Retrospective analysis of atazanavir therapeutic drug monitoring: is boosting with ritonavir necessary if atazanavir is used with tenofovir?

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BACKGROUND

- Tenofovir disoproxil fumarate (TDF) is known to decrease atazanavir (ATZ) exposure by 25% and minimum concentration (Cmin) by 40%;
- ATZ / ritonavir (RTV) 300 /100 mg once daily is recommended to overcome this interaction;
- Due to poor tolerability, RTV is often avoided and some patients on TDF receive ATZ 400 mg once daily without RTV;
- ATZ Cmin > 0,15 mg/L and genotypic inhibitory quotient (GIQ) > 0,1 mg/L/mutation, so called therapeutic values, have been associated with a greater likelihood of virologic response, and Cmin > 0,85 mg/L with more hyperbilirubinemia (Gonzalez de Requena et al, 6th IWCPHT, Québec, 2006).

STUDY OBJECTIVES

- Evaluate if ATZ 400 mg once daily without RTV can provide therapeutic Ctrough and GIQ when administered with TDF;
- Compare Ctrough and GIQ results in 4 groups (regimens given once daily and with ≥ 1 other NRTI):
  - ATZ 400 mg with TDF (no RTV)
  - ATZ 400 mg (no TDF, no RTV)
  - ATZ / RTV 300 mg / 100 mg with TDF
  - ATZ / RTV 300 mg / 100 mg (no TDF)
- Describe the virologic outcomes in a subset of patients

METHODS

- Retrospective study using TDM database
- Study approved by research and ethics board

Inclusion criteria

- HIV infected patients ≥ 18 years old
- At least one ATZ TDM sample between June 2006 and September 2010
- Samples between 12 and 26 hours post-dose
- Receiving ATZ 400 mg without RTV or ATZ / RTV 300 / 100 mg once daily

Exclusion criteria

- Missing data on NRTI use
- Pregnancy, hepatic impairment, or suspected non adherence noted by treating physician
- Concomitant use of CYP3A4 inhibitors or inducers, and/or gastric acid modifying agents

Pharmacokinetic sampling and analysis

- Validated LC/MS/MS assay used to quantify ATZ concentrations (inter-assay CV 5-7%; intra-assay CV 0.3-5%; limit of quantification 0.01 mg/L or 0.05 mg/L, varied in time)
- For samples not taken at 24 hours post-dose: the ATZ concentration was extrapolated at the end of the doing interval (Ctrough) using the product monograph mean ATZ half-lives
- Ctrough therapeutic target > 0.15 mg/L
- GIQ therapeutic target > 0.1 mg/L/mutation
- GIQ = Ctrough / # IAS-USA 2004 protease mutations present (as per Gonzalez de Requena et al, 6th IWCPHT, Québec, 2006)
- ATZ Ctrough supratherapeutic if > 0.85 mg/L

Statistical analysis

- Descriptive statistics with means, medians or %
- Continuous outcomes compared by Mann-Whitney U, frequencies compared by x^2 or Fisher's exact test, as appropriate

Figure 1 . Distribution of Ctrough among groups

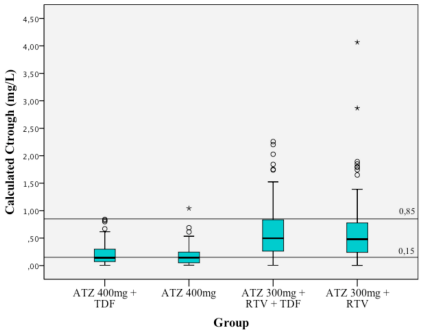
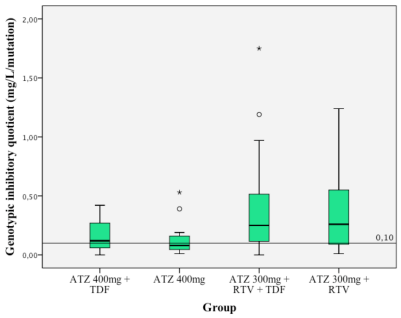


Figure 2. Distribution of GIQ among groups



RESULTS

379 samples / 284 patients kept in the analysis (956 / 421 excluded)

	ATZ 400 mg + TDF	ATZ 400 mg	ATZ/RTV 300/100 mg + TDF	ATZ/RTV 300/100 mg
# samples / # patients	51 / 33	91 /65	115 / 95	122 / 91
Mean age (SD), years	44 (11)	47 (9)	43 (9)	44 (9)
Mean weight (SD), kg	72.9 (14.3)	71.4 (9.9)	72.3 (12.6)	74.6 (14.5)
% male	75.8	89.2	71.6	86.8
% past protease inhibitor failure	21.6	6.6	29.6	14.8
# samples for virus with protease mutations (GIQ calculated)*	16	15	51	26
Mean # protease mutations (SD)	2 (1)	1 (1)	2 (1)	2 (2)
Median HIV RNA viral load, log_{10} (range)*	1.69 (1.69-3.8)	1.69 (1.69-3.1)	1.69 (1.69-5.6)	1.69 (1.69-4.5)
% undetectable HIV RNA viral load, log_{10}*	84.2	69.6	65.9	72.7
TDM RESULTS				
Median Ctrough (range), mg/L	0.14 (<0.01-0.84)	0.14 (0.01-1.04)	0.50 (0.01-2.26)[a]	0.48 (< 0.01-4.07)[d]
% therapeutic Ctrough (> 0.15 mg/L)	49.0	47.3	82.6[a]	84.4[d]
Median GIQ (range), mg/L/mutation	0.12 (<0.01-0.42)	0.08 (0.01-0.53)	0.25 (< 0.01 – 1.75)[b]	0.26 (0.01-1.24)[e]
% therapeutic GIQ (> 0.1 mg/L/mutation)	68.8	40.0	76.5[c]	73.1[f]
% supratherapeutic Ctrough (>0.85 mg/L)	0.0	1.1	24.3[a]	18.9[d]

*Protease mutations available for 108 samples and HIV viral load for 105 samples
a: vs ATZ/TDF p <0.001; b: vs ATZ/TDF p=0.049; c: vs ATZ/TDF p=0.528; d: vs ATZ p < 0.001; e: vs ATZ p=0.033; f: vs ATZ p=0.036; all comparisons between ATZ/TDF vs ATZ not significant.

Results stratified by population

Figure 3. Proportion of therapeutic Ctrough among patients without past protease inhibitor virologic failure (C trough > 0,15 mg/L)

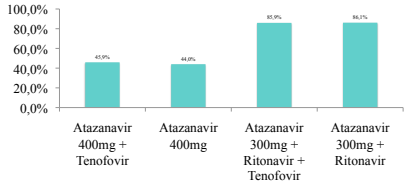
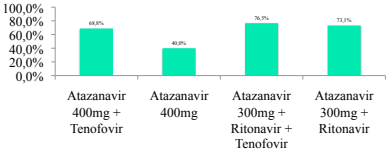


Figure 4. Proportion of therapeutic GIQ among patients with virus with protease mutations (GIQ > 0,10 mg/L/mutation)



- No statistical differences were observed with the proportions of undetectable HIV RNA (small sample size for this analysis).

DISCUSSION / CONCLUSIONS

- RTV but not TDF influenced the proportion of patients with therapeutic Ctrough and GIQ; this is consistent with other studies (Calcagno et al, JAIDS 2009);
- A low proportion of therapeutic Ctrough was noted in the ATZ/TDF (no RTV) group as in the ATZ (no RTV, no TDF) group (similar to Molto et al, TDM, 2007); the clinical relevance of these results are unclear;
- The Cmin target of 0.15 mg/L may not be appropriate in antiretroviral-naïve patients;
- Selection bias and adherence may have influenced the results;
- RTV boosting and TDM using GIQ is recommended in patients with protease mutations.

ACKNOWLEDGMENTS

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