P1026s: Pharmacokinetic Properties of Antiretroviral Therapy and Related Drugs during Pregnancy:
Second-line TB treatment arm

Jennifer Hughes, Desmond Tutu TB Centre, Cape Town, South Africa

IMPAACT TB Scientific Committee Meeting
17 June 2018
Drug-resistant tuberculosis (DR-TB) treatment

• Multidrug regimens, toxic, intolerable, expensive, long (20 months)
• At least 5 effective drugs
  • kanamycin, moxifloxacin (or levofloxacin), terizidone (or cycloserine), ethionamide (or prothionamide), hd-isoniazid, PAS
  • (pyrazinamide, ethambutol)

• PREGNANCY: kanamycin and ethionamide usually avoided, but rarely substituted (limited options, safety) – implications
  • Poor maternal treatment outcome – lower chance of treatment success; risk of acquisition of SLD resistance
  • Increased risk of transmission to newborn
Existing PK data for second-line TB drugs in pregnancy

• Two studies showed low peak serum concentrations for MFX and OFX, but...
• ... another reported peak serum concentrations comparable to non-pregnant adult target levels for MFX and LFX in C-sectioned women

• One PK study in 1977 reported low peak serum concentrations following a single dose of IM amikacin in 11 pregnant women

• One case report in 2017 of a woman with MDR-TB found a decreased exposure of linezolid (at 300mg twice daily) and moxifloxacin (at 400mg once daily) during pregnancy compared with post-partum measurements, but with a trend towards increased exposure of both drugs from the second to the third trimesters of pregnancy.
IMPAACT P1026s

• **Title:** PHARMACOKINETIC PROPERTIES OF ANTIRETROVIRAL AND RELATED DRUGS DURING PREGNANCY AND POSTPARTUM

• **Current version:** 10.0

• **Design:** Phase IV, prospective pharmacokinetic (PK) study

• **Objective:** To assess bioavailability of ART and TB drugs in T2, T3 and post-partum

• **Populations:** Pregnant and postpartum women receiving the following medicines as part of clinical care, and their infants

• **Study Arms:**
  - ARVs (without TB treatment) – darunavir, dolutegravir, TAF, cobicistat, elvitegravir
  - First line TB treatment with ARVs – EFV and lopinavir/ritonavir
  - First line TB treatment without ARVs
  - Second-line TB treatment +/- ARVs
  - ARVs (darunavir, atazanavir, cobicistat, efavirenz, tenofovir) with post-partum contraceptives (implants and combined oral)
Design of second-line TB arm

• Inclusion: >20 weeks pregnant, stable on any second-line TB drugs, with or without ART, for >2 weeks

• Enrollment target: 25 women with evaluable 3rd trimester PK data

• Enrollment after 20 weeks – then 5 study visits per patient:
  • 20-26 week PK
  • 30-38 week PK
  • (Labour and delivery – maternal plasma and cord blood *if possible*)
  • 2-8 week post partum PK
  • 16-24 week post partum, baby only (exit visit)

• Washout bloods in infant (only if mother HIV co-infected and on ART)

• Clinical care and all drugs provided by routine care providers
## Status update

<table>
<thead>
<tr>
<th>Arm</th>
<th>Number Enrolled</th>
<th>Target Accrual</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antepartum/HIV-infected Arms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAF 25 mg qd with COBI or ritonavir</td>
<td>15</td>
<td>25</td>
</tr>
<tr>
<td>ATZ/COBI</td>
<td>5</td>
<td>25</td>
</tr>
<tr>
<td><strong>Antepartum TB Arms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First line TB drugs with EFV</td>
<td>20</td>
<td>25</td>
</tr>
<tr>
<td>First line TB drugs with LPV/r</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>TB Only</td>
<td>14</td>
<td>25</td>
</tr>
<tr>
<td><strong>Second Line TB drugs (HIV-infected and uninfected)</strong></td>
<td>4*</td>
<td>25</td>
</tr>
<tr>
<td><strong>Postpartum Contraception Arms</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DRV/COBI or ATZ/COBI + oral contraceptives</td>
<td>1</td>
<td>25</td>
</tr>
<tr>
<td>DRV/COBI or ATZ/COBI + etonogestrel</td>
<td>2</td>
<td>25</td>
</tr>
</tbody>
</table>

Courtesy of FHI – as at 17 June 2018

* Two more consented, awaiting first PK session
Changing practice and way forward

• Recommendations for treatment of DR-TB in pregnancy
  • Updated WHO guidance for better treatment of DR-TB in adults and children
    • ‘new’ and repurposed drugs, and shorter regimens (9-12 months)
      • no evidence for use in pregnancy – excluded from trials
  • WHO guidance vs common practice (currently changing in South Africa)
  • Increasing access to clofazimine, linezolid, bedaquiline, delamanid

• New P2026s protocol
  • Focus on ‘new’ and repurposed drugs – CFZ, LZD, BDQ, DLM (and FQs)
    • BDQ – long half life, concern regarding high levels in maternal milk in rats
  • Inclusion of breastmilk PK analysis, particularly BDQ