

Darunavir: Review of its Efficacy as a Therapeutic Option for Treatment-Naïve and Treatment-Experienced Adults and Adolescents

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Abstract: Darunavir is a next-generation protease inhibitor that demonstrates potent *in vitro* activity against wild type strains of HIV type-1, as well as against numerous strains resistant to available protease inhibitors. Numerous trials conducted in naïve and in the treatment-experienced HIV-infected individuals have significantly demonstrated greater virological suppression when darunavir was added to an optimized background treatment compared with a control protease inhibitors. The drug is taken as two 400 mg tablets once daily plus 100 mg of ritonavir in naïve patients, while is taken as two 300 mg tablets plus 100 mg of ritonavir twice daily in experienced patients. Darunavir has a high genetic barrier and has a distinct resistance profile. Darunavir resistance-associated mutations have been defined as V11I, V32I, L33F, I47V, I50V, I54L/M, T74P, L76V, I84V, and L89V. The major adverse effects of darunavir therapy are nausea, diarrhea and rash; and as others protease inhibitors, increase of triglycerides and total cholesterol.

Keywords: darunavir, HIV type-1, protease inhibitor, *in vitro*

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Introduction

In 1983 the human immunodeficiency virus type 1 (HIV-1) was recognized as the primary cause of the acquired immunodeficiency syndrome (AIDS). After 25 years, HIV infection remains a significant cause of morbidity and mortality.¹ Major advances in HIV treatment have revolutionized patient care and prolonged survival, with the result that HIV infection can now be effectively managed as a chronic disease, at least in the industrialized countries. Particularly, combined antiretroviral therapy (cART) has completely changed the course of HIV infection, but current drugs do not eradicate the virus and lifelong treatment is necessary.^{2,3} The goals driving the decision to initiate cART therefore are to reduce HIV-related morbidity and prolong survival, improve quality of life, restore and preserve immunologic function, maximally and durably suppress viral load, and prevent vertical HIV transmission.⁴

At present there are 23 approved antiretroviral drugs, in six mechanistic classes with which to design combination regimens. These six classes include the nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), fusion inhibitors (FIs), CCR5 antagonists, and integrase inhibitors (INIs).

The initial selection of an antiretroviral regimen depends on the patient's characteristics, comorbidities, and drug susceptibility of the patient. Particularly, transmission of resistant variants in developed countries ranges from 5% to 20%.⁵ The selection is additionally influenced by factors like pill burden, frequency of dosing, drug interactions, poor adherence, tolerability, and short- and long-term adverse events profiles, and these treatment challenges continue to influence the use of the cART. Potential for emergence of resistance during therapy and subsequent treatment options may also affect the design of an initial regimen.⁶ Despite the availability of cART, a need still exists to develop antiretroviral agents that can sustain virological inhibition and have good tolerability in a broad range of HIV-infected patients. The darunavir (DRV) has been developed to meet this need.

Darunavir

DRV is an oral non-peptidic HIV-1 PIs that is used, together with a low boosting dose of ritonavir

(DRV/r), as part of an cART regimen in naïve and treatment-experienced patients with HIV infection, approved by the Food and Drug Administration on June 23, 2006 initially for experienced then naïve patients.⁷ It is a second-generation PIs, designed specifically to overcome problems with the older generation PIs: severe side effects and drug toxicities, higher therapeutic doses due to peptide-like character, and the emergence of drug resistance.⁸

Pharmacodynamics

DRV, like all PIs, selectively inhibits the cleavage of HIV gag and gag-pol polyproteins. Inhibition renders the viral particles unable to reproduce or infect.⁹ Inactivation of the protease enzyme is achieved through competitive binding of the enzyme in a “lock and key” manner. PIs act as false “keys” that disrupt protease activity through binding to the active enzyme site. DRV also inhibits dimerization of HIV-protease, thus inhibiting proteolytic activity and subsequent HIV-1 replication.¹⁰ The majority of PIs contain substantial peptide-like features. DRV is a nonpeptidic analogue of amprenavir, with a critical change at the terminal tetrahydrofuran (THF) group. Like amprenavir, DRV contains a sulphonamide group and instead of a single THF group, 2-THF groups are fused in the DRV compound to form a 2-THF moiety.^{11,12} This structural change leads to increased hydrogen bond interactions with more regions of the protease enzyme and an associated increase in binding energy.¹³ Conformational analysis has demonstrated that the agent is able to form a highly stable complex with protease, largely due to conformational flexibility and backbone interactions, which leads to less sensitivity of the biological activity and which results in continued enzyme inhibition in the presence of several mutations.¹⁴ With numerous hydrogen bonds, 2-THF was shown to closely and tightly bind to the backbone atoms of the S2 sub-site of the protease. Such tight interactions were consistently observed with mutant proteases and might therefore account for the unusually high resistance profile of DRV. Optimization attempts of the backbone binding in other sub-sites of the enzyme, through rational modifications of the isostere or tailor made P2 ligands, led to equally impressive inhibitors with excellent resistance profiles.



Pharmacokinetics

DRV is rapidly absorbed after oral administration, generally reaching peak plasma concentrations within 2.5–4 hours. Compared with a single dose of DRV 600 mg alone, DRV/r 600/100 mg twice daily had an increased absolute oral bioavailability (from \approx 37% to 82%).¹⁵ The bioavailability of oral DRV is increased by about 30% when taken with food. The type of meal does not affect exposure.¹⁶ Steady status is reached at 72 hours. Protein binding of DRV is high, at about 95%, bound primarily to plasma α_1 -acid glycoprotein.

DRV is primarily metabolized and eliminated by the hepatic CYP system and almost exclusively by isoenzyme CYP3A4. Total plasma concentration of DRV in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment was comparable with that in healthy subjects. However, the concentration of unbound DRV was approximately 55% (Child-Pugh Class A) and 100% (Child-Pugh Class B) higher, respectively. The clinical relevance of this increase is unknown, but caution should be used in this patient group.¹⁷ In an analysis of pharmacokinetic data from treatment-experienced patients in the POWER 1 and 3 studies, there were no differences in DRV exposure in patients co-infected with hepatitis B or C or patients without co-infection.¹⁸

In patients with renal impairment, no special precautions or dosage adjustments are required, in fact analysis showed that the pharmacokinetics of DRV were not significantly affected in HIV-infected patients with moderate renal impairment (CrCl between 30–60 mL/min).¹⁶

The pharmacokinetics of DRV/r in 74 treatment-experienced pediatric patients, aged 6 to 17 years and weighing at least 20 kg, showed that the administered

weight-based doses of DRV/r resulted in DRV exposure comparable to that in adults receiving DRV/r 600/100 mg. Population pharmacokinetic analysis in HIV-infected patients showed that DRV pharmacokinetics are not considerably different in the age range (18 to 75 years) evaluated in HIV infected patients. However, only limited data were available in patients above the age of 65 year, then caution is recommended in this group.^{19,20}

The pharmacokinetics of DRV/r in 18 patients showed that the median concentration in cerebrospinal fluid (CSF) was 56.9 ng/mL, while the median total plasma concentration was 4094 ng/mL and the median unbound plasma concentration was 542 ng/mL (DRV tends to bind with blood proteins, which interferes with ability to cross the blood-brain barrier). DRV concentrations in CSF also exceeded the IC₅₀ for wild-type HIV, with a median level 20.7 times the IC₅₀. DRV CSF concentrations also had a positive correlation with total plasma concentrations, but the association with unbound plasma levels was not significantly stronger. Sixty-two percent of DRV recipients had undetectable plasma viral load and 90% had undetectable CSF viral load. DRV is in the therapeutic range for inhibition of wild-type HIV and should contribute to control HIV replication in the nervous system as a component of effective antiretroviral therapy.²¹

Exposure to DRV/r was slightly higher in women than in men, but this is not considered clinically relevant.¹⁶ Adequate studies of DRV/r in pregnant women have not been performed and the drug should only be used in pregnancy if the potential benefit justifies the potential risk.²⁰

Table 1 summarize drug interactions of DRV with antiretrovirals and other drugs common use in clinical practice.

Table 1. Darunavir drug interactions in clinical practice.

Not recommended	cisapride, St John's Wort, midazolam, triazolam, rifampicin, astemizole, terfenadine, ergot alkaloids, anticonvulsants, lovastatine simvastatin
Caution, monitor dosage	antiarrhythmics, itraconazole, warfarin, calcium channel blockers, immunosuppressants
Caution, dose reduction of concomitant drugs	erectile dysfunction agents, atorvastin, pravastin
Darunavir dose reduction	clarithromycin, ketoconazole
Not clinically relevant	proton pump inhibitor, H2 receptor antagonist, efavirenz, nevirapine, NRTIs, raltegravir



Efficacy

DRV/r 600/100 mg, has demonstrated sustained efficacy and good safety in patients with a broad range of treatment experience.²² On the basis of the results in treatment-experienced patients once daily DRV/r was tested in HIV-naïve population.²³ The available data highlight that DRV/r is recommended for treatment-naïve and treatment-experienced adults and adolescents.⁴

Treatment-naïve patients

An initial cART regimen should be potent, durable, able to prevent or delay the onset of drug resistance and should also have good tolerability and a convenient dose schedule. On the basis of the results from POWER (Performance Of TMC114/r When evaluated in treatment-experienced patients with PI Resistance) studies in treatment experienced patients, once-daily DRV/r 800/100 mg was selected for patients with no previous treatment experience. The suitability of once-daily dosing in this population is supported by the long half-life of DRV in the presence of ritonavir. ARTEMIS (AntiRetroviral Therapy with TMC114 ExaMined In naïve Subjects) is a study assessing the efficacy and safety of DRV/r 800/100 mg as compared with lopinavir/ritonavir (LPV/r) in treatment-naïve HIV-1 infected patients over 192 weeks. It is a ran-

domized, phase III, open-label trial conducted across 26 countries.^{23,24} Treatment-naïve HIV-1 infected adult patients, with plasma HIV-RNA at least 5000 copies/mL were randomized to receive either DRV/r 800/100 mg or LPV/r 800/200 mg total daily dose. In addition, all patients received a fixed combination, tenofovir and emtricitabine.

The primary objective of the trial was to demonstrate non-inferiority of DRV/r 800/100 mg as compared with LPV/r 800/200 mg in virologic response at 48 weeks. Secondary objectives included evaluation of virologic and immunologic parameters over 192 weeks, evaluation of safety and tolerability and in the event of non-inferiority testing for superiority of DRV/r over LPV/r.

At weeks 48, 84% of DRV/r and 78% of LPV/r patients had a confirmed virologic response of HIV-1 RNA less than 50 copies/mL, demonstrating non-inferiority of DRV/r as compared with LPV/r. The median change from baseline in CD4 cell count at week 48 was similar between the groups. In patients with high baseline HIV-RNA (≥ 100000 copies/mL), LPV/r response rates (67%) were lower versus DRV/r (79%), resulting in a statistically significantly higher response rate with DRV/r.²² In the Figure 1, we have shown the comparison of boosted PIs in patients which have achieved virological suppression.

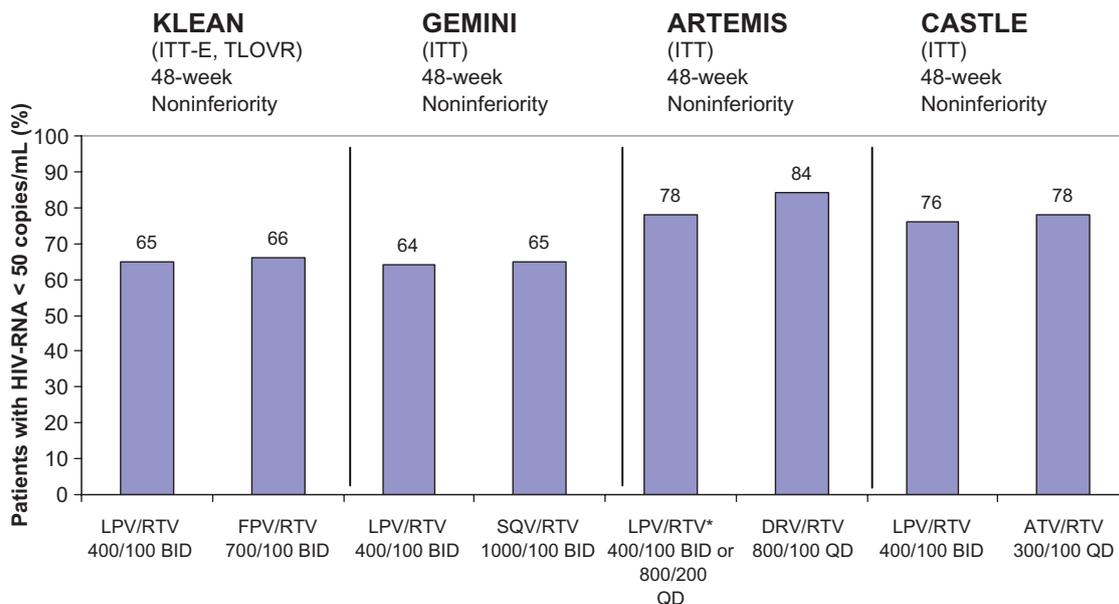


Figure 1. Comparison of boosted PIs in Antiretroviral-Naïve Patients: virological suppression.

*Use of LPV/RTV BID or QD as not randomized and was dependent on site and patient preference.



At week 96, 79% of patients receiving DRV/r vs. 71% of patients receiving LPV/r had a confirmed a viral load undetectable. The estimated difference in response for DRV/r vs. LPV/r was 8,4%, demonstrating non-inferiority of DRV/r relative to LPV/r. Further analysis showed, for those with a baseline CD4 cell count less than 200 cells/ μ l, that the response rate was higher in the DRV/r arm than in the LPV/r arm (79% vs. 65%). Response rates between arms were not significantly different for patients with HIV-1 RNA less than 100000 copies/mL or CD4 cell count at least 200 cells/ μ l at baseline.²⁴

These results demonstrate that DRV/r together with a fixed NRTIs background regimen was highly effective for treatment-naïve patients. Furthermore, 92% of DRV/r patients who had an undetectable viral load at week 48 remained undetectable at week 96, providing evidence of the continued potency in naïve patients.

Induction and maintenance

This treatment strategy involves starting with a highly potent combination regimen for the first six to twelve months (the induction regimen), then subtracting some of the drugs once most of the virus population has been eliminated (the maintenance regimen) and DRV/r, could be a good option.²⁵ In the MONET, the

first DRV monotherapy trial, the researchers recruited 256 Europeans with a viral load <50 copies for at least 6 months while taking a standard NNRTI regimen (43%) or PI regimen (57%).²⁶ No one could have DRV experience, and no one could have a history of virologic failure. The MONET team randomized 127 people to switch to 800/100 mg of DRV/r once daily alone and 129 to start once-daily DRV/r plus two NRTIs. Most study participants were white (91%), and most (81%) were men. Median CD4 count stood at 575 and median age at 43 years. People randomized to monotherapy had taken antiretrovirals longer (average 7.4 versus 6.4 years), and more of them had hepatitis C virus infection (19% versus 11%). Nine people in each treatment group stopped taking their assigned regimen. No new or unexpected treatment-related problems arose during the trial.

Defining failure as consecutive viral loads >50 copies, the investigators calculated a 48-week virologic response rate of 86.2% with monotherapy and 87.8% with triple therapy in a per-protocol analysis that excluded 10 patients with protocol violations and counted drug switches as failures. In an intent-to-treat analysis that included the 10 protocol violations, response rates were almost identical 84.3% with monotherapy and 85.3% with standard therapy (Fig. 2). And in an analysis that allowed switching, response

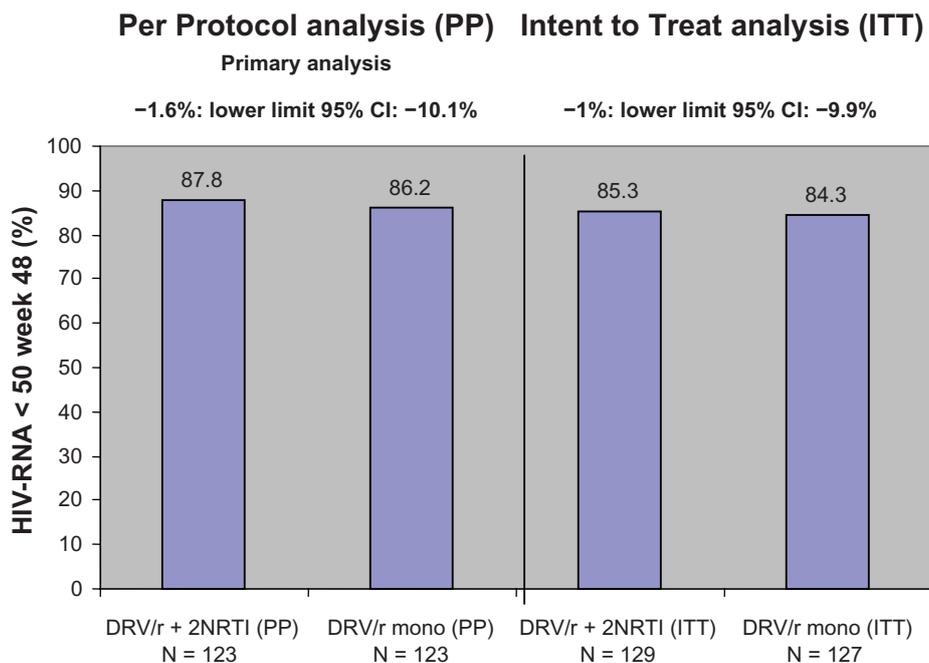


Figure 2. MONET Trial: darunavir/ritonavir monotherapy shows non-inferior efficacy to standard HAART. For patients with HIV-RNA < 50 copies/mL at baseline²⁵.



rates were 93.5% with monotherapy and 95.1% with triple therapy. All of these comparisons indicated that DRV/r monotherapy is not inferior to DRV/r plus two nucleosides in people who start one of these regimens with a viral load <50 copies. Eleven people in the monotherapy group and 7 in the triple-therapy group had two transient viral load readings above 50 copies, and 2 people in each group had a sustained viral load rebound above 400 copies. The investigators attributed most temporary or sustained rebounds to poor adherence or to emergence of other illnesses that may affect HIV load. At the last study visit, 124 of 127 people randomized to monotherapy and 126 of 129 randomized to triple therapy had a viral load under 50 (97.6% and 97.7%).

Arribas and coworkers searched for resistance mutations any time someone's viral load rose above 50 copies. Most of these 50-plus readings were transient blips. As already noted, people in the monotherapy group had more blips, a result reflecting findings in randomized trials of LPV/r monotherapy. All told, the MONET team had successful genotypes on 22 people taking monotherapy and 13 taking triple therapy. A new resistance mutation emerged in only one person in each study group. The M184V lamivudine/emtricitabine mutation and one primary PI mutation arose in 1 person taking DRV plus two NRTIs; one primary PI mutation and one DRV-related mutation evolved in a person on monotherapy. Neither of the two people with new PI mutations had phenotypic evidence of decreased viral susceptibility to DRV.

Compared with the MONET trial, a French trial of the same maintenance tactic proved less convincing for three reasons: in one of two 48-week analyses, DRV/r monotherapy was "not noninferior" to DRV/r triple-therapy maintenance; there were three virologic failures in people taking DRV/r monotherapy and none in the standard-therapy arm; and virologic response analyses used a viral load threshold of 400 copies instead of 50 copies.²⁷ The French MONOI trial (ANRS 136) enrolled 242 people with a viral load <400 copies for at least 18 months and fewer than 50 copies at entry. No one had taken DRV/r before, and no one had a record of virologic failure.

During an 8-week induction phase, everyone took DRV/r (600/100 mg twice daily) plus two NRTI. The 225 people who maintained viral suppression were randomized to continue twice-daily DRV/r plus two

NRTI (n = 113) or to switch to twice-daily DRV/r monotherapy (n = 112). Three quarters of MONOI participants were men. Median age was about 46 years, and starting CD4 counts were 582 in the triple-therapy arm and 585 in the monotherapy group. While 73% in the triple-drug group entered the trial taking a PI, 64% in the monotherapy arm were taking a PI-based regimen. About 20% in each group were taking a NNRTI-based combination, and the rest were taking three NRTI.

The MONOI team defined failure as consecutive viral loads >400 copies or treatment modification or discontinuation. In a per-protocol analysis, 99% in the triple-drug arm and 94.1% in the monotherapy arm met those response criteria by week 48. Those results indicated that DRV/r monotherapy is not inferior to DRV-based triple therapy in people like those in this trial.

The goal in both studies was to show non-inferiority of the DRV-only regimen. Both studies did so, although with some differences in the details.

In the MONET trial the primary endpoint was the proportion of patients whose viral load remained suppressed at the end of the first 48 weeks of the 96-week study. The DRV alone regimen was considered non-inferior if the difference was less than 12%.

In the intent-to-treat population 85.3% of the patients on three drugs maintained viral suppression, compared with 84.3% of those on DRV alone. The estimated difference of 1% had a 95% confidence interval whose lower limit was minus 9.9%—well within the minus 12% cut-off for non-inferiority. The per-protocol results were similar and also showed non-inferiority.

In the MONOI the per-protocol population, only 1% of those getting triple therapy failed, where failure was defined as two consecutive levels above 400 copies of HIV RNA per millilitres of plasma. That compared with 5.9% of those taking DRV only.

The 90% confidence interval of the 4.9% difference had a lower bound of minus 9%, which was within the specified minus 10% cut-off for non-inferiority.

In the intent-to-treat population, the results were similar, but the lower bound of the confidence interval fell outside the non-inferiority confidence interval. The results of the two studies combined suggest that DRV represents a viable alternative to standard triple therapy.



Treatment-experienced patients

POWER 1 and 2 are randomised, multinational (POWER 1: Australia, Brazil, Canada, Europe; POWER 2: Argentina, USA), 144-week phase IIB trials comparing the efficacy and safety of DRV/r with that of currently available in treatment-experienced HIV-1 infected patients. The first 24 week constituted a dose-finding phase: patients, aged ≥ 18 years, were HIV-infected adults with prior use of NRTIs, NNRTIs and one or more PIs for at least 3 months (prior enfuvirtide use was allowed), with plasma HIV-RNA > 1000 copies/mL and one or more primary PIs mutation, receiving a stable PI-containing regimen. Investigators selected an Optimized Background Therapy (OBT) for each patient based on genotypic resistance and treatment history (NNRTI were excluded) and then patients were randomized to receive one of four DRV/r doses or their investigator-selected control PI-based regimen (control PIs group) from baseline. The dose DRV/r 600/100 mg twice daily demonstrated the highest virological and immunological response.^{28,29}

After the primary 24-week efficacy analysis, patients in the control PI arm continued their assigned treatment whereas all patients receiving DRV/r were switched to DRV/r 600/100 mg twice daily for the longer-term, open-label phase of the randomized controlled trials: so the combined 48-, 96- and 144-week subgroup analyses included only those patients who received boosted DRV/r 600/100 mg twice daily.³⁰⁻³² At week 144, 48 (37%) patients in the DRV/r 600/100 mg twice daily group and 11 (9%) patients in the PIs group achieved HIV-RNA < 50 copies/mL. An increase of $\geq 1 \log_{10}$ HIV-RNA reduction was achieved by 67 (51%) patients in the DRV/r 600/100 mg twice daily group and 12 (10%) patients in the PI group. The median CD4 cell count increased from baseline by 97 cells/mm³ in the DRV/r 600/100 mg twice daily group and 4 cells/mm³ in the PI group.³²

In conclusion POWER studies confirm that DRV/r 600/100 mg twice-daily has long-term efficacy and is a treatment option in treatment-experienced patients.

The efficacy results of POWER 1 and 2 are confirmed by data from a large, non-randomized open-label analysis known as POWER 3. At 24 weeks, 65% of patients achieved a reduction in viral load of 1 \log_{10} or more versus baseline, and 40% of patients

reached < 50 HIV-RNA copies/mL. These results corroborate POWER 1 and POWER 2 studies.³³

In TITAN (TMC114/r In Treatment-experienced Patients Naïve to lopinavir) study, the efficacy and safety of DRV/r were assessed in lopinavir-naïve patients who had substantially less treatment experience than did those in the POWER trials.²² The aim of this study was to show non-inferiority of DRV/r 600/100 mg twice daily compared with lopinavir-ritonavir 400/100 mg twice daily, in terms of virological response, with both agents given in addition to an individually OBT. Lopinavir-ritonavir was chosen as comparator because of its efficacy and safety in PI-experienced patients in several randomized controlled trials.^{34,35}

It is a continuing, international, randomized, controlled, open-label, 96-week phase III trial. Patients aged ≥ 18 years who had received previous treatment with HAART for at least 12 weeks, lopinavir naïve, were eligible for study entry. Patients were assigned to an OBT, including at least two antiretroviral drugs (NRTI with or without NNRTI) and, then, were randomized in a 1:1 ratio to receive DRV/r 600/100 mg twice daily or LPV/r 400/100 mg twice daily.

The results showed that DRV/r was not only not-inferior to LPV/r, as determined by the primary endpoint of less than 400 copies/mL of HIV-RNA at week 48 but was also significantly better than boosted lopinavir at 48 and 96 weeks. In fact more patients in the population in the DRV/r group than in the lopinavir group had a viral load of < 400 copies/mL at week 48 (77% vs. 68%; mean difference of 9%).²² Similar results were recorded for this endpoint in the population at 96 weeks.²⁴ In addition significantly more patients in the DRV/r group than in the lopinavir group (71% vs. 60%) achieved a plasma viral load < 50 copies/mL at week 48. The proportion of patients achieving a viral load reduction from baseline of $\geq 1 \log_{10}$ copies/mL were higher in the DRV/r group than in the lopinavir group. The mean increase in CD4 cell count was not significantly different between treatment groups.²³

In conclusion DRV/r at a dose of 600/100 twice daily has demonstrated sustained efficacy in patients with a broad range of treatment experience.

In the TRIO trial³⁶ French researchers assessed the safety and efficacy of an antiretroviral regimen containing raltegravir, the NNRTI etravirine and the



DRV/r in treatment-experienced HIV patients with multidrug-resistant virus. This Phase II multicenter trial enrolled 103 treatment-experienced patients. Most (88%) were men. Participants had plasma viral load >1000 copies/mL, had not previously used the drugs under investigation, had a history of virological failure while on NNRTI, and had multiple HIV mutations conferring resistance to multiple drug classes. At baseline, the median viral load was 4 log₁₀ copies/mL and the median CD4 cell count was 255 cells/mm³ (nadir 79 cells/mm³). The median time since starting HIV treatment was 13 years, and 44% had a history of AIDS-defining events. Participants had a median of 4 primary PI resistance mutations, 6 NRTI resistance mutations, and 1 NNRTI resistance mutation. Almost all (96%) had 1–3 DRV resistance mutations and 65% had 1–3 etravirine resistance mutations. Background regimens included NRTI and the addition entry inhibitor enfuvirtide, whenever possible. The regimens of 83% of patients included NRTI (with a median genotypic sensitivity score = 0.5); 14 included enfuvirtide as part of their regimen, of whom 12 were enfuvirtide-naïve. The primary endpoint was the proportion of patients with undetectable viral load (<50 copies/mL) at week 24. The results showed that 57 patients (55%) had undetectable viral load at week 4; 91 patients (88%) had undetectable viral load at week 12. At week 24, 93 patients (90%) had viral load <50 copies/mL and 98 (95%) had viral load <400 copies/mL. The mean reduction in HIV RNA was 2.4 log₁₀. The median CD4 cell count increase was 99 cells/mm³.

Regimens containing the 3 study drugs were generally well tolerated. These findings show the potentially significant advantages of using 3 fully active oral drugs in treatment-experienced patients with multidrug-resistant HIV.

Treatment of children and adolescent

Combination antiretroviral therapy is recommended for all infants, children, and adolescent who are treated with antiretroviral agents. The current US and PENTA guidelines for using antiretrovirals in HIV-infected children are based largely on preliminary pediatric data and on studies in adult patients.³⁷ Understanding appropriate dosing of DRV/r in children is important because these drugs have proved

highly potent in adults with and without antiretroviral experience.

DELPHI (DRV Evaluation in Pediatric HIV-Infected, treatment-experienced patients; TMC114-C212) is a phase II trial designed to determine the appropriate DRV/r dose for treatment-experienced, HIV-1-infected children and adolescent aged 6–17 years, and to evaluate the long-term safety and efficacy of the recommended pediatric dose.³⁸ DRV/r 600/100 mg twice daily as a body-weight-adjusted dose is indicated for this pediatric patient population; the approval was based on the 24-week results of DELPHI. This trial included treatment-experienced HIV-1 infected patients aged 6–17 years, with body weight at least 20 kg, HIV-RNA greater than 1000 copies/mL and stable CD4. Patients were randomized in a 1:1 ratio to receive either the weight-adjusted, adult-equivalent dose of DRV/r 600/100 mg twice-daily (group A, DRV 9–15 mg/kg and ritonavir 1,5–2,5 mg/kg twice-daily) or a 20–33% higher dose of DRV/r twice-daily (group B, DRV 11–19 mg/kg and ritonavir 1,5–2,5 mg/kg twice-daily). Once the dose was selected all part I patients not on the selected dose were switched to receive it at a planned visit and all patients were scheduled to continue in part II. Part II evaluated the safety and efficacy of DRV/r at the selected dose over 48 weeks. All patients received DRV/r twice daily plus OBT. On the basis of the results of part I of this trial, the recommended DRV/r doses for treatment-experienced, HIV-infected children and adolescent with a body weight of 20–50 kg are DRV 11–19 mg/kg and ritonavir 1,5–2,5 mg/kg twice daily. DRV/r treatment was associated with at least a 1 log₁₀ reduction from baseline in HIV-RNA for almost two-thirds of patients, and undetectable HIV-1 RNA (<50 copies/mL) for almost half of all patients at week 48. Higher response rates were observed in younger patients (6–12 years) versus older patients (12–17 years). This difference is thought to be attributable to the greater antiretroviral treatment experience and higher degree of drug resistance in adolescent patients compared with children under 12 years old.

In treatment-experienced children and adolescents, the researchers conclude, DRV/r showed comparable exposure to adults with appropriate dose selection, favorable safety and tolerability, improved



body weight and significant virologic response. They propose that DRV/r is a valuable therapeutic option for this population.

Safety and tolerability

Tolerability data on DRV/r are available from all studies.^{22–24,26–33,39} The safety analysis in the POWER study adverse events reported with an incidence of 10% or greater in patients receiving DRV/r were diarrhea (20%), nausea (18%), headache (15%), rhinopharyngitis (14%), fatigue (12%), upper respiratory tract infection (12%) and herpes simplex (12%). Incidence of adverse events in the DRV/r groups were mostly lower than or similar to those of the control PIs group; in particular diarrhea, nausea and headache had a lower incidence in the DRV/r group. The incidence of herpes simplex infection was greater in the DRV/r than the control PIs group and the reason for this difference remains unclear. The most common laboratory abnormalities were increased triglycerides, increased pancreatic amylase and lipase (no cases of clinical pancreatitis were observed) and increased total cholesterol.

In TITAN study, DRV/r was generally safe and well tolerated, with few treatment discontinuations. In addition gastrointestinal adverse events were more frequent in lopinavir/ritonavir than DRV/r patients. The incidence of rash was similar in the two treatment groups. Triglyceride increase were more frequent with lopinavir/ritonavir than DRV/r, which may be related to the higher daily dose of ritonavir with lopinavir/ritonavir.

In ARTEMIS study, most adverse events were grade 1 or 2, and discontinuation due to adverse events were infrequent. The most common adverse events (regardless of severity and causality) were diarrhea, nausea, headache, upper respiratory tract infection, rhinopharyngitis, abdominal pain, vomiting, and cough. The overall incidence of laboratory abnormalities was comparable for DRV/r and lopinavir/ritonavir treatment groups. Mean increase in triglycerides and total cholesterol were more pronounced with lopinavir/ritonavir than with DRV/r.

Safety results of the week 48 analysis of DELPHI demonstrated a favorable overall tolerability profile for DRV/r in treatment-experienced pediatric patients. In addition an important clinical finding

was the positive effect of DRV/r treatment on growth parameters.³⁸

Dosing and administration

In treatment naïve patients, the recommended dosage is DRV/r 800/100 mg once-daily, while in treatment-experienced patients is DRV/r 600/100 mg twice-daily.

Recommended dose for treatment-experienced pediatric patients (6 to 17 years of age) for DRV/r is based on body weight: 20–30 kg, 375/50 mg; 30–40 kg, 450/60 mg and ≥ 40 kg, 600/100 mg, always twice daily.

There are insufficient data on the use of DRV/r in children less than 6 years of age or less than 20 kg body weight. Hence, DRV/r is not recommended for use in this group.

DRV is metabolized by the hepatic system. No dose adjustment is recommended in patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, however, DRV should be used with caution in these patients. No pharmacokinetic data are available in patients with severe hepatic impairment. Severe hepatic impairment could result in an increase of DRV exposure and a worsening of its safety profile. Therefore it must not be used in patients with severe hepatic impairment (Child-Pugh Class C).^{17,18}

Resistance

Several studies have looked at the prevalence of DRV-associated mutations in various populations. The mutations associated with DRV are V11I, V32I, L33F, I47V, I50M, I54M, T74P, L76V, I84V, and L89V.⁴⁰ To estimate to what extent DRV might be effective in patients failing distinct PIs in a clinical setting, the genotypic resistance scores for DRV were examined in a large clinical HIV-1 drug resistance database. All clinical specimens from HIV-infected patients failing PIs-based regimens referred for drug resistance testing between 1999 and 2007 to a reference centre in Madrid were analyzed. A total of 1021 genotypes from patients failing lopinavir (39.2%), nelfinavir (28.1%), saquinavir (14.5%), indinavir (13.7%), atazanavir (6.6%), fosamprenavir (5.3%), and tipranavir (1.1%) were identified. The prevalence of major DRV resistance mutations was: I50V



2.1%, I54M 1.3%, L76V 2.7%, and I84V 14.5%. For minor DRV resistance mutations, the rates were: V11I 3.3%, V32I 3.9%, L33F 11%, I47V 2.1%, I54L 2.3%, G73S 12.8%, and L89V 2.4%. Overall, 6.7% ($n = 68$) of the genotypes had 3 or more DRV resistance mutations, which corresponded to a mean total number of PIs resistance mutations of 12.3 ± 1.9 . In the multivariate analysis, prior fosamprenavir failure, prior saquinavir failure, the total number of PI resistance mutations, and the number of prior PIs used were all independently associated with having more DRV resistance mutations.⁴¹ In another study of treatment-experienced individuals, patients harboring viruses with amprenavir-specific resistance profiles, such as I50V or V32I + I47V, failed on DRV/r-containing regimens. These key amprenavir mutations were also selected at the time of failure, suggesting their impact on DRV efficacy.⁴² However this data are not confirmed by other authors.⁴³ Picchio and colleagues predicted phenotypic sensitivity to DRV, using over 56,000 sample genotypes with different levels of PIs resistance, from the Virco database from 2004–5.⁴⁴ Clinical and/or biological cut-offs using upper and lower levels for each PI (3.4 and 99.6 for DRV) were used to determine the relative sensitivity to DRV, defined as maximal, reduced, and minimal sensitivity. DRV showed a low proportion of samples (5%) with minimal and reduced responses. Recent study evaluate changes in 47 HIV-infected patients failing a tipranavir/r-including regimen. Genotypes were evaluated through the Stanford mutation score: patients were ranked for TPV/r and DRV/r resistance as susceptible (class 1), potential low-level (class 2), low-level (class 3), intermediate-level (class 4), and high-level resistance (class 5). At baseline (tipranavir initiation), the scoring for tipranavir/r was: class 3 = 4 (8.5%); class 4 = 31 (66%); and class 5 = 12 (25.5%). Corresponding scores for DRV/r were: class 2 = 1 (2%), class 3 = 12 (25.5%), class 4 = 32 (68%), and class 5 = 2 (4.5%). At tipranavir/r virological failure, a shift toward a higher tipranavir/r scoring class was seen in 16 (34.1%) patients ($P = 0.001$), whereas a shift toward a higher DRV/r scoring class was observed in 9 (19.2%) patients ($P = 0.2381$). After tipranavir/r virological failure, 25/47 patients (53%) were treated with a DRV/r. After 24 weeks, the median HIV-RNA decrease

was 3.04 (2.13–3.45) \log_{10} copies per milliliter in DRV/r group versus -0.04 (-0.44 ; 0.50) \log_{10} copies per milliliter in patients not treated with a DRV/r ($P < 0.0001$); CD4 increase was 126 (70–169) cells/mm³ in DRV/r group versus -42 (-121 ; 42) not treated with DRV/r ($P < 0.0001$). In conclusion the authors suggest that the treatment with tipranavir/r did not significantly increase the resistance score to DRV/r and did not preclude the efficacy of subsequent treatment with his treatment.⁴⁴

Conclusions

DRV/r is the first of a new generation of PIs and demonstrates potent antiviral activity against wild type strains of HIV-1 and against strains of HIV-1 that are resistant to other PIs.

The drug has demonstrates efficacy in naïve patient, in induction and maintenance strategy and when added to an OBT regimen in patients who have experienced treatment failure with multiple drug classes.

First-line DRV/r based regimen may provide the greatest opportunity to fully suppress HIV replication and to prevent the emergence of drug-resistant strains that can lead to treatment failure and compromise future drug treatment options.^{24,25,39} Hence, first-line ARV regimens should be potent and durable, prevent or delay the onset of drug resistance, and have good/excellent tolerability and a convenient dosing schedule. The results of the 48-week analysis of the ARTEMIS trial confirmed that DRV/r fulfils these criteria, including this PI in the current guidelines^{4,6} for use in treatment-naïve HIV patients. These 96-week results illustrate that the clinical response to DRV/r is both significant and persistent.³⁹

In HIV-infected population who had experienced virological failure, DRV/r could be added to at least one new agents from existing classes such as the new NNRTI etravirine,^{45,46} or a new agents of a new class as INIs or CCR5 inhibitors.^{47,48} Its high genetic barrier and resistance profile make it extremely useful in patients having failed a PI containing regimen.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been



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