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Etravirine protects the activity of darunavir in the DUET trials

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Abstract

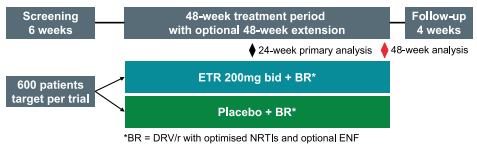
It has been shown in the TITAN study that darunavir (DRV) with low-dose ritonavir (DRV/r) was more effective than lopinavir with low-dose ritonavir (LPV/r) in protecting against the emergence of NRTI mutations. The protective effect of etravirine (ETR; TMC125) on the development of DRV resistance was studied in patients experiencing virological rebound in the ETR and placebo arms of the DUET trials.

In this analysis, patients with a virological rebound were defined as those who showed a virological response at earlier timepoints, but rebounded to >50 copies/mL in the DUET Week 48 dataset. Phenotyping and genotyping at baseline and endpoint were performed with the Antivirogram™ and virco®TYPE HIV-1 assays, respectively, if viral load was >1,000 copies/mL. Emerging mutations were those present at endpoint (i.e. the last available resistance test on treatment), but not at baseline. Patients who discontinued the trial for non-virological reasons were excluded.

Baseline DRV susceptibility was balanced across treatment arms: overall median (range) number of primary protease inhibitor (PI) mutations: four (0–8), DRV resistance-associated mutations (RAMs): two (0–8), DRV fold-change (FC): 6.40 (0.2–908.9) and 64% of patients had DRV FC ≤10 at baseline. Enfuvirtide (ENF) use and NRTI susceptibility were balanced between arms. Virological rebound occurred in 57 (11%) and 119 (22%) patients in the ETR and placebo arms, respectively. Among those experiencing a rebound, fewer patients in the ETR arm developed DRV RAMs (63% vs 96% in placebo, p<0.0001). The median number of emerging DRV RAMs was one and two in the ETR and placebo arms, respectively. The most frequently emerging DRV RAMs in the ETR and placebo arms were V32I (32% vs 60%) and I54L (16% vs 34%). DRV FC at rebound versus baseline increased 2.8-fold and 10.1-fold in the ETR and placebo arms, respectively (p<0.0001). Among the patients with virological rebound that had a DRV FC ≤10 at baseline, 47% in the ETR arm vs only 7% in the placebo arm still had a DRV FC ≤10 at endpoint.

In the DUET studies, ETR-treated patients experienced less virological rebound and loss of DRV susceptibility than those in the placebo arm. Among those with virological failure, ETR-treated patients showed less emergence of resistance to DRV.

DUET study design and major inclusion criteria



*BR = DRV/r with optimised NRTIs and optional ENF

- Plasma viral load >5,000 copies/mL and stable therapy for ≥8 weeks
- ≥1 NNRTI RAM, at screening or in documented historical genotype
- ≥3 primary PI mutations at screening
- DUET-1 and DUET-2 differ only in geographical 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

BR = background regimen

Objectives

- In the Phase III TITAN study,[1] DRV/r was shown to be more effective than LPV/r in protecting against the emergence of both PI and NRTI mutations in treatment-experienced, HIV-1-infected patients in the Week 48 analysis
  - the development of primary PI RAMs and loss of DRV susceptibility was rare in those patients taking DRV, especially those with lower baseline PI resistance and less PI experience
- The current study assessed whether treatment with ETR could protect against the development of resistance to DRV by comparing patients experiencing virological rebound in the ETR arm versus the placebo arm of the pooled Phase III DUET trials

[1]Madruga JV, et al. Lancet 2007;370:49–58

Methods

- The protective effect of ETR on DRV was determined by analysis of DRV resistance in patients experiencing virological rebound
- Patients with a virological rebound were defined as those who showed a confirmed virological response at earlier timepoints, but rebounded to a viral load >50 copies/mL on at least two consecutive timepoints thereafter in the Week 48 analysis
- Patients who discontinued the trial for non-virological reasons were excluded from the analysis
- Emerging mutations were those present at endpoint, but not at baseline
  - endpoint is defined as the last available timepoint during the treatment period, if the viral load was ≥1,000 copies/mL
- Phenotyping and genotyping at baseline and endpoint were performed with the Antivirogram™ and virco®TYPE HIV-1 assays, respectively, if viral load was >1,000 copies/mL
- 2007 DRV RAMs:[1] V11I, V32I, L33F, I47V, I50V, I54L, I54M, G74P, L76V, I84V, L89V

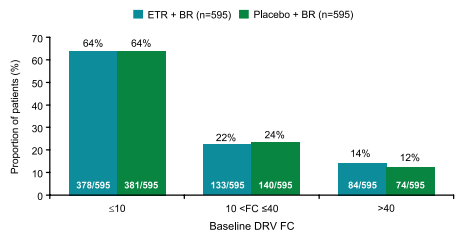
[1]De Meyer S, et al. 6th European HIV Drug Resistance Workshop, Budapest, Hungary, 26–28 March 2008. Abstract 54

Baseline characteristics and ARV background: overall population

Parameter	ETR + BR (n=599)	Placebo + BR (n=604)
Patient demographics		
Male, %	90	89
Caucasian, %	70	70
Disease characteristics		
Median viral load, log_{10} copies/mL (range)	4.8 (2.7–6.8)	4.8 (2.2–6.5)
Median CD4 cell count, cells/mm³ (range)	99 (1–789)	109 (0–912)
CDC category C, %	58	59
ENF use during DUET treatment period, %	45	47
Used ENF *de novo*	26	26
Number of mutations		
Median number PI RAMs (range)	4 (0–7)	4 (0–8)
Median number DRV RAMs (range)	2 (0–7)	2 (0–8)
Median DRV FC (range)	6.2 (0–909)	6.5 (0–752)
DRV FC ≤10, %	64	64

ARV = antiretroviral; CDC = Centers for Disease Control and Prevention

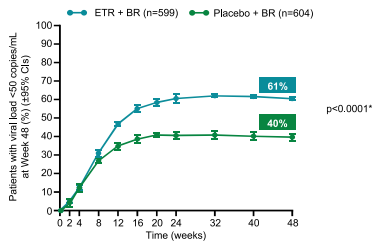
Baseline DRV sensitivity*



- There was no substantial difference in baseline DRV FC across treatment arms

*DRV sensitivity according to Antivirogram™

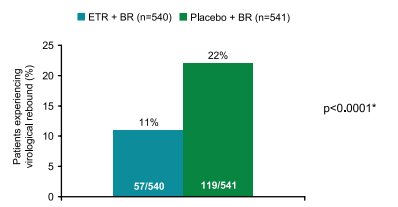
Response (<50 copies/mL) to Week 48 (ITT-TLOVR)



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

*p value vs placebo using logistic regression model
ITT = intent-to-treat; TLOVR = time-to-loss of virological response; CI = confidence interval

Virological rebound in the overall population in the Week 48 analysis



- Virological rebound was reported twice as often in the placebo + BR arm than in the ETR + BR arm (22% vs 11%, respectively) in this highly treatment-experienced patient population

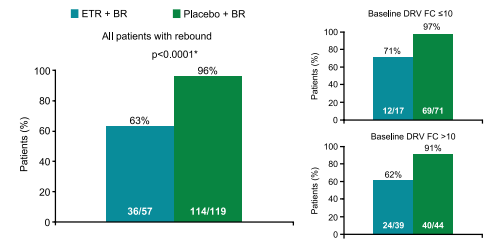
*Chi-square test

Baseline characteristics: virological rebound versus non-virological rebound patients

Parameter	Patients who experienced virological rebound		Patients who did not experience virological rebound	
	ETR + BR (n=57)	Placebo + BR (n=119)	ETR + BR (n=483)	Placebo + BR (n=422)
Baseline viral load, log_{10} copies/mL, median	4.9	4.9	4.8	4.8
ENF use during DUET treatment period, %	35	42	46	48
Used ENF *de novo*	14	17	27	30
Number of mutations				
Median number PI RAMs	5	4	4	4
Median number DRV RAMs	3	2	2	2
Median DRV FC	21.7	7.6	6.2	6.2
DRV FC ≤10, %	30	62	68	66
Number of sensitive NRTIs in BR, %				
0	60	64	52	51
1	28	25	30	33
>2	12	11	18	16

Baseline resistance data was available for 56 ETR- and 115 placebo-treated patients

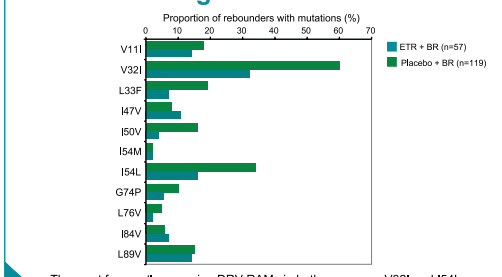
Proportion of virological rebounders with at least one emerging or new DRV RAM



- Among patients who experienced a virological rebound, a lower proportion of patients in the ETR + BR arm than in the placebo + BR arm developed DRV RAMs
  - in the overall population, the median number of emerging DRV RAMS was one for the ETR + BR arm and two for the placebo + BR arm

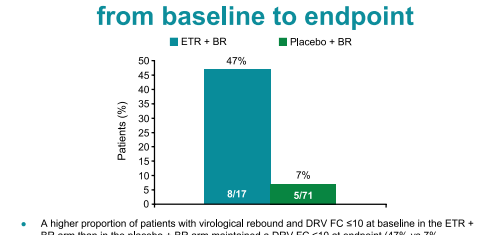
*Chi-square test

Emerging DRV mutations in virological rebounders



- The most frequently emerging DRV RAMs in both arms were V32I and I54L

Patients maintaining DRV FC ≤10 from baseline to endpoint



- A higher proportion of patients with virological rebound and DRV FC ≤10 at baseline in the ETR + BR arm than in the placebo + BR arm maintained a DRV FC ≤10 at endpoint (47% vs 7%, respectively)
- Overall, DRV FC at rebound versus baseline increased 2.8 and 10.1-fold in the ETR + BR and placebo + BR arms, respectively (p<0.0001)
  - in patients with baseline DRV FC ≤10, the increases were 4.0 and 15.6, respectively
  - in patients with baseline DRV FC >10, the increases were 2.3 and 5.0, respectively

Conclusions

- Among highly treatment-experienced patients in DUET, patients receiving placebo + BR experienced twice as much virological rebound as those receiving ETR + BR
- Among patients with virological rebound, a significantly lower proportion of ETR-treated patients showed development of DRV RAMs compared with placebo-treated patients
- Among patients with virological rebound and DRV FC ≤10 at baseline, a higher proportion of ETR-treated patients maintained a DRV FC ≤10 at endpoint versus placebo
- In the DUET studies, adding ETR to a DRV/r containing regimen protects the activity of DRV/r in cases of virological rebound in HIV-1-infected, highly treatment-experienced patients with existing PI resistance at baseline

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DUET-1

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DUET-2

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