Contents available at **PubMed**
**www.aidsreviews.com**

PERMANYER

**AIDS** Rev. 2017;19:105-112

# Darunavir Stands Up as Preferred HIV Protease Inhibitor

*Josep Mallolas*

*HIV/AIDS Unit, Infectious Disease Service, Hospital Clínic, University of Barcelona, Barcelona, Spain*

## Abstract

***Current antiretroviral therapy reaches and maintains viral suppression over the years in more than 90% of treated HIV-infected individuals. Although integrase inhibitors are the preferred third agent in antiretroviral therapy in the current guidelines, rilpivirine, a non-nucleoside reverse transcriptase inhibitor, and darunavir (DRV), a second-generation protease inhibitor, are the preferred third companion to be used along with a backbone of two nucleos(t)ide reverse transcriptase inhibitors as first-line triple HIV combination treatment. However, rilpivirine is not recommended in patients with plasma HIV-RNA above 100,000 copies/mL. Raltegravir requires uncomfortably twice daily dosing, whereas dolutegravir is often given as coformulation with abacavir, a drug that requires prior HLA-B5701 testing. Antiretroviral combinations based on DRV provide a unique robustness in terms of antiviral potency and resistance barrier, rendering this drug pivotal as part of rescue regimens for the treatment failures. Furthermore, dual antiretroviral therapy with DRV plus lamivudine has been tested with success as maintenance therapy. Finally, DRV has demonstrated its safety and efficacy in special patient populations, including pregnant women, pediatrics, HIV-2 infection, and individuals coinfected with viral hepatitis. Single-tablet regimens containing DRV coformulated with cobicistat alone or with other antiretrovirals should improve drug adherence. These fixed-dose combinations represent a step forward universal antiretroviral regimen, ensuring maximal efficacy, tolerability, and convenience.*** **(AIDS Rev. 2017;19:105-112)**

*Corresponding author: Josep Mallolas, mallolas@clinic.ub.es*

## Key words

***Darunavir. Drug resistance. Cobicistat. Coformulations. Dual therapy. Universal antiretroviral regimens.***

## Introduction

The first big change in antiretroviral therapy was made in the middle 90s when the first generation of protease inhibitors (namely, ritonavir, indinavir, and saquinavir) was licensed. Taken as triple combinations, these drugs improved survival dramatically even in patients with very advanced HIV/AIDS disease[1]. However, the drawbacks of those first therapies included a wide range of adverse events and large pill burden that coupled led to poor drug adherence and ultimately frequent virological failure[2].

The second generation of protease inhibitors appeared more than a decade later. Molecules such as atazanavir (ATV) and darunavir (DRV) had to be boosted with ritonavir to enhance their pharmacokinetic exposure and allow once-daily administration. The robust antiviral potency of these agents compared to antiretrovirals from other drug families positioned them as preferred choice for rescue interventions. In particular, DRV provided special advantages over other protease inhibitors in terms of antiviral potency, barrier to resistance, pill burden, and tolerability[3,4].

**Correspondence to:**
Josep Mallolas
HIV/AIDS Unit, Infectious Disease Service
Hospital Clínic, University of Barcelona, Barcelona, Spain
E-mail: mallolas@clinic.ub.es

The widespread use of antiretroviral regimens across larger HIV patient populations, including asymptomatic infected persons, provided the opportunity for easier recognition of long-term toxicities across distinct groups. Metabolic abnormalities, including insulin resistance and dyslipidemia, became a major subject using protease inhibitors[1,5]. Given that lopinavir (LPV) required a daily dosing of 200 mg of ritonavir (instead of 100 mg for DRV or ATV), it was particularly punished. To LPV, dismissal further contributed its poor gastrointestinal tolerance, namely, diarrhea[5].

Clinical development of DRV has been made with robust trials that have demonstrated the good performance of the drug in different scenarios, including treatment-naïve[6] and experienced populations, pregnant women[7], pediatric patients[8], HIV-2[9,10], coinfection with viral hepatitis including cirrhosis[11,12], and elderly people (Table 1)[13]. A dose of 800 mg boosted with ritonavir 100 mg (DRV/r) once daily was approved for drug-naïve HIV individuals, whereas DRV 600/100 twice daily was recommended for antiretroviral-experienced patients with DRV resistance-associated mutations[14].

In recent years, integrase inhibitors and new coformulations allowing treatment regimens with one pill once daily have been taking over the antiretroviral prescription market[15]. Nevertheless, protease inhibitors exhibit unique features that make them the most attractive for special groups, such as patients with poor drug adherence due to difficult social conditions (active drug use, neuropsychiatric illness, homeless, etc.) or individuals experiencing virological failure and with extensive drug resistance[1,14].

The advent of cobicistat, a new pharmacokinetic enhancer of DRV, represents a more favorable alternative option to ritonavir, with cleaner effects lacking residual antiretroviral activity and with less broader enzymatic inhibition of cytochromes and drug transporters[15]. A coformulation of DRV plus cobicistat is currently marketed.

## DRV for antiretroviral failures

The second generation of protease inhibitors, of which DRV is the prototype, exhibits improved tolerance, antiviral potency, and barrier to resistance. Given these unique features, the drug has been positioned as the preferred agent for rescue interventions. This is an important decision given that HIV cannot be cured (eradicated)[16] and the likelihood of changing any first-line regimen increases over time in HIV-infected persons[17,18].

DRV was initially considered for patients with a prior antiretroviral experience that had selected viruses with drug resistance mutations. The results of the POWER and TITAN studies confirmed the good performance of DRV in this setting. The Phase IIb trials POWER 1 and 2 were designed to evaluate the optimum dosage, long-term efficacy, safety, and tolerability (144 weeks) of DRV in

**Table 1. Good acceptability of DRV in special patient populations**

| Patient population | Comments | References |
|---|---|---|
| Antiretroviral naive | ARTEMIS trial (vs. LPV/r) | 23-25 |
| Antiretroviral failures | Dosing increased to DRV/r 600/100 BID or DRV/c 600/150 in the presence of DRV resistance-associated mutations | 19-21 |
| Switch therapy (maintenance) | Efficacious as triple, dual, and even monotherapy | 19, 20, 23-25, 34 |
| Pregnant women | No significant changes in drug exposure | 7 |
| Pediatric | Children ≥ 3-year-old | 8 |
| HIV-2 | Whereas amprenavir and atazanavir does not work well, HIV-2 is susceptible to DRV | 9, 10 |
| Hepatitis coinfection | No changes in DRV exposure in cirrhotics and good hepatic safety | 11, 12 |
| Elderly | No significant changes in DRV exposure | 13 |

DRV: Darunavir; LPV: Lopinavir.

treatment-experienced HIV patients who received one of four doses of DRV coadministered with ritonavir (DRV/r) (400/100 mg once daily, 800/100 mg once daily, 400/100 mg twice daily, or 600/100 mg twice daily) plus an optimized background regimen or an investigator-selected control protease inhibitor[19]. Both trials had two phases, with an initial 24-week dose finding and the second period with a follow-up over 144 weeks. All patients included had ≥ 1 primary resistance mutation and plasma HIV-RNA > 1000 copies/mL. The best results were obtained with the 600/100 mg BID dosing. This was the dose selected for the open-label phase of 144 weeks. Final results at week 24 showed 53% of undetectability in POWER 1 and 39% in POWER 2 compared to 18% and 7% in patients receiving control protease inhibitors, respectively. At week 144, the combined analysis of both POWER studies showed plasma HIV-RNA < 50 copies/mL in 37% of patients on DRV/r versus 9% on other protease inhibitors ($p < 0.001$). The DRV/r group also experienced a greater significant median increase in the CD4 count.

These results were confirmed in POWER 3 trial, another study that tested DVR/r 600/100 mg BID. Of note, DRV/r patients also experienced less adverse events than patients treated with other protease inhibitors[20].

The TITAN study was a Phase III trial performed in near 600 HIV-infected patients, all treatment-experienced but naïve to LPV/r. At week 48, the study demonstrated the non-inferiority of DRV/r and even superiority versus LPV/r. Overall, 77% of patients on DVR/r versus 68% on LPV/r had plasma HIV-RNA < 400 copies/mL[21]. These results were maintained at week 96.

## DRV for naive patients one pill once daily

To improve patient's adherence, interest has become focused on once daily administration of DVR/r. This was supported by the long half-life of boosted DRV (approximately 15 hours)[12], its antiviral activity against wild-type and multidrug-resistant HIV-1 isolates and its low propensity for developing resistance[22]. With these premises, the ARTEMIS trial was performed. It was a Phase III open-label study that assessed the efficacy and safety of QD DRV/r 800/100 mg compared with LPV/r 800/200 mg (total daily dose) in drug-naïve patients[23]. The study included nearly 700 patients and demonstrated the non-inferiority of DVR/r versus LPV/r. At week 48, plasma HIV-RNA < 50 copies/mL was achieved by 84% of DRV/r patients and 78% of LPV/r patients[24], at week 96, these figures were 79% versus 71%, respectively[25], and at week 192, 68.8% versus 57.2%[26]. Superiority of DVR/r versus LPV/r was found at weeks 96 and 192 supporting the sustainability of the virological response.

Elevations in triglycerides were less frequent with DRV/r than LPV/r group (5.9% vs. 16.0%, respectively) as increases in total cholesterol (24.3% vs. 32.7%, respectively). Likewise, gastrointestinal disturbances were more common with LPV/r than DRV/r[25].

Finally, individuals with high baseline plasma HIV-RNA (≥ 100,000 copies/mL) or low CD4 counts (< 200 cells/µl) represent a subset of patients prone to virological failure with many first-line antiretroviral regimens, including abacavir, rilpivirine, and raltegravir. This was not the case with DRV/r in the ARTEMIS study[25]. However in the FLAMINGO study, dolutegravir plus 2 NRTI had superiority vs DRV/r plus 2 NRTI specially among those patients included in the study with more than 100.000 copies/ml[27].

## DRV dual therapy

Following the high success of triple therapy with DRV/r plus to nucleos(t)ide inhibitors in terms of mortality, side effects, and convenience, interest steadily moved on testing whether less drug pressure could be attempted without compromising efficacy. To improve tolerance of combination regimens, reduce costs, and facilitate drug adherence, simplification strategies were investigated. Several approaches were tested, including reductions in dosages, longer intervals between dosing, and removal of some drugs allowing dual therapy or monotherapy[28].

Nucleoside-sparing regimens with dual therapy based on protease inhibitors were attractive since allowed to move off mitochondrial concerns of nucleoside analogs whereas keeping robustness against selection of drug resistance. One of the first studies examined virological outcomes in patients treated with dual therapy comprising DVR/r plus either raltegravir, maraviroc, or etravirine. Virological failure was low in patients treated with DVR/r 600/100 mg twice daily[29]. This

was one of the first proof of concept that dual therapy including DVR/r could work in treatment-experienced patients with suppressed viremia.

Another Italian study evaluated the efficacy of patients treated with triple therapy that switched to dual therapy based on either DRV/r, LPV/r, or ATV/r plus a second agent (raltegravir, maraviroc, etravirine, lamivudine, or tenofovir)[28]. Only dual therapy with DVR/r was associated with a lower risk of treatment discontinuation. In the adjusted model, however, only raltegravir taken as the second drug was associated with a lower risk of discontinuation[28].

A regimen combining raltegravir plus DRV/r includes two potent antiretrovirals, each with good tolerability and durable antiviral efficacy. The NEAT 001 study enrolled treatment-naive adults and compared raltegravir plus DRV/r with tenofovir/emtricitabine plus DRV/r, one of the recommended standard triple regimens at that time. The median follow-up was 123 weeks. Treatment failure occurred in 19% of patients treated with the nucleoside-sparing regimen and 15% of patients on the triple arm, demonstrating the non-inferiority of dual therapy[30]. However, in the subset of patients with more advanced HIV disease (high plasma HIV-RNA and low CD4 counts) triple therapy over performed dual therapy.

A dual regimen combining DRV/r plus rilpivirine was tested in the PROBE study[26]. Patients with prior toxicity associated with exposure to nucleoside analogs were enrolled in the study. Switching to DRV/r plus rilpivirine was virologically non-inferior compared to continuing with the same protease inhibitor plus either FTC/TDF or 3TC/ABC[26]. Whereas dual therapy did not affect the lipid profile and renal function, it was more friendly for the bone metabolism than standard triple therapy.

Lamivudine is one - if not the best-tolerated antiretroviral agent and is currently very cheap as generic. The dual regimen of DRV/r plus lamivudine has been examined in patients with suppressed viremia under triple standard combinations. Results so far have been very good, including analysis of patients with hepatitis C coinfection in whom no liver enzyme elevations were noticed[31]. A larger trial the DUAL trial was presented at Glasgow Congress on HIV Therapy this year with the 48 week results. An open-label non-inferiority study that randomised 249 patients with viral suppression on boosted DRV + two NRTIs to either switch to dual therapy with DRV/r plus lamivudine (3TC) or remain on triple therapy. The viral suppression (<50 copies/mL) at week 48 by ITT analysis was 89% vs 93% in the dual vs triple combination groups. This difference was tighter in the observed analysis when censoring discontinuations for non-virologic reasons: 97% vs 98%[32].

## DRV monotherapy

In the path for simplification, several authors have attempted DRV as monotherapy in special settings in an attempt to reduce costs and minimize drug-related toxicities[33].

The MONET and MONOI trials were among the first to evaluate DRV/r as monotherapy. The MONET trial recruited 256 patients with plasma HIV-RNA < 50 copies/mL and no history of virological failure. Patients were randomized to receive DRV/r 800/100 mg once daily either as monotherapy or along with two nucleoside reverse transcriptase inhibitors (triple therapy arm)[34]. The authors concluded that monotherapy was non-inferior to standard triple therapy in that population. Switched patients who experienced viral rebound could be successfully resuppressed by intensification with nucleoside analogs.

The MONOI study was a prospective, randomized, non-inferiority trial that compared DRV/r monotherapy versus DRV/r-based triple therapy in HIV-infected patients with viral load suppression under other regimens[35]. At week 96, the proportion of patients was lower but non-inferior in the monotherapy arm compared to the triple arm, being percentages 94% versus 99%, respectively.

The PIVOT trial compared the effectiveness, toxicity, and cost-effectiveness of boosted protease inhibitor monotherapy with standard triple therapy in a long-term, open-label, randomized, non-inferiority trial[36]. Patients with viral suppression under any triple regimen were randomized to keep on the same therapy or switch to a physician-selected ritonavir-boosted protease inhibitor monotherapy. DRV/r 800/100 mg once daily or LPV/r 400/100 mg twice daily was the most common. Virological rebounds were more frequent in the monotherapy arm although reintroduction of nucleoside analogs allowed to regain undetectability in most cases. The authors concluded that monotherapy with regular viral load monitoring and prompt reintroduction of combination

treatment for rebounds preserved future therapeutic options and did not change overall clinical outcomes or frequency of adverse effects[36]. None of the patients taking DRV or LPV developed drug resistance and fewer patients in the monotherapy group experienced an estimated glomerular filtration rate (eGFR) below 60 ml/minute/1.73 $m^2$ during follow-up.

In contrast with the results of prior studies, in the PROTEA trial[37], DRV/r monotherapy did not show non-inferiority versus triple therapy in the primary analysis at 48 weeks (86% vs. 95%, respectively). However, when reintroduction of nucleoside analogs was considered in the subset of patients on monotherapy experiencing viral rebound, virological outcomes at 96 weeks (89.1% vs. 89.7%, respectively)[38].

The possibility of simplified ART approaches that would use fewer than three drugs required that one of the components should have strong antiviral effect along with high resistance barrier in order to compensate for the lack of drug(s).

Previous studies have shown that PI/r-based regimens may work despite the accompanying drugs not displaying or in patients with poor drug adherence. The protective effect of these agents against drug resistance has resulted in a steadily fall of transmitted HIV drug resistance[39,40].

In summary, due to its unique pharmacodynamics/kinetic features, high resistance barrier, safety profile, good tolerability, potent antiviral effect, and availability as coformulation with other antiretrovirals, DRV stands up as the most attractive protease inhibitor with studies supporting monotherapy to avoid nucleoside toxicities in some circumstances. The higher rate of viral rebounds with this therapeutic option does not imply loss of therapeutic options since adding nucleosides allows to regain undetectability in most cases. The concern on viral rebound episodes, however, has prompted to prefer the dual therapy of boosted DRV plus lamivudine, which has a similar low cost.

## DRV boosted with cobicistat

DRV boosted with ritonavir has been the preferred recommended protease inhibitor in most HIV treatment guidelines, either in drug-naïve or treatment-experienced patients. Ritonavir has intrinsic antiviral activity against HIV, although doses much higher are needed to make recognizable this effect. The use of lower doses only allows recognition of its strong cytochrome P450 3A inhibitory effect. Ritonavir use is commonly associated with gastrointestinal disorders, dyslipidemia, and taste disturbances. DRV/r is administered once a day at doses of 800/100 mg in patients without resistance-associated mutations or twice daily at doses of 600/100 mg in patients with DRV-associated resistance changes. As expected, the use of higher ritonavir doses is associated with more intolerance.

Cobicistat is a structural analog of ritonavir, used as a pharmacokinetic enhancer with null antiviral activity[15]. The molecule strongly inhibits CYP3A and depicts chemical stability and solubility, which facilitates its coformulation as a fixed-dose combination (FDC) with other antiretrovirals. DRV plus cobicistat has been the first protease inhibitor coformulation of cobicistat in a single tablet[41]. Cobicistat has less pronounced effects on adipocytes than ritonavir and less potential for producing lipid metabolic abnormalities[19]. Its plasma half-life is 3.5 hours, with no potential for accumulation over time. Cobicistat binds in high proportion to plasma proteins (97-98%) and most of the drug (86%) is eliminated through the feces and a minimal amount (8%) through the urine. Studies in healthy volunteers have demonstrated the bioequivalence of DRV 800 mg plus cobicistat 150 mg fixed-dose coformulation versus single agents, administered under fasted, and fed conditions[42]. Given that DRV exposure was increased with food, DRV/c should be administered with food. The bioequivalence of DRV/c has also been demonstrated in comparison with DRV/r, with less metabolic effect and risk for drug interactions (Table 2)[43].

A Phase III, single-arm trial evaluated the safety, efficacy, and pharmacokinetics of DRV 800 mg plus cobicistat 150 mg once daily as a single tablet plus two investigator-selected nucleos(t)ide reverse transcriptase inhibitors in 313 HIV-infected adults without resistance mutations and mostly drug-naive. Patients had to have ≥ 1000 HIV-RNA copies/mL, eGFR ≥ 80 ml/min, and susceptibility to the two nucleosides[44]. At week 24, virological suppression was 82% and 81% through week 48, regardless baseline viral load below or above 100,000 copies/mL. Grade 3 or 4 adverse events occurred in 7%, mainly rash, with 5% leading to drug discontinuation. Pharmacokinetics, virologic,

**Table 2. Major studies with DRV**

| Trial | Design | No. patients | Comments | References |
|---|---|---|---|---|
| POWER | DRV/r + 2 nucleoside versus PI/r in failures | 110 | DRV/r BID superior | 19, 20 |
| PIVOT | DRV/r monotherapy in maintenance | 587 | Non-inferiority | 35 |
| TITAN | DRV/r versus LPV/r in failures | 595 | Non-inferiority | 21 |
| ARTEMIS | DRV/r versus LPV/r in naive | 689 | Superior, with adherence being important | 23-25 |
| NEAT-001 | DRV/r + raltegravir versus DRV/r+TDF/FTC | 805 | Non-inferior but in advanced HIV disease | 29 |
| DUAL | DRV/r + 3TC vs DRV/r plus TDF/FTC or ABC/3TC | 249 | Non-inferiority | - |
| PROBE | Dual DRV/r + rilpivirine versus triple standard therapy | 60 | Non-inferiority | 30 |
| MONOI | DRV/r maintenance | 242 | Non-inferiority | 34 |
| MONET | DRV/r monotherapy | 256 | Non-inferiority | 33 |
| PROTEA | DRV/r versus triple | 273 | Lower efficacy versus triple, especially with CD4 counts<200 cells/ul | 36, 37 |
| FLAMINGO | DRV/r vs Dolutegravir (+2nucs) | 484 | Dolutegravir superiority | 26 |
| AMBER | FDC of DRV/c + TAF/FTC | | Ongoing | NCT02431247 |
| EMERALD | FDC of DRV/c + TAF/FTC | | Ongoing | TMC114IFD3013 |

DRV: Darunavir; LPV: Lopinavir; TAF: Tenofovir alafenamide fumarate; FDC: Fixed-dose combination, FTC: Emtricitabine

and immunologic responses for DRV/c were similar to those previously seen with DRV/r 800/100 mg once daily[44].

Cobicistat has a renal excretion through glomerular filtration and secreted by the proximal tubule[45]. The pharmacokinetics of DRV/c was examined in patients with mild-to-moderate renal impairment[45]. A total of 73 patients with eGFR between 50 and 89 mL/min receiving ritonavir-boosted ATV or DRV-based regimens switched ritonavir to cobicistat in Phase III non-comparative open study. At week 48, 82% maintained virologic suppression. No clinically relevant changes in cystatin C were seen through week 96. The renal safety profile of cobicistat in this study was consistent with the long-term data in patients without renal impairment from the phase 3 studies.

Cobicistat inhibits CYP3A with similar potency than ritonavir. Cobicistat is currently available as a single agent (Tybost®). Cobicistat is a more specific CYP3A inhibitor than ritonavir and inhibits the intestinal transporters P-gp and breast cancer resistance protein. Thus, it increases the absorption of ATV, DRV, and tenofovir alafenamide[43]. Cobicistat depicts a limited effect on pregnane X receptor in contrast with ritonavir. Drugs whose exposure might be altered by ritonavir but unaltered by cobicistat are primarily metabolized by CYP-1A2, -2B6, -2C8, -2C9, and -2C19 or drugs undergoing glucoronidation. Cobicistat-boosted regimens are not recommended in the presence of efavirenz, etravirine, or nevirapine, whereas coadministration is feasible when using DRV with ritonavir[43].

## Future prospects for DRV

Several studies are ongoing testing DRV/c in triple therapy. The AMBER trial (NCT02431247) is a Phase III, multicenter, randomized, controlled study that evaluates the efficacy and safety of DRV/c plus emtricitabine/tenofovir alafenamide once-daily FDC versus a DRV/c coadministered with emtricitabine/tenofovir disoproxil fumarate

FDC in treatment-naive patients. The results will be available at the beginning of the year 2018.

The Emerald study (TMC114IFD3013) compares the efficacy, safety, and tolerability of an experimental once-daily single tablet of DRV/c plus FTC/TAF in patients currently suppressed under another boosted protease inhibitor plus FTC/TDF. Participants are randomized to stay on their current regimen or switch to the experimental regimen. The results will be available by the end of 2017.

## Conclusions

In the era of test and treat, where the United Nations AIDS Program and WHO have set the ambitious targets of 90/90/90, new efficacious, well tolerated, and simple therapeutic options are needed. DRV exhibits unique features as HIV-protease inhibitor. After ten years of experience with darunavir, its high barrier to resistance, intrinsic antiviral potency, and good long termtolerability has positioned DRV as one of the cornerstone of current antiretroviral regimens. The advent of cobicistat as pharmacoenhancer, with several advantages over ritonavir, and the opportunity for coformulation with multiple antiretrovirals has opened a new time where convenience (adherence) has become a matter of priority for long-term sustained treatment success. DRV/c has demonstrated good performance in multiple scenarios, as in severe immunosuppressed patients, patients with high-risk of non-adherence or in persons with nucleoside-associated toxicities. This versatility of DRV/c is very much appreciated, contributing to set up in practice the simplicity of universal antiretroviral for everyone and everywhere[45].

## References


1. Fernández-Montero JV, Barreiro P, Soriano V. HIV protease inhibitors: Recent clinical trials and recommendations on use. Expert Opin Pharmacother. 2009;10:1615-29.
2. Staszewski S, Morales-Ramirez J, Tashima K, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. N Engl J Med. 1999;341:1865-73.
3. Rabi SA, Laird GM, Durand CM, et al. Multi-step inhibition explains HIV-1 protease inhibitor pharmacodynamics and resistance. J Clin Invest. 2013;123:3848-60.
4. Llibre JM, Imaz A, Clotet B. From TMC114 to darunavir: Five years of data on efficacy. AIDS Rev. 2013;15:112-21.
5. Fernandez-Montero JV, Eugenia E, Barreiro P, Labarga P, Soriano V. Antiretroviral drug-related toxicities - Clinical spectrum, prevention, and management. Expert Opin Drug Saf. 2013;12:697-707.
6. Armenia D, Di Carlo D, Maffongelli G, et al. Virological response and resistance profile in HIV-1-infected patients starting darunavir-containing regimens. HIV Med. 2017;18:21-32.
7. Khoo S, Peytavin G, Burger D, et al. Pharmacokinetics and safety of darunavir/ritonavir in HIV-infected pregnant women. AIDS Rev. 2017;19:16-23.
8. Keating G. Darunavir: A review in pediatric HIV-1 infection. Paediatr Drugs. 2015;17:411-21.
9. Menéndez-Arias L, Alvarez M. Antiretroviral therapy and drug resistance in human immunodeficiency virus Type 2 infection. Antiviral Res. 2014;102:70-86.
10. de Mendoza C, Cabezas T, Caballero E, et al. HIV Type 2 epidemic in Spain: Challenges and missing opportunities. AIDS. 2017;31:1353-64.
11. Vispo E, Fernández-Montero JV, Labarga P, Barreiro P, Soriano V. Low risk of liver toxicity using the most recently approved antiretroviral agents but still increased in HIV-hepatitis C virus coinfected patients. AIDS. 2013;27:1187-8.
12. Curran A, Martí R, López RM, et al. Darunavir and ritonavir total and unbound plasmatic concentrations in HIV-HCV-coinfected patients with hepatic cirrhosis compared to those in HIV-monoinfected patients. Antimicrob Agents Chemother. 2015;59:6782-90.
13. Calza L, Colangeli V, Magistrelli E, et al. Plasma trough concentrations of darunavir/ritonavir and raltegravir in older patients with HIV-1 infection. HIV Med. 2017.
14. Capetti A, Cossu MV, Rizzardini G. Darunavir/cobicistat for the treatment of HIV-1: A new era for compact drugs with high genetic barrier to resistance. Expert Opin Pharmacother. 2015;16:2689-702.
15. Kakuda TN, Crauwels H, Opsomer M, et al. Darunavir/cobicistat once daily for the treatment of HIV. Expert Rev Anti Infect Ther. 2015;13:691-704.
16. Lederman MM, Cannon PM, Currier JS, et al. A cure for HIV infection: "Not in my lifetime" or "Just around the corner"? Pathog Immun. 2016;1:154-64.
17. O'Connor J, Smith C, Lampe FC, et al. Durability of viral suppression with first-line antiretroviral therapy in patients with HIV in the UK: An observational cohort study. Lancet HIV. 2017. pii: S2352-301830053-X.
18. Dharan NJ, Cooper DA. Long-term durability of HIV viral load suppression. Lancet HIV. 2017. pii: S2352-301830063-2.
19. Clotet B, Bellos N, Molina JM, et al. Efficacy and safety of darunavir-ritonavir at week 48 in treatment-experienced patients with HIV-1 infection in POWER 1 and 2: A pooled subgroup analysis of data from two randomised trials. Lancet. 2007;369:1169-78.
20. Molina JM, Cohen C, Katlama C, et al. Safety and efficacy of darunavir (TMC114) with low-dose ritonavir in treatment-experienced patients: 24-week results of POWER 3. J Acquir Immune Defic Syndr. 2007;46:24-31.
21. Bánhegyi D, Katlama C, de Cunha C, et al. Phase III TITAN week 96 final analysis: Efficacy/safety of darunavir/r (DRV/r) vs. lopinavir/r (LPV/r) in LPV-naïve, treatment-experienced patients. J Int AIDS Soc. 2008;11 Suppl 1:22.
22. Poveda E, de Mendoza C, Martin-Carbonero L, et al. Prevalence of darunavir resistance mutations in HIV-1-infected patients failing other protease inhibitors. J Antimicrob Chemother. 2007;60:885-8.
23. Ortiz R, Dejesus E, Khanlou H, et al. Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48. AIDS. 2008;22:1389-97.
24. Mills AM, Nelson M, Jayaweera D, et al. Once-daily darunavir/ritonavir vs. lopinavir/ritonavir in treatment-naive, HIV-1-infected patients: 96-week analysis. AIDS. 2009;23:1679-88.
25. Orkin C, DeJesus E, Khanlou H, et al. Final 192-week efficacy and safety of once-daily darunavir/ritonavir compared with lopinavir/ritonavir in HIV-1-infected treatment-naïve patients in the ARTEMIS trial. HIV Med. 2013;14:49-59.
26. Maggiolo F, Di Filippo E, Valenti D, Ortega P, Callegaro A. NRTI sparing therapy in virologically controlled HIV-1 infected subjects: Results of a controlled, randomized trial (PROBE). J Acquir Immune Defic Syndr. 2016;72:46-51.
27. Clotet B, Feinberg J, van Lunzen J, et al. Once-daily dolutegravir versus darunavir plus ritonavir in antiretroviral-naive adults with HIV-1 infection (FLAMINGO): 48 week results from the randomised open-label phase 3b study. Lancet 2014;383:22-31.
28. Latini A, Fabbiani M, Borghi V, et al. Switching to boosted protease inhibitor plus a second antiretroviral drug (dual therapy) for treatment simplification: A multicenter observational study. BMC Infect Dis. 2016;16:401.

29. Sterrantino G, Zaccarelli M, Di Biagio A, Biondi ML, Antinori A, Penco G; ARCA Study Group. Darunavir-based dual therapy of treatment-experienced HIV-infected patients: Analysis from a National Multicenter Database. Infection. 2015;43:339-43.
30. Raffi F, Babiker AG, Richert L, et al. Ritonavir-boosted darunavir combined with raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults infected with HIV-1: 96 week results from the NEAT001/ANRS143 randomised non-inferiority trial. Lancet. 2014;384:1942-51.
31. Casado JL, Bañón S, Moreno A, et al. Lamivudine plus darunavir boosted with ritonavir as simplification dual regimen in HIV-infected patients. J Int AIDS Soc. 2014;17 Suppl 3:19801.
32. Arribas J, Cahn P, Andrade-Villanueva J. Non-Inferiority of Dual-Therapy (DT) with Darunavir/Ritonavir (DRV/r) Plus 3TC Versus Triple-Therapy (TT) with DRV/r Plus TDF/FTC or ABC/3TC for Maintenance of Viral Suppression: 48-Week Results of the DUAL-GESIDA 8014 Trial. Glasgow Congress on HIV Therapy, 23-26, October; 2016.
33. Lambert-Niclot S, Flandre P, Valantin MA, et al. Similar evolution of cellular HIV-1 DNA level in darunavir/ritonavir monotherapy versus triple therapy in MONOI-ANRS136 trial over 96 weeks. PLoS One. 2012;7:e41390.
34. Arribas JR, Clumeck N, Nelson M, Hill A, van Delft Y, Moecklinghoff C. The MONET trial: Week 144 analysis of the efficacy of darunavir/ritonavir (DRV/r) monotherapy versus DRV/r plus two nucleoside reverse transcriptase inhibitors, for patients with viral load < 50 HIV-1 RNA copies/mL at baseline. HIV Med. 2012;13:398-405.
35. Valantin MA, Lambert-Niclot S, Flandre P, . Long-term efficacy of darunavir/ritonavir monotherapy in patients with HIV-1 viral suppression: Week 96 results from the MONOI-ANRS 136 study. J Antimicrob Chemother. 2012;67:691-5.
36. Paton NI, Stöhr W, Arenas-Pinto A, et al. Protease inhibitor monotherapy for long-term management of HIV infection: A randomised, controlled, open-label, non-inferiority trial. Lancet HIV. 2015;2:e417-26.
37. Antinori A, Arribas J, Fehr J, et al. The PROTEA trial: Darunavir/ritonavir with or without nucleoside analogues, for patients with HIV-1 RNA below 50 copies/mL. J Int AIDS Soc. 2014;17 4 Suppl 3:19525.
38. Girard PM, Antinori A, Arribas JR, et al. Week 96 efficacy and safety of darunavir/ritonavir monotherapy vs. darunavir/ritonavir with two nucleoside reverse transcriptase inhibitors in the PROTEA trial. HIV Med. 2017;18:5-12.
39. Rabi SA, Laird GM, Durand CM, Laskey S, Shan L. Multi-step inhibition explains HIV-1 protease inhibitor pharmacodynamics and resistance. J Clin Invest. 2013;123:3848-60.
40. Lathouwers E, Gupta S, Haddad M, Paquet A, de Meyer S, Baugh B. Trends in darunavir resistance-associated mutations and phenotypic resistance in commercially tested United States clinical samples between 2006 and 2012. AIDS Res Hum Retroviruses. 2015;31:628-35.
41. Curran A, Pérez-Valero I, Moltó J. Rezolsta® (Darunavir/Cobicistat): First boosted protease inhibitor co-formulated with cobicistat. AIDS Rev. 2015;17:114-20.
42. Kakuda TN, Van De Casteele T, Petrovic R, et al. Bioequivalence of a darunavir/cobicistat fixed-dose combination tablet versus single agents and food effect in healthy volunteers. Antivir Ther. 2014;19:597-606.
43. McDonald CK, Martorell C, Ramgopal M, et al. Cobicistat-boosted protease inhibitors in HIV-infected patients with mild to moderate renal impairment. HIV Clin Trials. 2014;15:269-73.
44. Navarro J, Curran A. Profile of once-daily darunavir/cobicistat fixed dose combination for the treatment of HIV/AIDS. HIV AIDS (Auckl). 2016;8:175-82.
45. Jacobson JM, Flexner CW. Universal antiretroviral regimens: Thinking beyond one-pill-once-a-day. Curr Opin HIV AIDS. 2017;12:343-50.