CONFERENCE CAHR 2020

CONGRÈS DE L'ACRV 2020

Association Between Untimed Plasma Atazanavir Levels and Renal and Gall Stones

Birgit Watson[1], Katherine A Baynes[1], Katherine J Lepik[1,2], Wendy Zhang[1], Kieran Atkinson[1], Karly Kondratowicz[1], Natalia Oliveira[1], Rolando Barrios[1], Chanson J Brumme[1,3]

1. BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; 2. Pharmacy Department, St. Paul's Hospital, Vancouver, BC, Canada; 3. Faculty of Medicine, University of British Columbia, BC, Canada

I HAVE NO CONFLICTS OF INTEREST TO DECLARE

Correspondence: bwatson@cfenet.ubc.ca
cbrumme@cfenet.ubc.ca

BRITISH COLUMBIA CENTRE *for* EXCELLENCE *in* HIV/AIDS

Program ID#: CSP11.01

Background

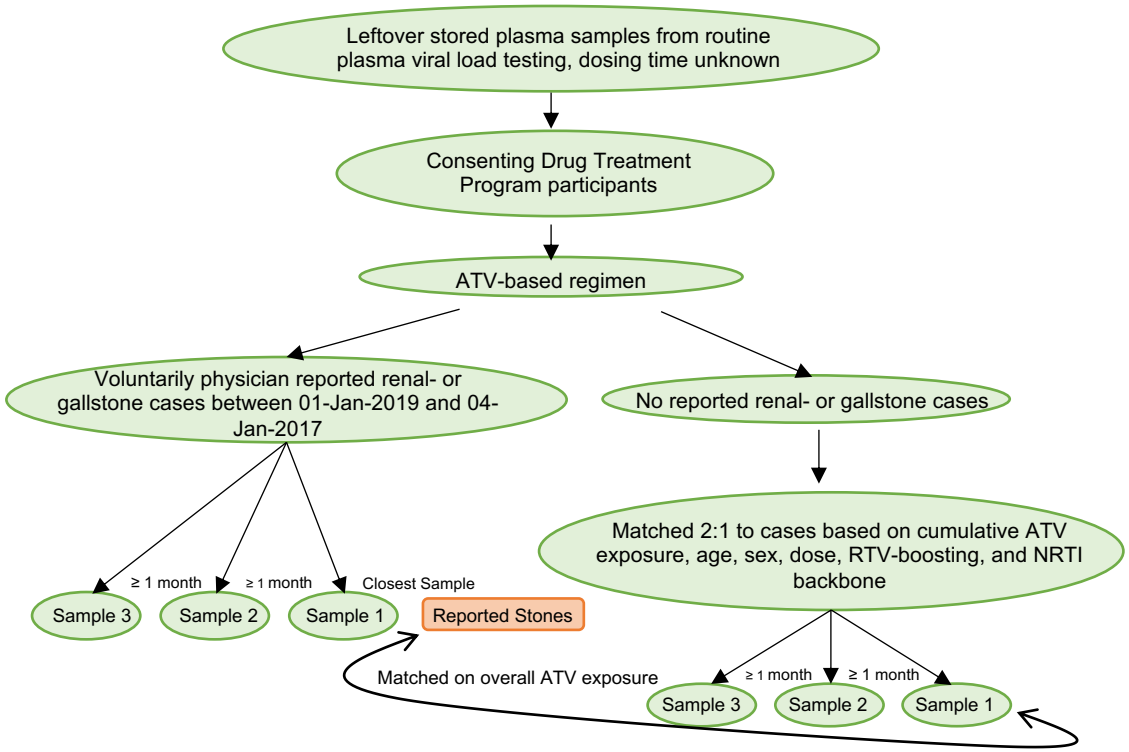
- Atazanavir (ATV) exposure has been associated with increased risk of renal- and gall stones (1)(2)
- Cumulative ATV exposure has been shown to increase risk (1)
- ATV containing stones have been identified in some patients (3)
- It has been reported that patients experiencing renal- or gallstones have significantly higher trough concentrations than patients with no ATV-related complications (2)
- We aim to determine whether reported renal- or gall stones in ATV-treated patients were associated with untimed ATV levels in HIV-1 patients
- Cases were identified from the BC Centre for Excellence in HIV/AIDS Pharmacovigilance program in which health care providers voluntarily report adverse effects related to ARV therapy

Untimed Drug Levels

- Drug levels vary based on pharmacokinetics, metabolism, drug absorption
- **"Untimed" drug levels (UDL)** - dosing time is unknown relative to plasma collection

Study Design

- Plasma samples are from leftover routine plasma viral load testing
- Cases: 3 pre-stone samples, latest selected sample closest to the date of reported stones
- Controls: 3 samples selected in order to match overall ATV exposure time
- All samples ≥1 month apart



1. Hamada Y et al. *Clin Infect Dis* 2012:55 (PMID 22820542); 2. Gervasoni C et al. *PLoS ONE* 2015:10 (PMID 25875091);
3. Anderson PL et al. *AIDS* 2007:21 (PMID 17457108).

Demographic and Clinical Characteristics

Baseline demographic characteristics and laboratory data for 156 participants (818 samples) who experienced renal- or gallstones (n=52) and were on Atazanavir (ATV) or Ritonavir-boosted ATV (ATV/r) antiretroviral therapy, and matching controls (n=104).

Parameters	Case (n=52)	Controls (n=104)
Male gender, %	80.8%	81.7%
Age at first ATV date, years	48 (Q1-Q3: 42-56)	47 (Q1-Q3: 43-54)
HAART backbone, %	37.1% 3TC/ABC	36.3% 3TC/ABC
	33.6% TDF/FTC	34.2% TDF/FTC
	3.9% 3TC/TDF	4.1% 3TC/TDF
	25.4% Other	25.5% Other
HAART including ATV/r, %	94.5%	95.2%
HAART including TDF, %	46.1%	46.9%
Median total exposure ATV, days	2346 (Q1-Q3: 1541-3279)	2123 (Q1-Q3: 1290-3150)
Detectable Viral Load (pVL ≥50 c/mL)	11.3%	20.1%
Participants with renal stones[a]	80.8%	
Participants with gallstones[a]	17.3%	
[a]1.92% experienced both		

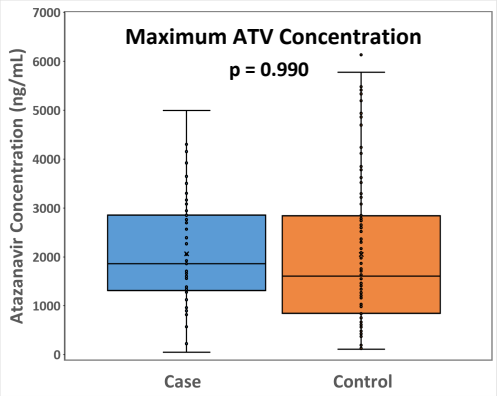
Analytical Method

- Validated HPLC-MS/MS method
- Sample processing: Internal standard addition, protein precipitation and dilution of filtrate
- 7-point calibration curve range: 27 - 6000 ng/mL
- $r^2 > 0.995$
- External quality control samples in serum and plasma

Statistical Analysis

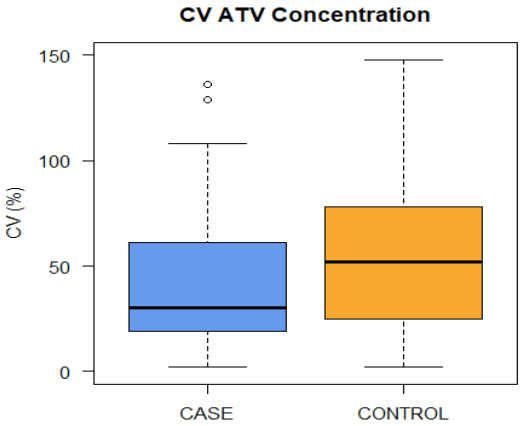
- Friedman test was used to compare the maximum ATV measurements between the 52 cases and 104 controls
- A one-sample Wilcoxon signed rank test was used to compare the ratio of the maximum ATV measurements
- Assessed potential confounding by variation in cART regimen in sub-analyses stratified by NRTI backbone (TDF vs. no TDF) and ritonavir boosting (yes vs. no)
- Analyses were conducted using SAS version 9.4 with a level of significance of 0.05

Distribution of Untimed ATV Concentrations in Cases and Controls



No Significant Difference in Maximum ATV concentrations between cases and controls.

Intra-patient variability of untimed ATV Concentrations



High intra-patient variability due to untimed drug levels shown in high coefficient of variation (CV).

Ratio of Maximum ATV Concentration

Median Ratio of maximum ATV plasma levels from the control to their case was 0.91 (Q1-Q3: 0.44-1.73) (p=0.40).

Sub-Analyses correcting for potential matching

		Case	Control	p-value
All evaluations	n	52	104	0.99
	Median (ng/mL)	1791	1671	
	Q1 (ng/mL)	1303	842.6	
	Q3 (ng/mL)	2852	2847	
Precisely matched[2] case-controls	n	40	70	0.53
	Median (ng/mL)	1878	1542	
	Q1 (ng/mL)	1348	845.5	
	Q3 (ng/mL)	2869	2849	
ATV/r 300/100mg OD	n	49	97	0.93
	Median (ng/mL)	1723	1726	
	Q1 (ng/mL)	1314	1030	
	Q3 (ng/mL)	2850	2849	
ATV 400mg[1]	n	3	7	0.48
	Median (ng/mL)	2050	617.1	
	Q1 (ng/mL)	50.1	372.0	
	Q3 (ng/mL)	2854	2846	
TDF backbone	n	24	49	0.80
	Median (ng/mL)	1470	1463	
	Q1 (ng/mL)	1286	774.6	
	Q3 (ng/mL)	2220	2741	
No TDF in regimen	n	28	55	0.73
	Median (ng/mL)	2005	1866	
	Q1 (ng/mL)	1650	1056	
	Q3 (ng/mL)	3024	3293	

[1]given either as 400mg OD or 200mg BID
[2]matched all fields (ATV exposure, age, sex, dose, RTV-boosting, NRTI backbone)

Sensitivity analysis for 'precisely-matched' case-control (all criteria matching) showed no differences in ATV concentrations (p = 0.53), similarly to sub analyses stratified by NRTI backbone (p = 0.80 and 0.73) or ritonavir boosting (p = 0.93 and 0.48).

Conclusions

No association was observed between reported renal- or gallstones and untimed atazanavir plasma levels in this small sample size of atazanavir-treated patients.

Atazanavir trough concentrations have shown an increased risk in renal- and gallstones. However, due to UDL testing limitations, untimed atazanavir plasma level monitoring may not be suitable for assessing risk of atazanavir-associated renal- or gallstones.