CONTACT INFORMATION
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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, 8th IWPCH, 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

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 0.3-5%; limit of quantification 0.01 mg/L or 0.05 mg/L, varied in time)

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

<table>
<thead>
<tr>
<th># samples / # patients</th>
<th>ATZ 400 mg + TDF</th>
<th>ATZ 400 mg</th>
<th>ATZ/RTV 300/100 mg + TDF</th>
<th>ATZ/RTV 300/100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATZ 400 mg with TDF</td>
<td>51 / 33</td>
<td>91 / 85</td>
<td>115 / 95</td>
<td>122 / 91</td>
</tr>
<tr>
<td>ATZ 400 mg (no TDF, no RTV)</td>
<td>44 (11)</td>
<td>47 (9)</td>
<td>43 (9)</td>
<td>44 (9)</td>
</tr>
<tr>
<td>ATZ / RTV 300 mg / 100 mg with TDF</td>
<td>72.9 (14.3)</td>
<td>71.4 (9.8)</td>
<td>72.3 (12.6)</td>
<td>74.6 (14.9)</td>
</tr>
<tr>
<td>ATZ / RTV 300 mg / 100 mg (no TDF)</td>
<td>75.8 (9.9)</td>
<td>79.2 (9.2)</td>
<td>71.6 (9.6)</td>
<td>86.8 (8.0)</td>
</tr>
</tbody>
</table>

% male
- ATZ 400 mg with TDF: 74.6%,
- ATZ 400 mg (no TDF, no RTV): 76.6%,
- ATZ / RTV 300 mg / 100 mg with TDF: 74.6%,
- ATZ / RTV 300 mg / 100 mg (no TDF): 76.6%

% past protease inhibitor failure
- 21.6% for ATZ 400 mg with TDF,
- 6.6% for ATZ 400 mg (no TDF, no RTV),
- 29.6% for ATZ / RTV 300 mg / 100 mg with TDF,
- 14.8% for ATZ / RTV 300 mg / 100 mg (no TDF)

% # samples for virus with protease mutations (GIQ calculated)*
- 21.6 for ATZ 400 mg with TDF,
- 16 for ATZ 400 mg (no TDF, no RTV),
- 15 for ATZ / RTV 300 mg / 100 mg with TDF,
- 14.8 for ATZ / RTV 300 mg / 100 mg (no TDF)

Statistical analysis
- Descriptive statistics with means, medians or %
- Continuous outcomes compared by Mann-Whitney U, frequencies compared by x² or Fisher’s exact test, as appropriate

RESULTS stratified by population

ORTH therapy:
- 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., AIDS 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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*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.