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Rezolsta® (Darunavir/Cobicistat): First Boosted Protease Inhibitor Co-formulated with Cobicistat

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Abstract

Rezolsta® (darunavir/cobicistat) is the first boosted protease inhibitor in a fixed-dose combination to be approved for the treatment of HIV infection. It contains darunavir, a protease inhibitor with a well-known safety and efficacy profile, and the new pharmacokinetic enhancer cobicistat. The convenience of this combination makes boosted darunavir easier to take, thus improving adherence. Exposure to darunavir is equivalent when it is administered with cobicistat or with ritonavir. Darunavir/cobicistat-based antiretroviral therapy has shown considerable efficacy and good tolerability in several clinical trials. Data from the single-arm, open-label, phase III GS-US-216-130 trial showed virological efficacy rates comparable to those from ARTEMIS and ODIN. Darunavir/cobicistat was well tolerated; most adverse events were mild and consisted of gastrointestinal disturbances. Cobicistat inhibits transporters of creatinine in kidney tubules, thus causing a minimal and reversible reduction in estimated glomerular filtration rate. Like ritonavir, cobicistat is a strong CYP3A4 inhibitor and, as such, shares most of its drug interactions. However, inhibition by cobicistat seems to be more specific than with ritonavir, and cobicistat has no inducer effect; therefore, differences in its drug interaction profile may be observed. **(AIDS Rev. 2015;17:114-20)**

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Key words

Darunavir. Cobicistat. Fixed-dose combination. HIV infection. Antiretroviral treatment.

Introduction

Guidelines for the management of antiretroviral treatment (ART) in HIV-infected patients recommend boosted darunavir as a preferred option for the initial ART regimen, regardless of baseline viral load or CD4 cell count[1]. Results from clinical trials show that darunavir/ritonavir 800/100 mg is efficacious in ART-naive and ART-experienced patients with no darunavir resistance-associated mutations (RAM), and data from clinical trials and clinical practice show that this option is well tolerated in the long term[2-4].

Like other protease inhibitors (PI), darunavir is extensively metabolized by the cytochrome P450 (CYP3A4) in the liver and the intestinal lumen[5]. Therefore, it needs to be coadministered with a pharmacokinetic enhancer able to increase plasma concentrations above the level needed to inhibit replication of HIV throughout the dosing interval.

Low-dose ritonavir (100 mg once or twice daily) has been used as a pharmacokinetic enhancer during recent decades[6]. Ritonavir is a potent CYP3A4 and

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Table 1. Pharmacokinetic studies comparing darunavir boosted with cobicistat or with ritonavir

	Geometric mean ratio (90% CI)		
Study	**AUC (mg.h/l)**	**C_{max} (mg/l)**	**C_{trough} (mg/l)**
Mathias, et al.[10] DRV 800 mg qd + RTV 100 mg qd DRV 800 mg qd + COBI 150 mg qd	1.02 (0.97-1.06)	1.03 (1.00-1.06)	0.69 (0.59-0.82)
Kakuda, et al. (GS003)[18] DRV 800 mg qd + RTV 100 mg qd DRV/COBI 800/150 mg qd	0.97 (0.92-1.02)	0.97 (0.92-1.01)	0.69 (0.60-0.81)
Kakuda, et al. (GS004)[18] DRV 800 mg qd + RTV 100 mg qd DRV/COBI 800/150 mg qd	0.99 (0.94-1.04)	1.00 (0.96-1.04)	0.74 (0.63-0.86)

DRV: darunavir; RTV: ritonavir; COBI: cobicistat; qd; once daily.

P-glycoprotein (P-gp) inhibitor that increases the oral bioavailability of other drugs such as darunavir, thus enabling once-daily or twice-daily administration[7]. However, ritonavir can produce undesirable adverse events and drug interactions. In addition, since ritonavir is active against HIV, it remains unclear whether boosting doses of ritonavir could generate resistance to PIs in the absence of a concomitant, fully active ART regimen[8].

Cobicistat (GS-9350) is a pharmacokinetic enhancer that was recently developed to boost other antiretroviral drugs. Results from clinical trials have shown that it can increase the plasma exposure of elvitegravir, atazanavir, and darunavir[9-13]. Compared with ritonavir, cobicistat has no intrinsic antiretroviral activity, is more selective than ritonavir in terms of inhibition of different isoenzymes of the cytochrome P450 system, and does not induce CYP isoenzymes or glucuronidation[14]. Given its chemical stability, cobicistat can be co-formulated as a fixed-dose combination (FDC), thereby reducing pill burden and medication errors[14].

The recently developed FDC of darunavir/cobicistat (800/150 mg, Rezolsta®)[15] is a convenient treatment option that has the potential to improve adherence to ART[16]. This review examines the pharmacokinetic profile of cobicistat-boosted darunavir and clinical data on the efficacy and safety profile and potential drug interactions of darunavir/cobicistat.

Pharmacokinetic data

Darunavir is rapidly absorbed after oral administration of darunavir/cobicistat 800/150 mg, with maximum concentrations generally achieved in 3.0-4.5 hours. When administered with food, the relative exposure of darunavir is 1.7-fold higher than without food. Therefore, darunavir/cobicistat should be taken with food[15,17].

A phase I clinical trial in healthy volunteers demonstrated that exposure to darunavir following darunavir/cobicistat 800/150 mg once daily, given either as single agents or as two candidate FDC formulations (GS003 and GS004), was comparable to exposure to darunavir/ritonavir 800/100 mg once daily (Table 1)[18]. Interestingly, this study also revealed an increase in darunavir concentrations at the end of the dosing interval (C24h) relative to previous timepoints (e.g. C20h) when darunavir was coadministered with ritonavir[18]. Although induction of glucuronidation by ritonavir and enterohepatic recycling of darunavir could potentially explain the late peak in darunavir plasma concentrations when it is given with ritonavir[19], the exact mechanism underlying this phenomenon remains unclear. Irrespective of the mechanism, this late peak meant that darunavir trough concentrations were 30% lower with cobicistat than with ritonavir[18]. Nonetheless, the difference may not be clinically relevant since trough concentrations remained about 25-times greater than the protein-binding-adjusted inhibitory concentration (IC_{50}) for HIV-1 strains with no darunavir RAMs[20].

Darunavir pharmacokinetic parameters were determined in 60 HIV-infected patients who received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily (administered as single agents), with an investigator-selected optimized background regimen[21]. Mean darunavir AUC, C_{max}, and C_{trough} were 81,646 ± 26,322 ng.h/ml, 7,663 ± 1,920 ng/ml, and 1,311 ± 969 ng/ml, respectively (Table 1)[21]. These results were comparable to those observed in healthy volunteers[17,18]. It is noteworthy that no relationship

Table 2. Safety summary of darunavir/cobicistat

Incidence (%)	GS-US-216-130[21] (n = 295)	GS-US-299-0102[23] (n = 153)	
Backbone	**TDF/FTC**	**TAF/FTC**	**TDF/FTC**
Any AEs, n (%)	270 (92)	NR	NR
Any drug-related AEs, n (%)	122 (41)	NR	NR
Grade 3-4 AEs, n (%)	21 (7)	NR	NR
AEs leading to discontinuation, n (%)	16 (5)	2 (2)	2 (4)
Diarrhea, n (%)	80 (27)	22 (21)	13 (26)
Nausea, n (%)	69 (23)	13 (13)	5 (10)
Upper respiratory tract infection, n (%)	43 (15)	16 (16)	7 (14)
Headache, n (%)	35 (12)	NR	NR
Rash, n (%)	7 (3.3)	12 (12)	4 (8)
Fatigue, n (%)	NR*	14 (14)	7 (14)

TDF: tenofovir disoproxil fumarate; FTC: emtricitabine; TAF: tenofovir alafenamide fumarate; AE: adverse events; NR: not reported.
*Grade 3-4 laboratory abnormalities in > 2% of the patients.

was observed between darunavir AUC or trough concentrations and virologic response or safety at week 24 or 48[21].

Efficacy and safety

The safety and efficacy profile of darunavir/cobicistat 800/150 mg administered once daily to HIV-infected patients was evaluated in a single-arm, open-label, phase III clinical trial (GS-US-216-130)[21] including 313 HIV-infected patients (295 ART-naive and 18 ART-experienced). The inclusion criteria were a screening genotype showing no darunavir RAMs and plasma HIV-1 RNA ≥ 1000 copies/ml. After inclusion, patients received darunavir 800 mg once daily in combination with cobicistat 150 mg once daily (administered as single agents), with an investigator-selected optimized background regimen consisting of tenofovir/emtricitabine in 96% of participants. The overall response rate was 82% at week 24 and 81% at week 48 (83% in ART-naive patients), and no differences were observed between patients whose baseline viral load was below or above 100,000 copies/ml[21]. These results are consistent with those previously observed with darunavir/ritonavir 800/100 mg once daily in the ARTEMIS and ODIN trials[2,3] (performed in the same settings for which darunavir/cobicistat has been approved)[15]. Darunavir/cobicistat 800/150 mg once daily was well tolerated during the study, and safety findings were consistent with those previously reported for darunavir and for cobicistat. Most adverse events were mild and consisted of gastrointestinal disturbances. Treatment-emergent grade 3 or 4 adverse events, regardless of causality, were reported in 21 (7%) patients, and only 16 (5%) patients discontinued treatment due to adverse events (Table 2)[21].

Similar results were reported in the randomized, double-blind, placebo-controlled clinical trial GS-US-299-102, which compared darunavir/cobicistat plus tenofovir disoproxil/emtricitabine or tenofovir alafenamide/emtricitabine (single-tablet regimen) in 150 treatment-naive HIV-infected adults[22]. By week 48, 84% of subjects randomized to receive tenofovir darunavir/cobicistat plus disoproxil/emtricitabine were virologically suppressed by FDA Snapshot (ITT), and only four patients (2.6%) had discontinued treatment due to adverse events (Table 2).

The renal safety profile of darunavir/cobicistat deserves special mention. Cobicistat is excreted through glomerular filtration and proximal renal tubular secretion. In the tubular cell, cobicistat inhibits creatinine secretion through the multidrug and toxin extrusion protein 1 (MATE1) transporter on the apical side of the tubular cell, but it does not interfere with tubular secretion of tenofovir[22]. Consequently, patients starting cobicistat experience an increase in plasma creatinine concentrations of about 0.05-0.1 mg/dl. This effect peaks four weeks after initiation of cobicistat, remains

constant during treatment, and disappears after cessation[24]. Inhibition of MATE1 by cobicistat eventually leads to a decrease of approximately 10 ml/min in the glomerular filtration rate (GFR) estimated according to the Cockcroft-Gault equation ($eGFR_{CG}$), while the actual GFR measured using iohexol clearance remains unaffected[25].

The effect of using cobicistat with darunavir on eGFR and proximal renal tubulopathy in patients without renal impairment was analyzed in GS-US-216-130[21]. As expected, levels of serum creatinine increased from baseline to week 2 (median 0.1 mg/dl) and then remained stable through week 48 (median 0.08 mg/dl increase from baseline). One patient who was receiving tenofovir/emtricitabine discontinued treatment owing to a renal tubular disorder that was resolved upon switching to abacavir/lamivudine plus darunavir/ritonavir.

Similar results were observed in patients with mild-to-moderate renal impairment who were receiving ART with ritonavir-boosted atazanavir (n = 52) or darunavir (n = 21) and who switched ritonavir for cobicistat (GS-US-236-118)[26]. No clinically relevant changes in cystatin C-based eGFR were seen through week 96 (–2.8 ml/min; –7.4 to 8.9), even though $eGFR_{CG}$ decreased more in patients starting with $eGFR_{CG}$ > 70 ml/min vs. < 70 ml/min (median [IQR], –7.6 ml/min [–15.2 to –3.6] vs. –3.1 ml/min [–5.1 to 0.5]). In this trial, two patients discontinued ART (one abnormal GFR and one hematuria/proteinuria). One patient experienced grade 1 hypophosphatemia, one patient grade 2 proteinuria, and three patients had an isolated increase of serum creatinine > 0.4 mg/dl. However, no cases of discontinuations due to proximal renal tubulopathy were reported.

Drug interactions with cobicistat: Comparison with ritonavir

As a pharmacokinetic enhancer, cobicistat inhibits CYP3A in a time- and concentration-dependent manner, much in the same way as ritonavir. Moreover, cobicistat acts as a weak inhibitor of CYP2D6 and has inhibitory effects (similar to those of ritonavir) on other enzymes and transporters, namely, P-gp in the liver and gut, breast cancer resistance protein (BCRP) in the gut, solute carrier organic anion transporters OATP1B1/3 in the liver, and MATE1 in the kidney[14,27,28]. Cobicistat is also a substrate of CYP and is metabolized through oxidation, mainly by CYP3A and, albeit to a lesser extent, by CYP2D6.

One of the main differences between ritonavir and cobicistat as boosters is that cobicistat is a more selective inhibitor of CYP3A and has no significant effect on other isoenzymes that can be inhibited by ritonavir at the concentrations achieved in clinical practice (e.g. 2C8 and 2C9)[14,29,30]. In addition, ritonavir acts as an inducer of some CYP isoenzymes *in vivo* (e.g. 1A2, 2C19, 2C8, 2C9, and 2B6), glucuronyl transferases (e.g. UGT1A4), and even P-gp[29,30]. Ritonavir also activates the pregnane X receptor (PXR), the main regulator of CYP3A expression, thus indicating a potential inducing effect on CYP3A4, even though the net effect is inhibition. In contrast, cobicistat does not exercise an inducer effect on CYP, glucuronyl transferases, or PXR[14].

Although the greater selectivity of CYP3A and the absence of an induction effect with cobicistat may reduce the risk of multidirectional or difficult-to-predict drug interactions compared with ritonavir, the mechanism of action of cobicistat means that most of its interactions are similar to those of ritonavir. However, data on drug interactions with cobicistat are scarce, and available clinical data are mainly from cobicistat/elvitegravir/tenofovir/emtricitabine FDC studies and not from studies of cobicistat administered to boost PIs. Furthermore, no drug interaction trials have been performed with the darunavir/cobicistat FDC. Thus, the potential interactions are assumed to be the same as those seen with darunavir/ritonavir. Table 3 shows the most relevant drug interactions of darunavir/cobicistat, including contraindicated drugs, according to its prescribing information[15].

When appropriate information is not available, clinicians usually extrapolate to cobicistat the data obtained with ritonavir. This option is useful most of the time as CYP3A is the major metabolic pathway and both drugs inhibit it in a similar fashion. However, a drug can sometimes be metabolized through other CYP isoenzymes or glucuronidation, both of which can in turn be affected by ritonavir (inhibited or induced) but not by cobicistat. Examples include olanzapine (CYP1A2 and glucuronidation), propofol (CYP2B6 and glucuronidation), lamotrigine and valproate (CYP2C9 and glucuronidation), gliclazide (CYP2C9 and 2C19), and mycophenolate and gemfibrozil (glucuronidation)[31]. Thus, physicians should be careful when extrapolating drug interaction data from ritonavir to cobicistat, especially in drugs metabolized by pathways other than CYP3A. In the same way, caution is required when switching from ritonavir to cobicistat for boosting during the first two weeks, especially if the dose of concomitant drugs has been adjusted during therapy with ritonavir[15].

Caution should be exercised when coadministering cobicistat with P-gp substrates, such as digoxin,

Table 3. Drugs contraindicated or not recommended with darunavir/cobicistat[31]

Drug class	Drug within class	Comments
Alpha1 adrenergic antagonist	Alfuzosin	Inhibition of CYP3A by COBI Coadministration contraindicated
Antianginal/ antiarrhythmic	Amiodarone, bepridil, dronedarone, quinidine, ranolazine, lidocaine	Inhibition of CYP3A by COBI Coadministration contraindicated
Anticoagulant/ platelet aggregation inhibitor	Apixaban, dabigatran, rivaroxaban ticagrelor	Inhibition of CYP3A/P-gp by COBI Coadministration not recommended
Ergot derivatives	Dihydroergotamine, ergometrine, ergotamine	Inhibition of CYP3A by COBI Coadministration contraindicated
Gastrointestinal motility agents	Cisapride	Inhibition of CYP3A by COBI Coadministration contraindicated
HMG-CoA reductase inhibitors	Lovastatin, simvastatin	Inhibition of CYP3A and transport by COBI Coadministration contraindicated
Antipsychotics/neuroleptics	Pimozide, quetiapine, sertindole	Inhibition of CYP2D6 by COBI Coadministration contraindicated
Phosphodiesterase 5 inhibitors	Sildenafil (for pulmonary arterial hypertension)	Inhibition of CYP3A by COBI Coadministration contraindicated
Corticosteroids	Budesonide, fluticasone	Inhibition of CYP3A by COBI Coadministration not recommended
Inhaled beta-agonists	Salmeterol	Inhibition of CYP3A by COBI Coadministration not recommended
Sedatives/hypnotics	Oral midazolam, triazolam	Inhibition of CYP3A by COBI Coadministration contraindicated
Direct-acting antivirals (HCV)	Boceprevir, telaprevir simeprevir	Coadministration not recommended Multidirectional interaction
Non-nucleoside reverse transcriptase inhibitors	Efavirenz*, nevirapine*, etravirine*	Induction of CYP3A by NNRTI Coadministration not recommended
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin	Induction of CYP3A by anticonvulsants Coadministration contraindicated
Antimycobacterials	Rifampicin rifabutin* rifapentine	Induction of CYP3A by rifamycins Coadministration contraindicated with rifampicin and not recommended with rifabutin and rifapentine
Endothelin receptor antagonists	Bosentan	Induction of CYP3A by bosentan Coadministration not recommended
Herbal supplements	*Hypericum perforatum* (St. John's wort).	Induction of CYP3A by *Hypericum* Coadministration contraindicated

If CYP3A is inhibited by cobicistat, plasma concentrations of the coadministered drug increase, with the subsequent risk of greater toxicity. If CYP3A is induced by another drug, darunavir and/or cobicistat plasma concentrations decrease, with the subsequent risk of virological failure.
COBI: cobicistat; HMG-CoA: 3-hydroxy-3-methylglutaryl coenzyme A.
*The prescribing recommendations for these drugs differ between darunavir/cobicistat and darunavir/ritonavir.

since plasma levels of the latter might be increased[27]. Additionally, owing to MATE1 inhibition, darunavir/cobicistat could theoretically increase metformin plasma concentrations, thus necessitating careful monitoring[32].

Cobicistat is a substrate of CYP3A. Coadministration with other inhibitors will increase cobicistat concentrations and, consequently, those of the boosted drug, potentially leading to increased toxicity. Conversely, coadministration with CYP3A inducers could decrease

cobicistat concentrations and its boosting effect and potentially increase the risk of virological failure. Examples of the former would be systemic azoles[3] and of the latter non-nucleoside reverse transcriptase inhibitors (NNRTI) such as etravirine, efavirenz, or nevirapine[15]. This potential interaction with NNRTI, which advises against coadministration with cobicistat[15], is a significant difference between cobicistat and ritonavir used as boosters.

Interaction of cobicistat with other antiretrovirals is not expected when cobicistat is used to boost elvitegravir as all the antiretrovirals are given in a single tablet. When cobicistat boosts a PI, potential interactions with other antiretrovirals must be taken into account. Furthermore, cobicistat cannot be used as a booster for PIs other than darunavir or atazanavir as no data are available[28]. The same applies to darunavir/cobicistat administered with other antiretrovirals that require boosting, such as PIs or elvitegravir, as pharmacokinetic enhancement might not be sufficiently strong to boost all drugs, with the subsequent risk of subtherapeutic plasma levels[15].

Cobicistat and ritonavir also differ with respect to coadministration of rifabutin, which is not recommended even with dose adjustments[15]. Other drugs frequently used in HIV-infected patients have been studied in combination with cobicistat and show no clinically relevant interactions. These include methadone[33], buprenorphine, naloxone[34], proton pump inhibitors, and antihistaminic drugs[35].

Given that the field of drug interactions is constantly changing, access to updated information is essential. Clinicians should consult specific sites, such as the Liverpool HIV drug interaction website (www.hiv-druginteractions.org), before prescribing new medications to patients receiving darunavir/cobicistat[31].

The role of Rezolsta® in current antiretroviral treatment

The main advantage of the FDC darunavir/cobicistat is its convenience (i.e. one pill less and one drug bottle less). It is also the first step towards a single-tablet PI regimen, probably with emtricitabine and tenofovir alafenamide, thanks to the better solubility of cobicistat compared with ritonavir[14].

Although integrase inhibitors are considered as the preferred option for the management of ART in some guidelines,[1] PI-based regimens may be the preferred option for patients with poor adherence, for whom a regimen with a high genetic barrier is desired. In these patients, it remains unclear whether it is better to use a simpler regimen in order to facilitate adherence (i.e. a single tablet) or to use a regimen with more pills but with a higher genetic barrier to avoid selection of resistance mutations (i.e. a boosted PI)[1]. Some physicians may prefer to start ART with boosted PIs in late presenters (i.e. patients with a low CD4 cell count and/or opportunistic infections at diagnosis of HIV infection) until the results of resistance tests are available and adherence is confirmed. The FDC darunavir/cobicistat simplifies the regimen while maintaining a high genetic barrier. Furthermore, having darunavir and cobicistat in an FDC eliminates the risk of selective nonadherence, where the patient takes only one of the two drugs (usually skipping ritonavir owing to its poorer tolerability), and the risk of taking them separately (loss of the ritonavir boosting effect with eventual subtherapeutic plasma drug concentrations). Finally, this FDC simplifies the ART regimen and reduces the risk of prescription errors.

Darunavir/cobicistat could improve convenience in well-tolerated and less expensive combinations[36]. In early rescue treatments, a boosted PI is usually the cornerstone of the antiretroviral regimen. Since darunavir/cobicistat can be used in patients with no darunavir RAMs, salvage regimens with a relatively low pill burden and once-daily administration can be designed[2]. Additionally, in selected patients, PI monotherapy can be used as a simplification strategy in a single-tablet regimen. Finally, dual therapy with a boosted PI plus lamivudine is among new simplification strategies currently under study. Such a strategy aims at preventing or solving NRTI-related toxicities while overcoming potential limitations of PI monotherapy.

Boosting with cobicistat is also subject to drawbacks. Drug interactions do not differ significantly from those of ritonavir, as CYP3A is the main metabolic pathway for most drugs. However, having a “cleaner” booster that diminishes the risk of off-target interactions is helpful, especially in our growing elderly population, for whom polypharmacy is increasingly frequent. The tolerability profile is also similar to that of ritonavir, with gastrointestinal and lipid disturbances as the main problems[14,18,36]. However, *in vitro* studies have shown that cobicistat does not affect lipid accumulation in adipocytes and causes less insulin resistance than ritonavir[14]. While cobicistat could lead to long-term tolerability benefits, more data and longer follow-up are necessary. Furthermore, inhibition of tubular creatinine secretion by cobicistat hampers estimation of renal function[24]. Many other antiretrovirals have a similar effect (e.g. ritonavir, dolutegravir, and rilpivirine)[37]. As clinicians caring for HIV-infected patients, we must familiarize

ourselves with the effects of these drugs or develop new tests for measuring actual renal function. Data on cobicistat in patients with impaired renal function show that the drug is safe in this population[25,38].

In conclusion, Rezolsta® (darunavir/cobicistat FDC) is a new, valuable, efficacious, and well-tolerated option for the treatment of HIV-infected patients. It makes boosted darunavir more convenient and has the potential to improve adherence. It also represents the first step towards a single-tablet PI regimen. Since cobicistat seems to be more specific than ritonavir as a pharmacokinetic enhancer, differences in drug interaction profile are possible.

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Conflict of interest

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