Correlation between atazanavir concentrations, clinical covariates and side effects

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Background

- ✓ In most European Countries atazanavir (ATV) is approved at the dosage of 300 mg once daily boosted with ritonavir.
- ✓ The highest probability of achieving undetectable viral load has been associated with ATV concentrations >150 ng/mL.
- ✓ Hyperbilirubinemia has been associated with ATV trough concentrations >800 ng/mL. No associations have been reported for other ATV-related complications.
- ✓ No clinical covariates affecting ATV concentrations have been conclusively identified.

Aims of the present study

- ✓ To investigate the potential associations between ATV plasma trough concentrations and drug-related adverse events.
- ✓ To assess the distribution of ATV plasma trough concentrations according to drug dosage.
- ✓ To identify clinical/demographic covariates significantly associated with ATV concentrations.

Methods

- ✓ ATV-related complications were defined as: total bilirubin >1.8 mg/dL with no UGT1A1*28 homozygous genotype, dyslipidemia (total cholesterol >200 mg/dL, triglycerides >180 mg/dL or statin therapy) and kidney stones (absence of urinary oxalate or urate crystals).
- ✓ ATV plasma trough concentrations were stratified as below, within or above the therapeutic thresholds.

Results 1

Table 1. Main characteristics of enrolled patient

Parameters	Patients (n=273)
Male gender, %	68%
Age, years	47±12
Naïve, %	21%
ATV therapy, days	926±844
HAART, %	54% tenofovir, 25% abacavir, 21% others
Body mass index, Kg/m^2	24±4
Creatinine, mg/dL	0.9±0.4
ALT, IU/L	47±48
CD4, cells/mL	587±246
HCV/HBV coinfection, %	30%

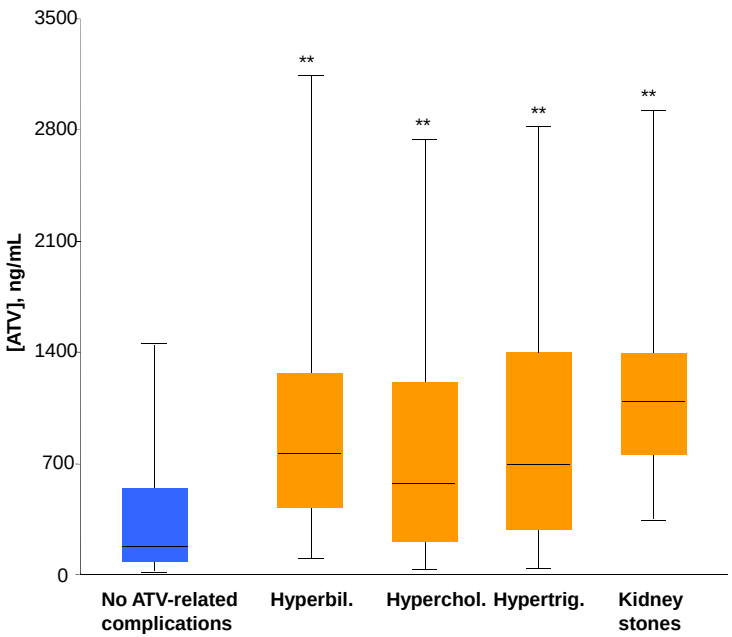
Results 2

Table 2. Comparison of the characteristics of HIV-positive patients that did or did not develop ATV-related complications.

Parametes	ATV-related AE YES (n=202)	ATV-related AE NO (n=71)	P-value
Atazanavir therapy, days	973±889	809±687	0.159
[Atazanavir], ng/mL	846±838	461±678	0.001
Ritonavir use, %	67%	52%	0.033*
HAART, %	56% TDF-based	48% TDF-based	0.201*
Male gender, %	71%	55%	0.014*
Age, years	48±11	43±11	0.003
Weight, Kg	70±14	66±16	0.110
Body mass index, Kg/m^2	24±4	23±4	0.323
Creatinine, mg/dL	0.9±0.5	0.8±0.2	0.119
ALT, IU/L	46±45	48±56	0.703
CD4, cells/mL	603±248	541±235	0.067
HCV or HBV co-infection, %	30%	39%	0.153*

AE: adverse events; * chi-square test

Figure 2. ATV plasma trough concentrations in patients that did or did not develop drug-related complications. (**p<0.001).



Results 3

Table 3. Distribution of ATV plasma trough concentrations according to daily drug dosage and therapeutic window

	ATV, ng/mL (mean ± SD)	Samples <150^	Samples 150-800^	Samples >800^
All evaluations (n=273)	766 ± 847	21.2%	44.3%	34.4%
ATV/r 300/100 mg qd (n=164)	939 ± 898	11.6%	44.5%	43.9%
ATV 400 mg* (n=76)	490 ± 651	35.5%	44.7%	19.8%
ATV 300 mg qd (n=25)	504 ± 812	44.0%	32.0%	24.0%
ATV 200/100 mg qd (n=8)	648 ± 709	0%	75.0%	25.0%

*given either as 400 mg qd or 200 mg bid; ^ng/mL

Table 4. Univariate and multivariate regression analysis of variables independently associated with ATV plasma trough concentrations

	Univariate		Multivariate	
Variable	r	p-value	r	p-value
Days of ATV therapy	-0.03	0.588		
Atazanavir dosage	-0.268	0.0001		
Gender	0.001	0.943		
Age	0.004	0.559		
Weight	0.004	0.422		
Body mass index	0.115	0.085		
ALT, IU/L	0.016	0.822		
Creatinine	0.001	0.926		
Co-infections	0.05	0.471		
Concomitant HAART	-0.051	0.497		
Number of drugs	0.048	0.366		
Ritonavir	0.357	<0.0001	0.291	<0.0001
Rosuvastatin	0.395	<0.0001	0.315	<0.0001
Proton pump inhibitors	0.010	0.922		

Conclusions

- ✓ High ATV plasma levels were significantly associated with metabolic and kidney ATV-related adverse events.
- ✓ A significant proportion of patients (mainly at the 300/100 mg qd dosage) had ATV plasma concentrations exceeding the upper therapeutic threshold.
- ✓ Rosuvastatin significantly increased ATV plasma concentrations in ritonavir-treated patients, despite its theoretical low potential for interactions with PIs.
- ✓ Individualized TDM-driven adjustments in ATV dosage may have potential advantages in terms of costs and toxicity.