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Original Article

Effectiveness of tipranavir versus darunavir as a salvage therapy in HIV-1 treatment-experienced patients

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Abstract

Introduction: Although both tipranavir (TPV) and darunavir (DRV) represent important options for the management of patients with multi-protease inhibitor (PI)-resistant human immunodeficiency virus (HIV), currently there are no studies comparing the effectiveness and safety of these two drugs in the Mexican population. The aim of this study was to compare the effectiveness of TPV versus DRV as a salvage therapy in HIV-1 treatment-experienced patients.

Methodology: This was a comparative, prospective, cohort study. Patients with HIV and triple-class drug resistance evaluated at the Hospital de Infectología "La Raza", National Medical Center, were included. All patients had the protease and retrotranscriptase genotype; resistance mutation interpretation was done using the Stanford database.

Results: A total of 35 HIV-1 triple-class drug-resistant patients were analyzed. All of them received tenofovir and raltegravir, 22 received darunavir/ritonavir (DRV/r), and 13 received tipranavir/ritonavir (TPV/r) therapies. The median baseline RNA HIV-1 viral load and CD4+ cell count were 4.34 log (interquartile range [IQR], 4.15–4.72) and 267 cells/mm^3 (IQR, 177–320) for the DRV/r group, and 4.14 log (IQR, 3.51–4.85) and 445 cells/mm^3 (IQR, 252–558) for the TPV/r group. At week 24 of treatment, 91% of patients receiving DRV/r and 100% of patients receiving TPV/r had an RNA HIV-1 viral load < 50 copies/mL and a CD4+ cell count of 339 cells/mm^3 (IQR, 252–447) and 556 cells/mm^3 (IQR, 364–659), respectively.

Conclusions: No significant difference was observed between DRV/r and TPV/r in terms of virological suppression in HIV-1 patients who were highly experienced in antiretroviral therapy.

Key words: HIV protease inhibitors; highly experienced patients; prospective study.

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Introduction

Antiretroviral drugs have been proven to control the progression of human immunodeficiency virus (HIV) disease and to prolong survival [1]. The introduction of protease inhibitors (PIs) in the management of HIV infection resulted in profound reductions in disease-related morbidity and mortality [1,2]. However, these benefits can be compromised by the development of drug resistance and treatment-associated complications, such as metabolic adverse effects, drug-drug interactions, and fat redistribution syndromes [3]. The development of new PIs with significant antiviral activity in individuals with extensive class resistance has emerged as an issue of paramount importance in the field of HIV therapy [2,3]. Tipranavir (TPV) and darunavir (DRV) are the first PIs that were developed for the management of infection caused by PI-resistant viruses, and each of these drugs exhibited potent *in vivo* and *in vitro* activity against HIV-1 strains with accumulated multiple mutations associated with resistance to this class of drugs [4]. Each of these drugs has been shown to be superior to equivalent PIs in randomized controlled trials of treatment-experienced patients [5,6]. Although both TPV and DRV represent important options for the management of patients with multi-PI-resistant HIV, currently there are no studies

comparing the effectiveness and safety of these two drugs in the Mexican population. The purpose of this study was to compare the virological and immunological effectiveness of TPV versus DRV as a salvage therapy in HIV-1 treatment-experienced patients.

Methodology

Study population and study design

After obtaining protocol research approval from the ethics and investigation committee in "La Raza" National Medical Center, a comparative, retrospective, cohort study of HIV-infected adults who were receiving either tipranavir/ritonavir (TPV/r)- or darunavir/ritonavir (DRV/r)-based antiretroviral therapy (ART) according to HIV-resistance testing was conducted. All HIV-1-infected patients followed at the Hospital de Infectología "La Raza", National Medical Center (a public national reference center that receives its HIV population not only from Mexico city but also from the rest of the country) who had triple-class drug resistance and in whom ART had failed (extensive resistance to PIs was considered as those patients who had had multiple PIs in their previous regimens used and who could be rescued with other PIs that had an extensive genetic barrier such as DRV or TPV), who were > 18 and < 65 years of age, had an HIV-1 RNA viral load > 1000 copies/mL prior to the initiation of TPV/r or DRV/r-based therapy, and had laboratory evaluations that included CD4+ cell counts and HIV-RNA viral load assessment for at least 24 weeks after the initiation of therapy, and who had provided informed consent, were included in the study. Patients who had hepatitis B virus (HBV), hepatitis C virus (HCV), or tuberculosis (TB) co-infections; cirrhosis; a creatinine clearance < 60 mL/min; a hypersensitivity reaction to any of the drugs, or who were pregnant, were excluded from the study. Patients receiving either TPV/r- or DRV/r-based therapy were identified by genotype; resistance mutation interpretation was done using the Stanford database. Patients received an individualized optimized background regimen (OBR) according to HIV-1 resistance testing and previous treatment-based regimen, and based on the investigator's decision, which was supported by a committee of multidrug resistance. This OBR included tenofovir plus raltegravir-based therapy. Drugs were administered as follows: tenofovir 300 mg orally once daily, raltegravir 400 mg orally twice daily, and either darunavir 600 mg orally twice daily boosted by ritonavir 100 mg orally twice daily or tipranavir 500 mg orally twice daily boosted by ritonavir 200 mg twice daily. Tenofovir was given alone in both groups. Baseline data, such as years on ART, number of previous treatment-based regimens, HIV-1 RNA viral load, CD4+ cell count, serum creatinine, clearance creatinine, serum total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, serum alanine transaminase (ALT), and serum aspartate transaminase (AST) were collected.

Virological and immunological endpoints

The primary endpoint of the study was the proportion of patients in each group with an HIV-1 RNA viral load < 50 copies/mL at week 24 of follow-up. Additional endpoints included changes in CD4+ cell count and metabolic parameters, such as serum creatinine, clearance creatinine calculated by the Modification in Diet of Renal Disease (MDRD) formulation, total cholesterol, HDL, LDL cholesterol, triglycerides, serum ALT, and serum AST, from the baseline to week 24 after the initiation of TPV/r- or DRV/r-based therapy.

Statistical analyses

The baseline characteristics of the two groups were summarized using medians and interquartile ranges (IQRs) for continuous variables and proportions for categorical variables. Fisher's exact test or the χ^2 test were used to compare categorical variables at week 24 in each group. The Wilcoxon rank-sum test was used to determine whether changes in CD4+ cell count, HIV-1 RNA viral load, serum creatinine, serum triglycerides, serum total cholesterol, HDL, LDL, and serum ALT and AST were significantly different from the baseline to week 24 of follow-up within each group. Moreover, the Mann-Whitney *U* test was used to compare these variables between groups. A p value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 20 (IBM, Armonk, USA).

Results

A total of 35 HIV-1 triple-class drug-resistant patients who received tenofovir and raltegravir plus DRV/r or TPV/r therapies were analyzed. Among these patients, 22 received DRV/r- and 13 received TPV/r-based regimens. In the DRV/r-based therapy group, 17 (77%) individuals were male and the median age was 47 years (IQR, 43.7–51.5 years); in contrast, in the TPV/r-based therapy group, 10 (76%) patients were male and the median age was 48 years (IQR, 41.5–52.5 years). The median of tenofovir disoproxil fumarate

(TDF) genotypic sensitivity score (GSS) score in the DRV group was 0.5 IQR (0.25–0.5), raltegravir GSS score 1 IQR (1–1), thus, the OBR GSS score was 1.5, and the median of the GSS score regimen was 2.25 IQR (2–2.25). In the TPV group, the median TDF GSS score was 0.5 IQR (0.25–0.5), raltegravir GSS score 1 IQR (1–1); the OBR GSS score was 1.5, and the median GSS score regimen was 2.25 IQR (2–2.25). The median TDF Stanford score was 25 IQR (25–35) in both DRV and TPV groups, which means that TDF had a low-level resistance. The baseline characteristics of the two groups are summarized in Table 1. Although there were no significant differences between the two groups regarding selected demographic variables such as age, HIV-1 RNA viral load, and CD4+ cell count, the two groups differed in variables such as the median number of years on ART prior to starting DRV/r- or TPV/r-based therapy: 14 (IQR, 9–17) and 8 (IQR, 7–1) years, respectively (p = 0.009). The Stanford score for each PI according to the presence of resistance-associated mutations in both groups were as follows: the number of DRV resistance-associated mutations was 0 in 5 patients, 1 in 10 patients, and 2 in 7 patients. The number of TPV resistance-associated mutations was 0 in 2 patients, 1 in 3 patients, 2 in 4, 3 in 3, and 4 in 1 patient. The median of DRV Stanford score was 5 IQR (0–20) and TPV Stanford score was 15 IQR (5–25), which mean fully active and low-potential resistance, respectively. Mutations such as I47V, I54M, T74P, and I84V were present as follows: 4 patients had I47V, 1 had I54M, and 3 had T74P in the DRV group, and only 3 patients had the I54M mutation in the TPV group. I47V, T74P, and I84V mutations were not presented in the TP group.

At week 24 of treatment (Table 2), 91% of patients receiving DRV/r and 100% of patients receiving TPV/r had a viral load < 50 copies/mL (p = 0.519); only one patient in the DRV/r group had detectable HIV-1 viral load at week 24. The median gain in CD4+ cell count from the baseline to week 24 was 339 cells/mm^3 (IQR, 252–447) and 556 cells/mm^3 (IQR, 364–659) for DRV/r and TPV/r, respectively (p = 0.058). In the

Table 1. Demographic and baseline characteristics according to treatment group.

Characteristics	Darunavir (n = 22)	Tipranavir (n = 13)	P value*
Male (%)	17 (77%)	10 (76%)	1.0
Age (years), median (IQR)	47 (44–51)	48 (41–52)	0.986
Years on ART, median (IQR)	14.5 (9–17)	8 (7–11)	0.009
Number of previous treatment-based regimens (IQR)	5 (4–6)	5 (4–6)	0.358
HIV-1 RNA viral load (log), median (IQR)	4.34 (4.15–4.72)	4.14 (3.51–4.85)	0.267
CD4+ cell count (cells/mm^3), median (IQR)	267 (177–320)	445 (252–558)	0.068
Cholesterol (mg/dL), median (IQR)	178 (145–218)	187 (163–207)	0.442
HDL-C (mg/dL), median (IQR)	39 (27–42)	40 (34–43)	0.401
LDL-C (mg/dL), median (IQR)	83 (55–112)	107 (74–114)	0.282
Triglycerides (mg/dL), median (IQR)	180 (146–258)	201 (181–265)	0.172
Serum creatinine (mg/dL), median (IQR)	0.8 (0.7–0.9)	0.8 (0.7–1.0)	0.728
Creatinine clearance (mL/min), median (IQR)	90 (78–99)	90 (73–99)	0.707
ALT (IU/L), median (IQR)	29 (19–42)	24 (20–49)	0.798
AST (IU/L), median (IQR)	27 (18–41)	22 (17–49)	0.973

IQR: interquartile range; ART: antiretroviral; HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; ALT: alanine transaminase; AST: aspartate transaminase; IU/L: international unit per liter; * P value statistically significant at < 0.05.

Table 2. Virological, immunological, and metabolic parameters at week 24 of follow-up according to treatment group.

Characteristics	Darunavir (n = 22)	Tipranavir (n = 13)	P value*
HIV-1 RNA viral load (log), median (IQR)	< 50 (91%)	< 50 (100%)	0.519
CD4+ cell count (cells/mm^3), median (IQR)	339 (252–447)	556 (364–659)	0.058
Cholesterol (mg/dL), median (IQR)	183 (151–262)	223 (191–309)	0.137
HDL-C (mg/dL), median (IQR)	38 (25–43)	33 (27–40)	0.561
LDL-C (mg/dL), median (IQR)	78 (58–119)	107 (86–127)	0.151
Triglycerides (mg/dL), median (IQR)	192 (154–287)	317 (245–408)	*0.005
Serum creatinine (mg/dL), median (IQR)	0.9 (0.8–1.0)	0.9 (0.8–1.1)	0.889
Creatinine clearance (mL/min), median (IQR)	88 (73–91)	81 (69–94)	0.383
ALT (IU/L), median (IQR)	30 (23–39)	22 (19–32)	0.060
AST (IU/L), median (IQR)	27 (20–38)	20 (18–26)	0.203

IQR: interquartile range; HDL-C: high-density lipoprotein cholesterol; LDL: low-density lipoprotein cholesterol; ALT: alanine transaminase; AST: aspartate transaminase; IU/L: international unit per liter; * P value statistically significant at < 0.05.

DRV/r-based therapy group, there were significant differences between the median creatinine at the baseline (0.8 mg/dL; IQR, 0.7–0.9) and at week 24 of follow-up (0.9 mg/dL; IQR, 0.8–1.0; p = 0.02), or in the median clearance creatinine calculated by the MDRD formulation at the baseline (90 mL/min; IQR, 78–99) and at week 24 (88 mL/min; IQR, 73–91; p = 0.002).

In the TPV/r-based therapy group, there were significant differences in the median baseline creatinine (0.8 mg/dL; IQR, 0.7–1.1) to week 24 of follow-up (0.9 mg/dL; IQR, 0.8–1.1; p = 0.03), median baseline total cholesterol (187 mg/dL; IQR, 163–207) to week 24 (223 m/dL; IQR, 191–309; p = 0.013), and median baseline triglycerides (201 mg/dL; IQR, 181–265) to week 24 (317 mg/dL; IQR, 245–408; p = 0.002).

In the DRV/r-based therapy group, there were no significant differences in the median total cholesterol at the baseline (178 mg/dL; IQR, 144–218) and at week 24 (183 mg/dL; IQR, 151–262; p = 0.167) and in the median baseline triglycerides (180 mg/dL; IQR, 146–259) at week 24 (192 mg/dL; IQR, 154–287; p = 0.305).

Similarly, no significant differences were noted between the two groups regarding the median changes in serum ALT (p = 0.06) and serum AST (p = 0.203) levels from the baseline to week 24.

Overall, the median change in serum cholesterol from the baseline through week 24 was not significantly different between the two groups (p = 0.137), whereas there was a significant difference in triglyceride levels (p = 0.005), which were higher in the TPV group.

None of the patients in each group discontinued therapy during the follow-up, and there were no hypersensitivity reactions to any of the drugs in the study.

Discussion

Our study provides the first data comparing the effectiveness and safety of DRV/r- and TPV/r-based regimens in a Mexican population. Although DRV has supplanted TPV as the preferred PI in patients with extensive resistance to this class of drug, our findings suggest that TPV remains a viable option in the setting of DRV intolerance or reduced susceptibility given the distinctive resistance profiles of the two drugs, as the virological and immunological effectiveness was similar between the two treatment groups [7].

Even though the two groups were similar regarding baseline virological and immunological effectiveness, important differences existed in the median number of years on ART prior to starting DRV/r- or TPV/r-based therapy (*i.e.*, a longer time was observed in the DRV group with more complex protease resistance mutations).

Patients receiving TPV had greater baseline CD4+ cell counts than did patients receiving DRV; however, this difference was not significant. Although clearly speculative, one of the explanations for this result might be the lower number of years on antiretroviral treatment prior to starting therapy observed in the TPV group.

Regarding renal function, there was a significant increase in the median baseline creatinine through week 24 of follow-up, and a decrease in the median baseline creatinine clearance in the group receiving DRV-based therapy, whereas in the TPV group, only a significant increase in serum creatinine was observed; however, when both groups were compared, these renal alterations were not significant. This renal impairment might be related to the use of tenofovir as an OBR, as previous studies have documented an imbalance in the input and output of the drug through proximal renal tubules that causes structural damage to tubular epithelial cells and encourages the development of tubular necrosis [8,9].

Regarding liver function, there were no significant alterations in ALT and AST levels from the baseline to week 24 in each of the groups, whereas regarding lipid parameters, only triglyceride levels exhibited a significant increase in the group receiving TPV-based therapy.

These findings are in contrast with those obtained in the POWER, TITAN, and RESIST trials, in which DRV (POWER and TITAN) and TPV (RESIST) were studied in comparison with other boosted PI-based regimens. Specifically, the POWER and TITAN [5,6] trials showed that 46% and 77% of patients in the DRV group, respectively, had an HIV-1 RNA viral load < 50 copies/mL, compared with our results of 91%. Moreover, here we used fully active raltegravir and tenofovir as an OBR, whereas the POWER and TITAN trials used reverse transcriptase inhibitors (and enfuvirtide in some cases) as the OBR, thus avoiding the use of raltegravir. Similarly, in the RESIST trials [10], the virological effectiveness in the TPV group was 20% compared with 100% of our patients who received TPV. Moreover, in the RESIST trial, raltegravir was not used as an OBR, and TPV had diminished activity. In contrast, in our study, TPV was completely active and we used raltegravir as an OBR, which probably led to a higher viral and immunological response compared with that observed in the RESIST study. In addition, this high percentage of patients who reached an HIV-1 RNA viral load < 50 copies/mL in both the DRV and TPV groups might be due to the small sample size used

here compared with the large number of patients that were included in those studies.

Our findings can be contrasted with those of Antoniou *et al*. [11] and the POTENT study [12], which were the first studies that compared the virological and immunological effectiveness of DRV and TPV plus OBR. In the POTENT study, the virological effectiveness was 30% in the TPV group and 22% in DRV group compared with our data. The POTENT study, similar to ours, did not find any difference in terms of virological and safety effectiveness in both groups, had a small sample size, and used raltegravir as the most common class agent in the OBR.

Antoniou *et al*. [11] did not find any significant differences in either of these endpoints or in metabolic parameters, only a significant increase in triglyceride level in the TPV-based regimen, as was observed in our study. However, those authors used different classes of OBR in each group, which might have influenced the virological response. In our study, we used only tenofovir and raltegravir as an OBR in both treatment groups, thus diminishing the possibility that the results were influenced by other drugs. In addition, both groups had the same median GSS regimen score considered necessary to reach undetectable viral load levels in both DRV and TPV regimens. The presence of resistance-associated mutations for each regimen (including OBR and IP) did not impact in terms of virological effectiveness.

Regarding metabolic parameters, the POWER trial [5] showed a significant increase in total cholesterol (7%) and triglyceride (15%) levels for the DRV-based regimen compared with 2% and 7%, respectively, observed in individuals who were randomized to boosted PI-based regimens. This finding was not observed in the DRV-based regimen used in our study. Similarly, the RESIST trial [10] showed a significant increase in triglyceride (30.8%), total cholesterol (4.3%), and ALT (10.1%) and AST (6.3%) levels in the TPV-based regimen compared with 23.1%, 0.7%, 3.3%, and 2.9%, respectively, observed in individuals who were randomized to boosted PI-based regimens. In our study, we did not observe an increase in either ALT or AST levels in the TPV-based regimen, as was observed in the RESIST trials; however, a significant increase in the baseline triglyceride levels through week 24 was observed within groups and after comparison between groups. This finding might be related to the higher dose of boosted ritonavir [13-15] detected in the TPV group (400 mg daily) compared with the lesser dose of boosted ritonavir in the DRV group (a higher dose led to an increase in triglycerides).

Our study had several limitations, including the small sample size and the lack of randomization. In addition, the majority of our patients were men (Table 1), which did not allow the extrapolation of our findings regarding the relative safety and effectiveness of each PI in women. Moreover, we can not generalize our results even for a predominantly male population, being limited to people with similar mutation profiles and for a period of 24 weeks. However, the data from this study are clinically relevant, given the lack of comparative trials of DRV- and TPV-based regimens in the Mexican population. In addition, observational studies may approximate more closely the effects of a specific treatment in clinical practice, because patients are assigned therapies based on individual characteristics rather than on randomization. It is necessary to continue the evaluation of these patients to 48 and 96 weeks, as tolerance to PIs such as TPV is lower after 24 weeks of treatment.

Conclusions

This study provides important comparative data regarding the virological and immunological effectiveness and safety of DRV- and TPV-based regimens, and found that there was no significant difference between DRV- and TPV-based regimens in terms of virological and immunological effectiveness in HIV-1 treatment-experienced patients. Additional data from observational studies or controlled trials comparing the two drugs would be necessary to clarify the role of each drug in the management of HIV-1 treatment-experienced patients.

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Authors' contributions

All authors were involved in revising the manuscript critically for important intellectual content, and contributed to the collection of data.

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