Towards physiologically-based pharmacokinetic modelling of darunavir / ritonavir in pregnancy.

Angela Colbers

On behalf of the co-authors: Rick Greupink, Luuk Swarts, Frans GM Russel, David Burger, and the PANNA network

Radboud university medical center, Nijmegen The Netherlands
Department of Pharmacy and Department of Pharmacology and Toxicology
A European clinical pharmacology network to investigate the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women
Outline PANNA study protocol

General study protocol, not specified per drug, 14 ARVs

cord blood at delivery

PK curve 3rd trimester
Appr wk 33 gestational age

PK curve postpartum
4-6 weeks after delivery

Samples: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after dosing
Physiological changes during pregnancy influencing pharmacokinetics (ADME) of ARVs

- Total body water ↑44%
- Plasma volume ↑50%
- Total body fat ↑35%
- Albumin conc. ↓31%
- GFR ↑37%
- Hepatic blood flow ↑42%
- CYP2D6 activity ↑48%
- CYP3A4 activity ↑38%
- Gastric pH ↑
- Gastric emptying and intestinal motility ↓
- Gastric pH ↑
- Plasma volume ↑50%
- Total body fat ↑35%
- Albumin conc. ↓31%
- GFR ↑37%
- Hepatic blood flow ↑42%
- CYP2D6 activity ↑48%
- CYP3A4 activity ↑38%
Pharmacokinetic Investigations of Antiretroviral agents in HIV-infected pregnant women: physiologically-based predictions and clinical validation

PIANO
AIM of PIANO

To generate mechanistic knowledge of the disposition of antiretroviral compounds in

1) healthy volunteers compared to
2) HIV-infected pregnant/matched post-partum controls and
3) the fetus (umbilical cord blood samples)

Ultimately leading to
• Improved assessment of safety/benefit ratios of antiretroviral drugs
• The development of rational dosing regimens for these compounds during pregnancy.
Simcyp pregnancy model
Simcyp pregnancy model

**Fig. 4.** Relative change in studied cytochrome P450 enzymes over gestational age to non-pregnant women. CYP = cytochrome P450.

**Fig. 5.** Fetal volume growth during pregnancy: performance of different functions vs actual data. The inset graph represents the expanded view of the first trimester values.
Method

- Choice of antiretroviral: **darunavir (DRV)**
- Development of PBPK model in Simcyp
  - **Step 1**: Develop PBPK model for single dose unboosted darunavir
  - **Step 2**: include ritonavir as booster: simulate single dose darunavir + ritonavir
  - **Step 3**: simulate steady state darunavir/r in non-pregnant population
  - **Step 4**: simulate steady state darunavir/r in pregnant population
Darunavir single dose – model without transporters

WSLM: well stirred liver model

Observed DRV: Sekar V et al. 7th International Workshop on Pharmacology of HIV Therapy; 2006, abstract 86
Darunavir and transporters?

*Xenobiotica, 2010; 40(3): 163–176*

**RESEARCH ARTICLE**

**Interaction of HIV protease inhibitors with OATP1B1, 1B3, and 2B1**

P. Annaert¹, Z.W. Ye¹, B. Stieger², and P. Augustijns¹

**HIV protease inhibitors are substrates for OATP1A2, OATP1B1 and OATP1B3 and lopinavir plasma concentrations are influenced by *SLCO1B1* polymorphisms**

Ruben C. Hartkoomᵃ, Wai San Kwanᵃ, Victoria Shallcrossᵃ, Ammara Chaikanᵃ, Neill Liptrottᶜ, Deirdre Eganᶜ, Enrique Salcedo Soraᵇ, Chloë E. Jamesᵃ, Sara Gibbonsᵃ, Pat G. Brayᵇ, David J. Backᵃ, Saye H. Khooᵃ and Andrew Owenᵃ

*Pharmacogenetics and Genomics 2010, 20:112–120*
Darunavir single dose – model WITH transporters

Darunavir 600mg unboosted

PLM: Permeability limited liver model, including Sinusoidal uptake OATPs, Canalicular efflux P-gp

Observed DRV: Sekar V et al. 7th International Workshop on Pharmacology of HIV Therapy; 2006, abstract 86
Darunavir/ritonavir single dose – with transporters

Observed DRV: Sekar V et al. 7th International Workshop on Pharmacology of HIV Therapy; 2006, abstract 86
Darunavir steady state PK parameters
Darunavir/ritonavir steady state

Observed DRV:
- Sekar V et al, ARTEMIS study, CROI 2008, Abstract 769
Darunavir in 3rd trimester of pregnancy

Observed DRV: Zorrilla et al, HIV Medicine (2013), PANNA data
## Darunavir AUC ratios in 3rd trimester in pregnancy

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Study</th>
<th>AUC ratio 3rd trimester/post-partum</th>
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</thead>
<tbody>
<tr>
<td>600/100 mg DRV/r BID</td>
<td>Zorrilla et al.</td>
<td>0.83</td>
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<td></td>
<td>PANNA</td>
<td>0.79</td>
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<tr>
<td></td>
<td>Capparelli et al.</td>
<td>0.74</td>
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<tr>
<td></td>
<td>Simcyp simulated</td>
<td>0.76</td>
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<tr>
<td>800/100 mg DRV/r QD</td>
<td>PANNA</td>
<td>0.67</td>
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<td></td>
<td>Capparelli et al.</td>
<td>0.76</td>
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<tr>
<td></td>
<td>Curran et al.</td>
<td>0.69</td>
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<td></td>
<td>Simcyp simulated</td>
<td>0.75</td>
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</tbody>
</table>
CONCLUSION

- Our data support the presence of a clinically relevant role of hepatic transporters in DRV pharmacokinetics.
- The described model could approximate boosting by ritonavir and the decrease in maternal DRV exposure during pregnancy.
- However, to ensure a better mechanistic basis of PBPK simulations, future in vitro experiments should focus on generating quantitative data concerning passive and transporter-mediated DRV uptake in hepatocytes, transporter abundance as well as data on the enteral re-uptake of unchanged DRV excreted via the bile.
FUTURE

• In vitro tests to determine the unknown variables in DRV file: Km/Vmax transporters, more detailed in vitro metabolism data

• In vitro tests to assess the inhibitory ability of RTV on DRV, both on metabolism and transporter level

• Use this information to build better PBPK models

• Use the same method for other ARVs
THANKS TO

Participants in PANNA study

Investigators of the PANNA study

Internship: Carlijn Litjens

PBPK expertise and Academic license Simcyp of pharmacology & toxicology department Radboudumc

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