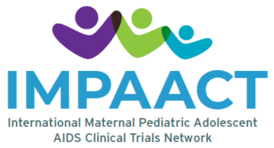
MDR-TB drugs in pregnancy

Jennifer Hughes, MD

TB Scientific Committee meeting

27 Oct 2023

Desmond Tutu TB Centre, Stellenbosch University, CRS 31790



2 Prevalence of TB in pregnancy

10.6 million new diagnoses of active TB

5.8 million

3.2 million

1 million

?

Incidence per 100 000 population per year

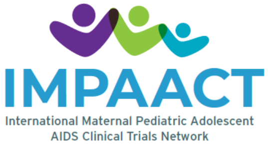
- 0–24
- 25–99
- 100–199
- 200–299
- ≥300
- No data
- Not applicable

WHO 2022

TB burden during pregnancy is likely high but not well quantified

RR/MDR-TB????

Urgent need for surveillance and reporting



3

TB incidence peaks during the reproductive age, irrespective of HIV status

Women in sub-Saharan Africa

Deluca JAIDS 2009

TB Cases per 100,000

700
600
500
400
300
200
100
0

0–14 15–24 25–34 35–44 45–54

Women in India

RNTCP Gender differentials in TB control 2004

400
300
200
100
0

16-19 20-25 26-30 31-35 36-40 41-45 46-50

Slide, courtesy, Amita Gupta

Increased adverse outcomes with TB during pregnancy

- **Mortality*** — **4-fold**
- **Morbidity** — **3-fold**
- **Hospitalization** — **10-fold**
- **Anemia** — **4-fold**
- **C-section** — **2-fold**
- **Miscarriage** — **9-fold**

*not significant

Maternal Outcomes

Study ID	OR (95% CI)	% weight	TB affected	TB total	Control affected	Control total
Maternal death						
A.Ali, 2011	5.25 (0.24, 112.66)	35.60	2	42	0	42
Tripathy, 2003	1.40 (0.08, 34.91)	32.34	1	111	0	51
Ricardo Figueroa- Damian- 1998	8.88 (0.35, 224.98)	32.06	1	26	0	75
Asuquo,2012	(Excluded)	0.00	0	24	0	72
N. Jana, 1994	(Excluded)	0.00	0	79	0	316
Subtotal ($I^2 = 0.0\%$, $P = 0.714$)	4.05 (0.65, 25.24)	100.00				
Maternal Morbidity						
Ricardo Figueroa- Damian- 2001	7.48 (2.09, 26.72)	10.75	8	35	4	105
N. Jana, 1999	2.05 (0.86, 4.88)	17.41	10	32	24	132
Ricardo Figueroa- Damian- 1998	4.57 (1.45, 14.37)	12.45	8	35	7	75
T.Bjerkedal, 1975	1.74 (1.34, 2.27)	34.02	62	542	8653	125 423
P.A. Kavganko, 2004	3.31 (1.89, 5.80)	25.37	58	98	39	120
Subtotal (I-squared = 60.3%, $P = 0.039$)	2.78 (1.70, 4.56)	100.00				
Antenatal admission						
N. Jana, 1999	9.58 (2.25, 40.80)	100.00	8	33	3	132
Subtotal ($I^2 = .\%$, $P = .$)	9.58 (2.25, 40.80)	100.00				
Anaemia						
A.Ali, 2011	3.08 (1.11, 8.56)	23.28	35	42	26	42
Adolfas Pranevièius,2003	6.70 (3.00, 14.97)	33.33	40	77	10	72
P.A. Kavganko, 2004	2.83 (1.47, 5.46)	43.38	32	98	18	120
Subtotal ($I^2 = 29.8\%$, $P = 0.241$)	3.55 (2.21, 5.71)	100.00				
C-section Delivery						
N. Jana, 1994	0.90 (0.45, 1.83)	22.80	11	79	48	316
N. Jana, 1999	3.44 (1.10, 10.74)	14.96	8	33	8	132
P.A. Kavganko, 2004	4.90 (1.95, 11.80)	18.93	22	98	7	120
T.Bjerkedal, 1975	2.38 (1.40, 4.06)	26.57	14	542	1238	112 530
Adolfas Pranevièius,2003	1.39 (0.50, 3.86)	16.73	10	77	7	72
Subtotal ($I^2 = 61.1\%$, $P = 0.036$)	2.10 (1.17, 3.79)	100.00				
Miscarriage						
T.Bjerkedal, 1975	8.06 (4.83, 16.67)	100.00	11	546	257	113 511
Subtotal ($I^2 = .\%$, $P = .$)	8.06 (4.83, 16.67)	100.00				

NOTE: weights are from random effects analysis

0.00444 | 1 | 225

Active TB better outcome | Active TB poorer outcomes

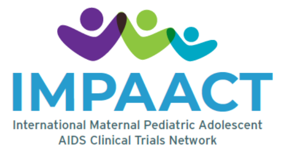
Includes:

3,384 pregnancies with active TB

and

119,448 without TB

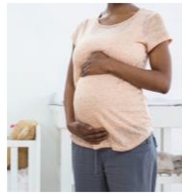
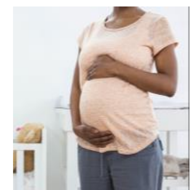
Sobhy BJOG 2017



WHO RR-TB treatment guidance 2022

Table A. List of recommendations in the 2022 update, where (a) is a new recommendation based on review of the new evidence and (b) is a reprinted recommendation where no new evidence was available or searched for the review.

1. The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen for MDR/RR-TB and pre-XDR-TB (a)	
1.1	WHO suggests the use of the 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than 9-month or longer (18-month) regimens in MDR/RR-TB patients. *(Conditional recommendation, very low certainty of evidence)*
2. The 9-month all-oral regimen for MDR/RR-TB (a)	
2.1	WHO suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded. *(Conditional recommendation, very low certainty of evidence)*
3. Longer regimens for MDR/RR-TB (b)	
3.1	In multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB) patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it. *(Conditional recommendation, very low certainty of evidence)*

	Group A: BDQ / LZD / FLQ Other: **Pretomanid**
	Group A: BDQ / LZD / FLQ Group B: CFZ Group C: PZA / EMB Other: high dose INH
	Group A: BDQ / LZD / FLQ Group B: CFZ / CS Group C: *(if options are limited)*

Existing peri-partum PK data for WHO Groups A & B drugs among people treated for RR-TB

WHO Group Drug Name	Group **A** Fluoroquinolones	Group **A** Bedaquiline	Group **A** Linezolid	Group **B** Clofazimine	Group **B** Terizidone
During pregnancy	Moxi: ♀ (n=1) *PK at 2T and 3T* *Van Kampenhout 2017*	♀♀♀♀♀♀♀♀♀ ♀♀♀♀ (n=13) *PK at ≥ 28 wks* *Court 2022*	♀ (n=1) *PK at 2T and 3T* *Van Kampenhout 2017*		
Post-partum	Moxi: ♀ (n=1) *PK at 8 wks PP* *Van Kampenhout 2017*	♀♀♀♀♀♀ (n=6) *PK at 6 wks PP* *Court 2022*	♀ (n=1) *PK at 8 wks PP* *Van Kampenhout 2017*		
Breastmilk and foetal transfer		FT: ♂♂♂♂ (n=4) BM: ♂ (n=1) *Court 2022*			
Safety	?? risk to foetus Assoc. with LBW	Sig. BM transfer Assoc. with LBW	Incr. exposures 2T → 3T → PP		

Recent / current PK studies of TB drugs in pregnancy

RECRUITING

Pharmacokinetic Properties of Antiretroviral and Anti-Tuberculosis Drugs During Pregnancy and Postpartum

IMPAACT 2026 (preceded by P1026s)

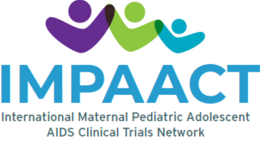
ClinicalTrials.gov ID NCT04518228

Sponsor National Institute of Allergy and Infectious Diseases (NIAID)

Information provided by National Institute of Allergy and Infectious Diseases (NIAID) (Responsible Party)

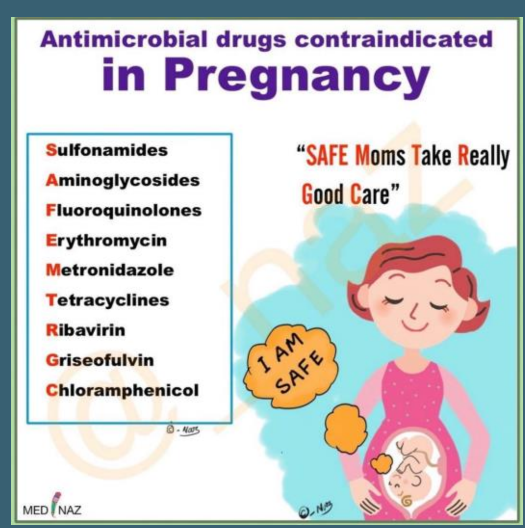
Last Update Posted 2023-01-05

- Sub-study of BEAT Tuberculosis (South Africa) – NCT04062201
- Observational cohort study in KZN, South Africa
- Others? *(Not published or on clinicaltrials.gov)*

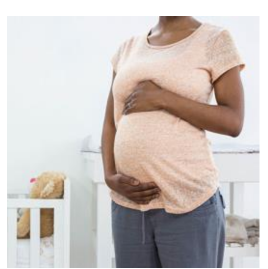


WHO GROUP	TB MEDICINE
Group A *Associated with better outcomes and mortality benefit*	Levofloxacin or Moxifloxacin
	Bedaquiline
	Linezolid
Group B *Associated with better outcomes*	Clofazimine
	Cycloserine / Terizidone
Group C *Potentially effective*	Ethambutol, delamanid, pyrazinamide, carbapenems, amikacin, ethionamide, PAS

RR-TB is treated for 6-18 mths with 4-5 effective drugs



2T (20-26 weeks) → 3T (30-38 weeks) → Delivery → 2-8 weeks post-partum

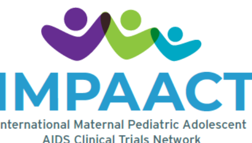


Intensive PK sampling:

pre-dose and 0, 2, 4, 6, 8, 12 hours post-dose

LFX plasma concentrations measured with HPLC TMSA

(P1026s)



Levofloxacin non-compartmental analysis results

Pharmacokinetic parameters	Second trimester (2T) (n = 6) Median [Q1, Q3]	Third trimester (3T) (n = 10) Median [Q1, Q3]	Post-partum (PP) (n = 8) Median [Q1, Q3]	2T vs PP (n = 4) GMR [90% CI]	3T vs PP (n = 7) GMR [90% CI]
C_{max} (µg/mL)	**10.31** [9.33, 12.10]	**10.55** [7.71, 11.00]	**10.61** [8.20, 12.70]	**0.86** [0.59, 1.25]	**0.98** [0.85, 1.12]
C_{min} (µg/mL)	**0.94** [0.85, 1.03]	**1.45** [0.04, 1.59]	**1.41** [0.16, 1.72]	**0.72** [0.17, 3.00]	**1.23** [0.24, 6.23]
AUC_{0-12} (µg*h/mL)	**69.01** [60.12, 77.14]	**77.64** [70.51, 85.05]	**80.23** [71.80, 97.73]	**0.75** [0.60, 0.95]	**0.94** [0.81, 1.08]
$T_{1/2}$ (h)	**6.28** [5.71, 6.64]	**8.71** [5.95, 10.19]	**8.17** [6.42, 9.30]	**0.84** [0.73, 0.97]	**1.11** [0.83, 1.50]
CL/F (litres/hr)	**13.43** [12.03, 15.45]	**12.88** [11.76, 14.18]	**11.38** [9.96, 13.64]	**1.33** [1.05, 1.67]	**1.07** [0.93, 1.23]
Vd/F (litres)	**108.92** [97.39, 159.31]	**167.86** [114.44, 206.86]	**134.96** [107.44, 198.01]	**1.12** [0.86, 1.44]	**1.16** [0.79, 1.72]

Cmax = maximum concentration; Cmin = minimum concentration; AUC = area under the curve; $T_{1/2}$ = half life; CL/F = clearance; Vd/F = volume of distribution; 2T = second trimester; Q1 = first quartile; Q3 = third quartile; 3T = third trimester; PP = post-partum; GMR = geometric mean ratio

Sociobehavioural research

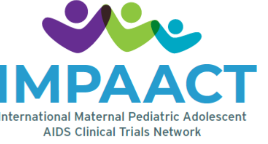
"What challenges do you encounter in accessing healthcare services while pregnant with RR-TB?"

"What concerns to you have about taking RR-TB drugs while pregnant? "

"What advice would you give to other people diagnosed with RR-TB while pregnant?"

- What are the perceptions, attitudes, beliefs, experiences and preferences of people receiving RR-TB treatment during pregnancy and post-partum?

- RR-TB diagnosed before vs after pregnancy test
- Stigma associated with RR-TB highlighted during pregnancy



THANKS!

Next steps: PK and safety 1026S: CFZ, MFX, Linezolid, BDQ: NCA and modeling

Any questions?

You can find me at

- jhughes@sun.ac.za