

# Week 8 response predicts Week 48 virological responses to tipranavir/r in the RESIST studies

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## Abstract

**Objectives:** To determine whether the extent of Week 8 viral load (VL) reduction from baseline could predict long-term virological responses to a tipranavir/ritonavir (TPV/r) based regimen.

**Methods:** Predictive value of Week 8 VL reductions for achieving undetectable VLs at Week 48 was assessed using RESIST data. Sensitivity, specificity, negative and positive predictive values were calculated for a range of cut off values.

**Results:** 1483 patients were randomised: 746 TPV/r; 737 control PI/r. 16.6% (124/746) of TPV/r patients initiated ENF ('new' ENF); 6.2% (46/746) recycled ENF ('old' ENF). At Week 48, 30.3% (22.7%) of TPV/r patients had VL <400 (50) copies/mL vs. 13.6% (10.2%) CPI/r patients (both: p<0.0001).

A VL reduction  $\geq 1.5$  log<sub>10</sub> copies/mL at Week 8 was predictive of VL <50 copies/mL at Week 48 in TPV/r patients. The Odds Ratio was 17.15 (95% CI 9.83, 29.91, p<0.001).

VL drop at Week 8 (log <sub>10</sub> copies/mL)	VL <50 copies/mL at Week 48		
	No N (%)	Yes N (%)	
<1.5	361 (96.0%)	15 (4.0%)	Negative predictive value = 96.0%
$\geq 1.5$	216 (58.4%)	154 (41.6%)	Positive predictive value = 41.6%
	Specificity = 62.6%	Sensitivity = 91.1%	

The proportion of patients with VL <50 copies/mL at Week 48 was higher with 'new' ENF (37.1%) vs. 'no/old' ENF (19.8%). A 1.5 log<sub>10</sub> copies/mL VL reduction at Week 8 was predictive in both subgroups: 45.4% with 1.5 log<sub>10</sub> copies/mL reduction vs. 7.4% without in 'new' ENF patients; 40.3% vs. 3.7% in 'no/old' ENF patients.

During first 8 weeks of TPV/r therapy, the risk of Grade 3/4 ALT was low: 3.0% TPV/r patients developed Grade 3/4 ALT vs. 1.4% CPI/r patients.

**Conclusions:** Patients taking a TPV/r based regimen who had a VL reduction  $\geq 1.5$  log<sub>10</sub> copies/mL at Week 8 were more likely to have an undetectable VL at Week 48.

## Introduction

Early virological responses in highly treatment experienced patients have been shown to be predictive of long term virological success [1]. In the TORO studies, patients who achieved a reduction in viral load (VL) of  $\geq 1.0$  log<sub>10</sub> copies/mL by Week 12 were more likely to have undetectable VLs at Week 96 than patients who did not have this degree of early virological response. In the RESIST studies, triple antiretroviral (ARV) class experienced patients were randomised to receive tipranavir/ritonavir (TPV/r) or a comparator ritonavir boosted protease inhibitor (CPI/r) plus an optimised background regimen (OBR) [2]. Patients are being followed for five years; Week 96 data have been presented [3,4].

The objective of this analysis was to determine whether the degree of the Week 8 VL reduction from baseline could predict long-term virological responses to a TPV/r based regimen in the RESIST studies.

## Methods

The predictive value of Week 8 VL reductions for achieving undetectable VLs at Week 48 was assessed using data from patients who had participated in the RESIST studies. Sensitivity, specificity, negative and positive predictive values were calculated for a range of cut off values in various patient groups to support the selection of a suitable threshold.

## Results

In the RESIST studies, 1483 patients were randomised: 746 to TPV/r; and 737 to CPI/r. In the TPV/r arm, 16.6% (124/746) of patients initiated enfuvirtide (ENF; 'new' ENF) and 6.2% (46/746) recycled ENF ('old' ENF) i.e. were enfuvirtide experienced but included the drug in their OBR. At Week 48, 22.7% (169/746) of TPV/r patients had a VL <50 copies/mL compared to 10.2% (75/737) of CPI/r patients (ITT NC=F) (p<0.0001). Nearly one-third (226/746; 30.3%) of TPV/r

Table 1: Positive and negative predictive value of VL reduction from baseline  $>1.5$  log<sub>10</sub> copies/mL at Week 8 with respect to achieving a VL <50 copies/mL at Week 48

VL drop at Week 8 (log <sub>10</sub> copies/mL)	VL <50 copies/mL at Week 48		
	No N (%)	Yes N (%)	
<1.5	361 (96.0%)	15 (4.0%)	Negative predictive value = 96.0%
$\geq 1.5$	216 (58.4%)	154 (41.6%)	Positive predictive value = 41.6%
	Specificity = 62.6%	Sensitivity = 91.1%	

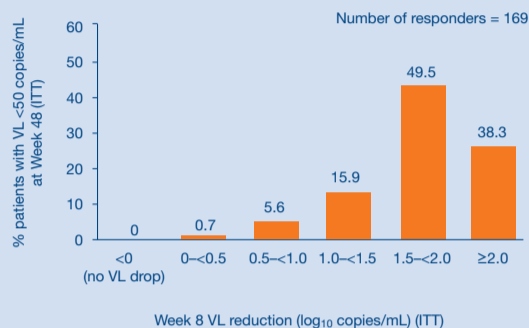


Figure 1: Viral load reduction at Week 8 in patients taking TPV/r who achieved a VL <50 copies/mL at Week 48 (ITT)

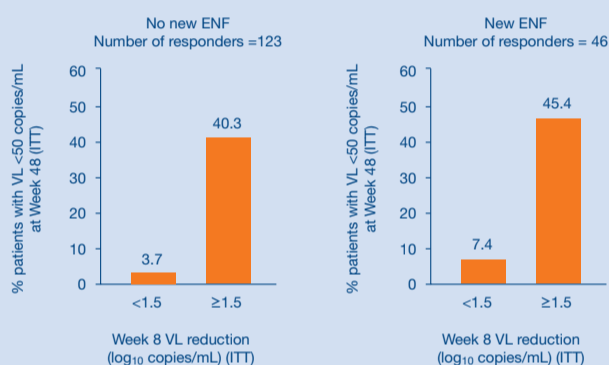


Figure 2: Viral load reduction at Week 8 in patients taking TPV/r plus or minus ENF who achieved a VL <50 copies/mL at Week 48 (ITT)

patients had a VL <400 copies/mL versus 13.6% of CPI/r patients (100/737) (ITT NC=F) (p<0.0001) at Week 48. Patients who took TPV/r plus ENF had better virological responses than those who took TPV/r without ENF: 29.4% (50/170) had VLs <50 copies/mL at Week 48 compared to 20.7% (119/576) (ITT NC=F). More than one-third (37.1%; 46/124) of 'new ENF' TPV/r patients achieved a VL <50 copies/mL at Week 48 compared to 19.8% (123/622) of 'no/old' ENF patients (ITT NC=F).

To determine a suitable threshold for predicting an undetectable (<50 copies/mL) VL at Week 48, sensitivity, specificity, negative and positive predictive values were calculated for a range of cut off values. With a cut off value above 1.5 log<sub>10</sub> copies/mL, the negative predictive value dropped below 95% and the sensitivity dropped below 90% with a relatively steep decline in sensitivity for higher cut off values. The positive predictive value reached a plateau with cut off values above 1.0 log<sub>10</sub> copies/mL, while the specificity showed a constant increase with increasing cut off values. Therefore a 1.5 log<sub>10</sub> copies/mL cut off value was selected.

In patients who took TPV/r, a VL reduction  $\geq 1.5$  log<sub>10</sub> copies/mL from baseline at Week 8 was predictive of having a VL <50 copies/mL at Week 48 (Table 1). The Odds Ratio was 17.15 (95% CI 9.83, 29.91, p<0.001), i.e. patients taking a TPV/r based regimen who experienced a VL reduction  $\geq 1.5$  log<sub>10</sub> copies/mL at Week 8 were ten times more likely to have an undetectable VL at Week 48 than patients who did not have an early virological response. The positive predictive value was 41.6% and the negative predictive value was 96.0% for this factor. The sensitivity of this association was 62.6% and its specificity was 91.1% (Table 1).

A 1.5 log<sub>10</sub> copies/mL VL reduction at Week 8 was predictive in various subgroups of TPV/r patients, classified by their ENF usage. Nearly one half of 'new' ENF patients (45.4%) who had a  $\geq 1.5$  log<sub>10</sub> copies/mL reduction in VL at Week 8 also had a VL <50 copies/mL at Week 48 compared to 7.4% of 'new ENF' patients who did not have an early virological response but did have VLs <50 copies/mL at Week 48. Similarly, 40.3% of 'no/old' ENF patients who experienced an early virological response had VLs <50 copies/mL at Week 48. By contrast, only 3.7% of 'no/old' ENF patients who did not have an early

virological response had VLs <50 copies/mL at Week 48 (Figure 2).

During the first eight weeks of TPV/r therapy, the risk of Grade 3/4 ALT elevations was low: 3.0% of TPV/r patients developed Grade 3/4 ALT levels compared to 1.4% of CPI/r patients. The frequency of Grade 3/4 transaminase elevations during TPV/r therapy is similar to that reported for other ritonavir-boosted PIs.

## Conclusions

- Patients taking a TPV/r based regimen who experienced a VL reduction  $\geq 1.5$  log<sub>10</sub> copies/mL at Week 8 were ten times more likely to have an undetectable VL at Week 48 than patients who did not have an early virological response (OR 17.15, p<0.001).
- An early virological response was also associated with a greater chance of achieving an undetectable VL at Week 48 in patients who took TPV/r plus ENF.
- During the first few weeks of TPV/r therapy, the risk of Grade 3/4 ALT elevations was low and comparable to the frequencies reported for other ritonavir-boosted PIs.
- Prescribing at least two active ARVs for this patient group is recommended by current guidelines as it is the most likely way to achieve virological and immunological responses i.e. undetectable VL and increased CD4 cell counts. Combining TPV/r and an ARV with a novel mechanism of action resulted in a substantial proportion of RESIST patients achieving these treatment goals.

## References

1. Raffi, F., et al. Clin Infect Dis, 2006. 42(6): p. 870-7.
2. Hicks, C.B., et al. Lancet, 2006. 368(9534): p. 466-75.
3. Farthing, C., et al. Tipranavir/r demonstrates superior and durable treatment response compared with comparator PI/r in highly treatment experienced (HTE) patients: Week 96 RESIST 1 and 2 results. In 46th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC). 2006. San Francisco. Abs. H-1385.
4. Gazzard, B., et al. Combined analysis of RESIST 96 week data: Durability and efficacy of tipranavir/r in treatment experienced patients. In 8th International Congress on Drug Therapy in HIV Infection. 2006. Glasgow, UK. Abs. P23.