Efficacy of the Protease Inhibitors Tipranavir plus Ritonavir in Treatment-Experienced Patients: 24-Week Analysis from the RESIST-1 Trial

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(See the article by Cahn et al. on pages 1347–56)

Background. Improved treatment options are needed for patients infected with multidrug-resistant human immunodeficiency virus type 1 (HIV-1). The nonpeptidic protease inhibitor tipranavir has demonstrated antiviral activity against many protease inhibitor–resistant HIV-1 isolates. The Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST-1) trial is an ongoing, open-label study comparing the efficacy and safety of ritonavir-boosted tipranavir (TPV/r) with an investigator-selected ritonavir-boosted comparator protease inhibitor (CPI/r) in treatment-experienced, HIV-1–infected patients.

Methods. Six hundred twenty antiretroviral-experienced patients were treated at 125 sites in North America and Australia. Before randomization, all patients underwent genotypic resistance testing, which investigators used to select a CPI/r and an optimized background regimen. Patients were randomized to receive TPV/r or CPI/r and were stratified on the basis of preselected protease inhibitor and enfuvirtide use. Treatment response was defined as a confirmed reduction in the HIV-1 load of ≥ 1 $\log_{10}$ less than the baseline level without treatment change at week 24.

Results. Mean baseline HIV-1 loads and $CD4^+$ cell counts were 4.74 $\log_{10}$ copies/mL and 164 cells/mm^3, respectively. At week 24, a total of 41.5% of patients in the TPV/r arm and 22.3% in the CPI/r arm had a ≥ 1-$\log_{10}$ reduction in the HIV-1 load (intent-to-treat population; $P < .0001$). Mean increases in the $CD4^+$ cell count of 54 and 24 cells/mm^3 occurred in the TPV/r and CPI/r groups, respectively. Adverse events were slightly more common in the TPV/r group and included diarrhea, nausea, and vomiting. Elevations in alanine and aspartate aminotransferase levels and in cholesterol/triglyceride levels were more frequent in the TPV/r group.

Conclusions. TPV/r demonstrated superior antiviral activity, compared with investigator-selected, ritonavir-boosted protease inhibitors, at week 24 in treatment-experienced patients with multidrug-resistant HIV-1 infection.

Protease inhibitor (PI)–based combination antiretroviral therapy has produced significant decreases in morbidity and mortality in patients with HIV-1 infection [1]; however, treatment failure still occurs [2–5] as a result of poor tolerability, lack of adherence, and challenging dosing regimens, all of which can lead to viral resistance [6–8]. Such issues may limit options for future therapy [9–11], particularly for patients who experience triple–drug class virologic failure and who may be at increased risk of death (3-year mortality rate, 15%) [12]. Therefore, despite the undisputed benefits of modern antiretroviral therapy regimens, newer agents with activity against drug-resistant HIV-1 are needed.

Tipranavir is a nonpeptidic PI of the dihydropyrone sulfonamide class with a structure differing from that

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of peptidic PIs, and in vitro studies have shown that it may be effective against virus strains that are resistant to available peptidic PIs [13–18]. Tipranavir is rapidly and extensively metabolized through the cytochrome P450 isoenzyme 3A [19–22] and must be coadministered with ritonavir to attain therapeutic concentrations [23]. Ritonavir-boosted tipranavir (TPV/r) has demonstrated potent antiviral activity in both treatment-naive and treatment-experienced patients [24, 25].

The Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST-1) trial is an ongoing, open-label, phase III multicenter study designed to evaluate the efficacy and safety of TPV/r (500 mg/200 mg twice per day, selected on the basis of phase II dose-ranging studies) and an investigator-selected, ritonavir-boosted, standard-of-care comparator PI (CPI/r), when given with an optimized background regimen to treatment-experienced, HIV-1–infected patients. A similar study (RESIST-2) has been conducted in Europe and Latin America [26]. The results of the 24-week interim analysis of RESIST-1 are presented here.

METHODS

Patients. HIV-1–infected adult patients were screened for baseline HIV-1 RNA levels $\geq$1000 copies/mL (i.e., the minimum level required for genotyping); documented baseline genotypic resistance demonstrating $\geq$1 primary PI mutation (codons 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M) [27]; no more than 2 PI resistance-associated mutations at codons 33, 82, 84, or 90; at least 3 consecutive months of experience with all antiretroviral therapy agents (nucleoside reverse-transcriptase inhibitors [NRTIs], nonnucleoside reverse-transcriptase inhibitor [NNRTIs], and PIs); experience with $\geq$2 PI-based regimens, one of which had to be the regimen at baseline. There was no restriction with regard to the $CD4^+$ cell count. Safety screening laboratory values of the Division of AIDS of the National Institutes of Health of grade $\geq$2 were exclusionary (grade 2 was allowed for total cholesterol and triglyceride levels). Other exclusion criteria included interruption in the antiretroviral treatment regimen for $\geq$7 consecutive days within 3 months of screening, prior tipranavir use, a positive pregnancy test result, or breast-feeding. Patients were excluded if they required other investigational medications, immunomodulatory drugs, or ethinyl estradiol within 30 days of study entry; if they were actively abusing substances that affected protocol participation; if they had an unacceptable medical history, as determined by the investigator (e.g., on the basis of exclusionary chest radiograph or electrocardiograph findings); or if they were unlikely to survive for 12 months. The protocol and written informed consent forms were reviewed and approved by an institutional review board or ethics committee before patients entered the study.

Study design. This ongoing, randomized, open-label, phase III study is being conducted at 125 sites in the United States, Canada, and Australia for a treatment period of 96 weeks. The main efficacy end point is treatment response, defined as the proportion of patients with a reduction in the HIV-1 load of $\geq$1 $\log_{10}$ after 24 weeks (confirmed by 2 consecutive measurements), without having experienced virologic failure, discontinued treatment with the study PI, introduced new antiretroviral agents because of a lack of treatment efficacy, neglected to maintain follow-up, or died. Other end points included the change from the baseline value in plasma HIV-1 RNA levels, achievement of an HIV-1 load <400 or <50 copies/mL, changes in the $CD4^+$ cell count during treatment, and safety measures.

Treatment. Before randomization, investigators selected both a CPI/r and an NRTI-based and NNRTI-based optimized background regimen (manufacturer's recommended dosages) for each patient on the basis of genotypic resistance screening findings and the patient's antiretroviral medication history. An expert resistance panel was available to help select the CPI/r. Patients were randomized to receive TPV/r or a preselected CPI/r (lopinavir-ritonavir, 400 mg/100 mg twice per day; indinavir-ritonavir, 800 mg/100 mg twice per day; saquinavir-ritonavir, 1000 mg/100 mg or 800 mg/200 mg twice per day; or amprenavir-ritonavir, 600 mg/100 mg twice per day). Randomization was stratified by both the preselected PI and the use of enfuvirtide. Tipranavir (250-mg capsules) was supplied by Boehringer Ingelheim, and CPIs and ritonavir were commercially acquired.

Changes to the treatment regimen were permitted only for reasons of toxicity and/or intolerance to the non-PI components of the regimen. After week 8, patients in the CPI/r arm had the option of discontinuing the assigned CPI because of a lack of initial virologic response (defined as a decrease in the HIV-1 load of <0.5 $\log_{10}$ from baseline or failure to achieve an HIV-1 load of <100,000 copies/mL despite having a 0.5-$\log_{10}$ decrease) or confirmed virologic failure (defined as an HIV-1 load of <1 $\log_{10}$ less than the baseline level confirmed on 2 consecutive assays or as 1 HIV-1 load of <1 $\log_{10}$ less than the baseline value followed by a permanent discontinuation of therapy) to receive TPV/r as part of a separate rollover study. This option was only permitted for participants who experienced confirmed HIV-1 load failure who had a measurable CPI blood concentration. Trough plasma drug concentrations for all PIs and ritonavir were determined at weeks 2, 4, and 28 (i.e., visits 4, 5, and 8). The ratio of the geometric mean trough plasma concentration for the PI to the IC_{50} (both unadjusted and protein adjusted) of the HIV isolate at study entry was calculated and correlated to subsequent virologic response.

Sample analysis. Plasma HIV-1 RNA levels were measured using the Amplicor HIV-1 Monitor Assay, version 1.5 (Roche), or the UltraSensitive method, version 1.5 (Roche). $CD4^+$ cell counts were measured using standard flow cytometry. All tests

were conducted by Covance Central Laboratory Services (Indianapolis, IN). HIV genotype resistance assessments were performed using the TruGene method, version 1.0, at screening; at weeks 4, 8, 16, and 24; and at end of treatment. Phenotypic drug resistance was determined in a randomly selected subset of 250 patients by Virco NV (Mechelen, Belgium) using Virco's Antivirogram assay. The Division of AIDS adverse events scale was used to grade adverse event intensity and several laboratory abnormalities, and the Common Toxicity Criteria scale was used to grade cholesterol levels.

Statistical analysis. Differences in treatment response at week 24 were analyzed by a 2-sided 95% CI, which was adjusted for preselected PI and enfuvirtide use [28]. A sample size of 247 patients per treatment arm provided 90% power to detect 15% superiority of tipranavir over CPIs in virologic response at 24 weeks, using a 2-sided Fisher's exact test. All efficacy analyses use the intent-to-treat, noncompleter-considered-failure analysis, in which missing values associated with premature discontinuation of treatment were considered to indicate treatment failure. Changes in the HIV-1 load and $CD4^+$ cell count over time were evaluated using the last-observation-carried-forward analysis.

RESULTS

Baseline Patient Characteristics

Between January 2003 and April 2004, a total of 1406 patients were screened for the RESIST-1 trial, and 630 patients were randomized (figure 1). Baseline characteristics were comparable between groups (table 1). The median number of genotypically available antiretrovirals in the optimized background regimen was 2 in the TPV/r group and 1 in the CPI/r group, and more patients in the TPV/r arm exhibited resistance to their preselected PI (54.3% vs. 60.5%). A higher proportion of patients in the CPI/r group than the TPV/r group had hepatitis C virus coinfection (7.4% vs. 3.2%).

Baseline Resistance Characteristics

Baseline genotypes identified a mean of 2 primary protease gene mutations from among 30N, 46I/L, 48V, 50V, 82A/F/L/T, 84V, or 90M, as well as a mean of 15 total protease gene mutations or polymorphisms. The median baseline phenotypic fold-change in susceptibility to tipranavir for the random sample of viral isolates was 1.9 times wild-type IC_{50}, compared with the following CPI IC_{50} values for the same specimens: 77.8-fold for lopinavir, 39.0-fold for indinavir, 27.2-fold for saquinavir, and 12.2-fold for amprenavir. The expert resistance panel was consulted for optimized background regimen selection in 154 (25%) of 620 cases, with 114 (74%) of their 154 recommendations being implemented. The optimized background regimen included a median of 1 genotypically active antiretroviral, including enfuvirtide (range, 0–4 antiretrovirals). The most common optimized background regimen (not including the CPI), which was received by 158 patients (25.5%), was 2 NRTIs. On the basis of the genotype test results, 176 patients (56.6%) in the TPV/r group and 183 patients (59.2%) in the CPI/r group were assigned a new PI.

Patient Disposition

Overall, 263 patients (84.6%) and 151 patients (48.9%) in the TPV/r and CPI/r groups, respectively, completed 24 weeks of treatment (figure 1). More patients in the TPV/r arm (199 patients [64.0%]) than in the CPI/r arm (136 patients [44.0%]) received study medication for at least 24 weeks. This resulted in a greater number of patient-exposure-years for the TPV/r arm (133.3 years) than for the CPI/r arm (115.8 years).

Efficacy End Points

Treatment response. Patients who received TPV/r demonstrated a significantly higher treatment response rate (according to intent-to-treat, noncompleter-considered-failure analysis), compared with CPI/r recipients (41.5% vs. 22.3%; $P < .0001$) (figure 2*A*). After response rates for the 2 arms were adjusted for different CPIs and enfuvirtide use, TPV/r had an 18.4% higher treatment response rate, compared with CPI/r (95% CI, 11.4%–25.3%). When treatment response rate was analyzed by the individual CPI, TPV/r was superior to each CPI (lopinavir group, 37.2% for tipranavir vs. 24.1% for lopinavir [$P = .0069$]; saquinavir group, 45.3% for tipranavir vs. 18.8% for saquinavir [$P = .0005$]; amprenavir group, 52.4% for tipranavir vs. 24.4% for amprenavir [$P = .0057$]; and indinavir group, 50.0% for tipranavir vs. 7.7% for indinavir [$P = .02$]).

A superior treatment response was also reported with the TPV/r group in patients with 3–4 or 5–6 primary PI-associated mutations at week 24, compared with the CPI/r group (3–4 mutations, 78 [42.9%] of 182 patients vs. 30 [15.5%] of 194 patients; 5–6 mutations, 2 [66.7%] of 3 patients vs. 1 [33.3%] of 3 patients). Furthermore, patients with 1–2 PI mutations at codons 33, 82, 84, or 90 in the TPV/r group had greater treatment response values than did comparable patients in the CPI/r group (1 mutation, 42 [46.2%] of 91 patients vs. 25 [32.5%] of 77 patients; 2 mutations, 81 [42.2%] of 192 patients vs. 36 [17.6%] of 204 patients). At week 24, when the treatment response was evaluated in 182 TPV/r recipients with an available baseline phenotype, there was a 47% response rate (54 of 115 patients) in patients with a baseline IC_{50} fold-change of <3, compared with 28% (19 of 67 patients) in those with a baseline IC_{50} fold-change of 3–8. Patients with a baseline HIV-1 load of <10,000 copies/mL were more likely to achieve a treatment response than were those with higher baseline HIV-1 loads (table 2).

Other efficacy end points. The 24-week mean reduction in HIV-1 load from baseline was significantly greater in the TPV/

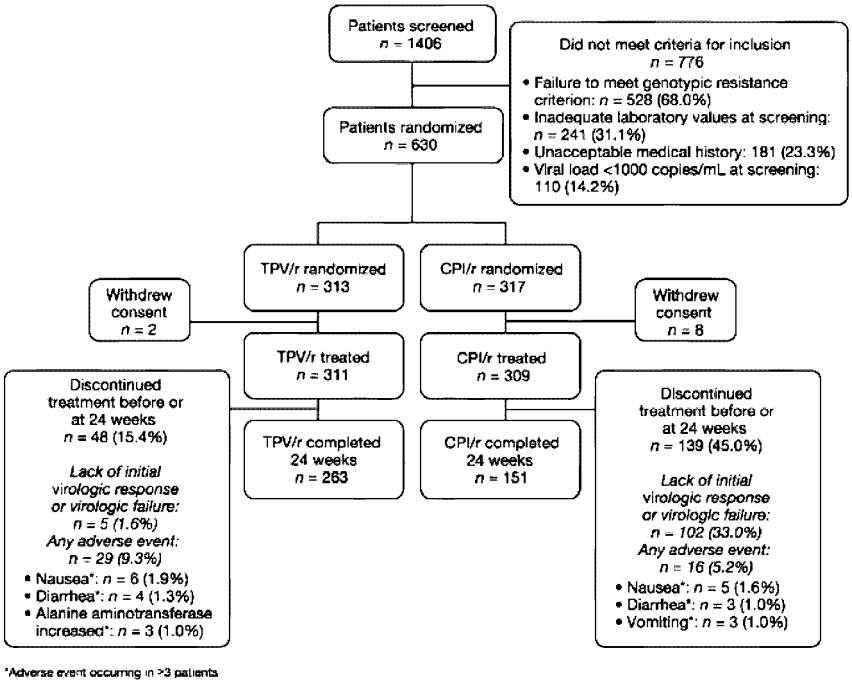

Figure 1. Patient disposition in a study of the efficacy of the protease inhibitors tipranavir and ritonavir. CPI/r, ritonavir-boosted comparator protease inhibitor; TPV/r, ritonavir-boosted tipranavir.

r group (-1.28 $\log_{10}$) than in the CPI/r group (-0.64 $\log_{10}$; $P < .001$) (figure 2*B*). More TPV/r recipients achieved an undetectable HIV-1 load (cutoff of <400 copies/mL, 34.7%; cutoff of <50 copies/mL, 25.1%), compared with CPI/r recipients (cutoff of <400 copies/mL, 16.5%; cutoff of <50 copies/mL, 10.0%; $P < .0001$) (figure 2*C*). Furthermore, among TPV/r and CPI/r recipients who received enfuvirtide, the proportion of patients with an undetectable HIV-1 load increased during treatment (for TPV/r recipients, 47.1% and 32.8% for cutoff values of <400 and <50 copies/mL, respectively; for CPI/r recipients, 21.9% and 14.3% for cutoff values of <400 and <50 copies/mL, respectively). The mean increase from baseline in the $CD4^+$ cell count was significantly greater in the TPV/r group than in the CPI/r group (+54 vs. +24 cells/mm^3; $P < .001$) (figure 2*D*).

The treatment response rate for TPV/r increased from 11.6% (5 of 43 patients), when the optimized background regimen contained no genotypically susceptible drugs, to 57.6% (19 of 33 patients), when there were ⩾3 genotypically susceptible drugs. Response rates with CPI/r ranged from 13.2% (7 of 53 patients), when there were no genotypically active drugs, to 41.0% (16 of 39 patients), when there were >3 active drugs. The addition of enfuvirtide to the optimized background regimen improved treatment response, from 31.3% to 58.0% in the TPV/r group and from 18.6% to 29.5% in the CPI/r group. The effect of enfuvirtide on treatment response was enhanced in TPV/r-treated patients who were enfuvirtide naive (66.7%), compared with enfuvirtide-experienced patients (31.0%).

Trough plasma concentrations were analyzed at weeks 2 and 4. Detectable plasma PI concentrations had to be documented before approval was granted for a switch of a patient from the CPI/r group to the TPV/r group. There was no difference in mean drug concentration measurements for patients who changed treatment group versus those who did not.

Safety

All 620 treated patients were included in the safety analysis. Most patients experienced at least 1 adverse event (90.7% of TPV/r recipients and 86.4% of CPI/r recipients) (table 3). The majority of adverse events in the 2 groups were graded as mild (in 78.5% of TPV/r recipients and 75.7% of CPI/r recipients) or moderate (in 59.8% of TPV/r recipients and 53.4% of CPI/r recipients) in intensity. In the TPV/r group, adverse events leading to discontinuation (⩾2 patients) were nausea, diarrhea, increased alanine aminotransferase (ALT) levels, vomiting, cerebrovascular accident, fatigue, pyrexia, and sepsis, whereas in the CPI/r group, adverse events leading to discontinuation (⩾2 patients) were nausea, diarrhea, vomiting, and abdominal pain (<2% of patients in all cases).

Serious adverse events were experienced by 55 patients (17.7%) in the TPV/r arm and 42 patients (13.6%) in the CPI/r arm; fever (TPV/r group, 1.9%; CPI/r group, 1.3%), diarrhea

Table 1. Baseline demographic characteristics of patients.

Characteristic	Treatment group		
	Overall (n = 620)	TPV/r arm (n = 311)	CPI/r arm (n = 309)
Male sex	565 (91.1)	278 (89.4)	287 (92.9)
Age, median years (range)	44 (24 –80)	45 (24–80)	43 (28–70)
Median no. of NRTIs used (range)	6 (2–8)	6 (2–8)	6 (2–8)
Median no. of NNRTIs used (range)	2 (0–3)	2 (0–3)	1 (0–3)
Median no. of PIs used (range)	4 (1–7)	4 (1–7)	4 (1–7)
HIV-1 load, median $\log_{10}$ copies/mL (range)	4.83 (2.01–6.31)	4.81 (2.34–6.13)	4.84 (2.01–6.31)
CD4$^+$ cell count, median cells/mm^3 (range)	123 (1–1184)	123 (1–860)	123 (1–1184)
Fusion inhibitor use	76 (12.3)	39 (12.5)	37 (12.0)
History of AIDS-defining illnesses	421 (67.9)	209 (67.2)	212 (68.6)
Median no. of primary protease mutations (range)	2.7 (0–5)	2.7 (0–5)	2.7 (0–5)
No. of protease mutations at 33, 82, 84, and 90[a]			
0	24 (3.9)	11 (3.5)	13 (4.2)
1	168 (27.1)	91 (29.3)	77 (24.9)
2	396 (63.9)	192 (61.7)	204 (66.0)
New PI selected that was not part of screening treatment regimen	359 (57.9)	176 (56.6)	183 (59.2)
Resistance to preselected PI			
Susceptible[b]	49 (7.9)	21 (6.8)	28 (9.1)
Possible resistance[c]	214 (34.5)	120 (38.6)	94 (30.4)
Resistance[d]	356 (57.4)	169 (54.3)	187 (60.5)
Median no. of genotypically available ARVs in the optimized background regimen (range)[e]	1 (0–4)	2 (0–4)	1 (0–4)
Treatment assignment			
Lopinavir	378 (61.0)	191 (61.4)	187 (60.5)
Indinavir	27 (4.4)	14 (4.5)	13 (4.2)
Saquinavir	128 (20.6)	64 (20.6)	64 (20.7)
Amprenavir	87 (14.0)	42 (13.5)	45 (14.6)
Enfuvirtide	224 (36.1)	119 (38.3)	105 (34.0)
Hepatitis virus coinfection status			
HBsAg and HCV RNA negative	559 (90.2)	286 (92.0)	273 (88.3)
HBsAg positive and HCV RNA negative	26 (4.2)	14 (4.5)	12 (3.9)
HBsAg negative and HCV RNA positive	31 (5.0)	10 (3.2)	21 (6.8)
HBsAg and HCV RNA positive	2 (0.3)	0	2 (0.6)
Missing	2 (0.3)	1 (0.3)	1 (0.3)
Hepatitis B antibody positive	335 (54.0)	171 (55.0)	164 (53.1)

NOTE. Data are no. (%) of subjects, unless otherwise indicated. ARV, antiretroviral; CPI/r, ritonavir-boosted comparator protease inhibitor; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; NNRTI, nonnucleoside reverse-transcriptase inhibitor; NRTI: nucleoside reverse-transcriptase inhibitor; TPV/r, ritonavir-boosted tipranavir.

[a] Individual codons were counted, not multiple polymorphisms. Mixture of wild-type and mutant are counted as mutants. V3I was not counted.
[b] No evidence of resistance detected using the HIV-1 genotyping method, versions 6.0 and 7.0 (TruGene).
[c] Possible resistance detected using the HIV-1 genotyping method, versions 6.0 and 7.0 (TruGene).
[d] Resistance detected using the HIV-1 genotyping method, versions 6.0 and 7.0 (TruGene).
[e] Found to be susceptible or possibly resistant (excluding the study PI) by the HIV-1 genotyping method, versions 6.0 and 7.0 (TruGene); enfuvirtide was always considered to be susceptible.

(TPV/r group, 1.6%; CPI/r group, 1.0%), and pneumonia (TPV/r group, 1.6%; CPI/r group, 0.6%) were the most common adverse events. Severe adverse events (grade 3 or 4 according to the Division of AIDS scoring system) were reported for 71 patients (22.8%) in the TPV/r arm and 56 patients (18.1%) in the CPI/r arm.

During the study, 15 types of AIDS-defining illnesses were acquired by 11 patients (3.5%) in the TPV/r group and 16 patients (5.2%) in the CPI/r group. There was a higher frequency of esophageal candidiasis in the CPI/r group (2.3% vs. 0.3%) and of wasting syndrome in the TPV/r group (1.0% vs. 0%). No other AIDS-defining illnesses were experienced by >2 patients in either group.

Laboratory abnormalities were generally more common in

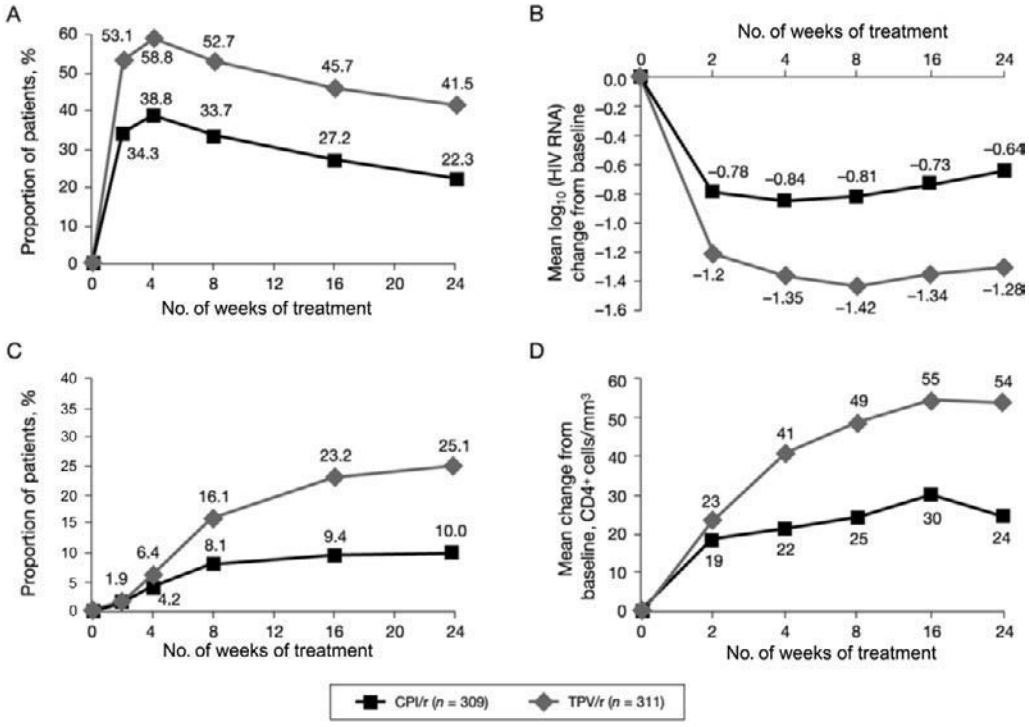

Figure 2. Comparison of virologic and immunologic responses in the ritonavir-boosted tipranavir (TPV/r) and ritonavir-boosted comparator protease inhibitor (CPI/r) groups over 24 weeks. *A,* Treatment response (defined as a confirmed $\geqslant$1-$\log_{10}$ reduction in the HIV-1 load). *B,* HIV-1 load reduction. *C,* Virologic response (defined as an HIV-1 load <50 copies/mL). *D,* $CD4^+$ cell count. For the TPV/r group, all 311 patients were analyzed for all variables except for the $CD4^+$ cell count, for which 1 data point was missing ($n = 310$). All 309 patients in the CPI/r arm were analyzed for all 4 response variables.

the TPV/r arm than in the CPI/r arm (table 2); most of these were mild or moderate and asymptomatic. Elevations in hepatic enzyme and plasma lipid levels were the most common grade 3 or 4 laboratory abnormalities reported. Among patients who experienced elevations in the ALT level, 15 (9.0%) were coinfected with hepatitis B or C virus, whereas 6 (4.4%) were not. Among patients who experienced elevated aspartate aminotransferase levels, 11 (6.6%) were coinfected with hepatitis B or C virus, and 3 (2.2%) were not. Seventeen of 21 TPV/r recipients with grade 3 or 4 liver function test results continued to received treatment without permanent discontinuation.

No patient with grade 3 or 4 elevated ALT or AST levels in either group developed treatment-onset hepatitis or related hepatic events. Some patients were concomitantly receiving potentially hepatotoxic drugs (13 [54.2%] of the 24 TPV/r-treated patients and 5 [62.5%] of the 8 CPI/r-treated patients with elevated ALT or AST levels).

There were 8 deaths (2.6%) in the TPV/r arm and 6 deaths (1.9%) in the CPI/r arm (6.0 and 5.2 deaths per 100 patient-exposure-years, respectively). None were judged to be related to treatment.

DISCUSSION

The results of this 24-week interim analysis demonstrate that, when TPV/r is used as part of antiretroviral combination therapy, it significantly suppresses viral replication and increases $CD4^+$ cell counts in genotypically screened, highly antiretroviral-treatment experienced patients with multidrug-resistant HIV-1 infection. A significantly greater proportion of patients randomized to receive TPV/r (41.5%), compared with CPI/r (22.3%), achieved an HIV-1 load reduction of $\geqslant$1 $\log_{10}$ after 24 weeks. In addition, patients in the TPV/r group experienced a significantly greater increase in $CD4^+$ cell counts than did those in the CPI/r group, although small imbalances in baseline characteristics may impact these results. These findings are important, because changes of this magnitude in virologic and immunologic markers have been associated with a decreased incidence of AIDS-defining events [29–32]. Furthermore, the level of suppression of HIV-1 replication observed at 24 weeks was comparable with that reported in the T-20 versus Optimized Regimen Only (TORO) trials of treatment-experienced patients, in which patients were randomized to receive enfuvirtide or an optimized background regimen alone [33, 34].

Table 2. Patients with a treatment response at week 24, according to baseline HIV-1 load.

Characteristic	Treatment group, no. of responders/ no. of evaluable patients (%)		
	Overall population	TPV/r arm	CPI/r arm
Total treated patients	198/620 (31.9)	129/311 (41.5)	69/309 (22.3)
Baseline HIV RNA level, copies/mL			
<1000	1/4 (25.0)	1/3 (33.3)	0/1 (0)
1000–10,000	40/93 (43.0)	24/45 (53.3)	16/48 (33.3)
>10,000 to 100,000	87/265 (32.8)	58/134 (43.3)	29/131 (22.1)
>100,000	70/258 (27.1)	46/129 (35.7)	24/129 (18.6)

NOTE. CPI/r, ritonavir-boosted comparator protease inhibitor; TPV/r, ritonavir-boosted tipranavir.

One treatment aim for patients with prior antiretroviral exposure and drug resistance is to reestablish maximum virologic suppression, and current guidelines recommend the addition of a newer PI boosted with ritonavir, with or without enfuvirtide, to a standard treatment regimen [35]. The results of the RESIST-1 trial demonstrated that increasing the number of background antiretroviral agents to which patients' isolates were susceptible enhanced the treatment response among both TPV/r recipients and CPI/r recipients. This was true for the TPV/r group when enfuvirtide, for which no level of cross-resistance was expected, was added; the proportion of treatment responders also increased (but less so) in the CPI/r arm. For TPV/r recipients who were enfuvirtide naive, the inclusion of enfuvirtide further enhanced the treatment response, compared with that of patients who had a history of prior enfuvirtide use. Similarly, having additional drugs beyond enfuvirtide in the optimized background regimen to which patients' isolates were susceptible increased the proportion of treatment responders.

Overall tolerability and the occurrence of adverse events were comparable between treatment arms. Most adverse events were mild or moderate in severity and were usually observed after administration of boosted PIs in a population with advanced immunodeficiency [36, 37]. Diarrhea, nausea, and fatigue were the most frequently occurring adverse events reported in both groups.

The grade 3 or 4 laboratory abnormalities observed in both treatment groups were similar, although some occurred more frequently in the TPV/r arm; asymptomatic elevations in ALT and AST levels and increases in triglyceride and cholesterol levels were more common among TPV/r recipients. Despite these abnormalities, most patients continued to receive TPV/r therapy. As seen with other boosted PIs, coinfection with hepatitis B or C virus and elevated transaminase levels at baseline increased the risk of elevated ALT or AST levels during treatment. Moreover, elevations in triglyceride levels were more common among patients who had high triglyceride values at baseline. One possible explanation for the observed increase in liver events and in triglyceride levels is the higher total daily dose of ritonavir used in TPV/r-treated patients (400 mg per day). Average ritonavir trough concentrations are lower in patients receiving TPV/r than in those who receive some other PIs (e.g., lopinavir and saquinavir) plus an optimized background regimen [38]; therefore, a higher daily dose of ritonavir was used in tipranavir-treated patients in this study.

Because the trial was open label, investigators may have been more prone to report adverse events for the investigational drug than for approved agents [39]. More importantly, CPI/r-treated patients were given the option of discontinuing treatment after 8 weeks in the event of a lack of initial virologic response or confirmed virologic failure, to join a TPV/r rollover study. Before week 24, a total of 33.0% of CPI/r recipients opted to discontinue receiving the study medication for these reasons, and most of these patients joined the rollover study. This led to a substantially longer treatment exposure among TPV/r recipients than among CPI/r recipients. This greater exposure may have led to an accumulation of adverse events (related or unrelated to the study drug) in the TPV/r arm.

In conclusion, the combination of TPV/r with an active optimized background regimen in antiretroviral-experienced patients resulted in significant improvements in virologic and immunologic responses through 24 weeks, compared with CPI/r and an optimized background regimen. This would suggest that TPV/r (500 mg/200 mg twice per day), as part of combination antiretroviral therapy, plays an important role in the achievement of effective viral suppression in patients infected with multidrug-resistant strains who have limited treatment options. The results of the 48-week analysis will determine the durability of TPV/r in achieving and maintaining effective viral suppression in this important patient population.

RESIST-1 STUDY GROUP

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Table 3. Adverse events (related or not related to treatment; grade 1–4) and laboratory abnormalities (grade 3–4) noted among study subjects.

Characteristic	Treatment group		
	Overall population (n = 620)	TPV/r arm (n = 311)	CPI/r arm (n = 309)
Adverse event			
Any[a]	549 (88.5)	282 (90.7)	267 (86.4)
Diarrhea	144 (23.2)	75 (24.1)	69 (22.3)
Nausea	131 (21.1)	64 (20.6)	67 (21.7)
Fatigue	96 (15.5)	47 (15.1)	49 (15.9)
Headache	65 (10.5)	37 (11.9)	28 (9.1)
Vomiting	57 (9.2)	32 (10.3)	25 (8.1)
Pyrexia	53 (8.5)	29 (9.3)	24 (7.8)
Upper respiratory tract infection	45 (7.3)	24 (7.7)	21 (6.8)
Injection site reaction	51 (8.2)	22 (7.1)	29 (9.4)
Grade 3 or 4 laboratory abnormalities			
Total no. of subjects	608	304	304
Elevated alanine aminotransferase level	25 (4.1)	21 (6.9)	4 (1.3)
Elevated aspartate aminotransferase level	19 (3.1)	14 (4.6)	5 (1.6)
Elevated amylase level	43 (7.0)	21 (6.9)	22 (7.2)
Elevated lipase level	14 (2.3)	9 (2.9)	5 (1.6)
Elevated cholesterol level	13 (2.1)	13 (4.2)	0
Elevated triglyceride level	104 (17.1)	66 (21.7)	38 (12.5)
Increased glucose level	11 (1.8)	6 (2.0)	5 (1.6)

NOTE. Data are no. (%) of subjects. CPI/r, ritonavir-boosted comparator protease inhibitor; TPV/r, ritonavir-boosted tipranavir.

[a] Averse events were observed in >5% of patients and were treatment related or not treatment related.

The Netherlands), and J. M. Schapiro (Stanford University, Stanford, CA).

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