

An Open-Label, Steady-State Investigation of the Pharmacokinetics (PK) of Tipranavir (TPV) and Ritonavir (RTV) and Their Effects on Cytochrome P-450 (3A4) Activity in Normal, Healthy Volunteers (BI 1182.5)

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SUMMARY

- The data demonstrate that RTV improves TPV concentrations with bid dosing
- TPV monotherapy did not achieve trough plasma concentrations above the target of 20 μM
 - 20 μM = 10x the protein-adjusted IC_{50} for multiple PI-resistant HIV
- All dosages of TPV/RTV (except 250 mg/200 mg) had median trough plasma concentrations above the target
- TPV induced the CYP3A4 enzyme system at all dosages; completely reversed by RTV co-administration
- RTV 200 mg provided more consistent CYP3A4 enzyme system inhibition at all TPV dosages

INTRODUCTION

Tipranavir (TPV) is the first in a new class of non-peptidic HIV protease inhibitors (NPPIs). TPV has shown in vitro activity against HIV resistant to multiple peptidic PIs. Phenotypic changes greater than 10-fold are rare; in one study, only 2 of 105 clinical isolates with more than 10-fold resistance to three or four other PIs had more than ten-fold resistance to TPV.¹ In another study, the mean IC_{50} of TPV against multiple PI-resistant HIV was $0.619 \pm 0.055 \mu\text{M}$ (maximum 0.86 μM).² These data suggest that TPV will be useful for patients who have become resistant to currently available PIs. In vivo, regimens containing TPV combined with low-dose RTV were effective in suppressing HIV viral load in patients who had previously failed two or more PI-containing regimens throughout 48 weeks.³ The objective of this study was to determine the optimum combination of TPV and low doses of RTV to be further evaluated in multidrug-experienced, HIV-positive patients.

METHODS

Study Design/Study Population

The study was an open-label, parallel-group, pharmacokinetic (PK) investigation of the interaction of multiple doses of TPV and RTV in HIV-negative, healthy volunteers. Subjects were not eligible if they were taking medications that might interact with the CYP3A4 enzyme system. The study was conducted at a single site (South Florida Bioavailability Clinic, Miami, FL).

Drug Dosages

Subjects were randomly assigned to treatment groups. Subjects took TPV alone during the first 11 days at doses of 250, 500, 750, 1000, and 1250 mg bid, and then the same TPV doses were co-administered with RTV (100 or 200 mg bid) for 21 days.

Treatment and Study Monitoring

Subjects were admitted overnight on study days 10, 17, 24, and 31 for intensive PK sampling the following day; the evening dose was taken at the clinic. For TPV/RTV PK determinations, blood was drawn: pre-dose (-10 min), 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, and 12 hours post-dose.

When subjects were not at the study site, they were instructed to take medication no less than 1 hour after a light snack; otherwise, medication was taken at least 1 hour before or 2.5 hours after regular meals. Doses were taken at 7:00 AM and 7:00 PM.

Adherence was monitored at each study visit by medication count and patient study diary card. Subjects were required to demonstrate 100% adherence and could be dropped from the study for nonadherence. Adverse events were monitored throughout the study and up to 21 days after the last dose of study medication.

Sample Analyses

TPV/RTV PK analysis

Plasma samples for TPV/RTV determination were measured by a validated liquid chromatography/mass spec/mass spec (LC/MS/MS) method at BAS Analytics, West Lafayette, IN.

CYP3A4 activity

The erythromycin breath test (ERMBT), which measures erythromycin metabolism, was used to measure TPV induction compared with RTV inhibition of CYP3A4 enzyme activity.

RESULTS

Study Population

- Data in Table 1 present demographic data for 113 randomized patients; 95 patients completed the study.

Table 1. Demographics

Gender	Male (%)	45 (39.8)	Female (%)	68 (60.2)
Age (years)	Mean	48.0	Median	47.0
	SD	15.2	Range	18-74
Race	White (%)	94 (83.2)	Asian	0
	Black (%)	19 (16.8)		
Weight (kg)	Mean	72.12	Median	73.00
	SD	11.95	Range	48.0-104.0

Pharmacokinetics of TPV and RTV

- With TPV alone, a dose-related increase in both C_{\min} and C_{\max} occurred, with median values of 1.81 and 72 μM , respectively, in the 1250 mg group (Table 2).
- With co-administration of RTV, increases in median C_{\min} and C_{\max} occurred beyond TPV alone and this increase appeared to be RTV dose-dependent (Figure 1 and 2).
- C_{\min} increased 20x with RTV. TPV dose combinations above 500 mg, with 100 mg RTV, resulted in mean C_{\min} levels above 20 μM , as did TPV dose combinations above 250 mg with 200 mg RTV. C_{\min} levels above 20 μM are 10-fold higher than the protein-adjusted IC_{50} for HIV resistant to other PIs (Figure 1).
- TPV C_{\max} increased approximately 4x with RTV (Figure 2).
- For subjects receiving RTV 100 mg bid, RTV morning trough concentrations (Figure 3) generally were below 1 $\mu\text{g/mL}$ at all 3 study days. For subjects receiving 200 mg RTV bid, morning troughs were generally higher and in some instances approached 4 $\mu\text{g/mL}$.

Figure 1. TPV Morning Trough Concentrations in the Absence and Presence of Co-administered RTV

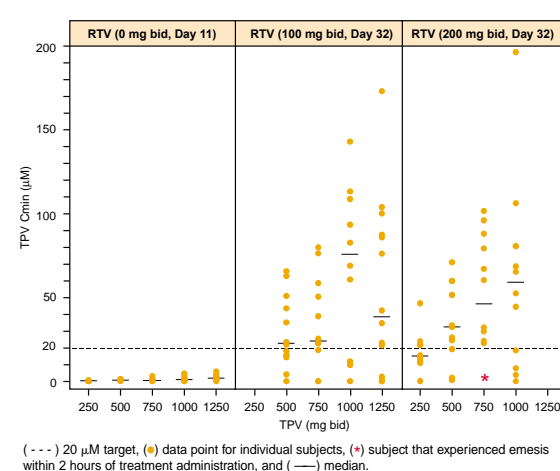


Figure 2. TPV C_{\max} in the Absence and Presence of Co-administered RTV

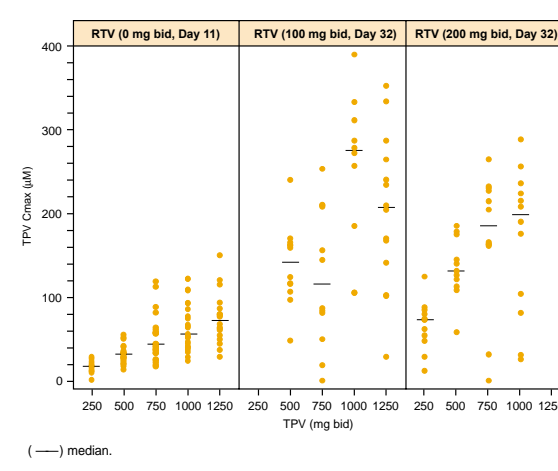


Figure 3. Morning Trough (C_{\min}) Plasma RTV Concentrations Over Course of Study

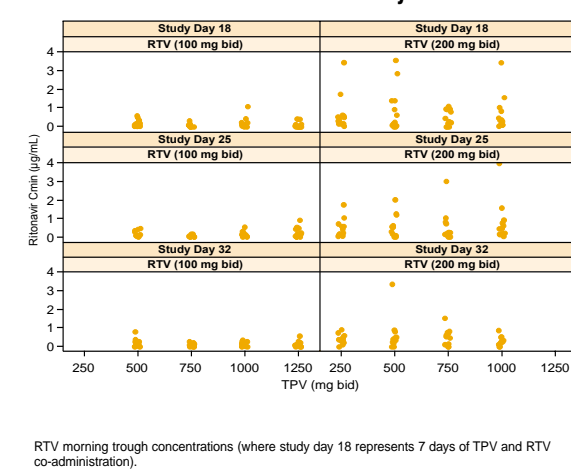


Figure 4. CYP3A4 Induction/Inhibition: ERMBT Assay Results Over Course of Study

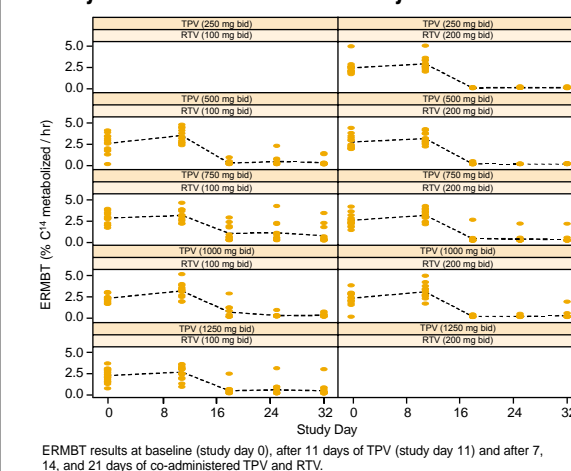


Table 2. Summary of Morning TPV C_{\min} and TPV C_{\max}

RTV Study Group (mg bid)	TPV (mg bid)					
	250	500	750	1000	1250	
Median TPV Morning C_{\min}, μM (range)						
100	10 days TPV alone		0.56 (0.25-1.27)	0.82 (0.21-1.21)	1.41 (.033-4.74)	1.81 (0.13-5.88)
	21 days RTV+TPV		22.58 (BLQ*-65.78)	25.42 (BLQ-80.02)	75.81 (BLQ-143.04)	38.41 (BLQ-173.05)
200	10 days TPV alone	0.28 (0.06-0.48)	0.75 (0.32-1.32)	0.60 (0.07-3.13)	0.83 (0.11-4.34)	
	21 days RTV + TPV	15.00 (0.10-46.53)	32.36 (0.72-71.02)	60.23* (BLQ-101.6)	58.92 (BLQ-173.05)	
Median TPV C_{\max}, μM (range)						
100	10 days TPV alone		28.36 (13.44-41.75)	38.00 (19.11-63.57)	71.15 (28.29-109.12)	72.11 (28.8-150.12)
	21 days		141.64 (48.01-240.30)	144.64 (18.62-253.50)	275.48 (105.19-390.20)	207.08 (28.84-352.66)
200	10 days TPV alone	17.48 (1.03-28.56)	33.63 (17.66-55.10)	44.36 (17.07-118.60)	53.01 (23.67-122.14)	
	21 days RTV + TPV	72.99 (11.99-124.57)	131.33 (57.98-185.35)	204.69 (31.45-264.83)	199.08 (25.84-288.67)	

*BLQ = below the limit of quantitation. *One patient value was not included because the patient had emesis within 2 hours of treatment administration.

Effects of TPV and RTV on the CYP3A4 Enzyme System

- ERMBT was used to measure cytochrome P-450 CYP3A4 activity in the liver. TPV is an inducer of CYP3A4 and RTV a potent inhibitor; results of the current study confirm this.
- After 11 days of TPV dosing, erythromycin metabolism increased, providing evidence that TPV induced CYP3A4 (Figure 4). After 7 days of TPV/RTV, erythromycin metabolism decreased. Inhibition was sustained over the remaining 2 weeks of TPV/RTV. The amount of inhibition, while substantial for both the 100 mg and 200 mg RTV doses, may be RTV dose-dependent as judged by slightly lower values and less variability in the 200 mg RTV group.

Adverse Events

- AEs (Table 3) were seen in 109/113 subjects (96.5%). No serious AEs were reported. Gastrointestinal AEs (91.2% of subjects) and headache were the most frequently reported. Only 6 subjects (5%) experienced AEs of moderate intensity.

Table 3. Selected Adverse Events by Treatment at Onset

AE	Number of Patients in Treatment Group With AE (%)		
	TPV Monotherapy n = 113	TPV + RTV 100 mg n = 54	TPV + RTV 200 mg n = 50
Diarrhea	78 (69.0%)	4 (7.4%)	7 (14%)
Nausea	56 (49.6%)	2 (3.7%)	3 (6%)
Vomiting	38 (33.6%)	3 (5.5%)	7 (14%)
Abdominal pain	19 (16.8%)	1 (1.9%)	1 (2%)
Headache	27 (23.9%)	6 (11.1%)	4 (8%)
Dizziness	15 (13.3%)	2 (3.7%)	2 (4%)

CONCLUSIONS

- Each dose of TPV/RTV studied (except TPV 250/RTV 200) produced plasma trough C_{\min} levels that achieved the target: 20 μM (10x the protein-adjusted IC_{50} for multiple-PI-resistant HIV).
- ERMBT data demonstrate RTV inhibition of the CYP3A4 enzyme system was the basis of the favorable PK profile of TPV/RTV, and that inhibition appeared more consistent with 200 mg RTV dose.
- Mild gastrointestinal effects with TPV/RTV were the most common AEs reported. No serious AEs occurred.

REFERENCES

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