

# Week 48 antiretroviral (ARV) response to darunavir (TMC114)/ritonavir and etravirine (TMC125) combination in patients with high level viral resistance

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## BACKGROUND

- Resistance and cross-resistance to ARVs remain a major reason for treatment failure and exhaustion of therapeutic options<sup>1</sup>.
- Development of new, potent and tolerable ARVs with improved resistance profiles is urgently needed for the growing number of subjects with multi-drug resistant HIV and otherwise limited treatment options.
- Furthermore, it is expected that the administration of two or more susceptible ARVs in this patient population would lead to enhanced treatment efficacy and durability<sup>1</sup>.
- Etravirine (TMC125) is a novel NNRTI designed to have a high genetic barrier to the development of resistance<sup>2</sup>. In a 7-day trial, etravirine monotherapy produced a mean change in viral load (VL) of  $-0.9 \log_{10}$  copies/mL in patients failing NNRTI-based therapy<sup>3</sup> and phase II trials in triple-class-experienced patients found that etravirine was generally safe and well tolerated and showed significant and sustained efficacy, suggesting that etravirine is the first NNRTI to show significant activity in patients with prior NNRTI failure<sup>4</sup>.
- A new formulation of etravirine is available today: 100 mg tablets with significantly improved bioavailability, dosage 200 mg bid showed a comparable exposure to 800 mg bid of previous formulation<sup>5</sup>.
- Darunavir (TMC114) is a potent, new non-peptidic protease inhibitor (PI) that, in combination with low dose ritonavir (RTV), has shown activity in naive and experienced patients. In these patients, darunavir/RTV produced a rapid and robust VL reduction and was well tolerated<sup>6</sup>. Moreover, darunavir has demonstrated long term efficacy in patients with PI resistance and has recently been approved for the treatment of HIV infection.
- We recently demonstrated the lack of a significant drug-drug interaction between etravirine and darunavir in HIV-infected patients<sup>7</sup>.
- We here present the week 48 results of the 11 highly experienced HIV patient who received etravirine and darunavir together for the first time.

## METHODS

### Study design and subjects:

- This was an open-label, single-arm study carried out at the Pharmacokinetic Unit of the St. Stephen's Centre, Chelsea and Westminster Hospital, London, UK. The study protocol was reviewed and approved by the Riverside Research Ethics Committee.
- Following screening procedures (days -14 to -1), all subjects were administered etravirine (200 mg bid) and darunavir/RTV (600/100 mg bid) together with two or more NRTIs, plus or minus enfuvirtide (ENF).

### Evaluations:

- Clinical laboratory tests, physical examination, ECG and vital signs were performed throughout the study.
- Plasma VLs were measured by real-time PCR (Roche COBAS TaqMan; lower limit of detection = 40 copies/mL).
- The immunologic effect of treatment was determined by changes in CD4 counts (absolute and %).
- Phenotypic and genotypic determinations were performed by Virco BVBA by means of the Antivirogram<sup>®</sup> and Virtual/Phenotype<sup>™</sup>, respectively.
- Primary PI mutations were identified according to the international AIDS Society Guidelines, October 2005.

## RESULTS

- 11 patients completed week 48; baseline demographic and clinical characteristics are summarised in Table 1. Two patients withdrew consent; one on screening and one on day 7 for personal reasons.
- All patients had viruses with high levels of resistance for all ARV classes (Tables 1 and 2).
- Two subjects showed wild type at screening but had extensive archived resistance documented by different tests performed in the past (Table 2).
- 6/11 patients had prior exposure to tipranavir and to enfuvirtide; only two used enfuvirtide for the first time (Table 2).
- At week 48, 9/11 patients had achieved an undetectable viral load, the two detectable viral loads were low: 166 and 465 copies/mL (Figure 1).
- Median (range) CD4 count increase and HIV RNA decline were 118 (75-293) cells/mm<sup>3</sup> and  $-2.7$  ( $2.2-3.8$ )  $\log_{10}$  copies/mL, respectively (Figures 2 and 3).
- Table 3 shows baseline and 48-week data for each patient.
- No new AIDS events, serious adverse events, or changes in laboratory safety were reported. Possibly drug related adverse events were: mild diarrhoea (n=1), headache (n=1), grade 1 skin rash (n=1), which all resolved with continuous dosing.

TABLE 1: Baseline demographics and clinical characteristics (n = 11)

Parameter	
<b>Sex (N)</b>	
Male	9
Female	2
<b>Age (years)</b>	
Median (range)	43 (38–56)
<b>Race (N)</b>	
Black	3
Caucasian	8
<b>Log<sub>10</sub> viral load (copies/ml)</b>	
Median (range)	4.6 (3.9–5.5)
<b>CD4 count (cells/mm<sup>3</sup>)</b>	
Median (range)	75 (3–490)
<b>NRTI-associated mutations (N)</b>	
Median range	7 (2–9)
<b>NNRTI-associated mutations (N)</b>	
Median (range)	2 (0–6)
<b>Primary PI mutations (N)</b>	
Median (range)	4 (0–5)
<b>PI resistance-associated mutations (N)</b>	
Median (range)	11 (2–13)

TABLE 2: Use of ENF and TPV; NRTI-associated mutations; NNRTI-associated mutations; PI-associated mutations; VL decrease and CD4 increase over 48 weeks of therapy (n = 11)

Subject ID	1	2	3	4	6	7	8	9	11	12	13
Use of ENF in the past	Y	N	Y	N	N	Y	Y	Y	N	Y	N
Current ENF	Y	N	Y	Y	N	Y	Y	N	Y	Y	Y
Use of TPV in the past	Y	N	N	N	Y	Y	Y	Y	N	Y	N
Baseline NRTI mutations	20R, 41L, 167N, 74I, 184V, 210W, 215Y, 219E, 228H	39A, 41L, 44D, 67G, 69A, 70R, 74V, 118I, 184V, 203K, 208Y, 210W, 211K, 215Y, 218E, 228H	44D, 67N, 69D, 70R, 118I, 181C, 184V, 215F, 219Q, 228H, 333E	62V, 65R, 75I, 77L, 115F, 116Y, 151M, 184V	41L, 43E, 44D, 62V, 118I, 184V, 210W, 215Y, 218E, 219R, 228H	20R, 65R, 184V	67N, 69X, 70R, 184V, 203K, 210W, 211K, 215N/S/Y, 219E, 228R	41L, 43E, 44A, 67N, 118I, 184I, 203K, 208Y, 210W, 211K, 215Y, 219R	43E, 62V, 67E, 69INS, 69S, 118I, 184I, 210W, 211K, 215Y, 228H	20R, 41L, 44D, 67N, 69D, 70R, 118I, 184V, 210W, 211Q, 215Y, 218E, 219Q, 228Q	41L, 67N, 75M, 118I, 184V, 210W, 211Q, 215Y, 218E, 219Q, 228Q
Baseline NNRTI mutations	103S, 106I, 108I	103N, 106I, 230L	101E, 135T, 181C, 189WT/I, 190A	None	None*	179I**	135V, 179I, 238T, 283I <sup>%</sup>	None***	179I <sup>%</sup>	89G, 103N, 135T, 179I, 221Y, 318F	135T
PI mutations at baseline	10I, 33I, 35D, 36I, 45R, 53V, 63P, 73C, 82C/F/L/R, 84V, 90M	10I, 13V, 20R, 33F, 35D, 36I, 48V, 50V, 54B, 82A, 89I	10F, 13V, 20R, 33F, 35D, 36I, 46WT/L, 54V, 63P, 71V, 73S, 82A, 90M	10I, 13V, 20T, 33F, 36L, 46I, 54V, 63P, 71T, 76V, 84V, 89V, 90M, 93L, 95F	10I, 20I, 33D, 36I, 47V, 48V, 54A, 63P, 63P, 71V, 74S, 82T, 85V, 90M, 93L	10V, 13V, 20R, 33F, 36I, 54V, 58E, 63P, 82A, 83D, 84V, 89I, 90M	36I, 63P <sup>^</sup>	10I, 46I, 48V, 54S, 74S, 77I, 82A, 84V, 85V	10I, 11I, 22V, 36L, 46I, 54V, 63P, 71V, 73S, 82A, 83D, 85V, 90M	10F, 20R, 35D, 36I, 60E, 63P, 71I, 74A, 82A, 93L	10V, 20R, 35D, 36I, 46L, 50V, 54V, 71V, 77I, 82A, 93L

\*Archived resistance: exposed to efavirenz in 1999–2000 and failed nevirapine in 2005; \*\*Archived resistance: 103N in 2002; \*\*\*Archived resistance: 103N in 2003; <sup>%</sup>Archived resistance: 103N, 98S, 179I, 189I, 283I; <sup>%%</sup>Archived resistance: 103N in 2003; <sup>^</sup>Archived resistance: 10I, 20I, 36I, 46I, 54V, 58E, 63P, 71V, 73S, 84V, 85V, 90M

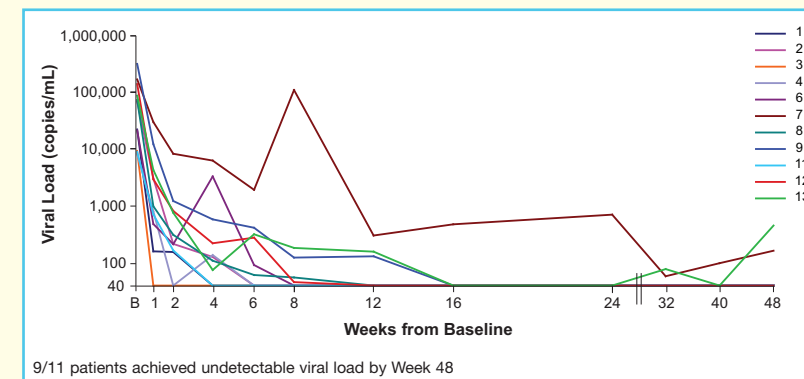


FIGURE 1: Change in viral load from baseline, by patient

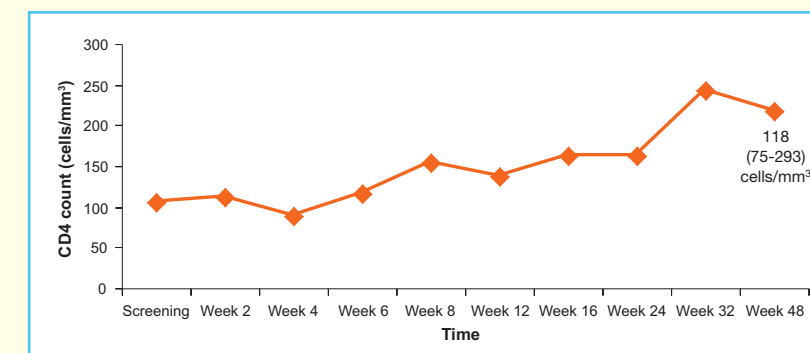


FIGURE 2: Median CD4 cell increase over 48 weeks in the 11 patients studied

TABLE 3: CD4 cell count and viral load at baseline and at Week 48, by patient

Patient #	CD4 cell count (cells/mm <sup>3</sup> )		HIV-1 RNA (copies/mL)	
	baseline	Week 48	baseline	Week 48
1	10	158	22,977	<40
2	50	168	71,665	<40
3	100	175	9,666	<40
4	157	245	8,483	<40
6	490	724	22,194	<40
7	3	296	176,802	166
8	156	268	76,701	<40
9	ND*	190	332,152	<40
11	401	399	9,313	<40
12	21	149	145,355	<40
13	110	402	91,802	465

\*ND = no data (baseline data not available due to clotted specimen; Week 2 = 9 cells/mm<sup>3</sup>)  
9/11 patients achieved undetectable VL by Week 48

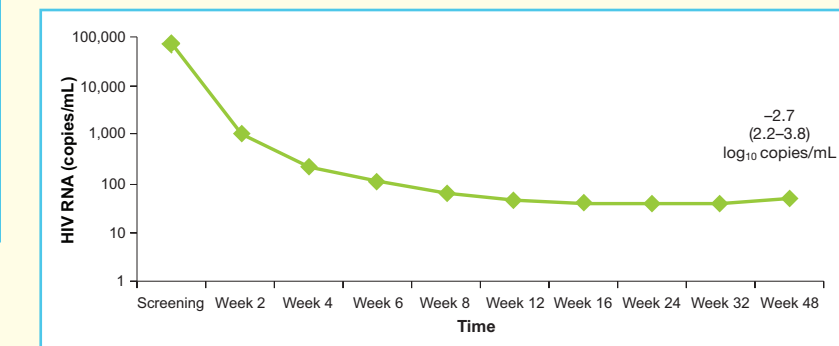


FIGURE 3: Median viral load (VL) decrease over 48 weeks in the 11 patients studied

## CONCLUSION

- The combination was well tolerated and showed efficacy over 48 weeks against three-class resistant HIV. Further studies of this combination are ongoing.

## References

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