

# Patients who responded to tipranavir/r (500/200 mg BID) plus new enfuvirtide (ENF) at Week 16 of RESIST studies maintain superior virologic and immunologic outcomes through Week 96

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## Abstract

**Background** Current guidelines recommend >2 active ARVs in treatment experienced patients (pts) to achieve undetectable viral load (VL) and improved immunologic response.

**Aim** To evaluate virologic and immunologic efficacy of tipranavir/r (TPV/r) plus a novel class ARV, e.g. enfuvirtide (ENF) in ARV experienced pts. Analysis focused on RESIST pts who took ENF and had early virologic response (VL <400 copies/mL). Virologic and immunologic efficacy was assessed over 96 weeks.

**Methods** Analysis of Wk 2, 16, 24, 48 and 96 efficacy data from RESIST.

**Results** 16.6% (124/746) of TPV/r and 97/737 (13.2%) CPI/r pts initiated ENF for first time (new ENF). At Wk 2, mean VL reduction from baseline in new ENF pts who took TPV/r was 1.62 vs. 1.11 log<sub>10</sub> copies/mL in those who took TPV/r without ENF. At Wk 16, 66/124 (53.2%) of new ENF pts in TPV/r arm had VL <400 copies/mL vs. 29/97 (29.9%) in CPI/r arm (ITT NCF). All but two of TPV/r pts (64/66; 97%) maintained VLs <400 copies/mL at Wk 24; 56/66 (84.8%) at Wk 48; and 48/66 (72.7%) at Wk 96 (ITT NCF). At last observation up to Wk 96, mean increase in CD4 cell count (cells/mm<sup>3</sup>) in new ENF pts was 125 in TPV/r vs. 42 in CPI/r (LOCF).

**Conclusions** RESIST patients taking TPV/r plus new ENF had superior early and durable virologic and immunologic outcomes vs. those taking CPI/r and new ENF. The majority of new ENF/TPV/r patients who had VL <400 copies/mL at Week 16 maintained this level of viral suppression through Week 96. Administering tipranavir/r plus a novel ARV results in substantial virologic and immunologic responses in a high proportion of treatment experienced patients.

## Introduction

- Currently, guidelines recommend the use of at least two active antiretroviral (ARV) drugs in the treatment of HIV positive patients who have failed previous therapeutic regimens [1,2]. The aim is to suppress viral replication and increase the CD4 cell count, thus protecting the patient from opportunistic infections and disease progression.
- The DHHS guidelines state: *Adding a drug with activity against drug-resistant virus (e.g., a potent ritonavir-boosted PI) and a drug with a new mechanism of action (e.g., HIV entry inhibitor) to an optimized background antiretroviral regimen can provide significant antiretroviral activity* [1]. In addition: *Tipranavir and darunavir are two new protease inhibitors approved for patients who are highly treatment experienced or have HIV-1 strains resistant to multiple PIs based on its demonstrated activity against PI-resistant viruses* [1].
- The BHIVA guidelines acknowledge that *The goals of treatment for the majority of treatment experienced patients have changed, and the new paradigm should be aiming for an undetectable and durable HIV plasma viral load suppression, wherever possible, leading to immunological improvement with lack of clinical progression and improvement in quality of life* [3].
- In the RESIST studies, patients who had prior experience with all three ARV drug classes including more than one protease inhibitor (PI) switched to tipranavir/r (TPV/r), enfuvirtide (ENF) and an optimized background regimen [4].
- The aim of this analysis was to evaluate the virologic and immunologic efficacy of TPV/r with or without ENF in treatment experienced patients who took part in the RESIST studies. The analysis focused on RESIST patients who took ENF for the first time ('new' ENF) and had an early virologic response (VL <400 copies/mL at Week 16). Virologic and immunologic efficacy was assessed over 96 weeks.

## Methods

An analysis of Week 2, 16, 24, 48 and 96 efficacy data from RESIST was conducted, using data from patients in the RESIST studies who took TPV/r or a comparator ritonavir boosted protease inhibitor (CPI/r) with or without 'new' ENF. All virologic analyses were Intent to Treat Non-Completer equals Failure (ITT NCF) unless otherwise stated. The immunologic analysis was Last Observation Carried Forward (LOCF).

## Results

Approximately one quarter of TPV/r patients took ENF: 170/746, 22.8%. One hundred and twenty-four patients in the TPV/r arm (16.6%; 124/746) initiated ENF for the first time ('new' ENF), while 6.2% (46/746) recycled or continued to take ENF ('old' ENF) at study initiation. There were 576 TPV/r patients who did not take ENF (576/746; 77.2%). A smaller proportion of CPI/r patients initiated ENF for the first time compared to TPV/r patients: 97/737 (13.2%).

Patients who took TPV/r plus ENF had more advanced HIV disease at baseline than patients who did not take ENF: median VL: 5.06 vs. 4.72 log<sub>10</sub> copies/mL; median CD4 cell count: 74 vs. 179 cells/mm<sup>3</sup>; proportion of patients with CDC Class C HIV disease: 65.3% vs. 57.8% (Table 1). Patients who took TPV/r plus ENF had taken more ARVs prior to enrollment than those who took TPV/r without ENF. The proportion of patients who were hepatitis co-infected was lower in the group of patients who took ENF: 5.3% vs. 11.8%. Other baseline characteristics, however, were similar. There were no differences between the 'new' and 'old' ENF groups (Table 2).

Table 1: Baseline demographic data by ENF use in the TPV/r arm of the RESIST trials

	TPV/r no ENF	TPV/r + ENF
Total treated	576	170
Age [years]		
Median	42	44
Range	17-80	17-67
Gender [N (%)]		
Male	477 (82.8)	152 (89.4)
Female	99 (17.2)	18 (10.6)
Race [N (%)]		
White	438 (76.0)	133 (78.2)
Black	69 (12.0)	25 (14.7)
Asian / Missing	69 (12.0)	12 (7.1)
Median baseline HIV-1 RNA [log <sub>10</sub> copies/mL]	4.72	5.06
Median baseline CD4+ cell count [cells/mm <sup>3</sup> ]	179	74
Prior ARV use		
Median prior PI use (range)	4 (1-7)	5 (1-7)
Median prior NRTI use (range)	5 (2-8)	6 (3-8)
Median prior NNRTI use (range)	1 (0-3)	2 (0-3)
Median number of FDA protease gene mutations <sup>a</sup>	4	5
Median number of IAS protease gene mutations <sup>b</sup>	10	11

<sup>a</sup>Number of mutations in the protease gene at positions (30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, 90).<sup>b</sup>Number of protease mutations out of (10FIRV, 13V, 16E, 20IMR, 24I, 30N, 32I, 33FIV, 35G, 36ILV, 43T, 46IL, 47AV, 48V, 50LV, 53L, 54ALMSTV, 58E, 60E, 62V, 63P, 69K, 71ILT, 73ACST, 74P, 77I, 82AFLST, 83D, 84V, 85V, 88DS, 90M, 93L).

Table 2: Baseline demographic data for 'new' and 'old' ENF TPV/r patients

	'New' ENF/TPV/r	'Old' ENF/TPV/r
Total treated	124	46
Age [years]		
Median	44	45
Range	17-67	33-61
Gender [N (%)]		
Male	109 (87.9)	43 (93.5)
Female	15 (12.1)	3 (6.5)
Race [N (%)]		
White	96 (77.4)	37 (80.4)
Black	19 (15.3)	6 (13.0)
Asian / Missing	9 (7.3)	3 (6.5)
Median baseline HIV-1 RNA [log <sub>10</sub> copies/mL]	5.07	5.01
Median baseline CD4+ cell count [cells/mm <sup>3</sup> ]	86	52
Prior ARV use		
Median prior PI use (range)	5 (1-7)	5 (3-7)
Median prior NRTI use (range)	6 (3-8)	6 (4-8)
Median prior NNRTI use (range)	2 (0-3)	2 (1-3)
Median number of FDA protease gene mutations <sup>a</sup>	5	5
Median number of IAS protease gene mutations <sup>b</sup>	11	12

<sup>a</sup>Number of mutations in the protease gene at positions (30, 32, 36, 46, 47, 48, 50, 53, 54, 73, 82, 84, 88, 90).<sup>b</sup>Number of protease mutations out of (10FIRV, 13V, 16E, 20IMR, 24I, 30N, 32I, 33FIV, 35G, 36ILV, 43T, 46IL, 47AV, 48V, 50LV, 53L, 54ALMSTV, 58E, 60E, 62V, 63P, 69K, 71ILT, 73ACST, 74P, 77I, 82AFLST, 83D, 84V, 85V, 88DS, 90M, 93L).

At Week 2, the mean VL reduction from baseline in 'new' ENF patients who took TPV/r was 1.62 vs. 1.11 log<sub>10</sub> copies/mL in those who took TPV/r without ENF (Figure 1). The comparable figures for the CPI/r arm were: -1.20 and -0.65 log<sub>10</sub> copies/mL in 'new' and 'no' ENF patients, respectively.

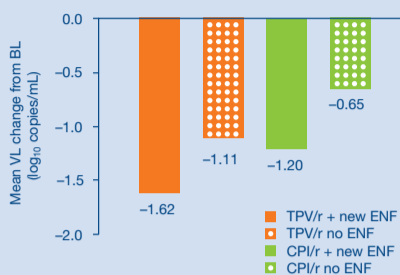


Figure 1: Mean viral load change from baseline at Week 2 in RESIST patients

At Week 16, 66/124 (53.2%) of new ENF patients in the TPV/r arm had VL <400 copies/mL vs. 29/97 (29.9%) in CPI/r arm (ITT NCF) (Figure 2). All but two of these 66 TPV/r patients (64/66; 97%) maintained VLs <400 copies/mL at Week 24; 56/66 (84.8%) at Week 48; and 48/66 (72.7%) at Week 96 (ITT NCF) (Figure 3).

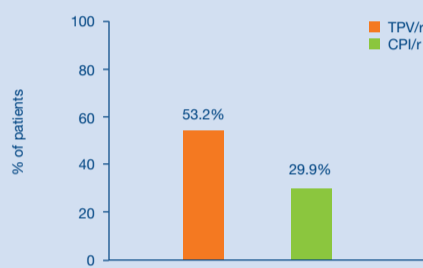


Figure 2: Proportion of RESIST patients who took 'new' ENF and who achieved a VL &lt;400 copies/mL at Week 16



Figure 3: Proportion of TPV/r patients who took 'new' ENF and who achieved a VL &lt;400 copies/mL at Week 16 and who subsequently maintained a VL &lt;400 copies/mL at Weeks 24, 48 and 96

At last observation up to Week 96, mean increases in the CD4 cell count in 'new' ENF patients were 125 cells/mm<sup>3</sup> in the TPV/r arm versus only 42 cells/mm<sup>3</sup> in the CPI/r arm (LOCF) (Figure 4). At last observation up to Week 96, the mean increase in the CD4 cell count in TPV/r patients who did not take ENF was 31 cells/mm<sup>3</sup> versus 21 cells/mm<sup>3</sup> in CPI/r patients who did not take ENF (LOCF).

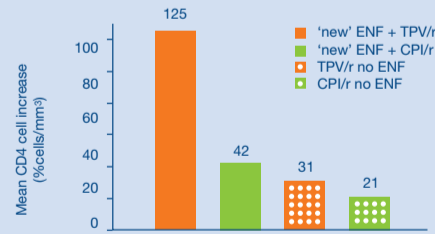


Figure 4: Mean CD4 cell changes in 'new' and 'no' ENF patients in the TPV/r and CPI/r arms of RESIST at last observation up to Week 96 (LOCF)

## Conclusions

- RESIST patients taking TPV/r plus 'new' ENF experienced highly effective antiviral activity, which was sustained in most patients throughout 96 weeks compared to those taking CPI/r and 'new' ENF. Immunologic outcomes were also greater in the TPV/r plus new ENF group.
- Over 70% of patients who took new ENF and TPV/r who had VL <400 copies/mL at Week 16 maintained this level of viral suppression through Week 96.
- Administering TPV/r plus a novel ARV results in substantial virologic and immunologic responses in a high proportion of treatment experienced patients.

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