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Patterns of Tipranavir Susceptibility and Cross-Resistance Among Patient Samples Submitted for Routine Resistance Testing

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BACKGROUND

- Tipranavir, the most recently approved protease inhibitor (PI), has a favorable activity profile among viruses resistant to other PIs.
- However the relative degree of cross-resistance between tipranavir and other PIs and in samples containing mutation clusters selected by other PIs is not fully understood.

METHODS

- The prevalence and patterns of tipranavir resistance and PI cross-resistance was characterized within a database containing phenotype (PhenoSense HIV) and genotype (GeneSeq HIV) results for 3564 samples containing at least one PI-selected mutation, submitted to the Monogram Clinical Reference Laboratory for routine resistance testing.
  - PI-selected mutations were defined as any non-wild type amino acid at position 23, 24, 30, 32, 46, 47, 48, 50, 54, 82 (except V82I), 84, 88, and 90.
- Samples with mixtures at major resistance-associated positions were removed.
- Only one sample per patient was included if repeats were present.
- Samples with extreme resistance too high to measure (IC_{50} higher than the maximum concentration tested in the assay) were assigned a drug-specific "Max FC" value for calculation purposes
- Samples were classified as tipranavir sensitive (S), partially sensitive (PS), or resistant (R) if the fold change in IC_{50} (FC) was less than the lower cut-off, between the lower and upper cut-off, or over the upper cut-off, respectively (see Table 1). For nelfinavir, the biological cut-off (3.6) was used to define samples as sensitive or having reduced susceptibility.

Table 1. Susceptibility Cut-off Values for Ritonavir-Boosted PIs

PI	Lower	Upper
Amprenavir (APV/r)	4	11.5
Atazanavir (ATV/r)	5.2	20*
Indinavir (IDV/r)	10	50*
Lopinavir (LPV/r)	9	55
Saquinavir (SQV/r)	2.3	12
Tipranavir (TPV/r)	2.0	8.0

*estimated upper cutoff, pending further analysis

Figure 1: Cross Resistance Plots

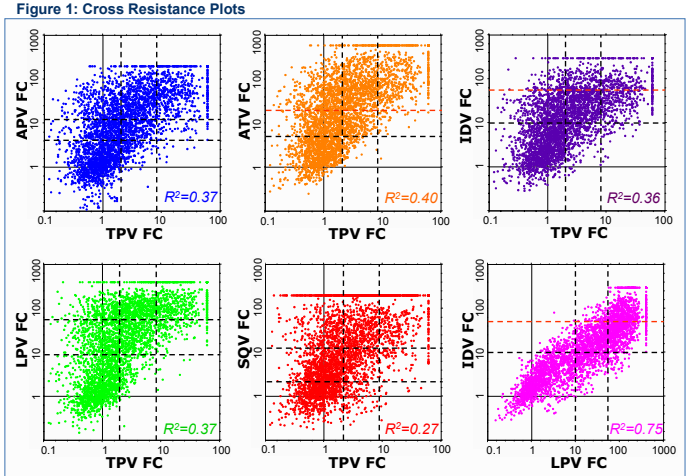
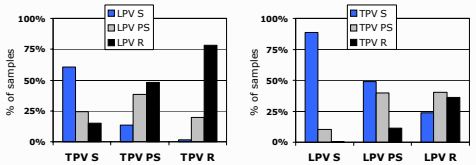


Table 2: Cross Resistance of Samples Grouped by Susceptibility to TPV (% of all samples)

TPV	2nd PI	2nd PI: APV	ATV	IDV	LPV	NFV	SQV
S	S	33%	27%	38%	34%	9.2%	23%
S	PS	10%	14%	15%	13%		19%
S	R	12%	14%	3.2%	8.2%	46%	14%
PS	S	4.2%	2.4%	6.6%	4.0%	0.9%	3.2%
PS	PS	7.2%	7.1%	16%	11%		8.4%
PS	R	17%	19%	6.2%	14%	28%	17%
R	S	0.3%	0.03%	1.1%	0.3%	0%	0.4%
R	PS	1.4%	1.0%	7.2%	3.1%		2.2%
R	R	14%	15%	7.5%	12%	16%	13%

Figure 2: TPV - LPV Cross Resistance of Samples Grouped by Susceptibility to TPV (left) or LPV (right)



78% of TPV-R samples are also resistant to LPV compared to 36% of LPV-R samples that are also resistant to TPV

Table 3: PI Susceptibility of Samples Defined by Primary Mutations

Mutation Grouping	N	TPV MFC*	TPV S	TPV PS	TPV R	APV MFC	APV S	APV PS	APV R	ATV MFC	ATV S	ATV PS	ATV R	IDV MFC	IDV S	IDV PS	IDV R	LPV MFC	LPV S	LPV PS	LPV R	NFV MFC	NFV S	NFV R	SQV MFC	SQV S	SQV PS	SQV R
D30N	22	0.3	100%	0%	0%	0.7	100%	0%	0%	2.4	95%	4.5%	0%	1.1	100%	0%	0%	0.8	100%	0%	0%	22.7	0%	100%	0.5	100%	0%	0%
D30N, N88D	169	0.9	95%	4.7%	0%	1.0	97%	3.0%	0%	3.7	72%	26%	1.8%	1.8	99%	1.2%	0%	1.1	99%	0.6%	0%	61.7	0%	100%	2.2	54%	44%	1.8%
V32I	6	0.7	100%	0%	0%	2.6	83%	0%	17%	5.2	50%	50%	0%	2.1	100%	0%	0%	1.0	100%	0%	0%	3.8	50%	50%	0.9	100%	0%	0%
V32I, M46IL, I47V	8	2.6	13%	88%	0%	9.7	0%	63%	38%	3.7	63%	25%	13%	5.2	75%	25%	0%	9.1	50%	50%	0%	6.5	38%	63%	1.0	88%	13%	0%
M46IL	30	1.2	87%	13%	0%	1.1	83%	17%	0%	1.2	97%	3.3%	0%	1.5	97%	3.3%	0%	1.1	97%	3.3%	0%	1.9	77%	23%	0.9	97%	0%	3.3%
I50V	3	0.3	100%	0%	0%	16.5	0%	33%	67%	1.1	100%	0%	0%	0.7	100%	0%	0%	4.0	100%	0%	0%	1.8	100%	0%	1.2	100%	0%	0%
M46IL, I50V	14	0.4	100%	0%	0%	18.1	0%	36%	64%	0.8	100%	0%	0%	1.0	100%	0%	0%	6.1	71%	29%	0%	2.2	79%	21%	1.2	100%	0%	0%
I50L	15	1.0	80%	6.7%	13%	1.3	80%	13%	6.7%	24.1	6.7%	40%	53%	0.7	100%	0%	0%	0.5	100%	0%	0%	1.3	80%	20%	0.5	93%	6.7%	0%
I54ALMSTV	21	1.2	71%	29%	0%	4.8	48%	29%	24%	1.9	76%	19%	4.8%	1.2	95%	4.8%	0%	1.7	100%	0%	0%	3.7	43%	57%	1.2	76%	19%	4.8%
V82A	21	1.1	100%	0%	0%	1.2	90%	10%	0%	1.4	95%	4.8%	0%	2.4	100%	0%	0%	2.5	95%	4.8%	0%	2.3	71%	29%	0.9	100%	0%	0%
V82L	4	2.2	50%	50%	0%	1.2	75%	25%	0%	1.6	75%	25%	0%	0.8	100%	0%	0%	1.0	100%	0%	0%	1.3	75%	25%	1.1	75%	25%	0%
V82L +/- others	22	23.5	9.1%	23%	68%	15.8	14%	36%	50%	77.2	14%	18%	68%	23.5	32%	32%	36%	14.6	36%	36%	27%	56.5	18%	82%	7.1	27%	23%	50%
I84V	20	2.2	45%	50%	5.0%	4.1	50%	40%	10%	3.0	75%	15%	10%	2.9	95%	5.0%	0%	3.0	90%	10%	0%	4.1	45%	55%	5.0	10%	70%	20%
N88S	17	0.9	100%	0%	0%	0.2	100%	0%	0%	17.6	18%	35%	47%	6.1	88%	12%	0%	0.8	100%	0%	0%	24.7	0%	100%	1.7	76%	24%	0%
L90M	298	1.0	91%	9.4%	0%	1.2	95%	4.7%	0.3%	1.8	83%	14%	3.0%	2.3	93%	6.7%	0%	1.2	99%	0.7%	0%	5.9	34%	66%	2.4	48%	44%	8.1%
L24I, M46IL, V82A	8	0.6	100%	0%	0%	4.1	50%	38%	13%	4.9	50%	38%	13%	6.8	63%	38%	0%	8.7	50%	50%	0%	6.5	25%	75%	1.2	75%	25%	0%
I54V, V82A, L90M	63	2.2	43%	54%	3.2%	4.0	48%	38%	14%	11.3	21%	43%	37%	18.0	24%	63%	13%	30.6	4.8%	62%	33%	33.2	0%	100%	10.1	1.6%	38%	60%
M46IL, I54V, V82A, L90M	90	2.8	38%	52%	10%	10.7	16%	38%	47%	27.4	14%	26%	60%	34.4	6%	74%	20%	71.9	0%	36%	64%	57.0	0%	100%	14.0	2.2%	21%	77%
M46IL, I47V, I54V, I84V, L90M	14	11.4	0%	29%	71%	57.0	0%	0%	100%	181.6	0%	7.1%	93%	147.4	0%	29%	71%	157.8	0%	0%	100%	128.0	0%	100%	1000	0%	0%	100%

*MFC: Median Fold Change in IC50 — 50-90% — >90%

RESULTS SUMMARY

- In the complete data set, 55.6%, 28.6%, and 15.8% of samples were susceptible, partially susceptible, or resistant to TPV/r, respectively.
- Linear regression coefficients (R^2) using log-transformed FC values between TPV and other PIs ranged between 0.27 – 0.40. For comparative purposes, the R^2 value for LPV vs. IDV is 0.75 (Figure 1).
- Among samples PS to TPV/r, the percentage susceptible to other PIs was 14% for APV/r, 8% for ATV/r, 23% for IDV/r, 14% for LPV/r, 3% for NFV, 11% for SQV/r.
- Of samples PS to LPV, the percentage susceptible to other PIs was 26% for APV/r, 16% for ATV/r, 34% for IDV/r, 3% for NFV, 17% for SQV/r, 49% for TPV/r.
- The median FC (MFC) to TPV was less than 2 in samples containing only one primary PI mutation except V82L (MFC 2.4, n=4); the percentage of samples that were PS to TPV was over 25% for I84V and V82L (Table 3).
- TPV MFC was elevated (2.1 to 2.8) in samples with the following mutation combinations: V32I/M46IL/I47V, I54V/V82A/L90M, and M46IL/I54V/V82A/L90M (n=5, 85, and 56, respectively). In these 3 groups, approximately 60-90% of samples had at least partial TPV resistance, but fewer than 10% were fully resistant (Table 3).

CONCLUSIONS

- Cross resistance between TPV and other approved PIs is lowest with NFV and SQV, highest with APV and ATV, but modest in any case.
- Viruses with single primary mutations remain largely sensitive to TPV, with the exception of I84V and V82L.

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