



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

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Summary

Background The continuing, randomised, multinational, phase IIB POWER 1 and 2 studies aim to evaluate efficacy and safety of darunavir in combination with low-dose ritonavir in treatment-experienced HIV-1-infected patients. We did a pooled subgroup analysis to update results at week 48 for patients receiving the recommended dose of darunavir-ritonavir compared with those receiving other protease inhibitors (PIs).

Methods After 24-week dose-finding phases and primary efficacy analyses, patients randomised to receive darunavir-ritonavir were given 600/100 mg twice daily, and patients receiving control PIs continued on assigned treatment into the longer-term, open-label phase; all patients continued on optimised background regimen. We assessed patients who had reached week 48 or discontinued earlier at the time of analysis; for the darunavir-ritonavir group, only patients who received 600/100 mg twice daily from baseline were included. Analyses were intention-to-treat. The POWER 2 study (TMC114-C202) is registered with ClinicalTrials.gov (NCT00071097).

Findings At week 48, 67 of 110 (61%) darunavir-ritonavir patients compared with 18 of 120 (15%) of control PI patients had viral load reductions of $1 \log_{10}$ copies per mL or greater from baseline (primary endpoint; difference in response rates 46%, 95% CI 35%–57%, $p < 0.0001$). Based on a logistic regression model including stratification factors (baseline number of primary PI mutations, use of enfuvirtide, baseline viral load) and study as covariates, the difference in response was 50% (odds ratio 11.72, 95% CI 5.75–23.89). In the darunavir-ritonavir group, rates of adverse events were mostly lower than or similar to those in the control group when corrected for treatment exposure. No unexpected safety concerns were identified.

Interpretation Efficacy responses with darunavir-ritonavir 600/100 mg twice daily plus optimised background regimen were greater than those with control PI and were sustained to at least week 48, with favourable safety and tolerability in treatment-experienced patients. This regimen could expand the treatment options available for such patients.

Introduction

A substantial need exists for antiretroviral therapies that offer increased efficacy in treatment-experienced patients with HIV-1 infection, a population whose extensive drug resistance restricts treatment options and has a severe effect on infection management.¹

Darunavir (TMC114), a new protease inhibitor (PI) with strong binding affinity for the HIV-1 protease, is highly potent in vitro against wild-type and multidrug-resistant HIV-1 strains.² POWER (Performance Of TMC114/r When evaluated in treatment-Experienced patients with PI Resistance) 1 and 2 (TMC114-C213 and TMC114-C202) are randomised, multinational, phase IIB trials comparing the efficacy and safety of darunavir co-administered with low-dose ritonavir (darunavir-ritonavir) with that of currently available PIs in treatment-experienced HIV-1-infected patients. In the 24-week primary efficacy analyses, patients receiving one of four darunavir-ritonavir doses plus an optimised background regimen had significantly

greater reductions in viral load and increases in CD4-positive T-lymphocyte (CD4) count than those who received investigator-selected control PIs plus optimised background regimen.^{3,4} In both studies, darunavir-ritonavir 600/100 mg twice daily showed the greatest efficacy, with 53% in POWER 1 and 39% of patients in POWER 2 reaching viral loads of less than 50 copies per mL compared with 18% and 7% of patients receiving control PIs, respectively. This dose has recently been approved in the USA⁵ and several other countries for the treatment of HIV infection in antiretroviral treatment-experienced adult patients, such as those with HIV-1 strains resistant to more than one PI.

Since inclusion criteria, study design, and objectives for the POWER 1 and 2 trials were almost identical, week 48 data from the two trials were combined. We compared pooled 48-week efficacy and safety data for patients randomised at baseline to receive the recommended darunavir-ritonavir 600/100 mg twice daily dose with patients who received control PIs.

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Methods

Patients

POWER 1 and 2 enrolled male and female adult patients (aged ≥ 18 years) with documented HIV-1 infection, plasma HIV RNA greater than 1000 copies per mL, and at least one primary PI mutation at screening, as defined by the March, 2003, International AIDS Society-USA (IAS-USA) guidelines (D30N, M46I/L, G48V, I50V/L, V82A/F/T/S, I84V and L90M).⁶ The proportion of patients with three or more primary PI mutations was initially limited to 30% in each study (based on this list, which was updated during the trial^{7,8}); in POWER 2, this cap was removed 11 months later to allow entry of a more treatment-experienced population. Patients were receiving a PI-containing regimen at screening (begun at least 8 weeks previously) and had previously used more than one nucleoside reverse transcriptase inhibitor (NRTI) for 3 months or longer, one or more non-nucleoside reverse transcriptase inhibitors (NNRTI) as part of a failing regimen, and at least one PI for a total period of 3 months or longer. Previous use of the fusion inhibitor enfuvirtide was permitted. Hepatitis B or C co-infected patients were included in POWER 1 if their condition was clinically stable and would not need treatment, but were excluded from POWER 2. Patients diagnosed with acute hepatitis A at screening were excluded from both trials; other major exclusion criteria included the presence of any currently active AIDS-defining illness, use of a treatment interruption schedule at screening, previous randomisation to a darunavir treatment arm, and use of investigational antiretroviral therapy at screening.

Written informed consent was obtained from all patients. Study protocols were reviewed and approved by the appropriate institutional ethics committees and health authorities, and were prepared in accordance with the Declaration of Helsinki.

Procedures

POWER 1 and 2 are multinational (POWER 1: Australia, Brazil, Canada, Europe; POWER 2: Argentina, USA), 144-week, phase IIB trials designed to assess the efficacy and safety of darunavir-ritonavir compared with that of currently available PIs.

Before randomisation, investigators selected an individually optimised PI-based regimen of one or more currently available PIs and an optimised background regimen (two or more NRTIs, with or without enfuvirtide) for each patient, on the basis of screening genotypic resistance (*Virtual Phenotype*, Virco, Belgium) and treatment history. Patients in POWER 2 were not allowed to receive NNRTIs during screening; NNRTIs were excluded from the optimised background regimen in both studies. Patients were stratified for number of primary PI mutations (one or none, two, or three or more),⁶ use of enfuvirtide in the optimised background regimen, and baseline plasma viral load (< 20000 or ≥ 20000 copies per mL), then randomised to receive either darunavir-

ritonavir (400/100 mg per day, 800/100 mg per day, 400/100 mg twice daily, or 600/100 mg twice daily) or their investigator-selected control PI-based regimen (control PI group) from baseline. All treatment allocations were done by dynamic randomisation using the minimisation technique with biased coin assignment⁹ via an interactive voice response system. Patients in the darunavir-ritonavir group of POWER 2 began their optimised background regimen 14 days after substituting darunavir-ritonavir for their failing PIs; patients in POWER 1 began their optimised background regimen plus darunavir-ritonavir at the same time, without the 14-day functional monotherapy period. All patients in the control PI arm began their optimised background regimen at baseline, along with their investigator-selected PI-based regimen. Investigational PIs were not allowed in the control PI arm, except for fosamprenavir and atazanavir (which had not yet received regulatory approval in all participating countries). Tipranavir was not included as a control PI because it was not available at the time of enrolment. Changes to the optimised background regimen and investigator-selected PIs were not permitted except for tolerability or toxicity reasons.

After the primary 24-week efficacy analysis cutoff date (Feb 1, 2005), patients in the control PI arm continued their assigned treatment whereas all patients receiving darunavir-ritonavir were switched to darunavir-ritonavir 600/100 mg twice daily (two darunavir 300 mg tablets plus ritonavir 100 mg capsule per intake) for the longer-term, open-label phase of the randomised, controlled trials. For darunavir-ritonavir patients, only 48-week efficacy and safety results for those who began treatment at baseline (week 0) with darunavir-ritonavir 600/100 mg twice daily (darunavir-ritonavir group) were included in the present analysis (cutoff date Sept 24, 2005); data from patients randomised to other darunavir-ritonavir doses at baseline who switched to darunavir-ritonavir 600/100 mg twice daily after the 24-week primary efficacy analyses were not included.

Virological failure leading to treatment discontinuation was defined as viral load reduction $< 0.5 \log_{10}$ copies per mL from baseline to week 12 and $< 1.0 \log_{10}$ copies per mL to week 12 or beyond (one subsequent confirmatory result was required). Patients who discontinued because of virological failure and were judged by the investigator to potentially benefit from darunavir-ritonavir therapy could be screened for inclusion in a rollover darunavir-ritonavir trial, to allow for regimen optimisation. A protocol amendment after the primary efficacy analysis cutoff date applied an additional definition of virological failure—not achieving a viral load of less than 50 copies per mL after 12 weeks of treatment (one confirmatory result was required) for patients in the control PI arm, to increase the likelihood of subsequent virological response in this group.

All endpoints were pre-defined in the protocol. The primary objective of the analysis was to compare this

response at week 48 between the treatment groups. The week 48 primary efficacy endpoint was confirmed virological response, defined as reduction in viral load of greater than $1.0 \log_{10}$ copies per mL from baseline (time-to-loss of virological response [TLOVR] algorithm). Secondary efficacy endpoints included the proportion of patients reaching viral loads less than 50 copies per mL (TLOVR), and changes from baseline in overall viral load (non-completer=failure analysis [NC=F]) and CD4 count (last observation carried forward analysis [LOCF]). Response (defined as viral load <50 copies per mL) to darunavir-ritonavir or control PIs was assessed at week 48 according to pre-defined subgroups. The effect of resistance on virological outcome was also evaluated.

The original primary endpoint was change in viral load, but this was amended on Dec 22, 2004, to the more conservative virological response endpoint, defined as a decrease of $1 \log_{10}$ or more compared with baseline, at the request of regulatory authorities and to have an endpoint that was more consistent with the most recent submissions to the US Food and Drugs Administration (FDA) of tipranavir and enfuvirtide. The power calculation was based on the change in viral load. To detect at least a $0.5 \log_{10}$ change in plasma viral load decrease of the highest compared with the lowest darunavir group (with a common SD of 1), with 80% power at a significance level of 5% (one-sided), 51 patients were needed per treatment group in both POWER trials. To account for the effect of discontinuations on the primary parameters, a total of 60 patients per group were needed for the intention-to-treat (ITT) analysis.

Viral load was measured with the Roche Amplicor HIV-1 monitor (Roche, Basel, Switzerland); immunological change was assessed by absolute and percentage CD4 counts. Phenotypic (Antivirogram, Virco) and genotypic resistance (*Virtual* Phenotype, Virco) were assessed at screening, days -14 and 1, and at weeks 2, 24, and 48, or at the withdrawal visit. Samples taken at other time points were analysed when judged appropriate by the protocol virologist on the basis of HIV-1 plasma viral load.

An independent data and safety monitoring board undertook continuous monitoring and objective assessment of adverse events and laboratory abnormalities, which were categorised according to a modified AIDS Clinical Trials Group grading severity list,¹⁰ classified using MedDRA preferred terms, and coded using version 6.1 of the MedDRA dictionary. Patients fasted for at least 8 h before blood sampling for biochemistry tests. Safety variables, including adverse events, serious adverse events, clinical laboratory evaluations (haematology, serum chemistry, and urinalysis), vital signs, and physical findings were assessed at screening, baseline, weekly during the first month, fortnightly during the second and third months, every 4 weeks until week 24, and every 8 weeks until week 48. A 12-lead electrocardiogram was recorded at screening, day -14, baseline, weeks 4, 12, 24, and 48, or

withdrawal. Unscheduled visits undertaken to obtain additional safety data and follow-up assessments were also taken into account.

Statistical analysis

An ITT analysis was done for efficacy and safety including all randomised patients who received at least one dose of study medication and had baseline or post-baseline data and follow-up safety data, irrespective of protocol compliance or ineligibility. Statistical analyses were adjusted for the three randomisation stratification factors (number of primary PI mutations, use of enfuvirtide in the optimised background regimen, and plasma viral load at screening). Sample sizes were determined as previously described.^{3,4} A logistic regression model, including treatment and all stratification variables, was applied to compare virological response between treatments. An ANCOVA model (including treatment and all stratification variables) was used to estimate the mean changes in viral load and CD4 count from baseline at week 48 (least squares means). Since the objective of the 24-week primary efficacy analysis (to compare all four darunavir-ritonavir doses with control PIs, and prove superiority of the optimum dose compared with control PIs after correction for multiplicity) was met, no corrections were implemented for multiple comparisons in the present analysis, the objective of which was to update the results after the 24-week primary analysis and focus on the week 48 timepoint for the recommended darunavir-ritonavir dose versus control PIs. An adjusted significance level could be applied by means of the Bonferroni correction resulting in a significance level of 0.00625, accounting for multiple analyses at weeks 24 and 48 and for multiple comparisons (four doses) versus control. The primary efficacy analysis was based on confirmed virological response (viral load reduction $\geq 1.0 \log_{10}$ copies per mL from baseline [TLOVR]) at week 48 for the darunavir-ritonavir arm compared with the control PI arm.¹¹ Patients who discontinued prematurely had their change in viral load levels imputed as zero (NC=F algorithm) in the ITT analysis and were considered to be treatment failures for virological response (TLOVR algorithm). Secondary efficacy endpoints were also evaluated.

The POWER 2 study (TMC114-C202) is registered with ClinicalTrials.gov, number NCT00071097.

Role of the funding source

The POWER 1 and 2 trials were designed and undertaken from September, 2003, by Tibotec, the study sponsor and developer of darunavir. The authors had full access to the data in both trials after they were unblinded and the corresponding author had final responsibility to submit the manuscript for publication. Tibotec was responsible for data collection and data analysis. An independent data and safety monitoring board was implemented for continued monitoring and

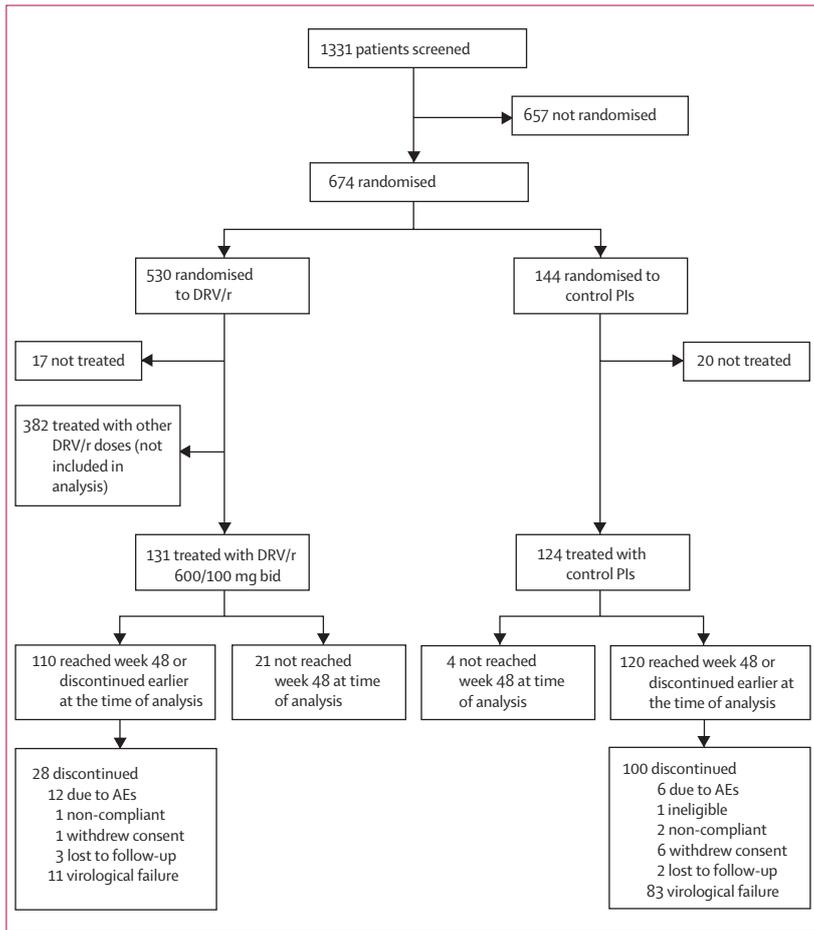


Figure 1: Combined trial profile of POWER 1 and POWER 2
 DRV/r=darunavir-ritonavir. bid=twice daily. AE=adverse event.

	Darunavir-ritonavir (n=131)	Control PIs (n=124)
Total discontinued	28 (21%)	100 (81%)
AE or HIV-related event	12 (9%)	6 (5%)
Ineligible to continue	0	1 (<1%)
Lost to follow-up	3 (2%)	2 (2%)
Non-compliant	1 (<1%)	2 (2%)
Virological failure	11 (8%)	83 (67%)
Withdrawal of consent	1 (<1%)	6 (5%)

Data are number (%). AE=adverse events.

Table 1: Reasons for discontinuation

objective assessment of all available antiviral activity data and adverse events. Data interpretation was done by EL and SS-G (authors employed by the sponsor) in conjunction with all other authors. The manuscript was drafted and author contributions collated by Emily de Looze (medical writer), Gardiner-Caldwell Communications; this service was funded by Tibotec. The data and the analysis were checked by three

independent groups: SGS International (the contract research organisation) cleaned the database and did the analysis. An internal SGS check was also done. Tibotec independently checked the data and the analysis by different means of checking and analysis programs. Additionally, the FDA reviewed the data and did an independent analysis confirming the accuracy of the results and conclusions.

Results

Figure 1 shows the study profile. From baseline (week 0), 131 (65 from POWER 1 and 66 from POWER 2) patients received darunavir-ritonavir 600/100 mg twice daily plus optimised background regimen and 124 (63 from POWER 1 and 61 from POWER 2) patients received control PIs plus optimised background regimen. At the time of analysis, 110 patients in the darunavir-ritonavir group and 120 patients in the control PI group had reached week 48 or discontinued earlier and were included with data from baseline. Since not all patients had reached week 48, those who had not were censored at their last available visit. The overall discontinuation rate was lower in the darunavir-ritonavir group than the control PI group (table 1). The high rate of discontinuation in the control PI group was mainly attributable to virological failure, which had a marked effect on overall treatment exposure between the two treatment groups (62.3 weeks in the darunavir-ritonavir groups versus 31.5 weeks in the control PI group). The higher drop-out rate in the control group did not drive the difference in efficacy between the treatment groups. The majority of the control PI patients discontinued from week 16 onwards because of virological failure. At week 12, 118 (95%) of the control patients were on treatment, and at this time the difference between the treatments was already established: 100 patients (76%) in the darunavir-ritonavir group and 29 (23%) in the control PI group had a decrease in viral load of 1 log₁₀ copies per mL or greater compared with baseline (difference 53%, 95% CI 42–63, p<0.0001). Multiple imputation techniques were applied to test sensitivity of the conclusions, including a LOCF method. All imputation methods resulted in the same conclusions of superiority of darunavir-ritonavir to control.

Demographics and baseline disease characteristics were similar between the treatment groups (table 2). Ritonavir was used as a pharmacokinetic enhancer in 121 (98%) of the control PI regimens, of which 92 (74%) were single-boosted and 29 (23%) were double-boosted. One patient received a single PI-based regimen and two received a double PI-based regimen. PIs used were lopinavir (45 patients, 36%), saquinavir (43, 35%), amprenavir or fosamprenavir (42, 34%), atazanavir (21, 17%), indinavir (three, 2%) and nelfinavir (one, <1%). In the control PI group, about 28% of patients received at least one PI to which they were sensitive during the treatment period, compared with only about

	Darunavir-ritonavir (n=131)	Control PIs (n=124)
Male	117 (89%)	109 (88%)
Mean age (years)	43.9 (8.6)	44.4 (7.1)
White	106 (81%)	90 (73%)
Mean duration of infection (years)	12.0 (4.4)	12.9 (4.7)
Mean viral load (log ₁₀ copies per mL)	4.6 (0.7)	4.5 (0.8)
Median CD4 count (cells per μL)	153 (3-776)	163 (3-1274)
CDC class C	47 (36%)	53 (43%)
Hepatitis B or C co-infection*	7 (11%)	13 (21%)
Mean duration previous NRTIs (months)	100 (48)	106 (45)
Mean duration previous NNRTIs (months)	29 (24)	23 (15)
Mean duration previous PIs (months)	65 (29)	65 (28)
Previous use ≥4 NRTIs	122 (93%)	119 (96%)
Previous use ≥1 NNRTI	127 (97%)	121 (98%)
Previous use ≥2 PIs	124 (95%)	123 (99%)
Previous enfuvirtide use (≥2 months)	25 (19%)	20 (16%)
Previous tipranavir use	5 (4%)	9 (7%)
≥3 primary PI mutations, as stratified†	51 (39%)	48 (39%)
≥3 primary PI mutations‡	71 (54%)	77 (62%)
≤1 DRV resistance-associated mutation	62 (47%)	56 (45%)
2 DRV resistance-associated mutations	40 (31%)	31 (25%)
≥3 DRV resistance-associated mutations	29 (22%)	37 (30%)
Median phenotypic DRV FC	4.3 (0.2-503.2)	3.3 (0.2-362.9)
Median phenotypic lopinavir FC	83.9 (0.8-152.4)	82.7 (0.4-130.5)

Data are number (%) unless otherwise stated. CDC=US Centers for Disease Control and Prevention. DRV=darunavir. *POWER 1 patients only (n=65 for darunavir-ritonavir group and n=63 for control PI group), active or non-active co-infection. †IAS-USA, March, 2003. ‡IAS-USA, March, 2005.⁸

Table 2: Baseline demographics and disease characteristics

8% of patients at screening, confirming that regimens were optimised as far as was possible.

The median numbers of primary PI mutations and IAS-USA PI resistance-associated mutations were three (range zero to five) and eight (zero to 12), respectively, in the darunavir-ritonavir group, and three (zero to five) and eight (one to 13), respectively, in the control PI group,⁸ confirming that the population had advanced HIV infection and extensive treatment experience. Darunavir resistance-associated mutations (V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, or L89V) were present in patients with a background of a higher overall number of IAS-USA PI mutations.¹² Baseline phenotypic susceptibility showed that 83 (64%) darunavir-ritonavir patients and 73 (61%) control PI patients were infected with virus with resistance to all commercially available PIs (excluding tipranavir, which was not available at the time of study enrolment; 87 [67%] patients in the darunavir-ritonavir group and 84 [70%] in the control PI group were susceptible to tipranavir); 26 (20%) and 22 (18%), respectively, were sensitive to one PI, and about 18% (45) in both groups were sensitive to two or more PIs.

Use of enfuvirtide in the optimised background regimen was stratified but not randomised and was similar between treatment groups: enfuvirtide was used for the first time (naive) by 42 (32%) patients in the darunavir-ritonavir group and 37 (30%) in the control PI group, and was re-used (non-naive) by 18 (14%) and 15 (12%), respectively. Demographics and baseline disease characteristics were similar between patients from the two groups in each enfuvirtide subgroup.

The week 48 primary efficacy endpoint was reached by a greater proportion of patients receiving darunavir-ritonavir compared with control PIs at all time points; this difference was sustained to at least week 48 of

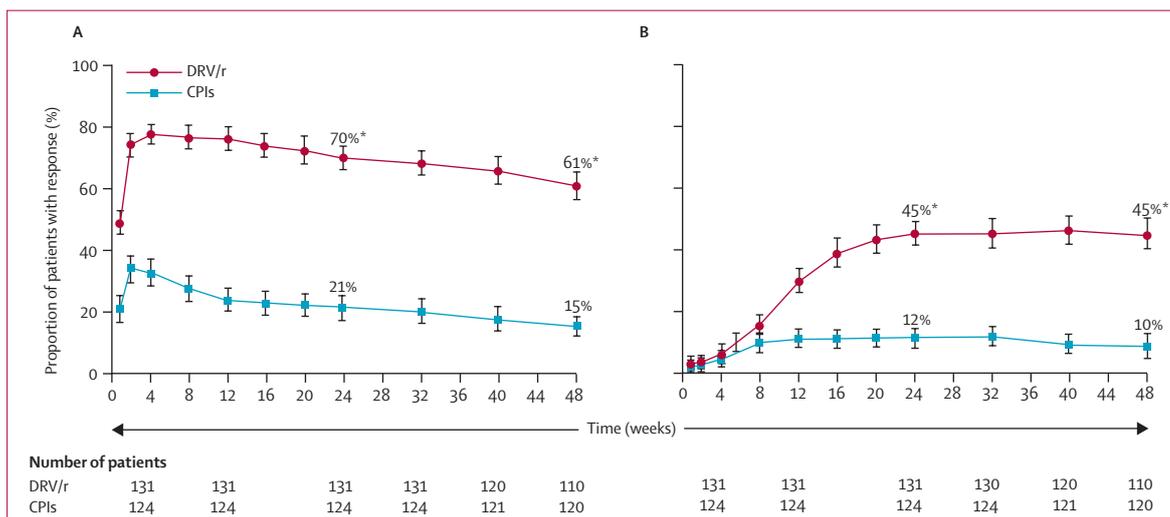


Figure 2: Week 48 virological response (ITT-TLOVR)

(A) Proportion of patients with viral load reduction ≥ 1.0 log₁₀ copies per mL from baseline. (B) Proportion of patients with viral load <50 copies per mL. Bars are SE. DRV/r=darunavir-ritonavir group. CPls=control protease inhibitor group. *p<0.0001 for DRV/r vs CPls.

	Darunavir-ritonavir		Control PIs		p
	N	n (%)	N	n (%)	
Enfuvirtide use in OBR					
Used, naive	36	29 (81%)	35	8 (23%)	<0.0001
Used, non-naive	13	4 (31%)	15	1 (7%)	0.1
Not used	61	34 (56%)	70	9 (13%)	<0.0001
Baseline viral load (copies per mL)					
≤20 000	35	29 (83%)	46	11 (24%)	<0.0001
20 000–100 000	46	19 (41%)	38	5 (13%)	0.005
>100 000	29	19 (66%)	36	2 (6%)	<0.0001
Primary PI mutations at baseline					
≤1	9	7 (78%)	16	2 (13%)	0.001
2	46	28 (61%)	30	8 (27%)	0.004
≥3	55	32 (58%)	74	8 (11%)	<0.0001
DRV-associated mutations at baseline					
≤1	50	34 (68%)	53	13 (25%)	<0.0001
2	33	24 (73%)	31	3 (10%)	<0.0001
≥3	27	9 (33%)	36	2 (6%)	0.004
Baseline phenotypic DRV FC					
≤10	70	51 (73%)	76	15 (20%)	<0.0001
10–40	29	13 (45%)	24	1 (4%)	0.0008
>40	10	2 (20%)	16	1 (6%)	0.3
Active NRTIs in OBR					
0	31	13 (42%)	32	0	<0.0001
1	48	33 (69%)	45	6 (13%)	<0.0001
≥2	28	19 (68%)	40	11 (28%)	0.001
Active ARVs in OBR					
0	25	7 (28%)	18	0	0.01
1	34	23 (68%)	40	2 (5%)	<0.0001
≥2	48	35 (73%)	60	15 (25%)	<0.0001

OBR=optimised background regimen. DRV=darunavir. ARV=antiretroviral. N=total number of patients in subgroup. n=number of patients viral load reduction $\geq 1.0 \log_{10}$ copies per mL from baseline.

Table 3: Proportion of patients with viral load reduction $\geq 1.0 \log_{10}$ copies per mL from baseline at week 48 by subgroup (ITT-TLOVR)

treatment (figure 2). Observed response rate at week 48 for the darunavir-ritonavir group was 61% (67 patients) and for the control PI group was 15% (18 patients; difference 46%, 95% CI 35–57, $p < 0.0001$). Based on a logistic regression model including the stratification factors (baseline number of primary PI mutations, use of enfuvirtide in the optimised background regimen, and baseline viral load) and study as covariates, the difference in response between the groups was 50% (odds ratio [OR] 11.72, 95% CI 5.75–23.89). The difference in response rates for the week 48 primary endpoint between darunavir-ritonavir and control PIs was maintained across all subgroups analysed (table 3). As might be expected in this population, patients who received a greater overall number of active antiretroviral agents (including NRTIs and enfuvirtide) in their optimised background regimen had higher response rates. Baseline phenotypic darunavir fold change in 50% effective concentration (FC) and number of darunavir

resistance-associated mutations at baseline were highly predictive of response.

The proportion of patients with viral load less than 50 copies per mL (ITT-TLOVR) was greater in the darunavir-ritonavir group than in the control PI group at all time points (figure 2); this difference was sustained to week 48, when 50 (45%) patients receiving darunavir-ritonavir reached a viral load of less than 50 copies per mL, compared with 12 (10%) patients receiving control PIs (difference 37%, 95% CI 25–46, $p < 0.0001$). Based on a logistic regression model using the same covariates as for the primary efficacy endpoint, the difference in response between the darunavir-ritonavir and control PI groups was 40% (OR 13.10, 95% CI 5.59–30.72). In total, 46% (60) of the darunavir-ritonavir patients and 81% (100) of the control PI patients never achieved a confirmed viral load of less than 50 copies per mL during study treatment. As with the primary efficacy endpoint, the difference in response rates between the groups was maintained across all subgroups (table 4). Similarly, the baseline number of darunavir resistance-associated mutations and baseline phenotypic darunavir FC were highly predictive of response in terms of reaching a viral load of less than 50 copies per mL.

Mean changes in plasma viral load from baseline at week 48 (NC=F) were -1.63 copies per mL (SD 1.31) for the darunavir-ritonavir group compared with $-0.35 \log_{10}$ copies per mL (0.77) for the control PI group ($p < 0.0001$). The difference in response rates was maintained across all subgroups. Mean changes from baseline in CD4 cell count were greater in the darunavir-ritonavir group than in the control PI group at all time points (102 cells per μL [SD 126.93] compared with 19 cells per μL [102.53] at week 48; $p < 0.0001$), in parallel with the virological responses (figure 3).

The safety analysis included all available data up to the database cutoff from all patients. Excluding enfuvirtide-associated injection-site reactions, adverse events reported with an incidence of 10% or greater in patients receiving darunavir-ritonavir were diarrhoea (26, 20%), nausea (24, 18%), headache (19, 15%), nasopharyngitis (18, 14%), fatigue (16, 12%), upper respiratory tract infection (16, 12%) and herpes simplex (16, 12%). Diarrhoea was reported with a higher incidence (35, 28%) in the control PI group, in addition to headache (25, 20%) and fatigue (21, 17%). Nausea was observed in 13% (16), nasopharyngitis in 11% (13), upper respiratory tract infection in 7% (8), and herpes simplex in 2% (2) of control PI patients. In an analysis per 100 patient-years of exposure to correct for difference in treatment exposure between the two treatment groups, incidences of adverse events in the darunavir-ritonavir groups were mostly lower than or similar to those of the control PI group; in particular, diarrhoea (16.6 vs 46.7 events per 100 patient-years), nausea (15.3 vs 21.3 events per 100 patient-years), and headache (12.1 vs 33.3 events per 100 patient-years) had a lower incidence in the darunavir-ritonavir group. The

incidence of herpes simplex infection was greater in the darunavir-ritonavir than the control PI group (10.2 vs 2.6 events per 100 patient-years). About a third of these events were reported concomitantly with immunological improvement observed within the first 12 weeks of treatment. For other adverse events that occurred at a higher frequency in the darunavir-ritonavir group than the control PI group, the differences in rates were relatively small, with the largest difference being for peripheral neuropathy (3.8 vs 0 events per 100 patient-years).

The majority of adverse events were grade 1 or 2 in severity. A low incidence of grade 3 and 4 adverse events was noted in both groups (table 5), with most occurring as isolated events. Overall, 26 (20%) darunavir-ritonavir patients and 17 (14%) control PI patients reported at least one serious adverse event. After adjustment for treatment exposure, the incidence of severe adverse events was 16.6 per 100 patient-years exposure in the darunavir-ritonavir group and 22.6 per 100 patient-years exposure in the control PI group. The majority of serious adverse events did not lead to treatment discontinuation. No particular serious adverse event was associated with either treatment group.

Five (4%) patients in the darunavir-ritonavir group died during the study, as a result of pulmonary embolism, overdose (illicit drug), anal cancer, death associated with peripheral neuropathy and pain management, and sepsis. One patient in the control PI group died because of a nosocomial infection 2 weeks after his last follow-up visit. All deaths were judged by the investigators (and confirmed by the data and safety monitoring board) to be unrelated or doubtfully related to study medication. When corrected for treatment exposure, the number of deaths was 3.2 per 100 patient-years of exposure for the darunavir-ritonavir arm.

The most common treatment-emergent grade 3 and 4 laboratory abnormalities were increased triglycerides (>8.4 mmol/L; 15% [20] of darunavir-ritonavir patients, 7% [8] of control PI patients), increased pancreatic amylase (>2× upper limit of normal [ULN]; 6% [8], 5% [6]), increased total cholesterol (>7.7 mmol/L; 7% [9], 2% [3]) and increased pancreatic lipase (>2×ULN; 5% [6], 1% [1]). No cases of clinical pancreatitis were observed in patients with lipase abnormalities. Grade 3–4 increases in alanine aminotransferase (>5×ULN) and aspartate aminotransferase (>5×ULN) were noted in 2% [3] and 3% [4], respectively, of patients in the darunavir-ritonavir group, and 2% [3] and 4% [5], respectively, of patients in the control PI group. No cases of hepatotoxicity were reported.

More patients used serum lipid-reducing agents in the control PI group than in the darunavir-ritonavir group during screening (27% [34] vs 20% [26]) and the treatment period (31% [38] vs 28% [36]). Changes in lipid measurements from baseline at week 48 were small in both groups. Mean changes were -0.60 (SD 2.67) for triglycerides, 0.25 mmol/L (1.39) for total cholesterol,

	Darunavir-ritonavir		Control PIs		p
	N	n (%)	N	n (%)	
Enfuvirtide use in OBR					
Used, naive	36	21 (58%)	35	4 (11%)	<0.0001
Used, non-naive	13	2 (15%)	15	1 (7%)	0.5
Not used	61	27 (44%)	70	7 (10%)	<0.0001
Baseline viral load (copies per mL)					
≤20 000	35	28 (80%)	46	9 (20%)	<0.0001
20 000–100 000	46	14 (30%)	38	2 (5%)	0.004
>100 000	29	8 (28%)	36	1 (3%)	0.004
Primary PI mutations at baseline					
≤1	9	6 (67%)	16	3 (19%)	0.02
2	46	20 (44%)	31	5 (17%)	0.02
≥3	55	24 (44%)	74	4 (5%)	<0.0001
DRV-associated mutations at baseline					
≤1	50	28 (56%)	53	9 (17%)	<0.0001
2	33	15 (46%)	30	2 (7%)	0.0004
≥3	27	7 (26%)	36	1 (3%)	0.006
Baseline phenotypic DRV FC					
≤10	70	39 (56%)	76	11 (15%)	<0.0001
10–40	29	10 (35%)	24	0	0.001
>40	10	0	16	0	..
Active NRTIs in OBR					
0	31	8 (26%)	32	0	0.002
1	48	28 (58%)	45	3 (7%)	<0.0001
≥2	28	13 (46%)	40	8 (20%)	0.02
Active ARVs in OBR					
0	25	5 (20%)	18	0	0.04
1	34	17 (50%)	40	1 (3%)	<0.0001
≥2	48	27 (56%)	60	10 (17%)	<0.0001

OBR=optimised background regimen. DRV=darunavir. ARV=antiretroviral.
N=total number of patients in subgroup. n=number of patients reaching viral load <50 copies per mL.

Table 4: Proportion of patients who reached a viral load <50 copies per mL at week 48 by subgroup (ITT-TLOVR)

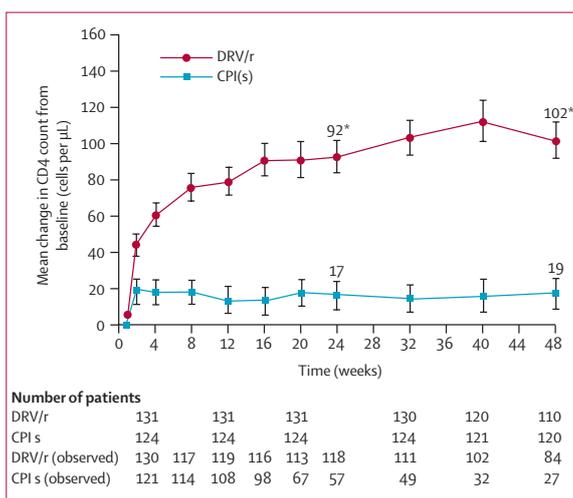


Figure 3: Mean changes over time from baseline to week 48 in CD4 count (LOCF)
Bars are SE. DRV/r=darunavir-ritonavir group. CPIs=control protease inhibitor group. *p<0.0001 for DRV/r vs CPIs.

	Darunavir-ritonavir (n=131)	Control PIs (n=124)
Abdominal pain	3	0
Neutropenia	2	3
Diarrhoea	2	2
Injection-site reaction*	2	1
Acute renal failure	2	1
Hip arthroplasty	2	0
Peripheral neuropathy	2	0
Anaemia	2	0
Weight decreased	2	0
Pneumonia	2	0
Fatigue	1	2
Hyperbilirubinaemia	0	3
Herpes zoster	0	2

*Associated with enfuvirtide use. Data are number of patients.

Table 5: AIDS Clinical Trials Group grade 3 or 4 adverse events recorded in ≥1% of patients in either treatment group up to week 48, regardless of causality

0.10 mmol/L (0.25) for high density lipoprotein, and 0.34 mmol/L (0.82) for low density lipoprotein in the darunavir-ritonavir group; corresponding values in the control PI group were -0.50 mmol/L (4.11), -0.26 mmol/L (1.59), 0.03 mmol/L (0.21), and -0.23 mmol/L (0.80). The overall mean concentrations of these lipid variables remained within the limits set by the National Cholesterol Expert Panel guidelines, except for triglycerides, which were higher than normal in both groups but were well below the “very high” cutoff of 5.65 mmol/L, and decreased slightly over the treatment period.¹³

No specific safety concerns relative to the overall darunavir-ritonavir patient population were identified for hepatitis B or C co-infected patients after 48 weeks of darunavir-ritonavir treatment.

Discussion

In this pooled analysis, after 48 weeks of treatment, virological and immunological responses of patients receiving darunavir-ritonavir 600/100 mg twice daily in the POWER 1 and 2 trials were greater than those of patients receiving currently available PIs. The maintenance of the difference in response rates to at least week 48 confirms and extends the results of the 24-week primary efficacy analyses.^{3,4} Furthermore, since CD4 increases of the magnitude seen in this analysis correlate with a reduction in the number of AIDS-related events or deaths,¹⁴ patients in the darunavir-ritonavir group might be less likely to have clinical progression of their disease than patients in the control PI group.

The 24-week primary efficacy analyses of POWER 1 and 2 identified a viral load of less than 50 copies per mL as a stringent yet realistic therapeutic goal for treatment-experienced patients, as opposed to the widely used endpoint of a reduction in viral load of

1 log₁₀ copies per mL or greater from baseline. In light of the recent IAS-USA recommendations, which were revised partly because of the approval of darunavir,¹⁵ the results of this 48-week analysis provide further evidence that a viral load of less than 50 copies per mL is an appropriate treatment goal. In this study, the proportion of patients with viral loads less than 50 copies per mL was maintained at around 45% from week 24 to week 48. These results are encouraging in this population, particularly as effective suppression of viral replication might prevent or delay the emergence of resistance. Response to darunavir-ritonavir in this analysis was affected by the number of darunavir resistance-associated mutations at baseline; the lower response rates in the control PI group might be accounted for by the darunavir resistance-associated mutations being present with a background of a high overall number of PI mutations.¹²

In the POWER 1 and 2 studies, enfuvirtide use was stratified but not randomised; patients who did not receive it as part of their optimised background regimen tended to have had shorter durations of HIV infection, lower baseline viral loads, and higher baseline CD4 cell counts compared with those who received enfuvirtide. In order to maximise patients' chances of maintaining this key response, the inclusion of other active agents in the optimised background regimen, especially those from new classes, should always be an aim during regimen selection. The results of the POWER studies showed that, in patients with limited options, the combination of darunavir-ritonavir with a new class, such as the fusion inhibitor enfuvirtide, had a substantial effect. The future availability of oral agents from other new classes should also provide potent alternatives expected to increase the likelihood of achieving a durable response.

During this 48-week analysis, darunavir-ritonavir was not associated with any new safety concerns. Although the reason for the difference in incidence of herpes simplex infection between the darunavir-ritonavir and control PI groups remains unclear, combination therapy with darunavir-ritonavir, like any other antiretroviral combination, might cause an inflammatory reaction to asymptomatic or residual opportunistic pathogens.¹⁶

The week 48 virological and immunological efficacy results for darunavir-ritonavir compare favourably with 48-week results reported for other currently available PIs in treatment-experienced patients, including ritonavir-boosted atazanavir,¹⁷ lopinavir,¹⁷ and tipranavir.¹⁸ Although the sample sizes are not comparable between the three studies, the results obtained with darunavir-ritonavir are important in this patient population because of the relatively large proportion of patients with an undetectable viral load after 48 weeks of treatment. Results of the present study also compare favourably with the 48-week results for enfuvirtide in a population of patients with extensive drug resistance.¹⁹

In these trials, 23% of patients in the control group used double-boosted PI regimens. Such regimens are also occasionally used in patients infected with HIV strains with established PI resistance, and in those with extensive NRTI or NNRTI resistance but with retained PI susceptibility. However, no benefit has been shown of double over single boosted PI therapy²⁰ or of dual PI therapy over single boosted PIs.²¹

Although the relatively small number of patients in POWER 1 and 2 is a possible limitation of this analysis, the consistent magnitudes of differences in responses over time to week 48 between the groups suggest the potential value of darunavir-ritonavir as a new antiretroviral agent. Although not all patients had reached week 48 or discontinued earlier at the time of this analysis, an ad-hoc analysis done when all patients had reached week 48 or discontinued earlier did not show any significant differences from the present results, either in terms of magnitude or in the differences in responses between the groups.²² Additionally, a larger group of patients (n=327) with a similar level of treatment experience are receiving darunavir-ritonavir 600/100 mg twice daily in the POWER 3 analysis, where similar efficacy and safety results have been observed to date.²³ The proportion of male patients in POWER 1 and 2 was high, but the effect of darunavir-ritonavir in female HIV-infected patients will be the focus of a currently recruiting study designed to evaluate the efficacy, safety, and tolerability of darunavir-ritonavir by sex and race.

The results of this combined analysis suggest that darunavir-ritonavir 600/100 mg twice daily, co-administered with an individually-optimised anti-retroviral regimen, is effective and well tolerated in treatment-experienced HIV-1-infected patients. This treatment is expected to fulfil the clinical need for a new PI capable of expanding the treatment options available for a treatment-experienced, drug-resistant population of patients. Darunavir-ritonavir is now being assessed in patients with less or no treatment experience in phase III trials.

POWER 1 and 2 study groups

In addition to the authors, the POWER 1 and 2 study groups included the following investigators and contributors to the design, conduct, and analysis of the study: ARGENTINA—P Cahn, I Cassetti, M Losso; AUSTRALIA—J Hoy, P Martinez, C Workman; AUSTRIA—A Rieger, N Vetter; BELGIUM—N Clumeck, F van Wanseele; BRAZIL—C A Da Cunha, B Grinstzejn, R Pedro, F Queiroz-Telles, A Timerman, J Valdez-Madruga; CANADA—P Junod, D Kilby, J McLeod, R O'Brien, A Rachlis, C Tsoukas, S Walmsley; FRANCE—J F Delfraissy, P M Girard, A Lafeuillade, F Raffi, J Reyes, W Rozenbaum, D Vittecoq; GERMANY—K Arasteh, H Carls, S Esser, H Jaeger, J Rockstroh, J A Rump, C K Schewe, D Schuster, S Staszewski; HUNGARY—D Banhegyi; ITALY—F Mazzotta, V Vullo; POLAND—A Boron-Kaczmarek; PORTUGAL—T Branco, R Sarmento-e-Castro, J Vera; SPAIN—K Aguirrebengoa, J M Gatell, J Gonzalez-Lahoz, J Iribarren, H Knobel, M J Perez-Elias, J J Picazo, I Santos; SWITZERLAND—E Bernasconi, M Opravil; UK—C Leen, A L Pozniak, E Wilkins; USA—B Barnett, J Baxter, G Beatty, S Becker, D Berger, C Borkert, D Brand, S Brown, A Burnside, T Campbell, A Collier, E De Jesus, R Liporace, J E Feinberg, I Frank, M Frank, J Gathe, S Green, J Hernandez, J Jemsek, H P Katner, D Kuritzkes,

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Contributors

B Clotet, N Bellos, J-M Molina, D Cooper, J-C Goffard, A Lazzarin, A Wöhrmann, C Katlama, T Wilkin, R Haubrich, C Cohen, C Farthing, D Jayaweera, M Markowitz, and P Ruane participated in the recruitment of patients and reporting of data for those patients. S Spinoso-Guzman and E Lefebvre contributed to the design of the trials. All authors approved the final version of the manuscript.

Conflict of interest statement

B Clotet has received consulting fees and lecture fees from Gilead, Roche, Bristol Myers Squibb, GlaxoSmithKline, Tibotec, Boehringer Ingelheim, Pfizer, and Abbott. N Bellos has served on speakers' bureaus and advisory boards for GlaxoSmithKline, Roche, Bristol Myers Squibb, and Gilead, and has received research support from all these companies, Pfizer, and Tibotec. J-M Molina has received consulting fees and lecture fees from Gilead, Roche, Bristol Myers Squibb, GlaxoSmithKline, Tibotec, and Abbott. D Cooper has received research support and honoraria from Johnson & Johnson including Tibotec. J-C Goffard has no contractual obligations, restrictions or conflicts of interest to disclose. A Lazzarin has received research grants and speaker or consulting honoraria from Gilead, Bristol Myers Squibb, Abbott, GlaxoSmithKline, Boehringer Ingelheim, Pfizer, Tibotec, and Roche. A Wöhrmann has had associations with Gilead and Abbott. C Katlama has had associations with Gilead, Roche, GlaxoSmithKline, Tibotec, Bristol Myers Squibb, and Boehringer Ingelheim. T Wilkin has served as an ad-hoc consultant for or received honoraria from Merck and Tibotec, and has received research support from Tibotec and Boehringer Ingelheim. On behalf of R Haubrich, the University of California has received funding to support research and consulting for the POWER 2 study. R Haubrich has received research support from GlaxoSmithKline and Pfizer; he has also acted as a consultant for or received honoraria from Bristol Myers Squibb, Monogram Bio, Tanox, Roche, Abbott, Boehringer Ingelheim, Gilead, and Virco. C Cohen has received research grants from Gilead, Bristol Myers Squibb, GlaxoSmithKline, Abbott, Roche, Tibotec, Boehringer Ingelheim, and Pfizer; he has received speaker honoraria from all these companies except Pfizer, and has acted as consultant for all these companies except Boehringer Ingelheim. C Farthing has received research grants from Gilead, Bristol Myers Squibb, Abbott, Roche, Tibotec, Boehringer Ingelheim, Pfizer, and has received speaker honoraria and acted as consultant for all of the above except Pfizer and Roche. D Jayaweera has received research support from GlaxoSmithKline, Bristol Myers Squibb, Roche, Abbott, Boehringer Ingelheim, and Tibotec. He has also acted as a consultant for or received honoraria from Bristol Myers Squibb, GlaxoSmithKline, Roche, Abbott, Tibotec, Boehringer Ingelheim, Gilead, and Virco. M Markowitz has received or currently receives research funding from Abbott, GlaxoSmithKline, Gilead, Merck, Boehringer Ingelheim, and Tibotec; he serves as paid consultant to Merck, GlaxoSmithKline, Gilead, and Sequoia Pharmaceuticals. P Ruane has received research support from GlaxoSmithKline, Gilead, and Roche, and has acted as a consultant for or received honoraria from Bristol Myers Squibb, Monogram, Roche, Tanox, Abbott, Boehringer Ingelheim, Gilead, GlaxoSmithKline, Tibotec and Virco. Sabrina Spinoso-Guzman and Eric Lefebvre are full-time employees of Tibotec.

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