Pharmacokinetic data used for this analysis came from AIDS Clinical Trial Group study A5202. Baseline characteristics, biomarker concentrations, and ATV clearances were summarized by treatment arms while other factors were adjusted. Biomarker concentrations were log-transformed. Slaviero et al. (2003) noted that plasma levels of ATV and/or its metabolites were inversely related to cytochrome P450 activity. ATP III, involving an unexplained source of variability in the pharmacokinetics and pharmacodynamics of statins, showed that ATP III was not significant. Several studies have demonstrated that chronic inflammation is associated with decreases in inflammatory and endothelial activation markers. While chronic inflammation associated with HIV infection may be a source of pharmacokinetic variability of antiretrovirals that are substrates or inhibitors of CYP3A or P450. Thus, the chronic inflammatory state associated with HIV infection may be a source of pharmacokinetic variability of antiretrovirals that are substrates or inhibitors of CYP3A or P450.

**Objectives**

1. To explore the relationship between ATV exposure and plasma concentrations of inflammatory and endothelial activation markers.
2. To explore the relationship between total bilirubin levels and plasma concentrations of inflammatory and endothelial activation markers.

**Methods**

**Data**

Pharmacokinetic data used for this analysis came from AIDS Clinical Trial Group study A5202, while inflammatory biomarker concentrations were measured as part of the A5224 substudy. Plasma samples for measurement of ATV concentrations were collected at weeks 4, 8, 16, and/or 24. A single ATV plasma apparent oral clearance value (CCL) for each individual was generated using a 1-compartment population pharmacokinetic model with first-order absorption and elimination.

**Statistical Analysis**

- Baseline characteristics, biomarker concentrations, and ATV clearances were summarized by proportions or medians with interquartile range.
- Biomarker concentrations were log-transformed.
- Spearman rank correlation tests were performed to determine the covariance between ATV CLF and biomarkers at week 24 and week 96, and trend from baseline at weeks 24 and 96. Correlations between total bilirubin and other biomarker concentrations were also assessed at all time points.
- P-values of <.05 were considered statistically significant.

**Results**

Table 2. Spearman correlation coefficients (r-values) between atazanavir clearance and biomarkers at weeks 24, 96, and changes from baseline

<table>
<thead>
<tr>
<th>Markers</th>
<th>ATV CL - Week 24 Markers</th>
<th>ATV CL - Week 96 Markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>hsCRP</td>
<td>0.12 (0.24)</td>
<td>-0.04 (0.07)</td>
</tr>
<tr>
<td>IL-6</td>
<td>0.01 (0.92)</td>
<td>-0.17 (0.01)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>0.07 (0.50)</td>
<td>-0.17 (0.01)</td>
</tr>
<tr>
<td>sTNFR-I</td>
<td>0.06 (0.06)</td>
<td>-0.13 (0.16)</td>
</tr>
<tr>
<td>sTNFR-Ⅱ</td>
<td>0.08 (0.41)</td>
<td>-0.20 (0.17)</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>0.11 (0.01)</td>
<td>-0.24 (0.04)</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.05 (0.87)</td>
<td>-0.22 (0.23)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>0.13 (0.10)</td>
<td>-0.04 (0.02)</td>
</tr>
</tbody>
</table>

**Table 1. Baseline Characteristics of Study Participants**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participants n=107</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, n (%)</td>
<td>Male 95 (89%) Female 12 (11%)</td>
</tr>
<tr>
<td>Race/Ethnicity, n (%)</td>
<td>Black, non-Hispanic 65 (61%), Hispanic 30 (28%), White, non-Hispanic 12 (11%)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37 (13, 43)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.8 (21.7, 28.1)</td>
</tr>
<tr>
<td>CD4 (cells/mm³)</td>
<td>524 (492, 564)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>14.1 (7.7, 4.5)</td>
</tr>
</tbody>
</table>

**Conclusions**

- The majority of inflammatory and endothelial activation markers were not significantly correlated with the exposure of ATV. sTNFR-II and sVCAM-1 were the only markers exhibiting correlation between ATV CLF at week 24 and week 96, respectively.
- Inflammatory-mediated interference of CYP3A may have been attenuated due to ATV-associated increases of bilirubin, which has anti-inflammatory properties. 6, 8
- Bilirubin concentrations were inversely correlated with each of the inflammatory markers at all time points (rho: -0.17 to -0.51, P = 0.0003 except hsCRP (P = 0.65). It remains to be determined if decreases in inflammatory and endothelial activation markers over time were due to suppression of HIV replication by the ARVs, increases in bilirubin, or both. Thus, more sophisticated models will examine relationships between biomarkers and ATV CLF.
- The effects of chronic infection due to HIV infection on ARV pharmacokinetics and the contribution of pharmacogenomics should be further assessed. Analysis should also include CYP metabolized agents that do not alter bilirubin concentrations.

**References**

2. Devereux EA, Chak L, Ross CA. Inflammation: an unexplained source of variability in the pharmacokinetics and pharmacodynamics of statins, showed that ATP III was not significant. Several studies have demonstrated that chronic inflammation is associated with decreases in inflammatory and endothelial activation markers. While chronic inflammation associated with HIV infection may be a source of pharmacokinetic variability of antiretrovirals that are substrates or inhibitors of CYP3A or P450.

**Abstract# 428**

**Inflammation Investigated as a Source of Atazanavir Pharmacokinetic Variability**

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**Background**

Inflammation is associated with the downregulation of drug metabolizing enzymes and transporters including cytochrome P450 (CYP) and P-glycoprotein (P-GP). Thus, the chronic inflammatory state associated with HIV infection may be a source of pharmacokinetic variability of antiretrovirals that are substrates or inhibitors of CYP3A or P-GP.

**Methods**

- The following biomarkers were assayed:
  - hsCRP
  - IL-6
  - TNF-α
  - sTNFR-I
  - sTNFR-II
  - sVCAM-1
  - sICAM-1
  - Total Bilirubin

**Results (cont’d)**

- The majority of inflammatory and endothelial activation markers were not significantly correlated with the exposure of ATV. sTNFR-II and sVCAM-1 were the only markers exhibiting correlation between ATV CLF at week 24 and week 96, respectively.
- Inflammatory-mediated interference of CYP3A may have been attenuated due to ATV-associated increases of bilirubin, which has anti-inflammatory properties.
- Bilirubin concentrations were inversely correlated with each of the inflammatory markers at all time points (rho: -0.17 to -0.51, P = 0.0003 except hsCRP (P = 0.65). It remains to be determined if decreases in inflammatory and endothelial activation markers over time were due to suppression of HIV replication by the ARVs, increases in bilirubin, or both. Thus, more sophisticated models will examine relationships between biomarkers and ATV CLF.
- The effects of chronic infection due to HIV infection on ARV pharmacokinetics and the contribution of pharmacogenomics should be further assessed. Analysis should also include CYP metabolized agents that do not alter bilirubin concentrations.