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The impact of background regimen on virologic response to etravirine: pooled 48-week analysis of DUET-1 and DUET-2

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Abstract

Background
DUET-1 and DUET-2 are ongoing, Phase III, randomized, double-blind, placebo-controlled trials investigating the efficacy, safety and tolerability of the next-generation NNRTI etravirine (ETR; TMC125) in HIV-infected, treatment-experienced patients.

Methods
Patients with documented NNRTI resistance, ≥3 primary protease inhibitor (PI) mutations and viral load >5000 copies/mL were randomized 1:1 to receive ETR 200mg bid or placebo bid with a background regimen (BR) consisting of darunavir with low-dose ritonavir (DRV/r), optimized NRTI(s) and optional enfuvirtide (ENF). The primary endpoint was the percentage of patients with a confirmed viral load <50 copies/mL. Baseline antiretroviral (ARV) sensitivity was determined by phenotypic sensitivity score (PSS). Subgroup analyses were conducted on the pooled DUET trial data to determine the impact of the BR on virologic response to ETR.

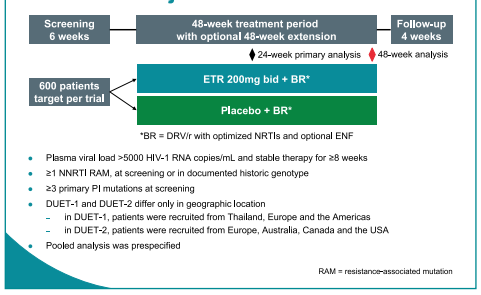
Results
ETR or placebo were administered to 599 and 604 patients, respectively. Baseline characteristics were comparable between the ETR and placebo groups with regards to median baseline viral load (both 4.8 $\log_{10}$ copies/mL), CD4 cell count (99 cells/mm^3 vs 109 cells/mm^3), overall ENF use (45.4% vs 46.7%), DRV sensitivity, NRTI sensitivity and median number of sensitive ARVs at baseline. The impact of the BR on virologic response is shown in the table.

	Responders (<50 copies/mL at Week 48), %			
	ETR + BR (n=599)	Placebo + BR (n=604)	Difference vs placebo group	p value
Effect of ENF sensitivity*				
Reuse or no use of ENF	57	33	24	<0.0001
De-novo ENF	71	58	13	0.0116
Effect of DRV sensitivity‡				
FC ≤10	74	58	16	<0.0001
10 < FC ≤40	63	28	35	<0.0001
FC >40	40	2	39	<0.0001
Effect of NRTI sensitivity				
0 sensitive NRTI	63	34	29	<0.0001
1 sensitive NRTI	70	52	18	<0.0001
≥2 sensitive NRTIs	76	66	10	0.1188
Effect of PSS				
0 sensitive ARV	46	6	40	<0.0001
1 sensitive ARV	63	32	31	<0.0001
≥2 sensitive ARVs	78	67	11	0.0022

ENF, DRV and NRTI sensitivity and PSS were significant predictors of response in both treatment groups.
p values derived from logistic regression model
*ENF was classed as sensitive if it had not been previously used; ‡DRV was classified as sensitive if a FC ≤10 was observed; FC = fold change

Conclusions
In general, the proportion of responders in each group increased with increasing numbers of sensitive ARVs in the BR. However, a significantly greater number of patients in the ETR group achieved an undetectable viral load (<50 copies/mL) compared with the placebo group at 48 weeks, irrespective of BR.

DUET study design and major inclusion criteria



Patient and disease baseline demographics

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Patient demographics		
Male, %	90	89
Caucasian, %	70	70
Disease characteristics		
Viral load, $\log_{10}$ copies/mL (median, range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
CD4 cells, cells/mL (median, range)	99 (1–789)	109 (0–912)
CDC category C, %	58	59
Prior ARV use		
NNRTIs used in screening period, %	12	12
10–15 ARVs, %	66	65
DRV/r, %	4	5
Detectable mutations		
≥2 NNRTI RAMs,[1] %	69	69
≥3 primary PI RAMs,[2] %	97	97

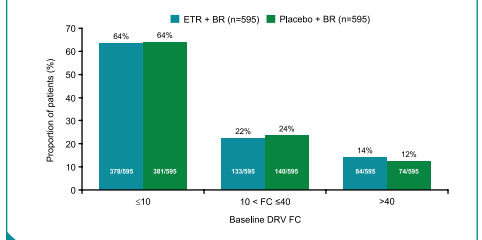
[1]Extended NNRTI RAM list. Tambuyzer L, et al. EHDRW 2007. Abstract 67
[2]Johnson M, et al. Top HIV Med 2005;13:125–31

ENF use prior to and during the DUET trials

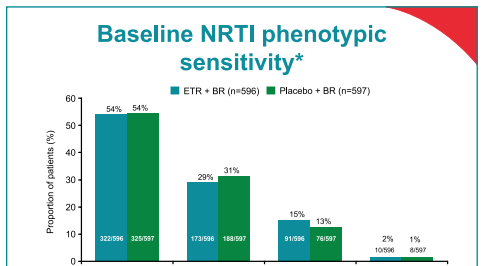
Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Previous ENF use, %		
Used ENF previously	40	42
Used ENF in screening period	18	21
ENF use during DUET treatment period, %	**45**	**47**
Used ENF *de novo*	26	26
Reused ENF	20	20
ENF not used during DUET treatment period, %	**55**	**53**
Discontinued ENF during DUET treatment period, %*	**18**	**21**
ENF *de novo*	14	18
Reused ENF	22	25

*In the case of tolerability problems, ENF could be discontinued or replaced by a NRTI

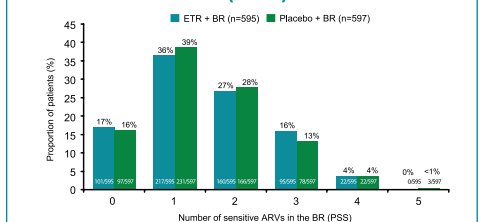
Baseline DRV sensitivity*



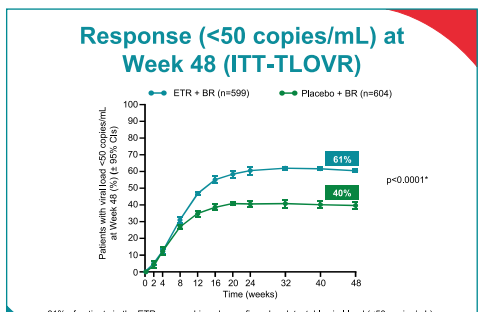
Baseline NRTI phenotypic sensitivity*



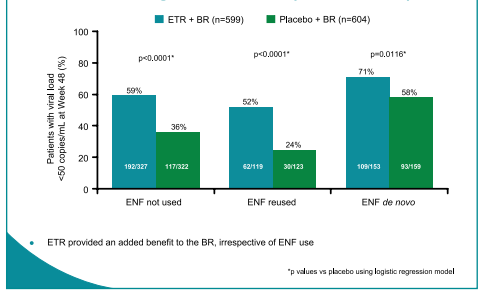
Number of sensitive ARVs in the BR (PSS)*



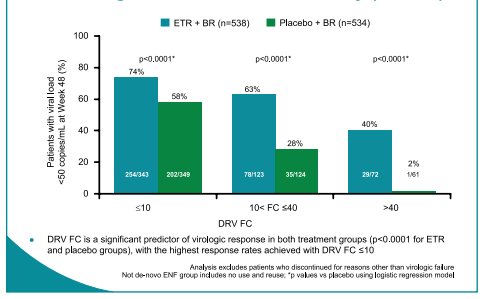
Response (<50 copies/mL) at Week 48 (ITT-TLOVR)



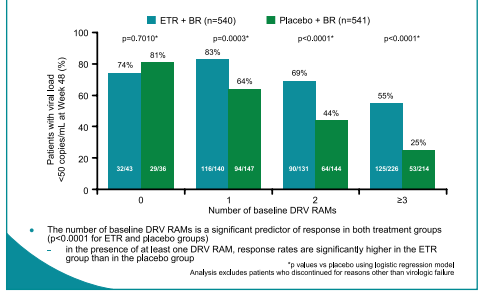
Response (<50 copies/mL) at Week 48 according to ENF use (ITT-TLOVR)



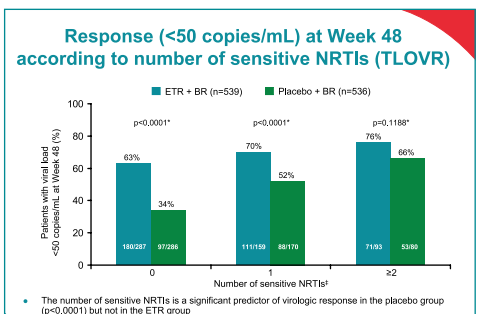
Response (<50 copies/mL) at Week 48 according to baseline DRV sensitivity (TLOVR)



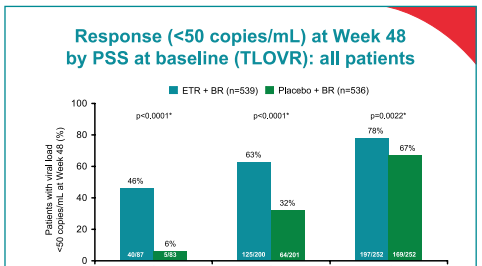
Response (<50 copies/mL) at Week 48 according to baseline DRV RAMs (TLOVR)



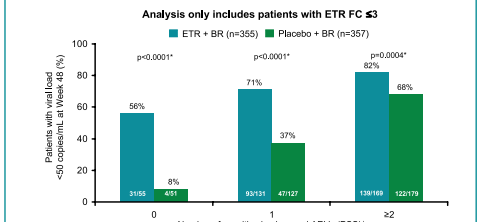
Response (<50 copies/mL) at Week 48 according to baseline DRV FC (TLOVR)



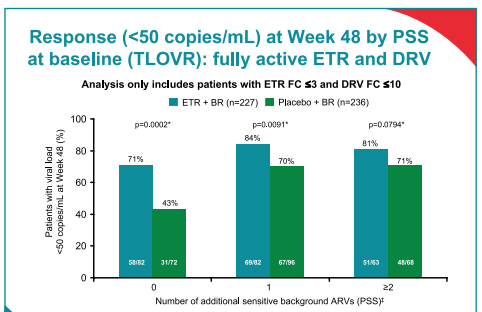
Response (<50 copies/mL) at Week 48 by PSS at baseline (TLOVR): all patients



Response (<50 copies/mL) at Week 48 by PSS at baseline (TLOVR): fully active ETR



Response (<50 copies/mL) at Week 48 by PSS at baseline (TLOVR): fully active ETR and DRV



Conclusions

- Superior virologic responses were achieved with ETR + BR versus placebo + BR, irrespective of ENF use, DRV FC and NRTI sensitivity, baseline DRV RAMs and PSS.
- The 82% response rate in patients with PSS ≥2 is comparable with the expected response rate from treatment-naïve patients when ETR FC ≤3.
- Even when given with no active drugs, ETR produced a significant virologic response compared with placebo.
- In line with treatment guidelines, at least two active ARVs should be used in ARV regimens.

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DUET-1

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DUET-2

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