SHORT COMMUNICATION

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Boosted Tipranavir versus Darunavir in Treatment-Experienced Patients

Observational Data from the Randomized POTENT Trial

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Abstract

Background: The POTENT trial compared the safety and efficacy of tipranavir/ritonavir (TPV/r) to darunavir/ritonavir (DRV/r), each with an optimized background regimen (OBR) in triple-class experienced HIV-1-infected patients with resistance to more than one protease inhibitor (PI).

Methodology/Principal Findings: POTENT was a prospective, open-label study of triple-class (PI, non-nucleoside reverse transcriptase inhibitors [NNRTI], nucleoside reverse transcriptase inhibitors [NRTI]), treatment-experienced, HIV-positive patients. Subjects were randomized to either TPV/r (500/200 mg twice daily) or DRV/r (600/100 mg twice daily) on a genotype-guided, investigator-selected OBR. CD4+ counts and HIV viral loads were assayed at key timepoints. The primary endpoint was time to virologic failure (viral load ≥500 copies/mL).

POTENT was prematurely terminated due to slow enrollment. Thirty-nine patients were treated with either TPV/r (n = 19) or DRV/r (n = 20); 82% were male, 77% White, with mean age of 43.6 years. Mean baseline HIV RNA was 3.9 $\log_{10}$ copies/mL. Median prior antiretrovirals was 11, with no prior raltegravir or maraviroc exposure. Raltegravir was the most common novel class agent in the OBRs (n = 14 TPV/r; n = 12 DRV/r). In both groups, patients achieved mean viral load decreases ≥2 $\log_{10}$ copies/mL by week 8, and by week 12 mean CD4+ counts rose by 40–50 cells/mm^3. Total observation time was 32 weeks. Drug-related adverse events were reported in 21% (TPV/r) and 25% (DRV/r) of patients.

Conclusions/Significance: TPV/r- and DRV/r-based regimens showed similar short-term safety and efficacy. These data support the use of next-generation PIs such as tipranavir or darunavir with novel class antiretroviral agents (integrase inhibitors, CCR5 antagonists, or fusion inhibitors).

Trial Registration: Clinicaltrials.gov NCT00517192

Introduction

Drug-resistance presents a major challenge to the successful long-term management of HIV-infected treatment-experienced patients. HIV protease inhibitors (PIs) have been used extensively since 1996. Due to the structural similarities of most PIs, emergence of resistance to one PI often

translated into cross-resistance to other PIs. This underscores the need for novel, potent PIs with distinct resistance profiles leading to minimal cross-resistance to other PIs. Tipranavir (TPV) is a potent, highly selective, nonpeptidic HIV PI. TPV plus low-dose ritonavir (TPV/r) [used in combination with other antiretroviral (ARV) drugs] was approved by the US FDA in 2005 for the treatment of HIV infection among treatment-experienced patients with PI-resistant virus.[1]

A study of >100 highly PI-resistant clinical isolates (with a greater than a 10-fold increase in the concentration that produces 50% inhibition [IC_{50}] to an average of more than six other PIs) demonstrated that 90% of these isolates remain susceptible to TPV. Only 8% and 2% of the isolates were shown to be moderately resistant and highly resistant, respectively, to TPV.[2] These laboratory observations have been confirmed in several clinical trials, including RESIST (Randomized Evaluation of Strategic Intervention in multidrug reSistant patients with Tipranavir),[3] Study 1182.51,[4,5] and Study 1182.52,[5] underlining the important role that TPV/r plays as a potent and efficacious treatment option for treatment-experienced patients.

Darunavir (DRV) is the newest PI approved by the FDA for the treatment of HIV-1 infection, with accelerated approval in 2006 for use in PI-resistant, treatment-experienced adults and in 2008 for use in treatment-naïve adults.[6] DRV is a potent nonpeptidic HIV-1 PI. DRV has been shown to be an efficacious, safe, and well tolerated component of ARV regimens for triple-class (PI, non-nucleoside reverse transcriptase inhibitors [NNRTI], nucleoside reverse transcriptase inhibitors [NRTI]), treatment-experienced patients who switched regimens in the prospective Darunavir Outcomes Study,[7,8] and in treatment-experienced patients undergoing early salvage therapy.[8] Since multiple mutations in the HIV protease are generally necessary for the virus to demonstrate significant resistance to DRV or TPV, these drugs exhibit a high genetic barrier to the emergence of novel resistant strains.[9,10]

The POTENT (PrOspecTive EvaluatioN of Tipranavir vs. Darunavir in Treatment Experienced Patients) trial compared the safety and efficacy of TPV/r versus DRV plus low-dose ritonavir (DRV/r) when each was combined with an optimized background regimen (OBR) in triple-class-experienced, HIV-infected patients with resistance to more than one PI. This head-to-head comparison of these two PIs in the same patient population was intended to provide data to help clinicians choose the appropriate ARV therapy for treatment-experienced patients.

The initial inclusion and exclusion criteria for patient enrollment in POTENT presented a challenge to study enrollment, given the availability of novel therapeutic agents, including raltegravir and maraviroc, at the time POTENT was attempting to recruit patients. Significant efforts to increase enrollment into the trial, including relaxing the enrollment criteria, did not result in improvements in patient recruitment. As a result, the POTENT trial was prematurely terminated. While the number of patients included in the trial and follow-up time are insufficient to draw definitive conclusions, these data provide short-term virologic and immunologic responses when initiating TPV/r or DRV/r combined with a novel agent such as raltegravir in this treatment-experienced patient population. In this brief report, we describe observed safety and efficacy data of the two study treatment arms with a focus on the concomitant use of novel agents as part of the OBR among treatment-experienced patients with multidrug-resistant HIV.

Methods

Ethics

The research was carried out in compliance with the POTENT protocol, the principles laid down in the Declaration of Helsinki (1996 Version), in accordance with the International Conference on Harmonization Harmonized Tripartite Guideline for Good Clinical Practice, and in accordance with applicable regulatory requirements. Participation in the POTENT trial was approved by the institutional review board (IRB) of each center involved in the study. This clinical study enrolled patients at 56 study sites in ten countries. The complete names and addresses of the centers (and their corresponding IRBs) that enrolled patients in the

POTENT trial can be found in table SI of the supplemental digital content (SDC), http://links.adisonline.com/DRZ/A4. Written informed consent was obtained from each patient, or their legal representative, prior to their participation in the study. Details of the clinical trial protocol can be found in the SDC (table SII). The CONSORT (Consolidated Standards of Reporting Trials) checklist can also be found in the SDC (table SIII).

Objectives

The POTENT study was designed as a randomized, open-label trial to compare the efficacy and safety of TPV/r (500/200 mg twice daily) with DRV/r (600/100 mg twice daily) in HIV-1-infected patients with triple-class (NRTI, NNRTI, and PI) treatment experience, who were harboring virus that was resistant to more than one PI at screening by virtual phenotype testing. Eligible patients were randomized to TPV/r or DRV/r, each combined with an investigator-selected OBR, with a planned follow-up treatment period of 50 weeks.

Participants

The inclusion criteria consisted of (i) signed informed consent; (ii) verification of triple-class treatment history with a minimum of 3 months duration for each class; (iii) documented viral resistance to more than one PI; (iv) OBR containing at least two active agents; (v) plasma viral load (VL) ≥500 copies/mL; and (vi) baseline laboratory values demonstrating reasonable organ system function. A CD4+ cell count ≥50 cells/mm^3 at screening was initially required, but this criterion was removed by a protocol amendment.

Exclusion criteria included (i) prior use of TPV or DRV; (ii) virtual phenotypic resistance to TPV or DRV; (iii) female patients who were pregnant, breastfeeding, or planning to become pregnant; (iv) patients with unresolved or unstable AIDS-defining illnesses; (v) active substance abuse; and (vi) use of agents with contraindications listed in the product monographs of TPV, DRV, or ritonavir. Patients who were unresponsive to treatment (VL decrease <1 $\log_{10}$ copies/mL after 12 weeks of treatment) or who at or after week 24 had a VL >400 copies/mL on two consecutive visits (at least 2 weeks apart) were to be removed from the study and initiate alternative ARV therapy in an attempt to establish better control of their HIV disease.

Description of Procedures or Investigations Undertaken

The POTENT trial was designed to enroll and treat 800 HIV-1-infected, antiretroviral-naïve patients who were to be randomly assigned (1 : 1) to one of the following open-label treatments: (i) TPV/r (500/200 mg twice daily); or (ii) DRV/r (600/100 mg twice daily). Both agents were administered in combination with other available ARVs selected by the investigator based on patient history and virtual phenotype screening results. The randomization lists were prepared by Boehringer Ingelheim, Inc., in cooperation with the contractor (Almac Clinical Technologies, Yardley, PA, USA) of the interactive voice response system in an automated fashion using validated randomization software (RS PMX™ CTM version 3.3.0, Rockwell Automation Solution GmbH, Karlsruhe, Germany). Patient randomization was stratified based on their background regimens, which were sorted according to their inclusion of zero, one, or two new classes of agents, and the resistance characteristics of the patient's virus to TPV/DRV (sensitive/sensitive, partially sensitive/sensitive, sensitive/partially sensitive, partially sensitive/partially sensitive) at initial screening. Access to the randomization lists was under the control of a central administrator (telephone/computer randomization). Patient enrollment commenced on 20 September 2007, and continued until trial closure on 1 July 2008.

The primary endpoint of POTENT was time to virologic failure using VL <50 copies/mL to determine virologic response and VL ≥500 copies/mL to define virologic rebound. The key secondary endpoint was treatment response at week 48. Other secondary endpoints included (i) changes from baseline in CD4+ cell count and viral load at each study visit; and (ii) new clinical events indicating AIDS progression or death.

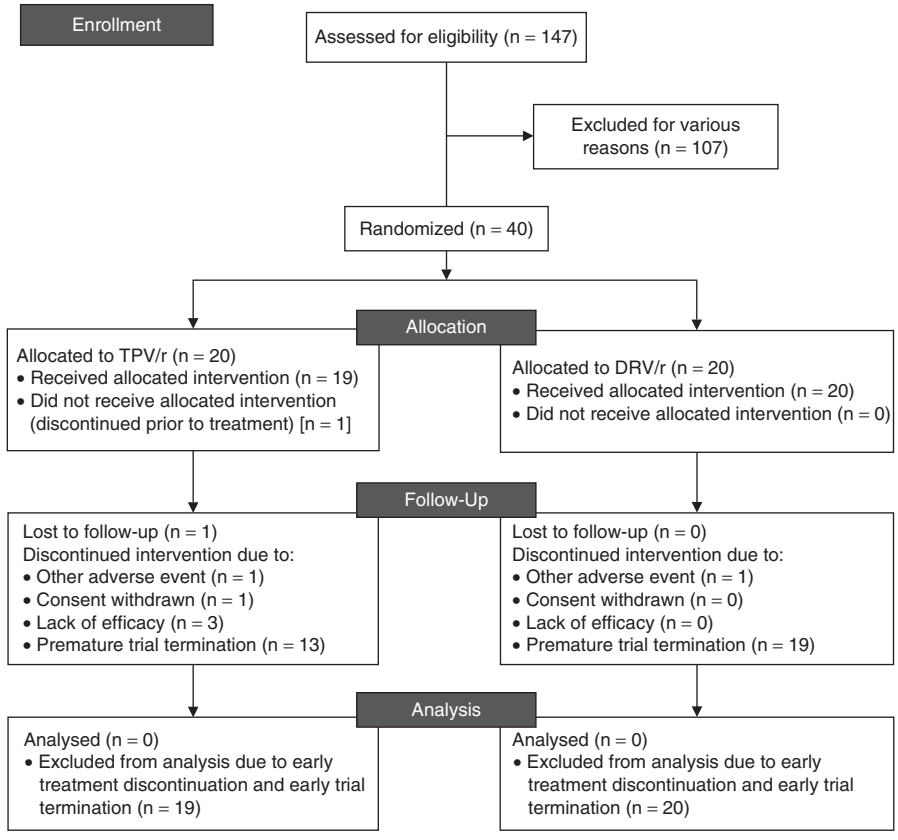

Fig. 1. Patient disposition flow chart. **DRV**/**r** = darunavir/ritonavir; **TPV**/**r** = tipranavir/ritonavir.

HIV VL was determined by the COBAS® AmpliPrep/COBAS® TaqMan® HIV tests (Roche Molecular Systems Inc, Branchburg, NJ, USA). The baseline VL was the geometric mean of the last two pretreatment VL determinations. CD4+ cell counts were assayed at the Covance Central Laboratory Service (Princeton, NJ, USA). The baseline CD4+ cell count was the mean of the last two pretreatment measures. Baseline samples for HIV genotyping were assayed in real-time using the virco® VirtualPhenotype™ method (VIRCO Lab Inc, Titusville, NJ, USA).

Adverse events (AEs) were monitored throughout the trial, were listed as non-serious or serious in accordance with the pre-established study criteria, and serious AEs were reported to the local Clinical Monitor as soon as the study personnel became aware of them.

Statistical Methods

As a result of the early termination of POTENT due to poor patient enrollment, statistical tests were not applied to the observational data that were collected.

Results

Despite efforts to improve enrollment, including amending the protocol to ease the entry criteria, only 40 of the planned 800 patients (5%) were randomized over an 8-month recruitment period. Of the 40 patients who were randomized, 39 were treated. As a result of the slow enrollment, the study was prematurely terminated and only short-term data, from 39 weeks of observation, are available to provide observational

virologic and immunologic responses in these patients.

Figure 1 presents the complete patient disposition results. Of the 39 patients who received treatment, 19 were treated with TPV/r and 20 were treated with DRV/r. Seven patients were prematurely discontinued from the trial, six in the TPV/r arm and one in the DRV/r arm. Reasons for discontinuation included AEs (n = 1 in each group), lack of efficacy (n = 3, TPV/r group), lost to follow-up (n = 1, TPV/r group), and withdrawal of patient consent (n = 1, TPV/r group). Of the six patients in the TPV/r group who interrupted treatment, three were for loss of efficacy when they experienced increased viral loads on treatment, following initial drops on treatment. The mean and median duration of treatment among TPV/r and DRV/r patients was 15.3 and 13.0 weeks, respectively, with an overall range of 0.6–37.4 weeks.

The baseline demographics are presented in table I. The mean age was 43.6 years, 82% were male, and 77% were White. Their baseline hepatitis status included six patients who were co-infected with hepatitis B or C: one patient in the DRV/r group was hepatitis B surface antigen (HBsAg) positive and five were HCV antibody positive (three in the TPV/r and two in the DRV/r groups). The mean baseline HIV RNA for all patients in both arms was 3.9 $\log_{10}$ copies/mL and the mean baseline CD4+ count was 283 cells/mm^3 in the TPV/r arm versus 338 cells/mm^3 in the DRV/r arm. The mean time since HIV diagnosis for all patients was 14.4 years. Nine patients in the TPV/r group and 12 in the DRV/r group had AIDS-related events (defined by the Centers for Disease Control and Prevention, Atlanta, GA, USA). The median number of prior ARV agents was 11. No patient had prior maraviroc or raltegravir exposure.

Of the newer drug classes, raltegravir was the agent most commonly included in the OBR for patients in both arms of the study (n = 14 and n = 12, TPV/r and DRV/r groups, respectively). Maraviroc was the next most common novel drug included as part of OBR (n = 4 and n = 2, TPV/r and DRV/r groups, respectively). Enfuvirtide was included in the OBR of three patients in each arm of the study. Resistance testing by virtual phenotypic analysis at baseline identified baseline sensitivities to TPV/r and DRV/r (table II).

The most commonly reported AEs and clinical laboratory abnormalities are listed in table III. Drug-related AEs were experienced by 21% and 25% of patients in the TPV/r and DRV/r groups, respectively. One patient in each arm experienced a drug-related AE that led to treatment discontinuation.

Baseline sensitivities to TPV/r and DRV/r were randomly distributed between the two

Table I. Patient baseline demographic data

	TPV/r (n = 19)	DRV/r (n = 20)	Total (n = 39)
Sex [n (%)]			
Male	15 (78.9)	17 (85.0)	32 (82.1)
Female	4 (21.1)	3 (15.0)	7 (17.9)
Ethnic origin [n (%)]			
White	14 (73.7)	16 (80.0)	30 (76.9)
Black	5 (26.3)	1 (5.0)	6 (15.4)
Asian	0 (0)	3 (15.0)	3 (7.7)
BMI (kg/m^2)			
Mean ± SD	24.9 ± 4.3	23.3 ± 3.0	24.0 ± 3.7
Median (range)	24.8 (18.7–33.2)	23.3 (18.7–33.0)	23.8 (18.7–33.2)
Age (y)			
Mean ± SD	44.3 ± 6.1	43.1 ± 6.2	43.6 ± 6.1
Median (range)	44.0 (33.0–53.0)	42.0 (34.0–63.0)	43.0 (33.0–63.0)

BMI = body mass index; **DRV/r** = darunavir/ritonavir; **TPV/r** = tipranavir/ritonavir.

Table II. Baseline sensitivities to tipranavir/ritonavir (TPV/r) and darunavir/ritonavir (DRV/r)

Baseline sensitivity	TPV/r (n) [n = 19]	DRV/r (n) [n = 20]
TPV-s/DRV-s	10	12
TPV-ps/DRV-s	4	5
TPV-s/DRV-ps	0	2
TPV-ps/DRV-ps	5	1

ps = partially sensitive; **s** = sensitive.

treatment arms, with 10 of 19 and 12 of 20 patient isolates being sensitive to both TPV and DRV in each treatment arm (TPV/r and DRV/r, respectively). While there appeared to be some imbalance between the arms in the number of patient isolates that were TPV-partially sensitive/DRV-partially sensitive (5 of 19 [26%] and 1 of 20 [5%], TPV/r and DRV/r arms respectively), the total number of patient isolates in each group were too small to allow meaningful statistical analysis, limiting any conclusions that might be drawn from these data.

The primary measures of therapeutic efficacy in the POTENT trial were change in $\log_{10}$ VL and change in CD4+ cell count from baseline values. In the setting of ARV therapy, these virologic and immunologic parameters are well established as surrogate markers for viral replication activity and relative immune health/reconstitution.[11,12] In both study arms, patients experienced favorable changes in VL and CD4+ cell count from baseline over the short-term course of treatment. These observational trends were observed for each study visit from week 2 through week 32 (note: only three patients in each arm had follow-up data to week 32).

Observed $\log_{10}$ changes in VL (figure 2) indicated a drop in VL >1.5 $\log_{10}$ copies/mL for both treatment arms by week 2, with mean reductions of ~2 $\log_{10}$ copies/mL by week 8, indicating short-term potent virologic activity for both TPV/r- and DRV/r-containing regimens in these treatment-experienced patients. At no timepoint were the changes in $\log_{10}$ HIV VL found to be different between the two treatment groups.

Observed changes in CD4+ cell counts from baseline (figure 3) showed similar increases in both treatment arms over the period of treatment/follow-up. By week 12, mean CD4+ counts rose by 40–50 cells/mm^3 in both arms. At no timepoint were the changes in CD4+ cell counts from baseline found to be different between the two treatment groups.

Discussion

The POTENT trial was designed as a head-to-head comparison of ritonavir-boosted TPV- versus DRV-containing regimens in treatment-experienced HIV-infected patients where the virus is resistant to more than one PI. These two agents have not been previously compared in a randomized clinical trial.

Limitations

Due to slow enrollment, only 39 patients were randomized and received study drugs prior to premature termination of the study. While data

Table III. Adverse events and laboratory abnormalities by treatment group

	TPV/r [n (%)] {n = 19}	DRV/r [n (%)] {n = 20}
Adverse events[a]		
Any	12 (63.2)	15 (75.0)
Serious	0 (0)	2 (10.0)
DAIDS G3	1 (5.3)	2 (10.0)
DAIDS G4	0 (0)	1 (5.0)
DR	4 (21.1)	5 (25.0)
DR leading to discontinuation	1 (5.3)	1 (5.0)
Gastrointestinal	5 (26.3)	5 (25.0)
Hepatobiliary disorders	1 (5.3)	0 (0)
Laboratory abnormalities		
DAIDS G3[b]	5 (26.3)	6 (30.0)
DAIDS G4[c]	0 (0)	4 (20.0)

a Unless associated with clinical symptoms, laboratory test abnormalities were not reported as adverse events.

b Eleven patients had a total of 41 G3 laboratory abnormalities, including changes in total cholesterol (n = 11), low-density lipoprotein cholesterol (n = 14), creatine phosphokinase (n = 4), glucose (n = 4), triglycerides (n = 2), and amylase (n = 2).

c Four DAIDS G4 abnormalities were observed in the DRV/r arm, none were seen in the TPV/r arm. One patient with G4 partial thromboplastin time at visit 7, one patient with G4 INR and PT at visit 4, and one patient with a G4 reduction in polymorphonuclear neutrophils.

DAIDS = Division of AIDS; **DR** = drug related; **DRV/r** = darunavir/ritonavir; **G** = grade; **INR** = International Normalized Ratio; **PT** = prothrombin time; **TPV/r** = tipranavir/ritonavir.

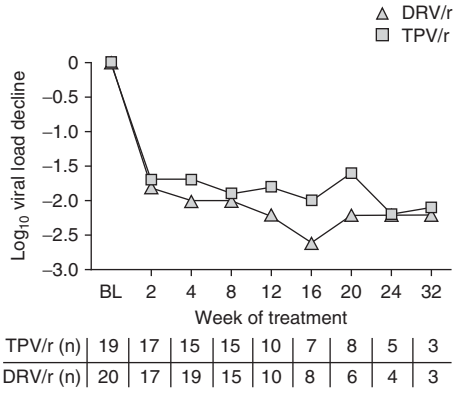

Fig. 2. Changes in log_{10} viral load from baseline. Log_{10} HIV viral loads were measured at each study visit (see Methods section), and individual patient values were normalized to their corresponding baseline (BL) values. Mean log_{10} declines for each treatment group at each timepoint are depicted in the graph. The table at the bottom presents the number of patients in each treatment arm at each timepoint. **DRV/r** = darunavir/ritonavir; **TPV/r** = tipranavir/ritonavir.

from the trial are insufficient to assess the primary and secondary endpoints in a statistically rigorous manner, they do provide observational data that demonstrated short-term virologic and immunologic benefits in highly treatment-experienced patients initiating either TPV/r or DRV/r in combination with an OBR.

Patients treated with a TPV/r- or DRV/r-containing regimen experienced similar safety and efficacy outcomes over the limited observation period in this small cohort of triple-class-experienced, HIV-infected patients who had previously not responded to other PIs. However, it should be noted that some of the clinical challenges with TPV treatment include compliance due to higher pill burden, and long-term side effects of this medication, both of which were difficult to measure in this study due to the low patient numbers, and the limited follow-up period.

The novel integrase inhibitor raltegravir was the most commonly used new agent in constructing a new OBR in the POTENT trial. In a recent subgroup analysis of a 48-week study[13] in treatment-experienced patients with drug-resistant HIV, raltegravir was compared with placebo, each arm in combination with an OBR that included TPV. In patients whose HIV was sensitive to TPV by genotypic or phenotypic assays, the combination of raltegravir plus TPV/r in the OBR demonstrated ~30–33% better response rates (HIV RNA <50 copies/mL at week 48) than patients taking placebo. In the same study, patients who first used DRV in combination with raltegravir demonstrated ~22% better response rate at week 48 than the placebo group.[13] This long-term improvement in virologic control demonstrated the viability of regimens that combine nonpeptidic PIs and novel class agents such as the integrase inhibitors. In another recent study of triple-class-experienced patients,[14] raltegravir in combination with OBR was demonstrated to have a robust and sustained antiviral effect through 96 weeks of treatment. Patients experienced mean changes in VL of −1.6 and −1.38 log_{10} copies/mL at 48 and 96 weeks, respectively. Additionally, 68% of patients had VLs <400 copies/mL and 55% had <50 copies/mL at 48 weeks. At 96 weeks, 55% and 48% of patients had VLs <400 copies/mL and <50 copies/mL, respectively.

The observational data from the POTENT trial demonstrated virologic and immunologic outcomes that indicate successful treatment with regimens containing TPV/r plus raltegravir. Both treatment arms (TPV/r and DRV/r) demonstrated good short-term efficacy and safety. The observed changes from baseline in VL were similar in both treatment groups. At week 24, all patients

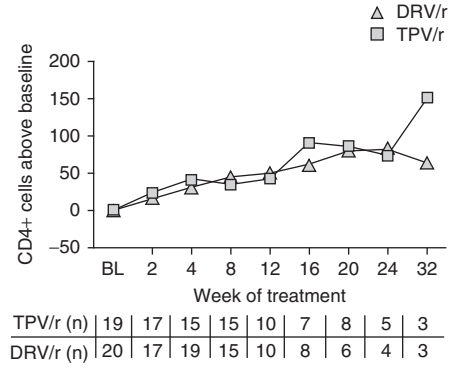

Fig. 3. Changes in CD4+ cell counts from baseline. CD4+ cell counts were measured at each study visit (see Methods section), and individual patient values were normalized to their corresponding baseline (BL) values. Mean CD4+ cell counts for each treatment group at each timepoint are depicted in the graph. The table at the bottom presents the number of patients in each treatment arm at each timepoint. **DRV/r** = darunavir/ritonavir; **TPV/r** = tipranavir/ritonavir.

achieved a VL <400 copies/mL, with all but one patient (in the TPV/r arm) achieving a VL <50 copies/mL. In addition, similar increases in CD4+ cell counts were observed in both treatment arms. Finally, the rates of serious AEs were similar between the two arms (0% and 10% for TPV/r and DRV/r, respectively). This information supports current treatment guidelines and re-emphasizes the clinical imperative of selecting active, potent agents when attempting to construct viable regimens in this patient population.

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Prezista® (Darunavir) was obtained commercially, as were the other drugs utilized in this study.

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