First report of dolutegravir unbound plasma concentrations during pregnancy in HIV-positive women

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19th International Workshop on Clinical Pharmacology of Antiviral Therapy
22-24 May 2018 in Baltimore, USA.
Disclosures - partners PANNA

- NEAT/PENTA
- Merck
- BMS
- Janssen
- ViiV Healthcare
- Gilead
A European clinical pharmacology network to investigate the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women
Dolutegravir in HIV+ pregnant women

- Antiretroviral treatment (ART) to reduce the risk of mother to child transmission and for the health of the mother

- Advice on dolutegravir (DTG) in guidelines on ART in pregnant HIV-positive women:
  - US: DTG listed a alternative agent[1]
  - EU: ART in pregnancy is the same as in non-pregnant women; women on DTG could continue their treatment[2]
  - WHO: delayed roll-out of DTG in LMIC; i.a. due to lack of data in pregnancy[3]

- Increasing data on safety and pharmacokinetics on the use of DTG in pregnancy[4]

Pharmacokinetics DTG in pregnancy

- Physiological changes in pregnancy may affect drug concentrations

- In pregnancy $\text{AUC}_{0-24h}$ and $C_{24h}$ DTG based on total drug concentrations were 5-29% and 44% lower, respectively, in third trimester compared to post partum \[1,2\]

- In general only that fraction of the drug concentration that is freely circulating or unbound plasma proteins in extracellular water can penetrate cell membranes and can exert its pharmacological effect

Plasma protein binding

- Serum albumine levels decrease in pregnancy

- Dolutegravir:
  - DTG is highly bound to human plasma proteins (>99.3% in vitro) and exhibits a low extraction rate [1]
  - Reduction of antiviral potency with increasing percentages of human serum albumin in vitro [2]

Changes in $C_{\text{Free}}$ are not always proportional to changes in $C_{\text{Total}}$ in case of altered pharmacokinetics >> Need to assess $C_{\text{Free}}$ for highly protein bound drugs in pregnancy.
Objectives

• To evaluate unbound DTG concentrations in pregnant HIV-positive women the 3\textsuperscript{rd} trimester and postpartum
Method

• DTG arm PANNA study:

* Blood samples: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after dosing

• Measuring unbound DTG in $C_{\text{min}}$ and $C_{\text{max}}$ samples selected from PK curves

PK curve* DTG 3$^{rd}$ trimester

~ 33wks GA

Cord blood at delivery (CB/MB ratio)

PK curve* DTG (reference) postpartum

4-6 weeks after delivery

Weeks ~ 30 32 34 36 38 40 2 4 6 8 10

*Blood samples: predose, 0.5, 1, 2, 3, 4, 6, 8, 12 and 24h after dosing
Method

- Obtainment of free drug-concentrations through ultrafiltration
  - 500 µL EDTA plasma
  - Centrifuge at 37°C; 20 min at 1650 rpm

- Quantification of DTG free drug concentrations in EDTA plasma with a validated LC-MS/MS quantification method

<table>
<thead>
<tr>
<th>Linear range (ng/mL)</th>
<th>Between run precision (% CV)</th>
<th>Between run accuracy (% Bias)</th>
<th>QC levels (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5-500</td>
<td>≤ 13.8%</td>
<td>0 ≥ bias ≤ 8.2%</td>
<td>0.5, 2.5, 30, 250, 500</td>
</tr>
</tbody>
</table>
Patient characteristics

- 9 women on dolutegravir 50mg QD included in 4 European hospitals (June ‘15 - June ‘17)
  - 3 women only 3rd trimester PK

<table>
<thead>
<tr>
<th>Demographics at delivery</th>
<th>Median (range) or n(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>30 (21-42)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38 (34-40)</td>
</tr>
<tr>
<td>HIV-1 RNA &lt; 50 cps/mL</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Regimen</td>
<td></td>
</tr>
<tr>
<td>DTG + TDF/FTC</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>DTG/ABC/3TC</td>
<td>4 (44%)</td>
</tr>
<tr>
<td>DTG + DRV/r +TDF</td>
<td>1 (12%)</td>
</tr>
<tr>
<td>DTG exposure in 1st trim</td>
<td>4 (44%)</td>
</tr>
</tbody>
</table>
## Results

<table>
<thead>
<tr>
<th></th>
<th>3rd Trimester</th>
<th>Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N 9</td>
<td>6</td>
</tr>
<tr>
<td>(C_{\text{min, unbound}}) ng/mL</td>
<td>4.0 (80)</td>
<td>4.2 (70)</td>
</tr>
<tr>
<td>(C_{\text{min, total}}) ng/mL</td>
<td>710 (102)</td>
<td>1070 (61)</td>
</tr>
<tr>
<td>Fraction unbound</td>
<td>% 0.63 (0.43-0.73)</td>
<td>0.33 (0.28-0.70)</td>
</tr>
<tr>
<td>(C_{\text{max, unbound}}) ng/mL</td>
<td>15 (33)</td>
<td>11 (33)</td>
</tr>
<tr>
<td>(C_{\text{max, total}}) ng/mL</td>
<td>3417 (31)</td>
<td>3350 (47)</td>
</tr>
<tr>
<td>Fraction unbound</td>
<td>% 0.40 (0.35-0.56)</td>
<td>0.29 (0.27-0.38)</td>
</tr>
</tbody>
</table>

Values are expressed as geometric mean (CV%), except for fraction unbound; median (IQR).
Individual unbound concentrations

![Graphs showing unbound DTG concentrations for Third trimester and Postpartum periods for both C_min and C_max.](image-url)
Free fraction versus $C_{\text{free}}$

Unbound DTG concentration (g/L) vs. free fraction (%)

- Blue dots: 3th trimester pregnancy
- Orange dots: postpartum
Free fraction vs albumin level

[Albumin], median (IQR)
- 3rd trimester (n=4)  36.5 (36-37) g/L
- post-partum (n=3)   39.0 (37-43) g/L
Discussion

- For $C_{\text{min}}$, total DTG concentrations were lower and free DTG concentrations were comparable in 3rd trimester vs post-partum; this could be the result of lower serum albumin concentrations in 3rd trimester.

- DTG fraction unbound;
  - Free fraction in 3rd trimester > post-partum; 0.40-0.63% vs 0.29-0.33%
  - Free fraction in non-pregnant in this study < free fraction in HIV-positive subjects in literature; ~0.29-0.33% vs ~0.49% [1]
  - Assay differences; cross validation with dialysis membrane sample preparation method

Conclusion

• In late pregnancy total dolutegravir exposure is lower, however unbound dolutegravir plasma $C_{\text{min}}$ seems unchanged in the 3rd trimester as compared to postpartum.

• Free fraction of DTG in pregnant women in the 3rd trimester in this study is $\sim0.4-0.63\%$.

• Although the sample size was small, these findings, coupled with the undetectable viral loads at delivery, suggest uncompromised efficacy of dolutegravir 50mg QD in pregnancy.
Acknowledgements

- Participants PANNA study
- Doctors and (research)nurses PANNA network
- Laboratory technicians dept. of pharmacy Radboudumc
- Stein Schalkwijk, MSc
- Dr. Angela Colbers (Projectmanager/ Investigator PANNA)
- Prof. Dr. David Burger (Principal Investigator PANNA)

Thank you for your attention