Pharmacological considerations on the use of ARVs in pregnancy

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Disclosures DM Burger

- Janssen: research grants, advisory board, speaker at symposia
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- Abbvie: advisory board, speaker at symposia
- Roche: research grant
- Bristol-Myers Squibb: research grants, advisory board
- Gilead: advisory board, speaker at symposia,

NB all payments have been invoiced by the financial department of Radboudumc
Famous quiz on Dutch players in Serie A
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Stefan de Vrij
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?
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Kevin Strootman

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Nigel de Jong

Kevin Strootman

Marten de Roon
Content


• Treatment of HIV-infected pregnant women
  • Where did we stand in 2005?
  • Major developments 2005 – 2015
  • Future perspective

• Conclusions
Available ARVs back in 2005 (n=17)

**NRTI**
- Abacavir (ABC)
- Didanosine (ddI)
- Emtricitabine (FTC)
- Lamivudine (3TC)
- Stavudine (d4T)
- Tenofovir (TDF)
- Zidovudine (AZT, ZDV)

**NNRTI**
- Efavirenz (EFV)
- Etravirine (ETR)
- Nevirapine (NVP)
- Rilpivirine (RPV)

**PI**
- Atazanavir (ATV)
- Darunavir (DRV)
- Fosamprenavir (FPV)
- Indinavir (IDV)
- Lopinavir (LPV)
- Nelfinavir (NFV)
- Ritonavir (RTV)
- Saquinavir (SQV)
- Tipranavir (TPV)

**Integrase inhibitor (II)**
- Raltegravir (RAL)
- Elvitegravir (EVG)
- Dolutegravir (DTG)

**Fusion inhibitor (FI)**
- Enfuvirtide (ENF, T-20)

**CCR5 Antagonist**
- Maraviroc (MVC)
**Currently available ARVs (n=25)**

### NRTI
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### CCR5 Antagonist
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There is a wealth of data comparing individual ARVs (1)
There is a wealth of data comparing individual ARVs (2)

Patel et al. Plos One 2014
ARV treatment in pregnancy: status 2005

- cART principally PI- (LPV/r, NFV) or NVP-based regimens
- Increased risk for NVP-toxicity at high CD4s already known
- NRTI backbone almost universally ZDV/3TC (concern about TDF bone toxicity)
- No EFV because of teratogenicity in monkeys
- Controversy about risk of pre-term birth (with PI-based therapy)
- No data on newer agents in pregnancy
- First PK data of ARVs in pregnancy presented
The pharmacokinetics of nelfinavir and M8 during pregnancy and post partum

Rolf P. G. van Heeswijk, PharmD, PhD, Yasmin Khaliq, PharmD, Keith D. Gallicano, PhD, Marc Bourbeau, BSc, Isabelle Seguin, Elizabeth J. Phillips, MD, and D. William Cameron, MD Ottawa and Toronto, Ontario, Canada, and Corona, Calif

AUC: -24%
Cmin: -57%
Reduced lopinavir exposure during pregnancy

Alice M. Stek\textsuperscript{a}, Mark Mirochnick\textsuperscript{b}, Edmund Capparelli\textsuperscript{c}, Brookie M. Best\textsuperscript{c}, Chengcheng Hu\textsuperscript{d}, Sandra K. Burchett\textsuperscript{e}, Carol Elgie\textsuperscript{f}, Diane T. Holland\textsuperscript{c}, Elizabeth Smith\textsuperscript{g}, Ruth Tuomala\textsuperscript{h}, Amanda Cotter\textsuperscript{i} and Jennifer S. Read\textsuperscript{j} for the PACTG 1026s study team\textsuperscript{*}

AUC: -28%  
Cmin: -56%
Why study pharmacokinetics of ARVs in pregnant women?

- Total body water \( \uparrow 44\% \)
- Plasma volume \( \uparrow 50\% \)
- Total body fat \( \uparrow 35\% \)
- Albumin conc. \( \downarrow 31\% \)
- Gastric pH \( \uparrow \)
- Gastric emptying and intestinal motility \( \downarrow \)
- Hepatic blood flow \( \uparrow 42\% \)
- CYP2D6 activity \( \uparrow 48\% \)
- CYP3A4 activity \( \uparrow 38\% \)
- GFR \( \uparrow 37\% \)
Why study pharmacokinetics of ARVs in pregnant women?

The recommended dose in a non-pregnant HIV-infected patient is not necessarily the optimal dose in a pregnant HIV-infected patient.
PANNA network

Dublin
2 centres

Cologne
Bonn
Berlin
München
Frankfurt

London
3 centres
+ 3 satellite sites

Nijmegen
Rotterdam
Amsterdam
Satellite Tilburg

Roma

Brussels

Granada

Barcelona
Cumulative patient inclusion

Number of patients


penna

Radboudumc
Summary of PK results from PANNA

Geometric mean ratios and 90% confidence intervals for AUCs pregnancy/postpartum
Are these PK differences leading to changes in dose recommendations?

• No general recommendation for an adjusted dose of a particular ARV in pregnancy, but....

• “Some experts say”:  
  • Increased dose of LPV/r (600/150mg BID or 500/125mg BID)  
  • Increased dose of ATV/r (400/100mg QD)  
  • DRV/r only BID in pregnancy (see below)  
  • Increased doses in case co-medication reducing [ARV], inadequate food intake, PI mutations, high body weight, etc.  
  • TDM may be helpful
Darunavir in pregnancy: BID or QD?

• Both PANNA & IMPAACT demonstrated approx. 35% decrease in AUC and 40—60% decrease in $C_{\text{min}}$ of DRV QD

• Pregnancy effects on DRV/r BID were less strong (and levels were higher postpartum)

• Significance of 40-60% decrease in DRV $C_{\text{min}}$ with QD administration (in patient without PI mutations)?
  • Perinatal guidelines/IMPAACT recommend BID
  • PANNA states that QD is possible in an adherent patient taking DRV/r with food and no other medication reducing DRV levels (and TDM)

Colbers et al. JAC 2015; Stek et al. JAIDS 2015
Safety concerns with ARVs: update 2016

• Concern remains about EFV toxicity (case reports); no overall increase in overall birth defects
  • *Initiation preferable after first 8 weeks of pregnancy*

• No evidence for human teratogenicity for TDF (can rule out 1.5-fold increase)
  • *No impact on infant birth weight or growth until 6 months of age (Ransom et al. JAIDS 2013)*
  • *Lower bone mineral content in newborns exposed to TDF in utero (Sibery et al. CID 2015 in press)*
  • *Cord blood/maternal blood ratio 0.83 so significant exposure*
  • *Dose increase recommended for women >90kg? (Best et al. HIV Med 2015)*

DHHS perinatal guidelines; update August 6, 2015
Safety concerns with ARVs: update EFV (1)

Safety of efavirenz in the first trimester of pregnancy: an updated systematic review and meta-analysis

Nathan Ford, Lynne Mofenson, Zara Shubber, Alexandra Calmy, Isabelle Andrieux-Meyer, Marco Vitoria, Nathan Shaffer and Françoise Renaud

AIDS 2014, 28 (Suppl 2):S123–S131
Safety concerns with ARVs: update EFV (2)

Association between Prenatal Exposure to Antiretroviral Therapy and Birth Defects: An Analysis of the French Perinatal Cohort Study (ANRS CO1/CO11)

Jeanne Sibiude, Laurent Mandelbrot, Stéphane Blanche, Jérôme Le Chenade, Naima Boullag-Bonnet, Albert Faye, Catherine Dollfus, Roland Tubiana, Damien Bonnet, Nathalie Lelong, Babak Khoshnood, Josiane Warszawski

Significant association between EFV and neurological defects (n=4)

Sibiude et al. Plos Med 2014

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Safety concerns with ARVs: update EFV (3)

Despite no overall increase in birth defects with EFV, guidelines stay at the safe side:

- “Initiation of EFV preferable after first 8 weeks of pregnancy”
- “Alternate ARV regimens should be strongly considered in women planning to become pregnant”
Preferred ARV regimens in pregnancy

- 3 main criteria
  - Established efficacy in non-pregnant patients
  - PK data supporting correct dose in pregnancy
  - No evidence for teratogenicity or adverse pregnancy outcome

- NRTI backbones: ABC/3TC, TDF/FTC, TDF/3TC, ZDV/3TC
- 3rd drug:
  - PI-based: ATV/r QD or DRV/r (only BID? See below)
  - NNRTI: EFV (after first 8 weeks)
  - InstI: RAL – more rapid decline in VL, esp. relevant for late presenters

DHHS perinatal guidelines; update August 6, 2015
HIV treatment of in pregnancy: we’re almost there

<table>
<thead>
<tr>
<th>Preferred PI Regimens</th>
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<tbody>
<tr>
<td>ATV/r plus a Preferred Two-NRTI</td>
<td>Once-daily administration. Extensive experience in pregnancy.</td>
</tr>
<tr>
<td>Backbone</td>
<td>Maternal hyperbilirubinemia</td>
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<tr>
<td>DRV/r plus a Preferred Two-NRTI</td>
<td>Better tolerated than LPV/r. PK data available. Increasing</td>
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<tr>
<td>Backbone</td>
<td>experience with use in pregnancy. Must be used twice daily in</td>
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<td>pregnancy.</td>
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<tr>
<th>Preferred NNRTI Regimen</th>
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<tr>
<td>EFV plus a Preferred Two-NRTI Backbone</td>
<td>Concern because of birth defects seen in primate study; risk</td>
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<tr>
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<td>in humans is unclear (see Teratogenicity and Table 7). Postpartum</td>
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<td></td>
<td>contraception must be ensured. Preferred regimen in women who</td>
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<td>require co-administration of drugs with significant interactions</td>
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<td>with PIs or the convenience of co- formulated, single-tablet,</td>
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<td>once-daily regimen.</td>
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<th>Preferred Integrase Inhibitor Regimen</th>
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<tr>
<td>RAL plus a Preferred Two-NRTI Backbone</td>
<td>PK data available and increasing experience in pregnancy. Rapid</td>
</tr>
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<td></td>
<td>viral load reduction. Useful when drug interactions with PI</td>
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<td></td>
<td>regimens are a concern. Twice-daily dosing required.</td>
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**Recommended Regimen Options**

(Drug classes and regimens within each class are arranged in alphabetical order.)

**INSTI-Based Regimens:**
- DTG/ABC/3TC—only for patients who are HLA-B*5701 negative (AI)
- DTG plus TDF/FTC (AI)
- EVG/cTDF/FTC—only for patients with pre-treatment estimated CrCl ≥70 mL/min (AI)
- RAL plus TDF/FTC (AI)

**PI-Based Regimens:**
- DRV/r plus TDF/FTC (AI)
HIV treatment of pregnant women in resource-limited countries

• WHO’s public health approach: one regimen (TDF/3TC/EFV) for all, including pregnant women (option B+)

• Teratogenicity problem detected by pharmacovigilance programs? (e.g., see Liu et al. AIDS 2014)

• CNS effects in women during pregnancy, in newborns in utero and through breastfeeding (e.g., infant [EFV] 10% of maternal [EFV]?)

• “Slow” VL decline by EFV-based regimens in late presenters?
Conclusions

• Significant progress has been made in treatment of HIV-pregnant women

• PK studies by international networks have contributed significantly to this knowledge

• Several concerns remain related to safety and preferred regimens

we’re closing the gap
and at het end
preferred regimens will be similar in pregnant and non-pregnant patients

Thank you for your attention!