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Cobicistat versus ritonavir boosting and differences in the drug–drug interaction profiles with co-medications

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Nearly all HIV PIs and the integrase inhibitor elvitegravir require a pharmacokinetic enhancer in order to achieve therapeutic plasma concentrations at the desired dose and frequency. Whereas ritonavir has been the only available pharmacokinetic enhancer for more than a decade, cobicistat has recently emerged as an alternative boosting agent. Cobicistat and ritonavir are equally strong inhibitors of cytochrome P450 (CYP) 3A4 and consequently were shown to be equivalent pharmacokinetic enhancers for elvitegravir and for the PIs atazanavir and darunavir. Since cobicistat is a more selective CYP inhibitor than ritonavir and is devoid of enzyme-inducing properties, differences are expected in their interaction profiles with some co-medications. Drugs whose exposure might be altered by ritonavir but unaltered by cobicistat are drugs primarily metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 or drugs undergoing mainly glucuronidation. Thus, co-medications should be systematically reviewed when switching the pharmacokinetic enhancer to anticipate potential dosage adjustments.

Introduction

The concept of pharmacokinetic boosting, whereby the metabolism of one drug is inhibited by another drug, was applied early on to HIV PIs in order to improve their effectiveness and convenience of use.[1] Over the past decade, boosting of PIs has been performed exclusively by using low doses (100–200 mg/day, except for with tipranavir) of ritonavir, a potent inhibitor of intestinal and hepatic cytochrome P450 (CYP) 3A and of P-glycoprotein (P-gp), to increase the absorption and prolong the $t_{\frac{1}{2}}$ of coadministered PIs.[2] The use of ritonavir as a boosting agent presents a number of disadvantages. Ritonavir has antiviral activity, which raises concern about the development of PI resistance if ritonavir is used as a booster in non-PI-containing regimens. In addition, ritonavir is poorly soluble, which limits its coformulation with other agents. Ritonavir also has issues of tolerability, and it inhibits or induces other drug-metabolizing enzymes, resulting in numerous unwanted drug–drug interactions (DDIs).[2] Consequently, novel boosting agents have been investigated.[3] Cobicistat, a structural analogue of ritonavir without antiviral activity and with improved physicochemical properties, is now available as an alternative pharmacokinetic enhancer.[3,4] Cobicistat inhibits CYP3A with a potency similar to that of ritonavir.[5] Cobicistat, at a dosage of 150 mg once daily, provides bioequivalent exposures of the PIs atazanavir (300 mg once daily)[6] and darunavir (800 mg once daily)[7] and of the integrase inhibitor elvitegravir (150 mg once daily)[8] compared with those observed with 100 mg of ritonavir once daily. Cobicistat is currently available as a single agent (Tybost®) or coformulated with atazanavir (Evotaz®), darunavir (Rezolsta®) or elvitegravir (Stribild®, Genvoya®). Although cobicistat (150 mg once daily) and ritonavir (100 mg once daily) are interchangeable as boosters of drugs metabolized by CYP3A,[9] cobicistat is a more specific CYP3A inhibitor than ritonavir and has no inducing properties. Consequently, differences are expected in their interaction profiles with some co-medications.

This commentary summarizes the effects of ritonavir and cobicistat on various CYPs and drug transporters and provides a list of co-medications predicted to be affected differently and which may require a dosage adjustment when switching boosting agent.

Effects of ritonavir and cobicistat on cytochromes and drug transporters

Ritonavir and cobicistat are equally potent inhibitors of CYP3A.[4] As summarized in Table 1, cobicistat is a more selective inhibitor of CYPs and, when clinically relevant concentrations are considered, has no inhibitory effects on CYP2C8 and is a weaker inhibitor of CYP2D6.[4]

Similarly to ritonavir, cobicistat inhibits the intestinal transporters P-gp and breast cancer resistance protein (BCRP), thereby increasing the absorption of coadministered substrates such as atazanavir, darunavir and tenofovir alafenamide.[11] At clinical concentrations, ritonavir and cobicistat also inhibit the hepatic transporters organic anion transporting polypeptides (OATPs) and multiantimicrobial extrusion protein 1 (MATE1), a transporter involved in the tubular secretion of creatinine.[12] Consequently, a

Table 1. Inhibitory and inducing effects of ritonavir and cobicistat on cytochromes and drug transporters[3,4,10–12]

	IC$_{50}$ (μM)	
	ritonavir	cobicistat
Cytochrome		
CYP1A2	>25	>25
CYP2B6	2.9	2.8
CYP2C8	2.8	>25
CYP2C9	4.4	>25
CYP2C19	>25	>25
CYP2D6	2.8	9.2
CYP3A4	0.11	0.15
Transporter		
P-gp	>20	36
BCRP	>20	59
OATP1B1	2.05	3.5
OATP1B3	1.83	1.88
MATE1	1.34	1.87
MATE2-K	>20	33.5
OAT1	>20	>100
OAT3	8.46	>100
OCT2	~20	14
PXR activation[a]	51%	10%

OAT, organic anion transporter.
[a]Potential to activate PXR.

small increase in serum creatinine with a related decrease in estimated glomerular filtration rate have been reported upon treatment with cobicistat- and ritonavir-based regimens. This effect has been shown to reflect mainly the inhibition of creatinine secretion by MATE1 rather than an actual impairment of the renal function.[13] Interestingly, when compared with those containing ritonavir, cobicistat-containing regimens have consistently shown higher serum creatinine concentrations,[6,9,14] even though they share similar IC$_{50}$ values for MATE1.[12] Cobicistat has been shown to be actively transported in the tubular cells by organic cation transporter 2 (OCT2).[12] Therefore, one explanation for the higher serum creatinine is that cobicistat accumulates preferentially in the tubular cells and thus achieves higher concentrations to inhibit MATE1.[12]

A key difference between ritonavir and cobicistat is their ability to activate the pregnane X receptor (PXR), which regulates the expression of various drug-metabolizing enzymes.[15] Cobicistat was shown to have a limited effect on PXR and therefore is unlikely to induce drug metabolism.[4] Conversely, ritonavir activates PXR and is known to induce CYP1A2, CYP2B6, CYP2C9 and CYP2C19 and glucuronidation.[16–19]

Co-medications affected differently by ritonavir and cobicistat

Based on the previous considerations, drugs undergoing major metabolism via CYP1A2, CYP2B6, CYP2C8, CYP2C9 or CYP2C19 or via glucuronidation, with no or minor involvement of CYP3A, are predicted to be affected differently by ritonavir than by cobicistat. Co-medications belonging to this category are presented in Table 2. The list has been established from the Liverpool HIV drug interaction database,[20] which contains information on the metabolic pathway and related risk of DDI with antiretroviral drugs for more than 600 co-medications. The differences in the interaction profiles for ritonavir and cobicistat are summarized as follows:

- exposure of drugs glucuronidated and/or metabolized by inducible CYPs and without CYP3A involvement are predicted to be decreased by ritonavir but not affected by cobicistat (e.g. lamotrigine)
- exposure of drugs glucuronidated and/or metabolized by inducible CYPs to a larger extent than CYP3A are predicted to be decreased by ritonavir but increased moderately by cobicistat (e.g. asenapine)
- exposure of drugs whose metabolism is subject to induction or inhibition are predicted to be decreased or increased by ritonavir but only increased by cobicistat (e.g. dihydrocodeine)

Importantly, cobicistat is licensed only as a once-daily boosting agent and therefore might not be able to overcome the effects of inducers. Thus, cobicistat-boosted regimens are not recommended in presence of efavirenz, etravirine or nevirapine, whereas coadministration is possible when using, for instance, darunavir twice daily with ritonavir (Table 2).[20]

Finally, although cobicistat has no inducing effects *per se*, it is also coformulated with elvitegravir, a modest inducer of CYP2C9, which might decrease the exposure of sensitive substrates such as the anticoagulants. Warfarin is a mixture of enantiomers, which are metabolized by different CYPs. *S*-warfarin (more potent) is metabolized by CYP2C9, whereas *R*-warfarin is metabolized by CYP1A2, CYP3A4 and CYP2C19.[21] Interestingly, elvitegravir/cobicistat was shown to decrease the exposure of warfarin, suggesting that CYP2C9 induction by elvitegravir has the stronger effect on warfarin metabolism compared with CYP3A inhibition by cobicistat.[22]

Conclusions

Although cobicistat and ritonavir are interchangeable as boosters of CYP3A, cobicistat is a more-specific CYP3A inhibitor than ritonavir and has no inducing properties. Consequently, co-medications primarily metabolized by CYP1A2, CYP2B6, CYP2C8, CYP2C9 and CYP2C19 or mainly glucuronidated are predicted to be affected differently by ritonavir and cobicistat. Therefore, co-medications should be systematically reviewed when switching pharmacokinetic enhancer in order to anticipate potential dosage adjustments.

Transparency declarations

The Liverpool HIV Drug Interactions web site (www.hiv-druginteractions.org) receives support from Merck, Janssen, Gilead, Boehringer Ingelheim, ViiV Healthcare and Bristol-Myers Squibb; editorial content remains independent. C. M. has received educational grants from AbbVie, Gilead and Bristol-Myers Squibb for her clinical service on DDIs. S. K. has received research funding from ViiV Healthcare, Janssen and Merck and travel

Table 2. Co-medications predicted to be affected differently by ritonavir versus cobicistat pharmacokinetic boosting

Therapeutic class	Drug	Metabolic pathway/comments	Ritonavir	Cobicistat
Anaesthetics	propofol	UGT1A9, UGT1A8 + CYP2B6	↓	↔
Analgesics	diamorphine	deacetylation + UGT2B7, UGT1A1	↓	↔
	dihydrocodeine	CYP2D6 + UGT2B7 > CYP3A4	↓↑	↑
	hydromorphone	UGT2B7	↓	↔
	morphine	UGT2B7, UGT1A1	↓	↔
	pethidine	CYP2B6 > CYP3A4	↓	↑
Antibacterials	sulfadiazine	CYP2C9	↓	↔
Anticoagulants	acenocoumarol	CYP2C9 > CYP1A2, CYP2C19	↓	↔
	eltrombopag	UGT1A1, UGT1A3 + CYP1A2, CYP2C8	↓	↔
	phenprocoumon	CYP2C9, CYP3A4	↓↑	↑
	warfarin	CYP2C9 > CYP1A2, CYP3A4, CYP2C19	↓	↑
Anticonvulsants	lamotrigine	UGT1A4	↓	↔
	valproate	UGT1A6, UGT1A9, UGT2B7 + CYP2C9, CYP2C19	↓	↔
Antidepressants	agomelatine	CYP1A2	↓	↔
	bupropion	CYP2B6	↓	↔
	duloxetine	CYP2D6, CYP1A2	↓↑	↑
	sertraline	CYP2B6 > CYP2C9, CYP2C19, CYP2D6, CYP3A4	↓	↑
Antidiabetics	gliclazide	CYP2C9 > CYP2C19	↓	↔
	glimepiride	CYP2C9	↓	↔
	glipizide	CYP2C9	↓	↔
	nateglinide	CYP2C9 > CYP3A4	↓↑	↑
	rosiglitazone	CYP2C8 > CYP2C9	↓	↔
	tolbutamide	CYP2C9 > CYP2C8, CYP2C19	↓	↔
Antiprotozoals	amodiaquine	CYP2C8	↑	↔
	atovaquone	glucuronidation	↓	↔
	proguanil	CYP2C19 > CYP3A4	↓	↔
Antipsychotics	asenapine	UGT1A4, CYP1A2, CYP3A4	↓	↑
	olanzapine	CYP1A2, UGT1A4	↓	↔
Antiretrovirals	efavirenz	cobicistat administered 150 mg once daily is not sufficient to overcome induction by efavirenz, etravirine or nevirapine	[a]	[b]
	etravirine		[a]	[b]
	nevirapine		[a]	[b]
β-Blockers	carvedilol	UGT1A1, UGT2B4, UGT2B7 + CYP2D6	↓↑	↑
	oxprenolol	glucuronidation	↓	↔
Bronchodilators	theophylline	CYP1A2	↓	↔
Contraceptives/HRT	oestradiol	CYP3A4, CYP1A2 + glucuronidation	↓	↑
	ethinyloestradiol	CYP3A4 > CYP2C9, glucuronidation	↓	↑
	norethisterone	CYP3A4, glucuronidation	↓	↑
Cytotoxics	anastrozole	CYP3A4 + UGT1A4	↓↑	↑
	dacarbazine	CYP1A2 > CYP2E1	↓	↔
	droloxifene	glucuronidation	↓	↔
	epirubicin	UGT2B7	↓	↔
	formestane	partly glucuronidation	↓	↔
	procarbazine	CYP2B6, CYP1A2	↓	↔
Gastrointestinal agents	alosetron	CYP1A2 > CYP2C9, CYP3A4	↓	↔
Antihypertensives	irbesartan	glucuronidation + CYP2C9	↓	↔
	labetalol	UGT1A1, UGT2B7	↓	↔
	losartan	CYP2C9	↓	↔
	torasemide	CYP2C9	↓	↔
Immunosuppressants	mycophenolate	UGT1A9, UGT2B7	↓	↔
Lipid-lowering agents	gemfibrozil	UGT2B7	↓	↔
	pitavastatin	UGT1A3, UGT2B7 > CYP2C9, CYP2C8	↓	↔

Continued

Table 2. *Continued*

Therapeutic class	Drug	Metabolic pathway/comments	Ritonavir	Cobicistat
Anti-Parkinson agents	apomorphine	glucuronidation, sulphation	↓	↔
	rasagiline	CYP1A2	↓	↔
	ropinirole	CYP1A2	↓	↔
Other	dexmedetomidine	UGT1A4, UGT2B10, CYP2A6	↓	↔

HRT, hormone replacement therapy; UGT, uridine diphosphate-glucuronosyltransferase; ↑, potential increase in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting; ↓, potential decrease in co-medication exposure by ritonavir or cobicistat pharmacokinetic boosting; ↔, no clinically significant effect on co-medication exposure.
Information on the metabolic pathway of the co-medication and on the description of the DDI can be found at the Liverpool HIV Drug Interactions web site.[20]
[a]Coadministration is possible when using 600/100 mg of darunavir/ritonavir twice daily, but it is not recommended with 300/100 mg of atazanavir/ritonavir once daily.
[b]Not recommended to be given with once-daily boosting with cobicistat (i.e. 150 mg once daily); cobicistat is not sufficient to overcome the induction effect of efavirenz, etravirine or nevirapine. Of note: cobicistat is not licensed as a twice-daily boosting agent.

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