

Boceprevir and Antiretroviral Pharmacokinetic Interactions in HIV/HCV Co-infected Persons: AIDS Clinical Trials Group Study A5309s

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Published online: 5 September 2017
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Abstract

Objective The objective of this study was to determine the magnitude of drug interactions between the hepatitis C virus (HCV) protease inhibitor boceprevir (BOC) and antiretroviral (ARV) agents in persons with HIV/HCV co-infection.

Methods Participants taking two nucleos(t)ide analogs with either efavirenz, raltegravir, or ritonavir-boosted atazanavir, darunavir, or lopinavir underwent intensive pharmacokinetic (PK) sampling for ARV 2 weeks before (week 2) and 2 weeks after initiating BOC (week 6) and for BOC at week 6. Geometric mean ratios (GMRs) and 90% confidence intervals (CIs) were used to compare ARV PK at weeks 2 and 6 and BOC PK at week 6 to historical data (HD) in healthy volunteers and HCV mono-infected patients.

Results ARV PK was available for 55 participants. BOC reduced atazanavir and darunavir exposures by 30 and 42%, respectively. BOC increased raltegravir maximum concentration (C_{max}) by 71%. BOC did not alter efavirenz PK. BOC PK was available for 53 participants. BOC exposures were similar in these HIV/HCV co-infected

participants compared with HD in healthy volunteers, but BOC minimum concentrations (C_{min}) were lower with all ARV agents (by 34–73%) compared with HD in HCV mono-infected patients.

Conclusions Effects of BOC on ARV PK in these HIV/HCV co-infected individuals were similar to prior studies in healthy volunteers. However, some differences in the effects of ARV on BOC PK were observed, indicating the magnitude of interactions may differ in HCV-infected individuals versus healthy volunteers. Findings highlight the need to conduct interaction studies with HCV therapies in the population likely to receive the combination.

Key Points

The effects of boceprevir on the pharmacokinetics of several antiretroviral agents were similar in HIV/hepatitis C virus (HCV) co-infected participants to those observed in prior studies in healthy volunteers.

Boceprevir exposures were similar in these HIV/HCV co-infected participants compared with historical data in healthy volunteers, but significantly lower boceprevir trough concentrations were observed with all antiretroviral cohorts compared with historic values in HCV mono-infected individuals.

Results highlight some differences in the magnitude of drug interactions for direct-acting antiviral agents in healthy volunteers compared with the HCV-infected population and indicate the need to conduct interaction studies in the population likely to receive the combination.

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1 Introduction

Drug interactions are a critical consideration in persons with HIV and hepatitis C virus (HCV) co-infection. The potential clinical consequences of an unexpected antiviral interaction include an increased incidence of adverse effects or therapeutic failure and the development of viral resistance. Despite the need to accurately characterize the extent of antiviral interactions in persons with HIV/HCV co-infection, there are challenges in studying these interactions in patients, and therefore most interaction studies are performed in healthy volunteers. However, there are uncertainties about extrapolating the results of drug interaction studies in healthy volunteers to HIV/HCV co-infected patients. The effects of liver functional status on the magnitude of drug interactions have not been well established. Available data suggest pathophysiologic alterations such as decreased drug uptake into the liver, a reduction in enzyme expression or function, and alterations in plasma protein binding can impact the extent of drug interactions [1]. The objective of this study was to evaluate the magnitude of drug interactions between the HCV NS3/4A protease inhibitor boceprevir (BOC) and several antiretroviral (ARV) agents, including the non-nucleoside reverse transcriptase inhibitor efavirenz (EFV), the integrase inhibitor raltegravir (RAL), and the ritonavir (RTV)-boosted protease inhibitors atazanavir (ATV), darunavir (DRV) and lopinavir (LPV), in persons with HIV and HCV co-infection.

2 Methods

AIDS Clinical Trials Group (ACTG) study A5309s was an intensive pharmacokinetic (PK) substudy of ACTG A5294 (NCT01482767), a prospective, phase 3, open-label study of BOC, peginterferon alfa-2b, and ribavirin in HCV/HIV co-infected participants [2]. Both A5294 and A5309s were approved by institutional review boards at the ACTG study sites. All participants provided written informed consent. All study procedures were in accordance with the Helsinki Declaration of 1975, as revised in 2000.

2.1 Subjects

Persons with HIV/HCV co-infection receiving peginterferon alfa-2b 1.5 mg/kg subcutaneously once a week and ribavirin 800–1400 mg daily based on body weight, administered in two divided doses, and intending to initiate BOC 800 mg three times daily with food could participate in this PK substudy. Allowed ARV regimens included two nucleoside reverse transcriptase inhibitors plus one of the

following: EFV 600 mg once daily, RAL 400 mg twice daily, ATV/RTV 300/100 mg once daily, DRV/RTV 600/100 mg twice daily, or LPV/RTV 400/100 mg twice daily. Participants could be naïve to HCV treatment or have failed prior interferon-based therapy. Participants with Child-Pugh class A cirrhosis (documented by liver biopsy or FibroSure™) were allowed provided they had no evidence of decompensated disease or hepatocellular carcinoma and platelet counts of greater than $80 \times 10^9/L$. Medications other than ARV with the potential to significantly alter BOC PK or be altered by BOC were excluded.

2.2 Design

Participants underwent intensive PK sampling for ARV 2 weeks before (week 2) and 2 weeks after initiating BOC (week 6), and intensive PK sampling for BOC at week 6. For these intensive PK visits, participants were admitted in the morning following an 8-h fast and offered a partially standardized breakfast (three options with similar fat and calorie content, 21 g and 600 kcal, respectively). Dosing of ARV and BOC (at week 6) was directly observed. Samples were collected at pre-dose and 1, 2, 3, 4, 6, and 8 h post-dose, and 12 and 24 h post-dose for twice daily and once daily ARV, respectively. Participants taking EFV and ATV/RTV in the evenings switched to morning dosing at least 3 days prior to the intensive PK visits. Adherence in the 3 days prior to the intensive PK visits was assessed using a medication diary.

2.3 Bioanalyses

2.3.1 Boceprevir (BOC) in Plasma

Blood samples for BOC quantification were cooled in an ice bath, approximately 4 °C, and then centrifuged for 15 min at 1500g within 30 min of collection. Following centrifugation, 1.5 mL of plasma was placed in pre-chilled cryovials containing 75 µL of 85% phosphoric acid. The vials were capped, mixed well and kept on wet ice until placed in a freezer for storage at –20 °C or colder.

BOC is administered as an approximately equal mixture of two diastereomers, SCH534128 (pharmacologically active) and SCH534129 (inactive), which rapidly interconvert in plasma. BOC concentrations are reported as the sum of SCH534128 and SCH534129, which were quantified by a validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) method (PPD, Middleton, WI, USA). SCH534128 and SCH534129 and internal standards (IS) 503034-d₉ and 629144-d₉ were isolated by solid-phase extraction and eluted from the solid-phase extraction plate. The extracts were dried and reconstituted. The final extract was analyzed by LC-MS/MS using positive ion

atmospheric pressure chemical ionization. The assay was validated over the SCH534128 concentration range of 5.20 to 5200 ng/mL and over the SCH534129 concentration range of 4.80 to 4800 ng/mL. SCH534128 assay imprecision (% CV) was $\leq 12.1\%$, and inaccuracy (bias, % difference) was within -7.12 to 3.59% . SCH534129 assay imprecision (% CV) was $\leq 10.3\%$, and inaccuracy (bias, % difference) was within -7.84 to 4.12% [3].

2.3.2 Antiretroviral (ARV) Agents in Plasma

ARV concentrations were determined using validated methods at the University at Buffalo Pharmacology Specialty Laboratory. DRV, EFV and LPV were measured using high performance liquid chromatography with ultraviolet detection (HPLC/UV) linear in the range of 0.100–16.0 mg/L for DRV and EFV, and 0.200–16.0 mg/L for LPV [4]. RAL, ATV, and RTV were measured using ultraperformance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Methods were validated using the Food and Drug Administration (FDA) bioanalytical guidance recommendations and externally reviewed for acceptance [5].

After addition of 750 μL of acetonitrile and 25 μL of the working IS solution (ATV-d₅ and RTV-d₆) to 250 μL of ethylenediaminetetraacetic acid (EDTA) human plasma, ATV and RTV were extracted via protein precipitation. The compounds were separated under gradient conditions and detected via electrospray coupled to a triple quadrupole mass spectrometer. Multiple reaction monitoring in positive mode was used, with ATV monitored at 706/168, ATV-IS at 711/144, RTV at 722/140 and RTV-IS at 728/146. The range of quantitation was 10–4000 ng/mL for both ATV and RTV; samples over the upper limit of dilution were diluted and reassayed. ATV assay imprecision (% CV) was $\leq 3.5\%$, and inaccuracy (bias, % difference) was within -13 to -6.3% . RTV assay imprecision (% CV) was $\leq 6.1\%$, and inaccuracy (bias, % error) was within -9.8 to -8.6% .

For analysis of RAL, plasma samples were prepared using an Oasis HLB 96-well solid phase extraction (Waters Corp., Milford, MA, USA) and included the addition of deuterated working IS solution to 250 μL of EDTA human plasma. Prior to sample extraction, samples were buffered with 250 μL of a 4% formic acid solution, and after elution, the eluant was diluted with 0.05% formic acid. The compounds were chromatographed under gradient conditions and detected via electrospray coupled to a triple quadrupole mass spectrometer. Multiple reaction monitoring in positive mode was used, with RAL monitored at 445/361 and RAL-d₃ at 448/364. The range of quantitation was 10–4000 ng/mL for RAL; samples over the upper limit of dilution were diluted and reassayed.

The laboratory participated successfully in proficiency testing programs for all compounds throughout the analysis period to assure accuracy and specificity [6–8].

2.4 Pharmacokinetic Analysis

Area under the concentration–time curve over the dosing interval (AUC_{0-T}) (8, 12, or 24 h) was estimated using the linear trapezoidal rule. If the pre-dose sample (C_{pre}) was missing, the concentration at the end of the dosing interval (C_T) was substituted for the C_{pre} in the calculation of AUC_{0-T} . If the C_T was missing, the C_{pre} was substituted in the calculation of the AUC_{0-T} . For participants who appeared to re-dose prior to obtaining the C_T (i.e., when C_T was more than 40% higher than the concentration at the previous sampling time), C_{pre} was substituted for the C_T in the calculation of the AUC_{0-T} in order to minimize over-estimation of AUC_{0-T} . Maximum concentration (C_{max}) and minimum concentration (C_{min}) were observed. Data were excluded from analysis if (1) participants missed more than one BOC or ARV dose in the 3 days leading up the intensive PK visits, (2) more than two samples were missing from the intensive PK profile, or (3) both the C_{pre} and C_T were missing.

2.5 Statistical Analysis

Geometric mean ratios (GMRs) and associated 90% confidence intervals (CIs) were used to compare ARV PK with versus without BOC (within-subject comparisons, week 6 vs week 2) and BOC PK at week 6 versus historical data in healthy volunteers. 90% CIs around the GMR were used as per FDA guidance [9], and 90% CIs excluding 1 were considered statistically significant. 90% CIs are nominal without adjustment for multiple comparisons. Historical data from healthy volunteers were used as the primary comparator because no intensive PK data from persons with HCV who received the commercial dose and formulation were available. The PK parameters in the BOC prescribing information [10] are values obtained from intensive sampling in healthy volunteers. BOC population PK modeling was previously performed in persons with HCV using samples and data obtained through sparse sampling in the phase 2 and 3 trials [11]. Formal statistical comparisons were performed with the BOC PK in healthy volunteers since these data were generated in a manner consistent with A5309s (i.e., from intensive sampling and non-compartmental analysis). However, the historical data from both healthy volunteers and the modeled data from HCV-infected subjects are provided and discussed for interpretation of study results. GMRs were used to compare BOC PK at week 6 versus historical modeled BOC data in HCV mono-infected patients.

3 Results

3.1 Participants

The first participant enrolled in A5309s in May 2012. Target enrollment for A5309s was 100 participants (20 in each of the ARV cohorts); however, the parent study A5294 closed to enrollment on December 20, 2013 because the study team and FDA determined the primary objectives could be addressed with adequate power using a reduced sample size. At that time, sixty-four participants were enrolled in A5309s: 24 on EFV, 22 on RAL, 11 on ATV/RTV, five on DRV/RTV, and two on LPV/RTV. Participant demographics are shown in Table 1. Most participants (88%) were male. Sixty-four percent of participants were HCV treatment naïve and 16% were cirrhotic. ARV PK was available for 55 participants, and BOC PK was available for 53 participants. A CONSORT diagram is provided in Fig. 1.

3.2 ARV Pharmacokinetics

Mean [standard deviation (SD)] ARV PK parameters with and without BOC, and the change in ARV PK with BOC, are shown in Table 2. BOC did not alter EFV PK. RAL AUC_{0-T} and C_{max} were 46 and 71% higher, respectively,

when administered with BOC, but there was wide variability in RAL PK, such that differences were not statistically significant. BOC reduced ATV AUC_{0-T} and C_{min} by 30 and 43%, respectively. BOC reduced DRV AUC_{0-T} , C_{max} , and C_{min} by 42, 32, and 64%, respectively. In the two participants on LPV/RTV, mean (SD) LPV AUC_{0-T} , C_{max} , and C_{min} were 67.62 (42.69) mg*h/L, 7.60 (4.40) mg/L, and 2.76 (3.63) mg/L, respectively, without BOC and 57.18 (2.62) mg*h/L, 7.28 (0.40) mg/L, and 1.90 (0.22) mg/L, respectively (not tabulated) with BOC, suggesting BOC reduced LPV concentrations. Figure 2 summarizes ARV concentration–time curves with and without BOC, and shows within-participant differences in ARV AUC with versus without BOC. RTV was also reduced with BOC. With ATV/RTV, the RTV AUC_{0-T} and C_{min} were reduced 44 and 69%, respectively. With DRV/RTV, RTV AUC_{0-T} and C_{min} were reduced 35 and 37%, respectively.

3.3 BOC Pharmacokinetics

Mean (SD) week 6 BOC PK by ARV cohort are shown in Table 3. To estimate the GMR and 90% CI, BOC PK was compared to historical data in 71 healthy volunteers [10]. In 71 healthy volunteers, mean (SD) BOC AUC_{0-T} , C_{max} , and C_{min} were 5.41 (1.47) mg*h/L, 1.72 (0.42) mg/L, and 0.09 (0.06) mg/L, respectively. BOC AUC_{0-T} , C_{max} , and

Table 1 Participant demographics ($n = 64$)

	Total ($n = 64$)	EFV ($n = 24$)	RAL ($n = 22$)	ATV/RTV ($n = 11$)	DRV/RTV ($n = 5$)	LPV/RTV ($n = 2$)
Age (years), mean (SD)	50.2 (7.7)	50.2 (6.4)	49.2 (8.1)	52.6 (9.2)	50.6 (8.2)	46.0 (12.7)
Weight (kg), mean (SD)	82.9 (16.5)	80.3 (14.9)	86.4 (20.9)	83.3 (11.7)	79.9 (13.7)	81.3 (17.4)
Male, number (%)	56 (88%)	19 (79%)	19 (86%)	11 (100%)	5 (100%)	2 (100%)
Race, number (%)						
White non-Hispanic	29 (45)	8 (33)	12 (55)	5 (45)	3 (60)	1 (50)
Black non-Hispanic	25 (39)	11 (46)	7 (32)	5 (45)	1 (20)	1 (50)
Hispanic	7 (11)	5 (21)	2 (9)	0 (0)	0 (0)	0 (0)
Other	3 (5)	0 (0)	1 (4)	1 (10)	1 (20)	0 (0)
Cirrhotic, number (%)	10 (16)	4 (17)	4 (18)	2 (18)	0 (0)	0 (0)
HCV treatment experienced, number (%)	23 (36)	12 (50)	5 (23)	3 (27)	3 (60)	0 (0)
Baseline HIV-1 RNA <50 copies/mL, number (%)	62 (98)	24 (100)	20 (95)*	11 (100)	5 (100)	2 (100)
Baseline CD4 (cells/mm ³), mean (SD)	662.1 (292.3)	596.6 (239.9)	583.7 (193.9)	847.2 (434.3)	870.4 (359.8)	772.5 (94.0)
NRTI regimen, number (%)						
Tenofovir disoproxil fumarate/ emtricitabine	50 (78)	20 (83)	17 (77)	8 (73)	4 (80)	1 (50)
abacavir/lamivudine	12 (19)	3 (13)	5 (23)	2 (18)	1 (20)	1 (50)
Other	2 (3)	1 (4)	0 (0)	1 (9)	0 (0)	0 (0)

ATV atazanavir, DRV darunavir, EFV efavirenz, HCV hepatitis C virus, LPV lopinavir, NRTI nucleoside reverse transcriptase inhibitor, RAL raltegravir, RTV ritonavir, SD standard deviation

* Baseline HIV-1 RNA missing for one subject on RAL

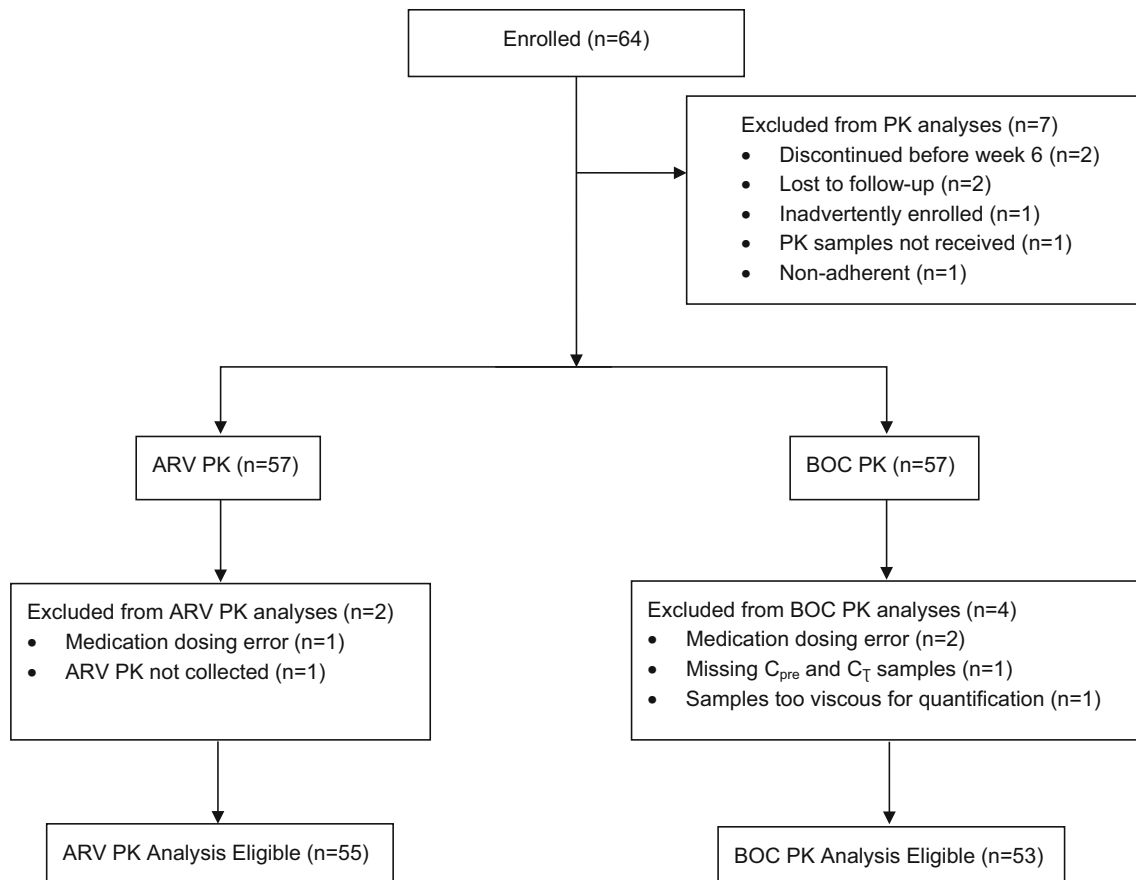


Fig. 1 CONSORT diagram showing subject disposition for PK analysis. *ARV* antiretroviral, *BOC* boceprevir, C_{pre} pre-dose sample, *PK* pharmacokinetic(s)

C_{min} were lower in participants on EFV by 12, 29, and 22%, respectively, compared with BOC PK in healthy volunteers. BOC AUC_{0-T} in those on RAL was 17% higher than the AUC_{0-T} in healthy volunteers. BOC C_{min} in those on ATV/RTV was 31% higher than in healthy volunteers, but the BOC AUC_{0-T} and C_{max} were not different. BOC AUC_{0-T} and C_{max} were not different in those on DRV/RTV relative to these values in healthy volunteers; however, the BOC C_{min} in those on DRV/RTV was 93% higher than the BOC C_{min} in healthy volunteers. Mean (SD) BOC AUC_{0-T} , C_{max} , and C_{min} in the two participants on LPV/RTV were 3.69 (1.25) $mg \cdot h/L$, 0.98 (0.27) mg/L , and 0.06 (0.02) mg/L , respectively (not tabulated). These values appear lower than the BOC AUC_{0-T} , C_{max} , and C_{min} in healthy volunteers.

As previously described, there are no intensive PK data in HCV-infected persons receiving the marketed BOC dose and formulation. However, there are BOC AUC_{0-T} , C_{max} , and C_{min} estimates generated through population PK modeling of samples obtained in phase 2 and 3 studies [11]. Population PK modeling of samples obtained through BOC trials determined a mean (SD) BOC AUC_{0-T} , C_{max} , and C_{min} in 271 HCV-infected patients to be 4.65 (1.58) $mg \cdot h/L$, 1.1 (0.4) mg/L , and 0.23 (0.11) mg/L , respectively. These

AUC_{0-T} and C_{max} estimates are lower than those observed in healthy volunteers, while the estimated C_{min} in HCV-infected persons was higher than that observed in healthy volunteers (0.23 vs 0.09 mg/L). If BOC PK in the ARV cohorts in A5309s were compared to these modeled data in HCV-infected persons rather than healthy volunteers, the mean BOC C_{min} in all ARV cohorts appears lower than the mean modeled C_{min} of 0.23 mg/L (Fig. 3).

4 Discussion

This study determined the magnitude of antiviral interactions in individuals with chronic liver disease and HIV co-infection. A 16–43% reduction in ATV concentrations and a 32–64% reduction in DRV concentrations were observed with the addition of BOC. There was no effect of BOC on EFV. In contrast to a previous study in healthy volunteers which found no effect of BOC on RAL PK [10], we observed an increase in RAL concentrations, though there was wide variability in RAL concentrations and the results were only statistically significant for C_{max} . In terms of the effects of ARV on BOC PK, interpretation is dependent on

Table 2 Mean (SD) antiretroviral pharmacokinetics and GMR (90% CI) with vs without BOC

	No.	No BOC (week 2)	With BOC (week 6)	GMR (90% CI)	GMR point estimate expressed as percentage change from week 2 (%)
ATV/RTV					
ATV AUC	11	35.20 (21.21)	23.75 (12.37)	0.70 (0.55–0.87)*	↓30
ATV C_{max}	11	2.66 (1.61)	2.14 (1.00)	0.84 (0.62–1.14)	↓16
ATV C_{min}	11	0.72 (0.48)	0.42 (0.35)	0.57 (0.42–0.76)*	↓43
RTV AUC	11	7.57 (3.82)	4.07 (1.45)	0.56 (0.46–0.68)*	↓44
RTV C_{max}	11	0.80 (0.54)	0.55 (0.20)	0.75 (0.54–1.04)	↓25
RTV C_{min}	11	0.06 (0.04)	0.03 (0.03)	0.31 (0.23–0.43)*	↓69
DRV/RTV					
DRV AUC	5	67.07 (14.58)	38.85 (9.40)	0.58 (0.53–0.63)*	↓42
DRV C_{max}	5	7.81 (1.45)	5.29 (1.02)	0.68 (0.64–0.71)*	↓32
DRV C_{min}	5	4.00 (1.24)	1.42 (0.46)	0.36 (0.27–0.48)*	↓64
RTV AUC	5	6.87 (3.14)	4.51 (1.92)	0.65 (0.55–0.78)*	↓35
RTV C_{max}	5	0.94 (0.51)	0.67 (0.28)	0.74 (0.52–1.04)	↓26
RTV C_{min}	5	0.3 (0.17)	0.19 (0.12)	0.63 (0.50–0.79)*	↓37
Efavirenz					
AUC	18	81.98 (76.82)	86.50 (73.76)	1.09 (0.97–1.22)	↑9
C_{max}	18	4.72 (3.42)	5.05 (3.31)	1.10 (0.97–1.24)	↑10
C_{min}	18	2.60 (3.09)	2.80 (2.91)	1.11 (0.96–1.27)	↑11
Raltegravir					
AUC	19	5.26 (7.11)	7.01 (5.12)	1.46 (1.00–2.12)	↑46
C_{max}	19	1.14 (1.57)	1.75 (1.41)	1.71 (1.08–2.70)*	↑71
C_{min}	19	0.09 (0.08)	0.09 (0.07)	1.09 (0.75–1.58)	↑9

AUC is in mg*h/L, C_{max} and C_{min} in mg/L; DRV/RTV is given as 600/100 mg twice daily. LPV/RTV not reported due to small sample size ($n = 2$)

↓ decrease, ↑ increase, ATV atazanavir, AUC area under the concentration–time curve, BOC boceprevir, CI confidence interval, C_{max} maximum concentration, C_{min} minimum concentration, DRV darunavir, GMR geometric mean ratio, LPV lopinavir, RTV ritonavir, SD standard deviation

* GMR CI excludes 1.0

the historical comparator. Relative to BOC PK in healthy volunteers, BOC C_{min} was 31 and 93% higher in these HIV/HCV co-infected individuals receiving ATV/RTV and DRV/RTV, BOC AUC was 17% higher in those on RAL, and BOC C_{max} was 29% lower in those on EFV. When compared with historical PK estimates using population PK modeling with sparse collection in HCV mono-infected subjects, the BOC C_{min} in all ARV cohorts was numerically lower than the modeled mean C_{min} of 0.23 mg/L.

The effect of BOC on ATV/RTV, DRV/RTV, and EFV PK in these HIV/HCV co-infected individuals was very similar to that observed in prior studies in healthy volunteers (Table 4). The mechanism(s) by which BOC reduces concentrations of RTV-boosted HIV protease inhibitors is unclear. BOC is a potent CYP3A4 inhibitor in vivo. The C_{max} and AUC for the CYP3A probe, midazolam, were increased 2.77-fold and 5.3-fold by BOC [10]. In vitro, BOC was not found to induce CYP enzymes [12]. However, both the AUC and C_{max} of escitalopram, a known substrate of CYP2C19, were reduced approximately 20%

in the presence of BOC [13]. Escitalopram's mean half-life was also accelerated from 31 to 22 h [13]. BOC was also found to increase metabolite formation of the HIV non-nucleoside reverse transcriptase inhibitor, etravirine, in a prior study [14], suggesting BOC may potentially induce CYP enzymes. Reductions in RTV concentrations by 25–69% likely contributed to the reductions in ATV, DRV, and LPV concentrations in our participants.

RAL AUC and C_{max} were increased 46 and 71% with the addition of BOC in these HIV/HCV co-infected participants. Though this effect on AUC did not reach statistical significance due to the wide interpatient variability in RAL PK, these increases are greater than previously observed in healthy volunteers (4 and 11%, respectively) [15]. Explanations for the discrepancy are unclear, but the prior study included a single dose of RAL in healthy volunteers, whereas our HIV-infected participants were receiving RAL as a component of their chronically suppressive ARV therapy. RAL is metabolized by uridine glucuronosyl transferase 1A1 (UGT1A1), but in vitro,

Fig. 2 ARV pharmacokinetics with vs without BOC. *Left panel* summary concentration-time plots for ARVs without (*solid yellow line*) and with (*dashed purple line*) concurrent BOC administration; geometric means of all subjects' hour-specific concentrations are plotted on the log scale. *Right panel* subject-specific ARV AUC_{0-T} without vs with BOC are plotted and connected. ARV antiretroviral, AUC_{0-T} area under the concentration-time curve over the dosing interval, BOC boceprevir

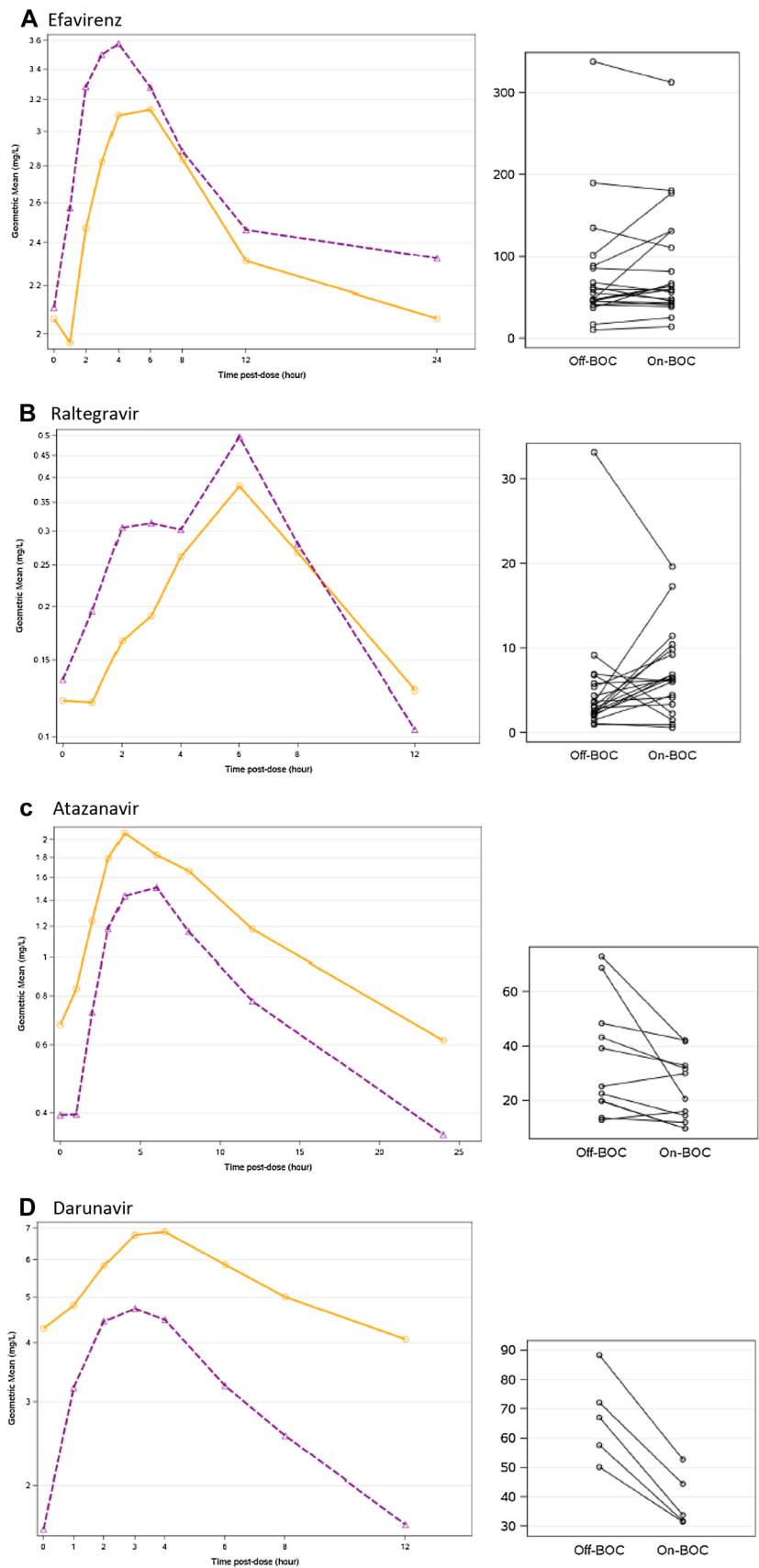


Table 3 Mean (SD) week 6 BOC PK by ARV cohort

	ARV	No.	Week 6 BOC PK	GMR (90% CI) vs historical data in healthy volunteers	GMR point estimate (%)	GMR vs modeled historical data in HCV+ mono-infected individuals
BOC AUC	EFV	19	4.80 (1.39)	0.88 (0.78–0.99)	↓12	1.05
BOC C_{max}		19	1.30 (0.63)	0.71 (0.61–0.84)*	↓29	1.17
BOC C_{min}		19	0.10 (0.09)	0.78 (0.49–1.24)	↓22	0.27
BOC AUC	RAL	18	6.35 (1.96)	1.17 (1.04–1.32)*	↑17	1.39
BOC C_{max}		18	1.76 (0.48)	1.00 (0.88–1.15)	↔	1.65
BOC C_{min}		18	0.12 (0.09)	1.29 (0.95–1.76)	↑29	0.44
BOC AUC	ATV/RTV	10	5.57 (1.22)	1.04 (0.90–1.20)	↑4	1.23
BOC C_{max}		10	1.74 (0.66)	0.97 (0.76–1.23)	↓3	1.59
BOC C_{min}		10	0.10 (0.03)	1.31 (1.05–1.64)*	↑31	0.44
BOC AUC	DRV/RTV	4	5.56 (1.68)	1.03 (0.72–1.46)	↑3	1.22
BOC C_{max}		4	1.51 (0.54)	0.85 (0.54–1.36)	↓15	1.41
BOC C_{min}		4	0.15 (0.07)	1.93 (1.37–2.73)*	↑93	0.66

To determine the GMR and 90% CI, BOC PK were compared to historical data in 71 healthy volunteers. Mean (SD) BOC AUC, C_{max} , and C_{min} in healthy volunteers are 5.41 (1.47) mg*h/L, 1.72 (0.42) mg/L, and 0.09 (0.06) mg/L, respectively. LPV/RTV not reported due to small sample size ($n = 2$)

↓ decrease, ↑ increase, ↔ no change, ARV antiretroviral, ATV atazanavir, AUC area under the concentration–time curve, BOC boceprevir, CI confidence interval, C_{max} maximum concentration, C_{min} minimum concentration, DRV darunavir, EFV efavirenz, GMR geometric mean ratio, HCV hepatitis C virus, LPV lopinavir, PK pharmacokinetics, RAL raltegravir, RTV ritonavir, SD standard deviation

* GMR excludes 1.0

BOC does not inhibit UGT1A1 [12]. Also, RAL C_{min} was not increased, which indicates BOC may increase the bioavailability of RAL either at the level of the gut or hepatic uptake. RAL is a substrate for P-glycoprotein (P-gp) and breast cancer resistance protein (BCRP) [16], but not human organic anion transporting polypeptide 1B1 (OATP1B1) [17]. BOC is only a weak inhibitor of P-gp, as evidenced by a 19% increase in the AUC of digoxin, a P-gp probe substrate [10]. BOC is a weak inhibitor of BCRP in vitro [18], but there are no data in vivo with BCRP probe substrates. RAL has a wide therapeutic index; thus it is unlikely that a 46% increase in RAL AUC and 71% increase in RAL C_{max} would have clinical implications.

Prior interaction studies in healthy volunteers found 32–35 and 45–57% lower BOC concentrations with DRV/RTV and LPV/RTV, respectively. BOC is a substrate of aldo-keto reductase (AKR) enzymes 1C2 and 1C3 and a substrate for CYP3A4. The mechanism for this effect is unclear, but may be due to induction of transporters or enzymes that transport or metabolize BOC or perhaps a protein binding displacement interaction whereby total concentrations of BOC are reduced while unbound concentrations are unchanged. Despite the magnitude of the interaction observed in healthy volunteers, similar rates of sustained virologic response (SVR or cure) were observed in HIV-infected patients (86% of whom were on a RTV-boosted HIV protease inhibitor) in the phase 2 study of peginterferon alfa-2b, ribavirin, and BOC to SVR rates

observed in HCV mono-infected patients [19]. This raises the question as to whether the magnitude of antiviral drug interactions is the same in persons with HCV (and potential hepatic impairment) as in healthy volunteers. EFV was also found to reduce BOC C_{min} , by 44%, in healthy volunteers through induction of CYP3A4 [10]. RAL did not change BOC AUC and C_{max} in a prior study in healthy volunteers [10]. Our study determined the effects of ARV on BOC by comparing BOC PK in HIV/HCV co-infected participants to historical data. While we might have expected greater reductions in BOC concentrations in those on DRV/RTV, LPV/RTV and EFV based on the prior studies in healthy volunteers, only the two participants on LPV/RTV had BOC concentrations lower than in healthy volunteers. BOC concentrations were only 12–29% lower in those on EFV relative to BOC concentrations in healthy volunteers, and BOC AUC and C_{min} were actually higher relative to healthy volunteers in those on ATV/RTV and DRV/RTV. In those on RAL, BOC AUC was 17% higher than in healthy volunteers. If we compare the BOC PK in our HIV/HCV co-infected individuals to modeled data in HCV mono-infected individuals, however, BOC C_{min} was lower in all ARV cohorts. BOC C_{min} was 73, 56, 56, and 34% lower in those on EFV, RAL, ATV/RTV, and DRV/RTV, respectively.

This study, A5309s, was an intensive PK substudy of ACTG A5294 (NCT01482767). A5294 was a prospective, phase 3, open-label study of BOC, peginterferon alfa-2b,

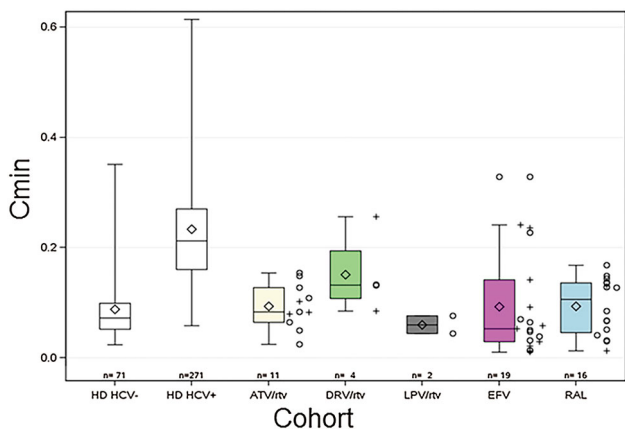


Fig. 3 Boceprevir C_{min} relative to HD in healthy volunteers (HD HCV-) and modeled data in HCV mono-infected patients (HD HCV+). Minimum, maximum and median, and 25th and 75th percentiles are shown as boxes and whiskers; means are indicated by diamond symbols. Individual subject values are also plotted: HCV-treatment naïve patients (open circles) and HCV-treatment experienced patients (+ symbols). *ATV* atazanavir, C_{min} minimum concentration, *DRV* darunavir, *EFV* efavirenz, *HCV* hepatitis C virus, *HD* historical data, *LPV* lopinavir, *RAL* raltegravir, *rtv* ritonavir

and ribavirin in HCV/HIV co-infected subjects [2]. The SVR rates in 135 treatment naïve and 122 treatment experienced participants were 36 and 30%, respectively. This SVR rate is significantly lower than that observed in the phase 2 trial of HIV/HCV co-infected participants (63%) [19] and lower than historical SVR rates observed in phase 3 trials of HCV mono-infected individuals (59–66%) [20, 21]. The majority of patients in A5294 were on EFV (42%) or RAL-containing (36%) ARV therapy. There was no signal of a particular ARV cohort having lower SVR rates; to the contrary, treatment naïve participants taking ATV/RTV had the highest rate of SVR observed in the study at 61%, but there were only 18 participants in this category. The strongest predictor of treatment outcome in A5294 was race, with blacks having significantly lower SVR rates. Roughly half of the A5294 participants were black.

This study evaluated the drug interaction potential of HCV and HIV medications in the patient population receiving the combination in clinical practice. This is a significant advantage in terms of the generalizability of study findings; however, there are some limitations. Given these are HIV-infected individuals on suppressive ARV therapy, ARV therapy was not discontinued in order to determine the PK of BOC alone, and thus BOC PK was compared to historical data. There were challenges with our BOC historical comparators since there were no intensive PK data in HCV-infected individuals on the commercial dose and formulation of BOC. There were also very few participants on RTV-boosted HIV protease inhibitors in this substudy, since recruitment was a function of enrollment in the parent study and the parent study opened first to those on EFV and RAL and HIV protease inhibitors were added in version 2.0. Given BOC was combined with pegylated interferon, which is not indicated in persons with decompensated (Child Pugh B or C) cirrhosis, there were very few participants in our study with more advanced liver disease. Advanced liver disease can be associated with portal hypertension which causes shunting of drug around the liver, reductions in hepatic uptake transporter and enzyme expression or function, and reductions in plasma protein binding due to a decrease in the amount of proteins synthesized, but also the quality of protein and competition for binding with endogenous substances (e.g., bilirubin). Sixteen percent of the participants had Child Pugh A cirrhosis, but the majority were non-cirrhotic. The magnitude of the interactions observed may differ in those with more advanced disease.

5 Conclusions

Overall, we found the effect of BOC on RTV-boosted HIV protease inhibitors and EFV PK in these HIV/HCV co-infected participants to be very similar to that observed in healthy volunteers, but BOC appeared to increase RAL

Table 4 Boceprevir interactions with antiretroviral agents in prior studies in healthy volunteers

	Antiretroviral pharmacokinetics			Boceprevir pharmacokinetics			References
	ΔAUC (%)	ΔC_{max} (%)	ΔC_{min} (%)	ΔAUC (%)	ΔC_{max} (%)	ΔC_{min} (%)	
ATV/RTV	↓35	↓25	↓49	↓5	↓7	↓18	[22]
BID DRV/RTV	↓44	↓36	↓59	↓32	↓25	↓35	[22]
BID LPV/RTV	↓34	↓30	↓43	↓45	↓50	↓57	[22]
EFV	↑20	↑11	ND	↓19	↓8	↓44	[10]
RAL	↑4	↑11	↓25	↓2	↓4	↓26	[10]

The table shows the change (Δ) in AUC, C_{max} and C_{min} for boceprevir and the antiretroviral agents

↓ decrease, ↑ increase, *ATV* atazanavir, *AUC* area under the concentration–time curve, *BID* twice daily, C_{max} maximum concentration, C_{min} minimum concentration, *DRV* darunavir, *EFV* efavirenz, *LPV* lopinavir, *ND* not determined, *RAL* raltegravir, *RTV* ritonavir

concentrations. While BOC PK in our participants was comparable to BOC PK in healthy volunteers, the BOC C_{\min} was lower in all ARV cohorts compared with historical data in HCV mono-infected patients. Additional PK-pharmacodynamic analysis would be required to determine whether BOC exposures contributed to the low rates of SVR observed in A5294; however, BOC is no longer marketed, and several newer HCV therapies have a lower potential for drug interactions with ARV.

Acknowledgements Preliminary data from this study were presented as a poster at the 15th International Workshop on Clinical Pharmacology of HIV and Hepatitis Therapy, Washington, DC, May 19–21, 2014.

We wish to acknowledge the study participants, the bioanalytical staff at the University of Buffalo Pharmacology Support Laboratory for performing the antiretroviral drug assays, and the following ACTG study sites and study personnel: Dr. Princy Kumar and Dr. Joseph Timpono, Georgetown University (Site 1008) ACTG CTU Grant 1U01AI069494; Mark Rodriguez, RN, BSN and Geyoul Kim RN, BSN, Washington University in St. Louis CRS (Site 2101) ACTG CTU Grant AI69439; Michelle Saemann, RN and Josette Robinson-Eaton, University of Cincinnati CRS (Site 2401) ACTG CTU Grant 2UM1-AI069501; Graham Ray and Thomas Campbell, University of Colorado Hospital CRS (Site 6101) ACTG CTU Grant 2UM1AI069432 and Grant UL1 TR001082; Kim Whitely, RN, Melissa Osborn, and Traci Davis, RN, MetroHealth Medical Center (Site 2503) ACTG CTU Grant AI69501 and the Clinical and Translational Science Collaborative of Cleveland, UL1TR000439; Roger Bedimo, MD and Deanna Rogers, Trinity Health & Wellness Center (Site 31443) ACTG CTU Grant U01 AI069471; Eric Helgeson, RN and Melvis Padullo, University of Washington ACTU CRS (Site 1401) ACTG CTU Grant UM AI-069481; Kristen Allen RN and Michael Chiccelly AS, Case CRS (Site 2501) ACTG CTU Grant AI069501; Vicki Bailey, RN and Husamettin Erdem, Vanderbilt Therapeutics Clinical Research Site (Site 3652) 2UM1AI069439-08, supported in part by the Vanderbilt CTSA grant UL1 TR000445; Dr. Richard Cindrich and Dr. Christina Koizumi, Bronx-Lebanon Hospital Center CRS (Site 31469) ACTG CTU Grant 2 UM1 AI069503-08; Lisa Klevens, BSN and Ramakrishna Prasad, MD, University of Pittsburgh CRS (Site 1001) ACTG CTU Grant UM1 AI069494, University of Pittsburgh CTSI Grant UL1 RR024153 and UL1TR000005; Mary Adams, RN, University of Rochester (Site 1101) ACTG CTU Grant 2UM1AI069511-08 and CRC Grant UL1 TR000042; Susan Koletar, MD and Kathy Watson, RN, the Ohio State University (Site 2301) ACTG CTU Grant UM1AI069494; Donna McGregor, NP and Kimberly Scarsi, PharmD, Northwestern University CRS (Site 2701) ACTG CTU Grant AI069471; Paul Sax MD and Cheryl Keenan, RN, BC, Brigham and Women's Hospital (Site 107) ACTG CTU Grant UM1AI069412; Beverly Sha, MD and Tondria Green, RN, Rush University Medical Center (Site 2702) ACTG CTU Grant AI069471; Peter Gordon, MD and Jolene Noel-Connor, RN, Columbia Physicians and Surgeons CRS (Site 30329) ACTG CTU Grant 2UM1-AI069470-08, UL1 TR000040 and UL1 RR024156.

Compliance with Ethical Standards

Conflict of interest Jennifer J. Kiser has no conflict of interest to declare. Darlene Lu has no conflict of interest to declare. Susan L. Rosenkranz has no conflict of interest to declare. Gene D. Morse has no conflict of interest to declare. Robin DiFrancesco has no conflict of interest to declare. Kenneth E. Sherman receives research support

(paid to institution) from Merck, Bristol Myers Squibb, AbbVie, and Gilead. Adeel A. Butt receives research support (paid to institution) from Gilead and Merck.

Funding The project described was supported by Award Number UM1AI068636 from the National Institute of Allergy and Infectious Diseases, the Statistical and Data Management Center (UM1AI68634), Merck & Co, Inc., Kenilworth, NJ, USA, the University at Buffalo Pharmacology Specialty Laboratory (UM1AI106701-01, CRB-SSS-S-12-002819, BRS-ACURE-S-12-002537), and K23 DK082621 (J. Kiser). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Allergy and Infectious Diseases or the National Institutes of Health.

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