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Activity of etravirine on different HIV-1 subtypes: Week 48 data of the pooled DUET trials and in-vitro susceptibility in treatment-naïve patients

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Abstract

Etravirine (ETR; TMC125) has shown good in-vitro activity against primary HIV-1 group M isolates from different subtypes and has demonstrated durable efficacy in treatment-experienced, HIV-1-infected patients in the Phase III DUET trials. In-vivo efficacy and in-vitro activity of ETR against different HIV-1 subtypes was further investigated.

DUET patients were randomised 1:1 to ETR (200mg bid) or placebo, both with a background regimen (BR) of NRTIs, darunavir (DRV) with low-dose ritonavir (DRV/r) and optional enfuvirtide (ENF). Subgroup analyses of the effect of HIV-1 subtype on the proportion of patients with viral load <50 HIV-1 RNA copies/mL (time-to-loss of virological response [TLOVR] imputation algorithm) were conducted on pooled Week 48 data. Genotype/subtype and phenotype determinations were performed using the virco®TYPE HIV-1 and Antivirogram™ assays, respectively. The effect of HIV-1 subtype on ETR fold-change in EC_{50} (FC) value was analysed in HIV-1 recombinant clinical isolates from treatment-naïve patients enrolled in other Tibotec trials (n=872) that included 49% of HIV-1 subtype non-B (18% CRF01_AE; 16% C; 5% A1; 3% CRF12_BF; 2% CRF02_AG; 1% F1; 3% other).

In DUET, HIV-1 subtype was available for 594 and 595 patients in the ETR and placebo arms, respectively. The majority of these (93.8%) harboured HIV-1 subtype B. Among the non-B subtypes, CRF12_BF (2.1%), F1 (1.2%), and CRF02_AG (0.8%) were most prevalent. Baseline disease characteristics (viral load, CD4, ETR FC, DRV FC, phenotypic sensitivity score [PSS]) were similar between patients with different subtypes, except for a higher number of sensitive NRTIs used in those with HIV-1 subtype non-B. In the ETR arm, virological responses at Week 48 were 59.9% (336/561) for HIV-1 subtype B vs 72.7% (24/33) for all other HIV-1 subtype non-B, as compared to an overall response of 60.6%.

These data were further supported by in-vitro results that indicated a comparable median (interquartile range) ETR FC in virus isolates from treatment-naïve patients infected with subtype B or non-B (1.1, 0.8–1.6 or 1.2, 0.8–1.7), respectively.

In the DUET studies, ETR was equally effective in suppressing viral replication in patients infected with HIV-1 subtype B or non-B. Furthermore, both subtype B and non-B HIV-1 recombinant clinical isolates from treatment-naïve patients exhibited comparable levels of in-vitro phenotypic susceptibility to ETR. These results confirmed the broad activity of ETR against HIV-1.

Data have been updated since abstract submission.

Background

- ETR is a next-generation NNRTI, with activity against NNRTI-resistant HIV-1 and a high genetic barrier to the development of resistance[1]
- ETR has shown good in-vitro activity against primary HIV-1 group M and group O isolates from different subtypes[1] and has demonstrated durable efficacy in treatment-experienced, HIV-1-infected patients in the Phase III DUET trials[2,3]

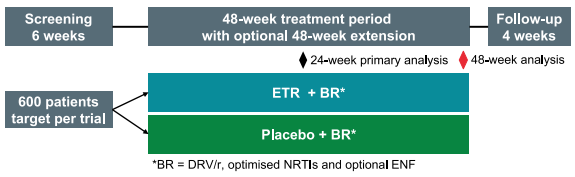
[1]Andries K, et al. Antimicrob Agents Chemother 2004;48:4680–86
[2]Trottier B, et al. CAHR 2008. Poster P167
[3]De Smedt G, et al. ISHEID 2008. Oral presentation

Objectives

- To investigate the virological response to ETR in DUET in patients infected with different HIV-1 subtypes
- To investigate the in-vitro activity of ETR in wild-type HIV-1 recombinant clinical isolates from treatment-naïve patients
  - genotypic variation due to HIV-1 subtype can be studied without the interference of resistance associated mutations
  - phenotypic clinical cut-off (CCO) values were defined previously[1] and can be applied to estimate the antiviral activity of ETR

[1]ETR FC = 3 and 13: Peeters M, et al. IHDRW 2008

DUET study design and major inclusion criteria



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

- 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 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

RAMs = resistance-associated mutations; PI = protease inhibitor

Methods

- Subgroup analyses of the effect of HIV-1 subtype on the proportion of patients with viral load <50 HIV-1 RNA copies/mL (TLOVR imputation algorithm) were conducted on pooled Week 48 DUET data
- Genotype and phenotype were determined by Virco
- HIV-1 subtype was determined by Virco as the best match between the protease/RT nucleotide sequence and the corresponding subtype consensus sequences from the LANL subtype reference subset[1]
- The effect of HIV-1 subtype on ETR FC was analysed in a panel of HIV-1 recombinant clinical isolates (n=673)
  - from treatment-naïve patients enrolled in other Tibotec-sponsored trials
  - no evidence of transmitted NRTI resistance or evidence of NNRTI resistance[2]

[1]http://hiv.lanl.gov; [2]Tambuyzer L, et al. EHDRW 2007
RT = reverse transcriptase

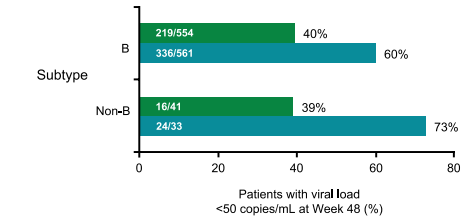
Distribution of HIV-1 subtypes in pooled DUET

HIV-1 subtype, n (%)	ETR + BR (N=594)	Placebo + BR (N=595)	All (N=1,189)
B	561 (94.4)	554 (93.1)	1,115 (93.8)
BF	13 (2.2)	12 (2.0)	25 (2.1)
F1	5 (0.8)	9 (1.5)	14 (1.2)
AG	6 (1.0)	3 (0.5)	9 (0.8)
Other	9 (1.5)	17 (2.9)	26 (2.2)
C	3	3	6
AE	2	2	4
BG	2	1	3
CPX	1	1	2
H	1	0	1
A1	0	5	5
D	0	4	4
G	0	1	1

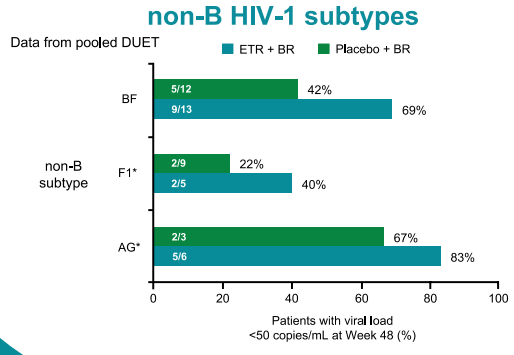
Baseline disease characteristics by HIV-1 subtype in pooled DUET

	ETR + BR		Placebo + BR	
	Subtype B (N=561)	Non-B (N=33)	Subtype B (N=554)	Non-B (N=41)
Median log_{10} viral load, copies/mL	4.8	5.0	4.8	4.9
Median $CD4^+$ cell count, cells/mm^3	100	79	109	81
Median ETR FC	1.7	1.5	1.5	1.9
Median DRV FC	6.5	4.3	6.6	4.9
De-novo use of ENF, %	25.1	33.3	26.9	24.4
≥1 sensitive NRTIs in BR, %	45.2	63.6	43.6	65.0
PSS, % 0	17.4	9.1	16.8	12.5
1	37.2	21.2	39.4	27.5
≥2	45.4	69.7	53.8	60.0

Virological response (<50 copies/mL) at Week 48 according to HIV-1 subtype

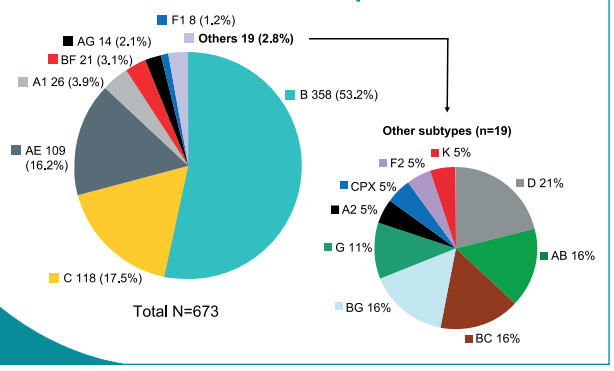


Virological response (<50 copies/mL) at Week 48 in the most prevalent non-B HIV-1 subtypes

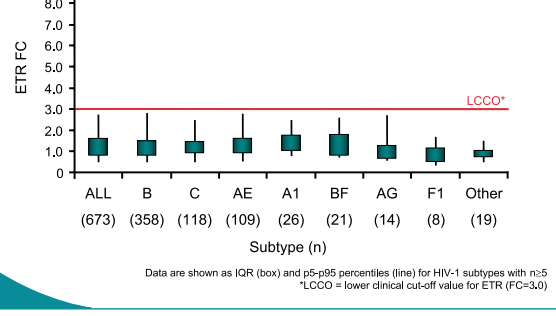


*Note that subgroups are small; n for the other subtypes is too small for data to be shown

Distribution of subtypes in a panel of HIV-1 recombinant clinical isolates from treatment-naive patients



ETR FC in B and non-B subtypes from treatment-naive HIV-1 recombinant clinical isolates



Data are shown as IQR (box) and p5-p95 percentiles (line) for HIV-1 subtypes with n≥5
*LCCO = lower clinical cut-off value for ETR (FC=3.0)

Conclusions

- In DUET, baseline disease characteristics (viral load, CD4, ETR FC, DRV FC) were similar between patients infected with different subtypes, except for a higher number of sensitive NRTIs used in those with HIV-1 subtype non-B
- ETR was equally effective in suppressing viral replication in patients infected with HIV-1 subtype B or various HIV-1 non-B subtypes
  - the additional effect of ETR on virological response as compared to placebo was similar in patients infected with HIV-1 subtype B or various HIV-1 non-B subtypes
- Further investigations were performed using HIV-1 recombinant clinical isolates from treatment-naïve patients infected with various HIV-1 subtypes
  - comparable median ETR FC values were observed irrespective of HIV-1 subtype
- These data confirm the activity of ETR against a broad range of HIV-1 subtypes

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This poster is available on-line at www.tibotec.com