A Comparison of the Pharmacokinetics of Dolutegravir in Pregnancy and Postpartum

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A European clinical pharmacology network to investigate the Pharmacokinetics of newly developed ANtiretroviral agents in HIV-infected pregNAnt women
Pregnancy and HIV+

- 1.5 million HIV-infected women deliver per year

- Mother-to-child-transmission (MTCT) of the HIV-virus while using antiretroviral medication during pregnancy; 20% to <2% chance

- Combination antiretroviral treatment (cART);

<table>
<thead>
<tr>
<th></th>
<th>Non-pregnant HIV+</th>
<th>Pregnant HIV+</th>
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<tbody>
<tr>
<td><strong>Backbone</strong></td>
<td>ABC/3TC</td>
<td>ABC/3TC</td>
</tr>
<tr>
<td></td>
<td>TDF or TAF/FTC</td>
<td>TDF/FTC or TDF/3TC</td>
</tr>
<tr>
<td><strong>Third agent</strong></td>
<td>PI or INSTI</td>
<td>PI or INSTI</td>
</tr>
<tr>
<td></td>
<td><strong>DRV/r</strong></td>
<td><strong>ATV/r, DRV/r or RAL</strong></td>
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<tr>
<td></td>
<td><strong>DTG, EVG or RAL</strong></td>
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Pregnancy and HIV+

- Pregnant women are excluded from clinical trials in development phase

- After marketing of the new drug, HIV+ women get pregnant using these new drugs

- Knowledge gaps:
  1. Placental passage
  2. Safety for the unborn child
  3. Pharmacokinetics in pregnancy
Why study pharmacokinetics of ARVs in pregnant women?

- Pregnancy may induce changes in PK of ARVs
- In many cases lower plasma concentrations are the result
- Adequate exposure to ARVs is necessary to maximalise VL reduction and prevent resistance
- Low VL is needed to prevent MTCT
Expected changes in pharmacokinetics of ARVs in pregnant women

- Gastric pH ↑
- Gastric emptying and intestinal motility ↓
- Total body water ↑
- Plasma volume ↑
- Total body fat ↑
- Albumin conc. ↓
- Hepatic blood flow ↑
- CYP2D6 activity ↑
- CYP3A4 activity ↑
- GFR ↑
Dolutegravir

- Dolutegravir is an integrase inhibitor recommended to be used in first line ARV treatment.

- Limited data is available about the pharmacokinetics of dolutegravir during pregnancy and the placental passage of dolutegravir
  - IMPAACT P1026s
Objectives

• To describe the pharmacokinetics of dolutegravir in the 3rd trimester of pregnant HIV-infected women and at post-partum

• To describe the safety of dolutegravir during pregnancy and the efficacy in terms of maternal viral load response and prevention of mother to child transmission

• To assess placental passage of dolutegravir
Method

3rd trimester
~ 33wks GA
PK curve dolutegravir

postpartum
4-6 weeks after delivery
PK curve dolutegravir (reference)

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

3rd trimester
~ 33wks GA
PK curve dolutegravir

postpartum
4-6 weeks after delivery
PK curve dolutegravir (reference)

Cord blood at delivery
(CB/MB ratio)

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

- 9 women on dolutegravir 50mg QD included in 4 European hospitals (June ‘15 - June ‘17).
  - 3 women only 3rd trimester PK, 1 woman was excluded from PK analysis

<table>
<thead>
<tr>
<th>Demographics at delivery</th>
<th>Median (range) or n(%)</th>
</tr>
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<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>Birth weight, grams</td>
<td>3180 (2120-3530)</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>
</tbody>
</table>
Plasma concentration vs. time curve
# Pharmacokinetic parameters

<table>
<thead>
<tr>
<th></th>
<th>3rd Trimester n=8; GA 34 (31-38) wks</th>
<th>Postpartum n=5; 6 (3-7) wks PP</th>
<th>GM ratio (90% CI) n=5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AUC\textsubscript{0-24h} (h*mg/L)</strong></td>
<td>42.9 (39)</td>
<td>44.8 (56)</td>
<td>0.95 (0.60-1.48)</td>
</tr>
<tr>
<td><strong>C\textsubscript{max} (mg/L)</strong></td>
<td>3.4 (33)</td>
<td>3.0 (41)</td>
<td>1.07 (0.78-1.47)</td>
</tr>
<tr>
<td><strong>C\textsubscript{24h} (mg/L)</strong></td>
<td>0.7 (109)</td>
<td>1.1 (71)</td>
<td>0.66 (0.32-1.36)</td>
</tr>
<tr>
<td><strong>T\textsubscript{max} (h)</strong></td>
<td>3.0 (1.0-4.5)</td>
<td>3.8 (0.5-8.0)</td>
<td>-</td>
</tr>
<tr>
<td><strong>CL/F (L/h)</strong></td>
<td>1.2 (39)</td>
<td>1.1 (56)</td>
<td>1.06 (0.67-1.66)</td>
</tr>
<tr>
<td><strong>T\textsubscript{1/2} (h)</strong></td>
<td>9.9 (50)</td>
<td>14.9 (27)</td>
<td>0.75 (0.58-0.98)</td>
</tr>
</tbody>
</table>

Values are expressed as geometric mean (CV%); except for T\textsubscript{max}, median (range).
Individual exposure and $C_{\text{trough}}$
Figure 2. Dolutegravir C$_{24}$ Ante- and Postpartum

<table>
<thead>
<tr>
<th>Parameter</th>
<th>2nd Trimester n = 9</th>
<th>3rd Trimester n = 15</th>
<th>Postpartum n = 9</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC$_{0-24}$ (mcg*hr/mL)</td>
<td>58.4 (47.6 - 64.5)</td>
<td>48.7 (40.3 - 57.6)</td>
<td>71.1 (58.0 - 83.1)</td>
</tr>
<tr>
<td>C$_{24}$ (mcg/mL)</td>
<td>0.86 (0.69 - 1.37)</td>
<td>0.91 (0.74 - 1.21)</td>
<td>1.70 (0.76 - 2.00)</td>
</tr>
</tbody>
</table>

CROI 2016; February 22-25; Boston, Massachusetts, USA; P438
Results ARVs

AUC GMR (90% CI) third trimester/postpartum

dolutegravir (n=5)
efavirenz (n=24)
rilpivirine (n=15)
etravirine (n=8)
maraviroc (n=15)
raltegravir (n=17)
ritonavir (DRV QD)
ritonavir (DRV BID)
ritonavir (ATV)
darunavir QD (n=9)
darunavir BID (n=5)
atazanavir (n=26)
abacavir (n=13)
tenofovir (n=27)
emtricitabine (n=24)
Results ARVs

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dolutegravir (n=5)
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darunavir QD (n=9)
darunavir BID (n=5)
atazanavir (n=26)
tenofovir (n=27)
emtricitabine (n=24)
CB/MB-ratio

- **FTC**: 1.63 (0.46–1.82), n=10
- **RAL**: 1.21 (1.13–4.53), n=9
- **EFV**: 0.81 (0.65–0.95), n=4
- **RAL**: 1.21 (1.13–4.53), n=9
- **TDF**: 0.82 (0.64–1.10), n=14
- **ABC**: 0.87 (0.73–1.03), n=4
- **RPV**: 0.5 (0.35–0.81), n=5
- **MVC**: 0.33 (0.03–0.56), n=10
- **ATV**: 0.20 (0.06–3.05), n=12
- **ETV**: 0.76 (0.19–4.25), n=6
- **EVG**: 1.0
- **DTG**: 1.4 (0.35–1.6), n=5
- **TDF**: 0.82 (0.64–1.10), n=14
- **DRV**: 0.13 (0.08–0.35), n=8
- **RTV**: <0.05, n=26

**Ratio = 1**

**Ratio = 1.75**
Safety & efficacy

- Approaching delivery all patients had a VL <50 cps/mL.
- 7/8 children were HIV un-infected (1 status unknown).
- One intrauterine fetal death (34 weeks of pregnancy) was reported due to cholestasis pregnancy syndrome.
- No further birth defects were reported.
- 2 SAE, not drug related; hospital admissions to rule out pre-eclampsia.
Conclusion

• Dolutegravir exposure and trough concentration in third trimester of pregnancy appear to be similar compared to postpartum
• Postpartum exposure is in line with literature ref. values

• Levels at the end of the dosing interval remain above the IC$_{90}$ for dolutegravir

• Dolutegravir efficiently crosses the placenta and therefore may have potential for pre-exposure prophylaxis

• PK results need to be confirmed in a larger group of patients
Acknowledgements

- Participants PANNA study
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- Prof. Dr. David Burger (Principal Investigator PANNA)
Partners PANNA

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- Merck
- BMS
- Janssen
- ViiV Healthcare
- Gilead
Thank you for your attention