Pharmacokinetic (PK) Interaction between the HIV Protease Inhibitors Tipranavir and Ritonavir

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Introduction

Tipranavir (PNU-140690)

- Non-peptidic HIV protease inhibitor (4-hydroxy-5,6-dihydro-2-pyrone)
- Active in vitro against laboratory strains of HIV-1 resistant to zidovudine or delavirdine
- Active in vitro against HIV-1 clinical isolates highly resistant to indinavir, ritonavir, nelfinavir, and saquinavir
- Metabolized primarily by cytochrome P450 3A (CYP3A)
- CYP3A inducer
- p-glycoprotein (Pgp) substrate

Introduction – (*Cont.)*

Ritonavir (Norvir®)

- Peptidic HIV protease inhibitor
- Metabolized primarily by cytochrome CYP3A, lesser by CYP2D6
- Enzyme inducer
- Potent inhibitor of human CYP3A-mediated metabolism
- Pgp inhibitor

Objectives

- Study I : To assess potential PK interaction between TPV and RTV
- Study II : To assess dose relationship of PK interaction

Methods (Study I & Study II)

Population

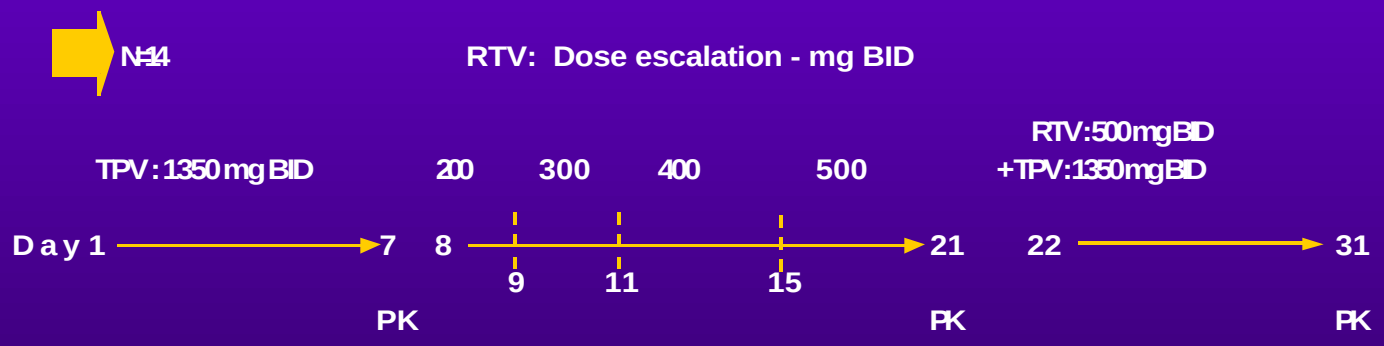
- Healthy males and females; age 18-55 years
- Study I : 10M completed; mean age of 28 years
- Study II : 13 (12M/1F) completed; mean age of 30 years

Methods (Study I & Study II)

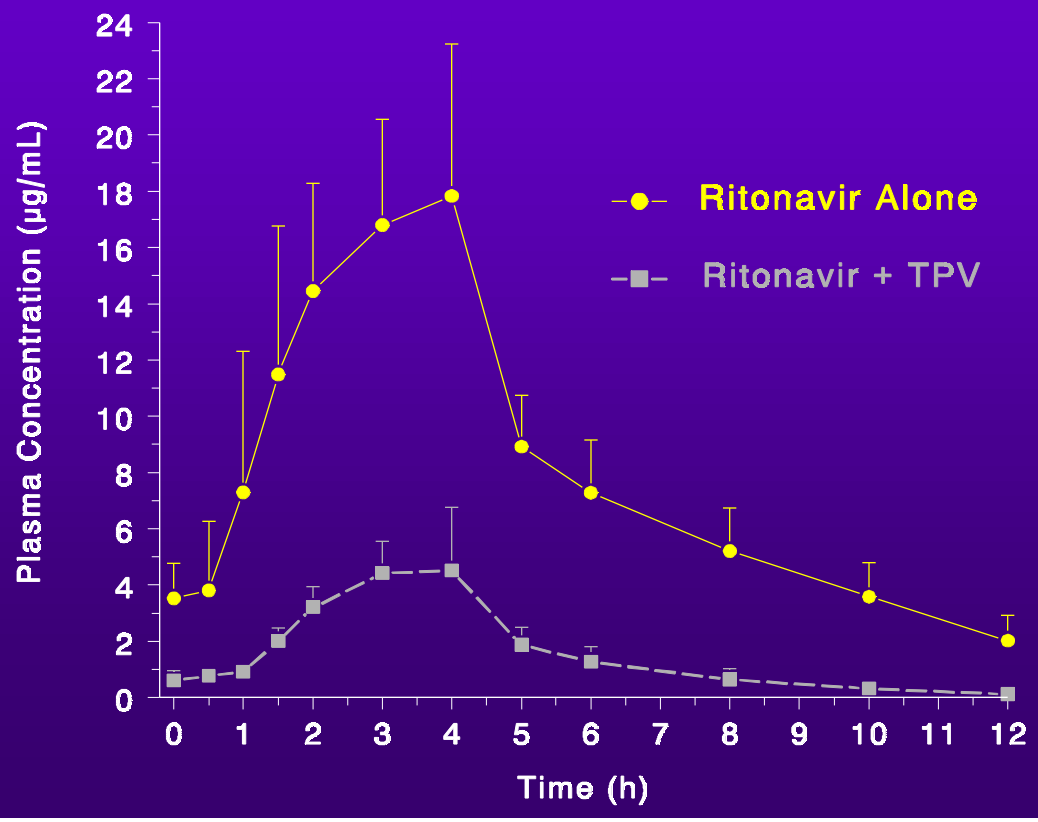
Analysis

- TPV and RTV in plasma : HPLC based – UV detection
- Pharmacokinetic parameters : non-compartmental techniques
- Statistical Methods : Non-parametric (Wilcoxon's Signed Rank Test)
  - Sample size based on ability to detect large (>50%) differences in steady-state PK

Study I : Flow diagram



Mean (+SD) Plasma RTV Concentrations (RTV 500 mg BID / TPV 1350 mg BID, N=10)



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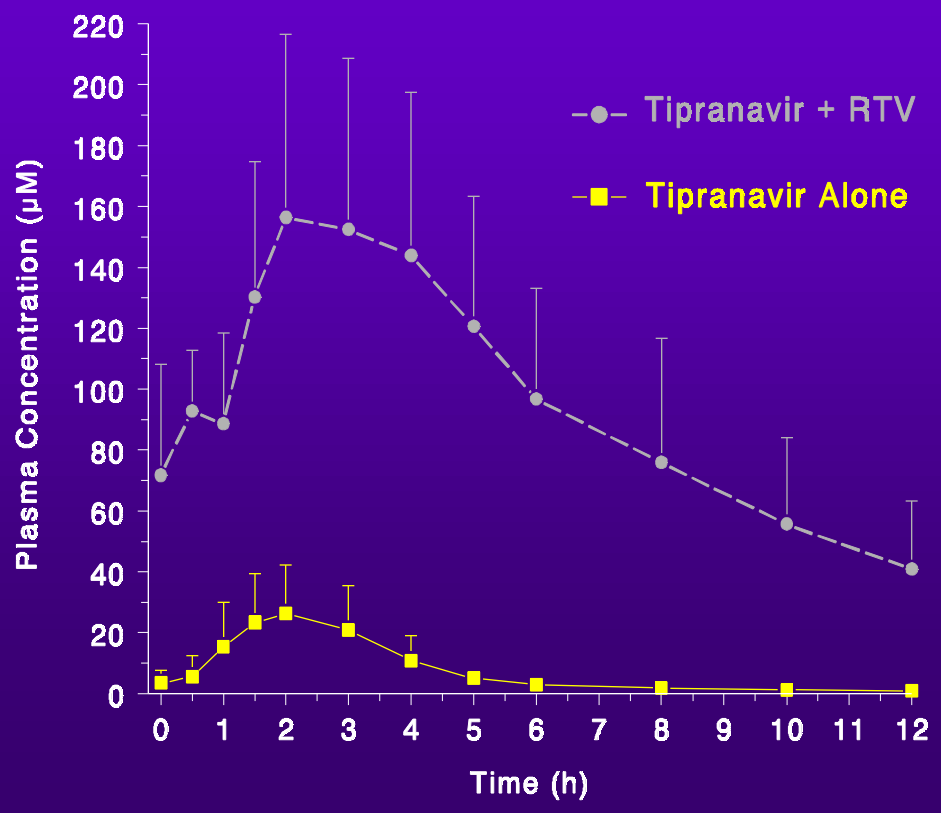
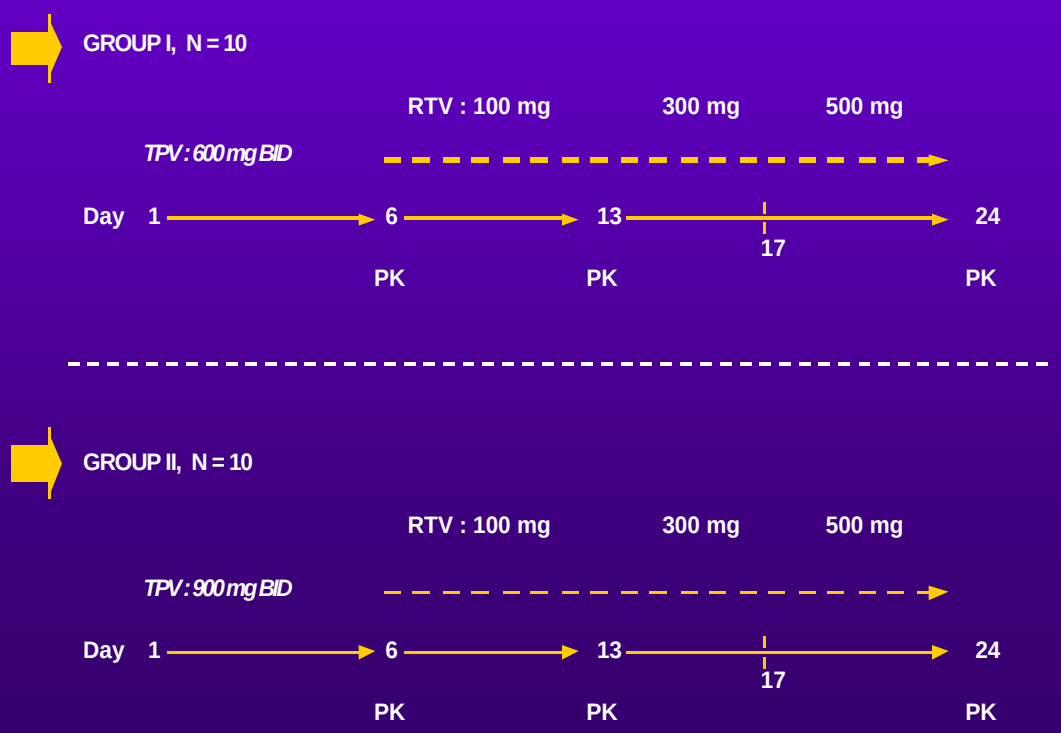


Conclusions (Study I)

- TPV significantly reduces RTV concentrations
- RTV has a pronounced effect in enhancing TPV concentrations
- RTV's effect on TPV is immediate, with no apparent accumulation of TPV
- TPV was well tolerated both when administered alone or concomitantly with RTV
- Further assessment is required to provide dosing recommendations

Study II : Flow diagram

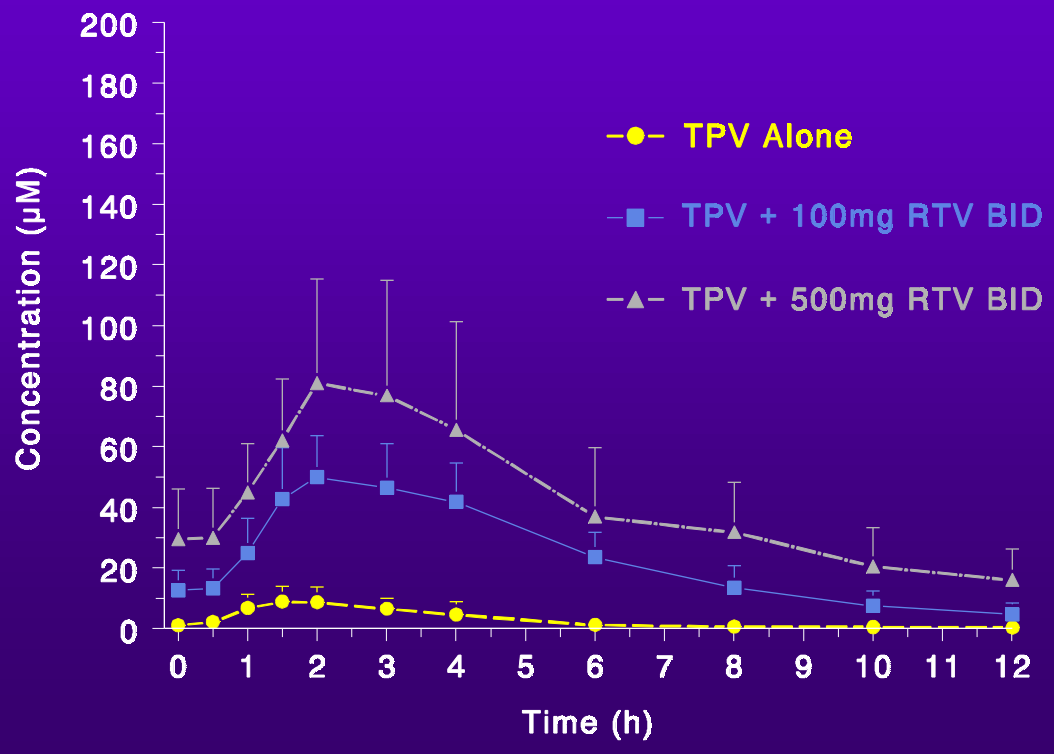


Median (Range) RTV Pharmacokinetic Parameters after RTV 500 mg BID Co-administered with TPV

Parameter	Ritonavir Alone*	Ritonavir + TPV 600 mg BID (N=7)	Ritonavir + TPV 900 mg BID (N=6)
CLpo (L/h)	5.1 (3.9-7.8)	19 (11-31)	19 (12-27)
AUC_{12} (µg·h/mL)	100 (64-128)	27 (16-44)	26 (19-40)
Css (µg/mL)	8.4 (5.3-10.7)	2.3 (1.4-3.7)	1.9 (1.6-3.4)
Cmin (µg/mL)	1.9 (1.0-3.9)	0.15 (0.08-0.53)	0.15 (0.09-0.62)
Cmax (µg/mL)	19 (12-28)	7.0 (4.8-8.5)	5.8 (3.9-7.9)
Tmax (h)	3.0 (1.0-4.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)
t? (h)	2.9 (2.6-4.4)	1.8 (1.5-2.2)	1.8 (1.5-2.7)

* Taken from the results of Study I

Mean (+SD) Plasma TPV Concentrations after TPV 600 mg BID Administered Alone or Concomitantly with RTV (N=7)

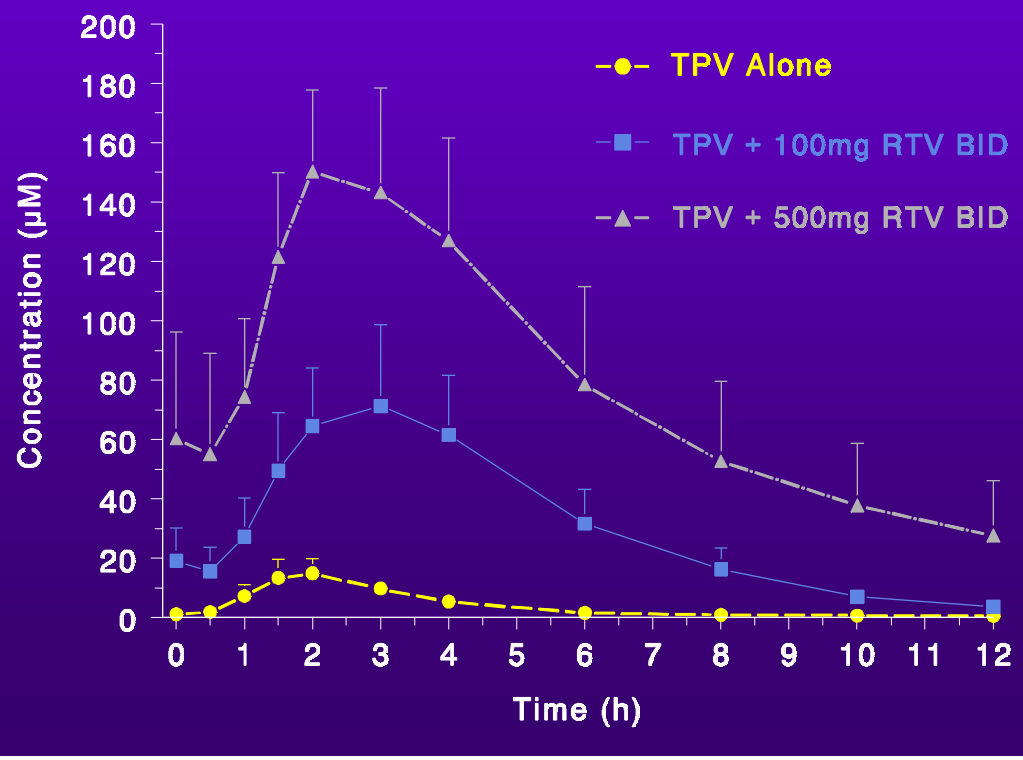


Median (Range) TPV Pharmacokinetic Parameters after TPV 600 mg BID Given Alone or Co-administered with RTV (N=7)

Parameter	Tipranavir Alone	Tipranavir + RTV 100 mg BID	Tipranavir + RTV 500 mg BID
CLpo (L/h)	31.3 (17.3-88.8)	3.35 (2.44-6.07) *'†	2.23 (1.02-4.79) *
AUC_{12} (µM·h)	32.5 (11.3-57.5)	297 (164-407) *'†	446 (207-972) *
Css (µM)	2.70 (0.94-4.79)	24.8 (13.7-34.0) *'†	37.2 (17.3-81.0) *
Cmin (µM)	0.341 (0.165-0.929)	3.14 (1.61-12.8) *'†	14.3 (4.70-32.5) *
Cmax (µM)	11.3 (4.18-19.1)	56.8 (32.5-75.4) *'†	78.6 (36.6-144.0) *
tmax (h)	2.0 (1.0-4.0)	2.0 (1.5-3.0)	2.0 (2.0-3.0)
t? (h)	3.9 (2.9-4.7)	2.4 (1.8-4.1) *	3.6 (2.8-4.8)

* Significantly different (p<.03) relative to TPV alone
† Significantly different (p<.03) relative to TPV + RTV 500 mg

Mean (±SD) Plasma TPV Concentrations after TPV 900 mg BID Administered Alone or Concomitantly with RTV (N=6)



Overall Conclusions

- RTV concentrations are significantly reduced by approximately same extent with TPV doses of 600, 900 or 1350 mg
- A low dose of RTV significantly enhances TPV exposure (~10-fold at 100 mg RTV)
- At a fixed dose of RTV, TPV Cmin increases with increasing dose of TPV
- At a fixed dose of TPV, TPV Cmin increases with increasing dose of RTV

Overall Conclusions - (*Cont.*)

- TPV appears to be a potent inducer of CYP3A
- RTV effect on TPV may be through inhibition of CYP3A and/or Pgp
- TPV may be administered twice daily when given with low dose RTV
- A higher dose strength SEC formulation of TPV, with 2-fold higher bioavailability than HFC, will result in reduced “pill burden”