J Antimicrob Chemother 2015; **70**: 1139–1145
doi:10.1093/jac/dku516 Advance Access publication 18 December 2014

Journal of Antimicrobial Chemotherapy

Reduced darunavir dose is as effective in maintaining HIV suppression as the standard dose in virologically suppressed HIV-infected patients: a randomized clinical trial

José Moltó[1,2]*, Marta Valle[2,3], Elena Ferrer[4], Pere Domingo[5], Adrian Curran[2,6], José Ramón Santos[1], María Gracia Mateo[5], María Silvana Di Yacovo[4], Cristina Miranda[1], Daniel Podzamczer[4] and Bonaventura Clotet[1,2,7,8] on behalf of the DRV600 Study Group†

[1]Fundació Lluita contra la Sida, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [2]Universitat Autònoma de Barcelona (UAB), Barcelona, Spain; [3]PKPD Modelling and Simulation, Institut de Recerca HSCSP-IIB St Pau, Barcelona, Spain; [4]Unitat VIH, IDIBELL-Hospital Universitari de Bellvitge, L'Hospitalet, Barcelona, Spain; [5]Internal Medicine Department, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain; [6]Infectious Diseases Department, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [7]Fundació IrsiCaixa, Hospital Universitari Germans Trias i Pujol, Badalona, Spain; [8]Universitat de Vic-Universitat Central de Catalunya (UVIC-UCC), Vic, Spain

*Corresponding author. Fundació Lluita contra la SIDA, Hospital Universitari Germans Trias i Pujol, Badalona, Spain. Tel: +34-93-497-88-87; Fax: +34-93-465-76-02; E-mail: jmolto@flsida.org
†Members are listed in the Acknowledgements section.

Received 25 September 2014; returned 5 November 2014; revised 20 November 2014; accepted 24 November 2014

Objectives: Maximizing ART efficiency is of growing interest. This study assessed the efficacy, safety, pharmacokinetics and economics of a darunavir dose-reduction strategy.

Methods: This was a multicentre, randomized, open-label clinical trial in HIV-infected patients with plasma HIV-1 RNA <50 copies/mL while receiving triple ART including 800 mg of darunavir once daily. Participants were randomized to continue 800 mg of darunavir (DRV800) or to 600 mg of darunavir (DRV600), both once daily. Treatment failure was defined as two consecutive HIV-1 RNA determinations >50 copies/mL or discontinuation of study treatment by week 48. The study was registered at https://www.clinicaltrialsregister.eu (trial number 2011-006272-39).

Results: Fifty participants were allocated to each arm. The mean (SD) CD4+ T cell count at baseline was 562 (303) cells/mm^3 and HIV-1 RNA had been <50 copies/mL for a median (IQR) of 106.9 (43.4–227.9) weeks before enrolment. At week 48 no treatment failure had occurred in 45/50 (90%) DRV600 patients and in 47/50 (94%) DRV800 patients (difference −4%; 95% CI lower limit, −12.9%). When only patients with virological data were considered, that endpoint was met by 45/48 (94%) in the DRV600 arm and 47/49 (96%) in the DRV800 arm (difference −2.2%; 95% CI lower limit, −9.6%). Darunavir exposure was similar in the two arms. The average reduction in annual cost per successfully treated DRV600-arm patient was US$7273.

Conclusions: The efficacy of a darunavir daily dose of 600 mg seemed to be similar to the efficacy of the standard 800 mg dose in virologically suppressed HIV-infected patients on triple ART. This strategy can potentially translate to substantial savings in the cost of care of HIV-infected patients.

Keywords: HIV infection, dose optimization, ART

Introduction

Improvement in ART has resulted in a dramatic decline in morbidity and mortality associated with HIV infection as well as decreased HIV transmission.[1–7] Based on these benefits, current guidelines for the management of HIV-infected patients promote expanded eligibility for ART, and the number of patients in treatment is expected to increase substantially in the near future.[8–10] However, meeting this goal in the present economy, in which economic restrictions affect many settings, remains challenging.

Since ART constitutes the largest portion of the total cost of care for HIV-infected patients, reducing the cost of antiretroviral drugs is essential to meet the current demand. In this regard, antiviral dose optimization is a possible strategy for maximizing ART efficiency.[11–13]

Selection of the dose of a drug for clinical development is based on Phase 2 dose-finding studies, in which a limited number of patients are included to evaluate the efficacy and safety of several doses. This process may be straightforward when a low dose is ineffective or a high dose is toxic. However, in many cases these Phase 2 trials reveal similar efficacy and safety over the dose range evaluated. The tendency, therefore, is to select the highest tolerated dose of the drug in an attempt to ensure efficacy, even though eventual drug interactions or adherence issues might lower drug concentrations. Nonetheless, choosing higher doses may result in higher costs and poor safety, and post-approval dose reductions have been necessary for some antiretroviral drugs.[14–16]

Since its approval for treating HIV infection, darunavir has been used to treat millions worldwide and is one of the preferred drugs for both initial and salvage therapy in HIV.[8,9] The pivotal POWER 1 and 2 clinical trials evaluated the efficacy and safety of four different doses of darunavir in combination with ritonavir (600 or 400 mg twice daily, and 800 or 400 mg once daily) in a population of treatment-experienced HIV-infected patients.[17–19] Because the highest virological response was obtained with 600/100 mg of darunavir/ritonavir twice daily, this dose was selected for further development, and it was subsequently approved for treatment-experienced patients. Additionally, in a subgroup analysis including only patients with no darunavir resistance mutations at baseline, the responses to the 800 mg once-daily and the 600 mg twice-daily doses were similar,[20] leading to approval of the single daily 800 mg dose for initial ART. However, that analysis showed that the once-daily darunavir doses of 400 and 800 mg had comparable efficacy in patients with viral strains that were fully susceptible to darunavir,[21] suggesting the possibility of using lower doses of darunavir in such patients.

Based on the above, we therefore aimed to test the hypothesis that reducing the daily darunavir dose from 800 to 600 mg in virologically suppressed HIV-positive patients with no darunavir resistance-associated mutations would maintain virological efficacy while reducing the cost associated with ART.

Methods

Design and participants

The DRV600 study was a 48 week randomized, open-label, multicentre clinical trial comparing the efficacy, safety, pharmacokinetics and economic impact of a reduced single daily dose of darunavir (600 mg) with the standard dose (800 mg) in virologically suppressed HIV-infected patients. The primary endpoint was the percentage of patients without treatment failure by week 48. Treatment failure was defined as the presence of two consecutive HIV-1 RNA determinations >50 copies/mL (virological failure) or discontinuation of randomized treatment for any reason. Secondary endpoints included the percentage of patients with adverse events or laboratory abnormalities leading to treatment discontinuation, changes in CD4+ T cell count or in darunavir concentrations in plasma during the follow-up, and the absolute annual cost per patient with virological response at 48 weeks.

Participants were recruited at four hospitals in the urban area of Barcelona, Spain. Eligible participants were HIV-infected patients aged ≥18 years who were on ART including 800/100 mg of darunavir/ritonavir once daily plus two NRTIs and who had had HIV-1 RNA levels in plasma <50 copies/mL for at least 12 weeks. Participants were excluded in the case of documented darunavir resistance-associated mutations or a prior history of virological failure while receiving PIs.

The trial was performed according to the stipulations of the Declaration of Helsinki and the protocol was approved by the participating hospitals' ethics committees and by Spanish national regulatory authorities. Each participant gave written informed consent before screening for eligibility criteria. The study was registered at https://www.clinicaltrialsregister.eu (trial number 2011-006272-39).

Interventions, data collection and procedures

After enrolment, patients were randomized (1:1) either to continue on the standard darunavir dose given as a single 800 mg pill (DRV800 group) or to a reduced darunavir daily dose of 600 mg also given as a single pill (DRV600 group). All patients continued receiving 100 mg of ritonavir once daily and the same NRTIs. Patients were encouraged to take their medication in the morning with food. The random allocation to a treatment group was carried out centrally based on a list of pseudorandom numbers drawn from a uniform distribution.

Demographic and clinical variables were recorded for each participant at enrolment. Clinical visits were scheduled at week 0 (baseline), week 4, week 12 and every 12 weeks thereafter until week 48. The visits included a physical examination, adverse event reporting and a blood work-up with biochemistry, plasma HIV-1 RNA, CD4+ T cell count and darunavir concentrations in plasma. Patients with confirmed viral rebound during the study were tested for HIV drug resistance mutations (genotypic tests) at the time of rebound.

Additionally, a full pharmacokinetic profile was obtained for 15 patients in each study arm who voluntarily agreed to participate in this pharmacokinetic substudy. These participants came to their usual HIV clinic in the morning for collection of serial blood samples to determine darunavir concentrations in plasma immediately before and 1, 2, 4, 6, 8, 10, 12 and 24 h after a witnessed dose of darunavir/ritonavir.

All laboratory determinations were performed locally with the exception of darunavir concentrations in plasma, which were determined by HPLC at a reference laboratory (IrsiCaixa, Barcelona, Spain) subscribed to an external quality assurance programme.[22]

Information on direct costs (cost of antiretroviral drugs and costs derived from treatment failure) was derived in US dollars from wholesale acquisition price lists.[9] Costs associated with virological failure included the costs of unscheduled determinations of HIV-1 RNA, genotypic resistance tests and antiretroviral drugs used for salvage ART. For patients who were lost to follow-up it was assumed that the patient had continued on ART with 800/100 mg of darunavir/ritonavir once daily plus tenofovir/emtricitabine up to week 48.

Statistical analysis

Data comparisons were carried out using SPSS version 15.0 statistical software (Chicago, IL, USA). Continuous variables were described as mean (SD) if they were normally distributed and as median (IQR) if not. Categorical data were summarized as absolute numbers and percentages. Comparisons were performed using parametric or non-parametric tests, as appropriate, for continuous variables, and the χ^2 test or Fisher's exact test for percentages.

The primary efficacy endpoint (absence of treatment failure) was evaluated considering all the patients randomized (ITT analysis); in addition we performed an analysis including only those patients with observed virological data at week 48, with missing values disregarded (observed data analysis).

For the pharmacokinetic substudy, individual darunavir pharmacokinetic parameters [C_{max}, AUC_{0-24} and concentration at the end of the dosing interval (C_{trough})] were calculated using non-compartmental analysis (Winnonlin version 2.0; Pharsight, Mountain View, CA, USA) and the two study arms were compared with the geometric mean ratio and its 90% CI.

For the cost–efficacy analysis, the incremental cost per successfully treated patient was calculated considering 1 year costs and 48 week efficacy for each treatment option (ITT).

Assuming 90% efficacy at week 48, we estimated that a sample size of 50 patients per treatment group would provide 80% power to detect a minimum difference of 15% in efficacy between the DRV600 and DRV800 arms, with an α risk of 0.05.

Results

Baseline characteristics and patient distribution

Figure 1 shows a flow chart of participants in the trial. Out of 105 patients screened from May 2012 to February 2013, a total of 100 fulfilled eligibility criteria and were enrolled and randomized (50 to each arm). Baseline characteristics were balanced between treatments (Table 1). Participants were mostly males, and 20% were coinfected by hepatitis C virus. Thirty-one patients (31%) were receiving their first antiretroviral regimen. The NRTI backbones were mainly tenofovir/emtricitabine (66%) or abacavir/lamivudine (33%). None of the patients had prior evidence of NRTI resistance-associated mutations. Viral load had been <50 copies/mL for a median of 106.9 (43.4–227.9) weeks before enrolment, and the mean CD4+ T cell count was 562 (303) cells/mm^3 at baseline. The mean nadir CD4+ T cell count was 199 (146) cells/mm^3. Fifty-eight (58%) and 19 (19%) patients had a nadir CD4+ T cell count <200 and <50 cells/mm^3, respectively.

Efficacy

The primary efficacy endpoint at week 48 (absence of treatment failure) was achieved by 45/50 (90%) and by 47/50 (94%) patients in the DRV600 and DRV800 groups, respectively (difference −4%; 95% CI lower limit, −12.9%). When only patients with virological data available at week 48 were considered (observed data analysis), 45/48 (94%) patients in the DRV600 arm and 47/49 (96%) patients in the DRV800 arm had HIV-1 RNA levels <50 copies/mL at the 48 week visit (difference −2.2%; 95% CI lower limit, −9.6%). The mean CD4+ T cell count remained stable over time in both arms.

Reasons for treatment discontinuation included virological failure, in three patients in the DRV600 arm and two patients in the DRV800 arm (Figure 1). Additionally, one participant in each arm was lost to follow-up and one cirrhotic patient in the DRV600 arm died during the trial.

Inconsistent adherence to ART was considered the main determinant of virological failure in four out of the five patients with HIV-1 RNA elevations. Valid genotypic results at the time of failure could be obtained for three patients, and showed no emergence of resistance mutations in either the protease or the reverse transcriptase gene. After additional adherence counselling, viral load returned to <50 copies/mL in four out of the five patients without changing the drugs in the antiretroviral regimen but increasing the dose of darunavir to 800 mg once daily in the three patients allocated to the DRV600 arm. The remaining patient did not continue to attend clinical appointments and he was lost to follow-up.

Safety

Overall, treatment was well tolerated and no patient discontinued ART due to drug-related adverse events. The most common grade ≥2 drug-related adverse events were gastrointestinal disturbances (four patients in the DRV600 arm and six patients in the DRV800 arm) and lipid elevations (five patients in the DRV800 arm and no patients in the DRV600 arm). One patient with liver cirrhosis developed spontaneous *Escherichia coli* bacteraemia during the trial and died of refractory septic shock.

Darunavir pharmacokinetics

The mean darunavir C_{trough} during the trial was 2.19 (1.50) mg/L in the DRV600 arm and 2.21 (1.44) mg/L in the DRV800 arm (P=0.942). The mean remained ∼40-fold higher than the protein binding-adjusted effective concentration (EC_{50}) for WT viral strains (0.055 mg/L)[23] in both arms.

Full darunavir plasma concentration–time curves were determined in 15 patients in each arm. Although patients in the DRV600 arm showed a slight decrease in darunavir exposure (Figure 2), no significant difference was observed in any of the primary pharmacokinetic parameters of darunavir between the two dosing regimens (Table 2).

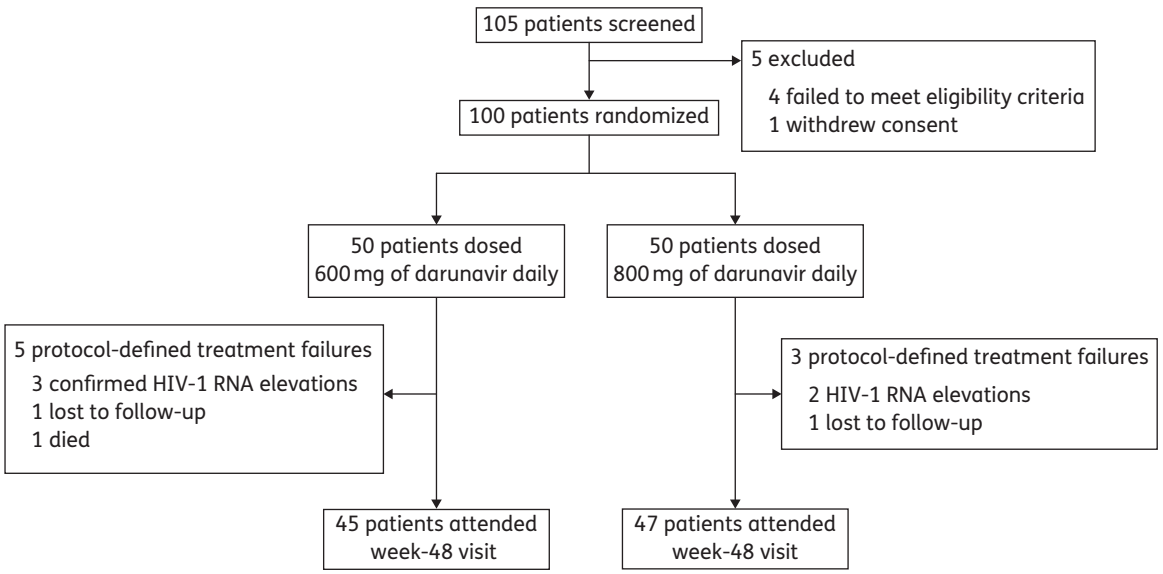

Figure 1. Flow chart showing patient distribution from screening until the week 48 endpoint of the DRV600 trial.

Table 1. Baseline demographic and clinical variables by treatment group

	600 mg of darunavir once daily ($n=50$)	800 mg of darunavir once daily ($n=50$)	Total ($n=100$)
Men, *n* (%)	40 (80)	41 (82)	81 (81)
Age (years), mean (SD)	45.6 (10.8)	44.8 (10.5)	45.2 (10.6)
HIV transmission route, *n* (%)			
homosexual/bisexual contact	21 (42)	25 (50)	46 (46)
heterosexual contact	18 (36)	16 (32)	34 (34)
intravenous drug user	8 (16)	6 (12)	14 (14)
other/unknown	3 (6)	3 (6)	6 (6)
Time since HIV infection diagnosis (years), mean (SD)	8.2 (6.8)	8.9 (7.2)	8.5 (7.0)
Hepatitis C virus coinfection, *n* (%)	13 (26)	7 (14)	20 (20)
No. of prior ART regimens, median (IQR)	1.5 (0–3.75)	1 (0–2.75)	1 (0–3)
NRTI backbone, *n* (%)			
TDF/FTC	32 (64)	34 (68)	66 (66)
ABC/3TC	17 (34)	16 (32)	33 (33)
CD4+ T cell count (cells/mm^3), mean (SD)	523 (331)	591 (272)	562 (303)
Nadir CD4+ T cell count (cells/mm^3), mean (SD)	197 (157)	201 (136)	199 (146)
<50 cells/mm^3, *n* (%)	11 (22)	8 (16)	19 (19)
Time since last HIV-1 RNA <50 copies/mL (weeks), median (IQR)	106.9 (40.3–252.4)	107.4 (55.4–219.0)	106.9 (43.4–227.9)
BMI (kg/m^2), mean (SD)	25.3 (3.4)	24.9 (3.5)	25.1 (3.5)

TDF/FTC, tenofovir/emtricitabine; ABC/3TC, abacavir/lamivudine.

Cost–efficacy analysis

The average absolute annual cost per patient with virological response at 48 weeks was US$40 311 in the DRV800 arm and US$33 038 in the DRV600 arm, resulting in a reduction in annual cost of US$7273 per patient successfully treated. Based on these results, one annual free ART with once-daily darunavir/ritonavir at 800/100 mg plus tenofovir/emtricitabine would potentially be obtained by switching six patients successfully to once-daily darunavir at 600 mg.

Discussion

We found that the 48 week efficacy of a less costly, reduced once-daily dose of darunavir (600 mg) was similar to the efficacy of the standard dose of 800 mg when combined with ritonavir plus two NRTIs in our virologically suppressed HIV-infected patients with no darunavir resistance-associated mutations or prior failure on PIs.

Our efficacy results were consistent with previous clinical trials on darunavir-based ART for HIV-infected patients with no PI resistance mutations,[24,25] even though the clinical scenario in our trial was different. In addition, consistent with the high genetic barrier of darunavir,[24–26] no resistance-associated mutations emerged after HIV-1 RNA elevations, and the viral load returned to undetectable levels in four out of five patients with virological failure, even though their antiretroviral drug regimens remained unchanged.

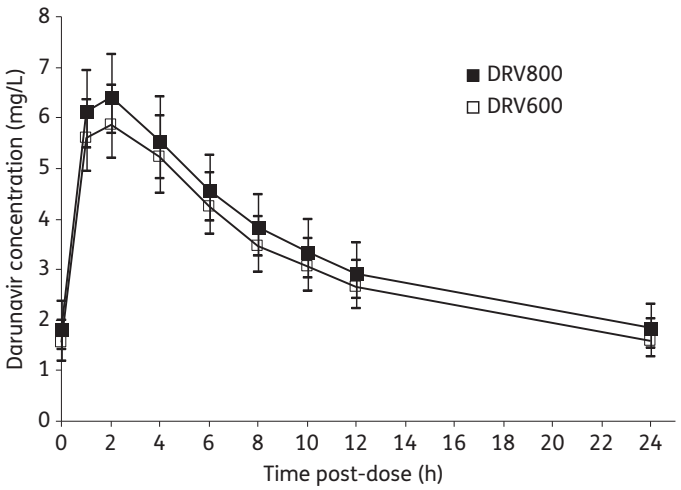

Figure 2. Geometric mean darunavir plasma concentration profiles of darunavir administered at a once-daily dose of either 600 mg (DRV600 arm, $n=15$) or 800 mg (DRV800 arm, $n=15$), with 100 mg of ritonavir. Error bars represent the 90% CI.

Although dose optimization of antiretroviral drugs is not a new concept, a growing interest in this strategy has developed in recent years. The optimum dose of antiretrovirals is not usually defined as the lowest effective dose during product development, and after a

Table 2. Comparison of darunavir pharmacokinetic parameters for darunavir administered at a daily dose of either 600 mg (DRV600 arm) or 800 mg (DRV800 arm) with 100 mg of ritonavir

	DRV600 (n=15), mean (90% CI)	DRV800 (n=15), mean (90% CI)	Geometric mean ratio, (90% CI)
AUC_{0-24} (mg·h/L)	76.66 (66.56–88.29)	83.99 (72.92–96.73)	0.91 (0.75–1.11)
C_{max} (mg/L)	6.52 (5.82–7.29)	6.63 (5.92–7.42)	0.98 (0.84–1.15)
C_{trough} (mg/L)	1.60 (1.26–2.02)	1.84 (1.45–2.32)	0.87 (0.63–1.21)

drug is launched emerging safety issues sometimes necessitate dose-reduction strategies, as has occurred with zidovudine, didanosine and stavudine.[14–16] Similarly, recently published results from the ENCORE1 clinical trial have shown non-inferior efficacy and fewer drug-related adverse events with a low daily dose of efavirenz (400 mg versus the standard one of 600 mg) in naive HIV-infected patients.[27] Not surprisingly, the reduction of the darunavir dose in our trial had little overall effect on safety. We attribute this finding to the fact that we limited enrolment to patients who were on a stable darunavir-containing ART; thus, all enrolled patients were already tolerating the drug. In addition, we note that Phase 2 dose-range studies were unable to demonstrate a clear relationship between dose or exposure and toxicity.[17–19,21]

Dose optimization aims not only at improving ART tolerability but also at reducing the associated costs.[11–13] Universal access to treatment for people living with HIV will expand ART to millions[6,10] and, since the costs will be huge, there are concerns about adequate funding for expanded access programmes.[28] Strategies that lower the cost of antiretroviral treatment are essential if we are to meet the demand. We estimated that a darunavir dose reduction to 600 mg once daily would yield annual savings of over US$7000 per patient successfully treated. This amount can be meaningful if it allows more patients to be treated within a fixed budget.

Inadequate drug exposure is among the potential concerns when evaluating lower doses of antiretrovirals. The darunavir pharmacokinetic parameters we observed were consistent with those previously reported.[21,29] Although there was a slight decline in darunavir concentration in the DRV600 group, the reduction was not statistically significant despite the 25% reduction in darunavir dose. Such a lack of correspondence is consistent with darunavir's non-linear dose–concentration curve found in dose-range studies, where less than dose-proportional changes in the darunavir AUC or C_{trough} were observed.[21] In addition, darunavir concentrations in plasma in both arms of our study remained far above the protein-binding adjusted EC_{50} for WT strains of HIV-1.[23,26] These results, together with efficacy, may raise the question of whether further decreases in darunavir dosing (e.g. to 400 mg once daily) might be feasible in this setting; however, it should be kept in mind that further decreases in darunavir exposure might put patients at risk of treatment failure. Moreover, Calcagno *et al.*[30] reported lower darunavir penetration in CSF when darunavir was given once instead of twice daily, which may increase the probability of suboptimal drug exposure in the CNS if the darunavir dose is further reduced. Therefore, darunavir concentrations and viral replication in anatomical reservoirs such as the CNS should be carefully assessed before implementing this strategy in clinical practice.

Our study provides unique information as it is the first comparative evaluation of the feasibility of a darunavir dose reduction. In addition, the evaluation of the average and incremental costs per individual with virological response at 48 weeks provides important information for both HIV healthcare providers and payers. This study thus facilitates the integration of information about ART costs and outcomes that is crucial for selecting the most efficient antiretroviral regimens. However, we acknowledge that, due to the relatively low number of participants, the present trial was not adequately powered to detect differences in efficacy below 15%, which might be clinically relevant. Therefore, our results should be confirmed in a fully powered non-inferiority trial. Another issue is that only patients with HIV-1 RNA <50 copies/mL at baseline were recruited in this study, making it impossible to predict the efficacy of the 600 mg of darunavir once-daily dose as a first-line ART.

In conclusion, the 48 week efficacy of a reduced once-daily darunavir dose of 600 mg seems to be similar to the efficacy of the standard 800 mg dose in combination with ritonavir and two NRTIs in virologically suppressed HIV-infected patients. This dose reduction strategy, which lowers the costs associated with ART, may have the potential to translate into substantial savings in care provision for millions of people worldwide. These results support further evaluation of this dose optimization strategy.

Acknowledgements

We thank the staff at the clinical sites where data were gathered for this study and the patients who participated. We also wish to acknowledge the contribution of Mary Ellen Kerans, who gave her advice on English language in the final version of the manuscript.

Members of the DRV600 Study Group

Hospital Universitari Germans Trias i Pujol (Badalona, Spain): Bonaventura Clotet, Josep Coll, Silvia Gel, Josep Maria Llibre, Cristina Miranda, José Moltó, Beatriz Mothe, Eugenia Negredo, Nuria Pérez-Álvarez, José Ramón Santos, Guillem Sirera. Hospital Universitari De Bellvitge (Barcelona, Spain): María Silvana DiYacovo, Elena Ferrer, Daniel Podzamczer, Nerea Rozas, Antonia Vila. Hospital De La Santa Creu I Sant Pau (Barcelona, Spain): Pere Domingo, María Del Mar Gutiérrez, Gracia Mateo, Marta Valle. Hospital Universitari Vall D'hebron (Barcelona, Spain): Joaquín Burgos, Adrian Curran, Jordi Navarro, Esteban Ribera.

Funding

This work was supported by the Spanish Health Department [Ministerio de Sanidad, Política Social e Igualdad (EC11-326)] and by the 'Lluita contra la SIDA' Foundation—Gala contra la Sida, Barcelona 2013. M. V. is supported by FIS trough grant CP04/00121 from the Spanish Health Department in

collaboration with Institut de Recerca de l'Hospital de la Santa Creu i Sant Pau, Barcelona, and is a member of CIBERSAM (a research network funded by the Spanish Health Ministry, Instituto de Salud Carlos III).

Transparency declarations

J. M., P. D., D. P. and B. C. have received research funding, consultancy fees and lecture sponsorships from and have served on advisory boards for various laboratories (MSD, Abbvie, Boehringer Ingelheim, Gilead Sciences, ViiV, Janssen-Cilag and Bristol-Myers Squibb). E. F. has received honoraria, speakers' fees and/or funds for research from Bristol-Myers Squibb, Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, MSD and ViiV. A. C. has received honoraria, speakers' fees and/or funds for research from Bristol-Myers Squibb, Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, MSD and ViiV. J. R. S. has received speakers' fees from Bristol-Myers Squibb, Abbvie, Boehringer Ingelheim, Gilead Sciences, Janssen-Cilag, MSD and ViiV. M. S. D. Y. has received consultancy fees from MSD, Boehringer Ingelheim, Janssen-Cilag, Bristol-Myers Squibb and ViiV. M. V., M. G. M. and C. M.: none to declare.

Author contributions

All authors substantially contributed to the study's conception, design and performance. J. M., E. F., P. D., A. C., J. R. S., M. G. M., M. S. D. Y., C. M., D. P. and B. C. all participated in recruiting significant numbers of participants and reported data from these patients. J. M., M. V., E. F., P. D., D. P. and A. C. had significant involvement in the data analyses. All authors were involved in the development of the primary manuscript and interpretation of data, and read and approved the final version.

References

1 Palella FJ, Delaney KM, Moorman AC *et al*. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med* 1998; **338**: 853–60.

2 Antiretroviral Therapy Cohort Collaboration. Life expectancy of individuals on combination antiretroviral therapy in high-income countries: a collaborative analysis of 14 cohort studies. *Lancet* 2008; **372**: 293–9.

3 Wood E, Kerr T, Marshall BD *et al*. Longitudinal community plasma HIV-1 RNA concentrations and incidence of HIV-1 among injecting drug users: prospective cohort study. *BMJ* 2009; **338**: b1649.

4 Montaner JS, Hogg R, Wood E *et al*. The case for expanding access to highly active antiretroviral therapy to curb the growth of the HIV epidemic. *Lancet* 2006; **368**: 531–6.

5 Cohen MS, Chen YQ, McCauley M *et al*. Prevention of HIV-1 infection with early antiretroviral therapy. *N Engl J Med* 2011; **365**: 493–505.

6 Delva W, Eaton JW, Meng F *et al*. HIV treatment as prevention: optimising the impact of expanded HIV treatment programmes. *PLoS Med* 2012; **9**: e1001258.

7 Rodger A, Bruun T, Cambiano V *et al*. HIV Transmission risk through condomless sex if HIV+ partner on suppressive ART: PARTNER Study. In: *Abstracts of the Twenty-first Conference on Retroviruses and Opportunistic Infections, Boston, MA, 2014*. Abstract 153LB. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

8 Thompson MA, Aberg JA, Hoy JF *et al*. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society—USA panel. *JAMA* 2012; **308**: 387–402.

9 Panel on Antiretroviral Guidelines for Adults and Adolescents. *Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents*. Department of Health and Human Services. http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf.

10 WHO. *Consolidated Guidelines on HIV Prevention, Diagnosis, Treatment and Care for Key Populations*. http://apps.who.int/iris/bitstream/10665/128048/1/9789241507431_eng.pdf?ua=1&ua=1.

11 Crawford KW, Ripin DH, Levin AD *et al*. Optimising the manufacture, formulation, and dose of antiretroviral drugs for more cost-efficient delivery in resource-limited settings: a consensus statement. *Lancet Infect Dis* 2012; **12**: 550–60.

12 Hill A, Ananworanich J, Calmy A. Dose optimization: a strategy to improve tolerability and lower antiretroviral drug prices in low and middle income countries. *Open Infect Dis J* 2010; **4**: 85–91.

13 Boyd MA, Cooper DA. Optimisation of HIV care and service delivery: doing more with less. *Lancet* 2012; **380**: 180–6.

14 Volberding PA, Lagakos SW, Koch MA *et al*. Zidovudine in asymptomatic human immunodeficiency virus infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. The AIDS Clinical Trials Group of the National Institute of Allergy and Infectious Diseases. *N Engl J Med* 1990; **322**: 941–9.

15 Kahn JO, Lagakos SW, Richman DD *et al*. A controlled trial comparing continued zidovudine with didanosine in human immunodeficiency virus infection. The NIAID AIDS Clinical Trials Group. *N Engl J Med* 1992; **327**: 581–7.

16 Hill A, Ruxrungtham K, Hanvanich M *et al*. Systematic review of clinical trials evaluating low doses of stavudine as part of antiretroviral treatment. *Expert Opin Pharmacother* 2007; **8**: 679–88.

17 Katlama C, Esposito R, Gatell JM *et al*. Efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients: 24-week results of POWER 1. *AIDS* 2007; **21**: 395–402.

18 Haubrich R, Berger D, Chiliade P *et al*. Week 24 efficacy and safety of TMC114/ritonavir in treatment-experienced HIV patients. *AIDS* 2007; **21**: F11–8.

19 Clotet B, Bellos N, Molina JM *et al*. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: a pooled subgroup analysis of data from two randomised trials. *Lancet* 2007; **369**: 1169–78.

20 de Meyer SMJ, Spinosa-Guzman S, Vangeneugden TJ *et al*. Efficacy of once-daily darunavir/ritonavir 800/100 mg in HIV-infected, treatment-experienced patients with no baseline resistance-associated mutations to darunavir. *J Acquir Immune Defic Syndr* 2008; **49**: 179–82.

21 Sekar V, De Meyer S, Vangeneugden T *et al*. Pharmacokinetic/pharmacodynamic (PK/PD) analyses of the POWER 1 and the POWER 2 trials in treatment-experienced HIV-infected patients. In: *Abstracts of the Thirteenth Conference on Retroviruses and Opportunistic Infections, Denver, CO, 2006*. Abstract J-121. Foundation for Retrovirology and Human Health, Alexandria, VA, USA.

22 Droste JA, Aarnoutse RE, Koopmans PP *et al*. Evaluation of antiretroviral drug measurements by an interlaboratory quality control program. *J Acquir Immune Defic Syndr* 2003; **32**: 287–91.

23 De Meyer S, Azijn H, Surleraux D *et al*. TMC114, a novel human immunodeficiency virus type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates. *Antimicrob Agents Chemother* 2005; **49**: 2314–21.

24 Orkin C, DeJesus E, Khanlou H *et al*. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. *HIV Med* 2013; **14**: 49–59.

25 Arribas JR, Clumeck N, Nelson M *et al*. The MONET trial: week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load <50 HIV-1 RNA copies/mL at baseline. *HIV Med* 2012; **13**: 398–405.

26 Llibre JM. First-line boosted protease inhibitor-based regimens in treatment-naive HIV-1-infected patients—making a good thing better. *AIDS Rev* 2009; **11**: 215–22.

27 ENCORE1 Study Group. Efficacy of 400 mg efavirenz versus standard 600 mg dose in HIV-infected, antiretroviral-naïve adults (ENCORE1): a randomized, double blind, placebo-controlled, non-inferiority trial. *Lancet* 2014; **383**: 1474–82.

28 Wilson D, Fraser N. Who pays and why? Costs, effectiveness, and feasibility of HIV treatment as prevention. *Clin Infect Dis* 2014; **59** Suppl 1: S28–31.

29 Deeks ED. Darunavir: a review of its use in the management of HIV-1 infection. *Drugs* 2014; **74**: 99–125.

30 Calcagno C, Yilmaz A, Cusato J *et al*. Determinants of darunavir cerebrospinal fluid concentrations: impact of once-daily dosing and pharmacogenetics. *AIDS* 2012; **26**: 1529–33.