

Resistance to Tipranavir Is Uncommon in a Randomized Trial of Tipranavir/Ritonavir (TPV/RTV) in Multiple PI-Failure Patients (BI 1182.2)

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SUMMARY

- Resistance to TPV (>10-fold IC₅₀ change) of HIV-1 clinical isolates was infrequent in this population of patients with exposure to multiple HIV protease inhibitors (PIs)
 - 1/41 patient isolates at baseline (2.4%)
- Reduced susceptibility to TPV (4- to 10-fold IC₅₀ change) of HIV-1 clinical isolates was not a frequent occurrence in this patient population
 - 5/41 patient isolates after more than 1 year of TPV treatment (12.2%)
- Treatment-emergent mutations at codon L33 (I, F, or V) plus V82T were found in 4/6 cases with reduced susceptibility to TPV
- TPV treatment did not appear to influence susceptibility to currently licensed peptidic PIs for the overall study population

INTRODUCTION

Tipranavir (TPV) is the first in a new class of non-peptidic protease inhibitors (NPPis). TPV has shown in vitro activity against HIV resistant to multiple peptidic PIs.¹ Passage of such HIV isolates in the presence of TPV selects for TPV-resistant strains after 2-3 months.² However, no specific mutations have been associated with this resistance.

As previously reported, TPV/ritonavir (RTV) therapy was effective in suppressing HIV over 48 weeks in patients who had previously failed 2 or more PI-containing regimens.³ This study characterizes development of TPV resistance in this study population.

METHODS

Study Design

- Phase II, open-label, parallel-group study in multiple PI-failure, NNRTI-naive population randomized to the following treatment groups:
 - Low-dose: TPV 500 mg bid (SEDDS)/RTV 100 mg bid [initially TPV 1200 mg bid (HFC)/RTV 100 mg bid]
 - High-dose: TPV 1000 mg bid (SEDDS)/RTV 100 mg bid [initially TPV 2400 mg bid (HFC)/RTV 200 mg bid]

Viral Load Testing

- Amplicor Monitor and Ultrasensitive Assays (Version 1.0)

Phenotyping

- Virco Antivirogram Assay

Genotyping

- Visible Genetics Trugene Assay

RESULTS

- HIV-1 from 35/41 (85.4%) patients did not have reduced TPV susceptibility (4- to 10-fold IC₅₀). Reduced susceptibility developed during TPV treatment in HIV-1 of 5 (12.2%) patients and resistance to TPV (>10-fold IC₅₀) was detected in HIV-1 of one patient at baseline (2.4%).

Table 1. Patient History of PI Exposure at Baseline by Fold Change in HIV-1 TPV IC₅₀: Reduced Susceptibility (≥4-Fold Change) vs Susceptible (<4-Fold Change)

TPV Treatment Group	Fold Change in TPV IC ₅₀			
	Low-dose TPV		High-dose TPV	
	≥4 n = 3	<4 n = 16	≥4 n = 3	<4 n = 19
	Number of Patients			
Indinavir (IDV)	1	5	3	9
Nelfinavir (NFV)	2	8	3	12
Ritonavir (RTV)	3	9	3	8
Saquinavir (SQV)	2	15	3	17

Table 2. Mean HIV RNA Change From Baseline (Log₁₀ Copies/mL) by TPV Treatment Group and Number of Baseline PI Mutations (ITT-as Randomized-LOCF)¹

TPV Treatment Group	Study Week	Number of Baseline PI Mutations ²				P Value ³
		≤5		>5		
		n	Δ HIV RNA	n	Δ HIV RNA	
Low-dose	Baseline ^a	12	4.61 ^a	7	4.34 ^a	
	24	12	-2.21	7	-2.37	0.65
	48	12	-2.39	7	-2.24	0.43
	80	12	-2.10	7	-1.52	0.29
High-dose	Baseline ^a	14	4.60 ^a	8	4.21 ^a	
	24	14	-1.98	8	-0.94	0.11
	48	14	-1.85	8	-1.33	0.36
	80	14	-1.88	8	-1.35	0.36

¹ITT-LOCF: intent-to-treat, all randomized patients, last observation carried forward, PI mutations: D30N, V32I, G48V, I50V, V82A/F/I/S, I84V, and L90M plus the following if present with one or more of the mutations previously listed: L10F/I/R/V, K20M/R, L24I, L33F, M36I, M46I/L, I47V, I54V/L, A71V/T, G73S/A, V77I, and N88D. ²Wilcoxon Rank Sum Test. ³Total viral load at baseline (HIV RNA copies/mL).

Figure 1. Treatment-Emergent HIV-1 Protease Gene Mutations at Last Patient Visit

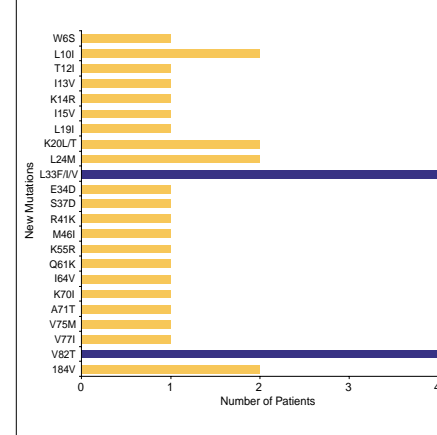


Figure 2. PI Susceptibility at Baseline for HIV-1 of the Total Study Population

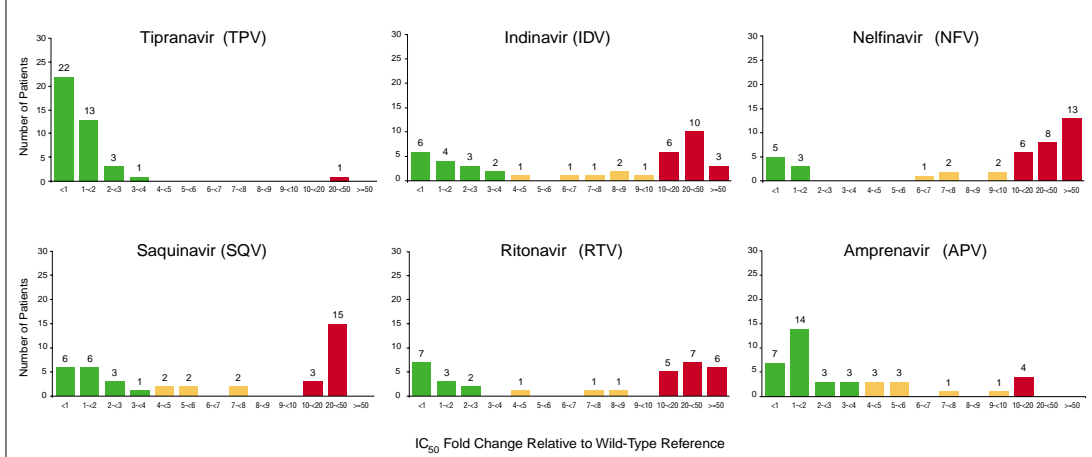


Table 3. Median HIV RNA Change From Baseline (Log₁₀ Copies/mL) by Presence or Absence of Major PI Cross-Resistance Mutations at Baseline (ITT-as Treated-LOCF)¹

TPV Treatment Group	Study Week	Baseline Major PI-Resistance Mutations				P Value ²
		No Major Mutations (includes D30N)		Any or All Major Mutations at Codons 46, 82, 84, 90		
		n	HIV RNA	n	HIV RNA	
Low-dose	Baseline ³	5	4.71	14	4.40	
	24	5	-2.56	14	-2.61	0.96
	48	5	-2.56	14	-2.68	0.61
High-dose	Baseline ³	5	4.70	17	4.35	
	24	5	-2.67	17	-2.43	0.81
	48	5	-2.64	17	-2.43	1.00

¹ITT-LOCF: intent-to-treat, as-treated, last observation carried forward. ²Wilcoxon Rank Sum Test. ³Total viral load at baseline (HIV RNA copies/mL).

Table 4. Number of Protease Gene Mutations at Baseline in HIV-1 With Continued TPV Susceptibility vs Reduced Susceptibility

TPV Treatment	TPV Phenotype	n	Standard Deviation				
			Mean	Minimum	Median	Maximum	
Low-dose	Susceptible ¹	14	11.57	4.22	3.00	11.50	17.00
	Reduced susceptibility ²	3	18.00	1.00	17.00	18.00	19.00
High-dose	Susceptible	19	10.21	3.24	6.00	10.00	19.00
	Reduced susceptibility	3	14.33	2.31	13.00	13.00	17.00
Total	Susceptible	33	10.79	3.69	3.00	11.00	19.00
	Reduced susceptibility	6	16.17	2.56	13.00	17.00	19.00

¹Susceptible: IC₅₀ fold change <4 relative to wild-type reference. ²Reduced susceptibility: IC₅₀ fold change ≥4 relative to wild-type reference

Table 5. PI Phenotype of HIV-1 for Total Study Population Pre- and Post-TPV Treatment

Timepoint	n	Median IC ₅₀ Fold Change ¹					
		TPV	APV	IDV	NFV	RTV	SQV
Day 1	40	0.80	1.70 ²	8.3	24.10	18.55	7.30
Week 24	6	2.25	2.00	13.95	30.45	45.70	28.70 ³
Week 48	4	2.50	0.95	4.90	6.30	28.55	5.40
Week 72	3	2.10	2.00	6.60	10.70	13.30	8.40
Week 80	5	0.50	2.70	1.40	8.60	4.30	2.00

¹Fold change relative to wild-type reference. ²n = 39. ³n = 5

Table 6. Change in Viral Load From Baseline (Log₁₀ Copies/mL) and IC₅₀ Fold Change in TPV Susceptibility

TPV Group	Dose	Patient Number	Study Week											
			Day 1 ¹		24		48		72		80		Early Discontinuation	
			Fold Change	HIV RNA	Fold Change	HIV RNA	Fold Change	HIV RNA	Fold Change	HIV RNA	Fold Change	HIV RNA	Fold Change	HIV RNA
TPV Susceptible (IC ₅₀ fold-change <4)	Low dose, n = 16	Group Mean	<4	4.57 ²	<4	4.49 ²	-2.69	-2.54	-2.55	-2.23	Not applicable	Not applicable	Not applicable	
	High dose, n = 19	Group Mean	<4	4.49 ²	<4	4.49 ²	-1.95	-1.94	-1.96	-1.96	Not applicable	Not applicable		
Reduced TPV Susceptibility (IC ₅₀ fold-change ≥4) ³	Low dose	111	23.7	4.47	3.5	-0.57					10.1	+0.38		
	151	2.3	4.17								6.3	-0.24		
	1142	1.3	3.85								Not applicable			
High dose	211	1.8	3.77								7.3	+1.43		
	261	0.3	4.43	3.6	-0.8	4.4	-0.84	3.0	-0.77	7.1	-1.14	Not applicable		
	262	1.1	4.83	4.4	+0.03	4.6	-0.3				Not applicable	-0.33		

¹Baseline fold change relative to reference HIV and absolute HIV RNA (log₁₀ copies/mL). ²Mean log₁₀ RNA copies/mL for patients whose HIV remained susceptible to TPV throughout the trial with viral loads below the limit of quantitation scored as 49 copies/mL. ³Individual patient log₁₀ RNA copies/mL and TPV IC₅₀ fold change values. ⁴Week 64 sample. ⁵Sample could not be amplified for genotyping

Table 7. Genotype and TPV IC₅₀ Fold Change for HIV-1 of Patients With Reduced Susceptibility to TPV

TPV Patient Group	#	Fold Change ¹	Study Week								
			Day 1 ² Mutations ³	24 Mutations	48 Mutations	72 Mutations	80 Mutations	Early Discontinuation (EDC) Mutations			
Low-dose	111	23.7	A22V, E35D, I13V, I62V, I64V, I84V, L10I, M36I, M46I, N83D, Q58E, E21EV, L63QE, Q180L, S37N, V11VF, W6RM	EDC ⁴	EDC	EDC	EDC	EDC	10.1	A22V, E35D, I13V, I62V, I64V, I84V, L10I, L63E, M36I, M46I, N83D, Q58E, S37N	
	151	2.3	E35D, I54V, I62V, I64V, I84V, L10I, M36I, M46I, N83D, Q58E, E21EV, L63QE, Q180L, S37N, V11VF, W6RM	3.5	I62V, I93L, L63P, Q61E, S37D, T12F	EDC	EDC	EDC	6.3	V3I, L10I, T12I, G16A, E35D, M36I, S37D, R41K, K43T, I54V, Q61E, I62V, L63P, A71V, V82T, I84V, L90M	
	1142	1.3	A71I, I54V, K55R, L10I, L63P, L90M, Q58E, R57K, V82A, E35ED, G73S, I62IV, M36IM, M46I, P79S, Q61K, S37D, W6SW	Below limit of detection (BLD) ⁵	BLD	7.9 ⁶	V3I, L10I, E35D, M36I, S37D, M46I, I54V, K55R, R57K, Q58E, I62V, L63P, A71T, V82T, L90M	3.6	V3I, L10I/L, I13V/I, L33F/L, E35D, M36I, S37D, M46I, I54V, K55R, R57K, Q58E, I62V, L63P, A71T, V82T, L90M	10.1	V3I, L10I, T12I, G16A, E35D, M36I, S37D, R41K, K43T, I54V, Q61E, I62V, L63P, A71V, V82T, I84V, L90M
High-dose	211	1.8	A71V, I13V, I54V, L24I, L64P, V82T, G73SG, I84IV, K14R, K20IM, L10IL, L89LV, S37N	EDC	EDC	EDC	EDC	EDC	7.3	A71V, G73S, I13V, I54V, I84V, K14R, K20IM, L, K70K, L10IV, L24IM, L, L33IV, L63P, L89V, Q61K, S37N, V82T	
	261	0.3	A71V, F53L, G16A, I54V, L24I, L63P, M36I, R41K, V82A, L10V, M46L, S37ND, T74S	3.6	A71V, E34D, F53L, G16A, I54V, K55R, L24M, L33IL, L63P, M36I, M46L, R41K, S37D, T74S, V82T	4.4	E34D, F53L, K55R, L10V, L24M, L33IL, L63P, M36I, M46L, R41K, S37D, T74S, V82T	3.0	V3I, L10V, G16A, L24M, L33I, E34D, M36I, S37D, R41K, M46L, F53L, I54V, K55R, L63P, I64V, T74S, V82T	7.1	V3I, L10V, G16A, L24M, L33I, E34D, M36I, S37D, R41K, M46L, F53L, I54V, K55R, L63P, I64V, T74S, V82T
	262	1.1	E35D, I85V, L10I, L63P, L90M, R41K, A71TIAV, F53LF, G73SG, I54IV, K20KM, K45KR, L33IL, M36I, M46IM, N88ND, S37N	4.4	A71V, E35D, I54V, I85V, K45R, L10I, L33I, L63P, L90M, K45KR, L33IL, M36I, M46I, N88ND, S37N, V82T	4.6	A71V, E35D, I54V, I84IV, I85V, K45KR, L10I, L33I, L63P, L90M, M36I, N88ND, R41K, S37ND, V82T	EDC	EDC	EDC	EDC

¹Baseline. ²Fold change in TPV IC₅₀ relative to wild-type reference. ³Protease gene mutations. ⁴Highlighted (in dark red) mutations are those that are treatment emergent. ⁵BLD = HIV RNA below the limit of detection of phenotyping and genotyping assays. ⁶Week 64 sample. ⁷Sample could not be amplified for phenotyping and genotyping

CONCLUSIONS

- Over the study 35/41 patients remained susceptible to TPV (Table 6)
- Two baseline characteristics were associated with reduced TPV susceptibility
 - PI exposure history (Table 1)
 - Number of protease gene mutations at baseline (Table 4)
- Number of baseline PI mutations (Table 2) or presence of major PI mutations at 46, 82, 84, and 90 (Table 3) did not influence the virologic response to TPV/RTV
- The V82T mutation combined with a L33 (I, F, or V) were treatment emergent in HIV-1 of 4/6 patients with reduced TPV susceptibility (Figure 1 and Table 7)
- HIV-1 isolates at baseline had a wide range of IC₅₀ fold values to currently licensed PIs. Most HIV were susceptible to TPV (Figure 2)
- TPV/RTV treatment did not influence susceptibility to other PIs (Table 5)

REFERENCES

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