0.62-0.91**	**<0.01**
History of AIDS	1.11	0.70-1.77	0.66
Treatment naïve	**0.42**	**0.23-0.75**	**<0.01**
Hepatitis B or C co-infection	0.96	0.58-1.58	0.87
ART duration per 1 year increment	**1.08**	**1.04-1.12**	**<0.01**

Table 3. Multivariate analysis to estimate the risk of >2 years treatment with ATV/r on cholelithiasis

	(n=890)			(n=851)		
	OR	95% CI	P value	OR	95% CI	P value
>2 years of ATV/r exposure	**2.10**	**1.13-3.88**	**0.02**	**1.81**	**0.92-3.54**	**0.09**
Age per 1 year increment	**1.01**	**0.98-1.04**	**0.01**	**1.03**	**1.01-1.05**	**<0.01**
Female sex	2.01	0.92-4.37	0.08	2.18	0.99-4.83	0.05
BMI per 1 kg/m^2 increment				1.00	0.98-1.02	0.88
Cirrhosis				**6.95**	**2.13-22.6**	**0.01**
Diabetes mellitus				1.02	0.42-2.48	0.97
HIV load per $\log_{10}$/ml increment				0.90	0.72-1.13	0.36
ART duration per 1 year increment				1.03	0.98-1.08	0.22

Conclusions

✓ Patients treated for >2 years with ATV/r were twice as likely to develop cholelithiasis than patients with no or <2 years of ATV/r exposure.

✓ Univariate analysis demonstrated a significant association between >2 years of ATV/r exposure and cholelithiasis(OR=2.22; 95%CI, 1.21–4.07; p=0.01), and the association almost persisted in multivariate analysis (adjusted OR= 1.81; 95%CI, 0.92-3.54; p=0.09).

✓ On the other hand, exposure to LPV/r or DRV/r, was not associated with cholelithiasis.

Reference:
1) Hamada *Clin Infect Dis* 2012; 55, 2) Rakotondravelo. *Clin Infect Dis* 2012; 55, 3) Courbon *J Antimicrob Chemother* 2012; 67 4) Jacques *Ann Pharmacother* 2010; 44, 5) Hamada *PLoS One* 2013; 8, 6) Barbara *Hepatology* 1987; 7

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