

ABSTRACT

BACKGROUND: TMC114 is a potent next-generation protease inhibitor (PI), active against wild type as well as PI-resistant protease gene mutations was 15 (range 8-26) and the median number of PI resistance associated mutations was 2 (range 1-6) for the L90M group. More than 80% of subjects had more than 1 primary PI mutation. All primary PI mutations, except L10F/IRV/V, K20M/R, L241, D30N, V32L, L33F, M36I, M46L/L, I47V, G48V, I50V/L, F53L, I54V/LAM, A71V/T, G73S/A, V77I, V82A/F/T/S, I84V, N88D/S, L90M, with the primary PI mutations presented in bold.

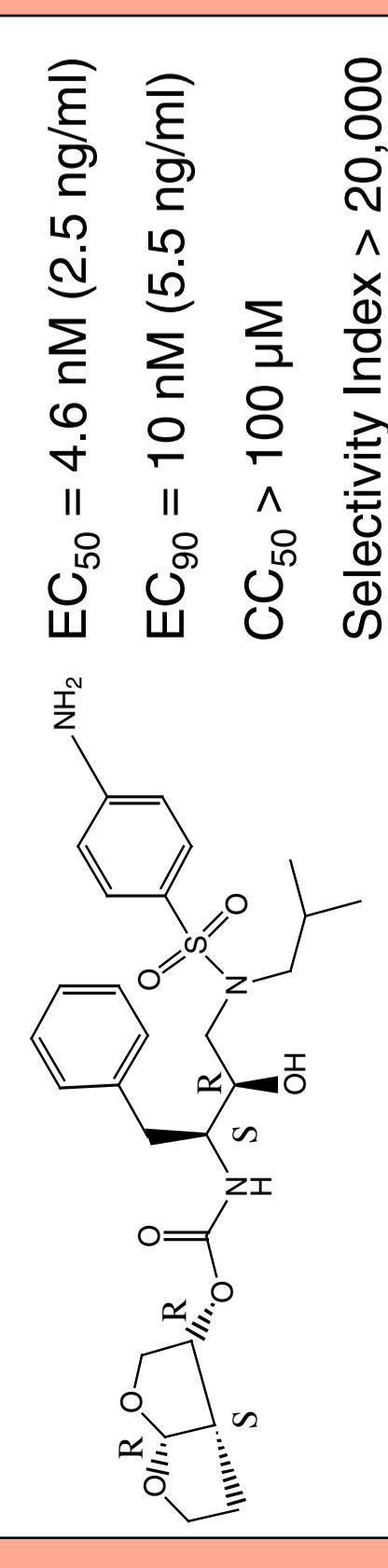
CONCLUSIONS: This study demonstrates the potent antiviral activity of TMC114, a next-generation PI, in multiple PI-experienced patients over 14 days. No mutation pattern influencing the response to treatment with TMC114 could be identified in this study.

RESULTS: Subjects in this study had a broad range of protease mutations at baseline. The median number of total protease gene mutations was 15 (range 8-26) and the median number of PI resistance associated mutations was 2 (range 1-6) for the L90M group. More than 80% of subjects had more than 1 primary PI mutation. All primary PI mutations, except L10F/IRV/V, K20M/R, L241, D30N, V32L, L33F, M36I, M46L/L, I47V, G48V, I50V/L, F53L, I54V/LAM, A71V/T, G73S/A, V77I, V82A/F/T/S, I84V, N88D/S, L90M, with the primary PI mutations presented in bold.

CONCLUSIONS: This study demonstrates the potent antiviral activity of TMC114, a next-generation PI, in multiple PI-experienced patients over 14 days. No mutation pattern influencing the response to treatment with TMC114 could be identified in this study.

INTRODUCTION

TMC114 is a next generation HIV protease inhibitor highly active against wild-type and PI resistant HIV.



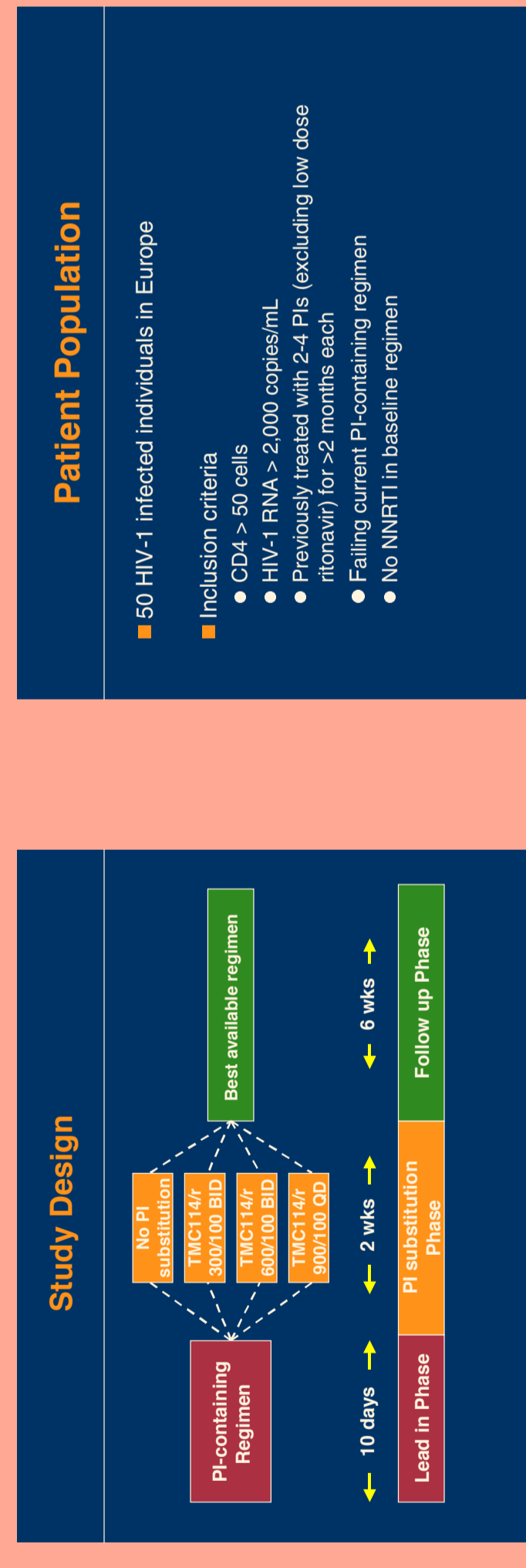
TMC114-C207 was an open, phase IIa, controlled, randomized trial to determine the antiviral activity, safety and tolerability of 14 days treatment with TMC114 boosted with low dose RTV in 50 multiple PI-experienced patients on a failing PI-containing regimen. These analyses focused on the phenotypic and genotypic resistance data of the patient samples. The influence of the baseline phenotypic and genotypic resistance on the virologic outcome was determined and phenotypic and genotypic changes between baseline and end-of-treatment were investigated.

METHODS

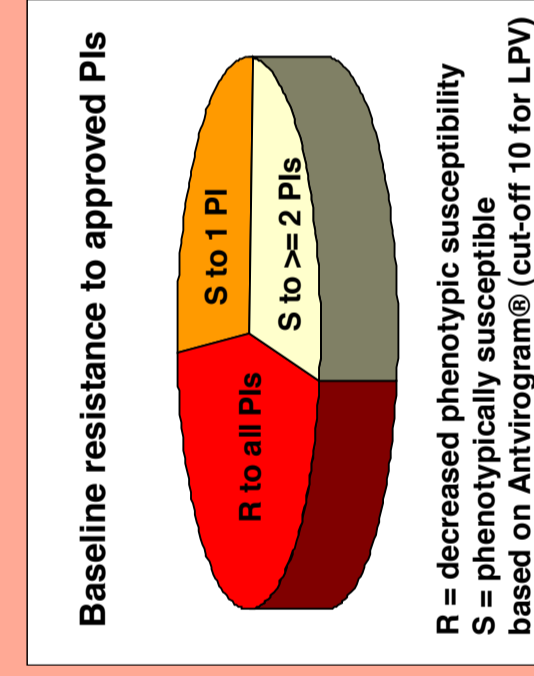
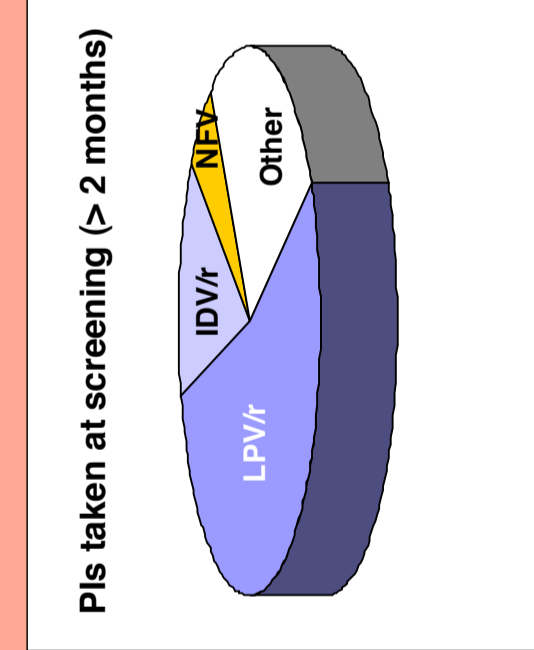
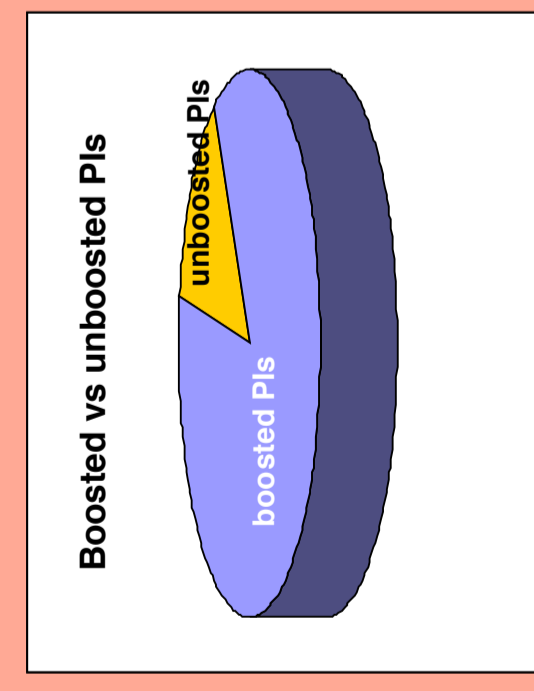
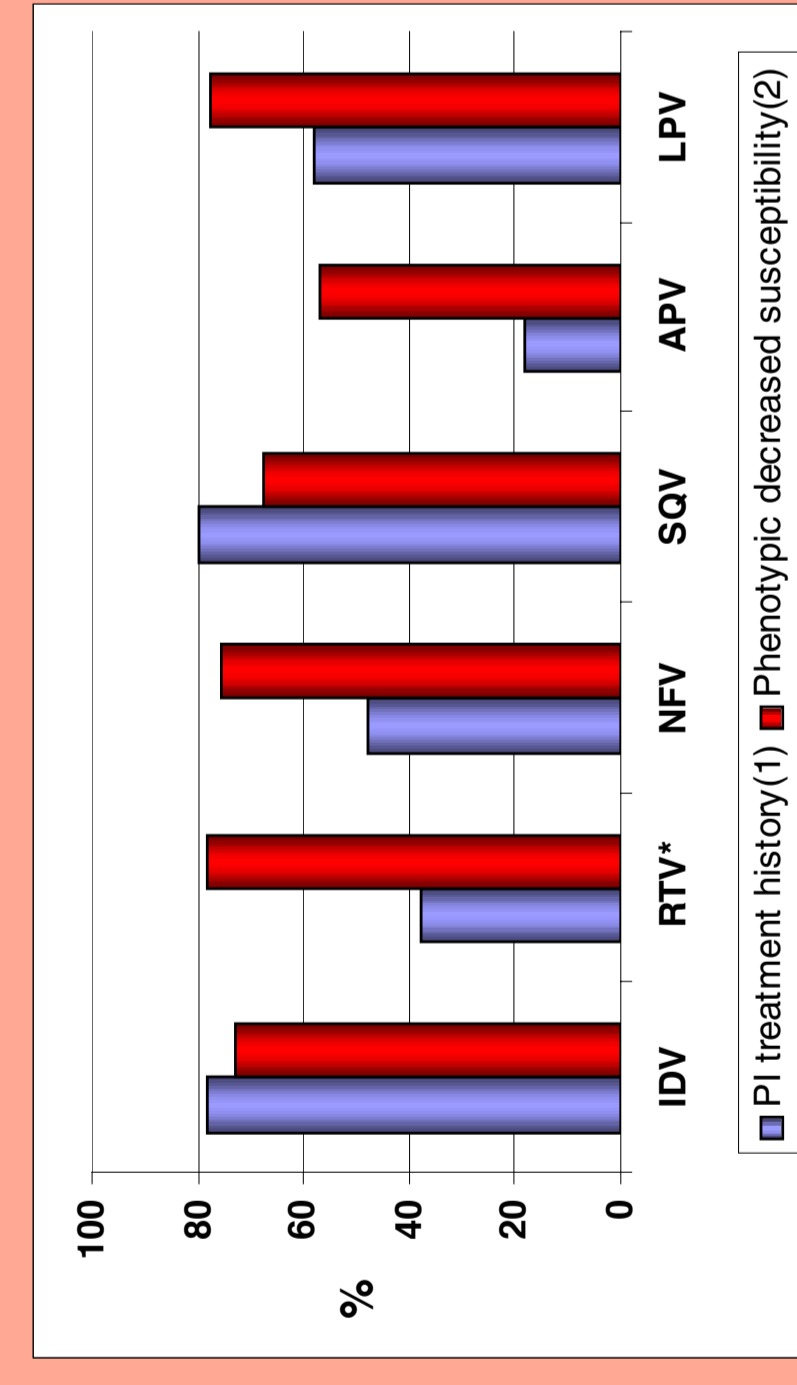
- Resistance determinations were performed on plasma samples taken at screening (within 28 days prior to treatment start), baseline (day 1), end-of-treatment (day 15) time-points and on additional time points for a selection of samples.
- Drug susceptibility profiles were determined using the Antivirogram® assay and mutational patterns were determined using *VirtualPhenotype*™.
- Analysis of individual clones was performed via endpoint dilution of cDNA of the protease and reverse transcriptase genes.
- PI resistance associated mutations were defined as L10F/IRV/V, K20M/R, L241, D30N, V32L, L33F, M36I, M46L/L, I47V, G48V, I50V/L, F53L, I54V/LAM, A71V/T, G73S/A, V77I, V82A/F/T/S, I84V, N88D/S, L90M, with the primary PI mutations presented in bold.
- Statistical methods: ANOVA models were applied to test the predictive value of geno- and phenotypes on the change in viral load. Pearson correlation was used to calculate a correlation coefficient.

CLINICAL TRIAL TMC114-C207

TMC114-C207 was an open, phase IIa, controlled, randomized trial. Fifty multiple PI-experienced subjects on a failing NRTI and PI containing regimen received TMC114 with low dose ritonavir (TMC114/r) at one of 3 doses as a substitution of their current PI or remained on their current regimen for 14 days. Afterwards, all patients switched to an investigator selected HAART regimen.



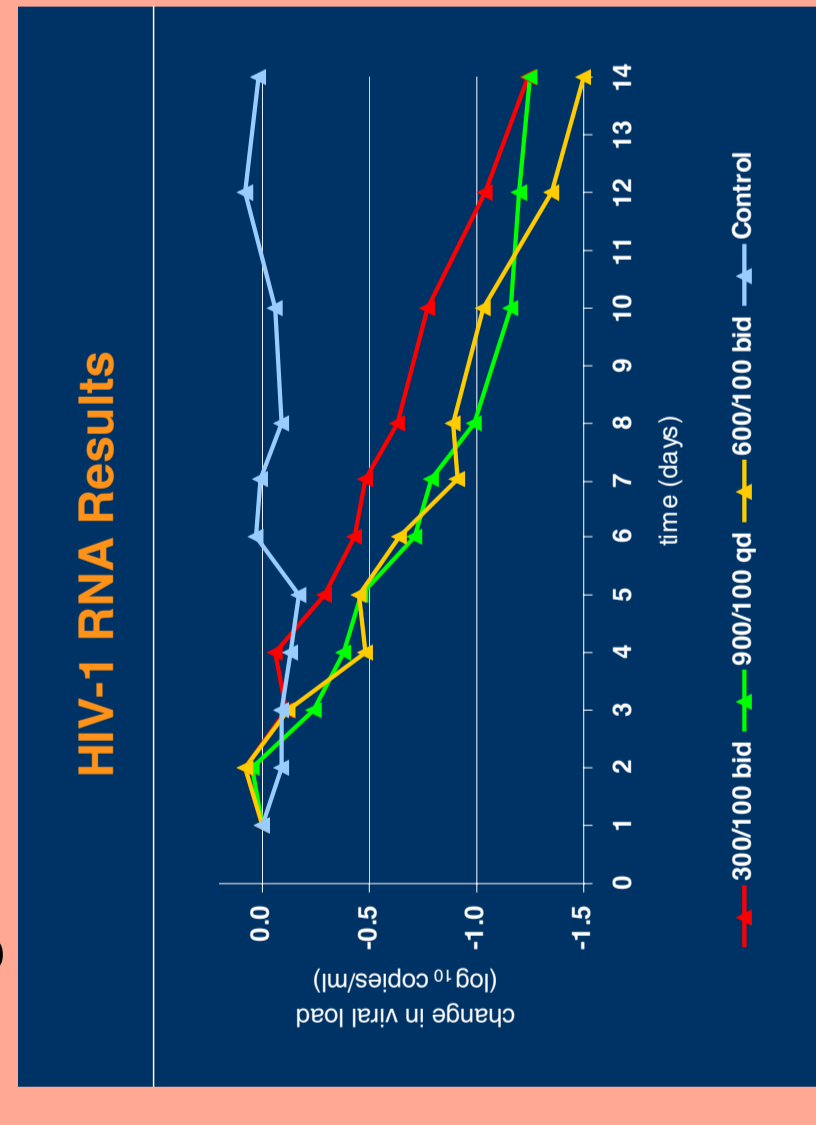
PI treatment history and resistance



Baseline viral genotype characteristics

- Primary PI mutations
 - Median = 3 (range 0-5)
 - All, except I50L and V82S present in at least 1 sample at baseline
 - > 80% of subjects had > 1 primary PI mutation at baseline
- PI resistance associated mutations
 - Median = 6 (range 1-11)
 - Total changes in protease
 - Median = 15 (range 8-26)

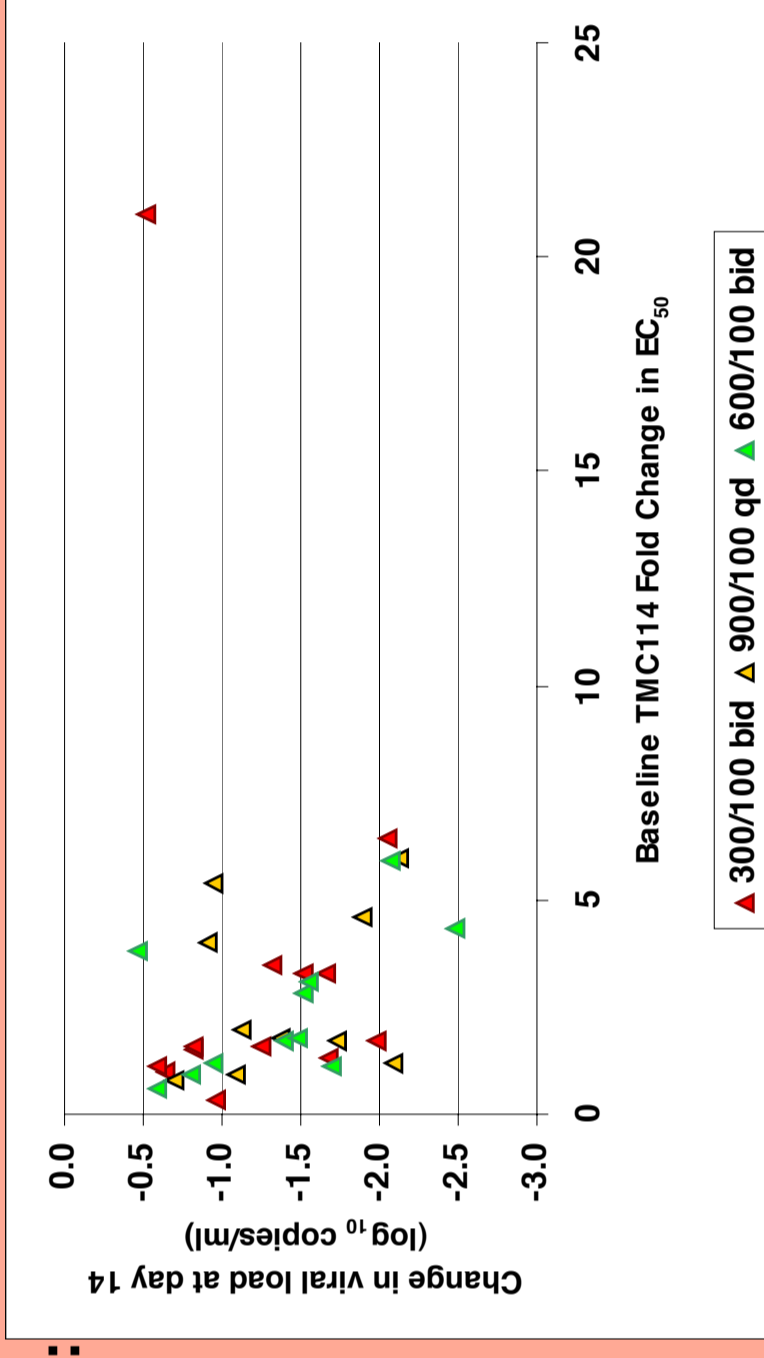
Viral load drop during treatment with TMC114/r



Overall, the median change in plasma HIV-1 RNA for the three TMC114/r groups at day 14 was -1.35 log₁₀ compared to +0.02 log₁₀ for the control group. No significant difference was observed between the 3 TMC114/r treatment arms.

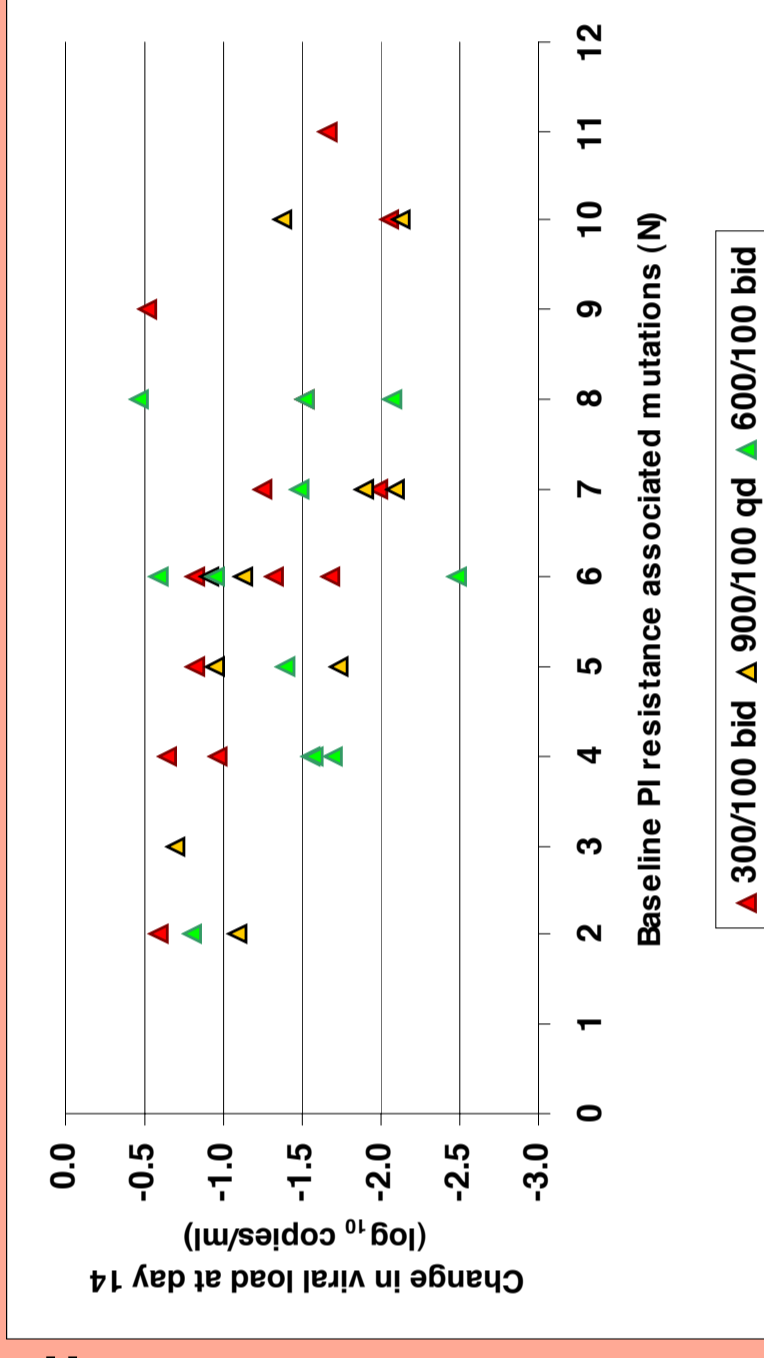
RESULTS

Influence of baseline TMC114 phenotype on virological response



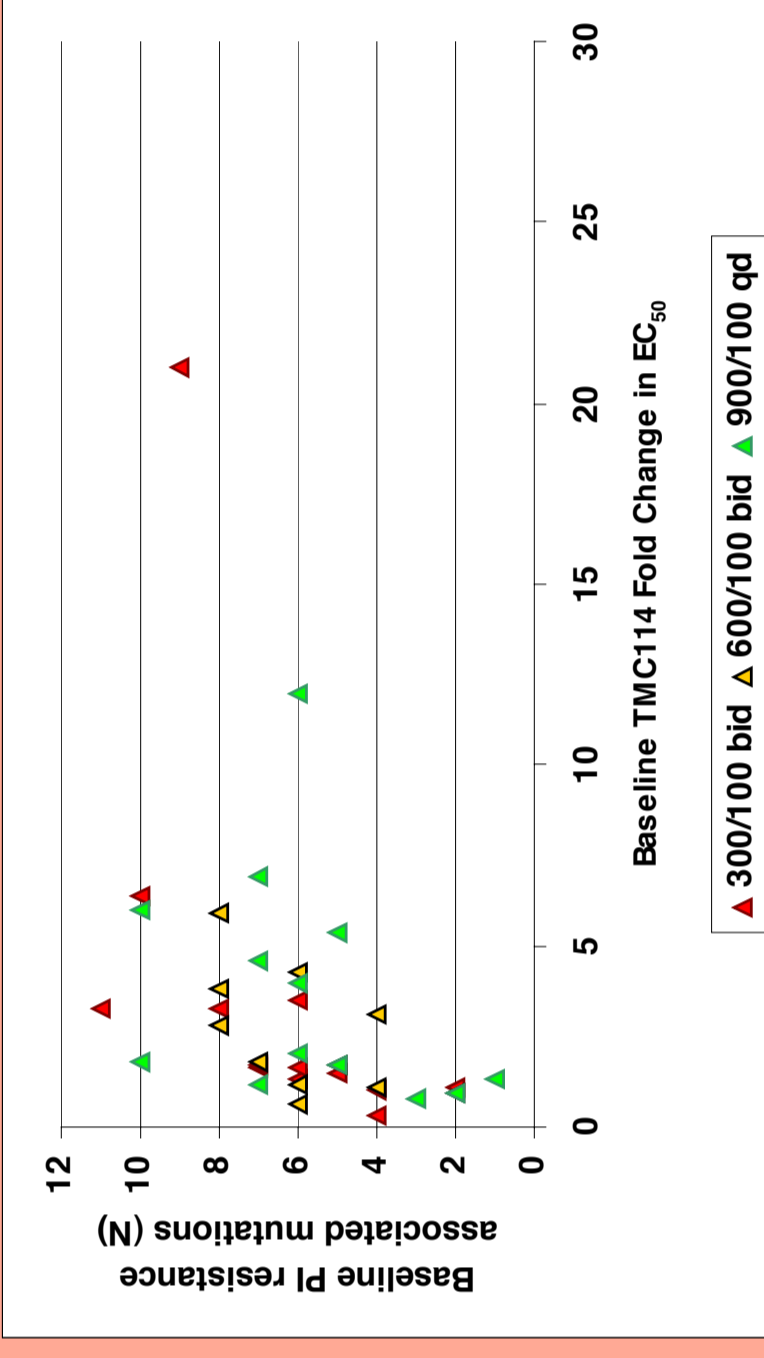
Baseline TMC114 phenotype was not predictive for the viral load change at day 14 (p=0.794). Moreover, in the integrated PK/PD analysis that is ongoing, pharmacokinetics appeared not to be a major determinant of outcome.

Influence of baseline genotype on virological response



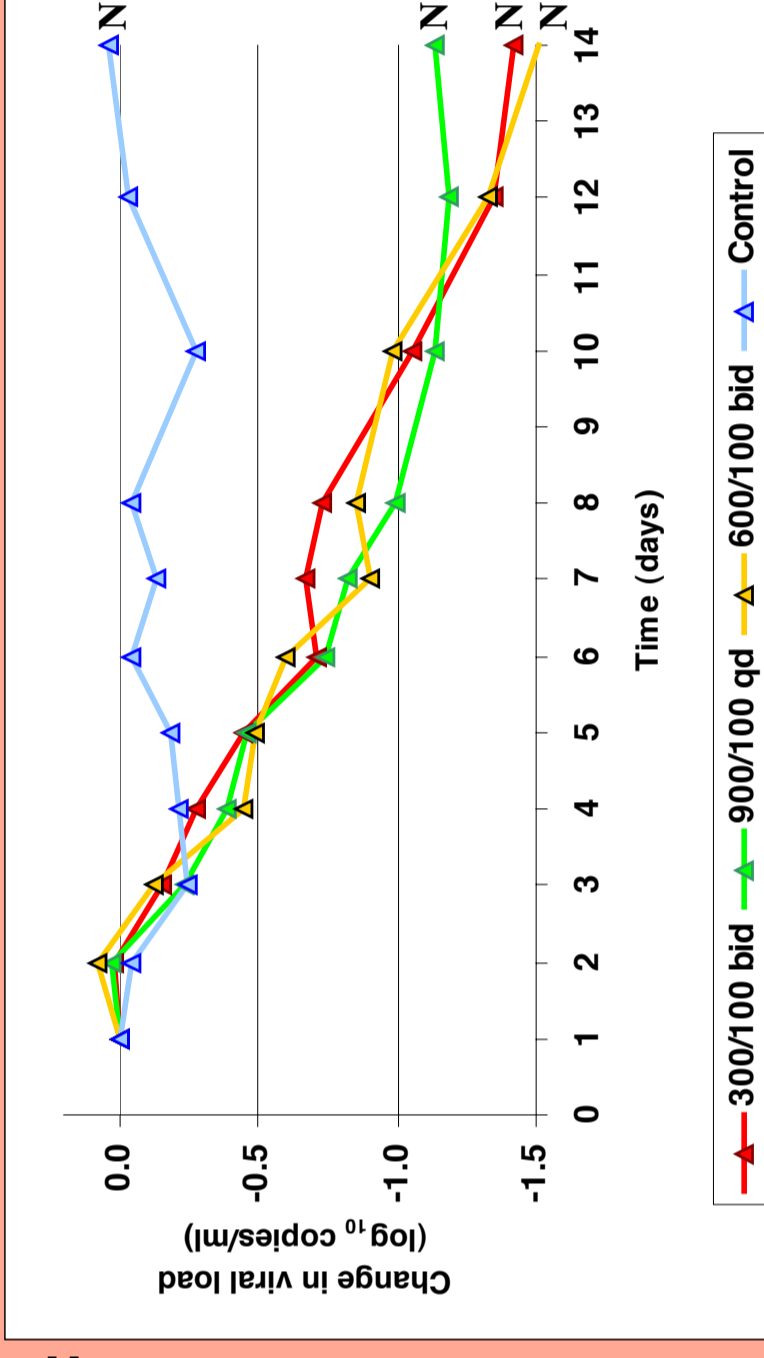
A higher number of PI resistance associated mutations at baseline was associated with a larger viral load drop at day 14 (p=0.017).

Correlation between baseline TMC114 phenotype and genotype



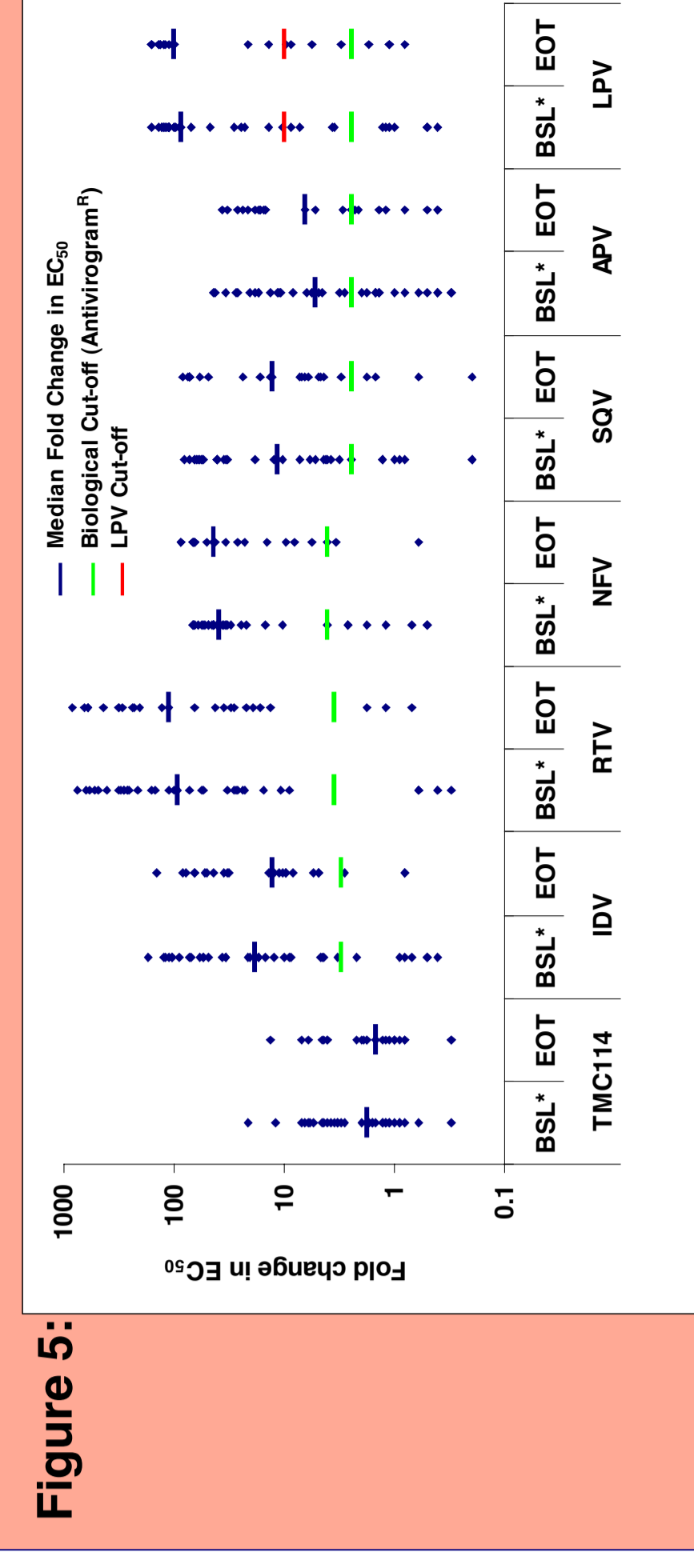
A correlation coefficient of 34% was found between baseline TMC114 fold change in EC₅₀ and number of baseline PI resistance associated mutations.

Viral load drop during treatment with TMC114/r of patients previously on a Kaletra failing regimen



The majority of patients entering the study (54%) were on a Kaletra containing failing regimen. The clinical outcome of this subgroup was analysed. Figure 4 shows that there is no difference between this subgroup and the entire study population.

Comparison of phenotypes from baseline and end-of-treatment



* baseline imputed values with screening values if no baseline values available
 • No significant differences between median fold changes in EC₅₀ of TMC114 or any of the approved PIs from baseline (BSL) and end-of-treatment (EOT) were found.

Comparison of genotypes from baseline and end-of-treatment

- Many genotypic changes were found between screening, baseline and end-of-treatment in the control as well as in the TMC114 groups.
- In 2 subjects primary PI mutations appeared after TMC114 treatment: V77V/I and I84V/I in subject T2070060 (300/100 bid, VL drop = -0.58 log₁₀ at day 14) and L90M in subject T2070037 (600/100 bid, VL drop = -2.49 log₁₀ at day 14).
- Genotypic analysis of all available plasma samples of subject T2070060, showed that L90L/M was also detected at day 3 (Figure 6). Moreover, L90M was detected in 2/29 individual clones of the screening sample (data not shown).
- Genotypic analysis of all available plasma samples of subject T2070037, showed that I84V/I was detected at day 14 and 15, but no longer in the follow up samples (Figure 7). Further analysis of individual clones is ongoing.

Figure 6: Subject T2070060 PI resistance associated mutations

Subject ID	Sample	PI resistance associated mutations		
		Screening	Baseline	End of Treatment
T2070060	Visit, Day 7	L10I, N88I	L10I, N88I	L10I, N88I
T2070060	Visit, Baseline	L10I, N88I	L10I, N88I	L10I, N88I
T2070060	Visit, Day 3	L10I, N88I	L10I, N88I	L10I, N88I, V77V, I84V
T2070060	Visit, Day 7	L10I, N88I	L10I, N88I	L10I, N88I, V77V, I84V
T2070060	Visit, Day 14	L10I, N88I	L10I, N88I	L10I, N88I, V77V, I84V, L90M
T2070060	Visit, Day 15	L10I, N88I	L10I, N88I	L10I, N88I, V77V, I84V, L90M
T2070060	Visit, Week 4	L10I, N88I	L10I, N88I	L10I, N88I, V77V, I84V, L90M
T2070060	Visit, Week 5	L10I, N88I	L10I, N88I	L10I, N88I, V77V, I84V, L90M

Figure 7: Subject T2070037 PI resistance associated mutations

Subject ID	Sample	PI resistance associated mutations		
		Screening	Baseline	End of Treatment
T2070037	Visit, Day 7	L10I, N88I	L10I, N88I	L10I, N88I
T2070037	Visit, Baseline	L10I, N88I	L10I, N88I	L10I, N88I
T2070037	Visit, Day 3	L10I, N88I	L10I, N88I	L10I, N88I
T2070037	Visit, Day 7	L10I, N88I	L10I, N88I	L10I, N88I
T2070037	Visit, Day 14	L10I, N88I	L10I, N88I	L10I, N88I, I84V, V82A
T2070037	Visit, Day 15	L10I, N88I	L10I, N88I	L10I, N88I, I84V, V82A
T2070037	Visit, Week 4	L10I, N88I	L10I, N88I	L10I, N88I, I84V, V82A
T2070037	Visit, Week 5	L10I, N88I	L10I, N88I	L10I, N88I, I84V, V82A

CONCLUSIONS

- TMC114 is effective in suppressing resistant HIV strains over 14 days in multiple PI-experienced patients failing on a PI-containing regimen.
- TMC114 susceptibility at baseline was not predictive for the virologic response in this group of patients.
- No mutation pattern(s) influencing the virologic response could be detected in this study.
- Larger and longer (phase II and III) studies will be used to further unravel the resistance pattern of TMC114.