

# Pharmacokinetics and Drug Interaction Profile of Cobicistat boosted-Elvitegravir with Atazanavir, Rosuvastatin or Rifabutin

S Ramanathan, H Wang, T Stondell,  
A Cheng, and BP Kearney  
Gilead Sciences, Inc., USA

13th International Workshop on Clinical Pharmacology of HIV Therapy

April 16-18, 2012

Barcelona, Spain

Abstract #O\_03

# Introduction

- Elvitegravir (EVG) Profile:
  - $\sim -2.0 \log_{10}$  mean change in HIV-1 RNA over 10 days as monotherapy<sup>1</sup>
  - High rates of efficacy, fewer CNS/psychiatric AEs as EVG/COBI/FTC/TDF (QUAD) vs. EFV/FTC/TDF (Atripla®) or Atazanavir/r + TVD in treatment-naïve patients<sup>2,3</sup>
  - Metabolized primarily via CYP3A, secondarily via UGT1A1/3
  - Boosted substantially by COBI 150 mg similar to RTV 100 mg
- EVG/r PK
  - EVG 150 mg  $\rightarrow$  85 mg with ATV; Rifabutin 300 mg QD  $\rightarrow$  150 mg QOD<sup>4</sup>
  - No data with newer (non-CYP3A) statins
- COBI Profile
  - Potent CYP3A inhibitor, weak 2D6 inhibitor, no effects on other CYPs or UGT
  - Similar inhibition as RTV of Pgp, BCRP (intestinal), OATP1B1/3 (liver)

<sup>1</sup> DeJesus E, et al. JAIDS 43(1):1-5, 2006; <sup>2</sup> Sax et al. CROI, 2012; <sup>3</sup> DeJesus et al. CROI, 2012; <sup>4</sup> German et al. IWCPHT, 2008

# Objective and Study Design

## Objective

- COBI-boosted EVG 85 mg plus ATV PK
- COBI-boosted EVG and statin (non-CYP3A) interaction
  - Rosuvastatin minimally metabolized (CYP2C9)
  - Substrate for BCRP, OATP1B1, OATP1B3
  - Dosing guidance for QUAD
- COBI-boosted EVG and dose-reduced rifabutin (150 mg QOD)
  - Dosing guidance for QUAD

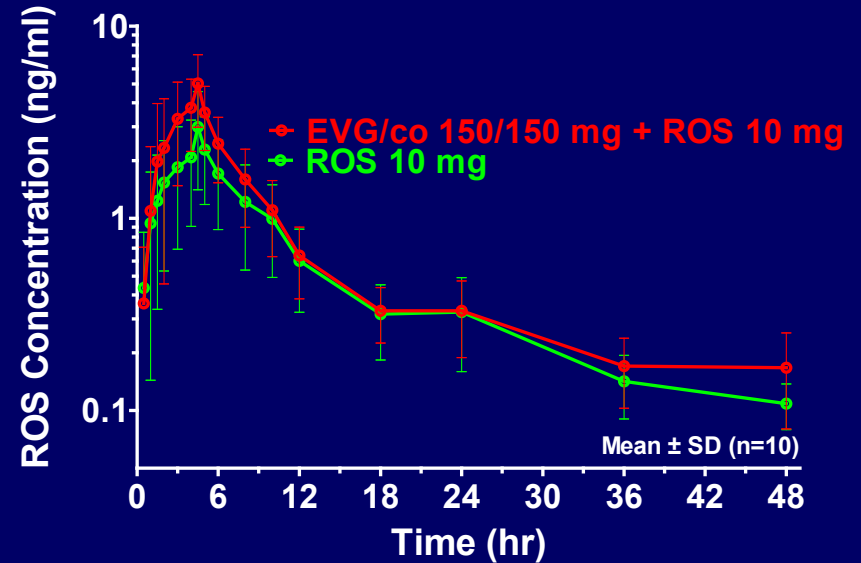
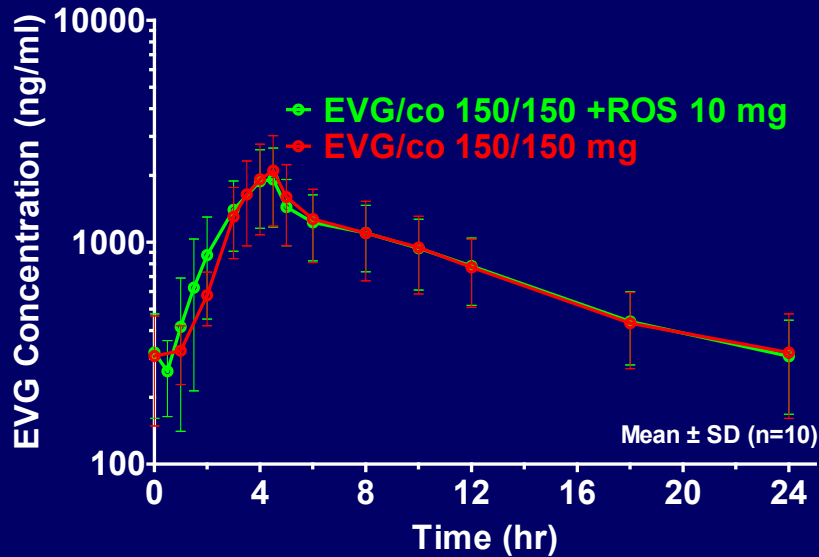
## Design

- Three cohorts with fixed-sequence crossover design
  - Rosuvastatin given as single dose
  - All other treatments given as multiple doses

# Demographics and Safety

- Demographics across three cohorts
  - Equal distribution by gender
  - Roughly 80% white, 20% black
  - Median age 35 years and BMI 28 kg/m<sup>2</sup>
- Safety Results
  - No Grade 4 or serious adverse events (serious AEs)
  - Five discontinuations during EVG/co plus ATV
    - Three Grade 3 hyperbilirubinemia, one Grade 3 rash, one Grade 2 abdominal pain
      - AEs generally consistent with ATV product labeling
      - Hyperbilirubinemia returned to baseline levels upon treatment discontinuation
  - Other AEs: constipation and headache, mostly Grade 1

# Elvitegravir and Rosuvastatin (ROS) PK

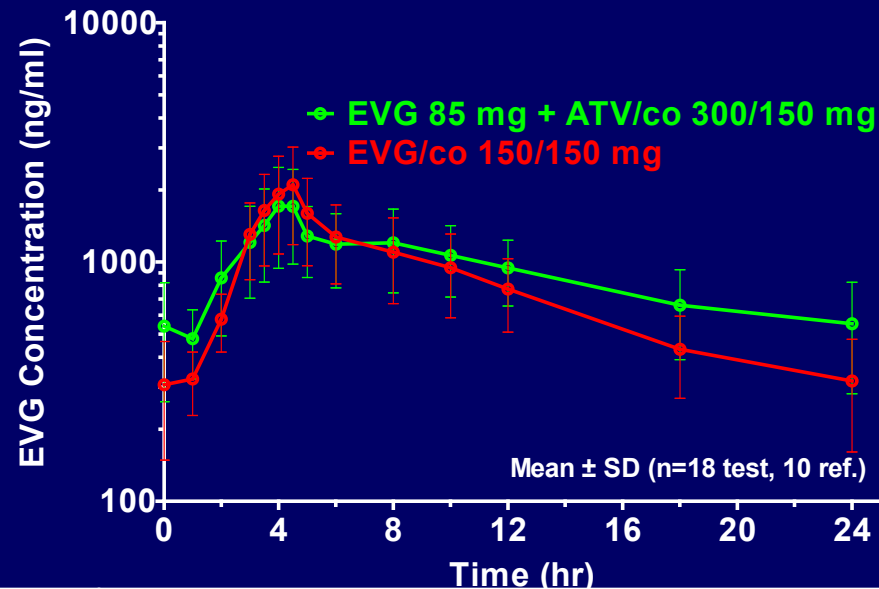
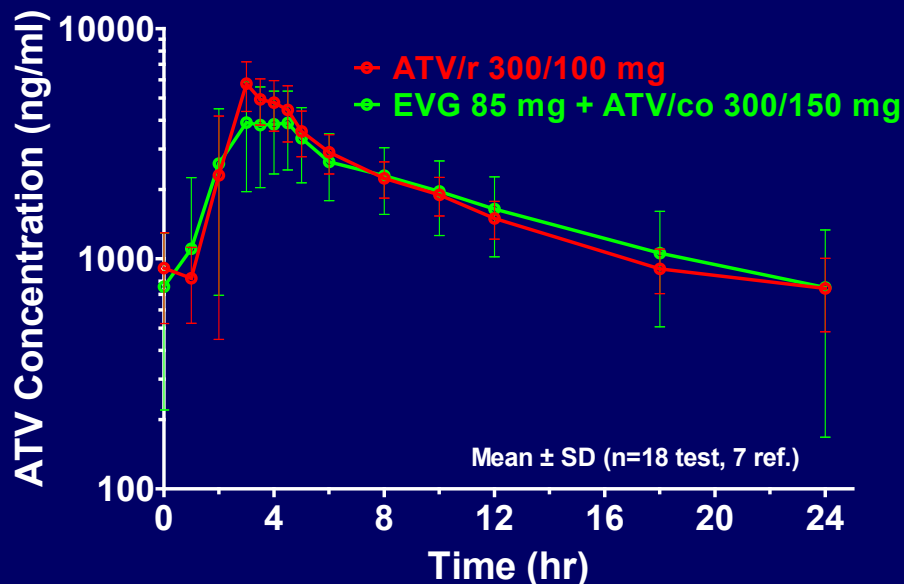


	Rosuvastatin PK		
Mean (%CV)	EVG/co + ROS	ROS	GMR (90% CI)
$AUC_{inf}$ (ng.hr/ml)	38 (40)	27 (41)	138 (114, 167)
$C_{max}$ (ng/ml)	5.0 (41)	2.7 (55)	189 (148, 242)
$T_{1/2}$ (hr) Median (Q1, Q3)	18 (17, 21)	21 (14, 27)	-

Presented at the 13<sup>th</sup> Int. W

- No ROS dose adjustment with QUAD per US PI
- EVG, COBI PK unaffected

# Elvitegravir and Atazanavir PK

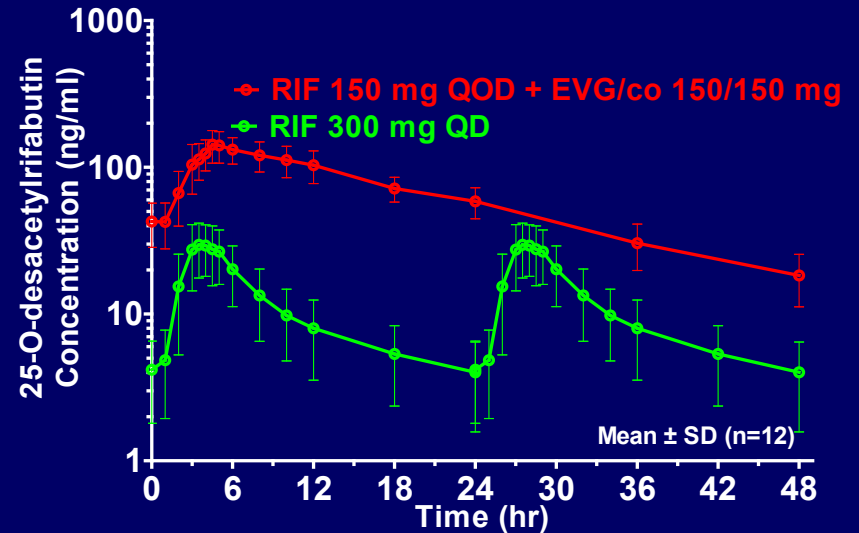
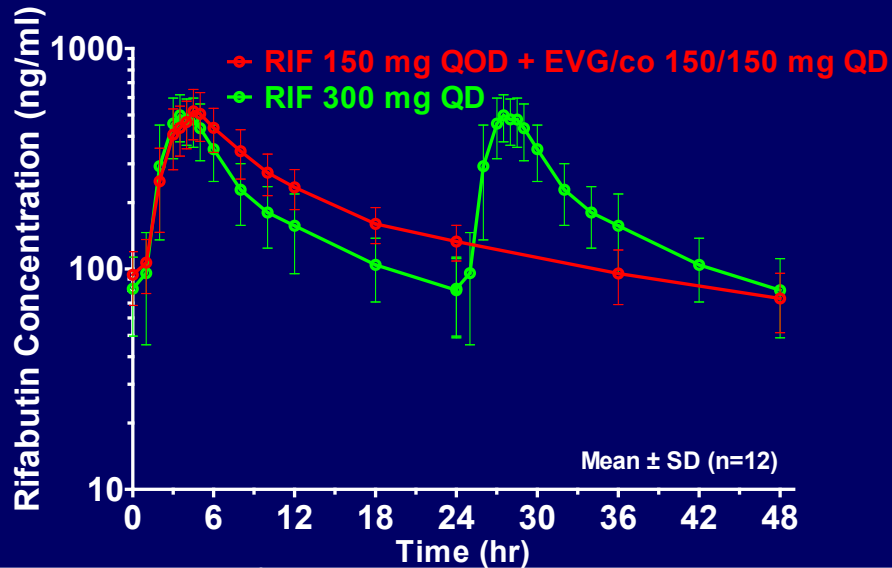


	ATV Exposures			EVG Exposures		
Mean (%CV)	EVG 85 mg + ATV/co	ATV/r	GMR (90% CI)	EVG 85 mg + ATV/co	EVG/co	GMR (90% CI)
$AUC_{\tau}$ (ng.hr/ml)	43000 (40)	43900 (16)	90.5 (73.4, 112)	21600 (35)	18700 (35)	117 (88, 156)
$C_{max}$ (ng/ml)	4660 (37)	5780 (24)	76.1 (59.1, 97.9)	1790 (43)	2150 (41)	84.2 (61.8, 115)
$C_{\tau}$ (ng/ml)	751 (78)	743 (35)	80.5 (55.6, 117)	553 (49)	318 (49)	183 (117, 286)

Presented at the 13<sup>th</sup> Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

- ATV, EVG, COBI PK comparable with reference/historical data

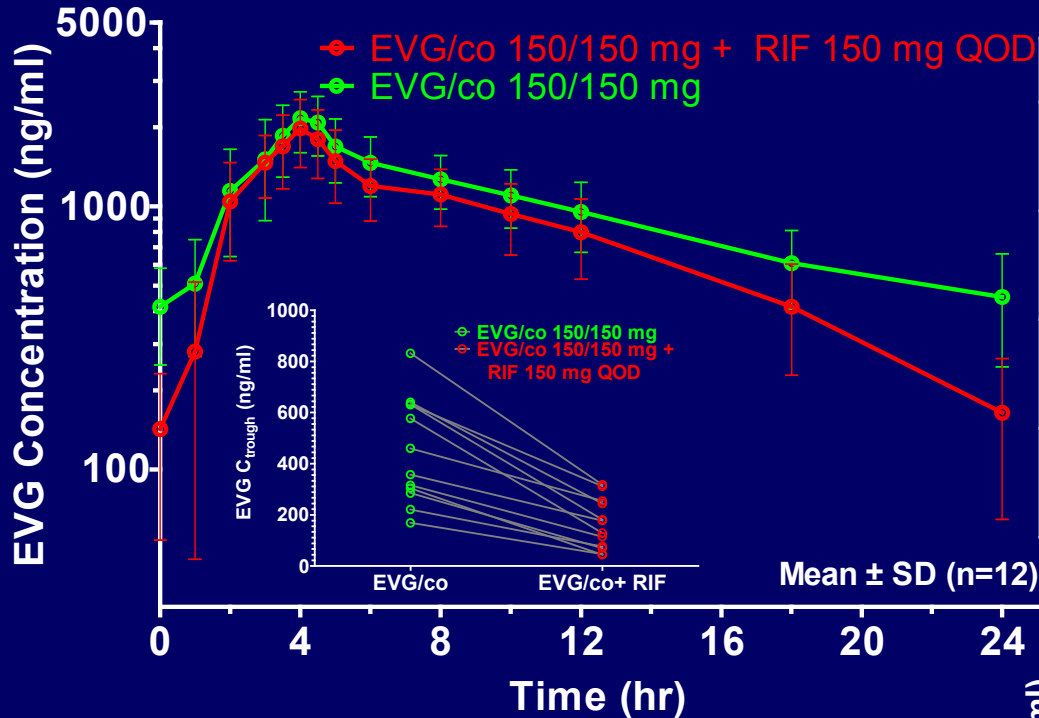
# Effect of EVG/co on Rifabutin/metabolite PK



Mean (%CV)	Rifabutin Exposures			25-O-desacetylriofabutin Exposures		
	Rifabutin + EVG/co	Rifabutin	GMR (90% CI)	Rifabutin + EVG/co	Rifabutin	GMR (90% CI)
AUC (ng.hr/ml)	8370 (13)	9320 (29)	92.4 (82.9, 103)	3010 (21)	518 (47)	625 (508, 769)
C <sub>max</sub> (ng/ml)	566 (17)	529 (27)	109 (98.5, 120)	150 (22)	32 (39)	484 (409, 574)
C <sub>tau</sub> (ng/ml)	74 (30)	80.1 (39)	93.9 (84.8, 104)	18.4 (39)	4.0 (61)	494 (404, 604)

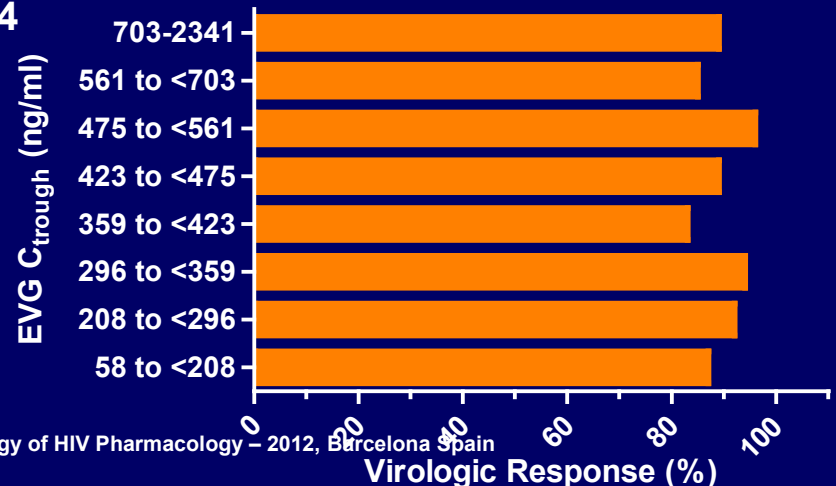
- Similar Rifabutin exposures, 21% higher antimycobacterial activity with EVG/co vs alone

# Effect of Rifabutin on EVG PK



Mean (%CV)	EVG Exposures		
	EVG/co + RIF	EVG/co	GMR (90% CI)
$AUC_{tau}$ (ng.hr/ml)	18400 (26)	23000 (24)	79.4 (74.1, 85.1)
$C_{max}$ (ng/ml)	2050 (25)	2250 (26)	91.1 (83.6, 99.4)
$C_{tau}$ (ng/ml)	164 (61)	452 (46)	32.9 (26.9, 40.1)

## QUAD Virologic Response vs EVG $C_{trough}$ Octile

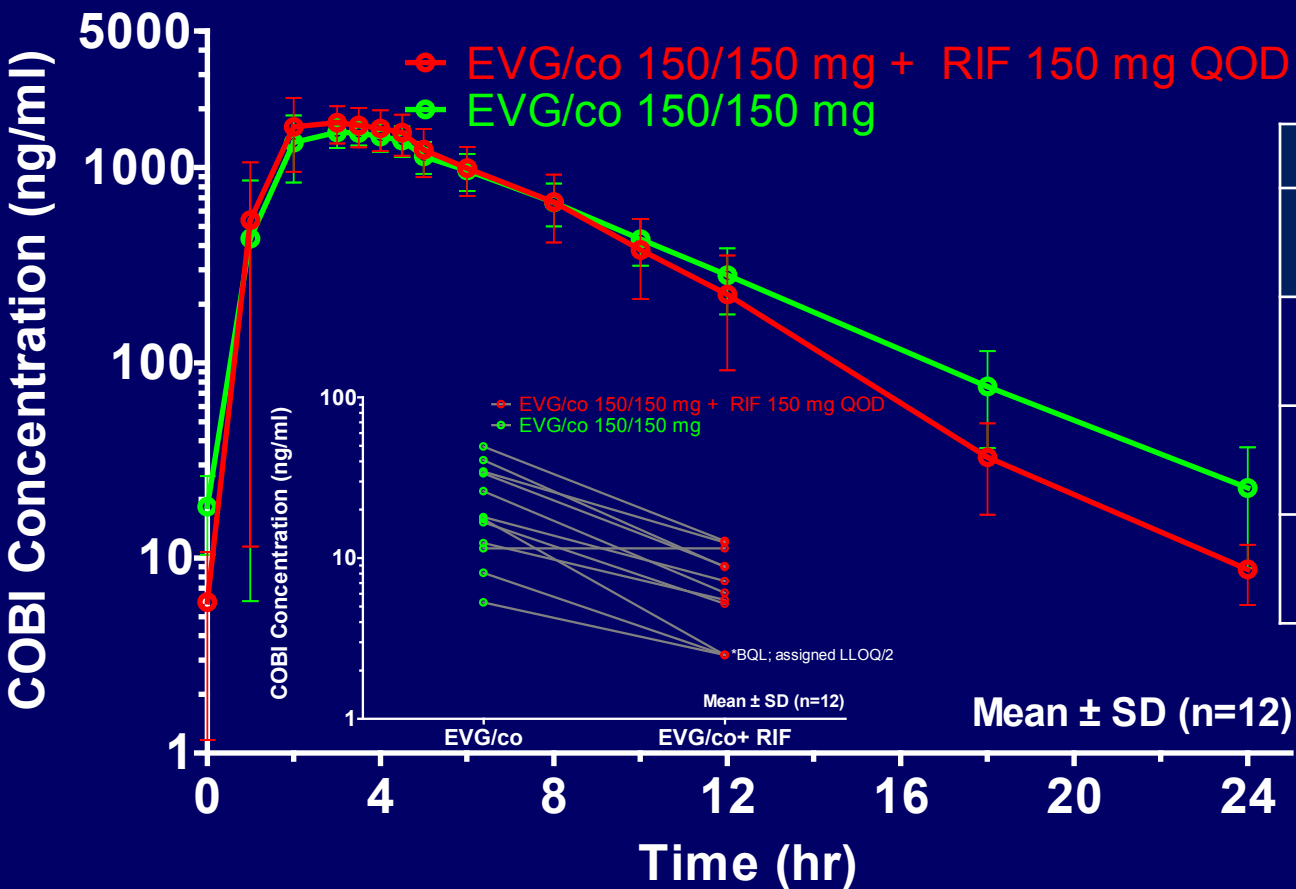


### EVG $C_{trough}$ lower with rifabutin

- Range (45-318 ng/ml) in Ph 3 bottom quartile
- Conservatively, QUAD codosing not recommended



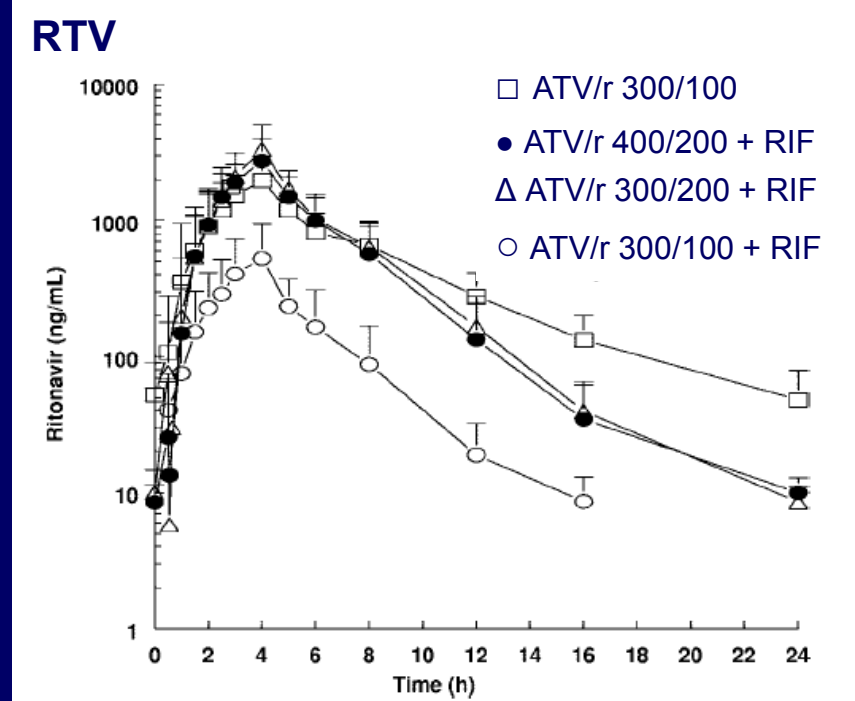
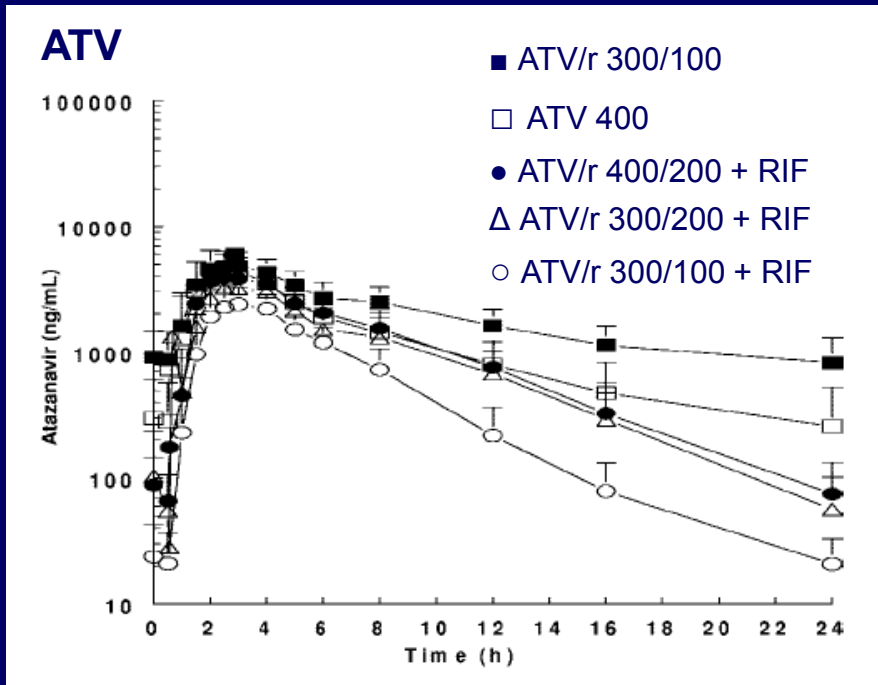
# Effect of Rifabutin on COBI PK



	COBI Exposures	
Mean (%CV)	EVG/co + RIF	EVG/co
AUC <sub>tau</sub> (ng.hr/ml)	11400 (29)	11200 (19)
C <sub>max</sub> (ng/ml)	1880 (29)	1640 (19)
C <sub>tau</sub> (ng/ml)	6.5 (72)	22.8 (61)

- COBI exposures lower with rifabutin

# Historical data: Effect of Rifampin on ATV, RTV



Dose (mg)	ATV 400	ATV/r 300/100	ATV/r 300/100+RIF	ATV/r 300/200+RIF	ATV/r 400/200+RIF
ATV Cmin (ng/ml)	187	707	18	43	53
RTV AUC (ng.h/ml)		10200	1520	11,900	11,300

Burger D M et al. Antimicrob. Agents Chemother. 2006;50:3336-3342  
 Figures shown with permission from Drs. Burger and Bertz

# Conclusions

- COBI-boosted EVG and Rosuvastatin: no clinically relevant interactions
  - No relevant effects based on inhibition of BCRP, OATP1B1 and OATP1B3 by EVG/COBI
  - No dose adjustment of rosuvastatin necessary with QUAD
- No clinically relevant interactions with COBI-boosted EVG 85 mg + ATV
  - Consistent with historical data on EVG/r
- EVG and COBI exposures lower with rifabutin
  - Coadministration with QUAD not recommended presently
  - Additional evaluation with antimycobacterial agents planned