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AIDS Rev. 2015;17:37-46

Pharmacokinetic Enhancement in HIV Antiretroviral Therapy: A Comparison of Ritonavir and Cobicistat

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Abstract

Inhibition of the cytochrome p450 3A4 enzyme system leads to increases in plasma concentrations of coadministered antiretroviral agents – a concept known as pharmacokinetic boosting. Ritonavir and cobicistat are potent inhibitors of cytochrome p450 3A4. Ritonavir was initially developed as an HIV protease inhibitor, but is currently used primarily as a pharmacokinetic boosting agent for other HIV and hepatitis C protease inhibitors. Cobicistat is a boosting agent for the integrase inhibitor elvitegravir and the protease inhibitors atazanavir and darunavir. Phase III data showed that atazanavir + cobicistat + tenofovir/emtricitabine had non-inferior efficacy and resulted in similar CD4 T-cell count increases to atazanavir + ritonavir + tenofovir/emtricitabine. The tolerability, gastrointestinal, and lipid profile of the cobicistat-containing regimen was comparable with the ritonavir-containing regimen. Primary HIV protease resistance mutations were not selected in either ritonavir or cobicistat arm virologic failures. Cobicistat-containing regimens have consistently shown higher serum creatinine increases and creatinine clearance decreases compared with ritonavir, and accurate assessment of glomerular filtration in the presence of cobicistat could only be made by using exogenous markers such as iohexol. Drugs contraindicated with cobicistat are consistent with those contraindicated with ritonavir-containing protease inhibitor regimens with respect to cytochrome p450 3A interactions. Information in this review may help clinicians assess the benefits and limitations of currently available pharmacokinetic enhancers when selecting the most appropriate treatment for their patients. **(AIDS Rev. 2015;17:37-46)**

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Key words

Ritonavir. Cobicistat. Protease inhibitor. Combination antiretroviral therapy. HIV.

Introduction

Pharmacokinetic (PK) boosting is a concept where alterations in metabolic rates of one pharmaceutical agent through the inhibitory effects of another agent lead to increases in plasma concentrations and prolongation of the half-life of the coadministered agent. This effect can lead to drug-drug interactions with associated toxicity, or when carefully characterized and managed it can: (i) allow for administration of a lower dose of the coadministered agent while maintaining therapeutic levels; (ii) reduce pill burden and dosing frequency; (iii) decrease effect of food; (iv) reduce variability of systemic exposure; and (v) increase overall treatment efficacy[1-3]. The introduction of PK boosting of protease inhibitors (PI) has advanced the therapy of HIV infection and ritonavir (RTV)-boosted PIs are included as preferred agents in guidelines for the treatment

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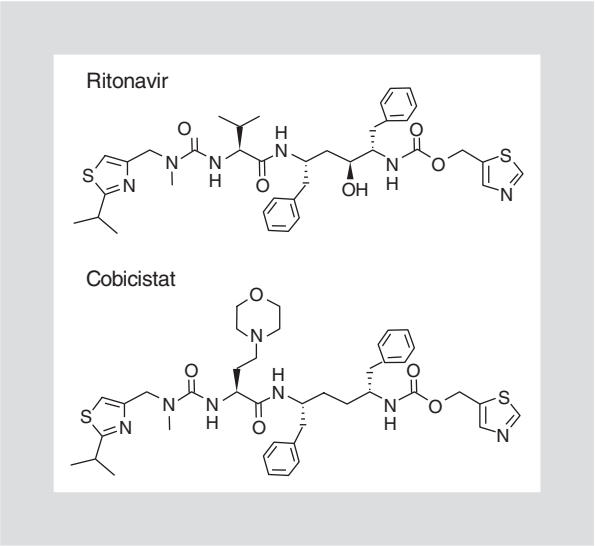

Figure 1. *Molecular structures of ritonavir and cobicistat.*

of HIV infection[4,5]. Ritonavir, a PI approved for treatment of HIV in combination with other antiretrovirals (ARV), was found to inhibit P-glycoprotein (P-gp) and cytochrome p450 (CYP450) enzymes, particularly the CYP450 3A4 isoform[6]. When coadministered with atazanavir (ATV), darunavir (DRV), or lopinavir (LPV), the PK boosting of these agents by RTV allows for once or twice daily dosing while maintaining a high inhibitory quotient (IQ = the minimum blood concentration [C_{min}] divided by the 50% inhibitory concentration [IC_{50}] of the drug). A high IQ reduces the risk of HIV resistance development and subsequent therapeutic failure[7-9]. Recently, cobicistat (COBI) has been developed as a booster for other ARV agents and clinical trials have demonstrated the ability of COBI to alter plasma exposure of the HIV integrase strand transfer inhibitor elvitegravir (EVG) and the HIV protease inhibitors ATV and DRV to similar extents as with RTV[10-14].

Relevant medical literature on COBI was identified by searching databases including BIOSIS Previews®, Derwent Drug File, Embase®, Embase® Alert, International Pharmaceutical Abstracts, MEDLINE®, SciSearch®: a Cited Reference Science Database. Search terms used included cobicistat or "GS-9350" or "GS 9350" or GS9350. This review focuses on studies that compare RTV and COBI in otherwise identical ARV regimens such as ATV + RTV + tenofovir/emtricitabine (TDF/FTC) versus ATV + COBI + TDF/FTC. We outline key similarities and differences between the two drugs with respect to PK boosting, non-intended drug-drug interactions, efficacy, safety, and tolerability profiles of ARV regimens containing either RTV or COBI.

Ritonavir

Ritonavir (Fig. 1) was originally approved by the FDA in 1996. The current FDA prescribing information of RTV states that RTV is an HIV PI indicated in combination with other ARV agents for the treatment of HIV-1 infection. Ritonavir was approved at a dose of 600 mg BID for the treatment of adult patients and based on body surface area for patients older than one month[6]. Treatment with a RTV-containing regimen resulted in decreased morbidity and mortality in HIV-infected patients compared with the standard-of-care, which could have consisted of up to two approved ARV agents when treating ARV-experienced patients or monotherapy when treating ARV-naive patients[6]. The use of RTV as an active ARV agent at the originally approved dose was limited by dose-related adverse events. The most commonly reported adverse events in clinical trials at a dose of 600 mg twice daily (BID) were diarrhea, nausea, vomiting, upper and lower abdominal pain, paresthesia, oral paresthesia, rash, and fatigue/asthenia[6]. In current practice, RTV is used almost exclusively at low doses (100-200 mg/day) solely to maintain therapeutic serum levels of other PIs used in combination[8,9]. The European Medicines Agency (EMA) RTV Summary of Product Characteristics (SmPC) states that RTV can be used at full dose as an ARV agent in combination with other ARVs to treat HIV infection , or at lower doses with other PIs (typically 100 or 200 mg/day – booster doses)[15]. In Europe, RTV is indicated for use in pediatric patients older than two years. Whereas the booster dose indication is not contained in the US RTV label, it is contained in the FDA labels of ATV[8,16,17], DRV[9,18], fosamprenavir (fAPV)[19,20], LPV[7,21], saquinavir (SQV)[22], tipranavir (TPV)[23,24], and indinavir (IDV)[25].

Cobicistat

Originally referred to as GS-9350 (Fig. 1), COBI was approved in the USA and Europe in 2012 for use as CYP450 3A inhibitor in the fixed-dose combination regimen of EVG + COBI + TDF/FTC. Subsequently COBI received approval in the EU as a pharmacokinetic enhancer of ATV 300 mg once daily or DRV 800 mg once daily as part of ARV combination therapy in HIV-1-infected adults[10,11]. The approved dose for COBI with EVG, ATV, and DRV is 150 mg once daily (QD) with food in adults, with no dosing recommendations in patients < 18 years of age. Preclinical results suggested that COBI might demonstrate improved tolerability, reduced gastrointestinal disturbances, smaller changes in plasma lipids, and fewer drug-drug interactions compared with RTV[13,14].

Table 1. Pharmacokinetic studies of atazanavir, darunavir, or tipranavir when boosted with cobicistat versus ritonavir

Study	Geometric mean ratio of the boosted-PI exposure		
	AUC	C_{max}	C_{tau}
ATV 300 mg + COBI 150 mg (n = 34) vs. ATV 300 mg + RTV 100 mg (n = 36)*	1.01 (0.945, 1.08)	0.923 (0.851, 1.00)	0.976 (0.88.1, 1.08)
DRV 600 mg + COBI 150 mg BID (n = 24) vs. DRV 600 mg + RTV 100 mg BID (n = 24)†	1.09 (1.04, 1.14)	1.08 (1.05, 1.12)	1.03 (0.932, 1.14)
DRV 800 mg + COBI 150 mg QD (n = 32) vs. DRV 800 mg + RTV 100 mg QD (n = 33)‡	0.97 (0.92, 1.02)	0.97 (0.92, 1.01)	0.69 (0.60, 0.81)
TPV 500 mg + COBI 150 mg BID (n = 12) vs. TPV 500 mg + RTV 200 mg BID (n = 12)†	0.462 (0.40, 0.534)	0.622 (0.549, 0.705)	0.144 (0.114, 0.176)

*Geometric mean ratio (95% CI)[30]; †Geometric mean ratio (90% CI)[29]; ‡Geometric mean ratio (90% CI)[27].
ATV: atazanavir; AUC: area under the concentration curve; BID: twice a day; C_{max}: maximum concentration; COBI: cobicistat; C_{tau}: concentration at the end of the dosing interval; DRV: darunavir; PI: protease inhibitor; QD: once a day; RTV: ritonavir; TPV: tipranavir.

Effects of ritonavir and cobicistat on systemic exposure of protease inhibitors

Ritonavir has been studied as a boosting agent with ATV, DRV, SQV, LPV, fAPV, TPV, and IDV[7,19-25], whereas COBI has been studied with ATV, DRV, and TPV[26-30]. Clinical trial data directly comparing RTV with COBI as a booster for ATV is available from two trials[31-33].

Ritonavir or cobicistat in combination with atazanavir

The efficacy and safety of an ARV regimen containing ATV boosted with RTV was demonstrated via two prospective, randomized, controlled, open-label phase III trials[16,17]. Based on the results from these trials, ATV 300 mg QD in combination with RTV 100 mg QD is approved for use in treatment-naive and experienced adult patients[8]. Phase I and II studies with COBI showed that ATV 300 mg QD administered with 150 mg of COBI provided bioequivalent steady-state area under the concentration curve (AUC), maximum concentration (C_{max}), and concentration at the end of the dosing interval (C_{tau}) of ATV compared with those observed with 100 mg of RTV (Table 1)[26,30].

Ritonavir or cobicistat in combination with darunavir

Based on phase III studies, DRV 800 mg QD or 600 mg BID, coadministered with 100 mg of RTV, is approved for use in treatment-naive and experienced adult patients[9,18]. The pharmacokinetics of DRV 800 mg QD administered with 150 mg COBI showed that the AUC and C_{max} of DRV were bioequivalent to those observed in the presence of RTV; however, trough levels of DRV were 30% lower with COBI than with RTV (Table 1)[27,28]. In the DRV 600 mg BID dosing regimen, the AUC, C_{max}, and minimum concentration (C_{trough}) of DRV + COBI were bioequivalent to levels achieved with DRV with 100 mg RTV BID[29].

Ritonavir or cobicistat in combination with tipranavir

The clinical efficacy and safety of TPV + RTV + optimized background regimen were established in the RESIST 1 and RESIST 2 studies in treatment-experienced patients[23,24]. A PK study in healthy volunteers given TPV with either COBI or RTV showed that TPV AUC, C_{max}, and C_{trough} exposures were substantially lower with COBI compared with levels observed with RTV (Table 1)[29].

Efficacy

Comparable rates of virologic suppression and CD4 cell gains were achieved in a 48-week phase II study of ATV + RTV + TDF/FTC versus ATV + COBI + TDF/FTC in 79 treatment-naive subjects[26]. In a 48-week phase III randomized, double blind, active-controlled study (n = 692), 85% of subjects in the ATV + COBI arm achieved HIV RNA < 50 copies/ml compared with 87% in the ATV + RTV arm (difference,

Table 2. Clinical and laboratory profiles of atazanavir + tenofovir/emtricitabine with either ritonavir or cobicistat after 48 weeks of therapy

	Phase II			Phase III		
	COBI (n = 50)	RTV (n = 29)	p value	COBI (n = 344)	RTV (n = 348)	p value
Lipids (mg/dl)						
– Fasting total cholesterol	+ 4	+ 4	0.85	+ 5	+9	0.081[33]
– Triglycerides	– 1	+ 7	0.67	+19	+32	0.063[33]
– LDL	+ 7	+ 1	0.28	NR	NR	0.32[32]
– HDL	+ 1	+ 5	0.26	NR	NR	0.69[32]
Gastrointestinal events (%)						
– All grades nausea	10	3	NR	17.7	16.4	0.69[33]
– All grades diarrhea	6	10	NR	15.4	20.4	0.09[33]
Bilirubin alterations (%)						
– Jaundice	NR	NR	NR	20.9	15.5	0.08
– Ocular icterus	12	14	NR	17.7	18.4	0.84
– Hyperbilirubinemia	96	100	NR	11.3	9.8	0.54[33]
– Grade 3-4 hyperbilirubinemia	63	45	0.16	65	57	0.02
Discontinuations due to AE (%)	4	3	NR	7.3	7.2	NR
– Jaundice/icterus	0	3	NR	5.2	3.7	NR
– GI events	1	0	NR	—	—	—

AE: adverse event; COBI: cobicistat; GI: gastrointestinal; HDL: high-density lipoprotein; LDL: low-density lipoprotein; NR: not reported; RTV: ritonavir.

–2.2%; 95% CI: –7.4 to 3.0), demonstrating non-inferiority of ATV + COBI to ATV + RTV[32,33]. The week 48 non-inferiority results have been confirmed through 144 weeks of therapy[34]. In this trial there were no differences in suppression of HIV-1 RNA to < 50 copies/ml when stratified by baseline HIV-1 RNA (≤ vs. > 100,000 copies/ml) or baseline $CD4^+$ T-cell count (≤ vs. > 350 cells/mm^3), or change from baseline in $CD4^+$ T-cell counts between the RTV and COBI arms.

Safety and tolerability

With full-dose RTV (1,200 mg/day), patients experienced substantial adverse effects, including oral paresthesia, gastrointestinal disturbances (nausea, vomiting, diarrhea, dyspepsia), and lipid elevations (most prominently hypertriglyceridemia)[6]. Although the tolerability profile of RTV may be associated with plasma exposure, RTV as a boosting agent (100-400 mg/day) likely contributes to gastrointestinal and lipid side effects experienced by some patients taking RTV-boosted PI-based regimens[35]. One of the stated objectives for the development of COBI as a new PK booster was to reduce the incidence of side effects believed to be caused by RTV. Early *in vitro* studies suggested a lower potential of COBI compared with RTV to cause clinical adverse events, including smaller alteration in lipid metabolism, fewer gastrointestinal disturbances, and fewer drug-drug interactions[13]. As with efficacy, the head-to-head tolerability comparisons of these agents are derived from two RTV or COBI boosted ATV + TDF/FTC randomized clinical trials.

Lipids

To date, COBI and RTV boosting of ATV in combination with TDF/FTC have shown no difference with respect to total cholesterol, triglycerides, LDL-C, or HDL changes with either agent (Table 2)[26,32,33].

Gastrointestinal tolerability

When administered with ATV, RTV and COBI showed a similar incidence of gastrointestinal adverse events with COBI (diarrhea, 6.0-15.4%; nausea, 10.0-17.7%) compared with RTV (diarrhea, 10.0-20.4%; nausea, 3.0-16.4%)[26,32,33]. In these studies, only one patient in the COBI arms and none in the RTV arms discontinued therapy due to gastrointestinal-related adverse events through 48 weeks of therapy (Table 2)[32].

Table 3. Cobicistat, ritonavir or placebo in subjects with normal renal function (creatinine clearance > 80 ml/min)[38]

	Placebo (n = 12)		COBI (n = 12)		RTV (n = 12)	
	Day 7	Day 14	Day 7	Day 14	Day 7	Day 14
SCr (SD)†	0.02 (0.08)	0.08 (0.17)	0.10 (0.09)*	0.01 (0.06)	0.01 (0.06)	–0.03 (0.06)
eGFR C-G (SD)‡	2.2 (9.10)	22.8 (59.9)	–9.9 (13.1)*	1.4 (11.5)	1.0 (8.62)	5.7 (8.21)*
eGFR MDRD (SD)§	2.2 (11.3)	23.7 (65.0)	–9.9 (12.2)*	1.1 (11.3)	0.4 (8.68)	0.3 (7.99)*
aGFR (SD)¶	4.7 (15.1)	0 (12.0)	–2.7 (8.71)	–2.5 (5.50)	2.2 (9.69)	–0.8 (6.28)
mGFR (SD)**	–0.2 (31.1)	25.5 (72.7)	–18.4 (23.9)*	–5.1 (31.5)	2.8 (35.0)	4.6 (22.8)

*P within-treatment group < 0.05.
†Serum creatinine (SCr): mg/dl.
‡Glomerular filtration rate estimated (eGFR) with the Cockcroft-Gault equation: ml/min.
§Glomerular filtration rate estimated with the modification of diet in renal disease (MDRD) equation: ml/min/1.73 m^2).
¶Actual glomerular filtration rate (aGFR) based on iohexol plasma clearance: ml/min.
**Measured glomerular filtration rate (mGFR) based on 24-hour urinary output and serum creatinine: ml/min.
COBI: cobicistat; RTV: ritonavir; SD: Standard deviation.

Hyperbilirubinemia

Atazanavir raises plasma bilirubin levels by inhibiting UDP glucuronyl transferase and likely through inhibition of the organic anion transporting polypeptides[36,37]. Although bilirubin elevation does not generally result in clinically relevant symptoms, hyperbilirubinemia can lead to jaundice and scleral icterus in some patients[17]. In the phase III trial comparing ATV + TDF/FTC with RTV or COBI, through 48 weeks 41% of subjects receiving COBI and 36% of subjects receiving RTV reported bilirubin-related adverse events, with a higher proportion of subjects in the COBI arm experiencing grade 3 and 4 laboratory hyperbilirubinemia compared with subjects in the RTV arm (65 vs. 57%; p = 0.023) (Table 2)[32]. Differences in treatment discontinuations due to bilirubin-related clinical endpoints between RTV and COBI were not observed through 144 weeks of therapy[32-34].

Renal Function

Serum creatinine and creatinine clearance

Increases from baseline in serum creatinine (SCr) concentration and decreases in creatinine clearance (CrCl) have been reported in clinical studies that compared COBI-containing regimens with RTV-containing regimens[26,32,33]. In these trials, patients with baseline CrCl < 70 ml/min were excluded. After 48 weeks of treatment with RTV or COBI in combination with ATV + TDF/FTC, mean SCr increased in patients in the COBI arm by 0.13 mg/dl compared with 0.09 mg/dl in the RTV arm (p < 0.001), and CrCl decreased by 13 ml/min in the COBI arm versus 9 ml/min in the RTV arm (p < 0.001)[33]. These changes remained similar after 144 weeks of therapy, with discontinuations due to renal events also similar between RTV and COBI at this time point[34].

Renal function laboratory markers

In view of the changes in SCr and CrCl observed in subjects exposed to COBI, studies were conducted to assess whether changes in CrCl with COBI exposure are caused by a true decrease in glomerular function. These studies include a comparison of changes in renal function with COBI (150 mg daily for 7 days), RTV (100 mg daily for 7 days) or placebo administered each to 12 HIV-negative healthy subjects with normal renal function (CrCl > 80 ml/min) (Table 3)[38], a single-arm study in 17 subjects with CrCl 50-70 ml/min at baseline that received COBI 150 mg daily for seven days[38], and an RTV to COBI switch study in 73 virologically suppressed patients treated with ATV + RTV + two nucleoside reverse transcriptase inhibitors (NRTI) (52 patients) or DRV + RTV + two NRTIs (21 patients)[39].

In the healthy subject study, renal function was assessed by CrCl (Cockcroft-Gault), estimated glomerular filtration rate (eGFR) calculated with the modification of diet in renal disease equation, measured GFR (mGFR, based on 24-hour urinary output and serum creatinine), and actual GFR (aGFR, based on iohexol plasma clearance). After seven days of RTV or COBI exposure, mean change from day 0 in SCr, CrCl, eGFR, and mGFR in the COBI arm were statistically different from the placebo arm (p < 0.05) (Table 3). In contrast, renal function measurements in the RTV

arms were not different from the placebo arm at day 7 or day 14. The cohort of subjects with renal impairment (CrCl 50-70 ml/min at baseline) receiving COBI showed significant increases in SCr at days 7 (0.24 mg/dl, SD: 0.13) and 14 (0.05 mg/dl, SD: 0.08) compared with baseline; the study did not include a placebo or a RTV comparator arm[38]. The switch study included patients on an ATV + RTV or DRV + RTV regimen with a CrCl between 50 to 89 ml/min at the time of switch of RTV to COBI. At baseline, 70% of subjects were receiving TDF and 48% of subjects had a median CrCl of 50 to < 70 ml/min. After 24 weeks of follow-up, a total of nine patients (12%) discontinued the study (five due to an adverse event of any kind). Switching RTV to COBI was associated with decreases from baseline in SCr-based CrCl and cystatin C-based eGFR. The decrease in CrCl was similar regardless of the presence of TDF in the NRTI backbone. A limitation of this study was that a control arm of patients who did not switch to COBI was not included. Evaluation of true eGFR with iohexol clearance was performed in a small subset of patients (13 of the 73 patients). This analysis showed that the iohexol clearance was within the pre-specified "lack of change window" (GLSM Ratio reference to baseline, 90% CI: 80-125%), however, baseline characteristics, including a breakdown of NRTI backbone and the use of TDF, ATV, or DRV was not reported in this analysis. Overall, these three studies consistently showed SCr increases from baseline with COBI. When compared with RTV, COBI had higher SCr increases and larger decreases in CrCl.

Proximal tubulopathy

In the ATV phase III study, five of the six subjects that discontinued due to renal events in the COBI arm and two of the five subjects that discontinued in the RTV arm within 48 weeks of therapy experienced proximal tubulopathy[33]. In the RTV to COBI switch study, new cases of proximal renal tubulopathy were not found after 24 weeks of follow-up[39,40]. The risk of proximal tubulopathy with RTV has been assessed among 254 patients exposed to RTV in a cross-sectional analysis of patients consecutively enrolled in the Aquitaine cohort. In this study, RTV was not found to be an independent risk factor for proximal tubulopathy[41].

Interactions with renal transporters

To better understand the mechanisms for the increase in SCr observed with COBI, *in vitro* experiments were conducted to assess the effects of RTV or COBI on the renal transporters believed to be involved in the active secretory clearance of creatinine: organic cation transporter 2 (OCT2), multidrug and toxin extrusion protein (MATE) 1, MATE2-K, p-glycoprotein (P-gp), multidrug resistance protein 2 (MRP2), and breast cancer resistance protein (BCRP)[42]. The investigators concluded that inhibition of MATE1 may be the mechanism for the increases in SCr in patients treated with COBI. Although the IC_{50} values for the inhibition of MATE1 by COBI (1.87 µm) and RTV (1.34 µm) were similar, clinical studies consistently show a differential increase in SCr with COBI compared with RTV[26,32,33]. Because COBI and RTV are highly bound to plasma proteins[6,11], the available amount of plasma free drug may not be enough to achieve the intracellular concentrations required to inhibit MATE1. Since the SCr changes are significantly larger with COBI compared with RTV, a mechanism may exist that preferentially accumulates COBI in the proximal tubular cells and selectively inhibits MATE1. An *in vitro* study investigated the interaction between COBI with basolateral transporters and found evidence suggesting that COBI is transported inside the proximal tubular cells by the OCT2 transporter[43]. This active transport of COBI, with associated increased intracellular concentrations, has been proposed as a potential mechanism for COBI inhibition of MATE1. Data on the uptake of RTV by proximal tubular cells are not currently available.

Drug-drug interactions (Fig. 2)

Boosting of ARV agents is an intentional drug-drug interaction that allows for desirable PK changes in drugs metabolized by CYP450 enzymes. However, some drug-drug interactions remain unpredictable, even in the environment of an enhanced understanding of the CYP450 enzyme system. Both COBI and RTV inhibit CYP450 3A4 with similar potency (IC_{50} values of 0.154 and 0.107 µm, respectively) and drugs contraindicated with COBI are consistent with drugs contraindicated with RTV-containing regimens with respect to CYP450 3A interactions[6,10,11]. The IC_{50} of RTV for CYP2D6 inhibition at 2.8 µm is lower than that of COBI at 9.2 µm[13], however recent data demonstrated greater increases in desipramine (a sensitive substrate of CYP2D6) levels with exposure to COBI 150 mg compared with exposure to RTV 100 mg[44,45]. *In vitro* inhibition of CYP450 1A2, 2B6, 2C19, 2C8, or 2C9 has not been observed at concentrations believed to be clinically relevant with either COBI or RTV[13]. Efavirenz pharmacokinetics (a CYP2B6 substrate) is not significantly affected by either RTV or COBI[11,45,46]. Both RTV and COBI

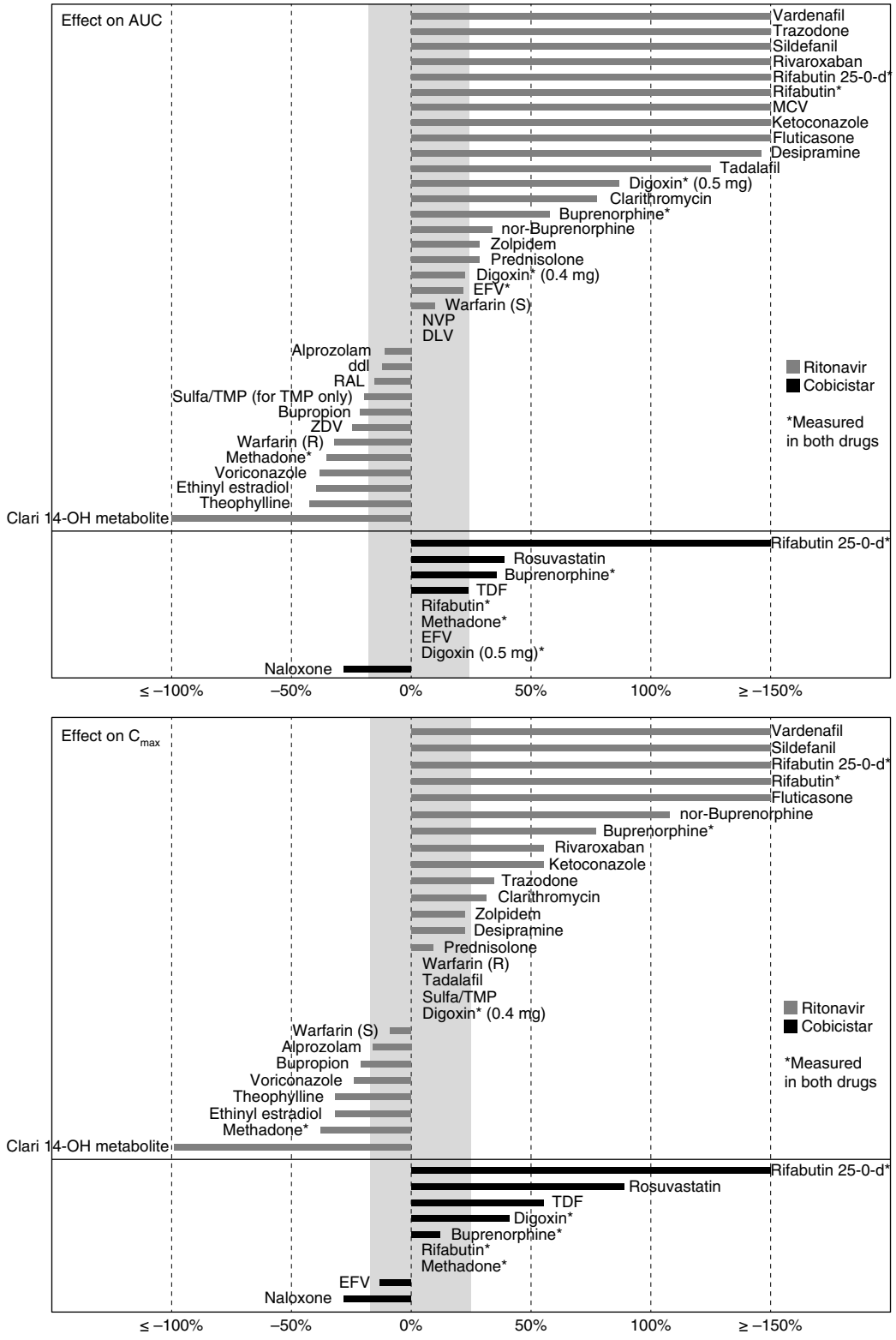

Figure 2. *Drug-drug interaction data per product European Medicines Agency Summary of Product Characteristics. Shaded area indicates traditional bioequivalence (80-125%)*[11,15].

inhibit P-gp, and the effects of COBI and RTV on P-gp substrates appear to be similar as evidenced by effects on digoxin[45]. Ritonavir has been shown to activate pregnane X receptor (PXR), which can result in induction of various metabolizing enzymes and induce metabolism of CYP450 3A, 1A2, 2B6, 2C9, and 2C19 as well as UGT *in vitro*; however, the net effect of RTV on CYP450 3A *in vivo* is inhibition[13]. Induction effects of COBI on these enzymes *in vivo* are currently unknown, but COBI shows a weak activation of PXR *in vitro*[13]. The effects of COBI and RTV on the different CYP450 isoforms, glucuronidation, P-gp or other potential enzyme systems (and the complex interactions between these) would make it very difficult to extrapolate drug-drug interaction data from RTV to COBI or *vice versa*. A summary of drug-drug interaction information included in the SmPCs for RTV and COBI is included in figure 2. Although the COBI SmPC drug-drug interaction section refers frequently to potential interactions, there is a relative paucity of PK study data when compared with the SmPC of RTV.

Interaction with tenofovir

In some patients, TDF can be associated with renal toxicities, including proximal renal tubulopathy and decreased glomerular filtration. Tenofovir-associated nephrotoxicity may not always be reversible, and TDF discontinuation can result in complete, partial, or no recovery of renal function. Coadministration of TDF with LPV/r, DRV + RTV, ATV + RTV, and SQV + RTV is associated with increases in TDF C_{max} (0-34%), AUC (0-37%), and C_{min} (23-51%), and monitoring for TDF-mediated toxicity is recommended for these combinations[47]. Similarly, increased TDF plasma exposures have been documented after coadministration with COBI. In a study of 42 subjects given EVG/COBI/TDF/FTC, TDF C_{max} and C_{tau} levels were increased by 30 and 24%, respectively, compared with TDF/FTC alone[48]. The investigators hypothesized that inhibition of gut P-gp by COBI may have been the reason for higher exposure of TDF, and that this effect might be transient. *In vitro* studies comparing the effects of RTV or COBI on the active transport of TDF by multidrug resistance protein 4 (MRP4), organic anion transporter 1 (OAT1), and organic anion transporter 3 (OAT3) concluded COBI and RTV do not alter renal transport of TDF[49].

Anti-HIV activity

Pharmacokinetic boosting of PIs results in increases in the IQ of the PI. As a result, PI-associated resistance development has significantly decreased in the boosting era[50]. Ritonavir has anti-HIV activity; thus, the question remains whether boosting doses of RTV could selectively drive PI resistance development in the absence of a concomitant, fully suppressive ARV regimen. Large clinical trials have shown that PI resistance mutations are very rare in therapy-naive patients failing PI + RTV-based regimens[16-18]. Cobicistat does not demonstrate measurable anti-HIV activity[13]. Primary PI resistance mutations were not selected among virologic failures in subjects treated with ATV + COBI + TDF/FTC, EVG/COBI/TDF/FTC or ATV + RTV + TDF/FTC[32,33,51,52]. However, during the review of the application for approval of EVG/COBI/TDF/FTC, the FDA highlighted a disproportionate number of substitutions in the protease sequence that developed on-treatment in the EVG + COBI + TDF/FTC treatment arm (9/14 subjects) compared with the EFV + TDF/FTC fixed-dose combination arm (4 of 15 subjects)[53]. Three of the nine protease substitutions in isolates from the EVG/COBI/TDF/FTC arm have been associated with resistance to PIs (M36I, D60E, and V77I). The clinical relevance of this finding was unclear because these protease substitutions can also be considered polymorphisms. The 144 week follow-up of the EVG/COBI/TDF/FTC versus ATV + RTV + TDF/FTC study did not detect any primary PI resistant mutations among eight subjects (2.3%) in the EVG/COBI/TDF/FTC arm that failed with emergent resistance mutations compared with two subjects (0.6%) in the ATV + RTV + TDF/FTC arm[54].

Use during pregnancy

Both RTV and COBI (in EVG/COBI/TDF/FTC) are pregnancy category B antiretroviral drugs[6,10]. The drugs should only be used if the benefits outweigh the potential risks to the fetus. Data on birth defects among women exposed to RTV during pregnancy have been collected by the Antiretroviral Pregnancy Registry[55]. The prevalence of birth defects among 2,096 prospective Registry reports of women with a first trimester exposure to RTV is 2.2/100 live births (96% CI: 1.6-3.0%). Although it is not known how many of these exposures represent full-dose RTV versus lower-dose RTV, this prevalence is not significantly different from the CDC's birth defects surveillance system (MACDP), which reported a total prevalence of birth defects identified among births from 1989 through 2003 of 2.72/100 live births (2.68-2.76)[55]. Through January 2013, no data have been published from the APR on the rate of birth defects of COBI or EVG/COBI/TDF/FTC. It is not known whether either RTV or COBI is excreted in human milk.

Discussion

Both COBI and RTV are effective PK enhancers, as it relates to inhibition of CYP450 3A4. The drugs differ in their potential to inhibit or induce other isoforms of the CYP450 enzyme system, as well as other metabolic pathways – as such, other drug-drug interactions can potentially differ between these agents. It may be appropriate not to assume that the drug-drug interactions identified for RTV would be identical of those of COBI.

Long-term efficacy data of RTV as a component of PI-based ART in both treatment-naive and -experienced patients is extensive, while fewer clinical trials have studied COBI. Both RTV and COBI have been compared in prospective, randomized clinical trials, when used in combination with ATV + TDF/FTC in ARV-naive adult patients. Results showed that the COBI-containing arms of these studies had non-inferior virologic outcomes compared with the RTV-containing arms through 144 weeks of therapy. Tolerability of these agents was comparable, specifically as it relates to gastrointestinal and lipid changes; however, grade III/IV hyperbilirubinemia occurred more frequently in the COBI arm of one study. The differential effect of COBI on renal function parameters compared with RTV has been attributed to inhibition of tubular secretion of creatinine due to the inhibitory effect on MATE1, even though the *in vitro* IC_{50} values for the inhibition of MATE1 by COBI and RTV are similar. Although the report suggesting intracellular accumulation of COBI via OCT2-mediated transport may help explain SCr elevations with COBI, the mechanisms responsible for the clinical differences between RTV and COBI related to SCR increases has not been elucidated yet. The US prescribing information of the EVG/COBI/TDF/FTC fixed-dose combination recommends that patients who experience a confirmed increase in SCr of > 0.4 mg per dl from baseline should be closely monitored for renal safety[10]. Accurate assessment of glomerular filtration in the presence of COBI required utilization of iohexol. This may present a clinical challenge, as the use of exogenous marker testing might be necessary to accurately assess whether changes in SCr or eGFR are the result of pathology versus a COBI-mediated effect.

A difference between COBI and RTV is COBI's lack of ARV activity. At boosting doses, the theoretical risk of RTV contributing to PI resistance development in previously ARV-naive patients failing PI-based therapy, in which RTV is used as a PK booster of the other PI , has not been confirmed[56]. Although COBI does not exhibit *in vitro* activity against HIV, it is structurally similar to RTV. Protease inhibitor-associated resistance primary mutations were not detected in patients failing therapy with the EVG/COBI/TDF/FTC fixed-dose combination or ATV + COBI + TDF/FTC, although substitutions in the PI sequence were observed. Compared with RTV, limited clinical data currently exist with the use of COBI in combination with PIs and longer-term follow-up in larger patient numbers is needed to assess the risk of PI-resistance development on failure.

In conclusion, both COBI and RTV are efficacious at PK boosting of the HIV PIs darunavir and atazanavir, due to their ability to inhibit CYP450 isozymes. Clinically important drug-drug interactions might differ between these agents and need to be evaluated for each drug on an individual basis. In general, the safety and tolerability of COBI and RTV are comparable; however, differences exist between the drugs with regards to their effects on serum creatinine and creatinine clearance. There are several studies ongoing that will further assess and characterize these differences and help health-care providers select the most appropriate ARV treatment for their patients.

Funding Source

AbbVie.

Conflict of interest/disclosure information

AbbVie provided financial support for the study and participated in the analysis and interpretation of data as well as the writing, review and approval of the manuscript. All authors are AbbVie employees and may hold Abbott or AbbVie stock or options. Medical writing support was provided by Rebecca Maag, who is also an AbbVie employee and may own Abbott or AbbVie stock. The authors wish to acknowledge John Fincke, Christine Ratajczak, Christos Argyropoulos, Camille Campbell-Pope, Dilek Arikan, and Angela Nilius for their contributions to this review.

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