

24-Week Efficacy and Safety of Tipranavir Boosted With Ritonavir (TPV/r) in Hepatitis B (HBV) or Hepatitis C (HCV) Co-Infected Patients

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ABSTRACT

BACKGROUND

The 2 Phase-III RESIST trials demonstrated the statistically superior efficacy of TPV/r over comparator ritonavir-boosted protease inhibitors (CPI/r). This analysis compares these treatment regimens in those HIV+ patients who were co-infected with HBV (HBsAg+) and/or HCV (HCV RNA+).

METHODS

Patients were randomized to receive TPV/r (500 mg/200 mg bid) or a preselected optimized CPI/r, plus an optimized background. Inclusion criteria required patients to have baseline laboratory test values and ALT/AST levels \leq DAIDS grade 1. Treatment response (TR) was defined as a confirmed ≥ 1 log₁₀ decrease in viral load from baseline.

RESULTS

In the 2 trials, 1483 patients were randomized and treated, and 1159 patients (582 in the TPV/r arm and 577 in the CPI/r arm) were available for analysis at 24 weeks. In the TPV/r arm, 4.0% were co-infected with HBV and 5.8% with HCV; 4 patients were HBV/HCV co-infected. There was no significant difference in TR between HBV+ (34.8% [8/23]) vs HBV- (41.4% [230/556]) patients. For HCV+ patients, TPV/r showed a TR of 47.1% (16/34) vs 40.9% (222/543) for CPI/r. TPV/r had a superior TR to CPI/r for HBV+ (34.8% vs 11.8%) and HCV+ (47.1% vs 24.5%) patients. Overall, viral hepatitis co-infected patients had a greater virologic response in the TPV/r arm than the CPI/r arm, with 38.6% [22/57] vs 15.5% [13/84] achieving a viral load <400 copies/mL and 26.3% [15/57] vs 10.7% [9/84] <50 copies/mL. The incidence of grade 3/4 ALT/AST abnormalities increased in co-infected patients in both arms (TPV 11.0%/6.8%; CPI 4.5%/3.7%) compared with HIV-only infected (TPV 5.4%/3.7%; CPI 1.3%/1.0%). TPV/r was generally well tolerated in this population, with a safety profile consistent with that of other ritonavir-boosted PI regimens in this population.

CONCLUSION

TPV/r treatment showed comparable efficacy in HIV+ patients with and without HBV and/or HCV co-infection.

INTRODUCTION

Tipranavir (TPV) is a non-peptidic protease inhibitor (NPI) with a resistance profile distinct from currently available PIs that is now approved. The companion Phase III RESIST-1 and RESIST-2 trials demonstrated that TPV/r was superior to a standard-of-care boosted PI at 24 weeks.^{1,2} TPV-based therapy produces potent, durable, and tolerable therapy in PI-experienced HIV-1-infected patients.^{3,4} In a 4-year follow-up study of treatment-experienced patients, TPV/r therapy was generally well tolerated and adverse events were not associated with treatment discontinuation.⁵ The trials were designed to allow combination of data from RESIST-1 and RESIST-2.

Advances in antiretroviral therapy have improved the life expectancy of HIV+ patients; consequently, liver disease related to hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection has emerged as a significant co-morbid disease among co-infected patients. In addition, co-infection may increase the likelihood of AIDS-defining events. Since TPV and ritonavir are metabolized by the liver and a substantial proportion of co-infected patients have advanced fibrosis or compensated cirrhosis, the efficacy and safety of TPV/r was analyzed in a subgroup of patients with hepatitis co-infection in the RESIST trials. These updated results, compared with those from HIV+ singly infected patients, are presented here.

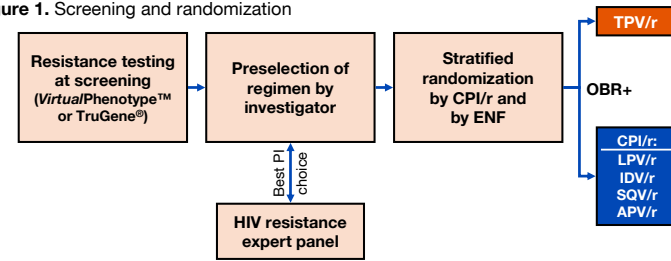
METHODS

The RESIST studies are Phase III, multicenter, open-label, randomized, comparative efficacy and safety studies of TPV/r 500 mg/200 mg twice daily compared with a genotypically defined, standard-of-care CPI/r (LPV/r, APV/r, SQV/r, or IDV/r) in HIV+ patients. At randomization, patients were stratified according to a preselected PI and T20 use. Inclusion criteria included:

- ≥ 18 years old
- ≥ 3 consecutive months of experience with all 3 classes of ARVs
- ≥ 2 PI-based regimens for at least 3 months, 1 of which was the current treatment regimen
- Any CD4+ cell count was permissible
- Viral load of ≥ 1000 copies/mL
- ≥ 1 primary protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, 90M
- ≤ 2 mutations at codons 33, 82, 84, 90
- Total cholesterol and triglycerides \leq DAIDS grade 2
- ALT $\leq 3.0 \times$ ULN and AST $\leq 2.5 \times$ ULN (\leq DAIDS grade 1)
- Co-infected patients were only allowed to enroll if their screening transaminases were ≤ 2.5 -fold above the upper limit of normal

STUDY DESIGN

Figure 1. Screening and randomization



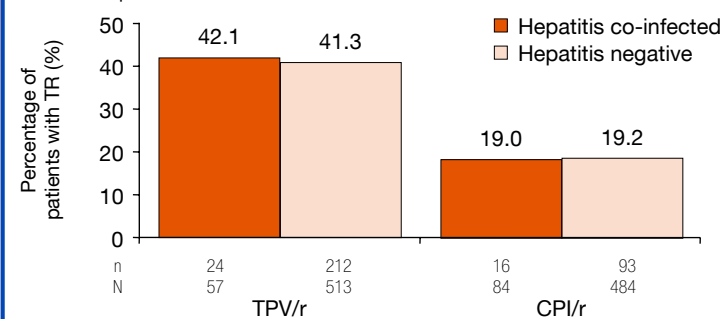
BASELINE DEMOGRAPHICS

Table 1. Baseline demographic characteristics

	TPV/r	CPI/r
Total treated	582	577
Age (years)	43.0 (17-80)	43.0 (21-72)
Gender (N, male [%])	503 (86.4)	516 (89.4)
Race (N, white [%])	430 (73.9)	414 (71.8)
Median baseline HIV-1 RNA (log ₁₀ copies/mL)	4.83	4.82
Hepatitis co-infected	4.72	4.82
Hepatitis negative	4.83	4.83
Median baseline CD4+ cell count (cells/mm ³)	155	158
Hepatitis co-infected	113	163
Hepatitis negative	159	155
HBV surface antigen+ and/or HCV RNA+ (N [%])	57 (9.8)	84 (14.6)
HBV	23	28
HCV	34	53

EFFICACY: TREATMENT RESPONSE

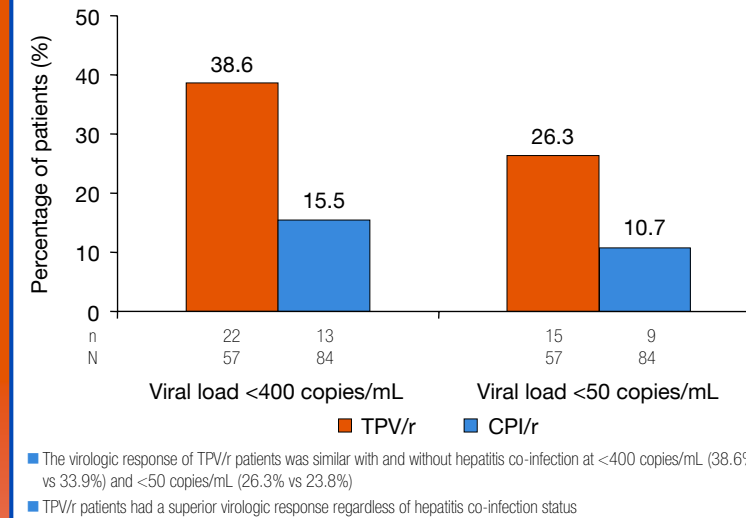
Figure 2. TPV/r patients had a greater treatment response at week 24 with or without hepatitis co-infection



- The overall treatment response (≥ 1 log₁₀ VL reduction) was 41.2% for TPV/r and 18.9% for CPI/r
- Patients with HCV or HBV co-infection had a similar treatment response as compared with the overall patients and patients not co-infected
- Patients taking TPV/r had a higher treatment response than patients in the CPI/r, regardless of hepatitis status

EFFICACY: VIROLOGIC RESPONSE

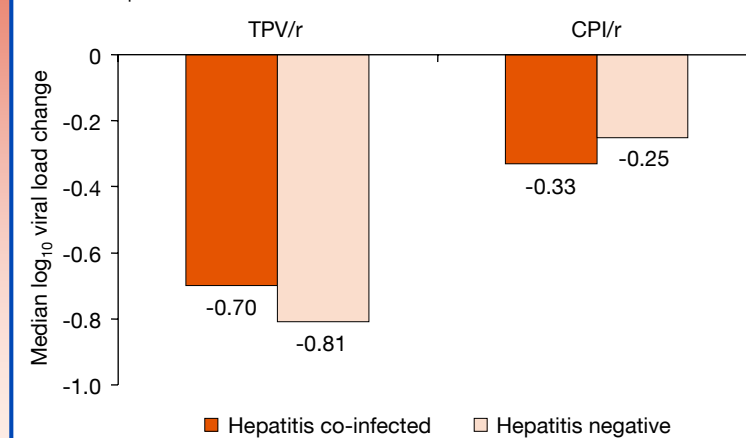
Figure 3. TPV/r patients had a greater virologic response compared with CPI/r at week 24 in patients with hepatitis co-infection



- The virologic response of TPV/r patients was similar with and without hepatitis co-infection at <400 copies/mL (38.6% vs 33.9%) and <50 copies/mL (26.3% vs 23.8%)
- TPV/r patients had a superior virologic response regardless of hepatitis co-infection status

EFFICACY: VIRAL LOAD CHANGE

Figure 4. Median baseline log₁₀ viral load change from baseline in patients with hepatitis co-infection at week 24



- TPV/r patients had a greater median viral load reduction than CPI/r, regardless of hepatitis co-infection status
- The median viral load reduction of TPV/r was similar with and without hepatitis co-infection

SAFETY: ADVERSE EVENTS

Table 2. Adverse events (AEs) in $\geq 5\%$ of all patients*

	Treatment group (N [%])			
	TPV/r (N=746)		CPI/r (N=736)	
	Hepatitis co-infected	Hepatitis negative	Hepatitis co-infected	Hepatitis negative
Total treated	76 (10.2)	665 (89.0)	113 (15.4)	620 (84.2)
Total with any AE	62 (81.6)	540 (81.2)	85 (75.2)	477 (76.9)
Diarrhea	16 (21.1)	155 (23.3)	22 (19.5)	125 (20.2)
Nausea	11 (14.5)	112 (16.8)	15 (13.3)	83 (13.4)
Pyrexia	8 (10.5)	59 (8.9)	9 (8.0)	43 (6.9)
Headache	8 (10.5)	69 (10.4)	10 (8.8)	44 (7.1)
Fatigue	7 (9.2)	62 (9.3)	5 (4.4)	57 (9.2)
Vomiting	6 (7.9)	55 (8.3)	10 (8.8)	40 (6.5)
Abdominal pain	6 (7.9)	37 (5.6)	8 (7.1)	29 (4.7)
Nasopharyngitis	6 (7.9)	32 (4.8)	4 (3.5)	24 (3.9)
Depression	6 (7.9)	19 (2.9)	4 (3.5)	27 (4.4)
Cough	5 (6.6)	29 (4.4)	9 (8.0)	26 (4.2)
Insomnia	4 (5.3)	20 (3.0)	8 (7.1)	27 (4.4)
Upper respiratory tract infection	4 (5.3)	25 (3.8)	3 (2.7)	27 (4.4)
Herpes simplex infection	4 (5.3)	28 (4.2)	1 (0.9)	19 (3.1)
Rash	3 (3.9)	36 (5.4)	5 (4.4)	32 (5.2)

*Safety data are for all patients randomized and treated, whereas efficacy data are for those patients with data available at 24 weeks

- The most reported AEs in the TPV/r group with hepatitis co-infection were diarrhea, nausea, pyrexia, headache, and fatigue
- These were also among most commonly reported AEs in the CPI/r hepatitis co-infected group
- In the TPV/r arm, both the types and frequencies of AEs were comparable in hepatitis negative and hepatitis co-infected patients
- No hepatic events occurred in $\geq 5\%$ of either hepatitis negative or hepatitis co-infected TPV/r patients
- The frequency of hepatobiliary events were similar in hepatitis negative and hepatitis co-infected patients

SAFETY: LABORATORY ANALYSIS

Table 3. Percentage of subjects with DAIDS grade 3/4 abnormalities for liver enzymes

	HIV only		HBV+		HCV+	
	TPV/r	CPI/r	TPV/r	CPI/r	TPV/r	CPI/r
ALT	8.4	1.5	17.4	5.0	14.3	7.4
AST	5.2	1.3	17.4	5.0	10.2	5.9

- The incidence of grade 3/4 AST or ALT levels was higher in both arms in patients with both HBV and HCV co-infection than in patients with only HIV infection
- These higher levels did not lead to symptomatic hepatic events
- The participants in the TPV/r arm experienced a higher rate of liver enzyme and lipid elevations; however, most laboratory abnormalities were asymptomatic and most patients remained on treatment without permanent discontinuation

SUMMARY

- The antiviral activity of TPV is not affected by HCV or HBV co-infection
- The treatment response rate was higher in the TPV/r arm than the CPI/r arm, regardless of co-infection status
- TPV/r was well tolerated in patients co-infected with HCV and/or HBV
- Patients with HCV or HBV co-infection are at an increased risk for developing transaminase elevations and therefore should be closely monitored
- The baseline presence of HCV or HBV was an independent risk factor for the development of elevated liver enzyme tests in both arms
- Most laboratory abnormalities were asymptomatic and not accompanied by jaundice or other signs of acute hepatitis or liver failure

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