Pharmacokinetic Interaction between Tenofovir and Atazanavir Coadministered with Ritonavir in Healthy Subjects

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BACKGROUND

- ATV is a potent, well-tolerated, QD HIV PI extensively studied in naive and experienced patients. ATV/RTV has demonstrated comparable efficacy in treatment-experienced patients to LPV/RTV regimens when used in combination with tenofovir (TDF) and other nucleosides.
- In a clinical trial, simultaneous administration of ATV/RTV 300/100 mg and TDF 300 mg QD in HIV-positive patients resulted in approximately 25% decrease in ATV exposure. This finding was unexpected as ATV is metabolized by CYP3A4 and tenofovir is not.

OBJECTIVES

Primary

To identify one or more dosing strategies that provide ATV/RTV and TDF exposures similar to each when dosed alone by assessing the pharmacokinetics (PK) of ATV, RTV and tenofovir

Secondary

¦ To assess the:

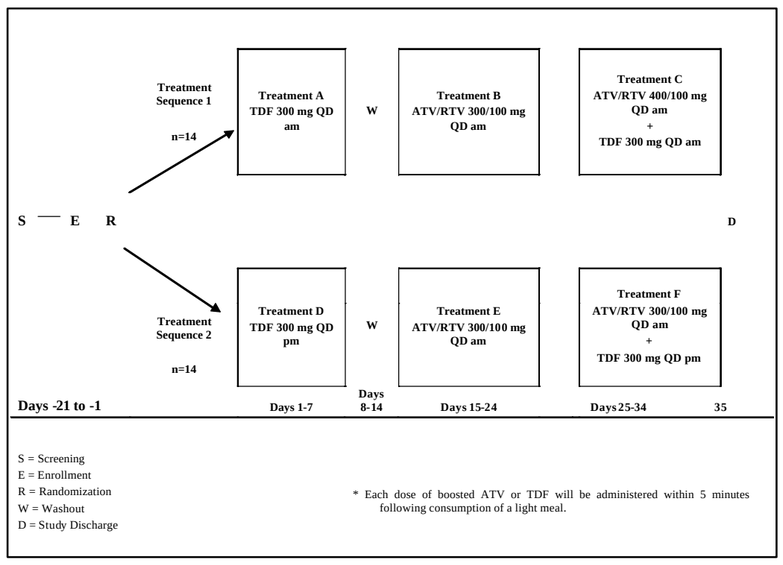
PK of ATV, RTV and Tenofovir

Safety and tolerability of ATV/RTV and TDF alone or in combination in healthy subjects

METHODS

- Randomized, open-label, multi-dose drug interaction study in 28 healthy adults randomized to receive TDF 300 mg QD for 7 days in the AM or PM
- After a washout period, all subjects received ATV/RTV 300/100 mg QD for 10 days in the AM, followed by either:
  - ATV/RTV 400/100 mg + TDF 300 mg simultaneously in the AM for 10 days (n=14), or
  - ATV/RTV 300/100 mg in the AM + TDF 300 mg in the PM (temporally separated) for 10 days (n=14)
- All study drugs were administered with a light meal.

Figure 1. Study Design



Pharmacokinetics

- ATV and RTV:
  - Intensive PK samples were evaluated on Days 24 and 34. C_{min} values were measured on specified days through Days 17 – 35
  - PK parameters: C_{max}, T_{max}, C_{min}, AUC(TAU), T-half following the AM dose
  - ATV and RTV measured by LC/MS/MS: LLQ = 5 ng/mL
- Tenofovir:
  - Intensive PK samples were collected in the PM following the PM dose and in the AM following the AM dose on Days 7 and 34. C_{min} values were measured on specified days through Days 4-8 and Days 27-35.
  - PK parameters: C_{max}, T_{max} and AUC(TAU)
  - Tenofovir measured by LC/MS/MS: LLQ = 1 ng/mL

Statistics

- To assess the effect of TDF on the PK of ATV and RTV and the effect of ATV/RTV on TDF, analyses of variance were performed on the log (C_{max}), log AUC(TAU), and log (C_{min}) of ATV, RTV and TDF separately
- The analyses for the two treatment sequences (TDF AM and PM) were performed 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.

Table 1. Subject Demographics

	ALL (n=28)	Treatment Sequence 1 (n=14)	Treatment Sequence 2 (n=14)
Age - Median (Range)	30 (18-50)	33 (18-50)	28.5 (19-43)
Sex, n (%)			
Male	18 (64.3)	8 (57.1)	10 (71.4)
Female	10 (35.7)	6 (42.9)	4 (28.6)
Race, n (%)			
Caucasian	19 (67.9)	9 (64.3)	10 (71.4)
Black	3 (10.7)	2 (14.3)	1 (7.1)
Hispanic	6 (21.4)	3 (21.4)	3 (21.4)

RESULTS

Figure 2. Mean (SD) Plasma Concentration-Time Profiles of ATV

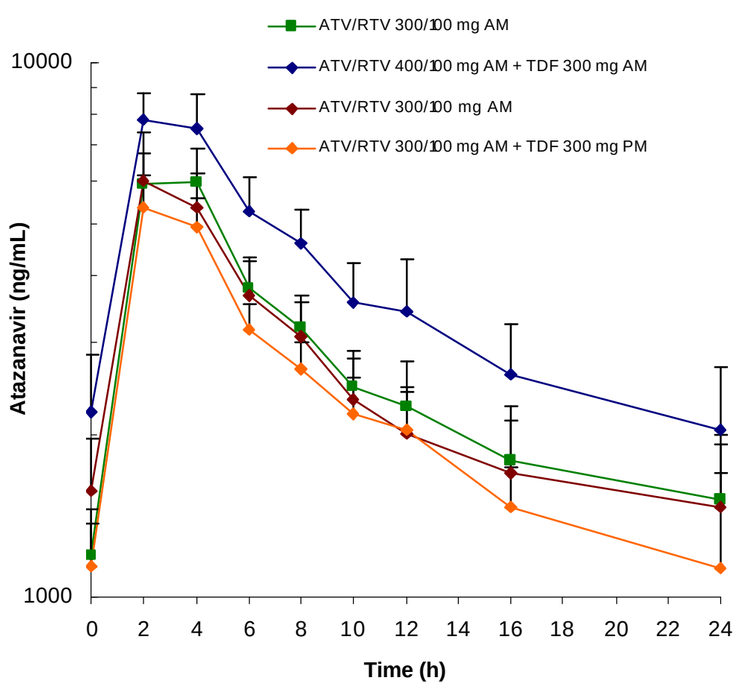


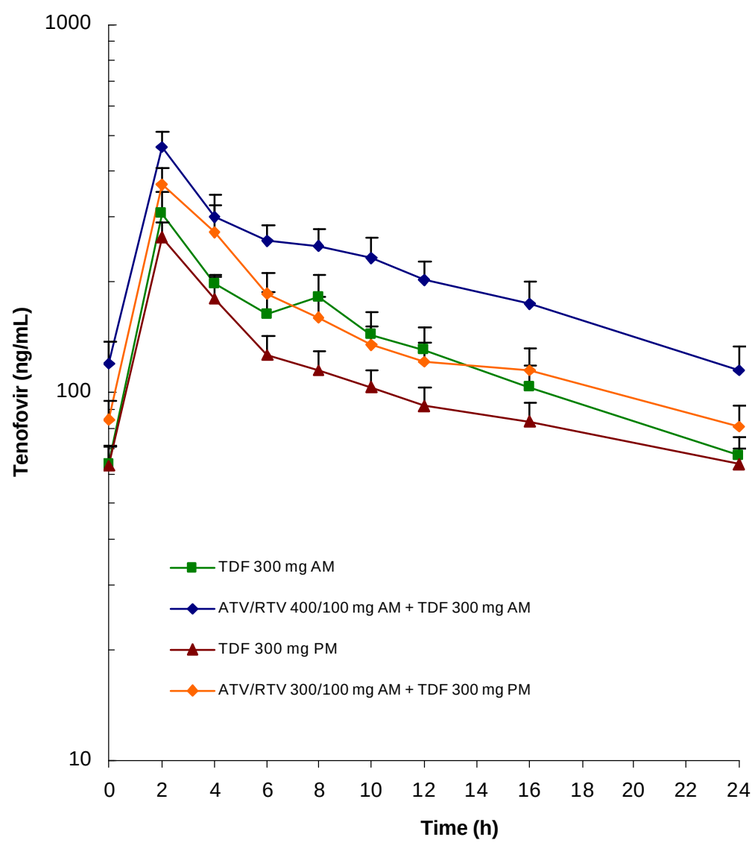
Table 2: Geometric Mean Ratios, CV% and 90% CI for ATV

PK Parameter	Treatment	Geometric Means (CV%)	Contrast	Ratios of Adjusted Geometric Means Point Estimates (90% CI)
AUC(TAU) (ng*hr/mL)	B	63612 (35)		
	C	87825 (35)	C vs. B	1.38 (1.32, 1.44)
	E	60322 (39)		
	F	53941 (28)	F vs. E	0.89 (0.82, 0.97)
C_{max} (ng/mL)	B	6564 (30)		
	C	8617 (24)	C vs. B	1.31 (1.24, 1.39)
	E	6448 (36)		
	F	5554 (26)	F vs. E	0.86 (0.80, 0.93)
C_{min} (ng/mL)	B	1276 (63)		
	C	1703 (63)	C vs. B	1.33 (1.24, 1.44)
	E	1289 (61)		
	F	1031 (44)	F vs. E	0.80 (0.73, 0.88)

Treatments: B=ATV/RTV 300/100 mg QD am; C=ATV/RTV 400/100 mg QD am + TDF 300 mg QD am; E=ATV/RTV 300/100 mg QD am; F=ATV/RTV 300/100 mg QD am + TDF 300 mg QD pm. CV=Coefficient of Variation, CI=Confidence Interval

- Median T_{max} for ATV ranged between 2 - 2.5 h for all 4 treatments.
- The pharmacokinetics of ATV was minimally affected by temporal separation of ATV/RTV and TDF.
- Although the study was not specifically powered to demonstrate bioequivalence, bioequivalence requirements were met for AUC and C_{max} for ATV in subjects who received ATV/RTV 300/100 mg in combination with TDF.

Figure 3. Mean (SD) Plasma Concentration-Time Profiles of Tenofovir



RESULTS (cont'd)

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

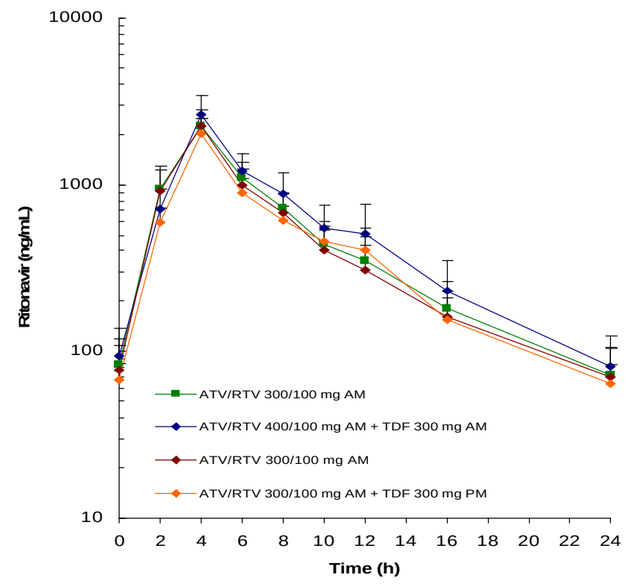
PK Parameter	Treatment	Geometric Means (CV%)	Contrast	Ratios of Adjusted Geometric Means Point Estimates (90% CI)
AUC(TAU) (ng*hr/mL)	B	3286 (24)		
	C	5101 (25)	C vs. A	1.55 (1.44, 1.68)
	E	2718 (21)		
	F	3669 (24)	F vs. D	1.37 (1.30, 1.45)
C_{max} (ng/mL)	B	359 (23)		
	C	499 (17)	C vs. A	1.39 (1.27, 1.53)
	E	327 (25)		
	F	436 (22)	F vs. D	1.34 (1.20, 1.51)
C_{min} (ng/mL)	B	64 (27)		
	C	109 (31)	C vs. A	1.70 (1.54, 1.87)
	E	63 (20)		
	F	78 (28)	F vs. D	1.29 (1.21, 1.36)

Treatments: A=TDF 300 mg QD am; C=ATV/RTV 400/100 mg QD am + TDF 300 mg QD am; D=TDF 300 mg QD pm; F=ATV/RTV 300/100 mg QD am + TDF 300 mg QD pm. CV = Coefficient of Variation, CI=Confidence Interval

The median T_{max} (hr) for tenofovir by treatment was:

- Treatment A: 2.00; Treatment C: 2.00
- Treatment D: 1.50; Treatment F: 1.75
- Tenofovir exposures (AUC) were moderately increased by 37% with temporal separation of ATV/RTV 300/100 mg and TDF.
- Simultaneous administration of ATV/RTV 400/100 mg and TDF further increased the tenofovir exposures (AUC) to 55%, likely due to the increased dose of ATV.

Figure 4. Mean (SD) Plasma Concentration-Time Profiles of RTV



No clinically relevant changes were observed in RTV concentrations

Table 4. Safety Results

Deaths - n (%)	0 (0)
Discontinuation due to AEs - n (%)	0 (0)
Serious AEs - n (%)	0 (0)
Most Frequent AEs (=5%) - n (%)	
Ocular (scleral) icterus	18 (67)
Jaundice	11 (41)
Nausea	10 (37)
Dizziness	8 (30)
Headache	8 (30)

Thirteen (13) subjects experienced a Grade 4 elevation in total bilirubin and 24 subjects experienced a Grade 3 elevation in total bilirubin. Among subjects who returned for a follow-up visit, total bilirubin return to normal. Follow-up bilirubin values were not available for two subjects who did not return for their follow-up visit after study discharge.

DISCUSSION

- Temporal separation of ATV/RTV 300/100 mg and TDF resulted in:
  - ATV AUC(TAU) and C_{max} values were slightly lower but within 14% of ATV/RTV 300/100 mg alone; C_{min} was slightly reduced by approximately 20%.
  - Increases in tenofovir C_{max}, AUC and C_{min} by 34%, 37%, and 29%, respectively. These increases were similar to those observed historically when TDF was administered with lopinavir/RTV.
- Simultaneous dosing of ATV/RTV 400/100 mg with TDF resulted in:
  - Increases of ATV C_{max}, AUC and C_{min} 31%, 38%, and 33%, respectively, relative to ATV/RTV 300/100 mg alone.
  - Tenofovir C_{max}, AUC and C_{min} were increased to a greater extent by 39%, 55%, and 70%, respectively, relative to TDF alone.
- RTV exposures were generally similar across all ATV/RTV regimens in the presence and absence of TDF.
- The administration of ATV/RTV and TDF either alone or in combination was safe and well tolerated.

CONCLUSIONS

- The results of the current study support the recommendation of co-administration of ATV/RTV 300/100 mg QD with TDF 300 mg QD.
- Temporal separation of ATV/RTV 300/100 mg and TDF 300 mg QD may not provide a significant clinical benefit compared to simultaneous dosing, since simultaneous dosing with ATV/RTV 300/100 mg and TDF was shown to be safe and efficacious in a long-term study in treatment-experienced HIV-infected subjects.
- Simultaneous dosing of ATV/RTV 400/100 mg and TDF is not recommended due to increases in ATV exposures and substantial increases in tenofovir exposures.