TUPE0047

48-week pooled analysis of DUET-1 and DUET-2: the impact of baseline characteristics on virologic response to etravirine

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Abstract

Background
Pooled 48-week analysis from the ongoing, randomized, double-blind, placebo-controlled DUET-1 and DUET-2 Phase III trials demonstrated the efficacy and safety of etravirine (ETR; TMC125) in treatment-experienced patients.

Methods
Treatment-experienced 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 or placebo bid plus background regimen (BR; darunavir with low-dose ritonavir [DRV/r], optimized NRTI[s] ± enfuvirtide [ENF]). The primary endpoint was the percentage of patients with confirmed viral load <50 copies/mL (intent-to-treat [ITT] population; time-to-loss of virologic response [TLOVR] algorithm). Subgroup analyses assessed the effect of baseline characteristics on response to ETR.

Results
One thousand, two hundred and three patients were included in the pooled analysis: 599 and 604 patients in the ETR and placebo groups, respectively. Baseline characteristics and demographics were comparable between treatment groups: male (90% vs 89%), median age (46 vs 45 years), Caucasian (70% vs 70%), viral load (both 4.8 $\log_{10}$ c/mL), CD4 cell count (99 cells/mm^3 vs 109 cells/mm^3), hepatitis B and/or C coinfection (13% vs 12%), and previous NNRTI use (92% vs 92%). The impact of baseline characteristics on virologic response is shown below.

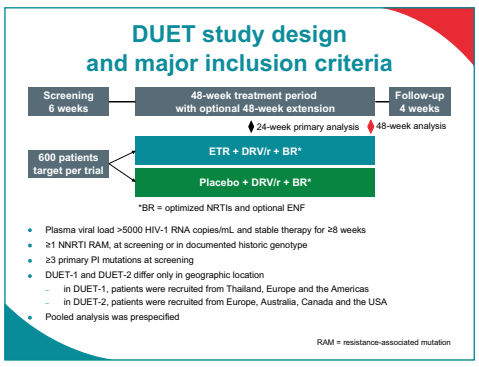
	Responders (<50 copies/mL at Week 48), % (patient numbers)			
	ETR + BR (n=599)	Placebo + BR (n=604)	Difference vs placebo group	p value
Effect by patient demographics				
Race				
Black	53 (37/70)	34 (24/70)	19	0.0150
Caucasian	61 (228/373)	41 (156/376)	20	<0.0001
Hispanic	57 (34/60)	36 (24/66)	20	0.0118
Effect of disease characteristics				
*Viral load				
<30 000c/mL	76 (125/165)	56 (97/174)	20	<0.0001
30 000–100 000c/mL	61 (126/206)	39 (82/213)	23	<0.0001
>100 000c/mL	49 (112/228)	28 (61/217)	21	<0.0001
*CD4 cell count				
<50 cells/mm^3	45 (96/213)	22 (45/209)	24	<0.0001
50–200 cells/mm^3	65 (136/208)	48 (99/208)	18	0.0002
200–350 cells/mm^3	74 (88/119)	52 (65/125)	22	0.0001
≥350 cells/mm^3	72 (42/58)	51 (31/61)	22	0.0061
Hepatitis B and/or C coinfection				
Negative	61 (304/495)	38 (190/495)	23	<0.0001
Positive	60 (43/72)	51 (34/67)	9	0.3028
***Effect of ENF use**				
ENF not used	59 (192/327)	36 (117/322)	22	<0.0001
ENF reused	52 (62/119)	24 (30/123)	28	<0.0001
ENF used *de novo*	71 (109/153)	58 (93/159)	13	0.0116

*Significant predictors of response in both treatment groups; p values derived from logistic regression model

The proportion of responders was also greater in the ETR versus placebo group when analyzed by gender, age, region, or previous NNRTI use.

Conclusions
At Week 48, consistently more patients in the ETR group achieved undetectable viral load <50 copies/mL than in the placebo group, irrespective of baseline characteristics. Baseline viral load, CD4 cell count and ENF were significant predictors of response in both treatment groups.

DUET study design and major inclusion criteria



*BR = optimized NRTIs and optional ENF

- Plasma viral load >5000 HIV-1 RNA copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historic genotype
- ≥3 primary PI mutations at screening
- DUET-1 and DUET-2 differ only in geographic location
  - in DUET-1, patients were recruited from Thailand, Europe and the Americas
  - in DUET-2, patients were recruited from Europe, Australia, Canada and the USA
- Pooled analysis was prespecified

RAM = resistance-associated mutation

Baseline demographics and background ARVs

Parameter, %	ETR + BR (n=599)	Placebo + BR (n=604)
Gender		
Male	90	89
Race		
Caucasian	70	70
Black	13	13
Hispanic	11	12
Prior ARV use		
Number of ARVs previously taken (median)	12	13
DRV/r	4	5
Previously used NVP	57	59
Previously used EFV	70	72
Detectable mutations		
≥2 NNRTI RAMs*	69	69
≥3 primary PI RAMs‡	97	97
BR		
Used ENF (total)	46	47
Reused ENF	20	20
Used ENF *de novo*	26	26
ENF not used	55	53
Active background agents (PSS) = 0	17	16
Active background agents (PSS) = 1	37	39

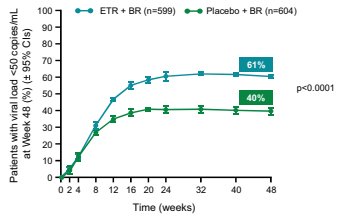
*From extended NNRTI RAM list (Tambuyzer L, et al. EHDRW 2007. Abstract 67); ‡From Johnson et al. Top HIV Med 2005;13:125-131

ARVs = antiretrovirals; PSS = phenotypic sensitivity score; NVP = nevirapine

Baseline disease characteristics

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Disease characteristics		
Duration of HIV infection, years, median (range)	14 (2.5–25.4)	14 (4.6–26.2)
CDC category C, %	58	59
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)
Viral load category (copies/mL)		
<30 000, %	28	29
30 000–100 000, %	34	35
>100 000, %	38	36
CD4 cell count category (cells/mm^3)		
<50, %	36	35
50–200, %	35	34
200–350, %	20	21
≥350, %	10	10
Hepatitis B/C coinfection		
Positive, %	13	12

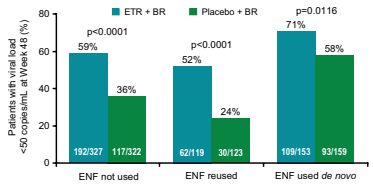
Response (<50 copies/mL) at Week 48 (ITT-TLOVR)



- 61% of patients in the ETR group achieved a confirmed undetectable viral load (<50 copies/mL) compared with 40% in the placebo group (p<0.0001)

CIs = confidence intervals; p value from logistic regression model

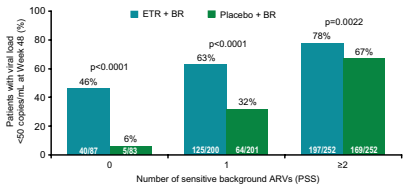
Response (<50 copies/mL) at Week 48 by ENF use (ITT-TLOVR)



- Irrespective of ENF use, patients in the ETR group achieved a significantly higher virologic response than patients in the placebo group
- ENF use was a significant predictor of response in both treatment groups (ETR: p=0.0018; placebo: p<0.0001)

All p values from logistic regression model

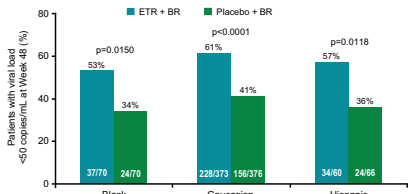
Response (<50 copies/mL) at Week 48 by PSS at baseline (TLOVR): all patients



- The difference in response rates between the ETR and placebo groups was most apparent in patients with no sensitive agents in their BR (40%)
- The number of sensitive background ARVs was a significant predictor of response in both treatment groups (p<0.0001)

All p values from logistic regression model; ENF was counted as sensitive if used *de novo*
DRV was counted as sensitive if FC ≤10; ETR not included in PSS calculation
Analysis excludes patients who discontinued for reasons other than virologic failure

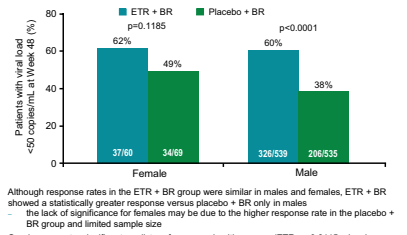
Response (<50 copies/mL) at Week 48 by race (ITT-TLOVR)



- ETR + BR showed superior virologic response versus placebo + BR, irrespective of race
- Race was not a significant predictor of response in either group (ETR: p=0.3757; placebo: p=0.6864)

All p values from logistic regression model.
Asian and other race subgroups were not analyzed separately due to low patient numbers

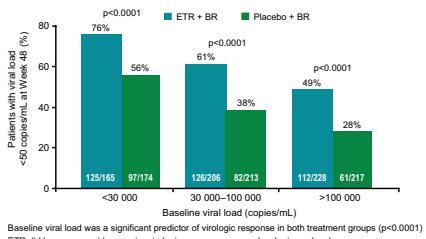
Response (<50 copies/mL) at Week 48 by gender (ITT-TLOVR)



- Although response rates in the ETR + BR group were similar in males and females, ETR + BR showed a statistically greater response versus placebo + BR only in males
  - the lack of significance for females may be due to the higher response rate in the placebo + BR group and limited sample size
- Gender was not a significant predictor of response in either group (ETR: p=0.8115; placebo: p=0.0703)

All p values from logistic regression model

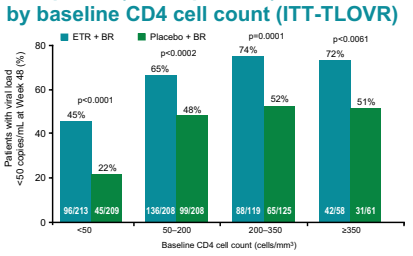
Response (<50 copies/mL) at Week 48 by baseline viral load (ITT-TLOVR)



- Baseline viral load was a significant predictor of virologic response in both treatment groups (p<0.0001)
- ETR did however provide superior virologic response versus placebo in each subgroup

All p values from logistic regression model

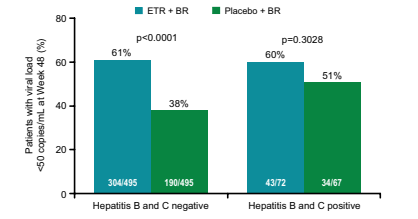
Response (<50 copies/mL) at Week 48 by baseline CD4 cell count (ITT-TLOVR)



- Baseline CD4 cell count was a significant predictor of virologic response (ETR: p=0.0012; placebo: p<0.0001)
- ETR did however provide superior virologic response versus placebo in each subgroup

All p values from logistic regression model

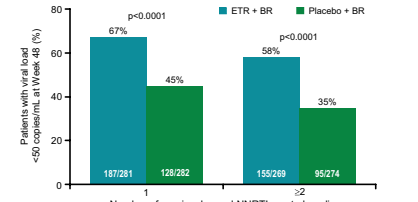
Response (<50 copies/mL) at Week 48 by hepatitis B and C coinfection (ITT-TLOVR)



- Hepatitis coinfection status was not a significant predictor of response in the ETR group (ETR p=0.7555; placebo p=0.0219)

All p values from logistic regression model

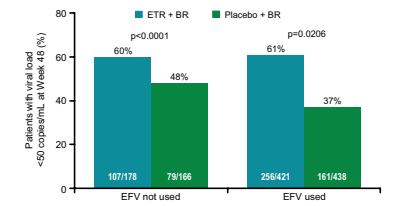
Response (<50 copies/mL) at Week 48 by previous NNRTI use (ITT-TLOVR)



- The number of previously used NNRTIs was a significant predictor of response in the ETR group (ETR: p=0.0052; placebo: p=0.0535)
- ETR provided superior viral load response versus placebo irrespective of the number of previously used NNRTIs

All p values from logistic regression model

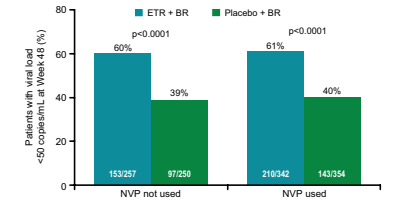
Response (<50 copies/mL) at Week 48 by previous EFV use (ITT-TLOVR)



- Previous EFV use was not a significant predictor of response in the ETR group (ETR: p=0.5647; placebo: p=0.0119)
- ETR provided superior viral load response versus placebo irrespective of previous EFV use

All p values from logistic regression model; EFV = efavirenz

Response (<50 copies/mL) at Week 48 by previous NVP use (ITT-TLOVR)



- Previous NVP use was not a significant predictor of response in either group (ETR: p=0.8995; placebo: p=0.6032)
- ETR provided superior viral load response versus placebo irrespective of previous NVP use

All p values from logistic regression model

Conclusions

- ETR + BR demonstrated superior virologic responses than placebo + BR in treatment-experienced patients at 48 weeks
  - 61% of patients in the ETR group achieved confirmed undetectable viral load (<50 copies/mL) compared with 40% in the placebo group.
- When analyzed by selected baseline characteristics, patients in the ETR group consistently achieved higher response rates than those in the placebo group, irrespective of ENF use, race, disease characteristics, or previous NNRTI use.
- Baseline viral load, CD4 cell count, ENF use and number of sensitive background ARVs were predictors of response in both treatment groups; nevertheless ETR provided added benefit in each subgroup.

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DUET-1
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