# Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis

M Loveday

VMC virtual meeting

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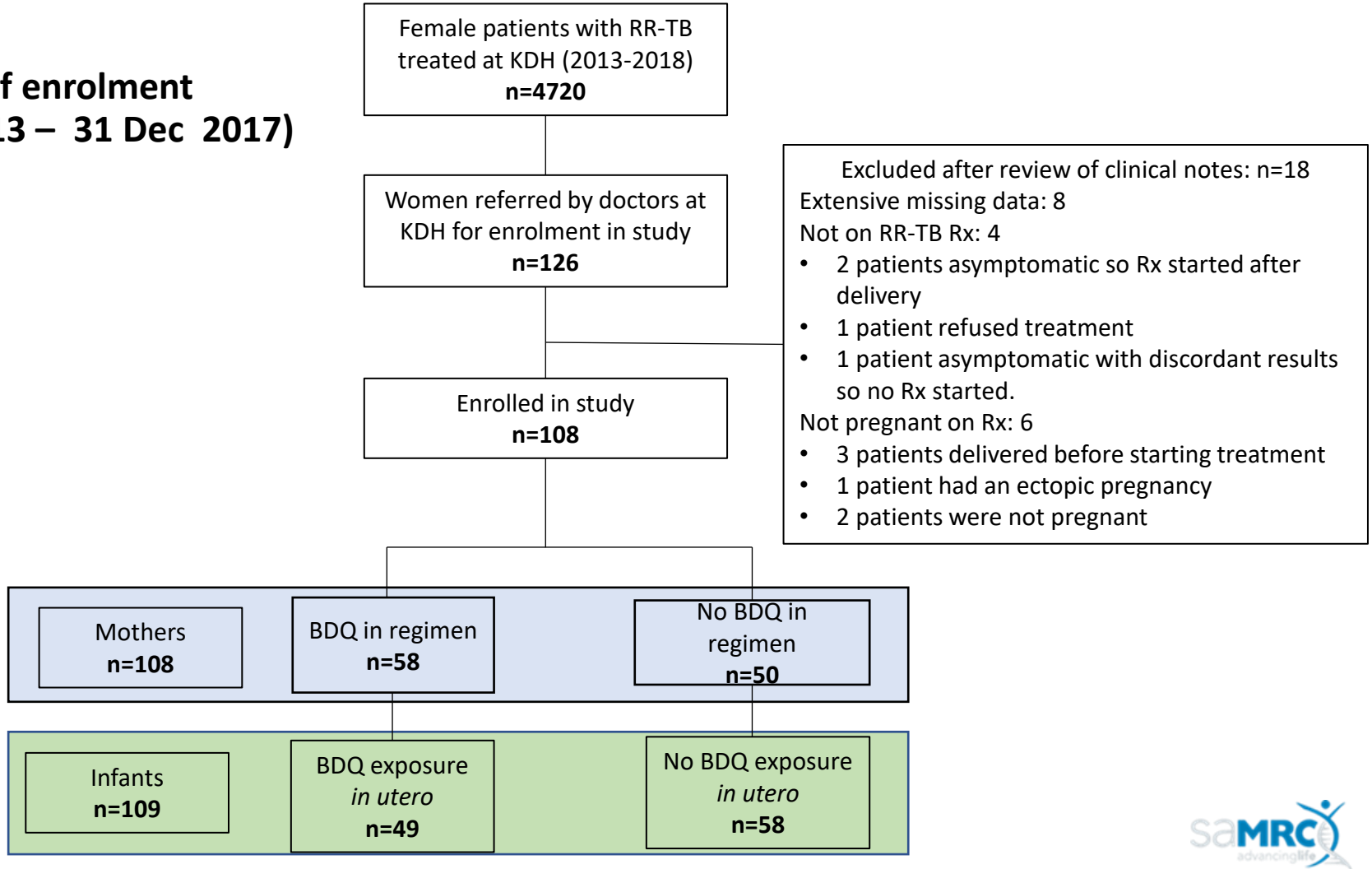
# Study Background

- 2013: Started enrolling pregnant women with RR/MDR-TB in an ongoing cohort.
  - **Objective:** To document treatment, pregnancy and infant outcomes amongst women treated for RR/MDR-TB in pregnancy.
  - **Methods:** Descriptive cohort analysis
    - A record review to document treatment and pregnancy outcomes;
    - An observational clinical assessment at 2, 6 and 12 months, to document infant outcomes.

Bedaquiline:

- 2013: Introduced into South Africa (limited initially to those with fluoroquinolone and/or injectable resistance, but then expanded to all RR/MDR-TBs
- 2016: NDoH recommended BDQ in pregnant women (although limited evidence on its use in pregnant women.)
- 2017: Study in animal models showed high levels of BDQ in breastmilk

# Schema of enrolment (1 Jan 2013 – 31 Dec 2017)



# Baseline clinical characteristics of pregnant women with RR-TB, stratified by bedaquiline exposure (n=108)

| | Clinical characteristics | BDQ in regimen N=58 | No BDQ N=50 | p-value |
|---|---|---|---|---|
| General characteristics | Age: years, mean; SD | 28.7; 6.08 | 27.0; 6.01 | 0.150 |
| TB characteristics | Culture positive at treatment initiation | 42/58 (72%) | 31/49 (63%) | 0.405 |
| | Previous TB or RR-TB | 19/35 (54%) | 19/47 (40%) | 0.265 |
| | Site of TB: Pulmonary | 57 (100%) | 51 (100%) | na |
| | Chest radiograph: extensive disease | 23/51 (45%) | 22/46 (48%) | 0.923 |
| | Resistance pattern: RR-TB/Rif-mono/MDR-TB | 45 (78%) | 38 (76%) | 1.000 |
| HIV characteristics | HIV-positive | 48 (83%) | 40 (80%) | 0.806 |
| | HIV- positive patients on ART before RR-TB treatment started | N=48<br>37 (77%) | N=40<br>37 (90%) | 0.155 |
| | Baseline CD4 count, cells/µl, median [IQR] | N=48<br>335 [138 - 500] | N=41<br>395 [219 - 540] | 0.352 |
| Pregnancy characteristics | Pregnant before RR-TB treatment started | 47 (81%) | 42 (84%) | 0.802 |
| | Gestational age at treatment start: weeks, median [IQR] | 23 [13 – 28] | 20.5 [15 – 28] | 0.905 |

# Maternal treatment, pregnancy and infant outcomes, stratified by bedaquiline exposure

| | Bedaquiline exposure | No bedaquiline exposure | p-value |
|---|---|---|---|
| **Maternal treatment outcomes** | N=58 | N=50 | 0.349 |
| Favourable treatment outcomes | 41 (71%) | 31 (62%) | |
| | | | |
| **Pregnancy outcomes** | N=49 | N=60 | 0.312 |
| Live births | 45 (92%) | 54 (90%) | 0.741 |
| Unfavourable pregnancy outcomes | 25 (51%) | 26 (43%) | |
| Preterm < 37 weeks | 13 (29%) | 15 (28%) | 0.903 |
| Low birth weight < 2500g | 20 (45%) | 13 (26%) | 0.034 |
| | | | |
| **Infant outcomes** | N=41 | N=45 | |
| Favourable infant outcomes | 36 (88%) | 36 (80%) | 0.136 |
| Weight gain: Thrive normally | 36 (88%) | 37 (82%) | 0.914 |
| Development: Normal development | 38 (93%) | 39 (86%) | 0.705 |

# Treatment details stratified by bedaquiline exposure

| | Bedaquiline exposure N=58 | No bedaquiline exposure N=50 | p-value |
|---|---|---|---|
| **Maternal treatment** | | | |
| Length of treatment: Days, median [IQR] | 552 [304 – 642] | 575 [394 – 669] | |
| Bedaquiline: Days, median [IQR] | 180 [29 – 196] | na | na |
| Treatment outcomes: | | | 0.349 |
| Cure | 35 (60%) | 24 (48%) | |
| Completed | 6 (11%) | 7 (14%) | |
| Default | 11 (19%) | 14 (28%) | |
| Died and failed | 4+2=6 (10%) | 4+1=5 (10%) | |
| **Foetal exposure** | | | |
| Foetal exposure to 2nd-line drugs: Days, median [IQR] | 110 [66 – 203] | 141 [70 - 213] | 0·562 |
| Foetal exposure to bedaquiline: Days, median [IQR] | 77 [28 - 140] | na | na |

# Newborn characteristics, stratified by bedaquiline exposure

| | Bedaquiline exposure N=49 | No bedaquiline exposure N=60 | p-value |
|---|---|---|---|
| Newborn characteristics | | | |
| Live births | 45 (92%) | 54 (90%) | 0.741 |
| Gestational age at delivery: weeks, mean; SD; (n=97) | 37.68; SD 2.93 | 37.82; SD 3.25 | 0.830 |
| Birth weight, grams, median [IQR] (n=93) | 2690 [2380 - 3095] | 2900 [2550 - 3270] | 0.179 |
| Low birth weight < 2500g | 20 (45%) | 13 (26%) | 0.034 |
| Foetal and neonatal deaths | 4 (8%) | 6 (10%) | |
| Stillbirth | 3 (5%) | 3 (6%) | |
| Miscarriage | 0 | 3 (6%) | |
| Termination of pregnancy | 1 (2%) | 0 | |

# Predictors of low birth weight

We identified risk factors of low birthweight in newborns exposed to BDQ vs those not exposed.

| | Unadjusted OR (95%CI) | p-value | aOR (95%CI) | p-value |
|---|---|---|---|---|
| **Maternal baseline characteristics** | | | | |
| Age ≥30 years | 2.10 (0.87 – 5.11) | 0.099 | | |
| Previous TB | 1.64 (0.62 – 4.33) | 0.322 | | |
| Increased resistance (pre-XDR/XDR-TB) | 0.85 (0.29 – 2.50) | 0.771 | | |
| Haemoglobin at treatment start | 0.88 ((0.67 – 1.16) | 0.359 | | |
| BMI at treatment start | 1.01 (0.93 – 1.10) | 0.791 | | |
| HIV-positive | 2.09 (0.62 – 6.96) | 0.232 | | |
| CD4 at treatment start | 1.00 (0.99 – 1.00) | 0.075 | | |
| **RR-tuberculosis drug exposure *in utero*** | | | | |
| Bedaquiline (BDQ) | 2.57 (1.06 – 6.20) | 0.036 | 3.18 (1.08 - 9.31) | 0.035 |
| Capreomycin (CAP) | 0.28 (0.10 – 0.84) | 0.023 | 0.31 (0.09 - 1.03) | 0.055 |
| Clofazamine (CFZ) | 3.42 (1.40 – 8.34) | 0.007 | 2.62 (0.91 - 7.55) | 0.075 |
| Levofloxacin (LVX) | 2.84 (1.17 – 6.88) | 0.021 | 3.97 (1.21 - 13.03) | 0.023 |
| Moxifloxacin (MXF) | 0.37 (0.15 – 0.91) | 0.031 | 0.30 (0.10 - 0.89) | 0.029 |

# Conclusion

**In mothers treated with Bedaquiline:**

- Favourable treatment outcomes were reported in 41/58 (71%) of the women.
- 45/49 (92%) babies were born alive.
- Low birth weight was reported in more of the babies exposed to BDQ than in babies not exposed (45% vs 26%; p=0.034).
- In univariate analysis, BDQ, clof, levo (drugs often used together), were all associated with an increased risk of low birth weight. After adjusting for confounders:
  - Foetal exposure to BDQ and levo had a 3- and 4-fold higher risk of LBW respectively.
- After 12 months 36/41 (88%) of the babies exposed to BDQ were thriving and developing normally compared to 36/45 (82%) of the babies not exposed to BDQ.

Loveday M, Hughes J, Sunkari B, Master I, Hlangu S, Reddy T, Chotoo S, Green N, Seddon JA. Maternal and infant outcomes among pregnant women treated for multidrug/rifampicin-resistant tuberculosis in South Africa. Clinical Infectious Diseases. 2021;72(7):1158–68

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# Updated comparison of maternal TB treatment, pregnancy and infant outcomes: 1st cohort vs 2nd cohort

| | 1st cohort (2013 – 2017) | 2nd cohort (2018 – 2021) |
|---|---|---|
| Still on treatment | | 11 |
| **Maternal treatment outcomes** | N=58 | N=27 |
| Favourable treatment outcomes | 41 (71%) | 16 (59%) |
| Unfavourable treatment outcomes | 17 (29%) | 11 (41%) |
| LTFU | 11 (19%) | 8 (30%) |
| **Pregnancy outcomes** | N=49 | N=32 |
| Live births | 45 (92%) | 32 (100%) |
| Favourable pregnancy outcomes | 24 (49%) | 19 (59%) |
| Unfavourable pregnancy outcomes | 25 (51%) | 13 (39%) |
| Foetal and neonatal deaths | 4 | 0 |
| Preterm < 37 weeks | 13 (29%) | 9 (28%) |
| Low birth weight < 2500g | 20 (45%) | 10 (31%) |
| **Infant outcomes** | N=41 | N=23 |
| Favourable infant outcomes | 36 (88%) | 18 (78%) |
| Weight gain: Thrive normally | 36 (88%) | 17 (74%) |
| Unfavourable infant outcomes | 5 (12%) | 5 (23%) |
| Developed TB in 1st year of life | 0 | 3 (13%) |

# 2018: Added a pharmacokinetic study component

## Objectives

- To explore the effect of pregnancy on BDQ pharmacokinetics:
  - What are BDQ concentrations in pregnant women? Do they vary pre- and post-partum?

To describe the exposure of BDQ in the breastmilk of mothers treated for RR/MDR-TB:

- What are these drug concentrations in breastmilk and babies exposed during pregnancy and breastfeeding?

## Methods

- A longitudinal PK study with PK sampling at 4 time-points over 6 hours in the 3rd trimester and at 6 weeks postpartum.
- Serial breastmilk samples from breastfeeding mothers, and a single plasma sample taken from breastfed and non-breastfed infants to assess BDQ exposure.
- Liquid chromatography–tandem mass spectrometry to perform the breastmilk and plasma BDQ assays, and population PK modelling to interpret BDQ concentrations.

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# Results

**13 pregnant women, all of whom were HIV-positive on ART**

We observed:

- Lower ante- and postpartum BDQ exposures in pregnant women than those reported in non-pregnant patients.
- There was no difference between ante- and postpartum BDQ pharmacokinetics.
- High BDQ concentrations in breastmilk with a milk to maternal plasma ratio: 14:1.
- In the 1 breastfed infant BDQ concentrations were similar to maternal plasma concentrations.
- In the 3 non-breastfed infants BDQ concentrations were detectable but lower than maternal plasma concentrations.

Court R, Gausi K, Mkhize B, et al. Bedaquiline exposure in pregnancy and breastfeeding in women with rifampicin-resistant tuberculosis. Br J Clin Pharmacol 2022;88:3548-58.

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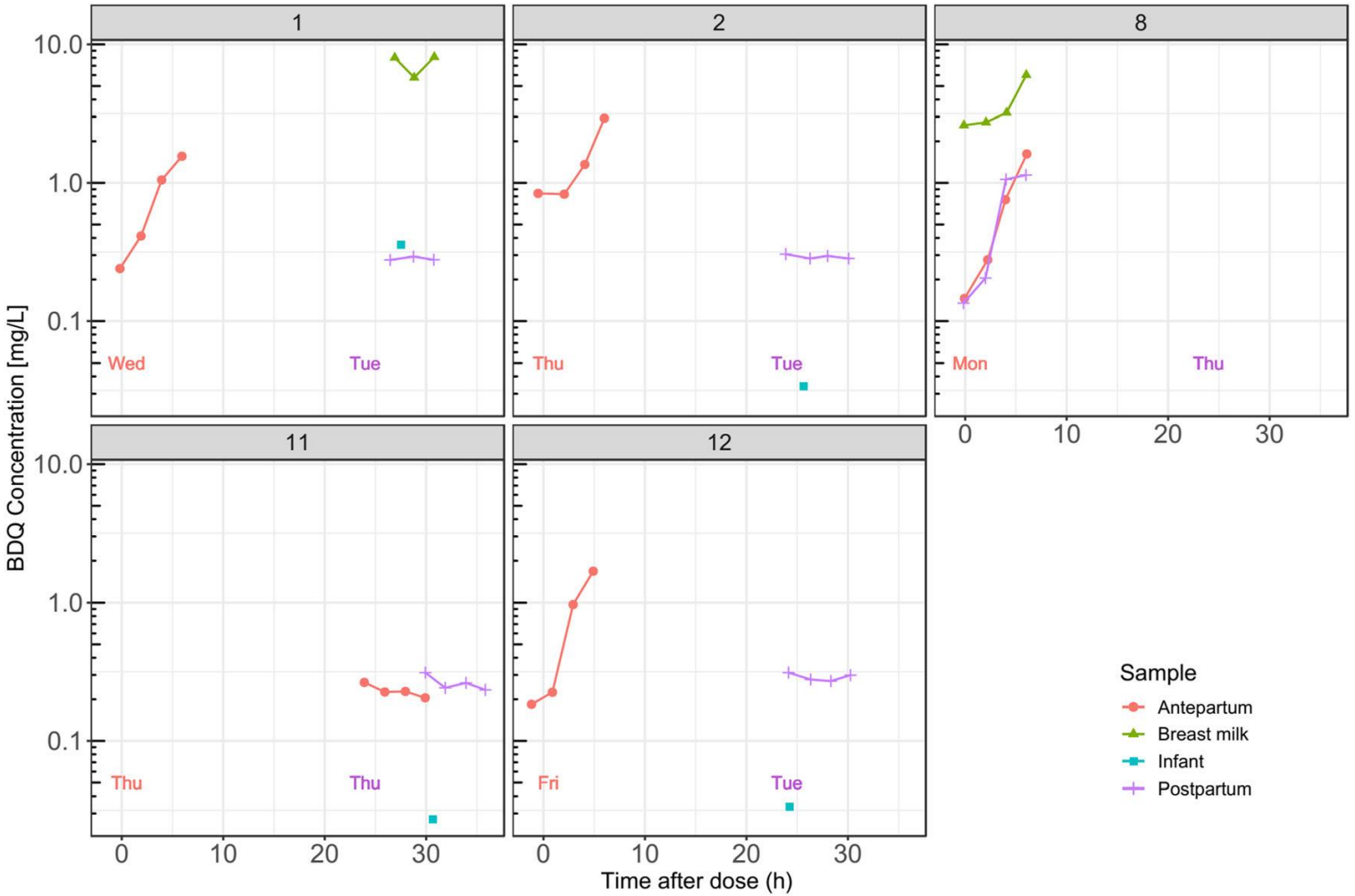
# Pharmacokinetics profiles of bedaquiline concentrations



## Study challenges

Our study participants (and most women with RR/MDR-TB in our setting) have limited resources, limited control over their lives and often limited support.

- Relying on public transport:
  - They may not arrive
  - May arrive late
- Medication:
  - BDQ is taken 3 days a week
  - May arrive without their medication
  - May have not taken medication for the last week
  - May come with 2 BDQ pills instead of 4
- Other challenges:
  - Covid
  - May arrive having been physically abused
  - May arrive having taken no treatment for a month and their infant is sick – losing weight, lethargic, coughing.

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**Contact details**
Marian.loveday@mrc.ac.za

**Thank you**