**RESULTS** (Cont’d)

- Median $T_{\text{max}}$ for TDF ranged between 1 and 2 h for all treatments
- $T_{\text{max}}$ was not calculated for TDF as the 24-h dosing interval proved inadequate to describe the terminal phase half-life for TDF
- TDF dosing was similar following AM and PM dosing of TDF alone
- Co-administration of ATV 400 mg AM with TDF 300 mg PM significantly increased the AUC(TAU), $C_{\text{max}}$, and $C_{\text{min}}$ of TDF compared to TDF 300 mg PM alone
- Co-administration of ATV 600 mg AM with TDF 300 mg AM significantly increased the AUC(TAU), $C_{\text{max}}$, and $C_{\text{min}}$ of TDF compared to TDF 300 mg AM alone

**Safety**

- No deaths, serious adverse events (SAEs) or discontinuations due to adverse events (AEs) occurred in this study
- The most frequent AEs were jaundice (61%), abdominal pain (33%), headache (22%), and nausea (22%)
- One subject experienced a Grade 4 elevation in total bilirubin and 7 subjects experienced Grade 3 elevations of total bilirubin. All total bilirubin levels returned to within normal range with follow-up after discharge from the study.
- Co-administration of ATV with TDF did not significantly affect the serum creatinine level in any subject.

**Discussion**

- Temporal separation of ATV 400 mg QD and TDF 300 mg QD by approximately 12 hours resulted in:
  - Decreases in ATV $C_{\text{max}}$, AUC, and $C_{\text{min}}$ of 10%, 17%, and 28%, respectively
  - Increases in TDF $C_{\text{max}}$, AUC, and $C_{\text{min}}$ of 44%, 37%, and 38%, respectively
- Simultaneous dosing of ATV 600 mg QD with TDF 300 mg QD resulted in:
  - Increases in ATV $C_{\text{max}}$, AUC, and $C_{\text{min}}$ of 27%, 36%, and 41%, respectively
  - Increases in TDF $C_{\text{max}}$, AUC, and $C_{\text{min}}$ of 41%, 59%, and 74%, respectively
- Increases in ATV and TDF exposures relative to temporal separation of ATV 400 mg QD and TDF 300 mg QD

**CONCLUSIONS**

- The administration of ATV and TDF either alone or in combination was safe and well tolerated.
- Neither of the dosing regimens employed in this study provided comparable exposures of either ATV or TDF, relative to either ATV 400 mg QD or TDF 300 mg QD alone.
- TDF concentrations were further increased when the ATV dose was increased from 400 mg to 600 mg.
- To compensate for the decrease in ATV exposures when ATV is co-administered with TDF, the combination of ATV/RTV at 300/100 mg QD has been recommended in the ATV label when ATV and TDF are administered together.

**REFERENCES**


**OBJECTIVES**

- Primary: To identify one or more dosing strategies that would provide ATV and TDF exposures comparable to each when dosed alone by assessing the PK of ATV and TDF.
- Secondary: To assess the safety and tolerability of ATV and TDF alone or in combination in healthy subjects.

**METHODS**

- Randomized, open-label, multi-dose drug interaction study in 18 healthy patients randomized to receive TDF 300 mg QD for 7 days in the AM or PM.
- After a washout period, all subjects received ATV 400 mg QD AM followed by ATV 400 mg QD AM + TDF 300 mg QD PM, followed by ATV 600 mg QD AM + TDF 300 mg QD AM, each for 7 days.
- All study doses were administered with a light meal.

**Figure 1: Study Design**

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**Pharmacokinetic Effects of Coadministration of Atazanavir and Tenofovir at Steady State**

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### METHODS (Cont’d)

**Pharmacokinetics**
- ATV: Intensive PK samples were evaluated on Days 20, 27, and 34. \( \text{C}_{\text{min}} \) values were measured on specified days through Days 18 – 35.
- PK parameters: \( \text{C}_{\text{max}} \), \( \text{T}_{\text{max}} \), \( \text{C}_{\text{min}} \), AUC(TAU), T-Half following the AM dose
- ATV measured by LC/MS/MS

**TDF:** Intensive PK samples were collected in the PM following the PM dose and in the AM following the AM dose on Days 7, 27, and 34. \( \text{C}_{\text{min}} \) values were collected prior to the PM dose during PM dosing and prior to the AM dose during AM dosing on specified days through Days 4 – 35.
- PK parameters: \( \text{C}_{\text{max}} \), \( \text{T}_{\text{max}} \), \( \text{C}_{\text{min}} \), AUC(TAU)
- TDF measured by LC/MS/MS

**Statistics**
- To assess the effect of TDF on the PK of ATV and the effect of ATV on the PK of TDF, analyses of variance were performed on the log(\( \text{C}_{\text{max}} \)), log(AUC(TAU)), and log(\( \text{C}_{\text{min}} \)) of ATV and TDF separately.
- Point estimates and 90% confidence intervals for differences on the log scale were exponentiated to obtain estimates for ratios of geometric means on the original scale.

### RESULTS (Cont’d)

**Demographics and Disposition**

**Table 1: Subject Demographics**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>ALL (n = 18)</th>
<th>Treatment: TDF AM + TDF 300 mg QD AM</th>
<th>Treatment: ATV 400 mg AM (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – Median (Range)</td>
<td>36 (20-50)</td>
<td>25 (19-40)</td>
<td>27 (20-50)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male: 11 (61), Female: 7 (39)</td>
<td>6 (40)</td>
<td>5 (61)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>Caucasian: 7 (39), Black: 3 (17), Hispanic: 8 (44)</td>
<td>5 (28)</td>
<td>2 (22)</td>
</tr>
</tbody>
</table>

Treatments: TDF AM + TDF 300 mg QD AM; ATV 400 + TDF PM=ATV 400 mg QD AM + TDF 300 mg QD PM; ATV 400 mg AM  + TDF 300 mg QD PM; ATV 600 mg AM + TDF 300 mg QD AM + TDF 300 mg QD AM.

- Of the 18 subjects enrolled and randomized in the study, 3 discontinued prior to study completion for non-safety reasons (participation in a concurrent study, family emergency, withdrawn consent). Fifteen (83%) subjects were clinically evaluable.

**Figure 2: Plot of Mean (SD) Plasma Concentration-Time Profiles of ATV**

**Figure 3: Plot of Mean (SD) Plasma Concentration-Time Profiles of TDF (PM and AM)**

**Table 2: Geometric Mean Ratios and 90% CI for ATV**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric Means</th>
<th>Contrast</th>
<th>Ratios of Geometric Means Point Estimate (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (TAU) (ng*hr/mL)</td>
<td>ATV 400 vs ATV 400 + TDF PM</td>
<td>0.83 (0.77, 0.88)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV 400 vs ATV 400 + TDF PM</td>
<td>1.36 (1.23, 1.52)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV 400 vs ATV 600 + TDF AM</td>
<td>0.72 (0.63, 0.82)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV 400 vs ATV 600 + TDF AM</td>
<td>1.41 (1.18, 1.68)</td>
<td></td>
</tr>
</tbody>
</table>

Treatments: ATV 400=ATV 400 mg QD AM; ATV 400 + TDF PM=ATV 400 mg QD AM + TDF 300 mg QD PM; ATV 600 + TDF AM=ATV 600 mg QD AM + TDF 300 mg QD PM (n = 15).

**Table 3: Adjusted Geometric Mean Ratios and 90% CI for Tenofovir**

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameter</th>
<th>Geometric Means</th>
<th>Contrast</th>
<th>Ratios of Geometric Means Point Estimate (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{\text{max}} (ng/mL)</td>
<td>ATV 400 vs ATV 400 + TDF PM</td>
<td>1.37 (1.29, 1.46)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV 400 vs ATV 600 + TDF AM</td>
<td>1.39 (1.44, 1.75)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV 400 vs ATV 600 + TDF AM</td>
<td>1.43 (1.27, 1.61)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ATV 400 vs ATV 600 + TDF AM</td>
<td>1.41 (1.24, 1.60)</td>
<td></td>
</tr>
</tbody>
</table>

Treatments: TDF AM + TDF 300 mg QD AM (n = 15); TDF PM + TDF 300 mg QD PM (n = 15); ATV 400 + TDF PM + ATV 400 mg QD AM + TDF 300 mg QD PM (n = 15); ATV 600 + TDF AM + ATV 600 mg QD AM + TDF 300 mg QD AM (n = 15).