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Physiologically-Based Pharmacokinetic Modeling of Rilpivirine During Pregnancy

Mary Gockenbach
Mary.Gockenbach@fda.hhs.gov
Division of Pediatrics and Maternal Health
US FOOD AND DRUG ADMINISTRATION

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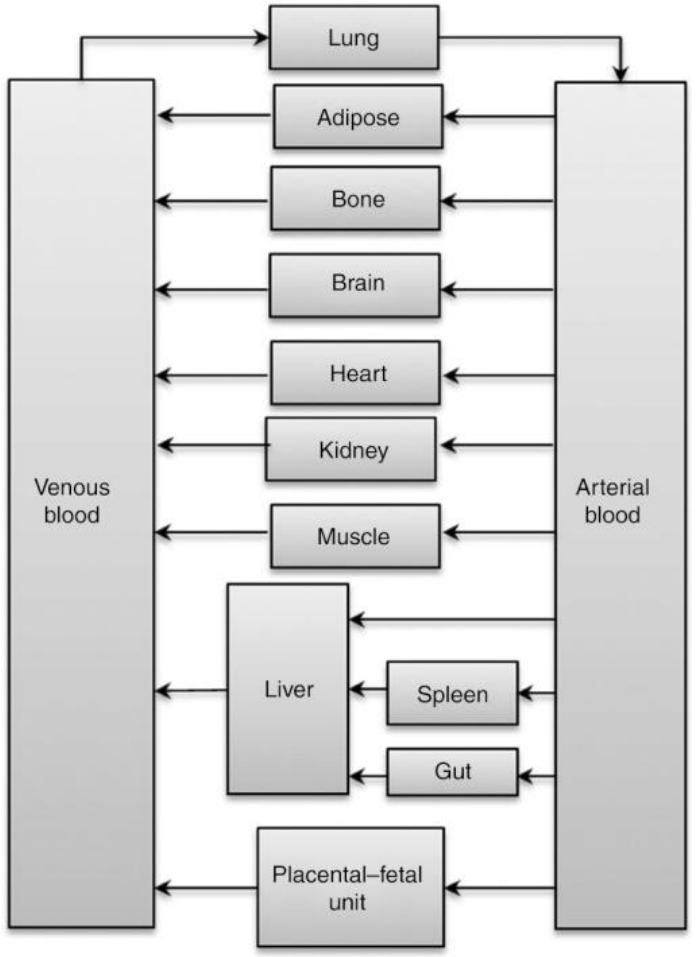
Introduction

- A physiologically-based pharmacokinetic (PBPK) modeling approach may be used to assess the effect of pregnancy on drug pharmacokinetics (PK).
- We developed a PBPK model for rilpivirine (RPV) using Simcyp® v16.1 with physicochemical, in vitro, and clinical PK parameters from literature.



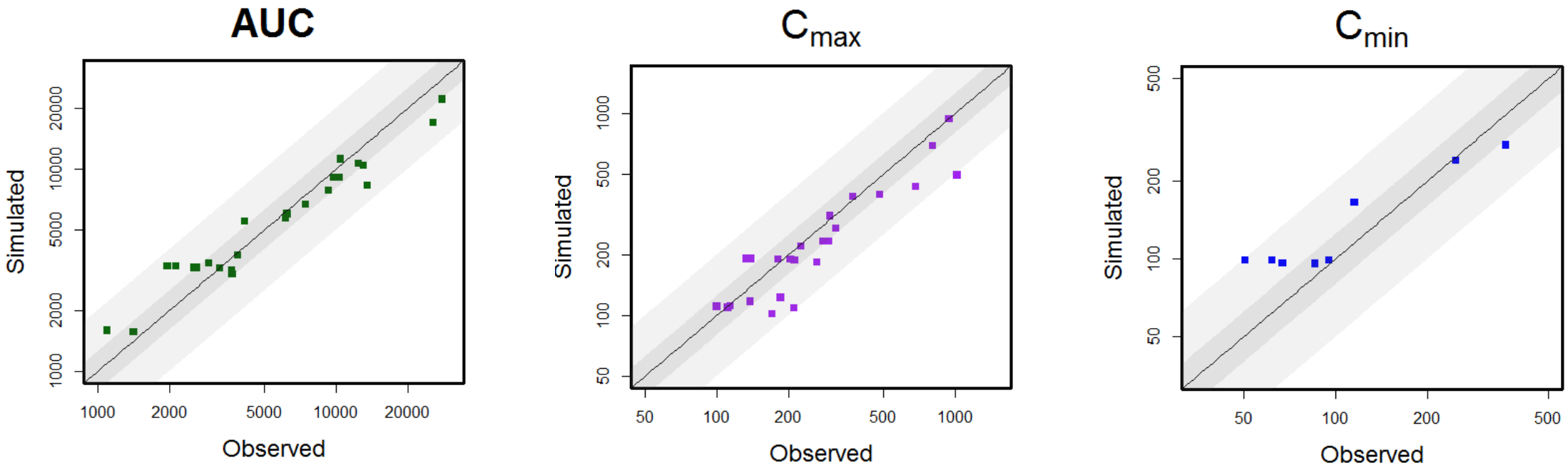
[1]

Methods

- The model built in the nonpregnant state was verified with PK data from clinical trials in healthy volunteers and adults living with HIV.
- The RPV model was then modified to account for the progressive physiological changes of pregnancy, including changes in:
    - albumin
    - CYP3A4 activity
    - glomerular filtration rate
- Predictions were verified from 3 clinicals trials in pregnant women living with HIV.

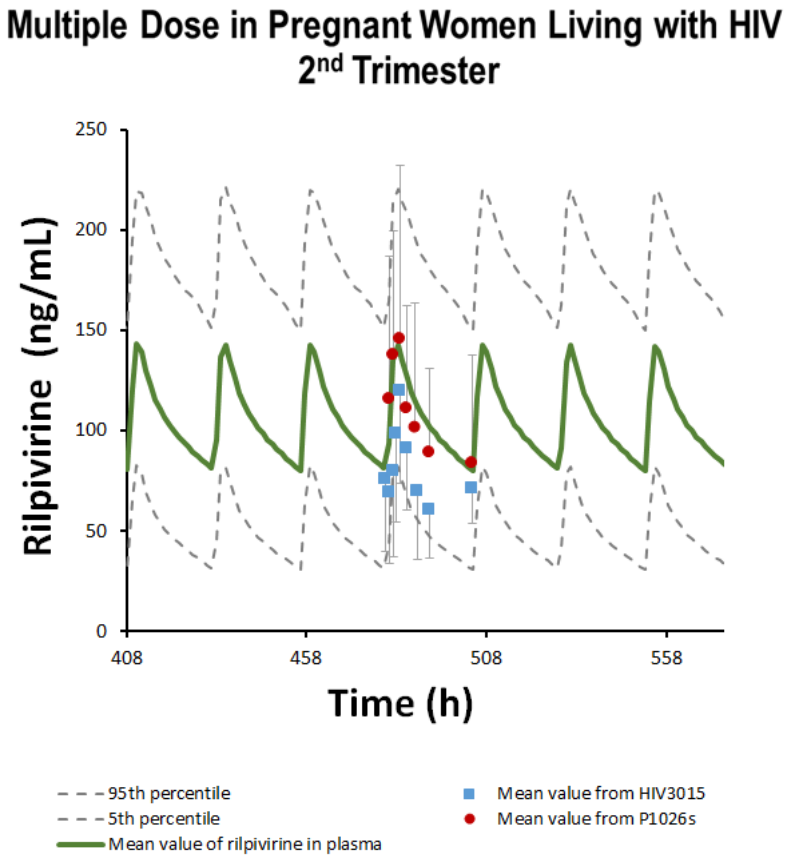
Results from the Nonpregnant State

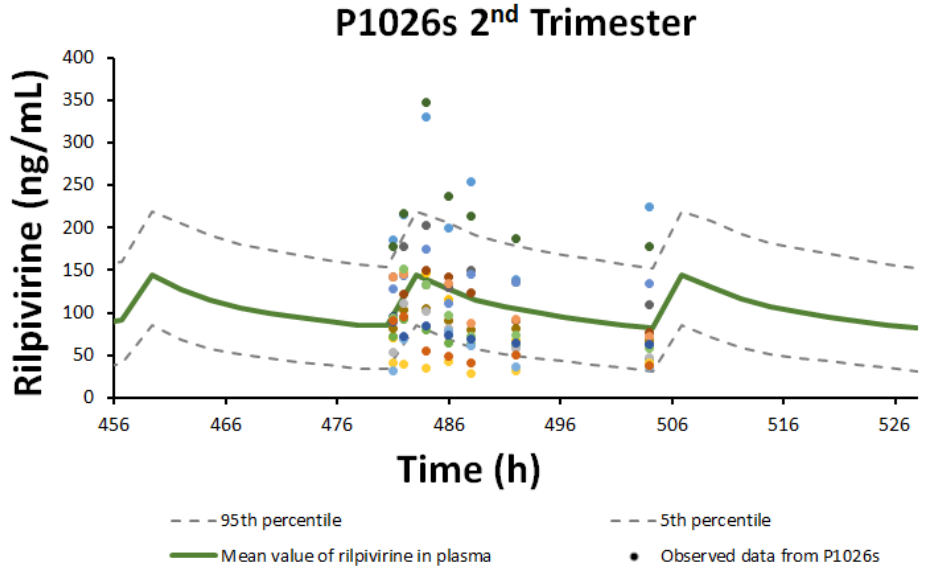
- Predictions for RPV PK fell within a 2-fold range of observed clinical values.



Results from 2nd Trimester

- Predictions for RPV PK fell within ± 50% of the mean observed clinical values.

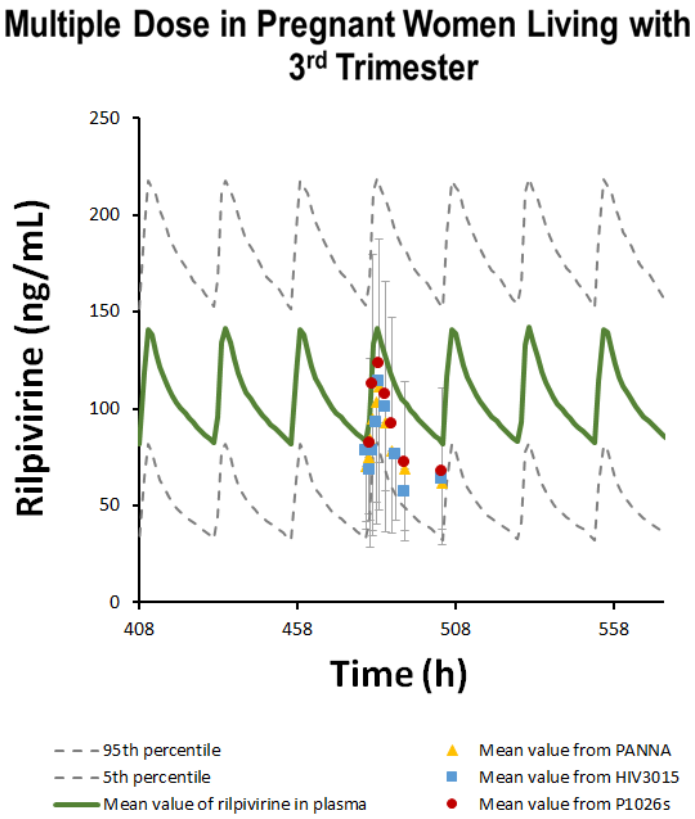


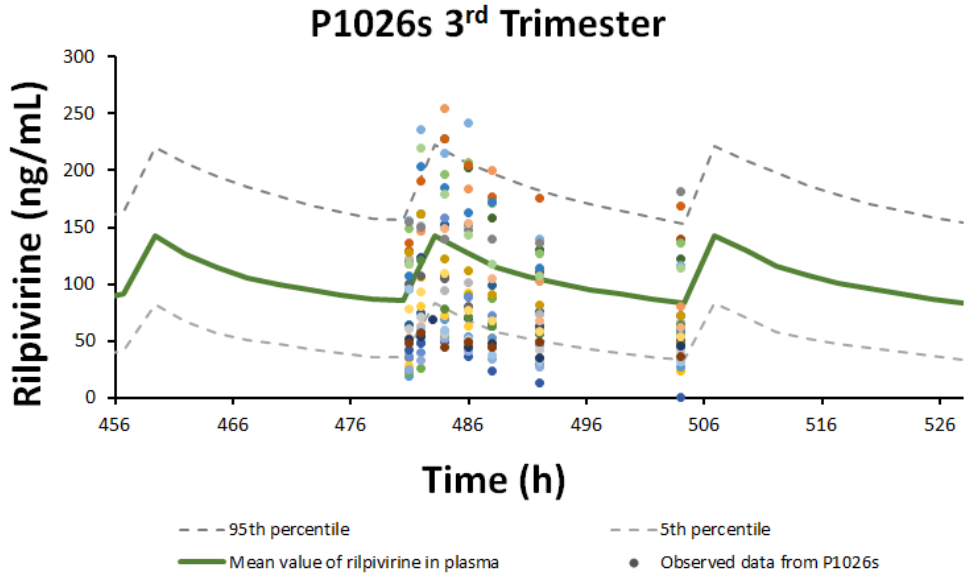


Model predictions vs PK from P1026s at 24 weeks			
	Predicted	Observed	Ratio
C_{max} (ng/ml)	140	142	0.99
AUC (ng.hr/ml)	2369	2090	1.13

Results from 3rd Trimester

- Predictions for RPV PK fell within ± 50% of the mean observed clinical values.





Model predictions vs PK from P1026s at 34 weeks			
	Predicted	Observed	Ratio
C_{max} (ng/ml)	139	124	1.12
AUC (ng.hr/ml)	2387	1700	1.40

Conclusion

- Progressive physiological changes during pregnancy incorporated in the model lead to:
  - Increase in the fraction of drug unbound in plasma (16 – 30%)
  - Increase in the volume of distribution (50 – 60%)
  - Increase in clearance (50%)
- Our PBPK model for RPV captured the effects of pregnancy on maternal exposure, with a predicted decrease in exposure of approximately 30% for AUC and C_{min} when compared with non-pregnant adults.
- Future work will investigate the effects of modifying the Simcyp® pregnant population using laboratory values collected from pregnant women living with HIV in the P1026s database.
- Additional antiretroviral compound models will be built to continue assessment of predictive performance of the pregnancy PBPK model.

Acknowledgments

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