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Risk Factors for Atazanavir (ATV)-Associated Urolithiasis: a Case-Control Study.

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BACKGROUND

- A high incidence of renal stones (23.7 cases per 1000 person-years) has been reported among patients receiving ATV/r containing ART (1). However, risk factors, clinical features and outcome of ATV-associated urolithiasis have not been fully investigated.
- To evaluate the risk factors for ATV-induced nephrolithiasis and to better describe clinical features and outcome we undertook a multicenter case-control study.

METHODS

- Retrospective multicenter case-control study.
- Cases were adults in whom an ATV-containing urolithiasis had been identified by spectroscopic analysis (either pure ATV or associated with proteins) from January 2008 to December 2012.
- Eligible patients were identified from the computerized database of 3 biochemistry laboratories, located in Paris.
- For each case, three controls were randomly selected among patients treated with ATV-based regimens for at least 6 months, no history of ATV-associated urolithiasis and matched to the closest date of ATV-associated urolithiasis defining-case.
- Patients' characteristics, treatment and outcome were retrieved from medical charts at diagnosis and 6-12 months later.
- A risk factor analysis was conducted to identify factors associated with the occurrence of ATV-containing urolithiasis. We used logistic regression modeling in an univariate analysis among all covariates. All factors with p < 0.05 were kept for a multivariate model selection. We selected for the multivariate analysis the most clinically relevant models.

BASELINE CHARACTERISTICS OF PATIENTS WITH ATV-ASSOCIATED UROLITHIASIS COMPARED WITH CONTROLS

	Controls (n=90)	Cases (n=30)	p
Male [n (%)]	68 (75.6%)	26 (86.7%)	0.31
Age (years) [median (range)]	47 [39, 52.8]	45.5 [42, 50.5]	0.85
Body Mass Index (BMI) (kg/m2) (median [IQR])	23 [21.1, 25.7]	22.8 [21.3, 24.2]	0.60
Duration of HIV infection (years) [median (range)]	12.0 [4.9, 18.3]	9.7 [4.2, 17.7]	0.47
CDC disease stage			0.20
A	48 (53.9%)	20 (66.7%)	
B	14 (15.7%)	1 (3.3%)	
C	27 (30.3%)	9 (30%)	
Nadir CD4 (cell count, cells/mL)	204 [112, 297]	209.5 [67, 313]	0.79
CD4+ cell count, cells/mL	492 [344, 657]	443 [401, 620]	0.77
Plasma HIV RNA > 50 cp/mL [n (%)]	59 (65.6%)	1 (3.3%)	< 0.001
Duration of ATV prior to urolithiasis (years) [median (range)]	1.9 [1.2, 3.2]	3.1 [2.2, 3.8]	< 0.009
Associated ARV therapy [(n) %]			
Ritonavir (100 mg od) [(n) %]	68 (75.6%)	29 (96.7%)	< 0.02
Lamivudine/emtricitabine	82 (91.1%)	26 (86.7%)	0.64
Abacavir	30 (33.3%)	10 (33.3%)	1.00
Zidovudine	6 (6.7%)	3 (10%)	0.69
Didanosine	11 (12.4%)	2 (6.7%)	0.51
Tenofovir	47 (52.8%)	16 (53.3%)	1.00
Baseline creatinine clearance* (median [IQR])	91.9 [77.5, 99.9]	81.5 [73.1, 98.2]	0.16
Chronic kidney disease** before urolithiasis [n (%)]	7 (7.9%)	4 (14.3%)	0.29
Prior treatment with indinavir (years) [(n) %]	18 (20%)	13 (44.8%)	< 0.02
Duration of indinavir (months) (median [IQR])	0 [0, 0]	0 [0, 32]	< 0.004
History of indinavir-urolithiasis [n (%)]	1 (1.2%)	8 (26.7%)	< 0.001
History of urolithiasis before ATV therapy [n (%)]	7 (7.8%)	11 (36.7%)	< 0.01
Diabetes [n (%)]	9 (10%)	1 (3.3%)	0.45
Serum calcium (mmol/L) (median [IQR])	2.3 [2.2, 2.4]	2.3 [2.3, 2.4]	0.96
Serum free bilirubin level (mmol/L) (median [IQR])	30.9 [17.7, 45]	49.1 [32.5, 56]	< 0.004

*: 6-12 months before ATV-associated urolithiasis occurrence
**: defined as creatinine clearance <60 mL/min (MDRD)

RISK FACTORS FOR UROLITHIASIS UNIVARIATE ANALYSIS

	OR	95% CI	p
Male sexe	2.1	0.66-6.69	0.21
BMI (kg/m2)	0.93	0.84-1.04	0.24
Age (years)	1	0.95-1.04	0.83
Plasma HIV RNA<50 cp/mL	0.07	0-0.44	< 0.006
Prior history of urolithiasis	6.86	2.35-20.03	< 0.001
Prior treatment with indinavir	3.25	1.33-7.96	< 0.01
Duration of ATV (per year)	1.37	1.04-1.79	< 0.03
Ritonavir (100 mg od)	9.38	1.21-72.9	< 0.04
Associated ARV therapy	0.8	0.34-1.85	0.6
Creatinine clearance (before lithiasis)	0.99	0.97-1.01	0.39
Serum free bilirubin level (per 2-fold increase)	1.02	1-1.04	< 0.02

RISK FACTORS FOR UROLITHIASIS MULTIIVARIATE ANALYSIS

	OR	95% CI	p
FIRST MODEL WITH 3 MAIN VARIABLES			
Duration of ATV (per year)	1.32	0.95-1.84	0.1
Serum free bilirubin level (per 2-fold increase)	2.31	1.18-4.52	0.01
Prior history of urolithiasis	3.66	0.88-15.2	0.07
ALTERNATIVE MODELS WITH 2 VARIABLES			
Serum free bilirubin level (per 2-fold increase)	1.94	1.12-3.36	0.02
Prior history of urolithiasis	4.79	1.44-15.98	0.01
Duration of ATV (per year)	1.42	1.04-1.93	0.03
Serum free bilirubin level (per 2-fold increase)	2.66	1.35-5.21	0.004

CLINICAL PRESENTATION AND OUTCOME OF 30 PATIENTS WITH ATV-ASSOCIATED UROLITHIASIS

Variable	n=30
Symptoms [n (%)]	
Renal colic/Lumbar and/or flank pain	27 (90.0%)
Macroscopic hematuria	19 (82.6%)
Créatinine clearance* [median (IQR)]	78.0 [45.6, 98.0]
Creatinine clearance* <60 mL/min [n (%)]	9 (34.6%)
Stone size (mm) [median (IQR)]	5.5 [3.9, 9.3]
Stone composition percentage [median (IQR)]	
ATV	89.0 [59.0, 95.0]
Proteins	7.5 [3.0, 10.0]
Calcium oxalate	0% [0%; 8%]
Calcium phosphate	0% [0%, 0%]
Stone location [n (%)]	
Pyelic	6 (33.3%)
Ureteral	11 (61.1%)
Bladder	1 (5.6%)
Ureteral dilatation [n (%)]	13 (54.2%)
Bilateral nephrolithiasis [n (%)]	4 (14.3%)
Treatment [n (%)]	
Medical	9 (31.0%)
Lithotripsy	2 (6.9%)
Urologic surgery	13 (44.8%)
ATV discontinuation [n (%)]	24 (82.8%)
Recurrence of urolithiasis [n (%)]	3 (10.7%)
Créatinine clearance* 6-12 months after ATV-associated urolithiasis [median (IQR)]	84.5 [69.4, 96.8]

*: MDRD

CONCLUSIONS

- In this study, ATV-associated urolithiasis was symptomatic, with renal colic and hematuria in most patients. It was associated with decreased creatinine clearance in a third of cases and frequently required urologic surgery. The urolithiasis occurrence led to ATV discontinuation in most patients.
- In univariate analysis, risk factors for ATV-urolithiasis were a history of urolithiasis, the prior use of indinavir, ATV duration, an undetectable HIV plasma RNA, the use of ritonavir as a booster and the serum free bilirubin level.
- Multivariate models retained ATV duration, serum free bilirubin level and a history of urolithiasis as independent factors associated with ATV-associated urolithiasis.

References

1. Hamada Y, Nishijima T, Watanabe K et al. High incidence of renal stones among HIV-Infected patients on ritonavir-boosted atazanavir than in those receiving other protease inhibitor–containing antiretroviral therapy, *Clin Infect Dis*. 2012 Nov;55(9):1262-9