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Impact of baseline NNRTI mutations on the virological response to TMC125 (etravirine; ETR) in the DUET-I and DUET-2 Phase III clinical trials

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Abstract

Background: TMC125 is a next-generation NNRTI, active against wild-type and NNRTI-resistant HIV-1, with a high genetic barrier to the development of resistance. Here, we identified baseline genotypic determinants of decreased virological response to TMC125 in the Phase III, double-blind, placebo-controlled DUET trials.

Methods: Effect of baseline genotype on virological response (<50 HIV-1 RNA copies/mL) to TMC125 at Week 24 was studied in patients not using enfuvirtide de novo, and excluding discontinuations for reasons other than virological failure (n=406). Decreased virological response was defined as a response that was at least 25% lower than that of the subgroup of patients without detectable NNRTI resistance-associated mutations (RAMs) at baseline. We studied 44 baseline reverse transcriptase (RT) mutations, but only analysed those present in ≥5 patients.

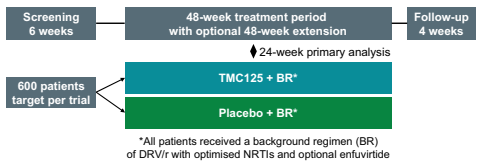
Results: The following RT mutations were associated with decreased virological response to TMC125 (TMC125 RAMs): V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S. Isolates with A98G, K101E, V179F, Y181C or G190A had more NNRTI RAMs than isolates without these mutations. V179F was never present without Y181C. V179F, Y181V and G190S had the largest impact on response, but were present in <5% of patients. Virological response decreased with increasing numbers of TMC125 RAMs. The largest decrease was in the subgroup of patients with ≥3 TMC125 RAMs at baseline. The virological response in patients who had Y181C without other TMC125 RAMs (but with other NNRTI RAMs) was comparable to that in patients without detectable NNRTI mutations; a decreased virological response was observed only in the subgroup of patients with Y181C plus two or more TMC125 RAMs.

Conclusions: Thirteen mutations, mainly occurring with other NNRTI RAMs, were associated with a decreased response to TMC125. The decrease was a function of the number of baseline TMC125 RAMs, with the largest impact in the subgroup of patients with ≥3 TMC125 RAMs.

Objectives

- To identify the baseline genotypic determinants of decreased virological response to TMC125, in the Phase III DUET-1 and DUET-2 trials (pooled data)
- To provide guidance in the interpretation of genotypic resistance information related to TMC125

DUET study design and major inclusion criteria



*All patients received a background regimen (BR) of DRV/r with optimised NRTIs and optional enfuvirtide

- DUET-1 and DUET-2 differed only in geographical location; pooled analysis was pre-specified
- Major inclusion criteria
  - plasma viral load >5,000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
  - ≥1 NNRTI RAMs,‡ at screening or in documented historical genotype
  - ≥3 primary PI RAMs at screening
- Patients recruited from Thailand, Australia, Europe and the Americas

‡From extended list of NNRTI RAMs (Tambuyzer L, et al. EHDRW 2007. Abstract 67); DRV/r = darunavir with low-dose ritonavir

Methods

- Effect of baseline genotype on the virological response to TMC125 was studied in the subgroup of patients not using enfuvirtide as a new drug, and excluding patients who discontinued for other reasons than virological failure (n=406)
- Virological responses in this Week 24 analysis are presented as the proportion of patients who achieved confirmed viral load <50 HIV-1 RNA copies/mL
- Decreased virological response was defined as a response that was at least 25% lower than that of the subgroup of patients without detectable NNRTI RAMs at baseline (n=52). These patients had NNRTI mutations from previous genotype
- RT mutations were included in the analysis if they were present at baseline in five or more patients

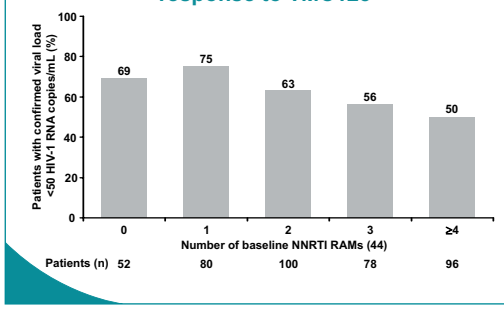
Total list of NNRTI RAMs (n=44)

V90I	A98G	L100I	K101E	K101P	K101Q	K103H	K103N	K103S
K103T	V106A	**V106I**	V106M	V108I	E138G	E138K	E138Q	V179D
V179E	V179F	V179G	V179I	Y181C	Y181I	Y181V	Y188C	Y188H
Y188L	V189I	G190A	G190C	G190E	G190Q	G190S	H221Y	P225H
F227C	F227L	M230I	M230L	P236L	K238N	K238T	Y318F	

14 NNRTI RAMs listed by IAS-USA[1]
27 Additional mutations found to be associated with resistance to NNRTIs[2,3]
3 Additional mutations associated with increased TMC125 fold-change, identified by linear regression analysis of recombinant clinical isolates
44 NNRTI RAMs in total

[1]Johnson M, et al. Topics in HIV Med 2006;14:125–130; [2]Tambuyzer L, et al. EHDRW 2007. Abstract 67; [3]Rimsky L, et al. IHDRW 2007. Abstract 63

The number of total baseline NNRTI RAMs (n=44) is not a good predictor of virological response to TMC125



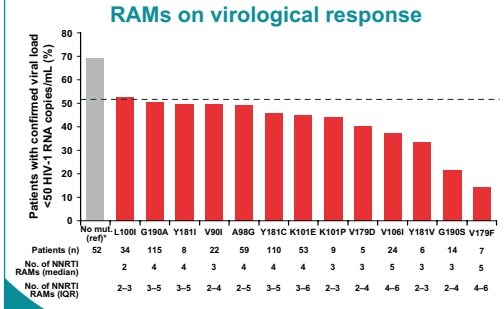
Identification of the TMC125 RAMs

V90I	A98G	L100I	K101E	K101P	K101Q		K103N	K103S
		V106I		V108I			E138Q	V179D
	V179F		V179I	Y181C	Y181I	Y181V		
Y188L	V189I	G190A				G190S	H221Y	P225H
	F227L					K238T	Y318F	

TMC125 RAMs Non-TMC125 RAMs

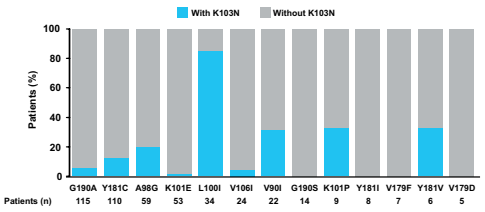
- 44 NNRTI RAMs were studied
- 26 NNRTI RAMs were present in ≥5 patients
- 13 TMC125 RAMs were identified at baseline to have a significant impact on virological response

The effect of baseline TMC125 RAMs on virological response



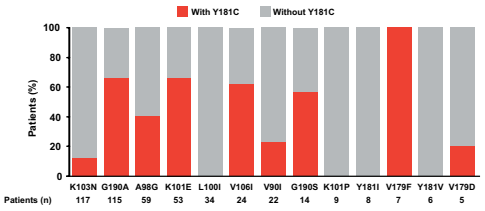
*No detectable baseline NNRTI RAMs from the list of 44; the 13 TMC125 RAMs are represented by red bars; IQR = interquartile range

Proportion of patients with K103N in the presence of specific TMC125 RAMs



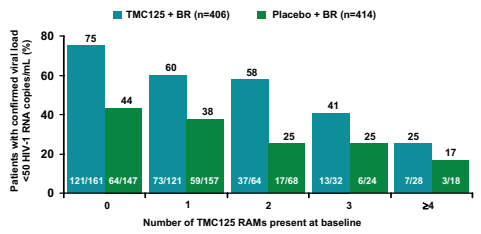
- L100I frequently occurred together with K103N
- The other TMC125 RAMs did not frequently occur together with K103N

Proportion of patients with Y181C in the presence of K103N or specific TMC125 RAMs



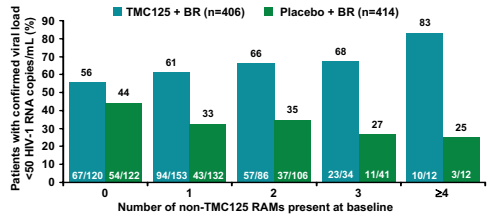
- G190A, K101E, V106I, G190S frequently occurred together with Y181C
- V179F always occurred together with Y181C
- K103N (which is not a TMC125 RAM) did not frequently occur together with Y181C

The number of baseline TMC125 RAMs correlated with the virological response (<50 copies/mL) to TMC125



Analysis excludes patients who used de-novo enfuvirtide or discontinued except for virological failure

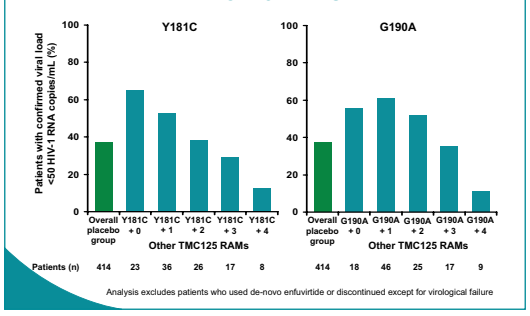
The number of baseline *non*-TMC125 RAMs did not correlate with the virological response (<50 copies /mL) to TMC125



- The non-TMC125 RAMs (n=13) are the NNRTI RAMs that were not identified to have an impact on response

Analysis excludes patients who used de-novo enfuvirtide or discontinued except for virological failure

Decreased virological response is only observed with multiple concomitant TMC125 RAMs



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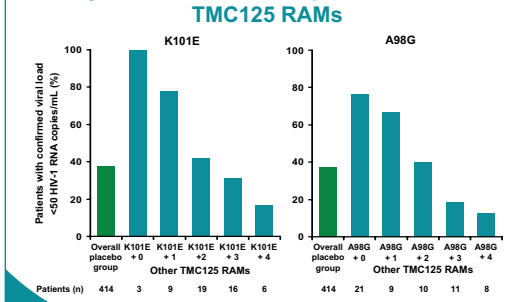
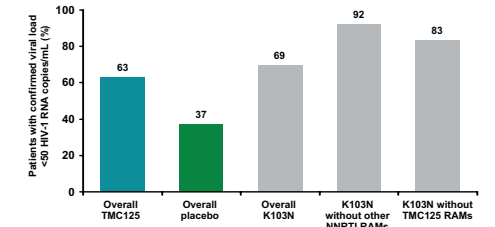


Analysis excludes patients who used de-novo enfuvirtide or discontinued except for virological failure

The presence of K103N was not associated with decreased virological response



Analysis excludes patients who used de-novo enfuvirtide or discontinued except for virological failure; K103N was the most prevalent NNRTI RAM in DUET

Conclusions

- Analysis of the pooled DUET data indicated that TMC125 has a unique resistance profile
  - no single mutation was identified to have a significant impact on virological response to TMC125
  - thirteen baseline RT mutations were associated with decreased virological response to TMC125 (TMC125 RAMs): V90I, A98G, L100I, K101E/P, V106I, V179D/F, Y181C/I/V and G190A/S.
- The majority of patients (86%) had <3 TMC125 RAMs, and these patients experienced the greatest benefit with TMC125 treatment.
- An increased number of baseline TMC125 RAMs was associated with a decreased virological response to TMC125.
- A high proportion of patients with K103N at baseline achieved a virological response (<50 copies/mL).
- These data provide guidance in the interpretation of genotypic resistance data related to TMC125.

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