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REVIEW

Cobicistat: a Novel Pharmacoenhancer for Co-Formulation with HIV Protease and Integrase Inhibitors

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ABSTRACT

Human immunodeficiency virus (HIV) therapy has evolved over the last 20 years from mono-drug therapy given five times daily to regimens consisting of three or four drugs combined in a single-tablet dosed once daily. To allow once-daily administration, several drugs require pharmacokinetic boosting by a concomitantly administered P-glycoprotein and cytochrome P450 inhibitor such as ritonavir. The availability of cobicistat provides an alternative to ritonavir to those who are intolerant to this drug, and the opportunity for co-formulated single-tablet regimens consisting of tenofovir/emtricitabine, cobicistat and elvitegravir, atazanavir or darunavir. The cobicistat/elvitegravir-based regimen is well tolerated and patients achieved high rates of HIV RNA suppression in clinical trials. Cobicistat inhibits renal tubular secretion of creatinine, resulting in increased serum creatinine concentrations and reduced estimated glomerular filtration rate, with a new set point reached after 4 weeks. Treatment limiting renal toxicity with cobicistat/elvitegravir and tenofovir disoproxil fumarate is infrequent and may be further reduced when cobicistat is co-formulated with tenofovir alafenamide fumarate, a novel formation of tenofovir currently undergoing clinical trials.

Keywords: Boosting; Cobicistat; eGFR; HIV; Infection; Pharmacology; Renal; Stribild; Virology

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INTRODUCTION

Since the introduction of zidovudine in 1987, human immunodeficiency virus (HIV) therapy has been revolutionised with the availability of over 30 agents across six drug classes. Current British HIV Association (BHIVA) guidelines recommend treatment with a nucleoside/nucleotide reverse transcriptase inhibitor (NRTI) backbone together with a non-nucleoside reverse transcriptase inhibitor (NNRTI), ritonavir-boosted protease inhibitor (PI), or integrase inhibitor (II) as a first-line therapy for the treatment-naïve HIV-positive individuals [1]. Whilst the majority of patients achieve an undetectable HIV RNA level on these treatments, high levels of adherence are required for successful treatment outcomes; recent clinical trials show significantly worse outcomes amongst sub-optimally adherent individuals (defined as adherence <95%) on NNRTI- and PI-based first-line regimens [2, 3]. Side effects remain the commonest reason for switching antiretroviral therapy [4, 5], and side effects are a common reason for late and missed doses [6]. Several agents [e.g. lamivudine, emtricitabine (FTC), efavirenz (EFV), nevirapine and raltegravir (RTG)] have a low genetic barrier to resistance and may be rendered ineffective by single nucleotide substitutions in the viral genome [7–9], while others [e.g. rilpivirine (RPV) and abacavir (ABC)] may have limited potency at high HIV viral load, are best avoided in patients with chronic kidney disease [e.g. tenofovir (TDF), atazanavir (ATV)], or in those at high risk of coronary heart disease (ABC), or should not be used in HLA B5701-positive patients (ABC) [1]. While many patients prefer a once-daily regimen consisting of a small number of tablets, some agents (e.g. RTG) require twice-daily dosing. As a result, antiretroviral therapy continuous to evolve as agents with favourable side-effect profiles, low pill burden, potency across viral loads, and limited cross resistance with existing antiretrovirals become available for use in clinical practice. Co-formulation of such drugs with the NRTI backbone into a single-tablet regimen is an attractive strategy to improve patient convenience, adherence, long-term outcomes and, in some countries, to lower prescription charges.

Cobicistat (COBI), a novel pharmacoenhancer, was recently licensed for the treatment of HIV infection when administered as Stribild® (Gilead Inc., Foster City, CA, USA), a single-tablet regimen containing COBI, elvitegravir (EVG), a novel II, and an NRTI backbone of TDF/FTC. Similar to many PI, EVG requires boosting in order to maintain therapeutic plasma concentrations. Co-administration of COBI maintains EVG plasma concentrations well above the protein-adjusted IC_{95} for wild-type HIV for more than 24 h, allowing once-daily administration [10]. COBI is also being developed as a pharmacoenhancer for HIV PI, with the potential to create fixed-dose combinations of COBI/ATV or COBI/darunavir (DRV). Finally, a novel formulation of tenofovir [tenofovir alafenamide fumarate (TAF)] is currently undergoing clinical trials which may lead to additional COBI-based combination tablets for HIV treatment [11]. In this review, we discuss the concept of pharmacoenhancing, the pharmacology of COBI, relevant clinical trial data and its potential role in clinical practice.\

METHODS

Clinical trials, pharmacokinetic and toxicity studies performed with COBI were reviewed for the purpose of this article. Relevant studies

were identified by searching the published literature (PubMed) and conference abstracts from January 2008 up to July 2013 for "cobicistat", "elvitegravir" and "Stribild". The analysis in this article is based on previously conducted studies, and does not involve any new studies of human or animal subjects performed by any of the authors.

RITONAVIR AND THE CONCEPT OF BOOSTING

Ritonavir (RTV) is an HIV PI which has been available since 1996. While its unfavourable side-effect profile at doses required to inhibit HIV replication limits its role as anti-HIV therapy, it has potent inhibitory effects on cytochrome P450 (CYP) and P-glycoprotein [12]. Inhibition of the efflux transporter P-glycoprotein results in increased drug absorption, and inhibition of CYP (especially 3A4) in reduced elimination of concomitantly administered medications. The pharmacokinetic profile of RTV has resulted in its widespread use as pharmacoenhancer of other PI, most commonly lopinavir, ATV and DRV. RTV prolongs the terminal elimination half-life of the co-administered PI and increases PI trough concentration, allowing once- or twice-daily administration of the "boosted" PI. This inhibitory effect on P-glycoprotein and CYP3A4 is achieved at low, sub-therapeutic doses (100–200 mg daily) that are generally better tolerated [12].

DRAWBACKS OF PHARMACOENHANCEMENT

Inhibition of CYP3A4 (and other CYP iso-enzymes) will affect concurrently administered medications metabolised by this pathway. COBI interactions are less widely studied than RTV; while data are awaited it may be necessary to draw on the experience with RTV when predicting likely COBI interactions. Some drugs cannot be co-administered with CYP3A4 inhibitors due to significant increases in concentrations of the co-administered agent (e.g. fluticasone, simvastatin) while others require dose adjustment (e.g. rifabutin, for which interaction data with RTV and COBI is available, and clarithromycin, for which only the interaction with RTV has been studied—advice for COBI is extrapolated from this). In addition, neither RTV nor COBI is 'clean' in terms of CYP inhibition; the impact of both on hepatic enzymes is more complex than CYP3A4 inhibition alone (Table 1) [10], further increasing the potential for important drug–drug interactions. The low doses of ritonavir used for boosting may still be associated with tolerability and toxicity issues [13, 14]. There is a paucity of data regarding the tolerability of COBI as a single agent but when used to boost ATV, adverse events and tolerability were similar for COBI and RTV [15].

Table 1 Inhibitory effect of COBI and RTV on cytochrome P450 iso-enzymes [10]

CYP	COBI	RTV
1A2	>25	>25
2B6	2.8	2.9
2C8	30	5.5
2C9	>25	4.4
2C19	>25	>25
2D6	9.2	2.8
3A4	0.2	0.2

Data are expressed as CYP iso-enzyme IC_{50} in micromoles/liter. A lower value reflects a greater inhibitory effect

COBI cobicistat, *RTV* ritonavir

PHARMACOENHANCERS: COBICISTAT COMPARED WITH RITONAVIR

Similar to RTV, COBI is a potent inhibitor of CYP3A enzymes but has no antiviral activity against HIV. It was specifically developed as a pharmacoenhancer to be used alongside drugs that are metabolised through CYP, specifically EVG and the PI ATV and DRV. While COBI and RTV have similar inhibitory effects on CYP3A4 and 2B6, COBI has a weaker (2D6) or no (2C8 and 2C9) inhibitory effect on other CYP enzymes (Table 1) [10]. Additional pharmacokinetic studies of COBI revealed <twofold increased desipramine exposure (reflecting limited CYP2D6 inhibition), minimally reduced EFV exposure (suggesting no relevant interactions with CYP2B6 substrates) and small increases in digoxin exposure consistent with inhibition of intestinal P-glycoprotein [16]. Similar to RTV, cimetidine and trimethoprim, COBI is an inhibitor of the renal multidrug and toxin extrusion protein 1 (MATE1) [17]. As a consequence, serum creatinine levels are increased by approximately 10–15%, and creatinine-based estimates of creatinine clearance are reduced by approximately 10% (10–15 mL/min) with COBI exposure [18, 19], a somewhat more pronounced effect than observed with RTV.

COBI at a dose of 150 mg once daily increases EVG exposure to a similar degree as RTV 100 mg (Table 2A); the EVG C_{tau} with COBI was 11-fold above the protein binding-adjusted IC_{95} (44.5 ng/mL) of wild-type HIV [10]. COBI/ATV and RTV/ATV co-administration results in similar ATV pharmacokinetic profiles (Table 2B, C) [15, 20]. The ATV C_{tau} with COBI was well above the protein binding-adjusted IC_{90} of wild-type HIV (14 ng/mL) and in >90% of visits above the Department of Health and Human Sciences (DHHS) recommended target of 150 ng/mL [20]. COBI and RTV are also similar in their ability to boost DRV when given once or twice daily (Table 2D, E) [21]. The 30% lower mean C_{tau} with once-daily COBI/DRV administration is 18 times over the protein binding-adjusted EC_{50} of wild-type HIV and the recommended target for wild-type virus (55 ng/mL). Similar DRV concentrations were observed when COBI/DRV twice daily was co-administered with EVG or etravirine [22]. By contrast, tipranavir exposure was inadequately boosted by COBI 150 mg as compared to RTV 200 mg (both given twice daily) [22].

The pharmacokinetic parameters of COBI are similar when taken fasted or with light meals; high-calorie, high-fat meals reduce COBI AUC_{tau} and C_{max} by 18–24%. By contrast, COBI-boosted EVG exposure is increased when given with food, with AUC_{tau} and C_{max} increased by 22–36% with light meals and by 56–91% with high-calorie, high-fat meals. Although it is recommended that Stribild is administered with food [23], the fasted EVG C_{24h} (250 ng/mL) was well over the protein-adjusted IC_{95} for wild-type HIV (44.5 ng/mL) [23], suggesting that Stribild should provide adequate EVG exposure in the vast majority of fasted patients. The pharmacokinetic parameters of COBI and EVG are not affected by co-administration of omeprazole, a proton pump inhibitor, or famotidine, an H_2-receptor antagonist [24]. Neither COBI nor EVG requires dose modification in patients with severe renal impairment (creatinine clearance <30 mL/min) [25] or moderate liver disease (Child–Pugh–Turcotte class B) [26].

A pharmacokinetic study of 32 patients switched from Atripla® (Bristol Myers Squibb, New York, NY, USA & Gilead Inc, Foster City, CA, USA) (fixed-dose combination of EFV and

Table 2 Relative effects of cobicistat vs. ritonavir on the pharmacokinetic profiles of elvitegravir, atazanavir and darunavir

Mean (CV%)	AUC_{0-24} (ng h/mL) geometric mean	C_{max} (ng/mL)	C_{trough} (ng/mL)
A. Pharmacokinetic profile of EVG (200 mg QD) when co-administered with COBI (150 mg QD) or RTV (100 mg QD) [10]			
COBI/EVG	27,000 (29.4)	2,660 (27.6)	490 (52.9)
RTV/EVG	22,500 (32.1)	2,500 (32.1)	409 (40.5)
B. Pharmacokinetic profile of ATV (300 mg QD) when co-administered with COBI (150 mg QD) or RTV (100 mg QD) [15]			
COBI/ATV	55,900 (28.2)	4,880 (24.9)	1,330 (42.7)
RTV/ATV	55,200 (27.6)	5,270 (23.6)	1,340 (40.8)
C. Week 48 pharmacokinetic profile of ATV (300 mg QD) when co-administered with COBI (150 mg QD) or RTV (100 mg QD) [20]			
COBI/ATV	41,300 (33)	3,880 (36)	655
RTV/ATV	49,900 (47)	4,390 (47)	785
D. Pharmacokinetic profile of DRV (800 mg QD) when co-administered with COBI (150 mg QD) or RTV (100 mg QD) [21]			
COBI/DRV	81,100 (31.0)	7,740 (21.8)	1,330 (66.8)
RTV/DRV	80,000 (34.0)	7,460 (20.3)	1,870 (83.3)
E. Pharmacokinetic profile of DRV (600 mg BID) when co-administered with COBI (150 mg BID) or RTV (100 mg BID) [22]			
COBI/DRV	73,400 (19)	9,040 (19)	3,960 (30)
RTV/DRV	67,900 (22)	8,390 (21)	3,800 (27)

ATV Atazanavir, *AUC* area under the concentration curve, *BID* twice daily, *C* concentration, *COBI* cobicistat, *CV* coefficient of variation, *DRV* darunavir, *EVG* elvitegravir, *QD* once daily, *RTV* ritonavir

TDF/FTC) to Stribild showed reduced EVG concentrations during the first week as a result of glucuronosyl transferase induction by EFV. However, the median EFV C_{tau} remained above the IC_{90} of wild-type HIV for at least 4 weeks and, by the end of the first week, the median EVG C_{tau} was threefold higher than the IC_{95}, suggesting that EFV activity is maintained while EVG concentrations reach therapeutic concentrations [27]. A phase IIIb study is evaluating the safety of a regimen switch from Atripla to Stribild in terms of continued viral suppression.

COBICISTAT AND DRUG–DRUG INTERACTIONS

Due to its inhibition of CYP enzymes, it is anticipated that COBI exposure will result in drug–drug interactions similar to those seen with RTV (see above). However, few studies have examined the effects of COBI on the plasma concentrations of other drugs and until the results of such studies emerge, it would appear prudent to avoid COBI in patients who require drugs with a narrow therapeutic index (e.g. cancer chemotherapy,

digoxin) or drugs that are contraindicated or require major dose adjustment in those on RTV. Further and up-to-date information is available on the HIV Drug Interactions webpage [28].

COBICISTAT-CONTAINING HIV THERAPY: RESULTS FROM THE PHASE III CLINICAL TRIALS PROGRAMME

The results of three studies have been presented to date; two studies investigated the efficacy and safety of Stribild [29–32], while the third study compared COBI with RTV, each co-administered with ATV and TDF/FTC [33].

The GS-US-236-0102 and 0103 studies are ongoing phase III, double-blind, randomised, placebo-controlled trials of antiretroviral-naïve HIV-1-positive adults [31, 32]. Patients with a baseline HIV RNA measurement of >5,000 copies/mL were randomised 1:1 to Stribild or Atripla [0102 study], or to Stribild or TDF/FTC/ATV/RTV [0103 study]. To be eligible, patients were required to have a creatinine clearance (calculated by Cockcroft-Gault) of ≥70 mL/min. The primary endpoint was the proportion of patients with an undetectable HIV RNA level (<50 copies/mL) at 48 weeks in the intention to treat population using the Food and Drug Administration (FDA) snapshot analysis. In both studies, Stribild was non-inferior to the comparator and associated with high rates (84–87%) of HIV RNA suppression throughout 96 weeks, low rates (2–3%) of treatment-emergent NRTI/II resistance, and less dizziness or abnormal dreams (vs. EFV) and diarrhoea (vs. ATV/RTV) (Table 3). The GS-US-216-0114 study is an ongoing phase III, double-blind, randomised, placebo-controlled trial of antiretroviral-naïve HIV-1-positive adults ($n = 692$) with baseline HIV RNA measurements of >5,000 copies/mL and creatinine clearance ≥70 mL/min who were randomised 1:1 to COBI 150 mg or RTV 100 mg, each given together with ATV 300 mg and TDF/FTC once daily [33]. At 48 weeks, the COBI/ATV regimen was non-inferior to the RTV/ATV regimen, with 85% and 87% of patients achieving HIV RNA <50 copies/mL, respectively. Adverse events, including bilirubin elevations, jaundice, nausea and diarrhoea, and study drug discontinuations due to adverse events occurred with equal frequency in both arms [33]. Other ongoing studies investigate a switch from TDF/FTC plus an NNRTI to Stribild (ClinicalTrials.gov identifier: NCT01495702) or TDF/FTC plus a RTV-boosted PI to Stribild (ClinicalTrials.gov identifier: NCT01495702), and the use of Stribild or COBI in patients with impaired renal function (creatinine clearance 50–89 mL/min; ClinicalTrials.gov identifier: NCT01363011). A small single-arm study confirmed the safety of a switch from TDF/FTC plus RTG to Stribild [34].

RENAL SAFETY

As described above, COBI inhibits the renal creatinine transporter MATE1. Although creatinine is freely filtered at the glomerulus, some 10–15% is actively secreted in the proximal tubule. Abrogation of tubular creatinine secretion results in mild increases in serum creatinine concentrations and mild reductions in estimated creatinine clearance. In healthy volunteers, COBI exposure resulted in reduced creatinine clearance (as measured with the Cockcroft-Gault formula) with minimal change in the actual (iohexol-measured) glomerular filtration rate (−9.9 vs. −2.7 mL/min in those with creatinine clearance

Table 3 Phase III trials of cobicistat-containing combination antiretroviral therapy regimens in treatment-naïve individuals

Study	Population	Treatment	Results	Comments
GS-US-0102 [28, 30]	$N = 700$, 89% male, median age 38, CD4 380 cells/mm^3, VL 4.75 log copies/mL	Stribild vs. Atripla (randomised 1:1, double-blind)	Stribild vs. Atripla (48w):	Stribild non-inferior to Atripla
			HIV RNA <50 copies/mL: 87.6% vs. 84.1% (difference 3.6%, 95% CI −1.6 to 8.8%)	Trend for better viral responses on Stribild for low (<100,000 copies/mL) and high baseline HIV RNA
			CD4 increases: 239 vs. 209 cells/mm^3, $p = 0.009$	At 96 weeks, non-inferiority in terms of viral suppression (84% vs. 82%, difference 2.7%, 95% CI −2.9 to 8.3%) was maintained, with emergent resistance observed in 3% of patients in each arm
			Virological failure: 14 (4%) vs. 17 (5%); 2% developed II and 2% NRTI resistance vs. 2% NNRTI and 1% NRTI mutations	
			Fasting lipids: smaller increases with Stribild ($p = 0.001$)	
			Treatment-emergent adverse events leading to discontinuation: 4% vs. 5%	
			Dizziness and abnormal dreams: 24–27% vs 7–15%	
			Diarrhoea and nausea were equally common in both arms (14–23%)	
GS-US-0103 [29, 31]	$N = 708$, 90% male, median age 38, CD4 360 cells/mm^3 VL 4.8 log copies/mL	Stribilid vs. TDF/FTC plus ATV/RTV (randomised 1:1, double-blind)	Stribild vs. TDF/FTC/ATV/RTV (48w):	COBI/EVG-containing regimen non-inferior to the PI-based regimen with a trend towards better viral responses with Stribild irrespective of baseline HIV RNA
			HIV RNA <50 copies/mL: 89.5% vs. 86.6% (difference 3.0%, 95% CI −1.9 to 7.8%)	At 96 weeks, rates of viral suppression were similar (87% vs. 85%, difference 1.1%, 95% CI −4.5 to 6.7%) with low cumulative resistance rates (2% vs. 0%)
			Similar CD4 increases: 207 vs. 211 cells/mm^3	Lower prevalence of diarrhoea with Stribild (∼5% vs. ∼10%)
			Virological failure: 12 (3%) vs. 8 (2%); 1% developed II and 1% NRTI resistance vs. no NRTI/PI resistance	
			Similar modest effects on fasting cholesterol ($P > 0.2$), smaller triglycerides increase with Stribild ($P = 0.006$)	
			Treatment-emergent adverse events leading to discontinuation: 4% vs. 5%	
			Diarrhoea and nausea were equally common in both arms (19–27%)	
GS-US-216-0114 [32]	$n = 692$, median age 38, CD4 352 cells/mm^3, mean VL 4.8 log copies/mL	Randomised 1:1 to COBI 150 mg or RTV 100 mg plus ATV 300 mg and TDF/FTC; double-blind	COBI vs. RTV (+TDF/FTC/ATV) (48w):	COBI-containing regimen non-inferior to the RTV-containing regimen
			HIV RNA <50 copies/mL: 85% vs. 87% (difference 2.2%, 95% CI −7.4 to 3.0%)	Consistent rates of viral suppression were observed across CD4 cell count and baseline HIV RNA strata
			Similar CD4 increases: 219 vs. 213 cells/mm^3	
			Virological failure: 20 (5.8%) vs. 14 (4.0%); 2 vs. 0 patients developed M184V; no PI mutations	
			Similar modest effects on fasting lipids	
			Treatment-emergent adverse events leading to discontinuation 7.3% vs. 7.2%	
			Adverse events, including bilirubin elevations, jaundice, nausea and diarrhoea, occurred with equal frequency in both arms	

ATV atazanavir, *COBI* cobicistat, *FTC* emtricitabine, *II* integrase inhibitor, *NNRTI* non-nucleoside reverse transcriptase inhibitor, *NRTI* nucleoside/nucleotide reverse transcriptase inhibitor, *PI* protease inhibitor, *RTV* ritonavir, *TDF* tenofovir disoproxil fumarate

≥80 mL/min, and −11.9 vs. −3.6 mL/min in those with creatinine clearance 50–79 mL/min) [35]. Baseline creatinine clearance (range 50–140 mL/min) did not affect the magnitude of the reduction in creatinine clearance with COBI exposure [35]. In the 0102 and 0103 studies, serum creatinine levels in the Stribild arm increased by approximately 10–15% in the first 4 weeks, and creatinine clearance declined by 10–15 mL/min [29, 30]. However, at 4 weeks a new "set point" was reached, with minimal subsequent change up to week 96 (−2.6 vs. −1.0 mL/min for Stribild and Atripla in the 0102 study, −1.8 vs. −4.4 mL/min for Stribild and TDF/FTC/ATV/RTV in the 0103 study) [18, 19]. In the 0114 study, patients in the COBI arm experienced greater reductions in creatinine clearance (−13 vs. −9 mL/min) than in the RTV arm [33].

Five patients (1.4%) in the 0102 study, all in the Stribild arm, had renal events (reported as elevated serum creatinine in two, renal failure in two, Fanconi syndrome in one; a total of four patients had evidence of proximal tubulopathy that led to study drug discontinuation before week 48) [29]. Further two patients (0.6%) in the Stribild arm discontinued study drug between weeks 48 and 96, because of renal adverse events consisting of serum creatinine elevations not accompanied by proximal tubulopathy [31]. In the 0103 study, five patients (Stribild arm 3, ATV/RTV arm 2) discontinued study drug due to renal events before week 96; none had evidence of proximal tubulopathy [32]. In the 0114 study, 1.7% and 1.4% of patients discontinued study medication for renal events in the COBI and RTV arms, and 5 vs. 2 cases had proximal tubulopathy [33].

The low rate of renal discontinuations and renal tubular disease suggests an overall favourable renal safety profile of Stribild and COBI. Indeed, data from patients with creatinine clearance 50–89 mL/min who initiated Stribild or substituted RTV with COBI observed no increased rate of renal toxicity or renal discontinuations [36]. The increases in serum creatinine concentration and the reductions in estimates of creatinine clearance and glomerular filtration rate are unlikely to be of clinical importance. Some of the renal discontinuations were likely to be due to patients meeting pre-specified criteria for discontinuation rather than secondary to overt renal toxicity. Nonetheless, the population included in the clinical trials was at low risk of kidney injury and despite this a small number developed significant renal tubular disease requiring drug discontinuation. The risk factors for TDF-induced Fanconi syndrome and renal tubular disease remain poorly defined but may point to an interaction between COBI and tenofovir at renal tubular level, as previously suggested for RTV [37]. Although such an interaction is not predicted by in vitro studies (Fig. 1), clinicians will need to remain alert to the nephrotoxic potential of Stribild in clinical practice.

DISCUSSION

Cobicistat provides an alternative to ritonavir as a pharmacoenhancer for antiretroviral therapy and as a component of Stribild; it offers an effective, well-tolerated, integrase inhibitor-based single-tablet regimen for HIV treatment. In terms of PI, co-formulations of COBI/ATV and COBI/DRV are in development. The low incidence of neuro-psychiatric side effects with COBI/EVG compared with EFV, and the lower prevalence of diarrhoea with COBI/ATV compared with RTV/ATV, makes it a potentially attractive alternative to these commonly prescribed agents. The reduced pill burden and once-daily administration

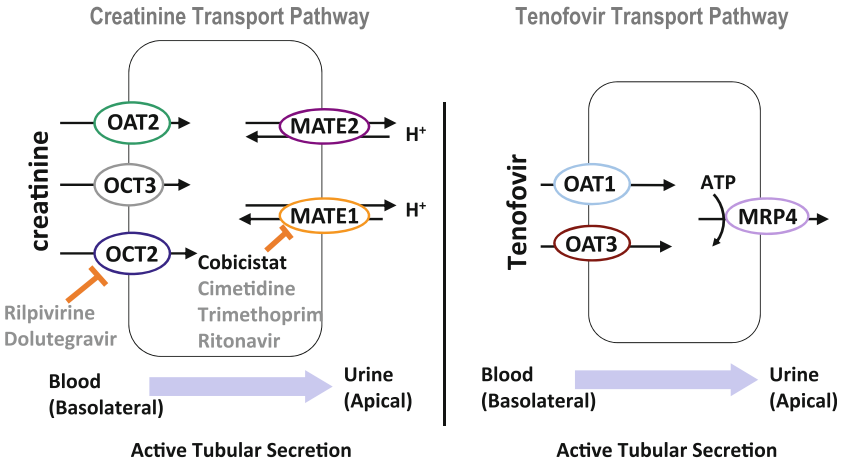

Fig. 1 Effect of various drugs on tubular creatinine secretion [17]. Tubular secretion of creatinine and tenofovir is mediated through distinct membrane transporter molecules. Based on in vitro experiments, no interaction between cobicistat and tenofovir is predicted. *MATE1–2* multidrug and toxin extrusion protein 1, *MRP4* multidrug resistance protein 4, *OAT1–3* organic anion transporter 1–3, *OCT 2–3* organic cation transporter 2–3

distinguish COBI/EVG from RTG, the only other II currently licensed. However, a single-tablet regimen based on the investigational integrase, dolutegravir, co-formulated with abacavir and lamivudine is expected to be licensed within the next 12 months and is currently under review by the FDA. Stribild's lack of interaction with acid-reducing agents distinguishes it from ATV and RPV.

There remain several data gaps, and widespread uptake of Stribild and COBI may be hampered by these. The male predominance and high median CD4 cell count of the phase III trial participants limit data in women and patients with low CD4 cell counts, opportunistic infections, malignancy or other serious co-morbidities, although the WAVES study, comparing Stribild to Truvada® (Gilead Inc., Foster City, CA, USA) plus RTV/ATV in women, is currently recruiting.

COBI is associated with drug–drug interactions, few of which have been studied to date. Although virological failure with Stribild was uncommon, patients that did fail commonly did so with dual-class resistance, and it remains unclear whether these viral isolates remain susceptible to dolutegravir. Also, Stribild is only licensed for use in patients with creatinine clearance ≥70 mL/min thus is not suitable for patients with renal impairment. The inclusion of TDF in Stribild makes it a less attractive option for patients with, or at risk of, osteoporosis, although the renal and bone concerns are likely to be less if TAF becomes the preferred tenofovir formulation of COBI-based single-tablet regimens. Finally, in an increasingly cost-conscious environment, the relative benefits of Stribild and COBI will have to be weighed against any incremental cost relative to current proprietary medications as well as forthcoming generic formulations.

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