

Health-Related Quality of Life with Tipranavir in Combination with an Optimized Background Regimen in 2 Randomized Clinical Trials

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ABSTRACT

BACKGROUND

Improving or preserving health-related quality of life (HRQOL) is an increasingly important goal in the treatment of HIV. We compared the impact of tipranavir vs comparator regimens on HRQOL in 2 randomized phase 3 clinical trials for ARV-experienced patients failing their current PI-based regimen.

METHODS

Patients were enrolled in 2 multinational phase 3 randomized open-label clinical trials in North America and Australia (RESIST-1); and Europe and Latin America (RESIST-2). Data are from the planned 24-week interim analyses. Tipranavir 500 BID boosted with ritonavir 200 BID (TPV/r) was evaluated vs boosted comparator PI (CPI/r) regimens selected based on genotype and treatment history. All patients received an optimized background regimen. Eligible patients had received prior NRTIs, NNRTIs, and at least 2 different PIs; had ≥ 1 primary PI mutation but ≤ 2 mutations at amino acids 33, 82, 84, and 90; and HIV RNA ≥ 1000 copies/mL. HRQOL was assessed at weeks 0, 8, 16, and 24 using the 35-item MOS-HIV, translated and validated in the relevant languages. Analyses included all randomized patients who received at least 1 dose of study drug and completed at least 1 survey. The primary outcome was change from baseline to 24 weeks in the Physical Health (PHS) and Mental (MHS) Summary scores. Exploratory analyses examined subscale scores. Multivariable longitudinal analyses used GEE modeling to explore treatment effects across all time points.

RESULTS

A total of 620 and 539 (full analysis set; FAS) patients were included in the RESIST-1 and RESIST-2 analyses. Patients on CPI/r were more likely to discontinue the study or were lost to follow-up (LTFU) at all time points after baseline (at 24 weeks: RESIST-1: 46% vs 15%; RESIST-2: 66% vs 43%). Larger differences between groups were observed in RESIST-2 compared with RESIST-1. In RESIST-2, at week 8, patients on TPV/r reported improvements in all MOS-HIV dimensions, with differences in change scores of 7.6 points for pain, 4.1 for cognitive functioning and 1.9 for PHS ($P < 0.05$ for all). At week 24, TPV/r patients had significantly larger changes in general health (6.2) and MHS (3.6). Using GEE, there was a non-significant trend favoring TPV/r. In RESIST-1, non-significant trends generally favored TPV/r. Treatment discontinuation raises the possibility that scores for the CPI/r arm may have been overestimated.

CONCLUSION

The results from this sample of ARV-experienced patients suggest that TPV/r does not adversely affect HRQOL. The impact of TPV/r on quality of life was at least as positive as that with comparator agents.

INTRODUCTION

HIV is a costly, chronic disease that exerts a significant toll on patients, caregivers, and the health care system. Without effective treatment, the functioning and well-being of patients with HIV invariably decrease over time.^{1,2} Health-related quality of life (HRQOL) measures the impact of an individual's health on his or her ability to perform and enjoy the activities of daily life.³

Declining HRQOL can have a significant impact on patients and caregivers, resulting in increases in both direct and indirect costs.^{4,5} Treatments that can prevent or delay disease progression while maintaining HRQOL can result in significant benefits to all health care stakeholders. This study measured QOL in 1114 PI-experienced HIV-1 patients who participated in the RESIST-1 and RESIST-2 trials and who were randomized to the TPV/r or CPI/r arms.

METHODS

The RESIST trials were conducted as randomized, open-label, international studies in HIV-positive, triple-class, 2-PI-experienced male and female patients who satisfied the following criteria:^{5,6}

- ≥ 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
- 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

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)

The Medical Outcomes Study-HIV Health Survey (MOS-HIV) is a brief, comprehensive QOL questionnaire that has been used extensively in studies of HIV and AIDS.⁷ The MOS-HIV reports physical health summary (PHS) and mental health summary (MHS) scores.

- Primary HRQOL study endpoint was change from baseline to 24 weeks in the MOS-HIV PHS and MHS summary scores
- QOL analyses performed on all randomized patients treated with ≥ 1 dose of study medication and ≥ 1 measurement using the MOS-HIV
- MOS-HIV was self-administered at baseline (0), 8, 16, and 24 weeks
- The 10 subscales of QOL included (1) general health perceptions (GH), (2) physical functioning (PF), (3) role functioning (RF), (4) pain (PN), (5) social functioning (SF), (6) mental health (MH), (7) energy (EN), (8) health distress (HD), (9) cognitive functioning (CF), and (10) overall quality of life (QL). In addition, one item assesses health transition (HT)
- Subscales of MOS-HIV are scored as a summated rating scale, from 0-100, higher scores indicate better QOL

Multivariable longitudinal analyses used generalized estimating equation (GEE) modeling to explore treatment effects across all time points.

BASILINE DEMOGRAPHICS

Table 1. Patient Demographics

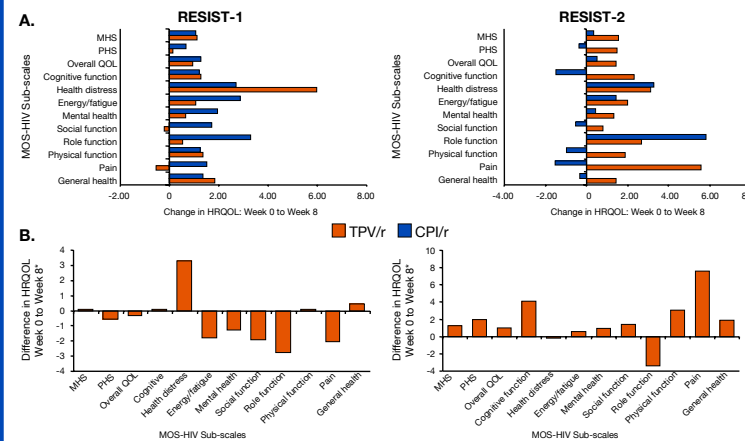
	RESIST-1		RESIST-2	
	TPV/r (n=311)	CPI/r (n=309)	TPV/r (n=271)	CPI/r (n=268)
Median age (years)	45	43	41	42
Male gender (%)	89.4	92.9	83	85.4
Race* (%)				
White	77.5	76.1	69.7	66.8
Black	21.9	22.3	5.5	4.1
Asian	0.6	1.6	0.7	1.1
Median baseline plasma HIV-1 RNA, log ₁₀ copies/mL	4.81	4.84	4.84	4.81
Median baseline CD4+ cell count, cells/mm ³	123	123	175	200

*Certain countries prohibit the collection of race data, therefore the race of all patients is not known.

■ No statistically significant differences ($P > 0.05$) found between the 2 study groups in baseline sociodemographic, clinical characteristics, or baseline MOS-HIV scale scores

RESULTS: CHANGE IN HRQOL FROM WEEKS 0 TO 8

Figure 1. (A) Change in HRQOL and (B) Difference in HRQOL from Weeks 0 to 8 for RESIST-1 and RESIST-2



*Positive value indicates TPV/r is better.

RESIST-1

- TPV/r patients experienced positive trends in all but 2 categories and significant improvement in 2 categories: decrease in health distress ($P < 0.001$) and increase in MHS ($P < 0.05$)
- CPI/r patients experienced significant improvement in 4 categories: health distress ($P < 0.05$), MHS ($P < 0.05$), energy/fatigue ($P < 0.01$), and mental health ($P < 0.05$)

RESIST-2

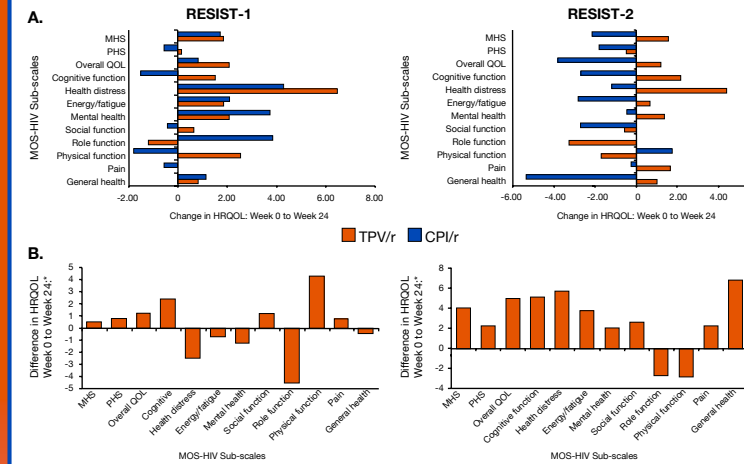
- TPV/r patients experienced positive trends in all categories and significant improvement in 5 categories: pain ($P < 0.001$), health distress ($P < 0.01$), increase in cognitive function ($P < 0.05$), PHS ($P < 0.01$), and MHS ($P < 0.01$)
- CPI/r patients experienced significant improvement in 2 categories: role function ($P < 0.05$) and health distress ($P < 0.01$)

Overall

- TPV/r was similar to CPI/r for RESIST-1 and superior to CPI/r for RESIST-2 at 8 weeks

RESULTS: CHANGE IN HRQOL FROM WEEKS 0 TO 24

Figure 2. (A) Change in HRQOL and (B) Difference in HRQOL from Weeks 0 to 24 for RESIST-1 and RESIST-2



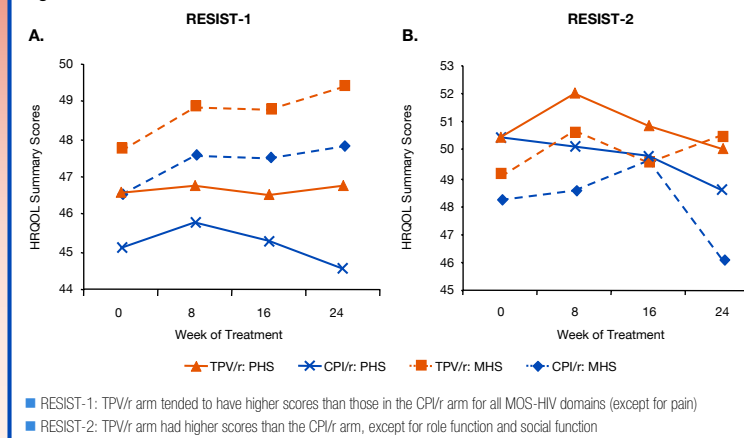
*Positive value indicates TPV/r is better.

RESIST-1

- TPV/r was superior to CPI/r for overall HRQOL scores, but there were no statistically significant differences between the groups
- The benefit of TPV/r over CPI/r was more pronounced than in RESIST-1. TPV/r patients had significantly better general health perceptions ($P < 0.05$) and overall mental health ($P < 0.05$) compared with CPI/r patients

RESULTS: MULTIVARIABLE ANALYSES OF HRQOL DATA SETS FOR THE RESIST STUDIES

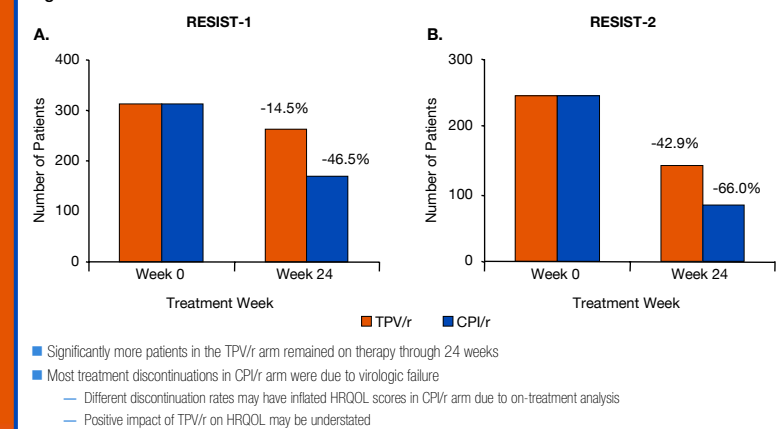
Figure 3. Trend in HRQOL Over Time: Weeks 0 to 24



- RESIST-1: TPV/r arm tended to have higher scores than those in the CPI/r arm for all MOS-HIV domains (except for pain)
- RESIST-2: TPV/r arm had higher scores than the CPI/r arm, except for role function and social function

RESULTS: DISCONTINUATION BY TREATMENT ARM

Figure 4. LTFU Rates in the RESIST Trials



SUMMARY

- For RESIST-1 and RESIST-2, TPV/r maintained HRQOL at least as well as CPI/r
- MOS-HIV scores for the TPV/r arm were superior to those for the CPI/r arm in both RESIST trials
- Differences in change scores between TPV/r and CPI/r were greater for RESIST-2 than for RESIST-1, with significant differences at week 8 and week 24
- Without effective treatment, it is likely that PI-experienced patients enrolled in these studies would have experienced declining function and well-being over time. In this context, the observed preservation of HRQOL can be considered a benefit
- Based upon the positive trend in HRQOL over the first 24 weeks, and the improved domain scores at time points throughout the study to date, TPV/r may provide important benefits to patients, caregivers, and payers through the maintenance of HRQOL

REFERENCES

- Bowie RD, Tobias MI, Williams T. *N Z Med J*. 1996;109:51-54.
- Weinfurt KP, Wilke RJ, Glick HA, Freimuth WW, Schulman KA. *Med Care*. 2000;38:404-410.
- Curtis JR, Deyo RA, Hudson LD. *Thorax*. 1994;49:162-170.
- Prachakul W, Grant JS. *J Assoc Nurses AIDS Care*. 2003;14:55-71.
- Hicks C, for the RESIST-1 study team. Presented at: 44th ICAAC; October 30-November 2, 2004; Washington, DC.
- Cahn P, and the RESIST-2 study team. Presented at: 7th International Congress on Drug Therapy in HIV Infection; November 14-18, 2004; Glasgow, Scotland.
- Wu AW, Rubin HR, Matthews WC, et al. *Med Care*. 1991;29:786-798.