Abstract #29

Phenotypic Susceptibility to TMC-114 and Tipranavir Before and After Lopinavir/ritonavir-based Treatment in Subjects Demonstrating Evolution of Lopinavir Resistance

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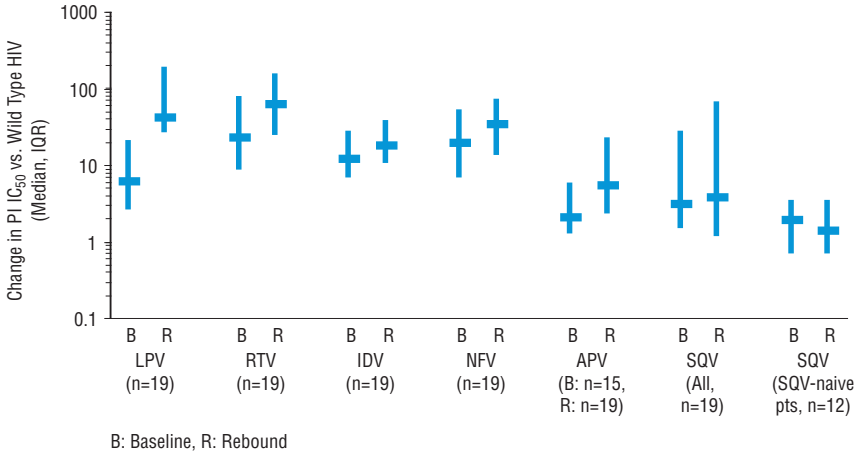
Background

- A previous analysis of 275 protease inhibitor-experienced subjects in two Phase 2 and one Phase 3 studies of lopinavir/ritonavir (LPV/r) identified 19 subjects with incremental evolution of LPV resistance during treatment with a LPV/r-based regimen (Mo 2005).
- Subjects with an intermediate level of LPV resistance at study baseline had the highest risk of demonstrating evolution of additional LPV resistance.
- Viral isolates from subjects with evolution of LPV resistance generally retained or developed a high degree of cross-resistance to ritonavir, indinavir, and nelfinavir, but a lower degree of resistance to saquinavir and amprenavir was observed (Figure 1).
- Changes in resistance to the new protease inhibitors TMC-114 (darunavir) and tipranavir (TPV) during evolution of LPV resistance have not previously been assessed.

Figure 1. Fold Change in Susceptibility to PIs in Patients Accumulating Incremental LPV Resistance During LPV/r Treatment



B: Baseline, R: Rebound

Methods

- For the current analysis, results from one Phase 2 study have been added, for a total of three Phase 2 and one Phase 3 studies (Table 1).

Table 1. Studies Analyzed

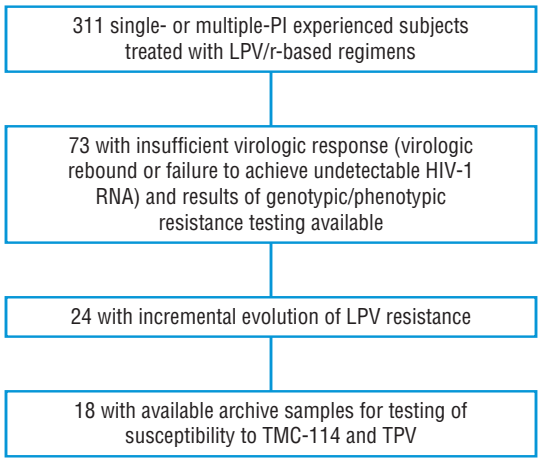
Study	N (LPV/r)	No. with Evolution of LPV Resistance	Duration (Weeks)	Entry Criteria
M97-765	70	6	144	NNRTI-naive, single PI-experienced
M98-957	57	5	72	NNRTI-naive, multiple PI-experienced
M98-888	148	7	48	NNRTI-naive, single PI-experienced
M99-049	36	6	48	≥1 NNRTI, ≥2 PIs

- For subjects with inadequate viral response (virologic rebound or failure to achieve undetectable plasma HIV-1 RNA) and no documented interruption of LPV/r, samples from baseline and the time of rebound were retrospectively submitted for genotypic and phenotypic drug resistance testing.
- Incremental evolution of LPV resistance was defined as >2.5-fold reduced susceptibility to LPV in the rebound sample compared to a WT virus (fold change, FC) as well as satisfying one or both of the following criteria:
  - Emergence of a new primary mutation in the PR gene associated with PI resistance (D30N, V32I, G48V, I50L/V, V82A/F/T/S, I84V, or L90M)
  - Emergence of a new secondary mutation (L10F/I/R/V, K20M/R, L24I, L33F, M36I, M46I/L, I47A/V, I54A/V/L/S, A71V/T, G73S/A, V77I, or N88D) accompanied by an increase greater than or equal to twofold in the LPV IC_{50} between baseline (pre-LPV/r treatment) and rebound.
- For the current analysis, subjects with evolution of LPV resistance and available archive samples had samples submitted for testing of phenotypic susceptibility to TMC-114 and tipranavir.
- TMC-114 was provided by Abbott to Monogram Biosciences in a blinded fashion.
- Viral susceptibility and replication capacity were determined by Monogram Biosciences using PhenoSense (Petropoulos 2000, Campbell 2003).

Results

- 18 subjects with available samples met inclusion criteria and had phenotypic resistance testing conducted (Figure 2) on samples prior to LPV/r-treatment ("baseline") and at virologic rebound during LPV/r treatment ("rebound"). No subject demonstrated 2.5 FC in LPV susceptibility between baseline and rebound without accompanying primary or secondary mutations.

Figure 2. Sample Selection



- Median TMC-114 FC was 1.4 at baseline and 2.7 at rebound, while median TPV FC was 1.9 at baseline and 1.8 at rebound (Figures 3-4).

Figure 3. Changes in Susceptibility to TMC-114 and TPV During LPV/r-Based Therapy

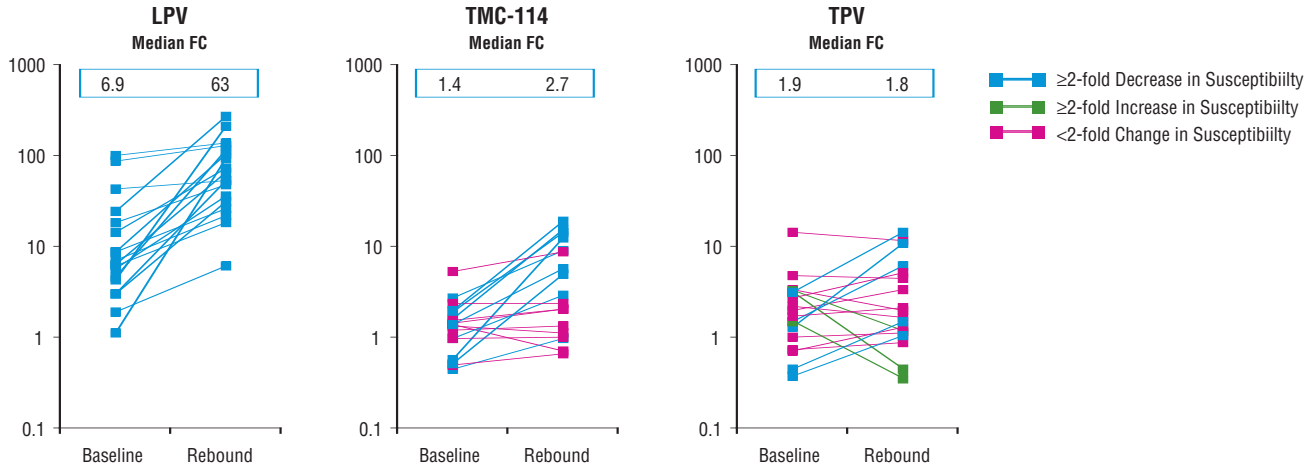
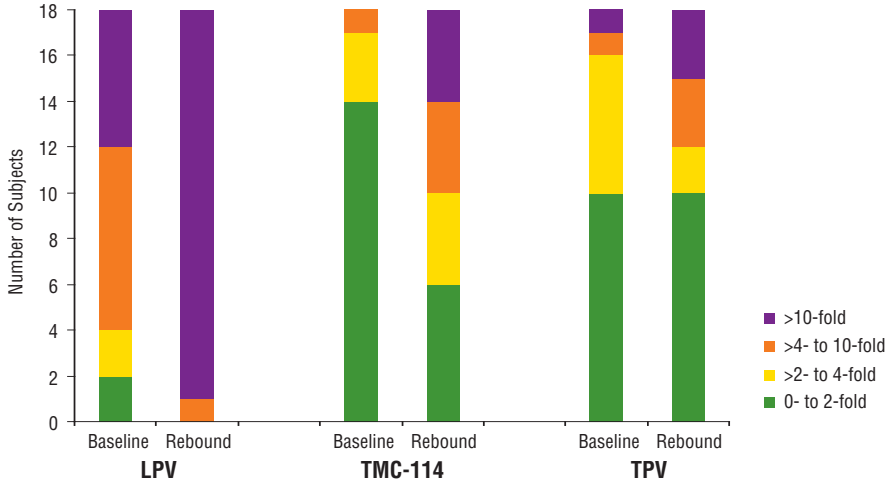


Figure 4. Susceptibility Changes by Category



- Isolates from 9 subjects demonstrated 2-fold decrease in TMC-114 susceptibility from baseline to rebound.
- Isolates from 5 subjects demonstrated 2-fold decrease, whereas isolates from 3 subjects demonstrated 2-fold increase in TPV susceptibility from baseline to rebound.

- Plasma HIV-1 RNA, genotype, and phenotype data for 3 subjects with >2-fold decrease in TPV susceptibility and rebound TPV FC >2-fold are displayed in Figures 5-7. Baseline and rebound data for the other 6 subjects with >2-fold increase in TMC-114 susceptibility are shown in Table 2.
  - Two of these 3 subjects demonstrated emergence of the L33F mutation at rebound.
  - All 3 subjects had mutations L10F/I, L90M, and either V82A or I84V at baseline, and all either had M46I and I54V mutations at baseline (n=2) or developed them at rebound (n=1).
- The emergence of an I50V mutation was observed in isolates from two subjects, with a corresponding 4- to 8-fold decreased susceptibility to TMC-114 (compared to baseline) but 3- to 4-fold *increased* susceptibility to TPV, and reductions in replication capacity of >85%. Increases in TPV susceptibility have previously been associated with the I50V mutation (Kohlbrenner 2004). Rebound isolates from the remaining subject with an increase in TPV susceptibility demonstrated emergence of mutations L24I, M46I, and F53F/L with decrease in RC of >90%.

Figure 5. Large Changes in TPV Susceptibility (Subject A)

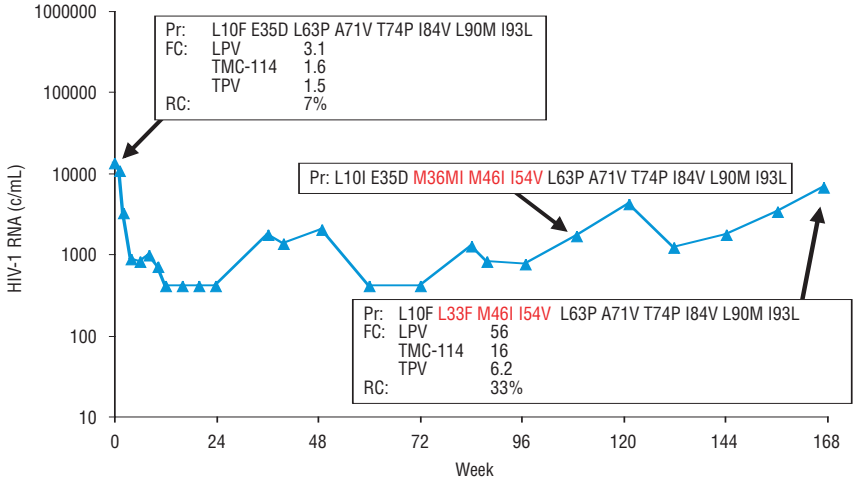


Figure 6. Large Changes in TPV Susceptibility (Subject B)

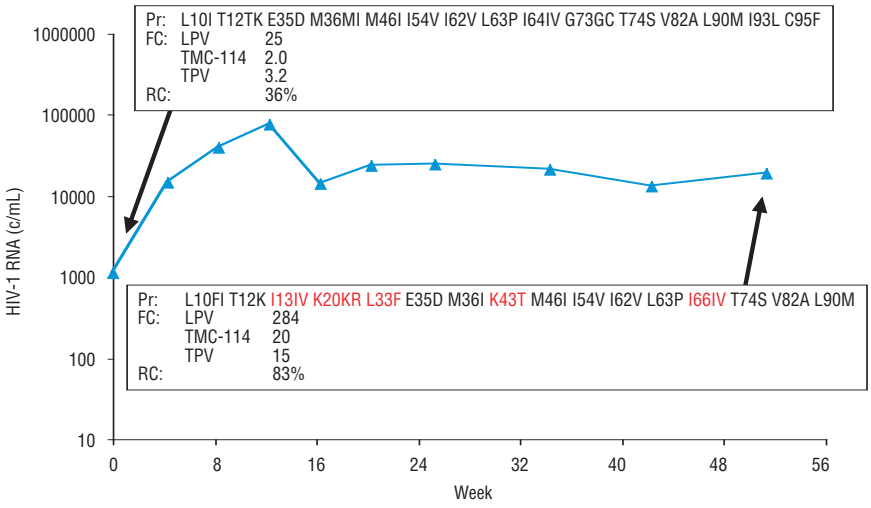
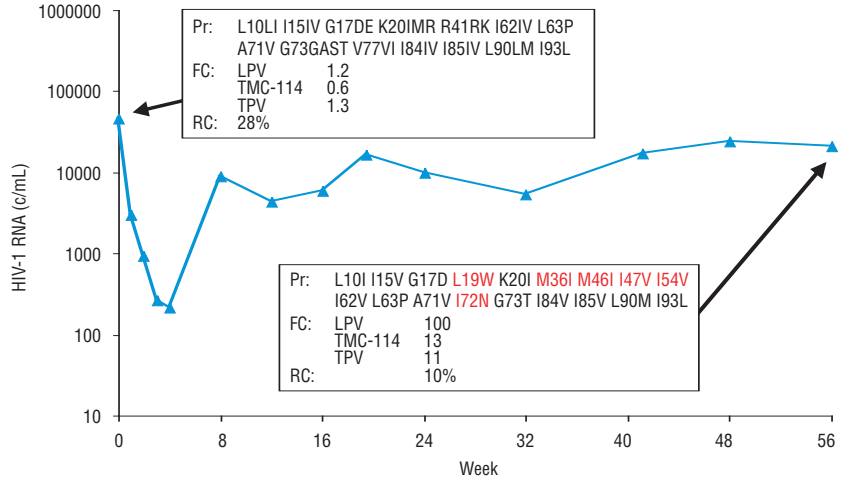


Figure 7. Large Changes in TPV Susceptibility (Subject C)



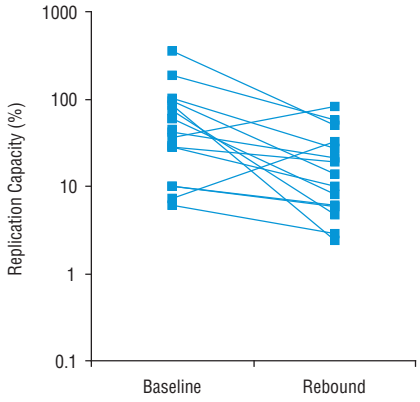
- Notably, 6 of the 9 subjects with >2-fold decreases in TMC-114 susceptibility (Figures 5–7 and Table 2) demonstrated the emergence of substitutions different from those associated with TMC-114 resistance to date (V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, I89V [de Meyer 2006]), highlighting the potential value of phenotypic resistance testing, especially for new compounds.

Table 2. Genotypic and Phenotypic Data for Subjects with >2-fold Decreases in TMC-114 Susceptibility

Subject	Visit	Replication Capacity (%)	LPV FC	TMC-114 FC	TPV FC	Protease Genotype
D	Baseline	59	9.07	2.72	2.2	L10I/V V32VI M46I I47V I62V L63P V77I Q92Q/K/R I93L C95F
	Rebound	8	109	9.32	1.66	L10I V32I M46I **I47A** I62V L63P V77I **V82V/I** Q92K I93L C95F
E	Baseline	41	4.76	0.98	1.03	L10M/I I13V Q18H S37D M46I K55R/K Q61H/Q L63P A71T I72T V77I N88S L90M I93L
	Rebound	21	123	2.98	1.12	L10I I13V **G16A** Q18H **L33F** S37D M46I **I54V** Q61H **I62V/I** L63P **A71L** I72T **L76V** V77I **V82A/V N88G** L90M I93L
F	Baseline	357	4.34	1.96	3.3	L10L/I I15V G16G/E K20R E35D M36I R41K I54I/V R57K Q61N L63L/H I64I/M K70K/R L89M L90L/M
	Rebound	427	226	15	1.18	L10V I15V G16E K20R E35D M36I R41K **M46I I50V** I54V **K55R** R57K Q61N I64I/L **A71V I72R V82A** L89I L90M **Q92K**
G	Baseline	6.1	7.34	0.44	0.75	L10L/I L24I R41K M46L I54V I62V L63P A71V T74A V77I V82A I93L
	Rebound	2.9	23	0.99	0.88	**L10L/F/I/V** L24I R41K M46L I54V I62V L63P A71V T74A V77VI V82A I93L
H	Baseline	96	91	1.4	1.52	L10I E34Q G48V I54S I62V L63P A71V I72V T74S V77I V82A I93L
	Rebound	14	134	5.81	0.35	L10I **L33L/F** E34Q **M46M/I/V** G48V **I50V** I54S I62V L63P A71V I72V T74S V77I V82A I93L
J	Baseline	9.9	3.07	0.51	0.37	V32I I47V Q61E L63P V82A I93L
	Rebound	6.1	33	5.14	1.04	**L10F** V32I **L33F M46I** I47V Q61E L63P V82A I93L

- Replication capacity decreased by a median of 64% (interquartile range: 40–86%) between baseline and rebound (n=17, Figure 8).
- Rebound isolates from 2 subjects with increases in RC both demonstrated emergence of the L33F mutation (Figures 5-6), although rebound isolates from 2 other subjects with emergence of L33F demonstrated 40-50% decreases in RC (Table 2).

Figure 8. Replication Capacity



Conclusions

- Evolution of lopinavir resistance during lopinavir/ritonavir-based treatment in protease inhibitor-experienced subjects was infrequently identified; additional resistance was observed in 8% of subjects treated for a median of 48 weeks.
- Evolution of incremental resistance to lopinavir/ritonavir generally resulted in lower replication capacity with relatively little change in susceptibility to tipranavir and modest changes in susceptibility to TMC-114 in some subjects.
- Tipranavir or TMC-114, guided by combination genotype/phenotype resistance testing, may be useful for salvage therapy following evolution of resistance on a lopinavir/ritonavir-based regimen.

References

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