Maternal DS-TB Treatment & Prevention

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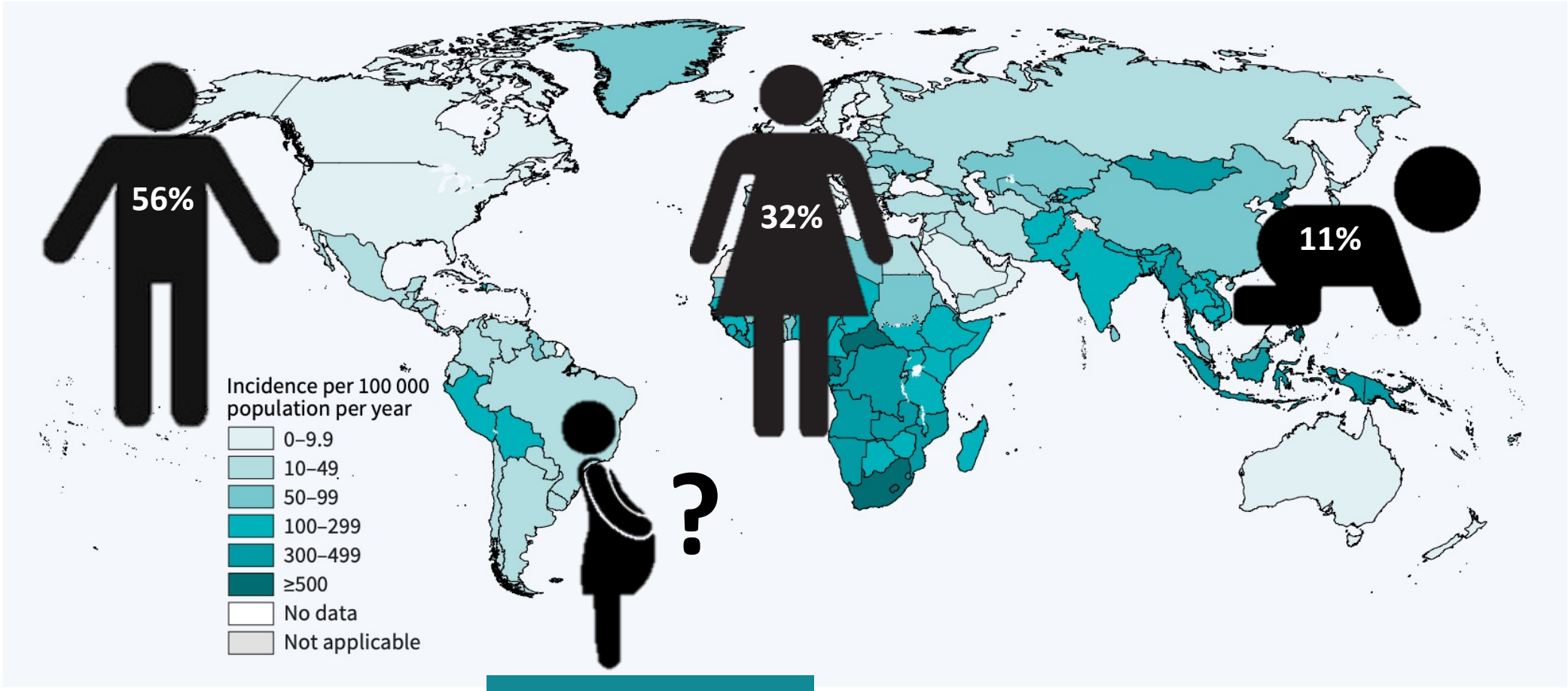
TB Burden in Pregnancy is Likely High but Unknown

10.6 million new diagnoses of TB disease in 2022

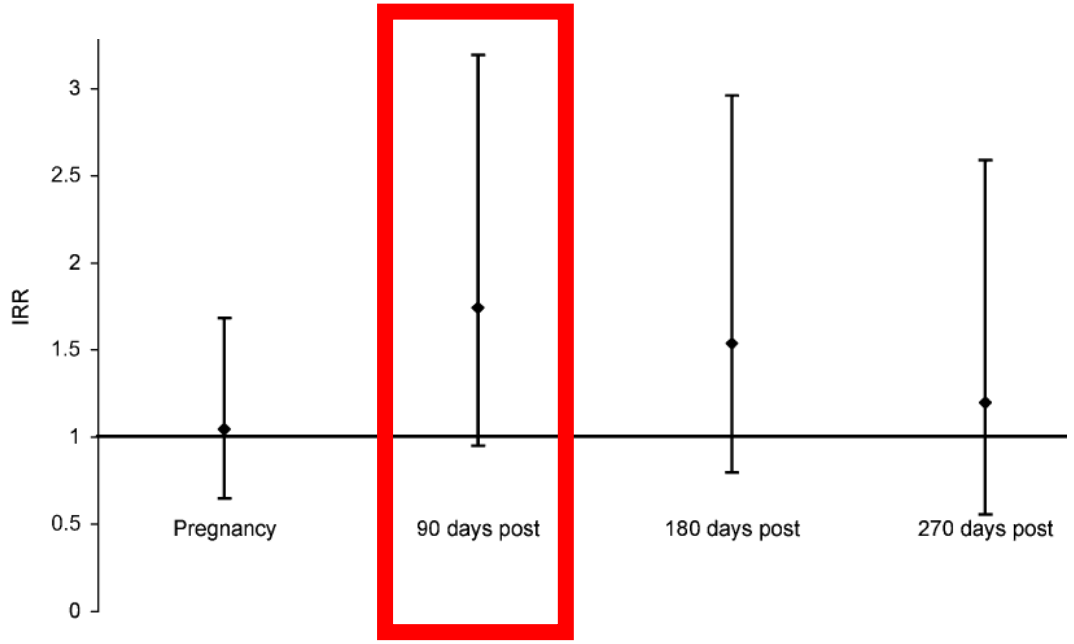


215,000 per year?

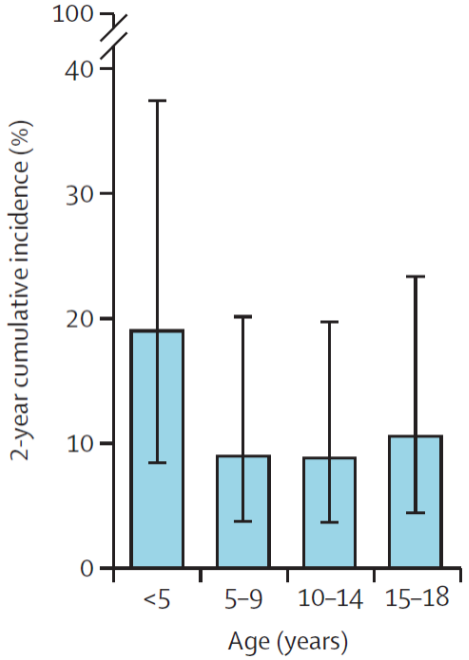
Slide adapted from Jyoti Mathad, Cornell

WHO Global TB Report 2022
Sugarman, et al. Lancet Global Health 2014

TB Risk in Peripartum Women and Children



TB incidence is **2x higher** postpartum than non-pregnant/non-postpartum



Other children in the household are also at high risk of disease

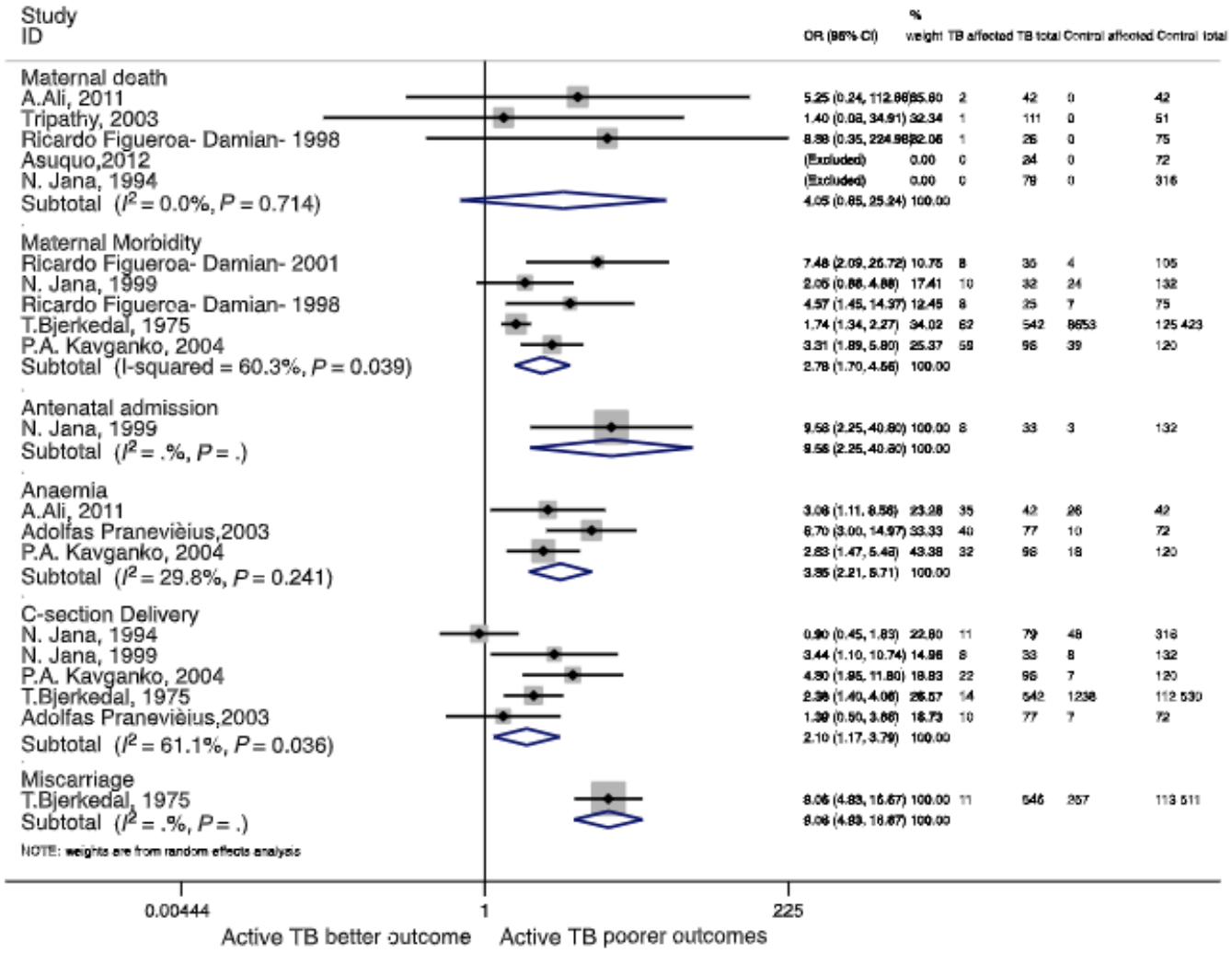
Zenner AJRCCM 2012

Slide adapted from Jyoti Mathad, Cornell

Martinez Lancet 2020

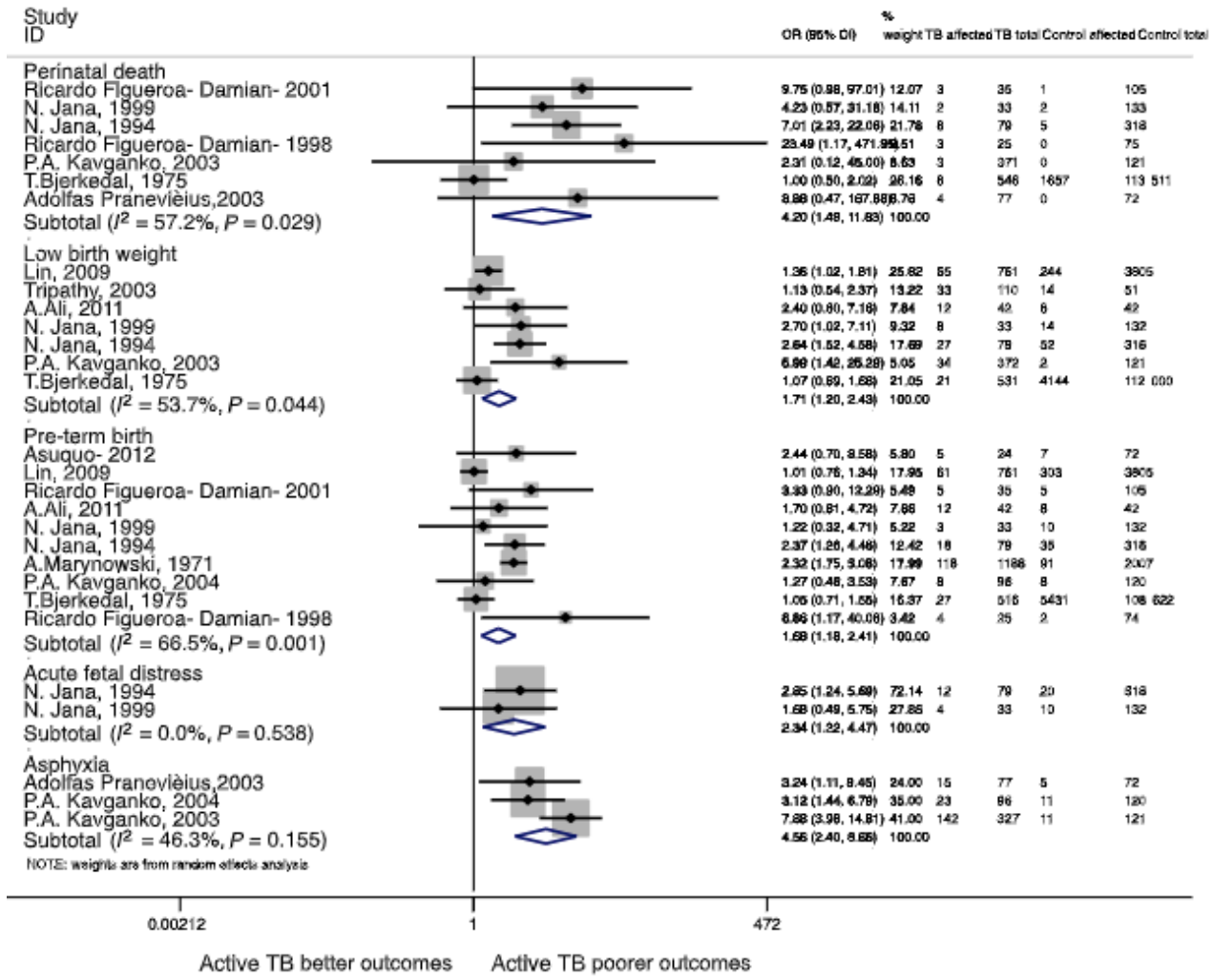
Increased Adverse Maternal and Pregnancy Outcomes

- 4-fold increased **maternal mortality**
- 3-fold increase **morbidity**
- 10-fold increased **hospitalization**
- 4-fold increase **anemia**
- 2-fold increase **cesarean**
- 9-fold increase **miscarriage**



Sobhy BJOG 2017

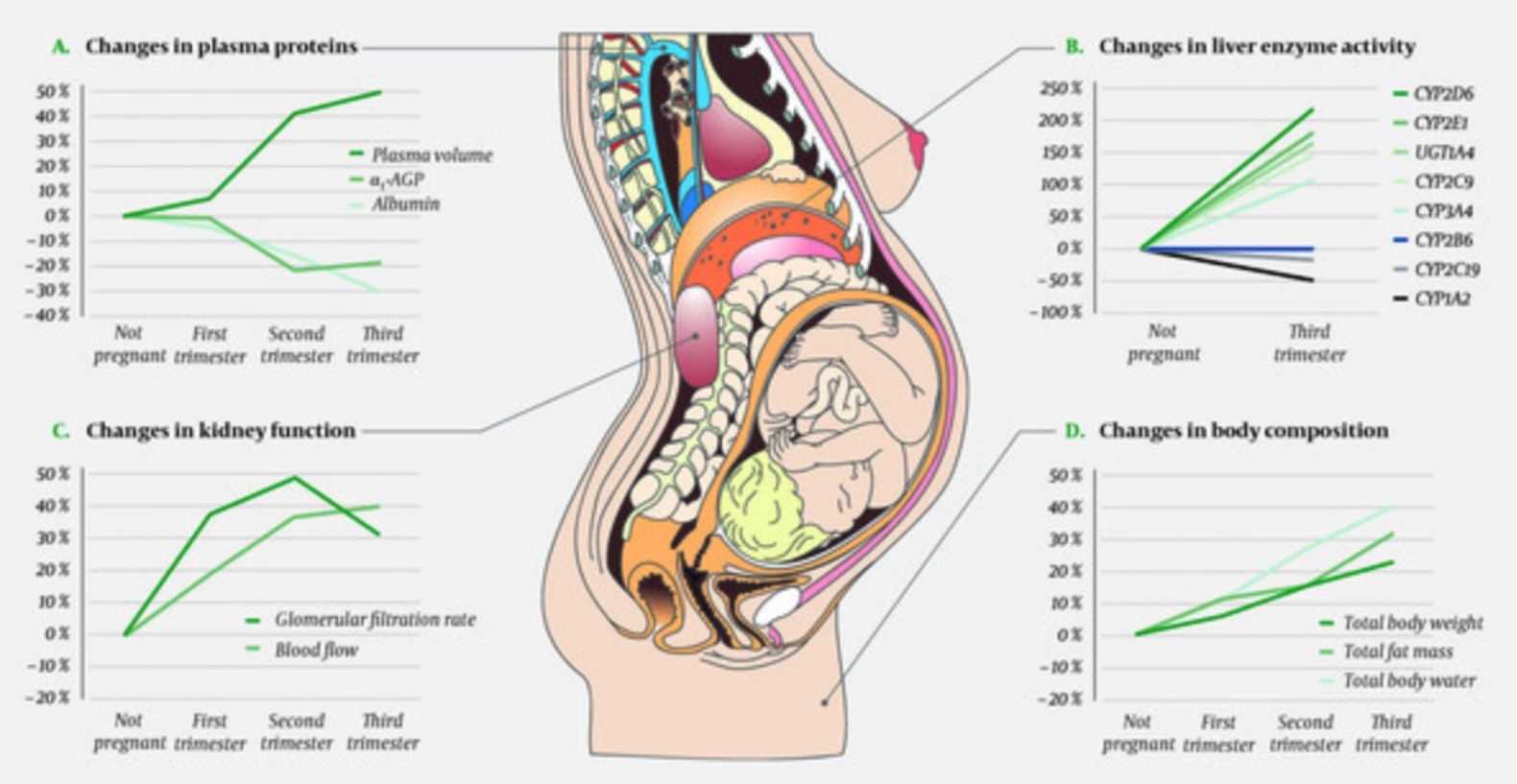
Increased Infant Adverse Outcomes



- 4-fold increased **perinatal death**
- 2-fold increase **LBW**
- 2-fold increased **PTB**
- 2-fold increase **acute fetal distress**
- 5-fold increase **birth asphyxia**

Sobhy BJOG 2017

Pregnancy-related Physiologic Changes that can Alter Drug Exposures



Key Physiologic Changes

- Changes in body composition
- Changes in plasma proteins
- Increased cardiac output
- Decreased lung capacity
- Changes in hepatic metabolism
- Decreased gastric emptying
- Decreased stomach pH
- Increased GFR

Tidsskr Nor Legeforen 2018

DS-TB Treatment during Pregnancy

Drug	Pharmacokinetics	Crosses Placenta	Fetal Toxicity	Chest feeding Compatibility	Terato-genicity	Concerns for Pregnant Persons
RIF	**No dose adjustment** Reduced CL in 3rd trimester (14%)	Yes	Hemorrhage	Yes (0.05-5%)	Yes	Many **DDIs** (DTG, PIs, OCP, etc.) Effect on embryo development in animals not humans **Bleeding risk**, may require vitamin K
INH	**No dose adjustment** Low exposures?*	Yes	CNS defects	Yes (< 5%)	No	**Hepatotoxicity** Possible Effects on embryo development, no teratogenicity
PZA	**No dose adjustment** No difference CL, F	**Unknown**	Jaundice	UD (excreted)	UD	**Unknown effect on fetus**; WHO and CDC recommendations differ
EMB	**No dose adjustment** No difference CL, F	Yes	Jaundice	UD (< 5%)	Yes	Increased teratogenicity (high doses) in animals but not humans

*Unclear if related to pregnancy, specimen handling, or NAT2

Gupta, et al. PLOS Medicine 2019; Abdelwahab, et al. AAC 2020; Denti, et al. AAC 2015

Pregnancy-related Immune Changes

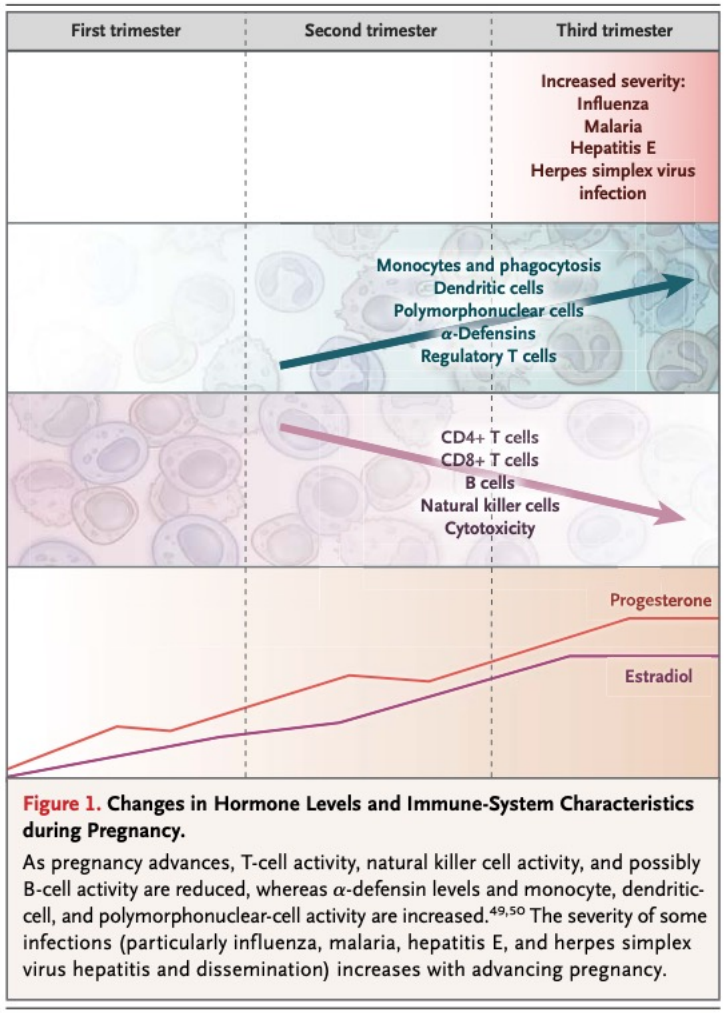


Figure 1. Changes in Hormone Levels and Immune-System Characteristics during Pregnancy.

As pregnancy advances, T-cell activity, natural killer cell activity, and possibly B-cell activity are reduced, whereas α-defensin levels and monocyte, dendritic-cell, and polymorphonuclear-cell activity are increased.[49,50] The severity of some infections (particularly influenza, malaria, hepatitis E, and herpes simplex virus hepatitis and dissemination) increases with advancing pregnancy.

- Immune alterations during pregnancy
  - May explain severity and susceptibility to some infections during pregnancy
  - Poorly understood
- Debate over whether:
  - Pregnancy increases TB risk
  - Pregnancy affects TB treatment outcomes

Do Pregnancy-related Immune Changes Alter DS-TB Treatment Outcomes?

DS-TB Treatment Outcomes in Pregnant Persons

- Cohort Cape Town, South Africa 2016:
  - 74 pregnant women with and without HIV diagnosed with TB in pregnancy or postpartum
  - 45% with unfavorable outcomes (LTFU 35%, Tx failure 3%, and Death 7%)
  - Poor outcomes associated with LBW infants (RR 3.8, CI 1.4-10.5)
  - Poor outcomes not associated with maternal HIV, EPTB, age, intra vs postpartum TB diagnosis, anemia, or bacteriologic confirmation
- Cohort Lima, Peru 2020
  - Women of child-bearing age with TB, with (n=36) and without (n=1298) pregnancy
  - 96.6% of pregnant vs 97.3% of non-pregnant women had successful treatment outcomes

When treated early and appropriately, pregnant persons can have successful TB treatment outcomes

Bekker, et al. PLoS One 2016; van der Water BMC ID 2020

HPMZ: What is Known About the Use of RPT and MFX During Pregnancy?

Drug	Pharmacokinetics	Crosses Placenta	Fetal Toxicity	Chest feeding Compatibility	Terato-genicity	Concerns for Pregnant Persons
RPT	**Unknown** Increases CL but no dose adj needed in 3HP	unknown	?	unknown	?	Many **DDIs** (DTG, PIs, OCP, etc.) **Unclear bleeding risk**, may require vitamin K
MFX	**No dose adjustment**	Yes	Possible bone	unknown	No	Increased teratogenicity (high doses) in animals but not humans
INH	**No dose adjustment** Low exposures?*	Yes	CNS defects	Yes (< 5%)	No	**Hepatotoxicity** Possible Effects on embryo development, no teratogenicity
PZA	**No dose adjustment** No difference CL, F	**Unknown**	Jaundice	UD (excreted)	UD	**Unknown effect on fetus**; WHO and CDC recommendations differ

Gupta, et al. PLOS Medicine 2019; Abdelwahab, et al. AAC 2020; Mathad, et al. CID 2022

RPT Use During Pregnancy

- Embryofetal toxicity and major fetal malformations in animal studies
  - Cleft palate, R aortic arch, delayed ossification, and increased ribs
  - ↓ BW & gestational survival
  - ↑ stillbirth, and ↑(slight) post-natal mortality

- PREVENT TB and iADHERE Trials of 3HP
  - No unexpected fetal loss or congenital anomalies
  - Preliminary reassurance when RPT needs to be used

- IMPAACT 2001
  - Generally safe, no treatment-related AEs (incl bleeding)
  - Not powered for safety

Moro, et. al, Annals ATS 2018; Mathad et al. CID 2022

FQ Restrictions in Pediatrics and Pregnancy are Largely Driven by Animal Studies

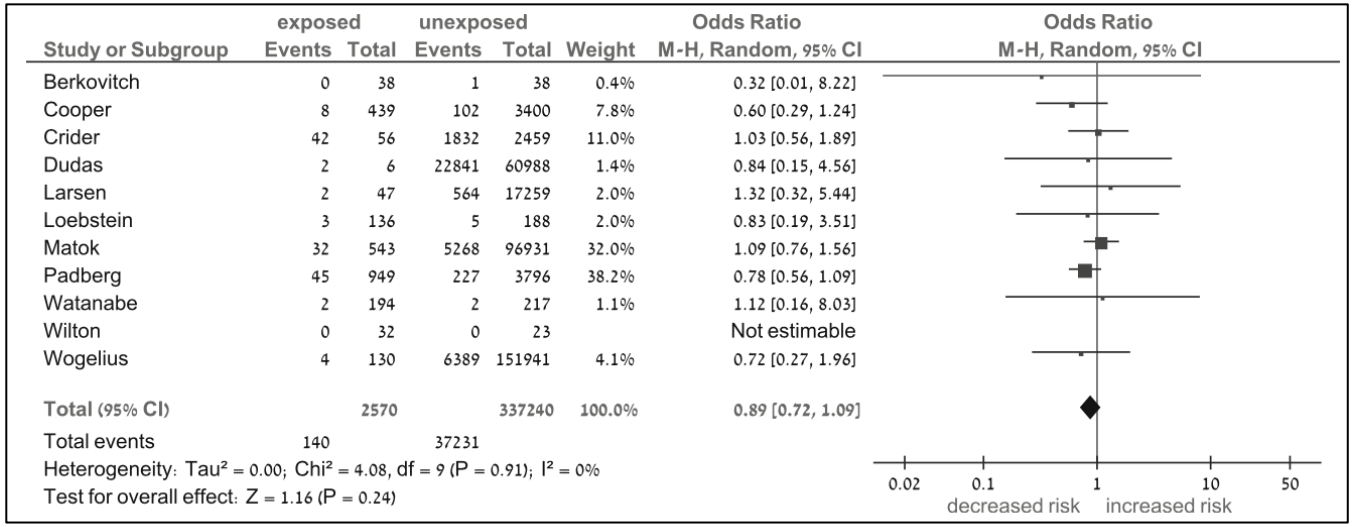
- FQ in Juvenile Beagle Dogs and Guinea Pigs
  - Cartilage damage and arthropathies → fetal bone malformation?

- Fetotoxicity but not teratogenicity in rats and rabbits
  - ↓ fetal birth weights, ↑ prenatal loss, ↑ neonatal death and ↑ therapy-related maternal mortality
  - Delayed fetal skeletal development
  - ↑ rib and vertebral malformations

- No adverse embryonic or fetal development *in monkeys*

Pregnancy Outcomes following FQ Exposure Systematic Review & Meta-analysis

- 12 studies
- 339,966 pregnancies
- >2500 FQ-exposed pregnancies
- Predominantly 1st trimester exposure



Study or Subgroup	exposed Events	exposed Total	unexposed Events	unexposed Total	Weight	Odds Ratio M-H, Random, 95% CI
Berkovitch	0	38	1	38	0.4%	0.32 [0.01, 8.22]
Cooper	8	439	102	3400	7.8%	0.60 [0.29, 1.24]
Crider	42	56	1832	2459	11.0%	1.03 [0.56, 1.89]
Dudas	2	6	22841	60988	1.4%	0.84 [0.15, 4.56]
Larsen	2	47	564	17259	2.0%	1.32 [0.32, 5.44]
Loebstein	3	136	5	188	2.0%	0.83 [0.19, 3.51]
Matok	32	543	5268	96931	32.0%	1.09 [0.76, 1.56]
Padberg	45	949	227	3796	38.2%	0.78 [0.56, 1.09]
Watanabe	2	194	2	217	1.1%	1.12 [0.16, 8.03]
Wilton	0	32	0	23		Not estimable
Wogelius	4	130	6389	151941	4.1%	0.72 [0.27, 1.96]
Total (95% CI)		2570		337240	100.0%	0.89 [0.72, 1.09]
Total events	140		37231			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 4.08$, df = 9 ($P = 0.91$); $I^2 = 0\%$

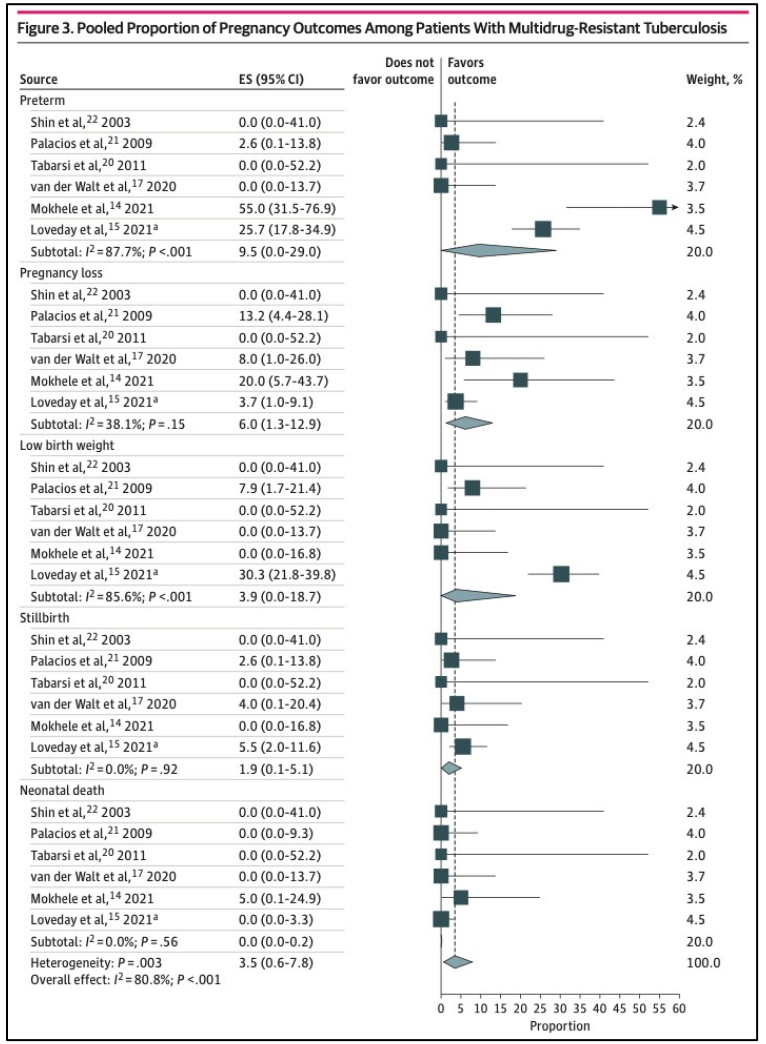
Test for overall effect: $Z = 1.16$ ($P = 0.24$)

- No increased risk of birth defects, stillbirths, prematurity or LBW with 1st trimester use
- Possible association between FQ use at any time of pregnancy and spontaneous abortion
  - Result driven by one study with important differences in controls
- Conclusion: Restrictions on prescribing FQ during the 1st trimester should be reconsidered
  - can lead to sub-optimal treatment of infection and undue excessive anxiety

Ziv, et al. Pharm Res 2018; Yefet et al. 2018; Loebstein, et. al. AAC 1998; Bar-Oz Eur J OBGYN and Repro Bio 2009

Safety of Prolonged MFX Use During Pregnancy

- Meta-analysis of 10 studies of DR-TB in pregnancy
- 288 women including 100+ on MFX
- Safety of prolonged FQ use during pregnancy
- Adverse Pregnancy Outcome
  - Prematurity, pregnancy loss, low birth weight, stillbirth
  - Similar/lower rates than gen population
  - No obvious safety concerns but small sample



Alene, et al. JAMA Network Open

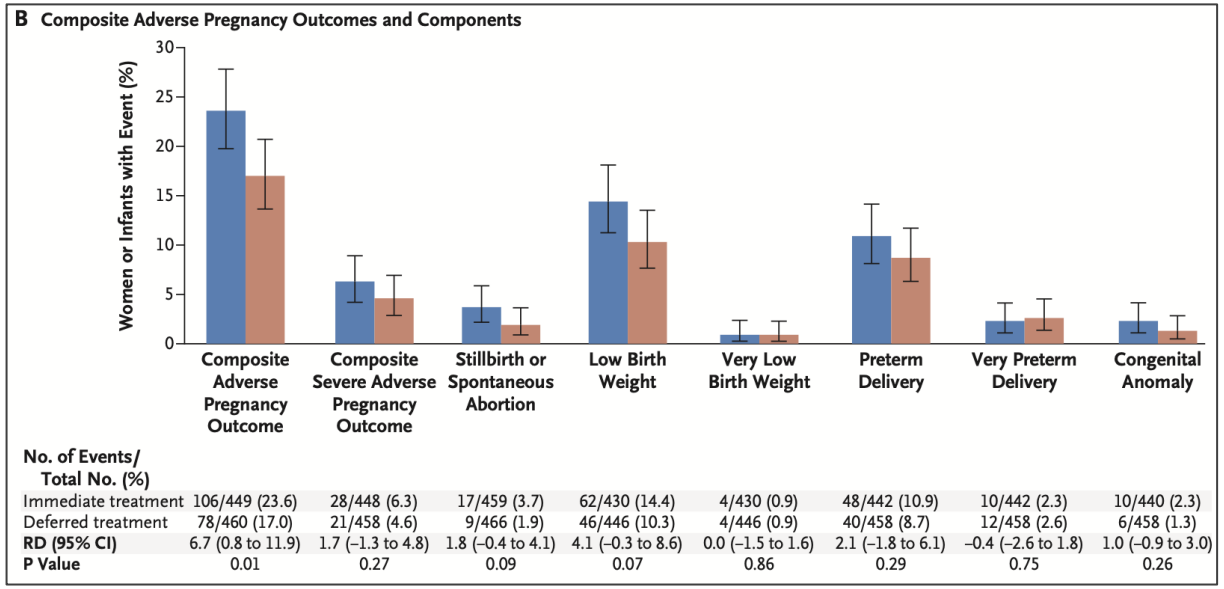
HPMZ for Pregnant Persons?

- Much disagreement about using moxifloxacin for DS-TB treatment
- No clear safety signals for H, P, M or Z in pregnant persons
- Evaluate its safety in a controlled setting with close follow up in a clinical trial setting

Maternal DS-TB Prevention

TB Apprise (P1078)

- Can IPT be safely initiated during pregnancy?
- Enrolled 956 HIV+ pregnant persons (14-34 weeks) in 8 high TB burden countries
- Randomized to initiate IPT during 2nd/3rd trimester vs postpartum

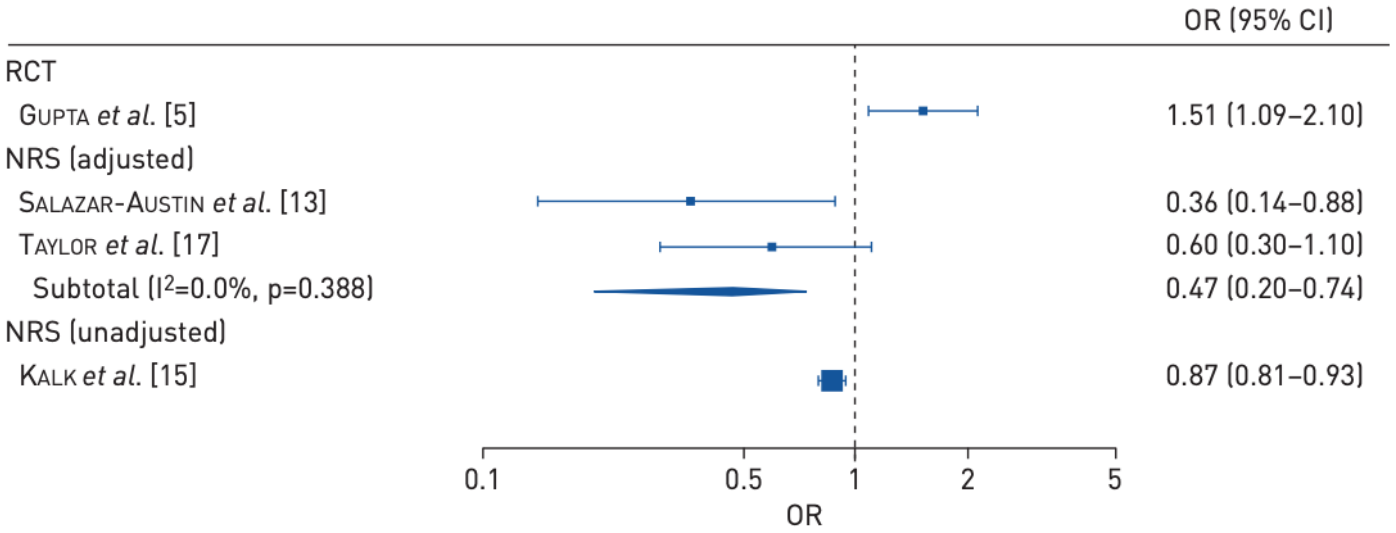


No. of Events/ Total No. (%)								
Immediate treatment	106/449 (23.6)	28/448 (6.3)	17/459 (3.7)	62/430 (14.4)	4/430 (0.9)	48/442 (10.9)	10/442 (2.3)	10/440 (2.3)
Deferred treatment	78/460 (17.0)	21/458 (4.6)	9/466 (1.9)	46/446 (10.3)	4/446 (0.9)	40/458 (8.7)	12/458 (2.6)	6/458 (1.3)
RD (95% CI)	6.7 (0.8 to 11.9)	1.7 (–1.3 to 4.8)	1.8 (–0.4 to 4.1)	4.1 (–0.3 to 8.6)	0.0 (–1.5 to 1.6)	2.1 (–1.8 to 6.1)	–0.4 (–2.6 to 1.8)	1.0 (–0.9 to 3.0)
P Value	0.01	0.27	0.09	0.07	0.86	0.29	0.75	0.26

- No differences in maternal or live-born infant outcomes, TB incidence or death
- More **adverse pregnancy outcomes** in those who received IPT during pregnancy than the postpartum period

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

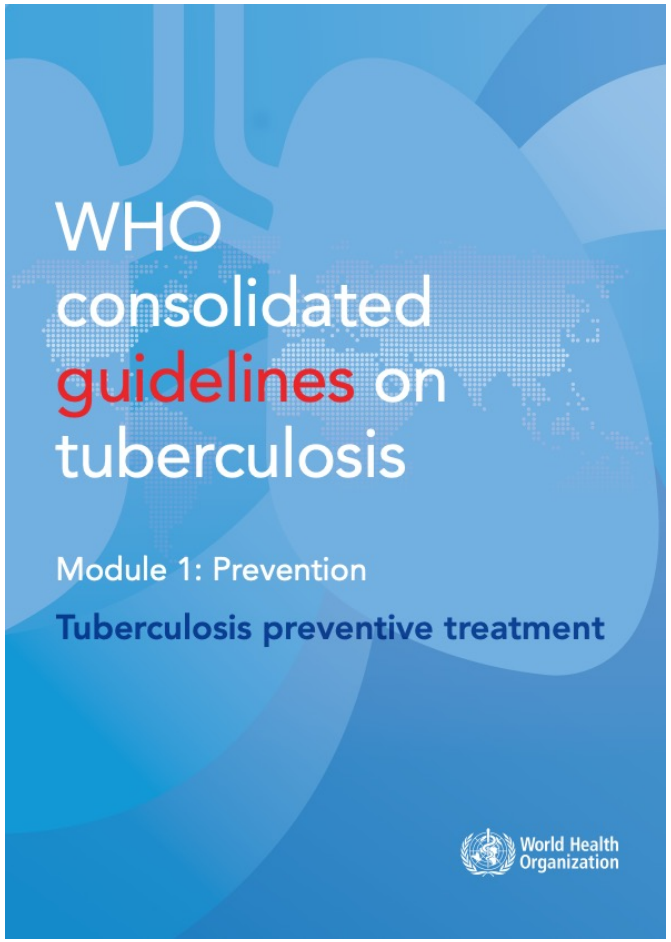
Composite Pregnancy Outcomes for Pregnant Persons with HIV with and without IPT



- **Inconsistent associations** between IPT and adverse pregnancy outcomes
- Weighing risk/benefit, **systematic deferral of IPT during pregnancy was not recommended**

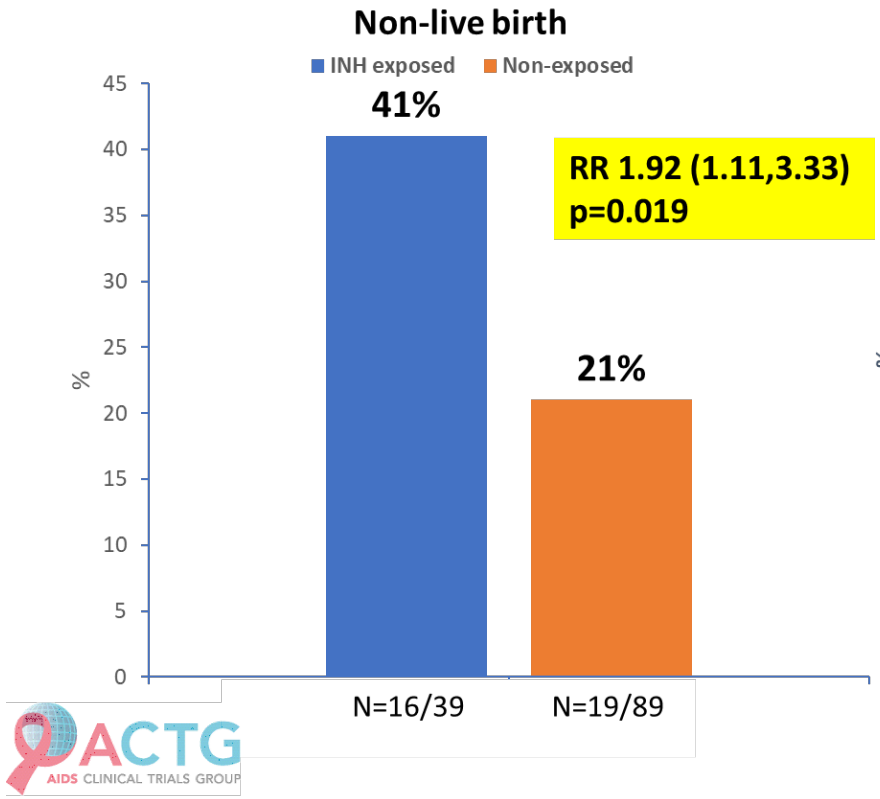
Hamada, et al. ERJ 2020

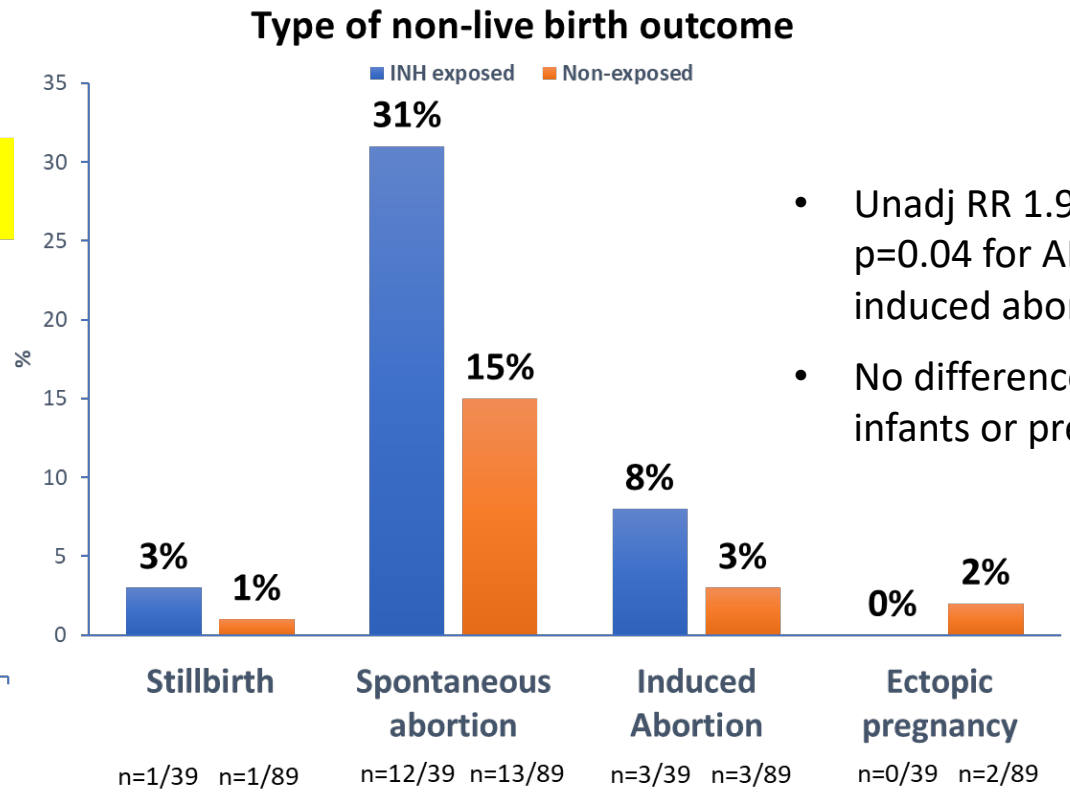
WHO Recommendation for TPT in Pregnant Persons



- Adults and adolescents living with HIV who are unlikely to have active TB should receive TPT as part of a comprehensive package of HIV care.
- Treatment should be given to those on antiretroviral treatment, **to pregnant women** and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable.
- *Strong recommendation, high certainty in the estimates of effect*

First Trimester INH Exposure and Pregnancy Outcome in A5279 / BRIEF-TB





- Unadj RR 1.94 (1.04, 3.61) p=0.04 for APO, excluding induced abortion
- No differences between LBW infants or preterm delivery

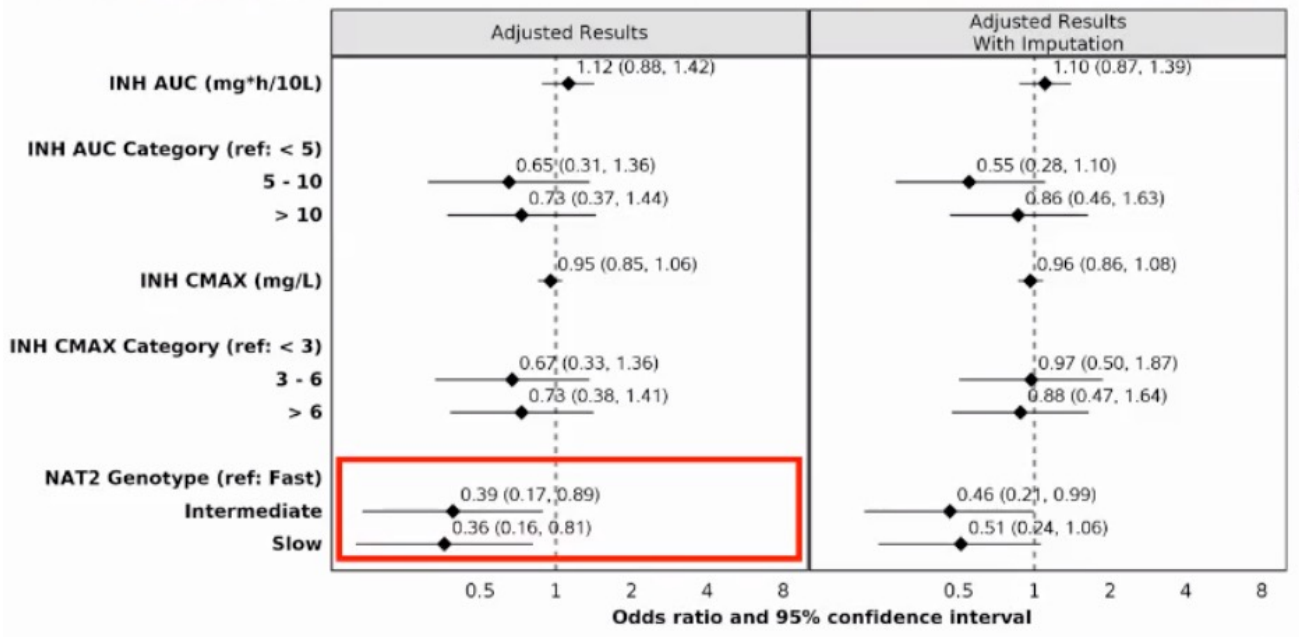
- First trimester INH exposure was associated with increased proportion of non-live births
- Counseling and contraception are needed for women of child-bearing age

Gupta, et al., CROI 2021

INH Acetylation Status May Predict Adverse Pregnancy Outcomes

Methods:

- Exploratory analysis
- Logistic regression with multiple imputation
  - Outcome associated with missing PK data
- Predictors:
  - INH & EFV exposures
  - INH acetylation status (NAT2)
  - EFV metabolism status (CYP2B6)
- Adjust: maternal age, CD4, VL, ART, MUAC, IGRA, pregnancy complications, smoking, hospitalization
- Outcome: Composite APO



Conclusions:

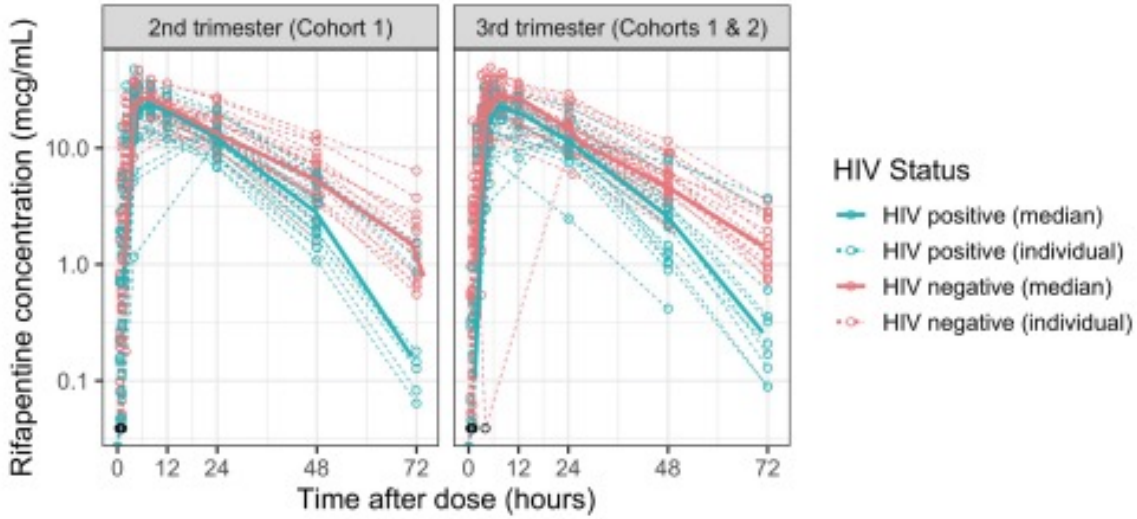
- Fast INH acetylators more likely to experience composite APO or have a LBW infant than intermediate/slow acetylators
- Not driven by INH exposures, may be driven by INH metabolites (?)

Aaron, et al., Union Conference 2022

IMPAACT 2001: PK & Safety of 3HP during Pregnancy

Methods

- 50 pregnant persons, 20 HIV+ on EFV
- 3HP initiated 2nd or 3rd trimester
- All with LTBI or recent contact



Parameter	HIV-positive	HIV-negative	% change vs. HIV-
Clearance, L/hr (RSE)	1.56 (7%)	1.20 (6%)	↑30%
AUC_{SS}, mg/L*hr (IQR)	522 (359-803)	786 (549-1171)	↓34%

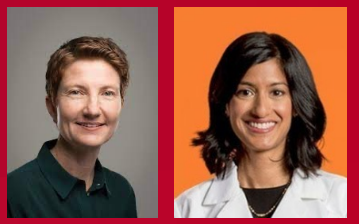
Conclusions

- No RPT dose adjustment needed
- Safe and tolerable, but **not powered for safety**
- Breastmilk and infant PK data pending

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Mathad, et al. CID 2022

DOLPHIN Moms Study Design



Phase IV RCT safety, tolerability of 1HP and 3HP with PK of DTG in pregnant women (20-34weeks gestation) with HIV

- **Design:** 2 arm, randomized, multicenter, open-label study
- **Study population:** Pregnant women with virally suppressed HIV on existing DTG-based ART
- **Primary outcome:**
  - Composite targeted safety and tolerability
    (maternal all-cause mortality, targeted SAEs, targeted pregnancy outcomes, permanent discontinuation 3HP or 1HP due to toxicity)
  - Population PK parameters DTG with and without HP (k_a, V_D, CI/F, AUC_{24} and C_t)
- **Duration:** 24 weeks postpartum (primary outcome at 12 weeks postpartum)

We hypothesize 1HP and 3HP will be similarly safe in pregnant women but will require DTG dose adjustment

2020 © IMPAACT4TB

TB Preventive Treatment during Pregnancy

Pregnancy is not a contraindication for TPT

Contraception should be offered to women of child-bearing age

Regimen	WHO assessed Safety	WHO/CDC Guidance	ART
6H	Safe for use* Some increased risk hepatoxicity	Preferred regimen B6 recommended while BF	No interaction
3RH	Safe for use*# Some increased risk hepatotoxicity Some increased risk bleeding	Recommended CDC: conditional	Interaction with DTG, PI, etc.
4R	May be safe, not safety/efficacy data available in this population# Some increased risk bleeding	Recommended CDC: conditional	Interaction with DTG, PI, etc.
3HP	Unknown	Not currently recommended	Interaction with DTG, need for dose adjustment unknown
1HP	Unknown	Not currently recommended	Interaction with DTG, need for dose adjustment unknown

*TB Apprise, use with caution. # Bleeding attributed to hypoprothrombinemia reported in infants and mothers following the use of rifampicin in late pregnancy. VitK recommended

Key Gaps in Maternal TB Treatment and Prevention

Treatment

- Can new shorter regimens be safely used for DS-TB and DR-TB in pregnancy and lactation?
  - BEAT-TB (BDLLC) – Union late breaker
  - HPMZ, BPALM, etc.
- Does dosing need to be modified?
  - IMPAACT 2026 (DS-TB and DR-TB drugs, not Pa)

Prevention

- What is the optimal timing to initiate TPT during pregnancy?
- Are short course regimens safe to use during pregnancy? – DOLPHIN Moms
- How should pregnant contacts of DR-TB patients be managed?

Optimized Approaches to Evaluate New Drugs and Regimens in Pregnancy

1. **Focused PK and safety studies** on DS-TB and DR-TB drugs and regimens
2. **Early inclusion** of children and women during second and third trimester and lactation in clinical trials
    - BEAT-TB
3. **Reconsent** women when pregnancy occurs allowing for informed choice to remain on study drug/regimen
    - endTB
4. **Pregnancy Registry** to improve our understanding of drug safety during pregnancy