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

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IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

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

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

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