

24-Week RESIST Study Analyses: The efficacy of tipranavir/ritonavir (TPV/r) is superior to lopinavir/ritonavir (LPV/r), and the TPV/r treatment response is enhanced by inclusion of genotypically active antiretrovirals in the optimized background regimen (OBR)

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ABSTRACT

BACKGROUND

RESIST-1 and -2 are ongoing phase 3, multicenter, open-label trials in treatment-experienced patients randomized to a standard-of-care regimen containing either a boosted comparator PI (CPI/r) or TPV/r. The objectives of these analyses were to compare the efficacy of TPV/r and LPV/r, and to assess the role of additional active drugs in the OBR.

METHODS

Patients with ≥3-class antiretroviral (ARV) experience, including ≥2 PI-based ARV regimens and ≥1 primary PI mutation, but ≤2 at amino acids 33, 82, 84, or 90 (TPV resistance mutations), and viral load (VL) ≥1000 copies/mL were eligible. Before randomization, an optimized CPI/r regimen (that could include enfuvirtide [T20] in the OBR) was selected. Then, patients received either TPV/r (500 mg/200 mg bid) or the preselected CPI/r (50% of investigators preselected LPV/r as optimized CPI/r) plus the OBR. The TPV/r and LPV/r treatment response was compared and the impact of active ARVs in the OBR was evaluated. Active drugs were defined as those with predicted ARV sensitivity based on interpretation of TruGene® or VirtualPhenotype™ assays. Treatment response was defined as a confirmed ≥1 log₁₀ decrease in VL from baseline.

RESULTS

1483 patients were randomized and treated in the 2 trials; 1159 were available for analysis at 24 weeks. Median baseline values: VL, 4.8 log₁₀ copies/mL; CD4+ cell count, 162 cells/mm³; number of protease gene mutations, 16. Patients had previously received a median 12 prior ARVs. At 24 weeks, treatment response (ITT-NCF) was seen in 39.6% (116/293) and 21.4% (62/290) in the TPV/r and LPV/r groups, respectively (*P*<0.05); 34% and 18% respectively had VLs <400 copies/mL; 24% and 11% respectively had <50 copies/mL; and CD4+ increase was +31 cells/mm³ and +6 cells/mm³, respectively. The 24-week treatment response increased in both the TPV/r and CPI/r groups with the use of more active background ARVs: 0 active background ARVs used (13.1% vs 9.1%, respectively), 1 (37.4% vs 12.9%), 2 (46.2% vs 19.9%), or ≥3 (54.7% vs 34.3%). A total of 24.7% of patients used T20. At week 24, the treatment response in patients using T20 was: TPV/r arm, 58.2%; CPI/r arm, 25.8%. The treatment response in patients not using T20 was: TPV/r arm, 34.9%; CPI/r arm, 16.9%.

CONCLUSION

The 24-week RESIST study results indicate that TPV/r was superior to LPV/r across multiple efficacy variables in these PI-experienced HIV-positive patients. The TPV/r treatment response is enhanced when combined with additional active ARVs.

INTRODUCTION

Tipranavir (TPV) is a non-peptidic protease inhibitor (NPI) with a resistance profile distinct from currently available PIs. It retains broad and potent in vitro antiviral activity against resistant HIV isolates and produces potent, durable, and tolerable therapy in treatment-naïve and PI-experienced HIV-1-infected patients.¹⁻⁴

The companion phase 3 trials, RESIST-1 and RESIST-2, are international, randomized, open-label studies in HIV-positive 2-PI-experienced patients designed to compare the efficacy and safety of TPV/r and comparator PI (CPI). Analyses of these 2 trials at 24 weeks have demonstrated that TPV/r was superior to CPI/r.^{5,6}

The planned analyses presented here compare the safety and efficacy of TPV/r vs LPV/r (the most frequently prescribed CPI across the 2 trials), and the effect of including active antiretrovirals, including enfuvirtide (T20) in the background regimen. LPV/r was the most frequently used comparator PI.

METHODS

RESIST studies were conducted in HIV-positive, triple-class, 2-PI-experienced male and female patients who satisfied the following criteria:

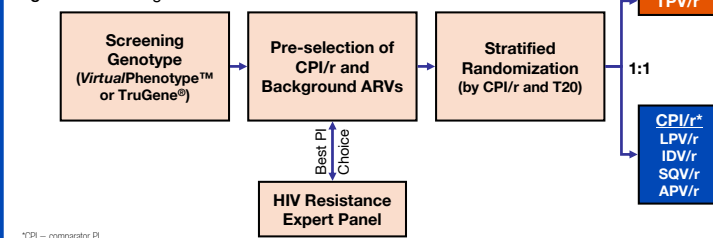
- ≥18 years old
- ≥3 consecutive months' experience with all 3 classes of ARVs
- ≥2 PI-based regimens for at least 3 months, 1 of which was the current treatment regimen
- Any CD4+ cell count was permissible
- VL of ≥1000 copies/mL
- ≥1 primary protease mutation at 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M
- ≤2 mutations at codons 33, 82, 84, 90 (key resistance mutations)

Key Exclusion Criteria

- All screening safety labs of DAIDS Grade 1 or greater
- Any recent drug holiday (7+ days in past 3 months)
- Use of investigational drugs or immunomodulatory drugs within 30 days of study entry
- Likely survival of <12 months (investigator opinion, no Karnofsky Score used)

STUDY DESIGN

Figure 1. Screening and Randomization



*CPI = comparator PI

■ Failures in CPI arm after week 8 could receive TPV in rollover study

BASELINE DEMOGRAPHICS

Table 1. Patient Demographics

	TPV/r	CPI/r
Total treated	582	577
Percent male	86.4	89.4
Median age (years)	43	43
Median baseline plasma HIV-1 RNA, (log ₁₀ copies/mL)	4.83	4.82
Median baseline CD4+ cell count, (cells/mm ³)	155	158
Median no. of protease gene mutations	16	16
Median prior ARV use	12	12
Median prior PI use	4	4
Prior T20 use, N (%)	69 (11.9)	68 (11.9)

RESULTS: STUDY MEDICATIONS

Table 2. Pre-selected Protease Inhibitor and T20

	TPV/r N (%)	CPI/r N (%)
Total treated	582 (100.0)	577 (100.0)
PI Strata		
LPV	293 (50.3)	290 (50.3)
APV	151 (25.9)	149 (25.8)
SQV	117 (20.1)	118 (20.5)
IDV	21 (3.6)	20 (3.5)
T20 Use	158 (27.1)	128 (22.2)

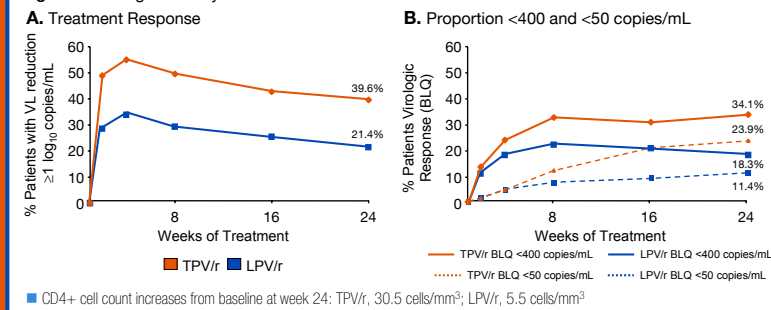
RESULTS: BASELINE PI CHARACTERISTICS

Table 3. CPI Treatment History and Resistance

	TPV/r N (%)	CPI/r N (%)
Total treated	582 (100.0)	577 (100.0)
New or Ongoing Pre-selected CPI		
CPI naïve	375 (64.4)	363 (62.9)
CPI in prior regimen	207 (35.6)	214 (37.1)
New or Ongoing Pre-selected LPV		
LPV naïve	128	122
LPV resistant	165	168
Resistance to Pre-selected PI		
Susceptible	76 (13.1)	80 (13.9)
Possibly resistant	135 (23.2)	112 (19.4)
Resistant	369 (63.4)	385 (66.7)
Missing	2 (0.3)	0 (0)
Resistant to LPV	105	91
Susceptible to LPV	187	199

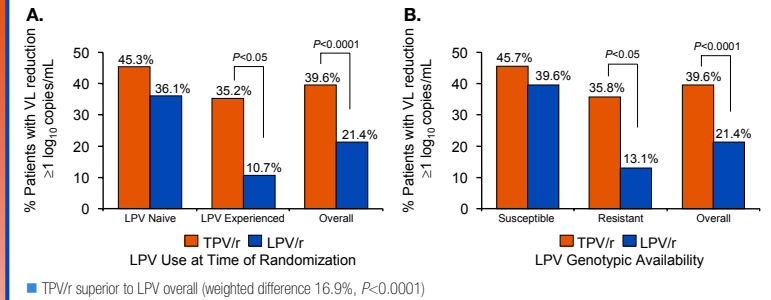
RESULTS: VIROLOGIC RESPONSE ACROSS TPV/r AND LPV/r STRATA

Figure 2. Virologic Efficacy Results for LPV/r Stratum



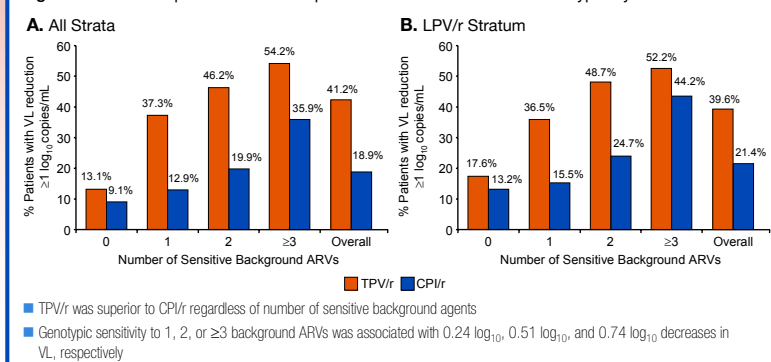
RESULTS: COMPARISON OF EFFICACY OF TPV/r AND LPV/r IN LPV STRATUM

Figure 3. 24-week Treatment Response of TPV/r- and LPV/r-treated Patients According to (A) LPV Use at Randomization and (B) LPV Sensitivity Predicted by Genotype



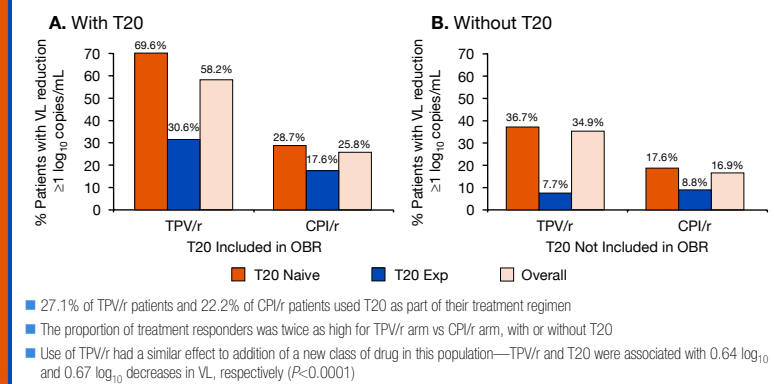
RESULTS: RELATIONSHIP OF TREATMENT RESPONSE TO NUMBER OF GENOTYPICALLY ACTIVE ARVS

Figure 4. Relationship of Treatment Response to Number of Included Genotypically Active ARVs



RESULTS: ADDITION OF T20 TO TREATMENT BACKGROUND OF TPV/r AND LPV/r PATIENTS

Figure 5. Effect of T20 on Treatment Response in the TPV/r and CPI/r Arms



SUMMARY

- TPV/r demonstrated superior treatment response to LPV/r (*P*<0.0001)
 - TPV was superior to LPV in all comparisons
- Safety profile with TPV/r was comparable to LPV/r
- Efficacy of both TPV/r and CPI/r was progressively enhanced by the number of active drugs in the OBR
 - TPV/r was always superior to CPI/r, regardless of number of background ARVs
- Addition of T20 to both TPV/r and CPI/r resulted in greater treatment response
 - TPV was superior to CPI/r with or without T20

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