From TMC114 to Darunavir: Five Years of Data on Efficacy

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Abstract

Five years after its initial approval, an overwhelming amount of pivotal data has come out on darunavir/ritonavir. It is the only antiretroviral that has been registered at two different doses, 800/100 mg once-daily or 600/100 mg twice-daily, allowing its administration throughout the entire course of HIV disease, from naive subjects without any HIV-1 resistance to heavily treatment-experienced subjects with widespread triple-class family resistance. Its binding affinity is more than 100-fold higher compared to other protease inhibitors, which poses extreme difficulties for wild-type viruses to develop* in vitro *resistance to darunavir. It is a preferred option for initial therapy as no subjects developing virologic failure select darunavir resistance mutations in this scenario. It is the default protease inhibitor for early and advanced salvage regimens in subjects with virologic failure. The once-daily darunavir dose has demonstrated non-inferior efficacy against the twice-daily dose in early stages of virologic failure in pretreated subjects without darunavir mutations, both doses retaining the genetic barrier against resistance seen in treatment-naives. With a high potency, superior genetic barrier to HIV-1 resistance development, and favorable pharmacokinetics, it meets the optimal requirements for being a candidate for once-daily antiretroviral monotherapy – a challenging proof-of-concept in HIV medicine. It has demonstrated non-inferior efficacy at 48 weeks against triple therapy in selected pretreated patients with suppressed plasma viremia, without evolution of protease resistance being seen up to 144 weeks. The present article summarizes the clinical implications of the key data on efficacy of darunavir.

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Key words

Darunavir. Antiretroviral treatment. Treatment-naive. HIV-1 treatment-experienced. Virologic failure.

Introduction

Since their introduction in 1995, protease inhibitors (PI) have become a cornerstone in antiretroviral therapy (ART), making history as the initial drivers in the decline in morbidity and mortality associated with HIV-1 infection[1]. Protease inhibitors work by blocking the ability of HIV-1 protease to convert the viral polypeptides *gag* and *gag-pol* into structural and enzymatic proteins during the final stages of viral particle maturation[1].

Crystal structures and molecular modeling were used to rationalize the broad spectrum profile resulting from the extension into the P2' pocket of the HIV-1 protease, and specifically identified compounds with exceptional broad spectrum activity against a panel of highly cross-resistant HIV-1 mutants, as well as having improved pharmacokinetic properties[2]. The X-ray and thermodynamic studies on both wild-type and mutant enzymes showed an extremely high enthalpy driven affinity of darunavir (DRV, previously known as TMC114, a fused heteroaromatic sulfonamide) for HIV-1 protease. *In vitro* selection of mutants resistant to DRV starting from wild-type virus proved to be extremely difficult; this was not the case for other PI[3-5]. The mechanistic

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explanation was evaluated on wild-type protease, demonstrating that the binding affinity of DRV was more than 100-fold higher compared to other PI, due to a very slow dissociation half-life (> 240 hours), much higher than for the other PI, including DRV's structural analogue amprenavir[1]. During the five years since approval by the FDA in June 2006 (February 2007 in Europe by the EMA), an overwhelming amount of data have confirmed that DRV coadministered with ritonavir (DRV/r) is a very effective PI with a high *in vitro* and *in vivo* potency against wild-type and multidrug-resistant HIV-1, and with a very high genetic barrier to the development of resistance.

POWER study, where everything started

Darunavir was first tested in very advanced patients with multidrug failure and triple-drug resistance and received its first accelerated approval with the phase IIb studies POWER 1 and 2[6,7]. These 24-week dose-finding trials compared the efficacy and safety of four doses of DRV plus low-dose ritonavir. Patients had one or more primary PI mutations (54% had ≥ 3, and 53% had ≥ 2 DRV resistance-associated mutations, RAM), had received two or more nucleoside reverse transcriptase inhibitors (NRTI), and had one or more non-nucleoside reverse transcriptase inhibitors (NNRTI) in a failing regimen, and prior enfuvirtide use (19%) was allowed. The list of DRV RAM included V11I, V32I, L33F, I47V, I50V, I54L, I54M, G73S, L76V, I84V, or L89V, and, unlike tipranavir, has remained unchanged so far, except for the substitution of G73S by T74P[8-10]. Of importance, the median fold change to lopinavir/ritonavir (LPV/r) at baseline was 83.9, thus indicating the high degree of exposure and resistance to PI at baseline[11]. Their median CD4 count was 153 cells/µl. All subjects received optimized background therapy plus DRV/r 400/100 mg once daily (QD), 800/100 mg QD, 400/100 mg twice daily (BID), or 600/100 mg BID, or a comparator PI. More DRV/r (45-77%) than comparator PI patients (14-25%) reached the primary endpoint of viral load reduction ≥ 1.0 $\log_{10}$ copies/ml at 24 weeks ($p < 0.001$). In addition, 18-53% of DRV/r patients (depending on the dose of DRV/r) and 7-18% of the comparator PI arm achieved viral load < 50 copies/ml ($p < 0.001$), and DRV/r demonstrated a greater CD4 cell increase (68-124 vs. 20 cells/ml; $p < 0.05$). The adverse event incidence with DRV/r was similar to the comparator PI, with lower incidences of diarrhea. Therefore, DRV/r was established as the default PI in salvage regimens, and 600/100 mg twice daily was chosen as the optimal dose in this scenario. At 48 weeks, 61% of patients initially assigned to DRV/r 600/100 mg BID (n = 131) versus 15% of controls had viral load reductions ≥ 1 $\log_{10}$ copies/ml ($p < 0.0001$), and the proportion of patients with viral load < 50 copies/ml (intent-to-treat time to loss of virologic response, ITT-TLOVR) was 45 vs. 10%, respectively (difference 37%; 95% CI: 25-46; $p < 0.0001$). In a subgroup analysis, the significant superiority of DRV/r was maintained independent of the activity of the NRTI, number of DRV-associated or primary PI RAM, baseline viral load, or use of enfuvirtide[11,12].

In an FDA requested study, the DRV/r 600/100 mg BID dose was further explored in 327 treatment-experienced subjects with virologic failure (VF) and baseline characteristics comparable to the POWER 1 and 2 studies without any control arm (POWER 3)[13]. Results confirmed what had been previously seen, and 65 and 40% achieved HIV-1 RNA reductions of ≥ 1 $\log_{10}$ and < 50 copies/ml, respectively, at week 24, with similar CD4 cell increases. Long-term (96-week) efficacy and safety data of the pooled POWER 1, 2, and 3 studies (including 467 individuals treated with DRV/r 600/100 mg BID) showed a high durability of the virologic suppression achieved in this advanced scenario, with 39% (vs. 9% in the comparator arm) maintaining < 50 copies/ml, an unthinkable rate at that time[14]. Subsequently DRV/r was explored also in the pivotal randomized studies of etravirine (DUET 1 and 2), undertaken later on in treatment-experienced adults with HIV-1 resistant strains. The control arm of the DUET studies was composed of DRV/r plus an optimized background regimen, reporting fully concordant efficacy rates (40% with viral load < 50 copies/ml at 48 weeks)[14]. Moreover, another trial (GRACE) evaluated sex-based differences in efficacy and adverse events over 48 weeks in treatment-experienced patients who initiated a DRV/r-based salvage therapy, and no sex-based statistical differences in virologic response or clinically relevant differences in adverse events were observed specifically in women[15]. Subsequently, the availability of new antiretrovirals not available during the conduct of the POWER studies has allowed increased rates of response in patients with multidrug-resistant virus who have few remaining treatment options. An ART regimen containing raltegravir, etravirine, and DRV/r has demonstrated rates of virologic suppression < 50 copies/ml (86% at 48 weeks) comparable to that of treatment-naive patients, currently a standard-of-care as long as individuals can construct a suppressive regimen with three active drugs[12,16-18]. Therefore, the goal of suppression of

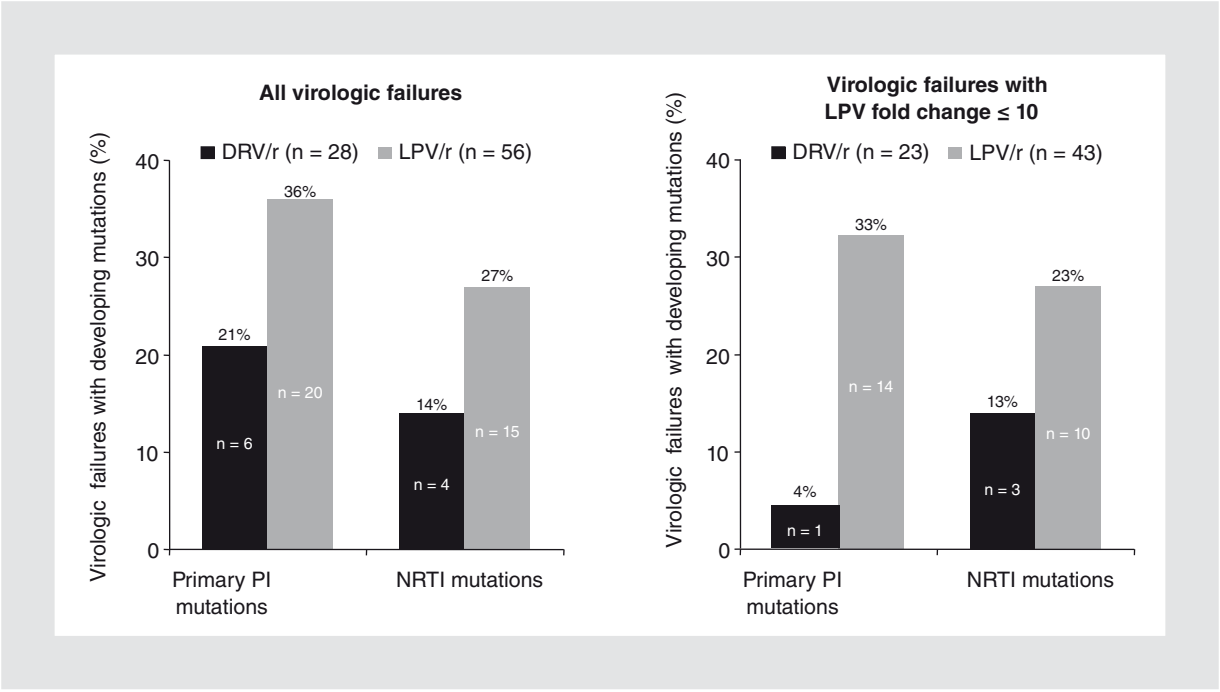


Figure 1. *Development of primary protease and nucleoside reverse transcriptase inhibitor resistance-associated mutations upon treatment failure (viral load ≥ 400 copies/ml) at 48 weeks in the TITAN trial. The figure shows the data in all virologic failures (left), and in the subset of subjects with complete lopinavir activity (fold change ≤ 10 in EC_{50}, right).*

plasma HIV-1 RNA below 50 copies/ml is now also feasible in advanced patients with multidrug-resistant HIV-1, particularly if the activity of DRV/r is preserved[12,17].

Defining superiority in earlier stages of virologic failure

Once established as the default PI/r in advanced failures with multidrug resistance, DRV/r was evaluated in earlier stages of VF. The TITAN study compared DRV/r 600/100 mg BID versus LPV/r 400/100 mg BID in 595 treatment-experienced patients who were naive to LPV/r. All subjects received optimized background therapy with at least two or three antiretrovirals from approved NRTI and/or NNRTI classes, and enfuvirtide was disallowed. This earlier scenario included 31% subjects naive to PI, 38% having received only one PI, 82% susceptible to four or more PI, 68% had ≥ 2 sensitive antiretrovirals in the background regimen, and the median CD4 count was 232 cells/ml[19]. Only 2 and 10% of the individuals had a fold change > 10 to DRV or LPV, respectively, in their arms. At week 48, significantly more DRV/r than LPV/r patients had HIV RNA < 50 copies/ml (71 vs. 60%, difference 11%; 95% CI: 3-19; p = 0.005), meeting the criterion for superiority of DRV/r – predefined Δ of -12% (results also seen in the 400 copies/ml analysis, the primary endpoint). There were no differences in the CD4 cell count increase. The rates of VF were lower in the DRV/r arm (10 vs. 22%) and fewer patients with VF with DRV/r (versus the LPV/r group) developed additional RAM: 21% (6/28) versus 36% (20/56) primary PI RAM, and 14% (4/28) versus 27% (15/56) NRTI RAM. These differences were also seen in a subanalysis that included only subjects who retained full LPV activity at baseline (defined as LPV fold change ≤ 10; Fig. 1). Therefore, DRV/r was not only associated with lower VF and limited resistance selection rates, but also with a better protection of the NRTI in the background regimen. Of interest, after treatment failure, 14% (4/28) in the DRV/r group compared with 32% (17/54) in the LPV/r group were susceptible to fewer NRTI than at baseline, and 11% (3/28) compared with 26% (14/54) had lost susceptibility to NRTI that were used in the background regimen[19]. In a subgroup analysis, DRV/r proved superiority against LPV/r in patients with a LPV fold change > 10 or with ≥ 1 IAS-USA primary PI RAM (a useful parameter in the clinic), even in cases where resistance testing indicates that both DRV and LPV are fully and equally susceptible and would be expected to provide similar clinical outcomes[20,21]. At 96 weeks, 60.4% of subjects treated with DRV/r maintained a plasma HIV-1 RNA < 50 copies/ml[22].

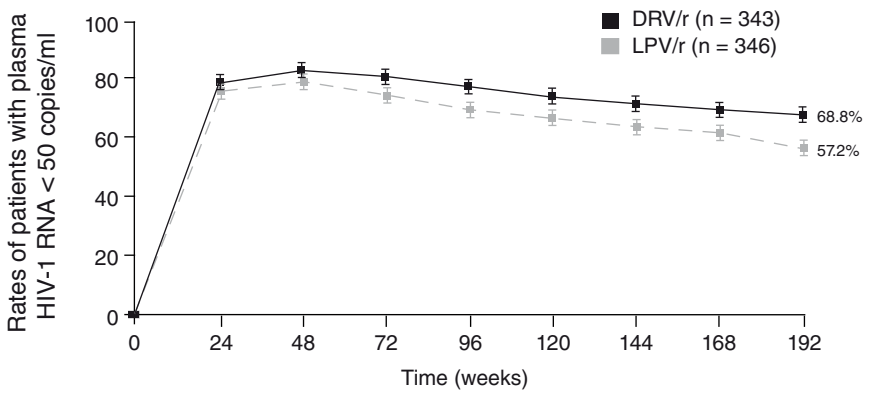
These data support the use of DRV/r as a preferred PI/r also in the scenario of early salvage therapy.

Expanding darunavir/ritonavir for treatment-naive HIV-infected patients: the ARTEMIS study

In the same breath of being established as the default PI/r in early and late salvage therapies, DRV/r was further explored in treatment-naive individuals. For the first time in HIV medicine, a different dose of an antiretroviral was explored and registered for these untreated subjects without HIV-1 resistance, not requiring so high inhibitory quotients of DRV. The ARTEMIS open-label trial compared the efficacy and safety of once-daily DRV/r (800/100 mg QD) with that of LPV/r (800/200 mg total daily dose, either BID [77%] or QD) plus fixed-dose tenofovir/emtricitabine in 689 treatment naives[23]. The median CD4 cell count was 225 cells/µl and randomization was stratified by plasma HIV-1 RNA (< 100 000, ≥ 100 000 copies/ml) and CD4 cell count (< 200, ≥ 200 cells/ml). At 48 weeks, 84% of DRV/r and 78% of LPV/r individuals achieved HIV-1 RNA < 50 copies/ml (estimated difference 5.6; 95% CI: –0.1-11), demonstrating non-inferiority of DRV/r as compared with LPV/r (p < 0.001; TLOVR). Darunavir/ritonavir had superior efficacy rates in patients with higher risk for VF, including those with higher viral loads (> 100,000 copies/ml, 79 vs. 67%, p < 0.05 at 48 weeks) and those with lower CD4 cell counts (< 200 cells/µl, 79 vs. 65%, p = 0.009 at 96 weeks), both at 48, 96, and 192 weeks[24,25]. These results are of paramount clinical relevance as all subjects were stratified by viral load and CD4 count at randomization. There were no differences in CD4 cell count increases. Darunavir/ritonavir had a lower incidence of possibly treatment-related grade 2-4 gastrointestinal adverse events (7 vs. 14%; p < 0.01) and treatment-related moderate-to-severe diarrhea (4 vs. 10%) than LPV/r, and adverse events leading to discontinuation (3 vs. 7%; p < 0.05). These significant differences in tolerability were maintained thereafter up to 192 weeks[24,25]. Additional sensitivity analyses including all the randomized subjects were incredibly robust. Considering that there were more discontinuations due to adverse events in the LPV/r arm, a subanalysis at 96 weeks that excluded patients who discontinued treatment for reasons other than VF (mainly toxicities or patients lost to follow-up) assessed the pure virologic response in 573 patients. The efficacy rate remained significantly higher in the DRV/r arm compared with LPV/r analysis of pure virologic efficacy (92.8 vs. 87.2%, respectively; p = 0.024; TLOVR non-VF censored population)[26]. Therefore, the significant difference in virologic response in favor of DRV/r could not be explained solely by tolerability differences between the two treatment groups. From 96 weeks on, there was a steady increase in the difference in efficacy between arms, with DRV/r being superior to LPV/r in all the follow-up period (Fig. 2)[25,26]. At 96 weeks, the VF rate was lower in DRV/r (12%, n = 40) versus LPV/r patients (17%, n = 59)[26]. No patient developed an IAS-USA PI RAM with either DRV/r or LPV/r, confirming the extremely high genetic barrier to resistance of PI/r in naives, and almost all developing minor PI RAM were polymorphic[12,26,27]. Part of the high genetic barrier to resistance of DRV/r lies in its pharmacokinetic properties. With a terminal half-life of 15 hours, the C_{trough} at 24 hours (median 2,041 ng/ml) still exceeded in 37-fold above the *in vitro* protein-binding corrected median effective concentration required to induce 50% response (EC_{50}) of 55 ng/ml (wild-type HIV-1), and all 335 patients checked in the ARTEMIS trial had C_{trough} levels above the EC_{50}[28]. Darunavir/ritonavir QD plus tenofovir/emtricitabine has been a preferred antiretroviral regimen (evidence AI) in initial therapy in all guidelines since the presentation of these data (Table 1)[29-32]. Furthermore, with the availability of the new 800 mg formulation of DRV, the daily pill number of the DRV/r QD plus tenofovir/emtricitabine regimen will be further reduced to three pills once daily. A new co-formulation including DRV 800 mg and a new pharmacoenhancer (Cobicistat, 150 mg) is in late-stage development.

Setting the limits of the darunavir/ritonavir once-daily dose

A sensitivity analysis of the dose-finding phase IIb studies POWER 1 and 2 in heavily treatment-experienced patients identified that the subgroup of patients with no baseline DRV RAM achieved similar virologic suppression rates (HIV-1 RNA < 50 copies/ml, ITT-TLOVR) with DRV/r 800/100 mg QD and DRV/r 600/100 mg BID (66.7% [14/21] and 62.1% [18/29], respectively)[33]. With that background, the ODIN study compared both DRV/r doses in very early salvage (earlier than in the TITAN study, Fig. 3), defined as treatment-experienced patients with no DRV RAM at screening[8,34]. All 590 subjects received an optimized background regimen with ≥ 2 NRTI. The median CD4 cell count was 228 cells/µl, 46% of the subjects had never received a PI (were failing in their first NNRTI regimen), their median number of primary PI drug-resistant mutations (DRM)



Time	48 weeks	96 weeks	192 weeks
Efficacy of DRV/r vs. LPV/r (ITT-TLOVR)	84 vs. 78%	79 vs. 71%	68.8 vs. 57.2%
Treatment difference, DRV/r vs. LPV/r (95%CI)	5.6 % (–0.1-11)	8.4% (1.9-14.8)	11.6% (4.4-18.8)

Figure 2. *Confirmed virologic response of HIV-1 RNA < 50 copies/ml in the predefined intent-to-treat time to loss of virologic response during the follow-up of the ARTEMIS study.*

Table 1.

Third drug	GESIDA	EACS	DHHS	IAS-USA	BHIVA
NNRTI	*TDF/FTC/EFV	TDF/FTC + EFV	TDF/FTC/EFV	TDF/FTC/EFV	TDF/FTC/EFV
	ABC/3TC + EFV	TDF/FTC + RPV			
	TDF/FTC/RPV	ABC/3TC + EFV		ABC/3TC/EFV	
	TDF/FTC + NVP	ABC/3TC + RPV			
		TDF/FTC + NVP			
PI	*TDF/FTC + ATV/r	TDF/FTC + ATV/r	TDF/FTC + ATV/r	ABC/3TC + DRV/r	TDF/FTC + ATV/r
	*TDF/FTC + DRV/r	TDF/FTC + DRV/r		TDF/FTC + ATV/r	
	TDF/FTC + LPV/r	TDF/FTC + LPV/r	TDF/FTC + DRV/r		TDF/FTC + DRV/r
	ABC/3TC + ATV/r	ABC/3TC + ATV/r		ABC/3TC + ATV/r	
	ABC/3TC + LPV/r	ABC/3TC + DRV/r			
		ABC/3TC + LPV/r			
INI	*TDF/FTC + RAL	TDF/FTC + RAL	TDF/FTC + RAL	TDF/FTC + RAL	TDF/FTC + RAL
	ABC/3TC + RAL				

GESIDA: Grupo de Estudio de SIDA; EACS: European AIDS Clinical Society; DHHS: US Department of Health and Human Services; IAS: International AIDS Society; BHIVA: British HIV Association; NNRTI: nonnucleoside reverse transcriptase inhibitor; PI: protease inhibitor; INI: integrase inhibitor; TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; RPV: rilpivirine; ABC: abacavir; 3TC: lamivudine; NVP: nevirapine; ATV: atazanavir; r: ritonavir; LPV: lopinavir; DRV: darunavir; RAL: raltegravir.

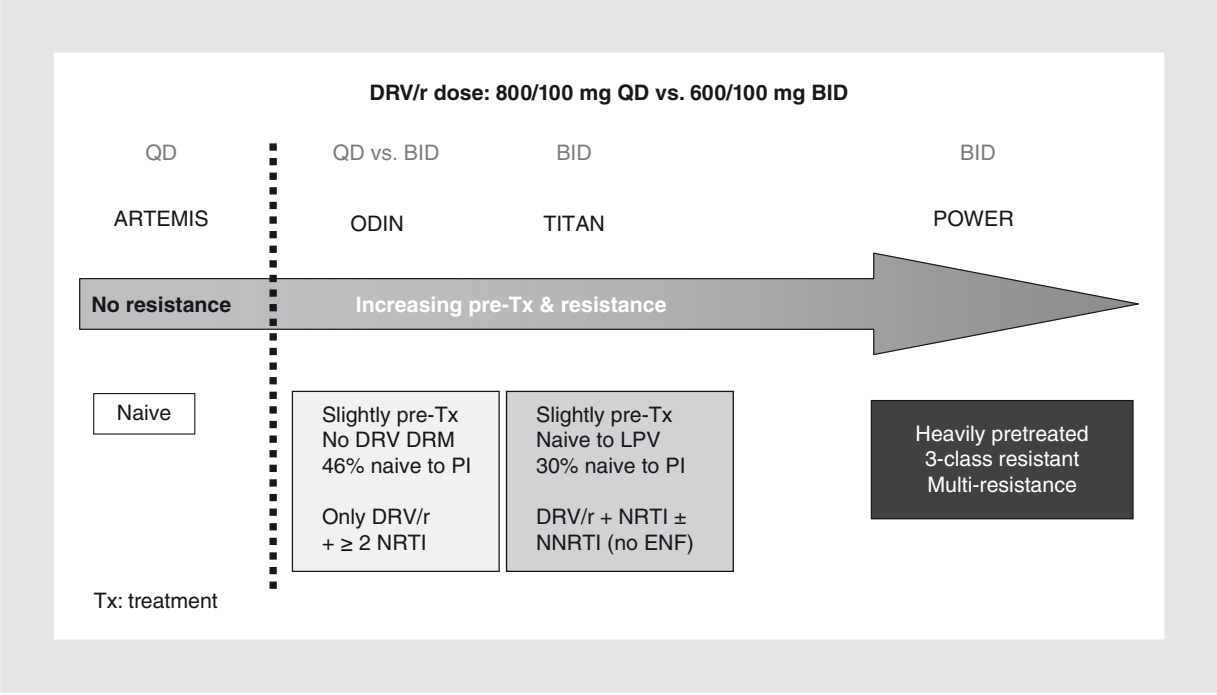


Figure 3. *Flow course of treatment with darunavir/ritonavir along the course of HIV-1 infection, with increasing rates of HIV-1 resistance. One drug, with two doses (800/100 mg once daily or 600/100 mg twice daily), is used throughout the entire course of HIV disease.*

was 0, with only 16% of them harboring ≥ 1 PI DRM, and 68-75% of them received a background regimen with ≥ 2 active NRTI[34]. At 48 weeks, 72.1% of the once-daily and 70.9% of the twice-daily patients achieved HIV-1 RNA < 50 copies/ml (ITT/TLOVR, treatment difference 1.2%; 95% CI: -6.1-8.5), therefore establishing non-inferiority of QD versus BID DRV/r. Both arms showed the same efficacy in subjects with high baseline viral load, defined as > 50,000 copies/ml, and had similar CD4 cell increases as well. Of those with paired baseline/endpoint genotypes, PI RAM developed in seven (11.7%) QD patients and four (9.5%) BID patients. Only one patient (out of 294) in the once-daily arm developed primary PI DRM, which included the DRV RAM V32I, L76V, and I84V (intermediate DRV resistance). Therefore, the genetic barrier of DRV in naives is maintained in earlier stages of VF. A subanalysis demonstrated that DRV/r QD would be non-inferior to BID in subjects who had not used previously PI, with no primary PI DRM at baseline, or who received a regimen with ≥ 2 active drugs (Fig. 4)[34]. In the remaining categories, particularly those subjects with at least one primary PI DRM at baseline, there was more uncertainty since the number of patients was too low. Once-daily DRV/r reported safety benefits, with a lower incidence of grade 2-4 triglyceride increases (5.2 vs. 11.0%; $p < 0.05$).

Meeting the requirements for monotherapy: a proof-of-concept

Darunavir/ritonavir meets the highest requirements for monotherapy as a switch strategy in treated patients with suppressed viremia, a path pioneered by LPV/r[35,36]. It has a high genetic barrier to resistance and favorable pharmacokinetics for once-daily dosing, albeit it needs ritonavir boosting with the potential impact on drug interactions and the lipid profile. Among the advantages, it may preserve future treatment options with other drug classes, avoid unnecessary exposure to drugs with potential for long-term toxicity, and it can lower the lifelong costs of ART[37,38]. MONET was an open-label trial that compared the switch to DRV/r 800/100 mg QD, either as monotherapy or with two NRTI, in 256 patients with HIV RNA < 50 copies/ml for 24 weeks on standard triple therapy without DRV, with either a NNRTI-based (43%), or a PI-based (57%) regimen[39]. In the primary per protocol switch equals failure analysis, 86.2% had HIV RNA < 50 copies/ml at week 48 in the monotherapy arm versus 87.8% in the triple-therapy arm (treatment difference –1.6%; 95% CI: –10.1-6.8; predefined Δ for non-inferiority –12%). At 96 weeks the rates (per protocol, TLOVR, switch equals failure) were 78 vs. 82%, respectively (difference –4.2%; 95% CI: –14.3-5.8), therefore not

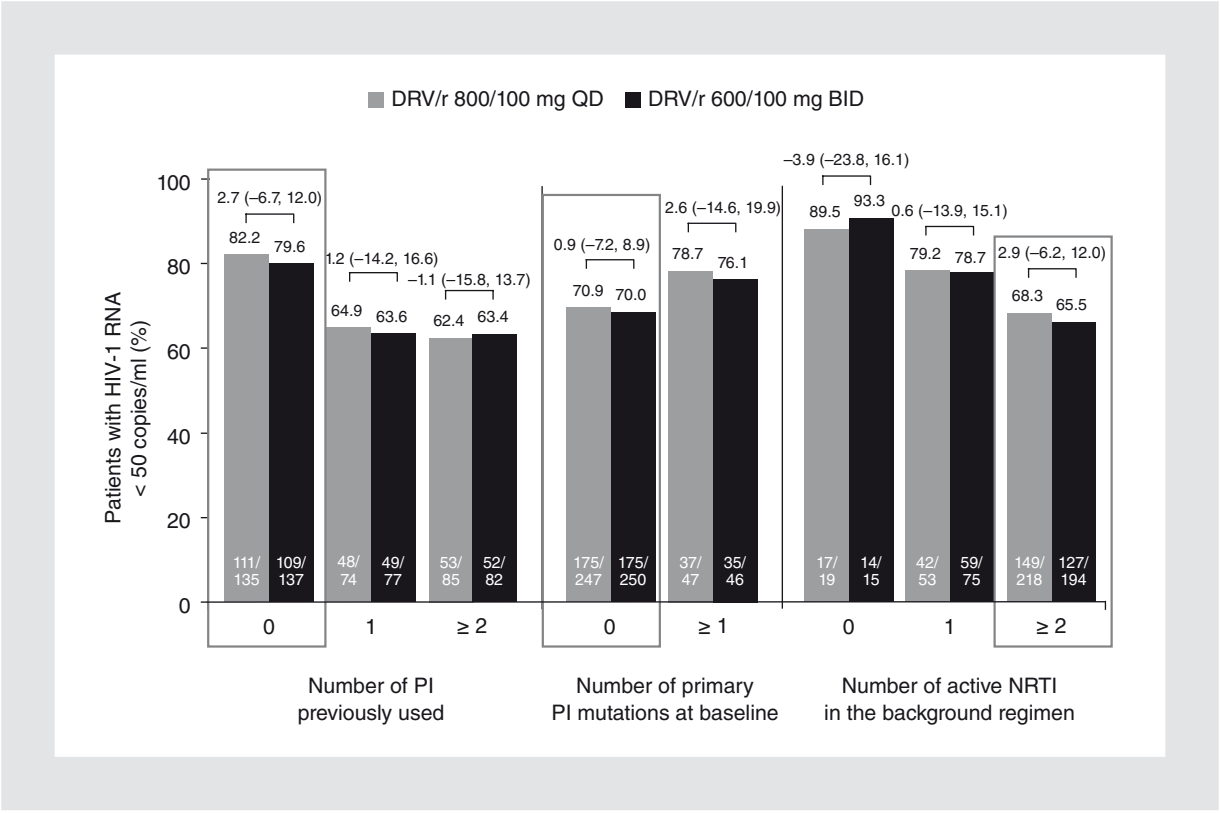


Figure 4. *Sensitivity analysis of the ODIN study comparing the virologic response rates of darunavir/ritonavir once daily vs. twice daily in very early salvage therapy by baseline surrogates of failure risk (difference in percentage of response [95% CI]). Darunavir/ritonavir once daily would be non-inferior to twice daily in subjects who had not previously used protease inhibitors, with no primary protease inhibitor drug-resistant mutations at baseline, or who received a regimen with ≥ 2 active drugs (highlighted with frames). The high number of subjects in these subgroups gives a high certainty to the analysis.*

meeting the non-inferiority of DRV/r monotherapy in the long term[40]. Similar results were seen at 144 weeks: 69 vs. 75%, respectively (difference: –5.9%; 95% CI: –16.9-5.1)[41]. A total of 63 patients had ≥ 1 HIV RNA ≥ 50 copies/ml (39 [30.7%] vs. 31 [24%], respectively). Most HIV RNA increases were transient and in the range of 50-200 copies/ml[42]. One patient per arm showed at least one PI mutation (L33F in the monotherapy arm [fold change to DRV 0.8], V82I/T and L90M in the triple arm; none developed DRV resistance). Both patients were re-suppressed to week 48, remaining within the same treatment. One patient in the triple therapy arm showed an NRTI mutation (M184V). No evidence for evolution of PI resistance has been seen up to 144 weeks, although the *Gag* cleavage site has not been assessed[43,44].

Nine patients per arm discontinued randomized treatment for either adverse events or other reasons (all patients in the study were new to DRV). The HIV-1 DNA levels remained stable in both arms at 144 weeks, and there were no differences in IL-6 or hs-CRP[45]. Therefore, there have been no data so far to suggest that the degree of HIV-1 suppression was lower in the monotherapy arm. Patients without hepatitis C virus coinfection (based on serology), and with baseline HIV RNA < 5 copies/ml (estimated by optical density by the Roche Amplicor assay, i.e. no virus detected) were most likely to show sustained HIV RNA suppression < 50 copies/ml on DRV/r monotherapy[46].

The absence of any resistance selection at failures (no "cost" seen at failure) suggested a different ITT switch-included analysis, not considering as failures those who reintroduced the NRTI and were re-suppressed after NRTI reintroduction. With this approach, monotherapy should fulfill the non-inferiority at both 96 and 144 weeks[40,41].

The MONOI-ANRS136 study assessed DRV/r monotherapy in 225 subjects using the 600/100 mg BID dose[47]. In the ITT analysis, the proportion of response to therapy was 87.5% with DRV/r monotherapy and 92% with DRV/r triple therapy (difference 4.5%; 90% CI: –11.2-2.1), excluding non-inferiority (predefined Δ –10%).

Three patients experienced VF on monotherapy and none on DRV/r triple drug. None had emergence of new DRV RAM. Factors associated with VF with DRV/r monotherapy were having an initial blip, shorter time of previous antiretroviral treatment, and an adherence < 100%[48]. Clonal analysis of the protease and Gag region found minority variants with DRV RAM at positions 32, 47, and 50 in one of the nine patients with VF[49]. At week 48, patients with viral load < 50 copies/ml were switched to DRV/r 800/100 mg QD until week 96. Throughout the 96-week follow-up, 66/112 (59%) and 79/113 (70%) patients consistently had plasma HIV-1 RNA < 50 copies/ml, respectively (p = 0.10)[50]. Despite a higher proportion of intermittent viremia in the monotherapy arm, a similar evolution of cellular HIV-1 DNA levels was observed in both arms at 96 weeks, suggesting a similar impact on the replenishment of the HIV-1 reservoirs[51].

The DRV/r monotherapy strategy has failed to show a benefit for the patient in terms of toxicity[39-41,47,50]. No significant differences were seen between arms, while rates of treatment-emergent grade 3 elevations in total cholesterol, alanine aminotransferase and/or aspartate aminotransferase, or discontinuation of study medication for adverse events were numerically higher in the monotherapy arm[39]. An improvement in vitamin D deficiency has been demonstrated in those who stopped efavirenz or zidovudine at the screening visit and switched to DRV/r, with or without two NRTI (not a benefit of monotherapy)[52]. Finally, body fat has also been assessed. A recent meta-analysis including six randomized trials of LPV/r or DRV/r monotherapy showed only significant improvements in lipoatrophy in those patients who were stopping zidovudine[53].

The body fat tissue was also assessed in a subgroup of subjects in the MONOI-ANRS136 study that included some subjects receiving thymidine analogues[54]. Body fat increased in patients on DRV/r monotherapy and triple therapy, with no difference between the arms over 96 weeks. The only difference found was a delayed increase in limb fat tissue in the triple-therapy arm in the first year. Therefore, those patients receiving PI/r monotherapy who had not stopped thymidine analogues (i.e. the Kreta study) showed no improvement in lipoatrophy[53,55]. Improvements of lipoatrophy in subjects stopping tenofovir or abacavir when starting PI/r monotherapy have not been shown so far.

There are still conflicting views about the ability of PI/r to protect the central nervous system (CNS) from HIV replication, one of the major reasons precluding the widespread use of this therapeutic strategy[56]. Both LPV and DRV achieve central system fluid (CSF) drug levels sufficient to fully suppress HIV replication. However, their CNS penetration-effectiveness score (a theoretical score) is substantially lower for PI/r monotherapy than for triple-drug therapy. No differences were observed in neuropsychiatric adverse events over 48 weeks in the MONET study[57]. Patients receiving PI/r monotherapy with either LPV/r or DRV/r who maintain full virologic suppression in plasma do not appear to be at a higher risk of discordant HIV replication in the CSF or of neuropsychiatric adverse events in clinical trials. However, two patients in the MONOI monotherapy arm developed neurological symptoms and their CSF investigation showed no abnormality, neither in cell number nor in protein level, but their CSF viral load was 330 and 580 copies/ml, respectively, contrasting with a suppressed plasma viremia > 50 copies/ml[47]. Anecdotal case reports of severe HIV-1 encephalitis or pachymeningitis in subjects with very low or even suppressed viremia treated with long-term PI/r monotherapy (mainly with LPV/r) have been plausibly reported, suggesting that the CNS could be a sanctuary for HIV replication[58,59]. In addition, a prospective randomized trial assessing the efficacy of HIV-1 suppression in the CNS with LPV/r monotherapy was prematurely stopped when six patients on monotherapy (none in continued triple-arm) demonstrated a VF in blood, five of them with elevated HIV-1 RNA load in CSF, and four with neurological symptoms[60]. The viral load was fully re-suppressed in all failing patients after resumption of the original combination therapy. All failures occurred in subjects with a nadir CD4 cell count < 200/µl[61].

Two trials (PIVOT [NCT01230580] and PROTEA [NCT01448707]) specifically evaluating the impact of DRV/r monotherapy in CNS are ongoing and hopefully will give light to this worrying issue.

Darunavir/ritonavir monotherapy could represent an outstanding strategy for cost saving in ART, currently a debate that has split some European countries down the middle among defenders, detractors, and Health System managers[37].

Darunavir/ritonavir has not received approval for its administration as a monotherapy, and US guidelines consider that this strategy cannot be recommended outside of a clinical trial owing to higher rates of VF than for combination therapy[30,31]. Spanish guidelines only consider monotherapy with LPV/r BID or DRV/r QD (evidence B-I) for patients with signs or symptoms of NRTI-related toxicity[32]. Candidates must also have no previous failure to PI-based treatment, undetectable

plasma viral load for ≥ 6 months, and excellent adherence. Finally, the European EACS guidelines are the only ones that consider that monotherapy might represent an option also for treatment simplification in patients without intolerance to NRTI[29].

Conclusions

A high enthalpy driven affinity of DRV for HIV-1 protease, a limited cross-resistance with prior PI failure, favorable pharmacokinetic properties, and a high potency have led to superior efficacy of DRV against other existing PI in early and advanced salvage regimens. Darunavir exhibits an extremely high genetic barrier to resistance in both treatment-naives or patients with early failure and limited antiretroviral exposure without DRV resistance mutations, preventing resistance development in VFs. With two different registered doses, it can offer optimal efficacy/tolerability ratios in early or advanced scenarios. Administered as a once-daily monotherapy in selected patients, it maintains its high genetic barrier to resistance as well, has demonstrated non-inferior efficacy against standard triple therapy at 48 weeks, and has no apparent cost at VF in clinical trials, as long as NRTI are reintroduced early.

Potential conflicts of interest

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