Efficacy, safety and pharmacokinetics of 900/100 mg of darunavir/ritonavir once daily in treatment-experienced patients

Adrian Curran1*, Mar Gutirerrez2, Elisabet Deig3, Gracia Mateo2, Rosa Maria Lopez4, Arkaitz Imaz1, Manuel Crespo1, Inma Ocaña1, Pere Domingo2 and Esteban Ribera1

1Infectious Diseases Department, Hospital Vall d’Hebron, Autonomous University of Barcelona, Barcelona, Spain; 2Infectious Diseases Unit, Hospital Sant Pau, Barcelona, Spain; 3Infectious Diseases Unit, Hospital Granollers, Barcelona, Spain; 4Pharmacology and Toxicology Laboratory, Biochemistry and Molecular Genetics Department, Hospital Clinic, Barcelona, Spain

*Corresponding author. Tel: +34-932746090; Fax: +34-934894091; E-mail: acurran@vhebron.net

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Objectives: To evaluate the virological efficacy, safety, tolerability and pharmacokinetics of a regimen containing 900/100 mg of ritonavir-boosted darunavir once daily in patients with antiretroviral experience but no darunavir resistance.

Patients and methods: An observational, prospective, multicentre study was conducted. Patients were included if 900/100 mg of darunavir/ritonavir once daily and at least one other active drug had been started due to virological failure, simplification or toxicity. Minimum follow-up was 24 weeks, or less if there was premature discontinuation of any drug or loss to follow-up. In a subgroup of patients, a complete 24 h pharmacokinetic study was performed by HPLC.

Results: One hundred and three patients (47 switch strategies, 56 early salvage therapies) were included. After 6 months, 85/103 (83%; 95% CI: 74%–89%) and 85/93 (91%; 95% CI: 84%–97%) patients had <50 copies/mL HIV-RNA by intention-to-treat and on-treatment analyses, respectively. The respective values were 42/47 (89%; 95% CI: 72%–96%) and 42/43 (98%; 95% CI: 88%–100%) in switch therapy, and 43/56 (77%; 95% CI: 64%–87%) and 43/50 (86%; 95% CI: 73%–94%) in salvage therapy. There was a significant increase in CD4 cell counts [+73 cells/mm3 (95% CI: 43%–102%), P<0.001]. There were no interruptions due to rash or liver toxicity. Significant decreases in cholesterol and triglycerides were seen in patients with abnormal lipids at baseline. Ten patients discontinued antiretrovirals (5 were lost to follow-up and 5 due to side effects). Twenty-five patients were included in the pharmacokinetic study. All patients had trough plasma concentrations >0.05 μg/mL.

Conclusions: Darunavir/ritonavir at 900/100 mg once daily is highly effective, safe and well tolerated in treatment-experienced patients with no darunavir resistance, both in early salvage and switch strategies. Adequate drug plasma levels were achieved in all patients.

Keywords: HIV infection, antiretroviral treatment, switch strategies, early salvage, drug plasma levels

Introduction

With the advent of new antiretroviral (ARV) drugs, the objective when treating any HIV-infected patient has become to achieve undetectable viral load, regardless of the previous treatment experience. However, in order to improve adherence and quality of life it is important to build a treatment with few or no side effects, with a low number of pills and administered once daily if possible.1,2

Since its appearance, ritonavir-boosted darunavir has shown its efficacy in different clinical settings. First, it demonstrated its superiority over an investigator-chosen comparator protease inhibitor (PI) in highly treatment-experienced patients in the POWER studies, given 600/100 mg twice daily.3 Later, in the TITAN study, in treatment-experienced but lopinavir-naive patients, darunavir/ritonavir twice daily demonstrated superiority over lopinavir/ritonavir.4 Lastly, given 800/100 mg once daily in the ARTEMIS trial in naive patients, darunavir/ritonavir showed non-inferiority after 48 weeks and even superiority after 96 weeks in front of lopinavir/ritonavir.5 Thus, darunavir/ritonavir became the first PI to be approved by the regulatory
agencies at two different daily dosages depending on the clinical setting.

Ritonavir-boosted darunavir has a terminal elimination half-life of 15 h,\(^5\) the longest of all PIs, which allows once-daily administration. Pharmacokinetic (PK) data obtained in the ARTEMIS trial with the 800/100 mg once-daily dosage in naive patients demonstrated adequate plasma levels in this setting. In treatment-experienced patients, 900/100 mg of darunavir/ritonavir once daily showed promising results in the TMC 114–C207 proof-of-principle trial; however, this trial was limited as it included only 13 patients in the once-daily arm.\(^7\) In the first 24 weeks of the POWER 1 and 2 trials, different darunavir/ritonavir dosages were also tested, including 800/100 mg once daily. Finally, the 600/100 mg twice-daily dosage was chosen, although a post hoc analysis of those patients with or without primary PI mutations but with no darunavir mutations at baseline showed similar efficacy with the 600/100 mg twice-daily (n=29) and 800/100 mg once-daily (n=23) doses.\(^8\)

All these results suggested a high potency, even in the presence of some PI-related mutations, good tolerability and a favourable PK profile, with both once- and twice-daily darunavir/ritonavir administration. The main advantages of darunavir/ritonavir once daily are a lower pill burden, better tolerability, lower metabolic impact (half ritonavir dose),\(^9,10\) improvement in adherence, and lower pharmaceutical cost due to lower darunavir and ritonavir doses.

In this study, the efficacy, safety and PK profile of darunavir/ritonavir once daily in early salvage therapies or switch strategies have been evaluated.

Methods
Subjects and design

A prospective, observational, multicentre study was carried out in three university hospitals in Barcelona, Spain.

Patients with previous ARV experience who started a new regimen including 900/100 mg of darunavir/ritonavir once daily between January 2008 and April 2009 were considered for the study. This regimen was decided by the physician in charge of each patient, who considered darunavir to be fully active based on prior resistance testing and/or prior treatment history, and once-daily dosing to be important for the patient. Other inclusion criteria were: age \(\geq 18\) years; ARV regimen containing at least one other active drug; and minimum follow-up of 24 weeks, or less in case of premature discontinuation of any drug, or loss to follow-up. The darunavir daily dose was 900 mg (3 \(\times\) 300 mg darunavir tablets), given that the 400 mg darunavir tablet was still not available in Spain when this study took place.

According to baseline characteristics, patients were divided into two groups: (i) switch, when the patient had complete virological suppression and treatment was changed for simplification, or due to clinical or laboratory toxicity; and (ii) early salvage, in patients with virological failure (confirmed viral load >50 copies/mL), no history of multiple virological failures with prior highly active ARV therapy (HAART), no previous treatment with new drugs of the classic or newer families (darunavir, tipranavir, etravirine, maraviroc or enfuvirtide) and a variable degree of resistance but with one or more active drugs available in at least two of the three classic families [nucleoside reverse transcriptase inhibitors (NNRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and PIs].

Demographic data (age, gender and race), hepatitis C virus (HCV) co-infection status and HIV-related data (transmission risk factor, years of infection, previous ARV regimens and reasons for discontinuation, and prior resistance testing if performed) were recorded for each patient. Genotypic resistance tests were performed using the Virco-TYPE HIV1 test (Virco BVBA, Mechelen, Belgium). All previous tests were taken into account to determine the potential susceptibility to ARV drugs. Drug resistance-associated mutations (RAMs) were considered as defined by the International AIDS Society, USA, guidelines.\(^11\)

Physical examination and laboratory tests (CD4 count, HIV-1 RNA, haematology, liver and kidney function tests, and fasting blood lipids) were performed at baseline and at weeks 12 and 24, as part of routine clinical care.

In the salvage and switch arms, effectiveness was measured as the percentage of patients achieving or maintaining viral suppression, defined as <50 copies/mL HIV-RNA after 24 weeks. True virological failure was defined as two consecutive determinations of >50 copies/mL HIV-RNA, separated by 4 weeks. Efficacy analyses were performed by intention-to-treat (ITT), where non-completion equalled failure, and on-treatment (OT).

The safety and tolerability of the study medications were assessed on the basis of clinical and laboratory adverse events, using the WHO toxicity grading scales.\(^12\)

ARV costs and savings were calculated with the laboratory selling prices plus 4% VAT, as published in the GESIDA 2010 guidelines.\(^13\) Savings are calculated considering the difference in price between darunavir once- and twice-daily dosing, as 600/100 mg of darunavir/ritonavir twice daily is the recommended dose for treatment-experienced patients.

The study protocol was approved by the institutional review boards of the participating centres and written informed consent was obtained from all patients.

PK study

In a subgroup of patients, a complete 24 h PK substudy was performed at steady-state. All subjects were instructed to take darunavir/ritonavir at 9:00 a.m. with breakfast during the week before the day of intensive PK assessment of drug concentrations. To assure that the dose was taken 24 h before the pre-dose analysis, patients completed a form with the exact time they took the preceding dose. On the day of assessment, patients came to the hospital between 8:15 and 8:45 a.m. after overnight fasting. Drugs were administered at the hospital at 9:00 a.m. with a standard breakfast. Blood samples were drawn pre-dose and at 1, 2, 3, 4, 6, 8 and 12 h post-dose. Since the pre-dose darunavir/ritonavir concentration was determined 24 h after the preceding dose, the value obtained at this time was also used for the 24 h post-dosing value in PK analysis (\(C_{24}=C_{0}=C_{\text{trough}}\)).

A precise and accurate simultaneous HPLC method with ultraviolet detection was developed and validated for darunavir and ritonavir. The HPLC system consisted of a Waters separation model 2695 and a Waters model 2487 absorbance UV detector coupled to Empower\(^\text{TM}\) software version 3.0 (Waters, Milford, MA, USA). Separation was performed at 25 °C on a Symmetry 300 mm \(\times\) 3.5 \(\mu\)m, C18 (3.5 \(\mu\)m, 4.6 \(\times\)150 mm) analytical column protected by Sentry Guard column Symmetry 300 mm \(\times\) 5 \(\mu\)m, C18 (5 \(\mu\)m, 3.9 \(\times\)20 mm) (Waters, Dublin, Ireland). The mobile phase was composed of a 10 mM potassium phosphate buffer (pH 5.5) (solvent A) and acetone:nitrite (solvent B). The mobile phase was delivered at 0.8 mL/min with a linear gradient program from time 0 (solvent A 60%/solvent B 40%) to 23 min (solvent A 45%/solvent B 55%); from time 23 to 26 min, the composition of the mobile phase was constant (solvent A 45%/solvent B 55%); from time 26 to 26.5 min, the mobile phase was changed to the initial gradient; and from time 26.5 to 29 min, the column was stabilized (solvent A 60%/solvent B 40%) before the next injection. Darunavir and ritonavir were detected simultaneously at 220 and 240 nm, respectively. A liquid–liquid extraction (diethyl ether) with an internal standard...
(A-86903) was used for sample preparation (1 mL of human plasma). An aliquot of 100 μL of reconstituted residue with methanol/water (50:50) was injected into the chromatographic system for a 29min run-time analysis. All validation steps were conducted according to the FDA guidelines for the validation of bioanalytical assays.14 The linearity range was 0.1–10 μg/mL. The limit of quantification and limit of detection were 0.1 and 0.05 μg/mL for both drugs, respectively. The intraday precision ranged from 0.9% to 2.9%, while the intraday accuracy ranged from −3.7% to 3.3%. The interday precision and accuracy were <3.4% and −3.0%, respectively. The mean recovery was 82.6% for darunavir and 89.1% for ritonavir. No interference was found between darunavir and ritonavir and endogenous compounds, other ARVs or other drugs commonly used, except for interference between darunavir and amprenavir.

The area under the plasma concentration–time curve from 0 to 24 h (AUC0–2 4) and oral clearance were assessed using a non-compartmental model using the linear/log trapezoidal rule with WinNonlin 3.3 (Pharsight Corp., Mountain View, CA, USA).

**Results**

**Patients and baseline characteristics**

One hundred and three patients were included in the study. Baseline characteristics are described in Table 1. Patients receiving darunavir as salvage therapy had significantly lower CD4 counts (P = 0.001) and lower triglycerides (P = 0.020) at baseline compared with switch patients.

In 59 (57%) patients, a resistance test before darunavir initiation was available. Of these patients, 21 (36%) had at least one thymidine-associated mutation, 8 (14%) had the K65R mutation, 22 (37%) had the M184V mutation, 16 (27%) had at least one major PI mutation (D30N, V32I, L33F, M46I/L, I47V, V82A/T, I84V, N88S and L90M), 4 had one darunavir RAM [V32I (1), L33F (2) and I84V (1)] and 1 had two darunavir RAMs (V32I and I47V).

Table 2 shows ARV drugs combined with darunavir/ritonavir. The most prescribed treatment was tenofovir plus emtricitabine in 57 (55%) patients. Darunavir/ritonavir was given with raltegravir in 19 patients and with etravirine in 6.

**Statistical analysis**

Statistical analyses were performed with the SPSS 15.0 statistical package (SPSS Inc., Chicago, IL, USA). Descriptive values are described as the mean ± SD. Changes from baseline in quantitative variables were calculated with the paired t-test or with the Wilcoxon signed ranks test. Comparisons between groups were performed with the independent samples t-test or the Mann–Whitney test. In the PK substudy, descriptive values for darunavir PK parameters are expressed as the median (interquartile range), geometric means [95% confidence interval (CI)] and coefficient of variation. Comparisons of darunavir PK parameters between subgroups were performed using a parametric statistical approach (analysis of variance) of in-transformed values followed by estimation of the 95% CI for the ratio of the geometric means.
Table 2. Antiretroviral drug associated with once-daily darunavir/ritonavir

<table>
<thead>
<tr>
<th>Background</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Only NRTI</td>
<td>76 (74%)</td>
</tr>
<tr>
<td>1 NRTI</td>
<td>6</td>
</tr>
<tr>
<td>TDF/FTC</td>
<td>57</td>
</tr>
<tr>
<td>ABC/3TC</td>
<td>6</td>
</tr>
<tr>
<td>other combinations</td>
<td>7</td>
</tr>
<tr>
<td>Raltegravir alone</td>
<td>19 (18%)</td>
</tr>
<tr>
<td>+NRTI</td>
<td>12</td>
</tr>
<tr>
<td>+NNRTI</td>
<td>2</td>
</tr>
<tr>
<td>+maraviroc</td>
<td>1</td>
</tr>
<tr>
<td>NNRTI etravine alone</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>etravine+NRTI</td>
<td>3</td>
</tr>
<tr>
<td>efavirenz+NRTI</td>
<td>2</td>
</tr>
</tbody>
</table>

NRTI, nucleoside reverse transcriptase inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; TDF/FTC, tenofovir/emtricitabine fixed-dose combination; ABC/3TC abacavir/lamivudine fixed-dose combination.

Patient disposition, plasma HIV-RNA levels and CD4 cell counts

At week 24, 93 (90%) patients remained on the initial treatment. Overall, 10 patients discontinued darunavir/ritonavir (5 patients were lost to follow-up and in the other 5 ARV therapy was changed or stopped because of related or unrelated side effects).

Virological outcomes are described in Figure 1. After 6 months, 85/103 (83%; 95% CI: 74%–89%) and 85/93 (91%; 95% CI: 84%–97%) of the patients had undetectable viral load (<50 copies/mL) by ITT and OT analyses, respectively. In switch strategies these values were 42/47 (89%; 95% CI: 72%–96%) and 42/43 (98%; 95% CI: 88%–100%), and in salvage therapy they were 43/50 (77%; 95% CI: 64%–87%) and 43/50 (86%; 95% CI: 73%–94%), respectively. Seven patients had a single determination of viral load of 50–200 copies/mL at week 24; when repeated 4 weeks later, the viral load was <50 copies/mL (blips).

True virological failure during darunavir/ritonavir treatment was observed in 8/103 (8%; 95% CI: 3%–15%) patients, with a confirmed viral load of 50–200 copies/mL in four of them and >200 copies/mL in the other four. Of the eight true virological failures, two were observed in the switch group and six in the salvage group, in which four patients failed to ever achieve a viral load of <50 copies/mL and two patients rebounded after being undetectable. The frequency of true virological failure in patients receiving darunavir/ritonavir with NRTIs was 8/76 (11%; 95% CI: 5%–20%); 2/34 (6%; 95% CI: 1%–20%) if the patient was taking two active NRTIs; and 6/42 (14%; 95% CI: 5%–29%) if one or none of the NRTIs was active (P = non-significant).

Of the 27 patients receiving darunavir/ritonavir associated with raltegravir or NNRTIs, 24 had <50 copies/mL HIV-RNA after 24 weeks and 3 were lost to follow-up. None of them had true virological failure. All seven patients receiving bitherapy (four with raltegravir and three with etravirine) had an undetectable viral load after 24 weeks.

Of the 13 patients previously receiving a double-boosted PI regimen, 11 (85%; 95% CI: 55%–98%) had a viral load of <50 copies/mL, one stopped treatment due to side effects and the other had a confirmed viral load of 50–200 copies/mL after 24 weeks.

Three out of four patients with darunavir-associated mutations, including the patient with two darunavir RAMs, had an undetectable viral load after 24 weeks. The fourth patient, with the L33F mutation, was lost to follow-up.

There was a significant increase in CD4 cell counts after 6 months (+73 cells/mm³ (95% CI: 43%–102%), P < 0.001). The CD4 increase was 111 cells/mm³ (95% CI: 67%–151%) in the salvage group and 33 cells/mm³ (95% CI: 6%–70%) in the switch group.

Safety and tolerability

Darunavir/ritonavir at 900/100 mg once daily was generally well tolerated. Five patients (5%) discontinued ARV therapy during follow-up due to side effects. The first, a 72-year-old patient with multiple cardiovascular risk factors, died from myocardial infarction. The second was diagnosed with an abdominal lymphoma with intestinal occlusion and all drugs had to be withdrawn. In the third patient, a previous depressive syndrome worsened and he decided to discontinue darunavir/ritonavir. The last two patients had gastrointestinal intolerance (one vomiting and one diarrhoea) and ARV treatment was discontinued.

No patients had rash or clinical symptoms of hepatitis, and there were no treatment interruptions due to clinical or laboratory liver toxicity. No patients had grade III or IV elevations of liver enzymes. Four patients presented grade II liver toxicity during follow-up without requiring treatment change: three at week 12, which spontaneously resolved at week 24; and one at week 24, which remained stable after 48 weeks. In two patients with grade II liver toxicity at baseline, transaminase levels decreased with darunavir/ritonavir therapy.

In the total population, there were no differences in cholesterol levels and a trend towards a decrease in triglycerides (from 230 to 194 mg/dL, P = 0.073) was observed after 24 weeks. Significant differences were found in patients with an abnormal lipid profile at baseline. In patients with high baseline triglycerides (>150 mg/dL), these decreased significantly after 6 months (from 341 to 253 mg/dL, P = 0.014) and this difference became greater with baseline triglycerides >250 mg/dL (from 484 to 316 mg/dL, P = 0.010). In the same way, significant differences were seen in total cholesterol levels in those patients with baseline values >200 mg/dL (from 248 to 231 mg/dL, P = 0.029), with no differences in the total/high-density lipoprotein cholesterol ratio.

Economic cost

The 900/100 mg of darunavir/ritonavir once-daily dose represented a saving of €1190 per month per patient compared with 600/100 mg of darunavir/ritonavir twice daily. Given that 103 patients were included during a follow-up of 6 months, this represents a total saving of €117420 during the study period.
PK study

Twenty-five patients were included in the complete 24 h PK substudy. The results of the PK analyses are summarized in Figure 2 and Table 3. All patients had a darunavir $C_{\text{min}}$ above the EC$_{50}$ for wild-type virus (0.055 mg/mL). All patients but one had $C_{\text{min}}$ values 10 times the darunavir EC$_{50}$ (0.55 mg/mL). The only patient with $C_{\text{min}}$ below this threshold had a $C_{\text{min}}$ of 0.45 mg/mL and after 6 months the viral load was <50 copies/mL.

There were no significant differences in darunavir PK parameters due to gender or HCV co-infection (Table 4). There were no trends or significant differences in darunavir plasma levels, irrespective of concomitant administration of other drugs, such as proton pump inhibitors ($n=2$), methadone ($n=3$), statins ($n=3$), benzodiazepines ($n=6$) or raltegravir ($n=4$).

Discussion

Darunavir/ritonavir is the only PI approved at two different daily dosages, 800/100 mg once daily in treatment-naive patients and 600/100 mg twice daily in treatment-experienced patients. The theoretical basis for this difference is that in patients with resistant virus, higher plasma drug concentrations are required to suppress viral replication and, thus, a higher dose...
administered twice daily has to be given. It seems reasonable that in treatment-experienced patients with no darunavir-associated mutations, this drug will perform as well as in treatment-naive patients when given once daily. In this sense, 83% and 91% of our patients, by ITT and OT analysis, respectively, had <50 copies/mL HIV-RNA after 24 weeks.

The few randomized studies conducted in the early salvage setting mainly compared boosted PIs with lopinavir/ritonavir, 

Table 3. PK parameters at steady-state in 25 patients treated with darunavir/ritonavir (900/100 mg once daily)

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Darunavir</th>
<th>Ritonavir</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{min}}, \mu g/mL$</td>
<td>1.83 (1.15–2.96)</td>
<td>0.06 (0.04–0.13)</td>
</tr>
<tr>
<td>geometric mean (95% CI)</td>
<td>1.80 (1.40–2.30)</td>
<td>0.07 (0.05–0.10)</td>
</tr>
<tr>
<td>coefficient of variation, %</td>
<td>101</td>
<td>30</td>
</tr>
<tr>
<td>$C_{\text{max}}, \mu g/mL$</td>
<td>8.19 (7.19–9.97)</td>
<td>0.67 (0.40–0.94)</td>
</tr>
<tr>
<td>geometric mean (95% CI)</td>
<td>8.34 (7.50–9.26)</td>
<td>0.64 (0.49–0.82)</td>
</tr>
<tr>
<td>coefficient of variation, %</td>
<td>12</td>
<td>139</td>
</tr>
<tr>
<td>$T_{\text{max}}, h$</td>
<td>2 (1–3.5)</td>
<td>4 (1.5–6)</td>
</tr>
<tr>
<td>geometric mean (95% CI)</td>
<td>2.09 (1.58–2.75)</td>
<td>2.92 (2.17–3.94)</td>
</tr>
<tr>
<td>coefficient of variation, %</td>
<td>91</td>
<td>67</td>
</tr>
<tr>
<td>$\text{AUC}_{0–24 h}, \mu g\cdot h/mL$</td>
<td>91.3 (72.9–122.6)</td>
<td>5.88 (4.93–8.30)</td>
</tr>
<tr>
<td>geometric mean (95% CI)</td>
<td>93.03 (79.68–108.53)</td>
<td>6.30 (5.09–7.80)</td>
</tr>
<tr>
<td>coefficient of variation, %</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>9.86 (7.37–12.35)</td>
<td>17.0 (12.1–20.3)</td>
</tr>
<tr>
<td>geometric mean (95% CI)</td>
<td>9.68 (8.29–11.29)</td>
<td>15.86 (12.82–19.65)</td>
</tr>
<tr>
<td>coefficient of variation, %</td>
<td>16</td>
<td>19</td>
</tr>
</tbody>
</table>

IQR, interquartile range; CI, confidence interval; $C_{\text{min}}$, minimum concentration; $C_{\text{max}}$, maximum concentration; $T_{\text{max}}$, timepoint of maximum concentration; $\text{AUC}_{0–24 h}$, area under the plasma concentration–time curve from 0 to 24 h; CL/F, oral clearance.

Figure 2. Median drug plasma concentration–time curves at steady-state in 25 patients treated with darunavir/ritonavir (900/100 mg once-daily). Error bars indicate interquartile ranges. Filled circles indicate darunavir concentrations. Open circles indicate ritonavir concentrations.
Darunavir/ritonavir 900/100 mg once daily in pre-treated patients

Table 4. Darunavir PK parameters depending on gender or HCV co-infection

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Gender</th>
<th></th>
<th></th>
<th>HCV</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>male (n=18)</td>
<td>female (n=7)</td>
<td>GMR (95% CI)</td>
<td>female/male</td>
<td>geometric mean (95% CI)</td>
</tr>
<tr>
<td>Cmin, μg/mL</td>
<td>1.74 (1.30–2.35)</td>
<td>1.95 (1.21–3.15)</td>
<td>1.12 (0.64–1.97)</td>
<td>1.23 (1.52–2.97)</td>
<td>1.50 (1.06–2.13)</td>
</tr>
<tr>
<td>Cmax, μg/mL</td>
<td>8.31 (7.32–9.44)</td>
<td>8.41 (6.65–10.32)</td>
<td>1.01 (0.80–1.29)</td>
<td>8.82 (7.62–10.21)</td>
<td>7.85 (6.74–9.13)</td>
</tr>
<tr>
<td>AUC, μg.h/mL</td>
<td>89.75 (74.66–107.88)</td>
<td>102.00 (75.94–137.00)</td>
<td>1.14 (0.80–1.61)</td>
<td>99.29 (80.08–123.22)</td>
<td>86.58 (69.20–108.42)</td>
</tr>
<tr>
<td>CL/F, L/h</td>
<td>10.03 (8.35–12.06)</td>
<td>8.83 (6.57–11.86)</td>
<td>0.88 (0.62–1.25)</td>
<td>9.06 (7.31–11.23)</td>
<td>10.39 (8.31–13.00)</td>
</tr>
</tbody>
</table>

P = non-significant for any parameter when comparing male versus female or HCV-negative versus HCV-positive.

GMR, geometric mean ratio; CI, confidence interval; HCV, hepatitis C virus; Cmin, minimum concentration; Cmax, maximum concentration; AUC, area under the plasma concentration–time curve; CL/F, oral clearance.

The gold standard at that time. Darunavir/ritonavir was the only drug that demonstrated superiority in front of lopinavir/ritonavir in the TITAN study.5 In this trial, the proportion of patients with <50 copies/mL HIV-RNA by ITT–time to loss of virological response (TLOVR) was 71% at 48 weeks. Although the darunavir/ritonavir dose used in the TITAN trial was 600/100 mg twice daily, these results are similar to those of our study performed in routine clinical practice with the administration of 900/100 mg once daily.

There is scarce previous clinical experience regarding the administration of once-daily darunavir/ritonavir in ARV-experienced patients,7,8 one being a post hoc analysis of a small number of patients in the POWER studies. Virological response rates (<50 copies/mL HIV-RNA by ITT) in these highly experienced patients, but with no baseline darunavir RAMs, were 67% and 62% with 800/100 mg of darunavir/ritonavir once daily and 600/100 mg of darunavir/ritonavir twice daily, respectively.8 Recently, the ODIN trial19 compared 600/100 mg of darunavir/ritonavir twice daily versus 800/100 mg once daily plus an optimized background regimen containing at least two active NNRTI, as salvage treatment in patients with no darunavir RAMs. The patients in the ODIN trial had a median of zero primary PI mutations and only 29% had previously received baseline lipidic parameters and even then the once-daily darunavir/ritonavir-based treatment did not have a deleterious effect on the lipid profile. Furthermore, in patients with abnormal lipid parameters at baseline, total cholesterol and triglycerides improved after 24 weeks of darunavir/ritonavir therapy. These benefits in lipid parameters with darunavir/ritonavir once daily have also been seen in the ODIN trial when compared with darunavir/ritonavir twice daily.20 However, our study was not powered for this analysis and these differences could be due to causes other than the reduction in darunavir/ritonavir dose.

Another benefit of once-daily darunavir/ritonavir administration is the cost, an issue that has become very important as HIV infection requires life-long therapy. The 900/100 mg of darunavir/ritonavir once daily (€523 per month per patient) and 800/100 mg once daily (€468 per month per patient) doses represent a saving of €190 and €245 per month per patient, respectively, compared with 600/100 mg of darunavir/ritonavir twice daily (€713 per month per patient), although the cost may vary between different countries and no formal cost analysis was done. The saving calculation in our study might have been overestimated (compared with darunavir/ritonavir twice
ritonavir-boosted PIs,26 with all the other advantages. We have Darunavir probably is more potent than the two conventional boosted PI-based regimen, if no darunavir resistance is present. can be especially evident are those previously receiving a double- can be an excellent option as a switch strategy.

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daily, which could have been the choice in salvage patients but not the first option in case of toxicity), but other current switch alternatives have the same price (etravirine costing €468 per month per patient) or are much more expensive (raltegravir and maraviroc cost €842 and €816 per month per patient, respectively) than once-daily darunavir/ritonavir, so the latter can be an excellent option as a switch strategy.

A subgroup of patients in whom all these potential benefits can be especially evident are those previously receiving a double-boosted PI-based regimen, if no darunavir resistance is present. Darunavir probably is more potent than the two conventional boosted PI-based regimen, if no darunavir resistance is present.

The PK data obtained from our study are important, given that most of the available information on the once-daily dosing from the ARTEMIS trial are population PK models extrapolated from C_{min}(in 335 patients), with complete curves performed in only nine patients. In our study, we present data of complete PK curves from 25 patients, which confirm the safety of the once-daily dose in those patients with no or little resistance to darunavir, as adequate darunavir plasma concentrations are achieved (the median C_{min}is >30 times the darunavir EC_{50} for wild-type virus and >3 times the darunavir EC_{50} for virus with a darunavir fold-change of 10). The median C_{min} in our study (1.83 μg/mL) is similar to the C_{min} in the ARTEMIS trial (2.04 μg/mL), to that in the 118 patients with 800/100 mg of darunavir/ritonavir once daily in the first weeks of the POWER studies (1.84 μg/mL) and to that in the once-daily arm of the ODIN trial (1.81 μg/mL). We have not observed differences in PK parameters depending on gender, HCV co-infection or other concomitant medications administered, but the latter has to be interpreted with caution due to the low number of patients.

Some limitations of this study have to be pointed out. First, the darunavir dose used is 900 mg, slightly higher than the 800 mg dose of the ARTEMIS and the ODIN trials. Until December 2009, the 400 mg darunavir tablet was not available in Spain and this is an observational analysis of data obtained from clinical practice. However, it is highly improbable that this 100 mg difference in the darunavir dose might have improved the results obtained in our patients with respect to the 800/100 mg dose, as plasma concentrations were far above the EC_{50} for susceptible virus. Also, the potential advantage of higher concentrations could have been outweighed by the fact of giving one extra pill. Thus, with the availability of the 400 mg darunavir tablet, probably the 800/100 mg dose can be used in these patients, as demonstrated in the ODIN trial. From December 2009, our patients taking 900/100 mg of darunavir/ritonavir once daily have been switched to 800/100 mg once daily, all after follow-up of ≥6 months with the 900/100 mg dose (no data with the 800/100 mg dose is included in the current analysis).

Another limitation of this study is the small number of previous mutations in the protease, which could make us consider these patients practically as PI-naive. However, some patients had previously failed on boosted or non-boosted PI-based regimens, so it is possible that some NRTI and/or PI-related mutations were archived, although they had not appeared in the resistance studies. In this setting it is important to give a potent PI as the basis of the treatment. Besides, in early salvage in the near future we will find even fewer resistance mutations both in the protease and in the reverse transcriptase. This is due to the use of ritonavir as a PI booster and to the fact that, nowadays, patients with virological failure have their treatment changed at an earlier point, avoiding the selection of mutations in the protease and, to a lesser extent, in the reverse transcriptase. Thus, once-daily darunavir/ritonavir will remain as an excellent treatment option.

Finally, being an observational study without a control group, there could have been a selection bias that could have influenced the positive outcomes. This is highly improbable, as darunavir/ritonavir once daily was administered to those patients with prior treatment failures and/or potential adherence problems to twice-daily regimens.

In summary, ritonavir-boosted darunavir given at 900/100 mg once daily is a highly effective, well-tolerated and safe alternative in ARV-experienced patients with no darunavir resistance as salvage or switch therapies.

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Transparency declarations

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Darunavir/ritonavir 900/100 mg once daily in pre-treated patients

Author contributions
A. C. and E. R. conceived the study, participated in its design, coordination and data analysis, and drafted the manuscript. M. G., E. D., G. M., A. I., M. C., J. O. and P. D. recruited patients, carried out the study protocol and supervised data integrity and analysis. R. M. L. performed the PK analysis and helped to draft the manuscript. All authors approved the final manuscript.

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