RESULTS (Cont'd)

- Median T_{max} for TDF ranged between 1 and 2 h for all treatments
- T-Half was not calculated for TDF as the 24-h dosing interval proved inadequate to describe the terminal phase half-life for TDF
- TDF exposures were 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_{max}, and C_{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_{max}, and C_{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_{max}, AUC, and C_{min} of 10%, 17%, and 28%, respectively
  - Increases in TDF C_{max}, AUC, and C_{min} of 43%, 37%, and 38%, respectively
- Simultaneous dosing of ATV 600 mg QD with TDF 300 mg QD resulted in:
  - Increases in ATV C_{max}, AUC, and C_{min} of 27%, 36%, and 41%, respectively
  - Increases in TDF C_{max}, AUC, and C_{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

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Pharmacokinetic Effects of Coadministration of Atazanavir and Tenofovir at Steady State

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BACKGROUND

- Atazanavir (ATV) is a potent, well-tolerated, once-daily HIV protease inhibitor extensively studied in naive and experienced patients
- In a previous study in treatment-experienced patients (Puzzle 2)[1] and in a separate pharmacokinetic (PK) analysis (AI424-113)[2], a bidirectional interaction was observed between ATV and tenofovir (TDF). ATV concentrations were decreased 23-28% when ATV was administered with ritonavir (RTV) and TDF in HIV patients and 11-20% in healthy volunteers. In healthy volunteers, TDF concentrations were increased by 29-37%
- Similarly, in a study in healthy volunteers (AI454-181)[3] in which TDF was co-administered with ATV 400 mg, ATV C_{max}, AUC, and C_{min} decreased by 21%, 25%, and 40%, respectively, while TDF C_{max}, AUC, and C_{min} increased by 14%, 24%, and 22%, respectively
- These findings were unexpected as ATV is primarily metabolized by CYP3A4 and TDF is primarily eliminated by renal elimination

OBJECTIVES

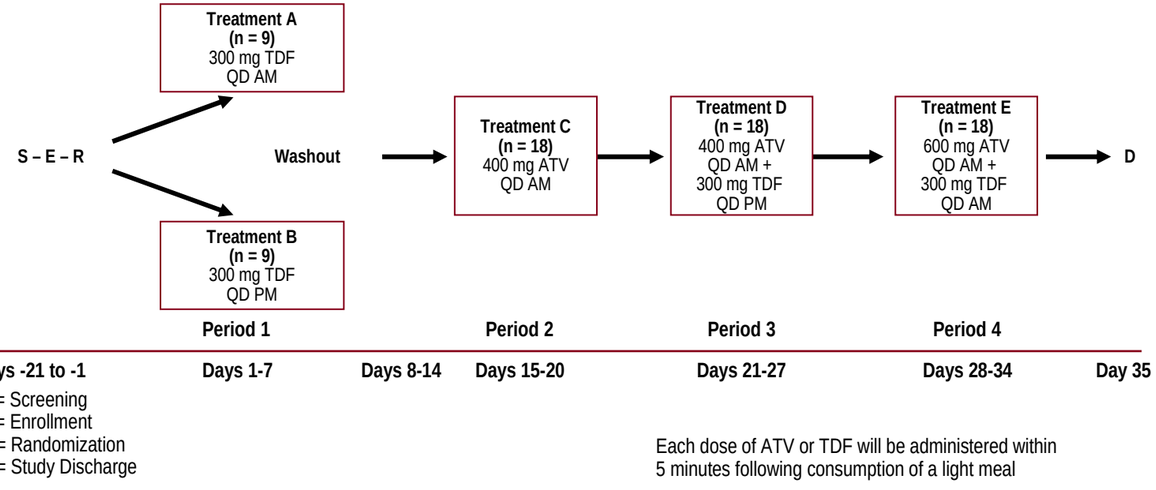
- Primary
  - To identify one or more dosing strategies that would provide ATV and TDF exposures comparable to each when dosed alone by assessing the PK of ATV and TDF
- Secondary
  - To assess the safety and tolerability of ATV and TDF alone or in combination in healthy subjects

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



S = Screening
E = Enrollment
R = Randomization
D = Study Discharge

Each dose of ATV or TDF will be administered within 5 minutes following consumption of a light meal

METHODS (Cont'd)

Pharmacokinetics

- ATV:
  - Intensive PK samples were evaluated on Days 20, 27, and 34. C_{min} values were measured on specified days through Days 18 – 35
  - PK parameters: C_{max}, T_{max}, C_{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. C_{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: C_{max}, T_{max}, C_{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(C_{max}), log(AUC(TAU)), and log(C_{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

Demographics and Disposition

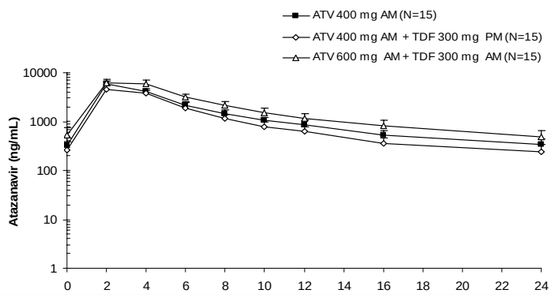
Table 1: Subject Demographics

	ALL (n = 18)	Treatments: TDF AM ATV 400 ATV 400 + TDF PM ATV 600 + TDF AM (n = 9)	Treatments: TDF PM ATV 400 ATV 400 + TDF PM ATV 600 + TDF AM (n = 9)
Age – Median (Range)	26 (19-50)	25 (19-43)	27 (20-50)
Sex, n (%)			
Male	11 (61)	6 (67)	5 (56)
Female	7 (39)	3 (33)	4 (44)
Race, n (%)			
Caucasian	7 (39)	5 (56)	2 (22)
Black	3 (17)	2 (22)	1 (11)
Hispanic	8 (44)	2 (22)	6 (67)

Treatments: TDF AM =TDF 300 mg QD AM; TDF PM =TDF 300 mg QD PM; 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 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



RESULTS (Cont'd)

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

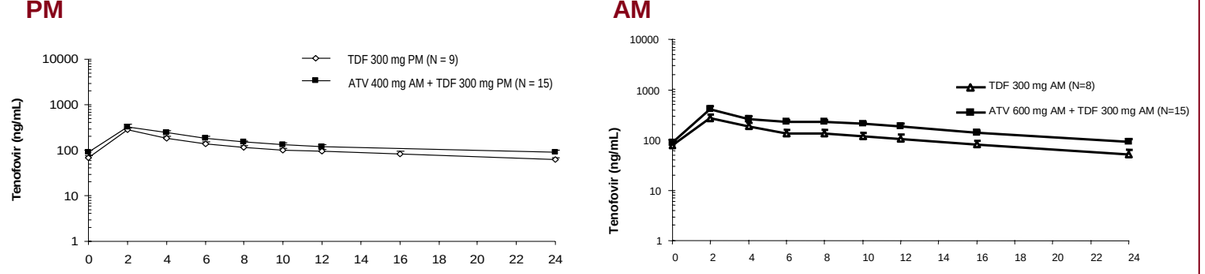


Table 2: Geometric Mean Ratios and 90% CI for ATV

Pharmacokinetic Parameter	Geometric Means Original Scale		Contrast	Ratios of Geometric Means Point Estimate (90% CI)
AUC (TAU) (ng*hr/mL)	ATV 400	33714		
	ATV 400 + TDF PM	27823	ATV 400 + TDF PM vs ATV 400	0.83 (0.77, 0.88)
	ATV 600 + TDF AM	46012	ATV 600 + TDF AM vs ATV 400	1.36 (1.23, 1.52)
C_{max} (ng/mL)	ATV 400	6037		
	ATV 400 + TDF PM	5439	ATV 400 + TDF PM vs ATV 400	0.90 (0.84, 0.97)
	ATV 600 + TDF AM	7649	ATV 600 + TDF AM vs ATV 400	1.27 (1.13, 1.42)
C_{min} (ng/mL)	ATV 400	273		
	ATV 400 + TDF PM	195	ATV 400 + TDF PM vs ATV 400	0.72 (0.63, 0.82)
	ATV 600 + TDF AM	384	ATV 600 + TDF AM vs ATV 400	1.41 (1.18, 1.68)

Treatments: ATV 400=ATV 400 mg QD AM (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)

- Median T_{max} for ATV ranged between 2 and 2.5 h for all treatments
- Mean T-half life of ATV ranged from 6.9 to 8.7 h across all treatments
- Co-administration of TDF 300 mg PM with ATV 400 mg AM decreased the AUC (TAU) and C_{min} of ATV compared to ATV 400 mg AM alone
- Co-administration of TDF 300 mg AM with ATV 600 mg AM significantly increased the AUC (TAU), C_{max}, and C_{min} of ATV compared to ATV 400 mg AM alone

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

Pharmacokinetic Parameter	Adjusted Geometric Means Original Scale		Contrast	Ratios of Geometric Means Point Estimate (90% CI)
AUC (TAU) (ng*hr/mL)	TDF AM	2751		
	TDF PM	2706		
	ATV 400 + TDF PM	3715	ATV 400 + TDF PM vs TDF PM	1.37 (1.29, 1.46)
	ATV 600 + TDF AM	4373	ATV 600 + TDF AM vs TDF AM	1.59 (1.44, 1.75)
C_{max} (ng/mL)	TDF AM	336		
	TDF PM	348		
	ATV 400 + TDF PM	498	ATV 400 + TDF PM vs TDF PM	1.43 (1.27, 1.61)
	ATV 600 + TDF AM	473	ATV 600 + TDF AM vs TDF AM	1.41 (1.24, 1.60)
C_{min} (ng/mL)	TDF AM	51		
	TDF PM	60		
	ATV 400 + TDF PM	83	ATV 400 + TDF PM vs TDF PM	1.38 (1.30, 1.47)
	ATV 600 + TDF AM	88	ATV 600 + TDF AM vs TDF AM	1.74 (1.53, 1.98)

Treatments: TDF AM =TDF 300 mg QD AM (n=8); TDF PM =TDF 300 mg QD PM (n=9); 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)