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Cobicistat versus Ritonavir: Similar Pharmacokinetic Enhancers But Some Important Differences

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Introduction

Sustained viral load suppression is a key goal of antiretroviral therapy and is related to adequate drug exposure.[1] Pharmacokinetic enhancing strategies utilize either a low dose of the protease inhibitor (PI) ritonavir, or the pharmacokinetic enhancer cobicistat. Both drugs are potent inhibitors of the CYP3A4 isoenzyme and achieve the desired goal of boosting plasma drug concentrations and prolonging half-life of the CYP3A substrate (i.e., atazanavir, darunavir, or elvitegravir) they are paired with.

Ritonavir, initially launched as a PI in 1996 at 600 mg twice daily for use with other antiretrovirals for treatment of HIV[2] was plagued by high pill burden, poor tolerability, need for dose escalation, and drug interactions. Use of ritonavir then evolved to that of a pharmacokinetic enhancer. At doses of 100 mg once or twice daily, ritonavir was better tolerated and effective in enhancing the pharmacokinetic profile of partner PIs through inhibition of intestinal and hepatic CYP3A4 and P-glycoprotein (P-gp), resulting in increases in the area under the curve (AUC), maximum concentration (Cmax) and half-life.[3] This allowed less frequent dosing, lower pill burden, reduced impact of food on bioavailability, reduced variability of systemic drug exposure and improved treatment efficacy.[4]

Cobicistat was approved as a pharmacokinetic enhancing agent in 2012 to address limitations of ritonavir such as co-formulation difficulties secondary to poor water solubility and drug interactions secondary to its broad effects on CYP isoenzymes and drug transporters. Cobicistat is generally considered to be an equipotent inhibitor of CYP3A4 and

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P-gp as ritonavir, and is co-formulated with the PIs darunavir and atazanavir and the integrase inhibitor elvitegravir.

However, there are important pharmacokinetic distinctions between cobicistat and ritonavir which may lead to clinically significant differences in drug interaction outcomes. This review aims to compare and contrast the pharmacological characteristics, pharmacokinetic boosting data, and drug interactions studies for ritonavir and cobicistat with an emphasis on relevance to clinical practice. A discussion on considerations when switching from one booster to another is included to guide clinicians.

Data Sources

We performed a search of MEDLINE database (1985 to April 2017) using the following search terms: cobicistat, ritonavir, drug interactions, pharmacokinetic, booster, pharmacokinetic enhancer, HIV, antiretrovirals. Conference abstracts, reference lists of relevant articles, and product monographs were also reviewed. Search results were limited to studies conducted in humans and published in the English language.

Pharmacokinetics/Pharmacodynamics

Ritonavir

Ritonavir is a potent inhibitor of CYP3A4 isoenzyme, and also inhibits CYP2D6, CYP2C19, CYP2C8 and CYP2C9.[3–5] In addition, ritonavir inhibits P-gp and the cellular transport mechanism via this efflux pump. Inhibition of P-gp may contribute to the drug boosting effects through disruption of the active transport of PIs out of cells from the intestinal tract, liver and kidneys. Furthermore, ritonavir is a known inducer of CYP1A2, CYP2B6, CYP2C9, CYP2C19 and the uridine 5′-diphospho-glucuronosyltransferase (UGT) family.[6] Other drug transporters inhibited by ritonavir include the breast cancer resistance protein (BCRP), the organic anion transporting polypeptides (OATPs) located in the liver and multiantimicrobial extrusion protein 1 (MATE1).[7]

The major metabolite of ritonavir is isopropylthiazole which displays similar antiviral activity to the parent compound. Ritonavir undergoes extensive hepatic metabolism primarily through CYP3A4 and to a lesser degree CYP2D6. The majority of elimination is in the faeces with the remaining in the urine. The elimination half-life of the parent compound is between 3 to 5 hours. No dosage adjustments are required for ritonavir in patients with renal failure or mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment.[2]

Cobicistat

Cobicistat is a structural analogue of ritonavir without antiviral activity. It has improved physiochemical properties compared to ritonavir and is a potent inhibitor of CYP3A and a weak inhibitor of CYP2D6. Cobicistat inhibits the transporters P-gp, BCRP, OATP1B1 and OATP1B3.[8] Cobicistat 150 mg once daily has a pharmacokinetic boosting effect comparable with ritonavir 100 mg once daily.[9]

In contrast to ritonavir, cobicistat does not demonstrate any enzyme inducing effects on CYP450, UGT or P-gp.[8] There is reduced activation of the pregnane X receptor which regulates expression of different drug-metabolizing enzymes and demonstrates the reduced impact of cobicistat on concomitant medications.[10] Cobicistat inhibits renal cation transporters including OATPs and MATE1. MATE1 is involved in the renal tubular secretion of creatinine, and studies involving cobicistat and ritonavir have identified 10–15% increases in serum creatinine concentrations with no impairment of actual renal function.[11] The rise of serum creatinine with cobicistat is more pronounced compared to ritonavir, which may be explained by active transport of cobicistat in the tubular cells by organic cation transporter (OCT2) leading to accumulation of cobicistat and greater inhibition of MATE1.[10] In a randomized study comparing atazanavir boosted with cobicistat versus ritonavir in combination with emtricitabine/tenofovir disoproxil fumarate (TDF) in treatment naïve patients, median increases in serum creatinine were higher in the cobicistat arm compared to the ritonavir arm (0.13 mg/dL vs. 0.09 mg/dL, respectively, $P<0.001$); these changes were observed as early as week 2 and remained stable after week 8.[12]

Metabolism of cobicistat is predominantly by CYP3A4 and to a lesser degree CYP2D6. However, overall metabolism in the body is minimal as 99% is excreted unchanged (90% faeces, 10% urine) and the metabolites formed exhibit negligible clinical activity. No dosage adjustments are necessary for patients with renal failure or mild to moderate hepatic impairment. There are no data available relating to dosage adjustments in severe hepatic impairment.[8]

Pharmacokinetic Boosting (Atazanavir, Darunavir, Elvitegravir, Tipranavir)

The pharmacokinetic effects of cobicistat versus ritonavir on the properties of atazanavir, darunavir, elvitegravir and tipranavir are summarized in Table 1. For atazanavir, bioequivalent exposures in volunteers[13] were further supported by a phase II study conducted in HIV-1 infected treatment-naïve participants, where cobicistat 150 mg and ritonavir 100 mg were found to be bioequivalent based on AUC tau, Cmax, and Ctau.[14]

A phase I, multiple-dose, cross-over study found that cobicistat 150 mg provided equivalent darunavir Cmax and AUCtau, but bioequivalence was not established for darunavir Ctau compared to ritonavir 100 mg.[15] Similarly, a randomized, three-way crossover trial evaluated the oral bioavailability of darunavir 800 mg/ritonavir 100 mg daily and two fixed dose combinations (FDC) of darunavir 800 mg/cobicistat 150 mg daily in healthy volunteers; darunavir AUC24h was comparable with both boosters, while a slightly lower darunavir Cmin was seen with the cobicistat FDCs versus ritonavir.[16] These differences are not considered to be clinically significant in treatment-naïve patients.

Cobicistat and ritonavir equally effectively boost elvitegravir.[15] A study evaluating the bioavailability and pharmacokinetics of a FDC tablet (elvitegravir/cobicistat/emtricitabine/TDF) showed bioequivalent exposures for elvitegravir AUCtau and Cmax, but a lower Ctau compared to elvitegravir/ritonavir.[17]

In contrast, cobicistat is not an adequate booster for the PI tipranavir. In a fixed-sequence crossover study, the pharmacokinetics of tipranavir 500 mg twice daily with either cobicistat 150 mg twice daily or ritonavir 200 mg twice daily were assessed. When combined with cobicistat, tipranavir concentrations were significantly lower compared to those achieved with ritonavir.[18] It is interesting to speculate whether a higher dose of cobicistat (i.e., 300 mg twice daily) would have been more successful, given that for tipranavir the effective boosting dose of ritonavir is double the usual twice daily boosting dose for other PIs.

Cobicistat interactions with other antiretrovirals

Cobicistat has been investigated as a booster for two antiretrovirals simultaneously. Interactions between cobicistat-boosted agents and other antiretrovirals may need to be considered when managing treatment-experienced patients who require non-traditional antiretroviral combinations. Drug interaction studies involving cobicistat-boosted elvitegravir or darunavir plus other antiretrovirals are described below. Drug interaction studies involving atazanavir/cobicistat with other antiretrovirals have not been conducted.

NNRTIs with cobicistat-boosted elvitegravir or darunavir

a. *Efavirenz plus elvitegravir/cobicistat*. In a three-period study, healthy subjects received elvitegravir/cobicistat/emtricitabine/TDF on days 1 to 7 followed by a washout, efavirenz/emtricitabine/TDF on days 15 to 28, and elvitegravir/cobicistat/emtricitabine/TDF on days 29 to 62. At day 35, elvitegravir AUC, Cmax and Ctau were reduced by 37%, 19%, and 67%, respectively compared to day 7. Mean elvitegravir Ctrough was 3-fold and 5- fold higher than protein-adjusted IC95 of wild-type virus on days 35 and 42, respectively, and 7-8 fold higher at 5 weeks post switch. Cobicistat Ctau was reduced 35% at day 14 post-switch compared to day 7, and cobicistat AUC returned to normal by day 42. Over the duration of the 5 week period post switch, all patients had efavirenz Ctrough above IC90. These results indicate that patients on efavirenz-containing regimens may be switched immediately to a elvitegravir/cobicistat regimen without dose adjustment, since efavirenz concentrations remain therapeutic during the initial period of lower elvitegravir exposures. However, long-term co-administration of efavirenz and elvitegravir/cobicistat should be avoided since elvitegravir concentrations will be subtherapeutic.[18]

b. *Etravirine plus elvitegravir/ritonavir*. In healthy subjects, no clinically relevant pharmacokinetic changes were observed when elvitegravir 150 mg/ritonavir 100 mg daily and etravirine 200 mg twice daily were coadministered.[19] There are no data regarding etravirine with cobicistat-boosted elvitegravir.

c. *Etravirine plus darunavir/cobicistat*. In a study assessing the pharmacokinetics of darunavir 600 mg/cobicistat 150 mg twice daily alone or with etravirine 200 mg twice daily, darunavir exposures were not significantly affected by coadministration with etravirine, and etravirine exposures were comparable to historical data.[20] However, darunavir/cobicistat is only available as an 800 mg/150 mg coformulation approved for once daily dosing. Although a phase II

single arm study in HIV-infected subjects of darunavir 800 mg/ritonavir 100 mg daily plus etravirine 400 mg daily showed no significant changes in either darunavir or etravirine with coadministration,[21] an open-label, fixed sequence study in 30 HIV-infected subjects showed marked reductions in cobicistat (30% reduction AUC, 66% reduction in C24h) and 56% reduction in darunavir C24h with coadministration of darunavir 800 mg/cobicistat 150 mg and etravirine 400 mg daily compared to darunavir/cobicistat administered alone.[22] The darunavir/cobicistat monograph states that coadministration of etravirine is not recommended.[23] If therapy with both etravirine and darunavir is required, ritonavir may be the preferred booster.

Elvitegravir plus a Protease Inhibitor Using Cobicistat as a dual antiretroviral booster

a. *Atazanavir plus elvitegravir/cobicistat.* A study in healthy subjects compared elvitegravir 85 mg/cobicistat 150 mg plus atazanavir 300 mg daily to either elvitegravir 150 mg/cobicistat 150 mg daily or atazanavir 300 mg/ritonavir 100 mg daily. Elvitegravir Ctau increased more than 80% when dosed with atazanavir/cobicistat. All atazanavir, elvitegravir and cobicistat pharmacokinetics were comparable with reference or historical data.[24] However, elvitegravir is not available as an 85 mg dose with cobicistat.

b. *Darunavir plus elvitegravir/cobicistat.* Cobicistat appears to be an effective dual booster of darunavir and elvitegravir when administered twice daily. In a study assessing the kinetics of darunavir 600 mg/cobicistat 150 mg twice daily plus elvitegravir 150 mg daily compared to darunavir 600 mg/cobicistat 150 mg twice daily alone, darunavir exposures were not significantly affected by coadministration with elvitegravir, and elvitegravir exposures were comparable to historical reference data.[20] However, observations with once daily dosing are conflicting. When darunavir 800 mg was administered with elvitegravir 150 mg/cobicistat 150 mg once daily in healthy volunteers, elvitegravir Ctrough was approximately 50% lower compared to exposures achieved with elvitegravir/cobicistat/TDF/emtricitabine without darunavir, and darunavir Ctrough was 20% lower compared to darunavir 800 mg administered with cobicistat 150 mg daily alone.[20] In a retrospective case series of HIV-infected, treatment-experienced subjects receiving darunavir 800 mg plus elvitegravir/cobicistat/TDF/emtricitabine once daily, median darunavir Ctrough were 80% lower compared to historical population data. Elvitegravir concentrations were not measured in this study. All patients reported 100% adherence, and only one patient had a darunavir resistance-association mutation. Detectable minor increases in HIV viral load were observed in three patients.[25] In contrast, a pharmacokinetic substudy of a simplification trial involving darunavir 800 mg plus elvitegravir/cobicistat/TAF/emtricitabine in treatment-experienced, HIV-infected subjects, both darunavir and elvitegravir exposures were similar to historical controls.[26] The reasons for these varying results are unclear, but may be related to significant interpatient variability or differences in pharmacokinetics between HIV-infected subjects versus healthy controls.

Drug Interaction Studies (non-antiretrovirals): Cobicistat versus ritonavir

There are limited drug interaction studies evaluating cobicistat and concomitant medications and drug interactions are often inferred based on the pharmacokinetic properties of cobicistat. For instance, drug interaction studies were initially not conducted with atazanavir/cobicistat and recommendations from the product monograph include predicted interactions as well as results of drug interaction studies of unboosted atazanavir, atazanavir/ritonavir, cobicistat alone or as a booster for another agent.[27] Similarly, drug interaction information in the elvitegravir/cobicistat/TDF/emtricitabine monograph includes studies involving the coformulated product, or elvitegravir with either cobicistat or ritonavir (as well as any pertinent interactions for emtricitabine or TDF). While this approach is generally appropriate, differences between the effects of cobicistat versus ritonavir on certain metabolizing enzymes and transporters may result in different and sometimes opposite effects on the disposition of coadministered medications. It is notable that the darunavir/cobicistat monograph states that the interaction profile of darunavir is dependent upon which pharmacokinetic booster is used, and highlights instances when drug interaction recommendations for darunavir/cobicistat are different from those for darunavir/ritonavir. Examples of similarities and differences between ritonavir versus cobicistat-boosted agents are described below and summarized in Tables 2 to 4.

Gastric acid reducing agents

The pharmacokinetics of elvitegravir boosted with either cobicistat or ritonavir are not impacted by acid-reducing agents such as H2-blockers or proton pump inhibitors.[28] In healthy subjects receiving darunavir 400 mg/ritonavir 100 mg twice daily, administration of ranitidine 150 mg twice daily or omeprazole 20 mg daily did not alter darunavir or ritonavir AUC.[29]

It is important to also consider which antiretroviral is being boosted by ritonavir or cobicistat. In contrast to elvitegravir and darunavir, atazanavir absorption is dependent upon gastric pH. With respect to coadministration of H2-receptor antagonists, recommendations for atazanavir boosted with either cobicistat or ritonavir are similar for treatment-naïve patients or in treatment-experienced patients not receiving concomitant TDF. Boosted atazanavir should be administered simultaneously with or at least 10 hours after a dose of the H2-receptor antagonist. However, the recommendations in treatment-experienced patients who are also taking TDF vary according to the booster used. In this situation, a dose of atazanavir 400 mg with ritonavir 100 mg is recommended;[30] since atazanavir/cobicistat is a fixed-dose coformulated product, such a dose adjustment is not possible and use of atazanavir/cobicistat is not recommended.[27] Of note, unlike TDF, pharmacokinetic data suggest that TAF does not significantly impact the pharmacokinetics of atazanavir/ritonavir and standard boosted atazanavir doses may be used.[31]

CYP3A4 substrates

Dose finding studies confirmed potent CYP3A4 inhibitory effects of cobicistat at doses of 100-200 mg as evidenced by a 95% reduction in midazolam clearance. This was comparable to a 96% reduction in midazolam clearance seen with ritonavir 100 mg once daily.[32] A

number of case reports highlight the potential for serious interactions with cobicistat via CYP3A4 inhibition. An HIV-infected man developed iatrogenic Cushing's syndrome due to an interaction between elvitegravir/cobicistat and fluticasone nasal drops.[33] A patient undergoing treatment for Hodgkin's lymphoma developed severe peripheral neuropathy, thought to be secondary to an interaction between elvitegravir/cobicistat and vinblastine.[34] Several cases of significantly elevated tacrolimus concentrations and toxicity have been reported in HIV-infected renal transplant patients following coadministration of elvitegravir/cobicistat and tacrolimus.[35–37] Extensive bruising and elevated rivaroxaban concentrations were observed in a patient on elvitegravir/cobicistat,[38] while severe acute leg ischemia occurred following ingestion of an ergotamine-containing preparation by a patient on elvitegravir/cobicistat.[39] Of note, while ergot alkaloids, fluticasone and tacrolimus are mentioned in the product monographs for elvitegravir/cobicistat, vinblastine and rivaroxaban are not. These reports reinforce the importance of avoiding cobicistat or ritonavir with drugs that have narrow therapeutic indices, or close monitoring with dose adjustment of therapy if coadministration is required.

Coadministration with CYP3A4 inducers

An open-label fixed sequence study of elvitegravir 150 mg/cobicistat 150 mg daily and carbamazepine 100 mg twice daily for 3 days followed by 200 mg twice daily up until day 41 in 14 healthy subjects demonstrated a 43% increase in the AUC of carbamazepine and a 69% and 97% decrease in elvitegravir AUC and Ctau, respectively.[40] Carbamazepine is contraindicated with elvitegravir,[28] atazanavir/cobicistat[27] and darunavir/cobicistat, and an alternative anticonvulsant should be used if possible.[41]

With ritonavir-boosted PIs, recommendations on coadministration are different. The atazanavir/ritonavir product monograph states that carbamazepine concentrations may be increased and atazanavir concentrations may be decreased. Therapeutic drug monitoring of both agents may be helpful, with close monitoring and dose adjustments as necessary.[30] For darunavir/ritonavir, the manufacturer suggests monitoring for carbamazepine efficacy/toxicity; a 25-50% reduction in carbamazepine dose may be necessary, while dosage adjustment for darunavir/ritonavir is likely not required.[41] However, clinicians should be aware that these recommendations are based on results of an interaction study in healthy volunteers where coadministration of darunavir 600 mg/ritonavir 100 mg twice daily plus carbamazepine 200 mg twice daily resulted in 14% reduction in darunavir Cmin with no change in AUC, a 54% increase in Cmin and 45% increase in AUC of carbamazepine and 52% reduction in Cmin and 54% reduction in the AUC of carbamazepine-epoxide compared to either drug administered alone. It is unclear whether darunavir exposures would be similarly unaffected if administered at a once-daily dose in the presence of carbamazepine. Therefore, close monitoring is recommended if coadministration is required.

Rifabutin, an antimycobacterial agent, is also an inducer of CYP3A4. The metabolism of rifabutin involves first pass metabolism by CYP3A4 in the intestine, and CYP3A4 metabolism in the liver of the active metabolite 25-desacetyl metabolite.[42] Initially, rifabutin was studied with ritonavir-boosted elvitegravir. Healthy subjects received elvitegravir 300 mg/ritonavir 100 mg daily alone and with rifabutin 150 mg every other day versus rifabutin

300 mg daily.[43] The pharmacokinetics of elvitegravir, ritonavir and rifabutin were within the no-effect boundary, although AUC of 25-desacetyl metabolite increased 951% . In contrast, in a pharmacokinetic study of healthy volunteers, coadministration of rifabutin 150 mg every other day and elvitegravir 150 mg/cobicistat 150 mg daily resulted in a 67% decrease in elvitegravir Ctau compared to elvitegravir/cobicistat administered alone, and 625% increase in AUC of 25-desacetyl metabolite.[24] A subsequent pharmacokinetic study demonstrated that increasing cobicistat to 150 mg twice daily mitigated the effect of rifabutin on elvitegravir concentrations.[44] However, the practicality of this strategy is limited given that cobicistat is not licensed for more than once daily dosing and cobicistat as a sole agent may not be readily available. Therefore, if rifabutin use is required, an alternative antiretroviral regimen should be considered.

Recently, an in vitro study demonstrated that ritonavir was more potent than cobicistat in overcoming rifampin-induced increase in darunavir clearance.[45] These findings, along with the etravirine, tipranavir, carbamazepine and rifabutin interaction studies suggest that cobicistat may not be as effective as ritonavir in overcoming CYP3A4 induction in the presence of concomitant inducers. Therefore, coadministration of cobicistat-regimens with moderate-potent enzyme inducers should be avoided.

Other CYP450 enzymes and drug transporters

At boosting doses, cobicistat and ritonavir are weak CYP2D6 inhibitors. In healthy volunteers, cobicistat 150 mg daily increased desipramine AUC 58–65%,[46] while desipramine AUC was increased 26% with ritonavir 100 mg twice daily[47] and increased 145% with ritonavir 500 mg twice daily.[2] This example serves as a reminder to be cognizant of the ritonavir dose used in drug interaction studies, since CYP-mediated inhibition is often dose-related and effects observed with high dose ritonavir may not occur at the same magnitude at lower doses.[48]

One of the principal differences between cobicistat and ritonavir is the impact on other CYP isoenzymes. As previously stated, ritonavir induces CYP1A2, CYP2B6, CYP2C9, CYP2C19 and UGT,[6] whereas cobicistat is not known to induce these enzymes. A study in healthy volunteers taking the CYP2B6 substrate sertraline 50 mg and elvitegravir/cobicistat/TAF/emtricitabine found no clinically relevant changes in sertraline pharmacokinetics.[49] In contrast, sertraline AUC was decreased 49% when coadministered with darunavir 400 mg/ritonavir 100 mg twice daily, suggesting a potent CYP2B6 induction effect of ritonavir.[41] Ritonavir 100 mg twice daily has been shown to reduce exposures of bupropion, another CYP2B6 substrate by 21% and 57% when given either alone or with lopinavir 400 mg twice daily, respectively.[50–51] The product monographs for ritonavir-boosted darunavir,[41] lopinavir/ritonavir,[48] and ritonavir[2] state that bupropion exposures may be decreased and dose titration may be required. In contrast, product monographs for cobicistat-boosted darunavir[23] or elvitegravir[28] mention the possibility of increased sertraline or bupropion concentrations.

Methadone undergoes oxidative metabolism in the liver by CYP2B6, CYP3A4, CYP2C19, CYP2D6, and CYP2C8. R-methadone and S-methadone concentrations were not significantly impacted by elvitegravir/cobicistat and symptoms of opioid withdrawal or

toxicity were not observed.[52] Ritonavir boosted PIs, on the other hand, have been shown to decrease R- and S-methadone concentrations, and monitoring for withdrawal symptoms and need for dose adjustment is recommended.[53–54]

Warfarin is also a mixture of two enantiomers: the S-enantiomer is more potent and is primarily metabolized by CYP2C9, and the R-enantiomer is metabolized primarily via CYP1A2, CYP3A4, and CYP2C19.[55] Ritonavir-boosted PIs have been shown to decrease warfarin concentrations via CYP2C9 induction.[56] This interaction would not be expected when cobicistat is administered with darunavir or atazanavir. This is illustrated in a case report of an HIV-positive individual stabilized on warfarin 10 mg daily and atazanavir/ritonavir-based therapy. When atazanavir/ritonavir was replaced with darunavir/cobicistat, the patient experienced increased INR and bleeding, and a 60% reduction in warfarin dose was required.[57] Of note, elvitegravir modestly induces CYP2C9;[28] a 60% increase in warfarin dose was required to maintain therapeutic INR after therapy with elvitegravir/cobicistat/emtricitabine/TDF was initiated.[55] Therefore, pharmacological properties of both the specific pharmacokinetic enhancer as well as the coadministered boosted antiretroviral need to be considered when considering potential drug interactions with warfarin.

Buprenorphine is metabolized to its active metabolite, nor-buprenorphine, via CYP3A4, CYP 3A5, CYP3A7 and CYP2C8; nor-buprenorphine is further metabolized via CYP3A4 and both the parent and metabolite undergo subsequent glucuronidation.[58] In HIV seronegative subjects stabilized on buprenorphine/naloxone, elvitegravir 150 mg/cobicistat 150 mg daily increased buprenorphine and nor-buprenorphine AUCtau by 35% and 42%, respectively, and decreased naloxone AUCtau 28%. These changes did not result in opioid toxicity or withdrawal symptoms and these agents may be co-administered without dosage adjustments.[58] Similarly, there was no change in buprenorphine exposures and a 46% increase in AUC of norbuprenorphine when coadministered with darunavir 600 mg/ritonavir 100 mg twice daily.[41] In contrast, atazanavir inhibits UGT1A1 in addition to CYP3A4; thus, slightly larger increases in buprenorphine and norbuprenorphine exposures are observed in the presence of atazanavir or atazanavir/ritonavir. With atazanavir 300 mg/ritonavir 100 mg, AUC of buprenorphine and norbuprenorphine increased 67% and 105%, respectively, and increased 93% and 76%, respectively, when coadministered with atazanavir 400 mg once daily.[30] A priori dose adjustments of buprenorphine are not required with either elvitegravir/cobicistat[28] or darunavir boosted with either cobicistat[23] or ritonavir.[41] In contrast, when coadministered with atazanavir alone or with a booster, monitoring for increased buprenorphine effects is recommended and dose adjustment may be necessary.[30]

Ethinyl estradiol is extensively metabolized by CYP3A4, CYP2C9, and UGT, in particular UGT1A1.[59] Recommendations on coadministration with boosted antiretrovirals vary according to the booster used as well as the antiretroviral it is combined with. Ethinyl estradiol exposures are decreased 19% in the presence of atazanavir/ritonavir, presumably secondary to UGT induction by ritonavir,[60] and the manufacturer recommends use of an oral contraceptive with a minimum 30 μg ethinyl estradiol content. However, when coadministered with unboosted atazanavir, ethinyl estradiol concentrations are increased 48% due to UGT1A1 inhibition by atazanavir,[61] and in this case, an oral contraceptive with no more than 30 ug ethinyl estradiol is recommended.[30] With atazanavir/cobicistat, the

manufacturer suggests consideration of non-hormonal contraception based on the unboosted atazanavir-hormonal contraceptive interaction data.[27] In contrast, ethinyl estradiol AUC and Cmin were reduced 25% and 44%, respectively when administered with elvitegravir/cobicistat/TDF/emtricitabine.[62] These results may reflect CYP2C9 induction by elvitegravir; therefore, oral contraceptives with at least 30 mcg of ethinyl estradiol should be used in combination with elvitegravir/cobicistat/TDF/emtricitabine.

The prodrug dabigatran etexilate (DE) is converted to dabigatran by esterase-catalyzed hydrolysis in plasma and the liver. DE is a substrate of P-gp; thus, concomitant use of potent P-gp inducers or inhibitors may affect exposures of DE and impact the amount of DE available for conversion to dabigatran. A healthy volunteer study assessed DE in the presence of cobicistat 150 mg daily. With simultaneous administration, dabigatran AUC increased 127%, thrombin time at 24hrs (TTlast) increased 46-51%, and AUC for TT increased by 30-33%. Spacing administration of cobicistat and DE by two hours did not mitigate the interaction. In contrast, no significant effect was observed on dabigatran exposures when ritonavir 100 mg was administered simultaneously.[63] Case reports showed no interaction when dabigatran 110 mg or 150 mg twice daily was administered to patients on lopinavir/ritonavir[64] and atazanavir/ritonavir,[65] respectively, with dabigatran Ctrough similar to those observed in the RE-LY trial.[66] Interestingly, although these data appear to suggest a greater effect of cobicistat on dabigatran exposures compared to ritonavir, dabigatran is not mentioned in the elvitegravir/cobicistat or atazanavir/cobicistat monographs. For both ritonavir- and cobicistat-boosted darunavir, the manufacturer recommends use of this combination with caution, and avoidance in subjects with severe renal impairment. Similar precautions should also be considered when using dabigatran with elvitegravir/cobicistat or atazanavir/cobicistat.

Rosuvastatin is a substrate for BCRP, OATP1B1, OATP1B3, and OAT3, with CYP2C9 being a minor pathway of disposition.[67] In healthy subjects, elvitegravir/cobicistat increased rosuvastatin Cmax 89% and AUCinf by 38%, however these drugs may be coadministered without dose adjustment.[68] In contrast, mean rosuvastatin AUC increased 48% and 93% and Cmax increased 144% and 277% in the presence of darunavir 600 mg/ritonavir 100 mg twice daily,[69] and darunavir 800 mg/cobicistat 150 mg daily, respectively.[70] Similarly, rosuvastatin AUC increased 213% and 242% and Cmax increased 600% and 958%, when coadministered with atazanavir 300 mg/ritonavir 100 mg daily[71] or atazanavir 300 mg/cobicistat 150 mg daily, respectively.[70] The greater increases in rosuvastatin exposures with boosted PIs versus elvitegravir/cobicistat may be due to additional inhibitory effects of atazanavir and darunavir on BCRP and OATP1B1 transporters.[72–73] While the elvitegravir/cobicistat monograph states that dose modifications are not required with rosuvastatin, recommendations for cobicistat-boosted PIs are similar to those with ritonavir-boosted PIs plus rosuvastatin, i.e., use of the lowest possible dose of rosuvastatin.

Making switches from a ritonavir-boosted regimen to a cobicistat-boosted regimen

Clinicians and patients may elect to switch from a ritonavir-boosted to a cobicistat-boosted regimen or vice versa for a number of reasons. Studies involving switches from ritonavir to cobicistat-boosted regimens have shown greater treatment satisfaction and minimal differences or improvements in adverse effects.[74–76] Use of a cobicistat-containing coformulation reduces pill burden and number of prescriptions (an important consideration for patients with out-of-pocket co-payments), and ensures that the boosting agent is always dosed at the same time as the accompanying antiretroviral. Conversely, some patients may find a coformulated tablet too large, and prefer to take individual agents. In addition, a commercial oral liquid formulation of ritonavir is available for patients who have difficulty swallowing tablets.[2]

Generally, when switching from ritonavir to cobicistat, the lack of enzyme inducing activity with cobicistat should be considered. Concentrations of coadministered drugs which are substrates of CYP1A2, CYP2B6, CYP2C9, CYP2C19, and UGT may increase, and close monitoring with potential dose adjustments are recommended. A recent pharmacokinetic switch study in 12 HIV-infected patients on dolutegravir 50 mg daily plus darunavir 800 mg/ritonavir 100 mg daily illustrates this point. After patients were switched to darunavir 800 mg/cobicistat 150 mg daily with dolutegravir, darunavir exposures remained stable, but dolutegravir Ctrough increased 100%. The authors hypothesized that dolutegravir exposures may have decreased secondary to ritonavir induction of glucuronidation; switching to cobicistat removed the UGT induction effect resulting in increased in dolutegravir concentrations.[77] Similarly, when switching from a cobicistat- to a ritonavir-boosted regimen, exposures of comedications which are substrates of these enzymes may decrease, and dose increases may be required to maintain therapeutic effect. The onset and dissolution of enzyme inducing activity may take 1-2 weeks and appropriate clinical monitoring and potential dose adjustments should be planned within this time frame.

Consideration should also be given to the pharmacological characteristics of the agent being boosted as well as the booster as highlighted by interactions with warfarin. As previously discussed, cobicistat lacks induction properties, and increased INR was observed following a switch from a ritonavir-boosted PI to a cobicistat-boosted PI in a patient on stable warfarin.[57] However, if a patient on a ritonavir boosted PI was changed to elvitegravir/cobicistat, then a noticeable change in INR may not occurre, since elvitegravir itself induces CYP2C9.[55] Other interaction combinations such as those involving gastric-acid reducing agents, oral contraceptives, or buprenorphine serve as examples where important pharmacological differences between individual antiretrovirals and specific boosting agents can be associated with different interaction outcomes.

Summary

Cobicistat and ritonavir are generally considered equivalent pharmacokinetic boosters, with similar inhibitory effects on CYP3A4, CYP2D6, P-gp, and other transporters. Similar exposures of elvitegravir, atazanavir and darunavir are achieved when combined with either

booster. In the presence of inducers such as etravirine, rifamycins or anticonvulsants, cobicistat may not be as effective as ritonavir in terms of inhibiting CYP3A4. Pharmacokinetic drug interaction data for cobicistat are often extrapolated from ritonavir-boosted antiretrovirals; however this approach may not be appropriate, since cobicistat is not associated with enzyme inducing properties. Significant problems can arise when switching from a ritonavir-boosted regimen to a cobicistat-boosted regimen or vice versa in patients stabilized on a dose of a relevant substrate agent. Clinicians should be aware of these important differences and distinctions when assessing and managing potential drug interactions with ritonavir or cobicistat-based regimens, particularly in patients with multiple comorbidities and concomitant medications. Depending on the co-medications used, additional monitoring and/or dose adjustments may be required. Since new interaction data are continually emerging, clinicians are encouraged to utilize HIV specific drug interaction resources, such as www.hiv-druginteractions.org or http://app.hivclinic.ca, for up to date information.

References

1. Higgins N, Tseng A, Sheehan N, la Porte C. Antiretroviral therapeutic drug monitoring in Canada: current status and recommendations for clinical practice. Can J Hosp Pharm. 2009; 62:500–9. [PubMed: 22478939]
2. AbbVie Corporation. Norvir (ritonavir) Prescribing Information. Saint-Laurent, QC: 2017.
3. Zeldin RK, Petruschke RA. Pharmacological and therapeutic properties of ritonavir-boosted protease inhibitor therapy in HIV-infected patients. J Antimicrob Chemother. 2004; 53:4–9. Epub 2003/12/06. DOI: 10.1093/jac/dkh029 [PubMed: 14657084]
4. Renjifo B, van Wyk J, Salem AH, Bow D, Ng J, Norton M. Pharmacokinetic enhancement in HIV antiretroviral therapy: a comparison of ritonavir and cobicistat. AIDS reviews. 2015; 17:37–46. Epub 2015/01/15. [PubMed: 25586481]
5. Larson KB, Wang K, Delille C, Otofokun I, Acosta EP. Pharmacokinetic enhancers in HIV therapeutics. Clin Pharmacokinet. 2014; 53:865–72. Epub 2014/08/29. DOI: 10.1007/s40262-014-0167-9 [PubMed: 25164142]
6. Foisy M, Yakiwchuk E, Hughes C. Induction effects of ritonavir: implications for drug interactions. Ann Pharmacother. 2008; 42:1048–59. [PubMed: 18577765]
7. Kis O, Robillard K, Chan GN, Bendayan R. The complexities of antiretroviral drug-drug interactions: role of ABC and SLC transporters. Trends in pharmacological sciences. 2010; 31:22–35. Epub 2009/12/17. DOI: 10.1016/j.tips.2009.10.001 [PubMed: 20004485]
8. Gilead Sciences Canada Inc. Tybost (cobicistat) Product Monograph. Mississauga, ON: 2016.
9. Nathan B, Bayley J, Waters L, Post FA. Cobicistat: a novel pharmacoenhancer for co-formulation with HIV protease and integrase inhibitors. Infectious diseases and therapy. 2013; 2:111–22. Epub 2014/08/20. DOI: 10.1007/s40121-013-0013-7 [PubMed: 25134475]
10. Marzolini C, Gibbons S, Khoo S, Back D. Cobicistat versus ritonavir boosting and differences in the drug-drug interaction profiles with co-medications. J Antimicrob Chemother. 2016; 71:1755–8. Epub 2016/03/08. DOI: 10.1093/jac/dkw032 [PubMed: 26945713]
11. German P, Liu HC, Szwarcberg J, et al. Effect of cobicistat on glomerular filtration rate in subjects with normal and impaired renal function. J Acquir Immune Defic Syndr. 2012; 61:32–40. Epub 2012/06/27. DOI: 10.1097/QAI.0b013e3182645648 [PubMed: 22732469]
12. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer of atazanavir plus emtricitabine/tenofovir disoproxil fumarate in treatment-naive HIV type 1-infected patients: week 48 results. J Infect Dis. 2013; 208:32–9. Epub 2013/03/28. DOI: 10.1093/infdis/jit122 [PubMed: 23532097]

13. Ramanathan, S., Warren, D., Wei, L., Kearney, BP. Pharmacokinetic boosting of atazanavir with the pharmacoenhancer GS-9350 versus ritonavir [abstract A1-1301]; 49th Interscience Conference on Antimicrobial Agents and Chemotherapy; San Francisco. 2009.

14. Elion R, Cohen C, Gathe J, et al. Phase 2 study of cobicistat versus ritonavir each with once-daily atazanavir and fixed-dose emtricitabine/tenofovir DF in the initial treatment of HIV infection. AIDS. 2011; 25:1881–6. Epub 2011/08/04. DOI: 10.1097/QAD.0b013e32834b4d48 [PubMed: 21811136]

15. Mathias, A., Liu, H., Warren, D., Sekar, V., Kearney, B. Relative bioavailability and pharmacokinetics of darunavir when boosted with the pharmacoenhancer GS-9350 versus ritonavir [abstract 28]; 11th International Workshop on Clinical Pharmacology of HIV Therapy; Sorrento, Italy. 2010.

16. Kakuda TN, Opsomer M, Timmers M, et al. Pharmacokinetics of darunavir in fixed-dose combination with cobicistat compared with coadministration of darunavir and ritonavir as single agents in healthy volunteers. J Clin Pharmacol. 2014; 54:949–57. Epub 2014/03/20. DOI: 10.1002/jcph.290 [PubMed: 24644095]

17. German P, Warren D, West S, Hui J, Kearney BP. Pharmacokinetics and bioavailability of an integrase and novel pharmacoenhancer-containing single-tablet fixed-dose combination regimen for the treatment of HIV. J Acquir Immune Defic Syndr. 2010; 55:323–9. [PubMed: 20683270]

18. Ramanathan S, Custodio JM, Wei X, et al. Pharmacokinetics of co-formulated elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate after switch from efavirenz/emtricitabine/tenofovir disoproxil fumarate in healthy subjects. J Acquir Immune Defic Syndr. 2016; 72:281–8. Epub 2016/02/18. DOI: 10.1097/qai.0000000000000959 [PubMed: 26885802]

19. Ramanathan S, Kakuda TN, Mack R, West S, Kearney BP. Pharmacokinetics of elvitegravir and etravirine following coadministration of ritonavir-boosted elvitegravir and etravirine. Antiviral Ther. 2008; 13:1011–7.

20. Ramanathan, S., Wang, H., Szwarcberg, J., Kearney, BP. Safety/tolerability, pharmacokinetics and boosting of twice-daily cobicistat administered alone or in combination with darunavir or tipranavir [abstract P_08]; 13th International Workshop on Clinical Pharmacology of HIV Therapy; Barcelona, Spain. 2012.

21. DeJesus E, Lalezari JP, Osiyemi OO, et al. Pharmacokinetics of once-daily etravirine without and with once-daily darunavir/ritonavir in antiretroviral-naive HIV type-1-infected adults. Antivir Ther. 2010; 15:711–20. Epub 2010/08/17. DOI: 10.3851/imp1562 [PubMed: 20710052]

22. Molto, J., Curran, A., Valle, M., et al. Pharmacokinetics of darunavir/cobicistat and etravirine alone and coadministered in HIV-infected patients [abstract O_03]; 18th International Workshop on Clinical Pharmacology of Antiviral Therapy; Chicago, IL. 2017.

23. Janssen Inc. Prezcobix (darunavir/cobicistat) Product Monograph. Toronto: 2015.

24. Ramanathan, S., Wang, H., Stondell, T., Cheng, A., Kearney, BP. Pharmacokinetics and drug interaction profile of cobicistat boosted-elvitegravir with atazanavir, rosuvastatin or rifabutin [abstract O_03]; 13th International Workshop on Clinical Pharmacology of HIV Therapy; Barcelona, Spain. 2012.

25. Ricard, F., Wong, A., Lebouche, B., et al. Low darunavir concentrations in patients receiving Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate) and darunavir once daily [abstract 50]; 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; Washington, DC. 2015.

26. Huhn G, Tebas P, Gallant J, et al. A randomized, open-label trial to evaluate switching to elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide plus darunavir in treatment-experienced HIV-1-infected adults. J Acq Immune Def Syndr. 2017; 74:193–200. DOI: 10.1097/QAI.0000000000001193

27. Bristol-Myers Squibb Canada. Evotaz (atazanavir/cobicistat) Product Monograph. Montreal, Canada: 2016.

28. Gilead Sciences Canada Inc. Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate) Product Monograph. Mississauga, ON: 2014.

29. Sekar VJ, Lefebvre E, De Paepe E, et al. Pharmacokinetic interaction between darunavir boosted with ritonavir and omeprazole or ranitidine in human immunodeficiency virus-negative healthy

volunteers. Antimicrob Agents Chemother. 2007; 51:958–61. Epub 2007/01/11. DOI: 10.1128/aac.01203-06 [PubMed: 17210768]

30. Bristol-Myers Squibb Canada. Reyataz (atazanavir) Product Monograph. Montreal, QC: 2016.
31. Lawson, EB., Martin, H., McCallister, S., Shao, Y., Vimal, M., Kearney, BP. Drug interactions between tenofovir alafenamide and HIV antiretroviral agents [abstract H-1012]; 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); Washington, DC. 2014.
32. Mathias AA, German P, Murray BP, et al. Pharmacokinetics and pharmacodynamics of GS-9350: a novel pharmacokinetic enhancer without anti-HIV activity. Clin Pharmacol Ther. 2010; 87:322–9. Epub 2010/01/01. DOI: 10.1038/clpt.2009.228 [PubMed: 20043009]
33. Lewis J, Turtle L, Khoo S, Nsutebu E. A case of iatrogenic adrenal suppression after co-administration of cobicistat and fluticasone nasal drops. AIDS. 2014; 28:2636–7. [PubMed: 25574967]
34. Bidon D, Bauler S, Venon M-D, Dupont C. Cobicistat–vinblastine interaction and severe peripheral neuropathy. AIDS. 2015; 29:1120–1. [PubMed: 26125146]
35. Han Z, Kane BM, Petty LA, Josephson MA, Sutor J, Pursell KJ. Cobicistat significantly increases tacrolimus serum concentrations in a renal transplant recipient with human immunodeficiency virus infection. Pharmacotherapy. 2016; 36:e50–e3. Epub 2016/04/05. DOI: 10.1002/phar.1752 [PubMed: 27041642]
36. Camargo JF, Chin-Beckford N. Antiretroviral therapy combo pills in HIV+ kidney transplant recipients: first do no harm. Ann Pharmacother. 2017; 51:520–1. Epub 2017/02/07. DOI: 10.1177/1060028017692601 [PubMed: 28161972]
37. Patel SJ, Kuten SA, Musick WL, Gaber AO, Monsour HP, Knight RJ. Combination drug products for HIV-a word of caution for the transplant clinician. Am J Transplant. 2016; 16:2479–82. Epub 2016/04/19. DOI: 10.1111/ajt.13826 [PubMed: 27089541]
38. Yoong D, Naccarato M, Gough K. Extensive bruising and elevated rivaroxaban plasma concentration in a patient receiving cobicistat-boosted elvitegravir. Ann Pharmacother. 2017; 1060028017702677. Epub 2017/03/30. doi: 10.1177/1060028017702677
39. Navarro J, Curran A, Burgos J, et al. Acute leg ischaemia in an HIV-infected patient receiving antiretroviral treatment. Antivir Ther. 2017; 22:89–90. Epub 2016/10/21. DOI: 10.3851/imp3075 [PubMed: 27546463]
40. Custodio, JM., Shao, Y., Begley, R., et al. Pharmacokinetics and drug interaction profile of cobicistat-boosted elvitegravir with carbamazepine [abstract H-1011]; 54th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC); Washington, DC. 2014.
41. Janssen Inc. Prezista (darunavir) Product Monograph. Toronto, Ontario: 2016.
42. Regazzi, MB., Cusato, M., Matteelli, A., et al. Pharmacokinetic evaluation of rifabutin and its active metabolite LM565 in combination with lopinavir in HIV-infected subjects with mycobacterial disease (MD); 12th International Workshop on Clinical Pharmacology of HIV Therapy; Miami, FL. 2011.
43. German, P., West, S., Hui, J., Kearney, BP. Pharmacokinetic interaction between elvitegravir/ritonavir and dose-adjusted rifabutin (abstract P19); 9th International Workshop on Clinical Pharmacology of HIV Therapy; New Orleans, LA. 2008.
44. Custodio, J., Shao, Y., Begley, R., et al. Pharmacokinetics of boosted-elvitegravir in combination with rifabutin, utilizing twice daily administration of cobicistat to overcome induction [abstract THPDB0102]; 20th International AIDS Conference; Melbourne, Australia. 2014.
45. Roberts O, Khoo S, Owen A, Siccardi M. Interaction of rifampin and darunavir-ritonavir or darunavir-cobicistat in vitro. Antimicrob Agents Chemother. 2017; 61 Epub 2017/02/15. doi: 10.1128/aac.01776-16
46. German, P., Mathias, A., Wei, L., Murray, B., Warren, D., Kearney, BP. The effect of cobicistat on cytochrome P450 2D6, 2B6 and P-glycoprotein using phenotypic probes [abstract O_01]; 12th International Workshop on Clinical Pharmacology of HIV Therapy; Miami, USA. 2011.
47. Aarnoutse RE, Kleinnijenhuis J, Koopmans PP, et al. Effect of low-dose ritonavir (100 mg twice daily) on the activity of cytochrome P450 2D6 in healthy volunteers. Clin Pharmacol Ther. 2005; 78:664–74. Epub 2005/12/13. DOI: 10.1016/j.clpt.2005.09.001 [PubMed: 16338282]

48. AbbVie Corporation. Kaletra (lopinavir/ritonavir) Prescribing Information. Saint Laurent, Canada: 2016.
49. Custodio, J., West, S., Das, M., Nichols, A., Kearney, BP., Zack, J. Evaluation of the drug interaction potential between elvitegravir/cobicistat/emtrictabine/tenofovir alafenamide and sertraline [abstract 73]; 16th International Workshop on Clinical Pharmacology of HIV & Hepatitis Therapy; Washington, DC. 2015.
50. Park J, Vousden M, Brittain C, et al. Dose-related reduction in bupropion plasma concentrations by ritonavir. J Clin Pharmacol. 2010; 50:1180–7. [PubMed: 20484617]
51. Hogeland GW, Swindells S, McNabb JC, Kashuba AD, Yee GC, Lindley CM. Lopinavir/ritonavir reduces bupropion plasma concentrations in healthy subjects. Clin Pharmacol Ther. 2007; 81:69–75. Epub 2006/12/23. DOI: 10.1038/sj.clpt.6100027 [PubMed: 17186001]
52. Bruce RD, Winkle P, Custodio JM, et al. Investigation of the interactions between methadone and elvitegravir-cobicistat in subjects receiving chronic methadone maintenance. Antimicrob Agents Chemother. 2013; 57:6154–7. Epub 2013/10/02. DOI: 10.1128/aac.01229-13 [PubMed: 24080665]
53. McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. Clinical Infectious Diseases. 2003; 37:476–82. [PubMed: 12905130]
54. Sekar V, Tomaka F, Lefebevre E, et al. Pharmacokinetic interactions between darunavir/ritonavir and opioid maintenace therapy using methadone or buprenorphine/naloxone. J Clin Pharmacol. 2011; 51:271–8. DOI: 10.1177/0091270010365558 [PubMed: 20421512]
55. Good BL, Gomes DC, Fulco PP. An unexpected interaction between warfarin and cobicistat-boosted elvitegravir. AIDS. 2015; 29:985–6. [PubMed: 25909832]
56. Liedtke MD, Rathbun RC. Warfarin-antiretroviral interactions. Ann Pharmacother. 2009; 43:322–8. Epub 2009/02/07. DOI: 10.1345/aph.1L497 [PubMed: 19196837]
57. Tseng AL, Luetkehoelter J, Walmsley SL. Increase in international normalized ratio after switching from atazanavir/ritonavir to darunavir/cobicistat in a patient on warfarin: boosters are not always equal. AIDS. 2017; 31:175–6. Epub 2016/11/30. DOI: 10.1097/qad.0000000000001275 [PubMed: 27898595]
58. Bruce RD, Winkle P, Custodio J, et al. The pharmacokinetic and pharmacodynamic interactions between buprenorphine/naloxone and elvitegravir/cobicistat in subjects receiving chronic buprenorphine/naloxone treatment. J Acq Immune Def Syndr. 2013; 63:480–4.
59. Tseng A, Hills-Nieminen C. Drug interactions between antiretrovirals and hormonal contraceptives. Expert Opin Drug Metab Toxicol. 2013; 9:559–72. Epub 2013/02/22. DOI: 10.1517/17425255.2013.772579 [PubMed: 23425052]
60. Zhang J, Chung E, Yones C, et al. The effect of atazanavir/ritonavir on the pharmacokinetics of an oral contraceptive containing ethinyl estradiol and norgestimate in healthy women. Antivir Ther. 2011; 16:157–64. [PubMed: 21447864]
61. Tackett, D., Child, M., Agarwala, S., et al. Atazanavir: a summary of two pharmacokinetic drug interaction studies in healthy subjects [abstract 543]; 10th Conference on Retroviruses and Opportunistic Infections; Boston. 2003.
62. German, P., Wang, M., Warren, D., Kearney, BP. Pharmacokinetic interaction between norgestimate/ethinyl estradiol and elvitegravir/cobicistat/emtricitabine/tenofovir single tablet regimen [abstract O_17]; 12th International Workshop on Clinical Pharmacology of HIV Therapy; Miami, USA. 2011.
63. Brooks, KM., Gordon, LA., Penzak, S., et al. Cobicistat, but not ritonavir, increases dabigatran exposure [abstract 409]; Conference on Retroviruses and Opportunistic Infections (CROI); Seattle, WA. 2017.
64. Barco S, Coppens M, van den Dool EJ, van de Kerkhof D, Stroobants AK, Middeldorp S. Successful co-administration of dabigatran etexilate and protease inhibitors ritonavir/lopinavir in a patient with atrial fibrillation. Thromb Haemost. 2014; 112:836–8. Epub 2014/07/06. DOI: 10.1160/th14-03-0214 [PubMed: 24990596]
65. Perram J, Joseph J, Holloway C. Novel oral anticoagulants and HIV: dabigatran use with antiretrovirals. BMJ case reports. 2015; 2015 Epub 2015/11/22. doi: 10.1136/bcr-2015-211651

66. Reilly PA, Lehr T, Haertter S, et al. The effect of dabigatran plasma concentrations and patient characteristics on the frequency of ischemic stroke and major bleeding in atrial fibrillation patients: the RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). Journal of the American College of Cardiology. 2014; 63:321–8. Epub 2013/10/01. DOI: 10.1016/j.jacc.2013.07.104 [PubMed: 24076487]

67. Elsby R, Hilgendorf C, Fenner K. Understanding the critical disposition pathways of statins to assess drug-drug interaction risk during drug development: it's not just about OATP1B1. Clin Pharmacol Ther. 2012; 92:584–98. Epub 2012/10/11. DOI: 10.1038/clpt.2012.163 [PubMed: 23047648]

68. Custodio JM, Wang H, Hao J, et al. Pharmacokinetics of cobicistat boosted-elvitegravir administered in combination with rosuvastatin. J Clin Pharmacol. 2014; 54:649–56. Epub 2014/01/01. DOI: 10.1002/jcph.256 [PubMed: 24375014]

69. Samineni D, Desai P, Sallans L, Fichtenbaum C. Steady-state pharmacokinetic interactions of darunavir/ritonavir with lipid-lowering agent rosuvastatin. J Clin Pharmacol. 2012; 52:922–31. [PubMed: 21712498]

70. Custodio, J., West, S., SenGupta, D., et al. Evaluation of the drug-drug interaction potential between cobicistat-boosted protease inhibitors and statins [abstract O_04]; 18th International Workshop on Clinical Pharmacology of Antiviral Therapy; Chicago, IL. 2017.

71. Busti AJ, Bain AM, Hall RG, et al. Effects of atazanavir/ritonavir or fosamprenavir/ritonavir on the pharmacokinetics of rosuvastatin. J Cardiovasc Pharmacol. 2008; 51:605–10. [PubMed: 18520949]

72. Bierman WF, Scheffer GL, Schoonderwoerd A, et al. Protease inhibitors atazanavir, lopinavir and ritonavir are potent blockers, but poor substrates, of ABC transporters in a broad panel of ABC transporter-overexpressing cell lines. J Antimicrob Chemother. 2010; 65:1672–80. Epub 2010/06/17. DOI: 10.1093/jac/dkq209 [PubMed: 20551216]

73. Elsby R, Martin P, Surry D, Sharma P, Fenner K. Solitary inhibition of the breast cancer resistance protein efflux transporter results in a clinically significant drug-drug interaction with rosuvastatin by causing up to a 2-fold increase in statin exposure. Drug Metab Dispos. 2016; 44:398–408. Epub 2015/12/25. DOI: 10.1124/dmd.115.066795 [PubMed: 26700956]

74. Arribas J, Rizzardini G, Arasteh K, et al. Simplification to Stribild vs continuation of RTV-boosted DRV with FTC and TDF in virologically suppressed HIV adults: a STRATEGY-PI subgroup analysis. Journal of the International AIDS Society. 2014; 17:19805. Epub 2014/11/15. doi: 10.7448/ias.17.4.19805 [PubMed: 25397549]

75. Arribas JR, Pialoux G, Gathe J, et al. Simplification to coformulated elvitegravir, cobicistat, emtricitabine, and tenofovir versus continuation of ritonavir-boosted protease inhibitor with emtricitabine and tenofovir in adults with virologically suppressed HIV (STRATEGY-PI): 48 week results of a randomised, open-label, phase 3b, non-inferiority trial. The Lancet infectious diseases. 2014; 14:581–9. Epub 2014/06/09. DOI: 10.1016/s1473-3099(14)70782-0 [PubMed: 24908551]

76. McDonald CK, Martorell C, Ramgopal M, et al. Cobicistat-boosted protease inhibitors in HIV-infected patients with mild to moderate renal impairment. HIV Clin Trials. 2014; 15:269–73. Epub 2014/12/01. DOI: 10.1310/hct1506-269 [PubMed: 25433666]

77. Gervasoni C, Riva A, Cozzi V, et al. Effects of ritonavir and cobicistat on dolutegravir exposure: when the booster can make the difference. J Antimicrob Chemother. 2017 Mar 3. [Epub ahead of print].

Table 1

Pharmacokinetic parameters of elvitegravir, atazanavir, darunavir, and tipranavir boosted with either cobicistat or ritonavir

	Cobicistat as Booster	Ritonavir as Booster	Antiretroviral kinetics (Cobi vs RTV)	Availability:	
				Fixed dose combination	Single Tablet Regimen
Elvitegravir once daily	150/150 mg	150/100 mg	Equivalent[17]	n/a Elvitegravir and cobicistat licensed as individual products (Viteka and Tybost) although not generally available.	Stribild Genvoya
AUC_{tau} (ng*hr/mL)	27000 (29.4)	22500 (23.4)			
C_{max} (ng/mL)	2660 (27.6)	2500 (32.1)			
C_{tau} (ng/mL)	490 (52.9)	410 (40.5)			
Atazanavir once daily	300/150 mg	300/100 mg	Equivalent[13]	Evotaz	n/a
AUC_{tau} (ng*hr/mL)	55900 (28)	55200 (28)			
C_{max} (ng/mL)	4880 (25)	5270 (2)			
C_{tau} (ng/mL)	1330 (43)	1340 (41)			
Darunavir once daily	800/150 mg	800/100 mg	Similar AUC, Cmax, 31% decrease in Ctrough[16]	Prezcobix (Rezolsta – EU)	*Upcoming*: darunavir/cobi/FTC/TAF
AUC_{tau} (ng*hr/mL)	76490 (27.3)	78410 (26.7)			
C_{max} (ng/mL)	6917 (20.1)	6973 (21.9)			
C_{tau} (ng/mL)	1478 (63.2)	2015 (42.3)			
Darunavir twice daily	600/150 mg	600/100 mg	Equivalent[20]	n/a	n/a
AUC_{tau} (ng*hr/mL)	73400 (19)	67900 (22)			
C_{max} (ng/mL)	9040 (19)	8390 (21)			
C_{tau} (ng/mL)	3960 (30)	3800 (27)			
Tipranavir twice daily	500/150 mg	500/200 mg	54% decrease in AUC, 86% decrease in Ctau[20]	n/a	n/a
AUC_{tau} (ng*hr/mL)	239 (39)	505 (31)			
C_{max} (ng/mL)	45.1 (35)	70.4 (23)			
C_{tau} (ng/mL)	2.6 (41)	18.6 (51)			

Data expressed as mean (CV%)

Key: cobi = cobicistat, EU=European Union, FTC = emtricitabine, n/a = not available, RTV=ritonavir, TAF = tenofovir alafenamide

Table 2

Elvitegravir interactions

	Elvitegravir Dose/Booster used	Change in elvitegravir	Change in coadministered drug	Comment
Antiretrovirals				
Atazanavir 300 mg[24]	85 mg/cobicistat 150 mg	17% increase AUC, 83% increase Ctau	10% decrease Cmin, 19% decrease Ctau (vs. atazanavir 300/ritonavir 100 mg)	Lower dose of elvitegravir used in this study not commercially available.
Darunavir 800 mg QD[20]	150 mg/150 mg cobicistat	20% decrease AUC, 52% decrease Cmin	3% decrease AUC, 21% decrease Ctrough	Healthy volunteer study.
Darunavir 800 mg QD[26]	150 mg/150 mg cobicistat (coformulated with tenofovir alafenamide/emtricitabine)	Similar to historical controls	Similar to historical controls	PK substudy in treatment-experienced patients.
Darunavir 600 mg BID[20]	150 mg QD with 150 mg cobicistat BID	Comparable to historical data	Similar to kinetics of darunavir 600 mg/cobicistat 150 mg BID alone.	This dose of darunavir not available coformulated with cobicistat.
Efavirenz[18]	150 mg/150 mg cobicistat	37% decrease AUC, 67% decrease Ctau (day 35)		Study examined kinetics of elvitegravir/cobicistat/TDF/emtricitabine after stopping efavirenz/TDF/emtricitabine. Efavirenz and elvitegravir were not given simultaneously.
Etravirine[19]	150 mg/ritonavir 100 mg daily	No clinically relevant changes	No clinically relevant changes	Note that this study used ritonavir as a booster.
Comedications				
Acid-reducing agents:				
Antacids[28]	50 mg/ritonavir 100 mg	2-20% decrease AUC (separated) or 45% decrease AUC (simultaneous administration)		Separate elvitegravir/cobicistat and antacids by at least 2 hours.
Famotidine[28]	150 mg/150 mg cobicistat	3% increase AUC, 7-18% increase Cmin		Interaction not considered clinically significant.
Omeprazole[28]	50 mg/100 mg ritonavir	1% decrease AUC, 6% decrease Cmin		Various elvitegravir doses used.
Omeprazole[28]	50/150 mg cobicistat 150/150 mg cobicistat	10% increase elvitegravir AUC 5% increase elvitegravir AUC		
Buprenorphine[58]	150 mg/150 mg cobicistat		35% increase AUC, 66% increase Cmin	No dose adjustment required.

	Elvitegravir Dose/Booster used	Change in elvitegravir	Change in coadministered drug	Comment
Carbamazepine[40]	150 mg/150 mg cobicistat	69% decrease AUC, 97% decrease Cmin	43% increase AUC, 51% increase Cmin	Coadministration is contraindicated.
Digoxin[28]	150 mg cobicistat alone	n/a	8% increase AUC, 41% increase Cmax	Administer with caution, clinical monitoring recommended.
Ketoconazole[28]	150 mg/ritonavir 100 mg	48% increase AUC, 67% increase Cmin		Do not exceed 200 mg daily of ketoconazole.
Ledipasvir/sofosbuvir[28]	150 mg/150 mg cobicistat	2% increase AUC, 36% increase Cmin	78% increase AUC, 91% increase Cmin (ledipasvir)	
Methadone[52]	150 mg/150 mg cobicistat		R-methadone: 7% increase AUC, 10% increase Cmin S-methadone: 2% increase Cmin	Dose adjustment not required.
Norgestimate/ethinyl estradiol[62]	150 mg/150 mg cobicistat		Norgestimate: 126% increase AUC, 167% increase Cmin. Ethinyl estradiol: 25% decrease AUC, 44% decrease Cmin	
Rifabutin 150 mg every other day[24]	150 mg/150 mg cobicistat	21% decrease AUC, 67% decrease Cmin	25-0-desacetyl-rifabutin: 625% increase AUC	A subsequent study using cobicistat 150 mg twice daily with elvitegravir 150 mg daily yielded favourable elvitegravir exposures, and a 41% increase rifabutin Ctau.[44]
Rifabutin 150 mg every other day[43]	300 mg/100 mg ritonavir	Equivalent to elvitegravir 300/ ritonavir 100 mg alone	25-0-desacetyl-rifabutin: 951% AUC increase,	Note that the elvitegravir dose used was twice the licensed dose.
Rosuvastatin[68]	150/150 mg cobicistat	2% increase AUC, 2% decrease Cmin	38% increase AUC, 43% increase Cmin	Dose adjustment not required.

Table 3

Atazanavir Interactions – differences in monograph recommendations

	Atazanavir/cobicistat[27]	**Atazanavir/ritonavir[30] (*not including unboosted atazanavir)**
Antiretrovirals		
Ritonavir or ritonavir-containing products	Contraindicated.	Use 100 mg with 300 mg atazanavir.
NNRTIs	Efavirenz, etravirine, nevirapine: Do not coadminister.	Efavirenz: treatment-naïve – use atazanavir 400 mg with ritonavir 100 mg. Treatment-experienced: do not coadminister.
Antiarrhythmics (digoxin)	Titrate digoxin dose and monitor digoxin concentrations.	Pharmacokinetic studies not performed; use with caution.
Antibacterials, macrolide (clarithromycin)	Consider alternative antibiotic.	Reduce clarithromycin dose by 50% with atazanavir. Coadministration with atazanavir/ritonavir not studied.
Anticancer agents (dasatinib, nilotinib, vinblastine, vincristine)	Potential for increased adverse events; dosage reduction of dasatinib and nilotinib may be necessary.	Not mentioned.
Anticonvulsants	Carbamazepine, phenobarbital, phenytoin: **contraindicated**. Lamotrigine: effect **unknown**. Monitor lamotrigine concentrations.	Carbamazepine, phenobarbital, phenytoin: **dose reduction of anticonvulsant may be needed**. Lamotrigine: potential **decrease** in lamotrigine; dose adjustment may be required.
Antidepressants (SSRIs)	Potential for increased SSRI concentrations. Dose titration may be required.	Not mentioned.
Antifungals	Ketoconazole, itraconazole: use with caution. Specific dosing recommendations not available. Voriconazole: effects unknown. Do not coadminister unless benefits outweigh risks. Clinical monitoring may be needed.	Ketoconazole, itraconazole: use high doses (>200 mg/day) with caution. Voriconazole: In patients with functioning CYP2C19 allele: decreased atazanavir and voriconazole. Do not use unless benefits outweigh risks. Monitor for voriconazole adverse events and loss of voriconazole or atazanavir efficacy. In patients without a functional CYP2C19 allele: decreased atazanavir and increased voriconazole.
Beta 2-adrenoreceptor agonists (salmeterol)	Contraindicated.	Should not be coadministered.
Benzodiazepines (midazolam)	Parenteral midazolam: Use with caution, with close clinical monitoring for respiratory depression and/or prolonged sedation; consider dosage adjustment.	Oral midazolam: Contraindicated. Parenteral midazolam: Use with caution, with close clinical monitoring for respiratory depression and/or prolonged sedation; consider dosage adjustment.
Corticosteroids (dexamethasone)	Reduction in atazanavir and cobicistat. Consider alternate corticosteroid.	Not mentioned.
HMG-CoA reductase inhibitors (rosuvastatin)	Do not exceed rosuvastatin 10 mg daily.	Use lowest dose possible.
H2-receptor antagonists (famotidine)	In treatment-experienced patients also on tenofovir DF: **do not coadminister**.	In treatment-experienced patients also on tenofovir DF: **use atazanavir 400 mg with ritonavir 100 mg once daily**.
Hormonal contraceptives	**Increased** concentrations of ethinyl estradiol and norethindrone; consider alternate non-hormonal forms of contraception.	**Decreased** ethinyl estradiol and increased norgestimate metabolite; use oral contraceptive containing at least 30 mcg of ethinyl estradiol.
Opioids (fentanyl)	Increased fentanyl. Monitor for therapeutic and adverse effects.	Not mentioned.

	Atazanavir/cobicistat[27]	**Atazanavir/ritonavir[30] (*not including unboosted atazanavir)**
Proton pump inhibitors (omeprazole)	Treatment-naïve: do not exceed doses comparable to omeprazole 20 mg daily. Treatment-experienced: not recommended.	Not recommended. If needed, use atazanavir 400 mg with 100 mg ritonavir and do not exceed doses comparable to omeprazole 20 mg daily.
PDE5 inhibitors (vardenafil)	Do not coadminister.	Contraindicated.

Table 4

Darunavir Interactions – differences in monograph recommendations

	Darunavir/cobicistat[23]	**Darunavir/ritonavir[41]**
Antiretrovirals		
NNRTI	Efavirenz, etravirine, nevirapine: coadministration **not recommended**. Rilpivirine: no dose adjustment required.	Rilpivirine: use with caution. Efavirenz, etravirine: **May be used without dose adjustment**. Nevirapine: no dose adjustment necessary. Potential for hepatotoxicity.
Protease inhibitors (atazanavir)	Do not coadminister.	Atazanavir may be coadministered.
Anticoagulants (warfarin)	Effect on warfarin unknown. Monitor INR.	Decreased warfarin. Monitor INR.
Anticonvulsants (carbamazepine, phenobarbital, phenytoin)	Contraindicated.	Carbamazepine: Monitor carbamazepine concentrations; may require 25-50% dose reduction. Phenobarbital, phenytoin: do not coadminister.
Antimalarials (artemether/lumefantrine)	**Increased** artemether and lumafantrine. Use with caution.	**Decreased** aremether and metabolite and increased lumafantrine.
Endothelin receptor antagonists (bosentan)	**Decreased darunavir**, cobicistat, increased bosentan. Monitor and adjust bosentan dose if necessary.	Increased bosentan. In patients on stable darunavir/ritonavir: start bosentan 62.5 mg once daily or every other day. In patients on bosentan: discontinue bosentan at least 36 hours prior to initiation of darunavir/ritonavir and then restart at 62.5 mg daily or every other day at least 10 days following initiation.
Inhaled beta agonist (salmeterol)	Contraindicated.	Coadministration not recommended.
Antidepressants (sertraline, paroxetine)	**Increased** antidepressant concentrations. Monitor and adjust antidepressant dose if necessary.	**Decreased** sertraline and paroxetine concentrations; titrate SSRI dose based on response.