Pharmacokinetic interaction between etravirine or rilpivirine and telaprevir in healthy volunteers: a randomised, two-way crossover trial

TN Kakuda, L Leopold, S Nijs, A Vandevoorde, H Crauwels, K Bertelsen, M Stevens, J Witek, Y van Delft, F Tomaka, RMW Hoetelmans

janssen
PHARMACEUTICAL COMPANIES OF Johnson & Johnson

13th International HIV Clinical Pharmacology Workshop Barcelona, Spain, April 2012 [abstract O_18]

Introduction

- HIV/HCV co-infected patients may need combined treatment with antiretrovirals and anti-HCV drugs.
- Etravirine (TMC125, ETR)
  - CYP3A: substrate and (weak) inducer
  - CYP2C9 and CYP2C19: substrate and (weak) inhibitor
  - P-glycoprotein: inhibitor
- Rilpivirine (TMC278, RPV)
  - CYP3A: substrate
- Telaprevir (VX-950, TVR)
  - CYP3A: substrate and (potent) inhibitor
  - P-glycoprotein: substrate and moderate inhibitor

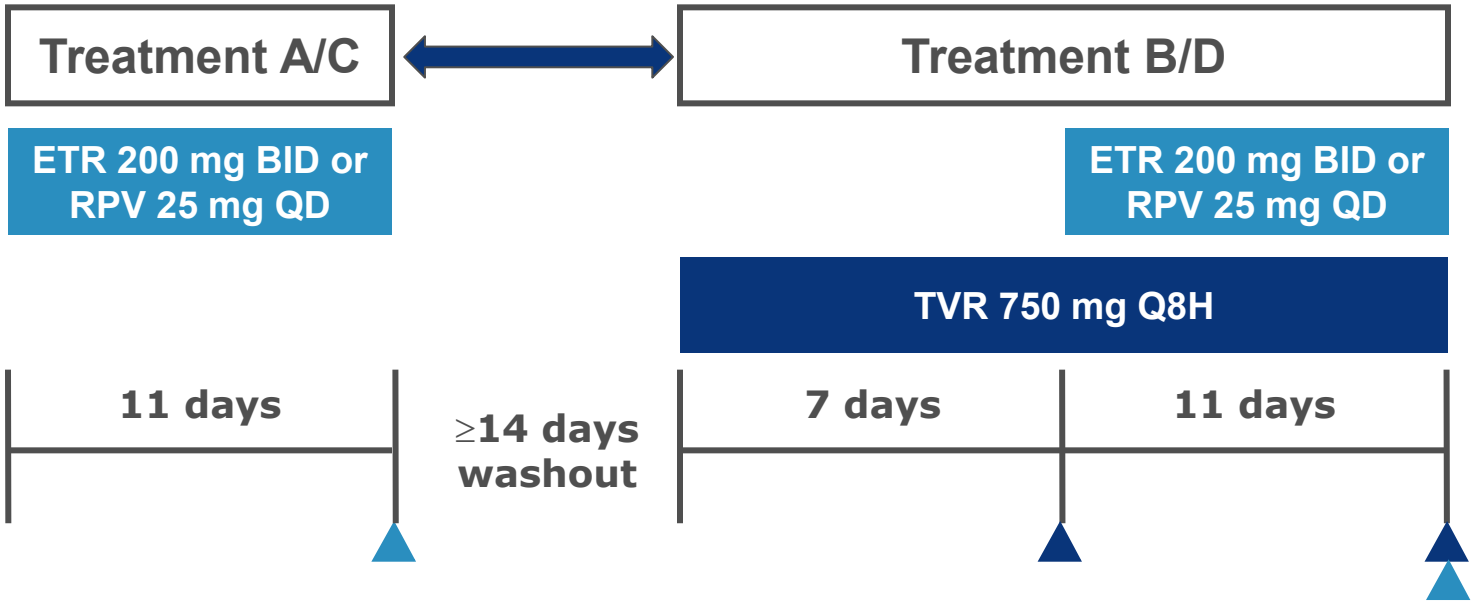
Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

Objectives

- Primary
  - Determine the effect of ETR or RPV on TVR PK and the effect of TVR on the PK of ETR or RPV when co-administered at steady-state and under fed conditions
- Secondary
  - Short-term safety and tolerability of ETR, RPV or TVR alone and in combination (ETR+TVR or RPV+TVR)

Study design

- 2 panels: ETR (A/B) and RPV (C/D), n=16 healthy volunteers



▲ TVR PK over 8 hours determined on Day 11 and Day 18

▲ ETR or RPV PK over 12 or 24 hours, respectively, determined on Day 11 and Day 18

All drugs taken under fed conditions. Plasma concentrations collected pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 8, 9, 12, 16 and 24 hours post-dose, as applicable.

Safety and tolerability assessments were performed throughout the trial until at least 7 days after the last trial medication intake

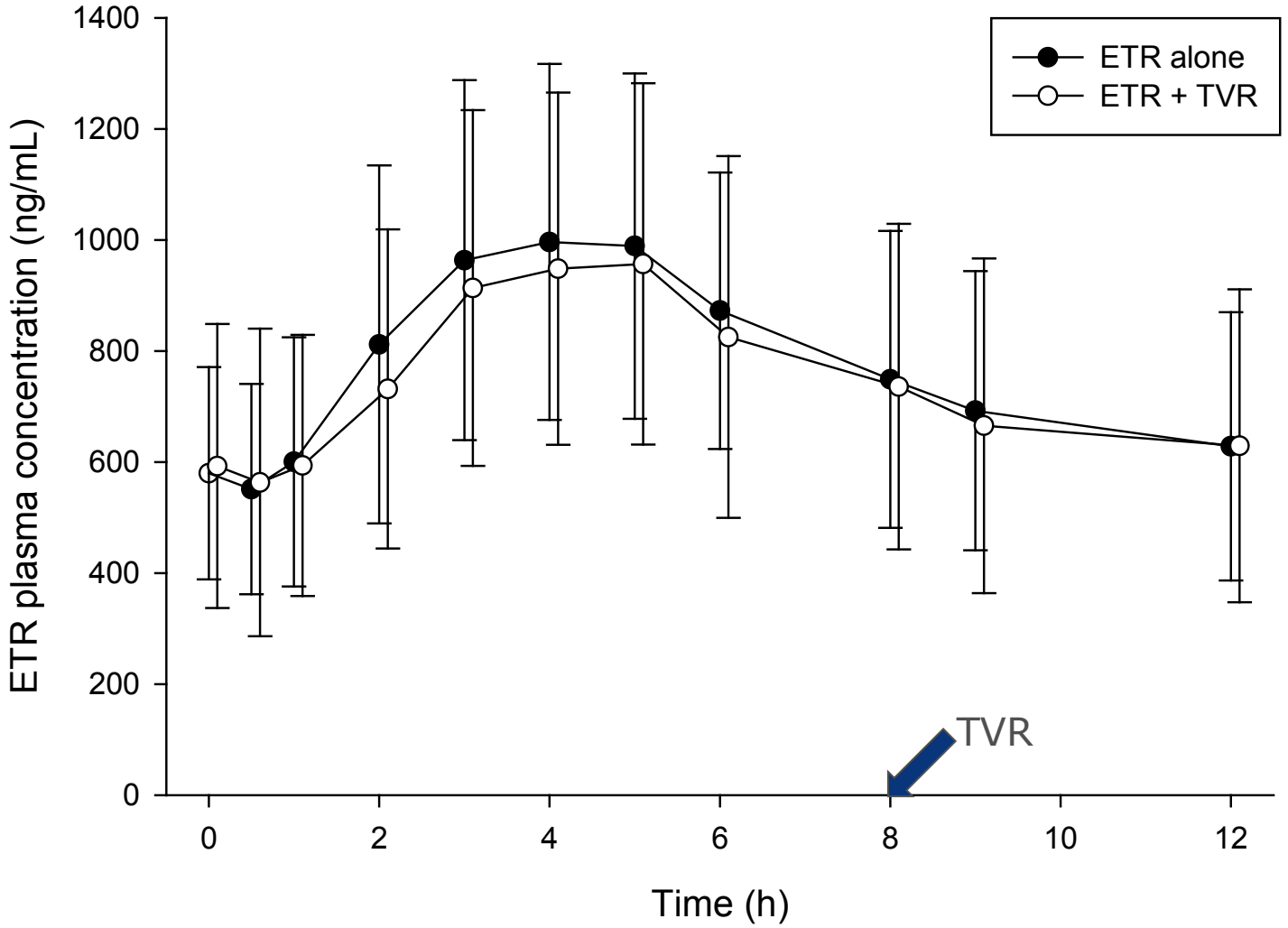
Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

Etravirine Panel: Subject Disposition and safety

- Overall, 11/17 were male, with median age 48 years. 14/17 subjects (82%) completed the whole study. One subject withdrew consent. Two patients discontinued treatment for adverse events:
  - AE, rash: 1 subject, drug-related (permanent discontinuation)
  - SAE, myocardial ischemia, 1 subject, not drug-related (resolved after 5 days)
- Grade 1-4 clinical adverse events:
  - 10/15 (67%) in ETR phase
  - 10/16 (63%) in TVR phase
  - 11/15 (73%) in ETR + TVR phase

  Most common adverse events were headache (8 subjects) and pruritis (3 subjects)
- Median changes in laboratory parameters, ECG and vital signs were generally minor and not clinically relevant.

Mean (SD) etravirine plasma concentration over time, with or without telaprevir



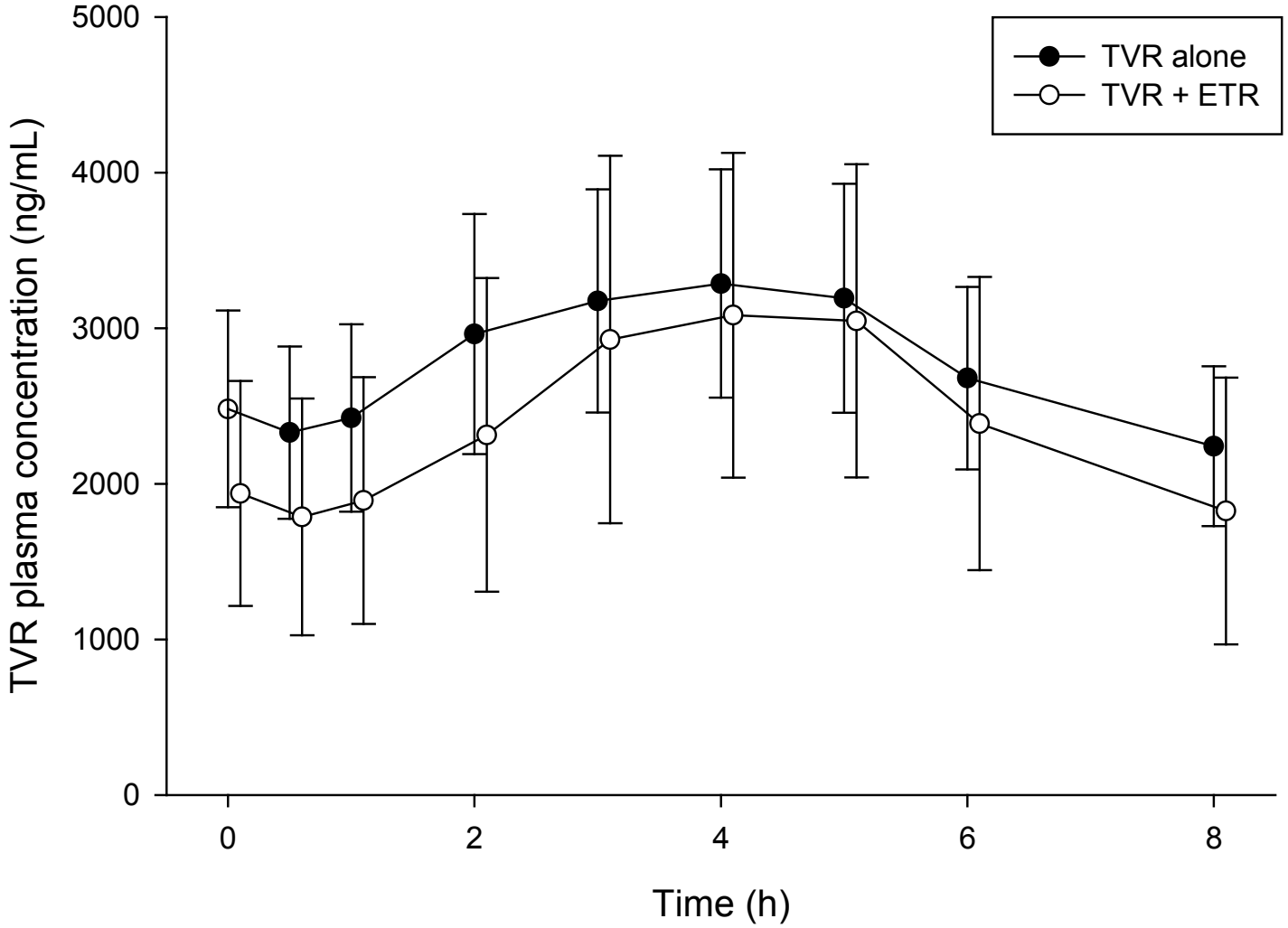
Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

Etravirine statistics, with or without telaprevir:

Parameter	LSmeans		LSmeans ratio	90% CI
	200 mg etravirine BID	200 mg etravirine BID + 750 mg telaprevir q8h		
C_{min}, ng/mL	529.7	514.3	0.97	0.86 - 1.10
C_{max}, ng/mL	1041	964.9	0.93	0.84 - 1.03
AUC_{12h}, ng.h/mL	9184	8629	0.94	0.85 - 1.04

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

Mean (SD) telaprevir plasma concentration over time, with or without etravirine



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

Telaprevir statistics, with or without etravirine

Parameter	LSmeans		LSmeans ratio	90% CI
	750 mg telaprevir q8h	200 mg etravirine BID + 750 mg telaprevir q8h		
C_{min}, ng/mL	2027	1520	0.75	0.61 - 0.92
C_{max}, ng/mL	3533	3175	0.90	0.79 - 1.02
AUC_{8h}, ng.h/mL	22100	18470	0.84	0.71 - 0.98

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

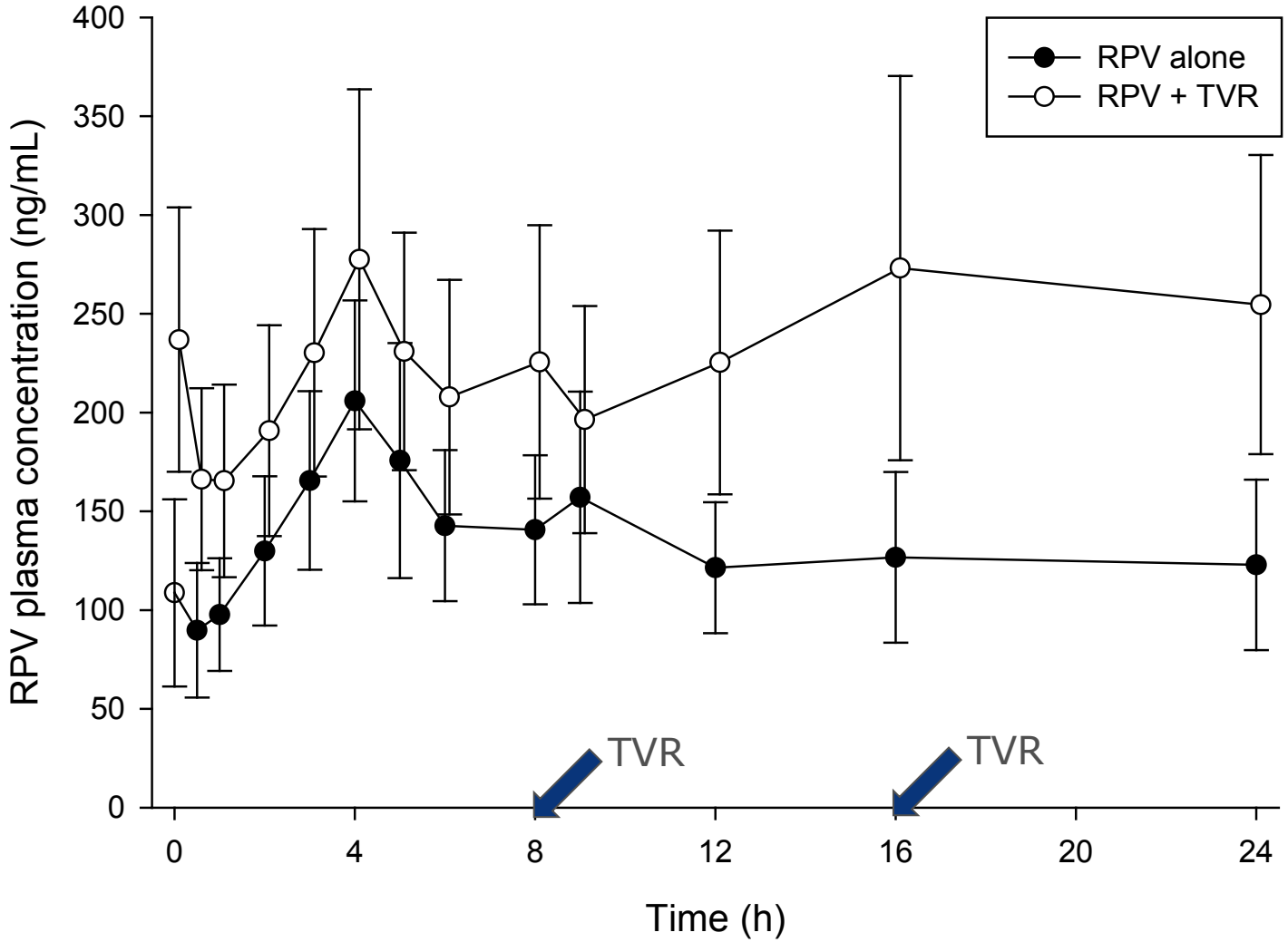
Rilpivirine Panel: Subject Disposition and safety

- Overall, 8/16 subjects were male, with median age of 42 years. 14/16 subjects completed the study (88%). No subjects discontinued treatment for adverse events. One subject withdrew consent, 1 discontinued for other reasons. There were no serious adverse events reported.
- Grade 1-4 clinical adverse events:
  - 12/16 (75%) in RPV phase
  - 9/14 (64%) in TVR phase
  - 12/14 (86%) in RPV + TVR phase

Most common adverse events were headache (10 subjects), acne and abdominal discomfort (4 subjects each)

- Highest mean changes in QTcF
  - +12.8ms in RPV phase
  - +7.8ms during TVR phase
  - +15.8ms in RPV + TVR phase
- There were increases in QTcF in 8 subjects >30ms which did not lead to abnormal values.

Mean (SD) rilpivirine plasma concentration over time, with or without telaprevir



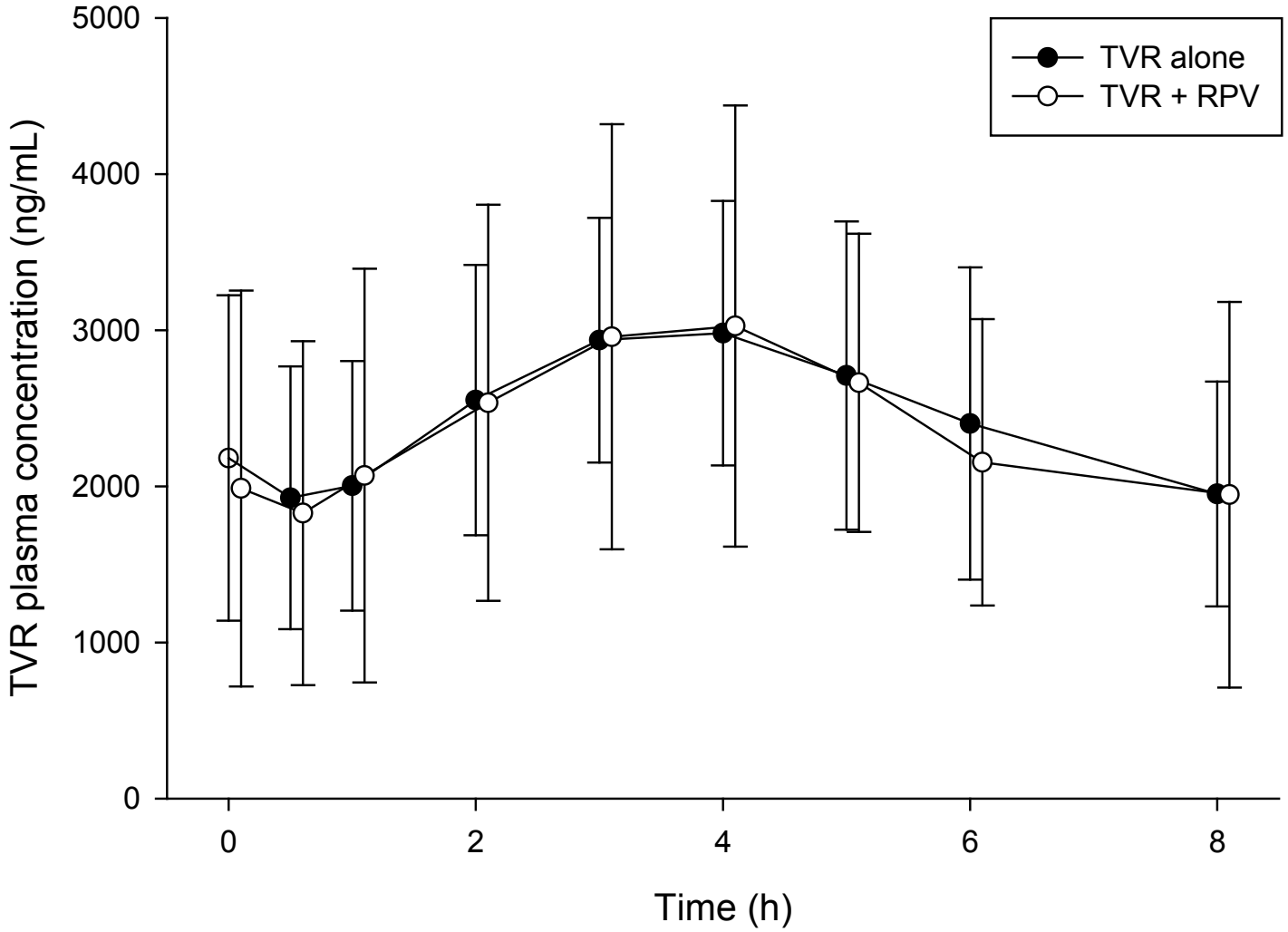
Presented at the 13th Int. Workshop on Clin. Pharmacology of HIV Pharmacology – 2012, Barcelona Spain

Rilpivirine statistics, with or without telaprevir:

Parameter	LSmeans		LSmeans ratio	90% CI
	25 mg rilpivirine QD	750 mg telaprevir q8h + 25 mg rilpivirine QD		
C_{min}, ng/mL	81.89	154.4	1.89	1.51 - 2.35
C_{max}, ng/mL[b]	204.9	300.7	1.47	1.19 - 1.80
AUC_{24h}, ng.h/mL	3116	5564	1.79	1.45 - 2.20

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

Mean (SD) telaprevir plasma concentration over time, with or without rilpivirine



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

Telaprevir statistics, with or without rilpivirine

Parameter	LSmeans		LSmeans ratio	90% CI
	Panel 2: 750 mg telaprevir q8h	Panel 2: 750 mg telaprevir q8h + 25 mg rilpivirine QD		
C_{min}, ng/mL	1631	1411	0.87	0.67 - 1.12
C_{max}, ng/mL	3051	2913	0.95	0.78 - 1.17
AUC_{8h}, ng.h/mL	18910	17480	0.92	0.75 - 1.13

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

Conclusions

- Co-administration of telaprevir and etravirine
  - No change in etravirine
  - Slight decrease in telaprevir (AUC_{8h} ↓ 16%)
  - No dose adjustment necessary for either antiviral
- Co-administration of telaprevir and rilpivirine
  - Increase in RPV (AUC_{24h} ↑ 1.8-fold, C_{max} ↑ 1.5-fold) likely due to CYP3A inhibition by TVR
    - Changes in RPV PK not clinically relevent for QTc prolongation
  - Slight decrease in TVR (AUC_{8h} ↓ 8%)
  - No dose adjustment necessary for either antiviral

Acknowledgements

- Thanks to the volunteers who took part in the trial

- Thanks to the study investigators and coordinators, and the data management, bioanalysis and statistics groups for their work on the trial