Tuberculosis in Pregnant and Postpartum Women

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Hot Topics in TB

Heartland National TB Center in San Antonio, Texas

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- I have no financial relationships with commercial entities to disclose

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  - UNITAID
  - Indian Department of Biotechnology and Indian Council of Medical Research
  - Foundations (Gilead, Wyncote, Ujala)

- Any opinions expressed are my own and not of any of my sponsors.

Overview

- Global TB burden and epidemiology
- Impact on maternal-child health outcomes
- Screening for active disease and TB infection in pregnancy/ postpartum
- Treatment for TB and TBI
- Ongoing research

Patient Presentation

- HPI: 26 yo Indian female G2P1 @ 10 weeks gestational age presenting with vaginal bleeding and abdominal pain

- Diagnosed with pulmonary TB at ~6 weeks gestational age
  - Sputum AFB positive 2+
  - Anti TB therapy started

- Ultrasound now shows signs of gestational failure

BJMC, Sassoon Hospital Pune Case, Dr. Shilpa Naik

Case Report

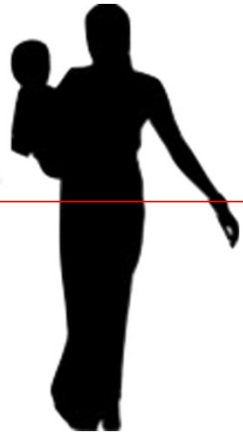
Untreated Active Tuberculosis in Pregnancy with Intraocular Dissemination: A Case Report and Review of the Literature

- 26 y.o. Ghanaian pregnant female with gestational diabetes and prior PPD+
- 4 months of cough
- No chest radiograph done until after delivery due to fear of radiation exposure
  - DELAY in diagnosis
- Dissemination to eye causing optic atrophy, chorioretinitis, uveitis
- Neonate separated from mother, formula fed and provided INH/B6

Rezai Case reports in Pulmonology 2015

Bedaquiline and Linezolid for Extensively Drug-Resistant Tuberculosis in Pregnant Woman

Marie Jaspard, Elisabeth Elefant-Amoura, Isabelle Melonio, Inès De Montgolfier, Nicolas Veziris, Eric Caumes

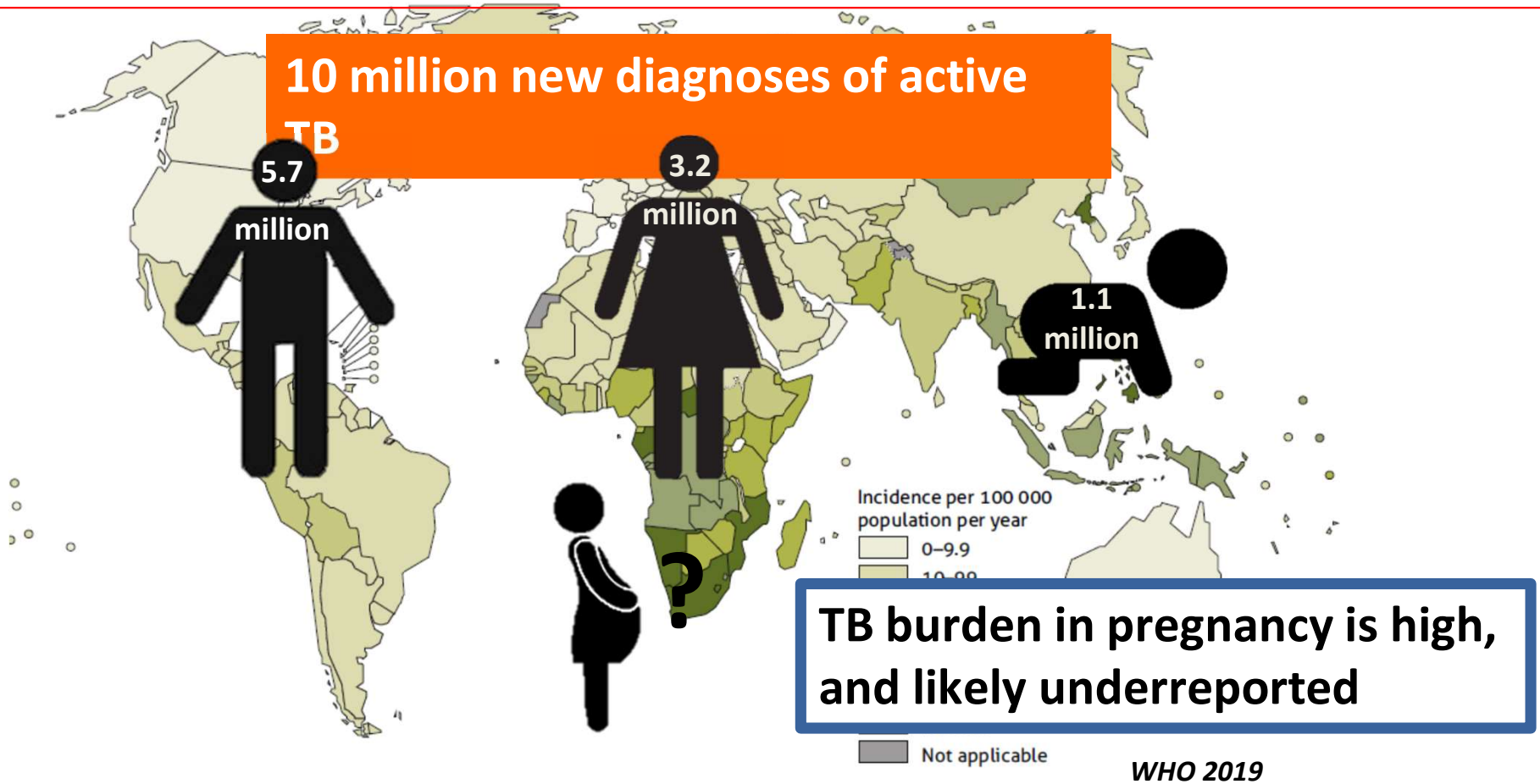


- 33 yo woman developed MDR TB in Republic of Georgia in 2008, relapsed in 2012 then developed XDR TB in 2014.
  - Incomplete treatment with PZA, cycloserine, PAS, amox/clav, capreomycin, levofloxacin, prothanimide, clarithro, clofazamine.
- Became pregnant and not on treatment. At 31 weeks sought care in France. She had chronic cough, cavitary lung lesion, no weight loss. Fetus had no abnormalities.
  - Resistance to INH, RIF, low level FQ, EMB, ethionamide, AG but susceptible to cycloserine, PAS, bedaqualline, linezolid
  - At 36 weeks gestation: **bedaqualline, linezolid** 600mg/d, PAS, cycloserine, levofloxacin initiated
  - At 39 weeks delivered FT healthy baby, placenta negative for MTB, infant negative for TB by gastric washings, Xray, and was separated from mom as still smear+
  - Mom completed 24 month treatment. Baby well at 2 years with normal growth

EID Vol 23, No 10, October 2017

What is the burden of TB in pregnancy?

Global TB burden



TB burden in pregnancy is high, and likely underreported

WHO 2019
Sugarman, Lancet Global Health 2014

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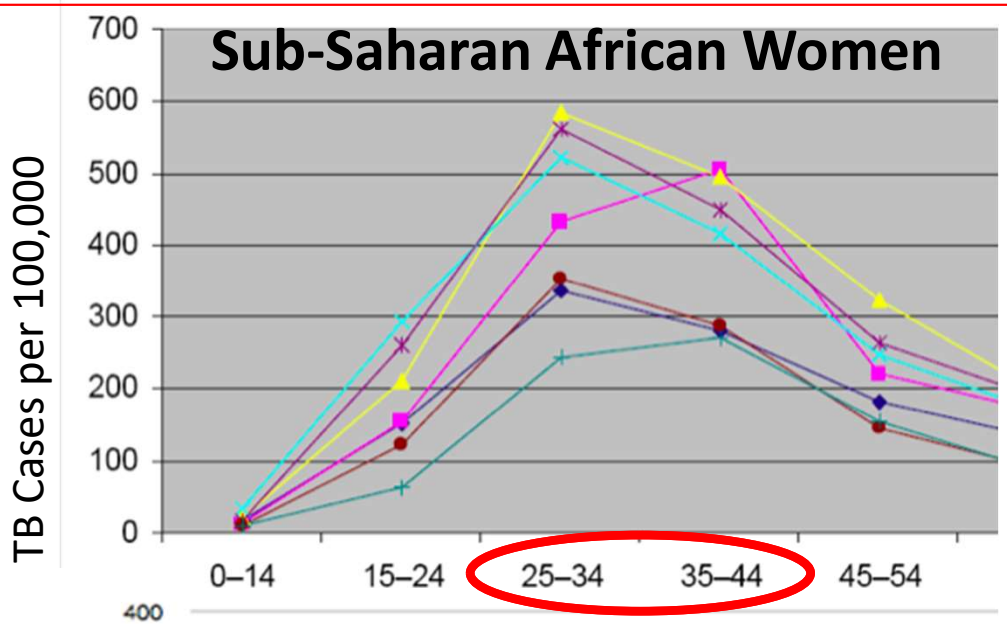
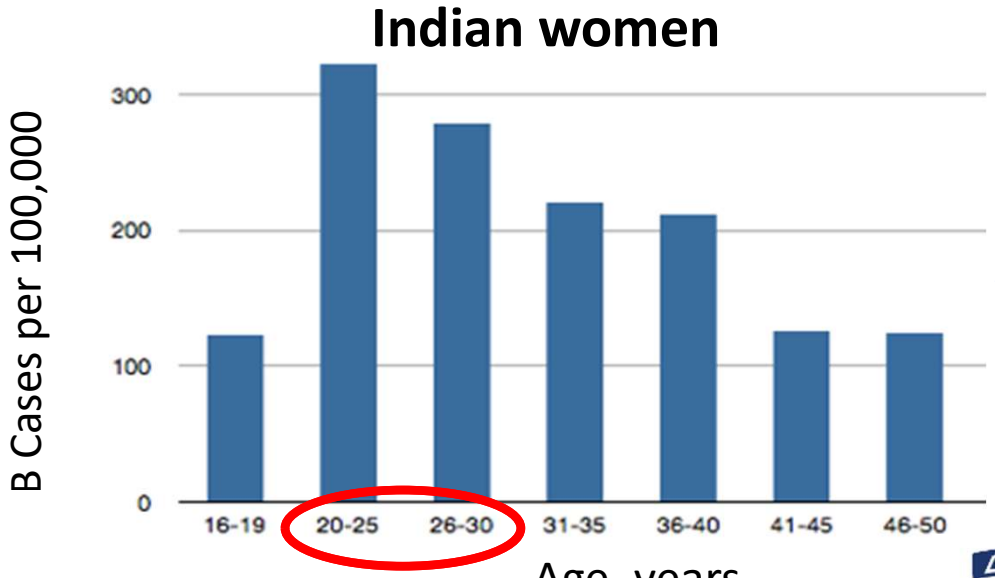
Peak TB incidence in women of reproductive age irrespective of HIV



Deluca JAIDS 2009



RNTCP: Gender differentials in TB control 2004

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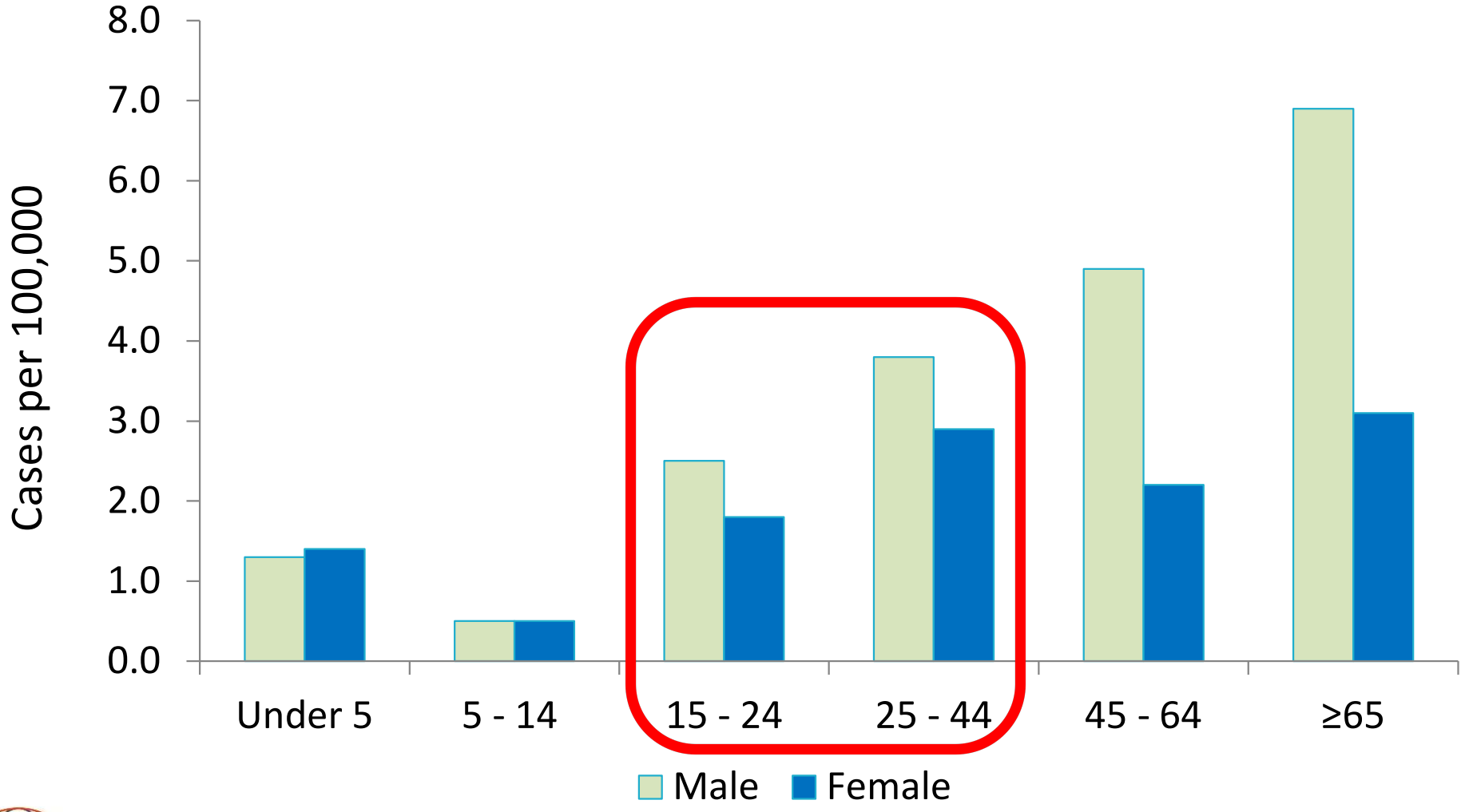
US TB Epidemiology

TB Case Rates by Age Group and Sex, United States, 2014



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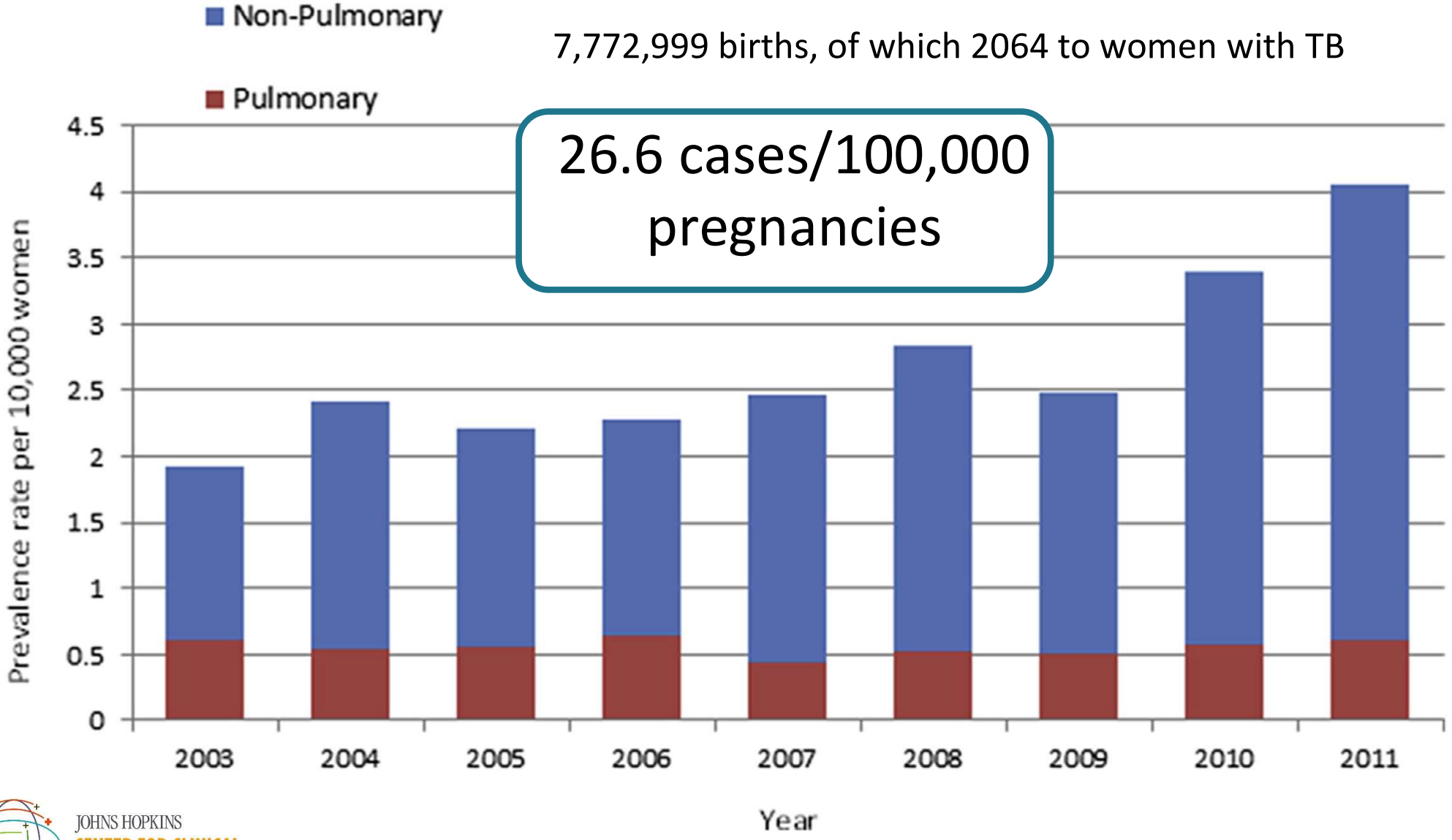
CDC 2014

US TB Epidemiology in Pregnancy

Prevalence of Pulmonary and Non-pulmonary TB, 2003-2011



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El-Messidi AJOG 2016

Prevalence of TB in pregnancy

- No national reporting for high burden countries
- Data based on individual screening studies

Active TB

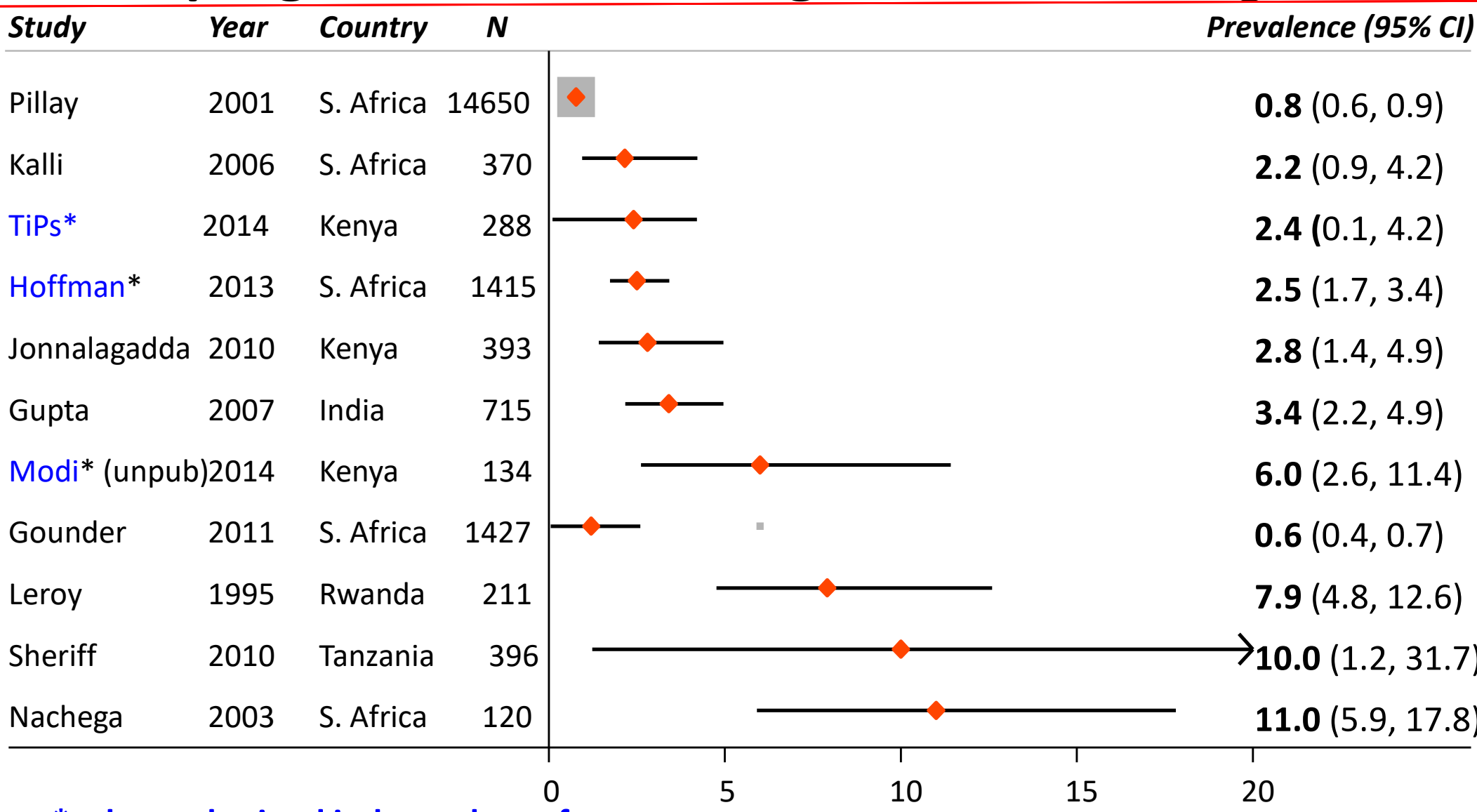
Study Site	HIV-negative	HIV-positive
Low burden countries	0.06-0.25%	1%
High-burden countries	0.07-0.53%	0.69-11%

Latent TB

Study Site	HIV-negative	HIV-positive
Low burden countries	10-23%	11-26%
High-burden countries	18-34%	21-49%

Mathad & Gupta, CID 2012

Prevalence of TB disease in HIV-infected pregnant women in high burden settings



*culture obtained independent of symptoms

Prevalence: 0.6-11%

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Slide courtesy of Sylvia LaCourse, Univ of Washington

Global estimate of TB in pregnancy

	Mean (95% uncertainty range)	Rate per 1000 pregnant women (95% uncertainty range)	Percentage of global burden
All countries combined	216 500 (192 100–247 000)	2·1 (1·8–2·4)	..
African Region	89 400 (74 200–110 500)	3·6 (3·0–4·5)	41%
Region of the Americas	4800 (3900–6000)	0·4 (0·3–0·5)	2%
Eastern Mediterranean Region	28 500 (19 700–41 900)	2·3 (1·6–3·4)	13%
European Region	4900 (3800–6300)	0·6 (0·5–0·8)	2%
South-East Asia Region	67 500 (52 000–87 100)	2·4 (1·9–3·1)	31%
Western Pacific Region	21 400 (19 400–23 700)	1·1 (1·0–1·2)	10%

Table 2: Total number of active tuberculosis cases in pregnant women, rate per 1000 pregnant women and percentage of global burden by WHO region and combined

Based on total population, crude birth rate, age distribution, TB case notification by age/sex

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Sugarman, Lancet Global Health 2014

Revisiting The Burden Of TB In Pregnant And Post-partum Women

WHO Region	Pregnancy	Postpartum
	Mean (95% uncertainty range)	Mean (95% uncertainty range)
All countries combined	150 600 (119 800, 181 300)	49 000(39 000, 59 000)
AFR	60 900 (48 300, 73 400)	19 000 (15 700, 23 900)
AMR	3 000 (2 500, 3 500)	1000 (800 , 1 100)
EMR	16 300 (9 000, 23 500)	5 300 (2 900, 7 700)
EUR	2 800 (2 100, 3 500)	900 (700, 1 100)
SEA	54 300 (27 700, 81 000)	17 700 (9 000, 26 400)
WPR	13 300 (8 500, 18 200)	4 300 (2 800, 5 900)

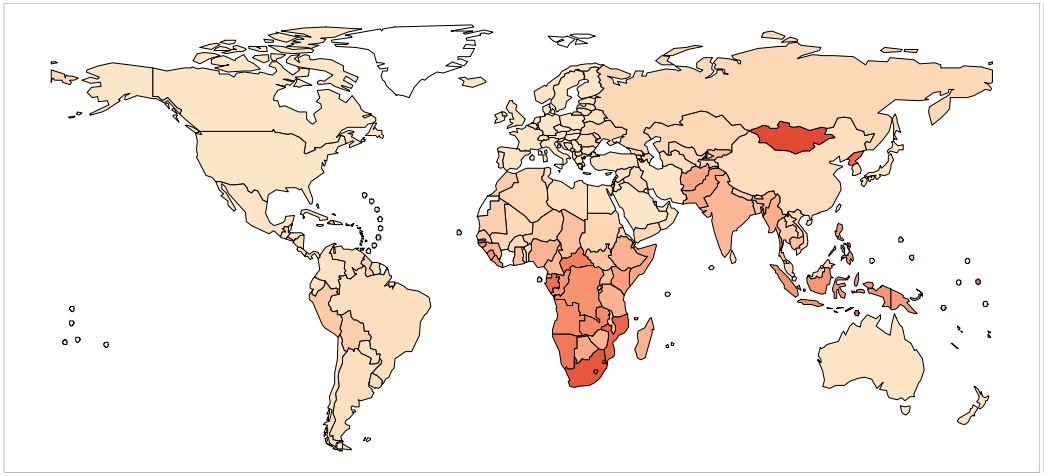
+ Prevalence potentially lower than previously estimated

- Data on TB in pregnancy and postpartum not routinely collected

HOW DO WE IMPROVE OUR ESTIMATES IF WE DON'T ACTUALLY REPORT TB CASES IN PREGNANCY?

Mafirakureva Union Conference 2019

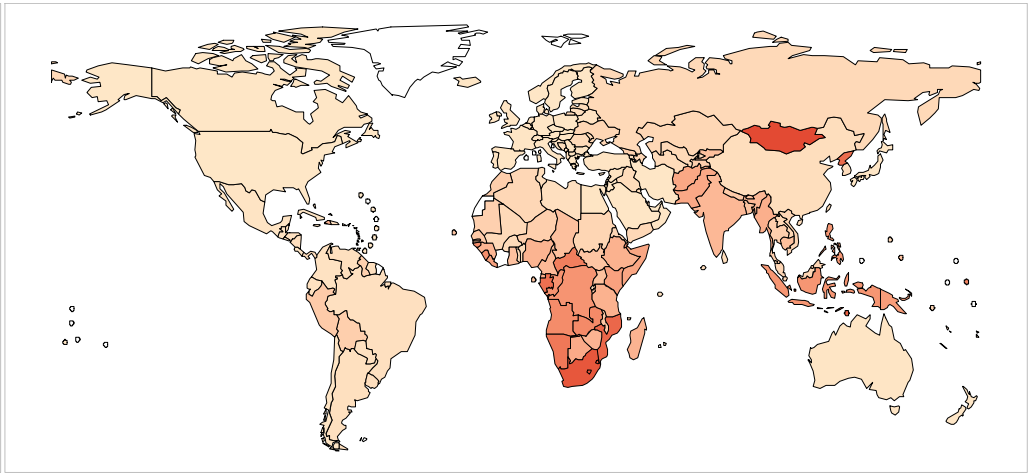
Revisiting The Burden Of TB In Pregnant And Post-partum Women



Estimated number of TB incident cases per 1000 pregnant women

0 1 2 3 4

PREGNANCY



Estimated number of TB incident cases per 1000 pregnant women

0.0 0.5 1.0

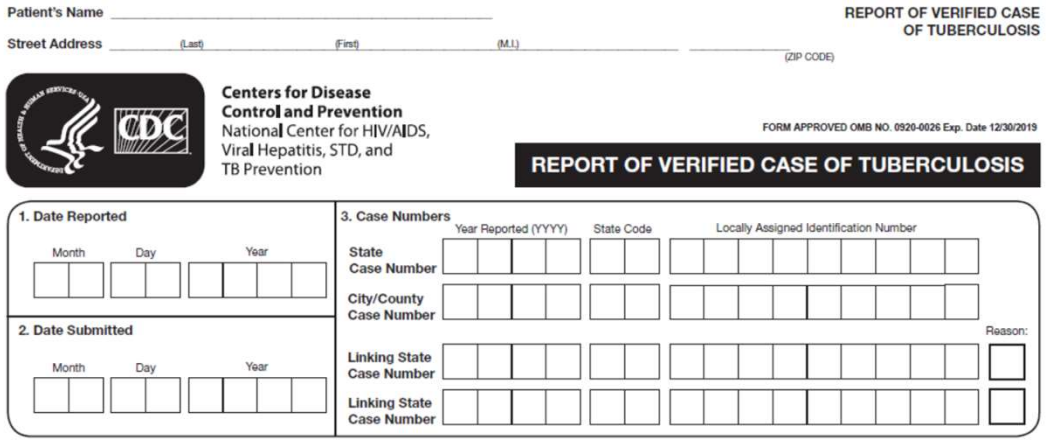
POSTPARTUM

HOW DO WE GET PREGNANCY ESTIMATES IN FUTURE GLOBAL TB REPORTS?

Mafirakureva Union Conference 2019

Pregnancy Status In The U.S. National Tuberculosis Surveillance System (NTSS)

- TB in pregnancy not currently captured under routine surveillance in US
- CDC 2020 Revision of the Report of Verified Case of Tuberculosis (RVCT)
- Opportunity to improve our understanding of TB outcomes among pregnant women using surveillance data



Patient's Name _____ REPORT OF VERIFIED CASE OF TUBERCULOSIS

Street Address _____ (Last) _____ (First) _____ (M.I.) _____ (ZIP CODE)

Centers for Disease Control and Prevention
National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

FORM APPROVED OMB NO. 0920-0026 Exp. Date 12/30/2019

REPORT OF VERIFIED CASE OF TUBERCULOSIS

1. Date Reported — Month Day Year

2. Date Submitted — Month Day Year

3. Case Numbers — Year Reported (YYYY) | State Code | Locally Assigned Identification Number

State Case Number

City/County Case Number

Reason:

Linking State Case Number

Linking State Case Number

The "wish list":

- ✅ Pregnancy
- ✅ Gestational age
- ✅ Postpartum
- ✅ Infant outcome

Brostrom Union Conference 2019

Pregnancy Status In The U.S. National Tuberculosis Surveillance System (NTSS)

Comprehensive Pregnancy Variables Considered

Demographics

If female, pregnancy status of the patient at time of diagnostic evaluation:

___delivered or miscarried within 12 weeks prior to TB diagnosis

___pregnant at the time of diagnostic evaluation

___no pregnancy

___unknown

Additional Risk Factors

___delivered or miscarried within 12 weeks prior to diagnosis

___undergoing IVF or other fertility trtmt

Final TB Disease Case Outcome

If pregnant at the time of diagnostic evaluation or pregnant during treatment:

___maternal complications during delivery

___spontaneous or induced abortion

___live or still birth

___premature birth

___low birth weight

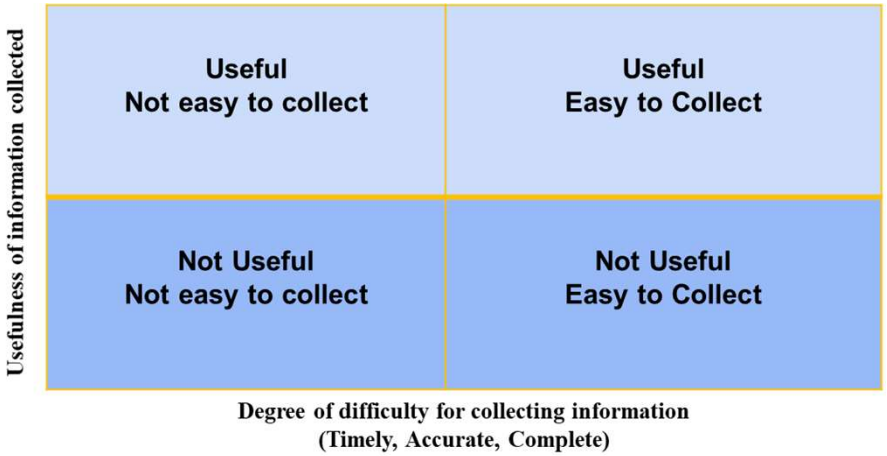
___congenital abnormality (specify)

___fetal death

___maternal death

___TB transmission to infant

Pregnancy Status In The U.S. National Tuberculosis Surveillance System (NTSS)



✅ **Pregnancy**

☑ Gestational age

☑ Postpartum

☑ Infant outcome

Some of the New Questions Added:

Is the Patient Pregnant? (Yes/No/Unknown)

CD4 results for patients with reported positive HIV status

A1c results for with diabetes mellitus

IS PREGNANCY STATUS OF TB CASES ROUTINELY COLLECTED IN YOUR SETTING?

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Impact of Maternal TB on maternal-infant outcomes?

Risk of complications in pregnancy TB vs. no TB

Maternal complications

- Pre-eclampsia & eclampsia (2 fold)
- Vaginal bleeding (2 fold)
- Hospitalization (12 fold)
- Miscarriage (10 fold)
- Increased maternal mortality

Jana Int J Gyn Obstet 1994
Jana NEJM 1999
Chin HC BJOG 2010
Bjerkedal 1975

Bothalmley 2001
Pillay Lancet ID 2000;
Mathad CID 2012
Gupta CID 2007

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Risk of complications in pregnancy TB vs. no TB

Fetal and infant complications

- Fetal death (increased)
- Low birth weight (2 fold)
- Lower Apgar scores
- Prematurity (2 fold)
- Small for gestational age (2 fold)
- Perinatal death (increased)
- congenital TB (rare)
- Increased HIV transmission (2 fold)

Jana Int J Gyn Obstet 1994
Jana NEJM 1999
Chin HC BJOG 2010

Khan AIDS 2001;
Pillay Lancet ID 2000;
Gupta JID 2011

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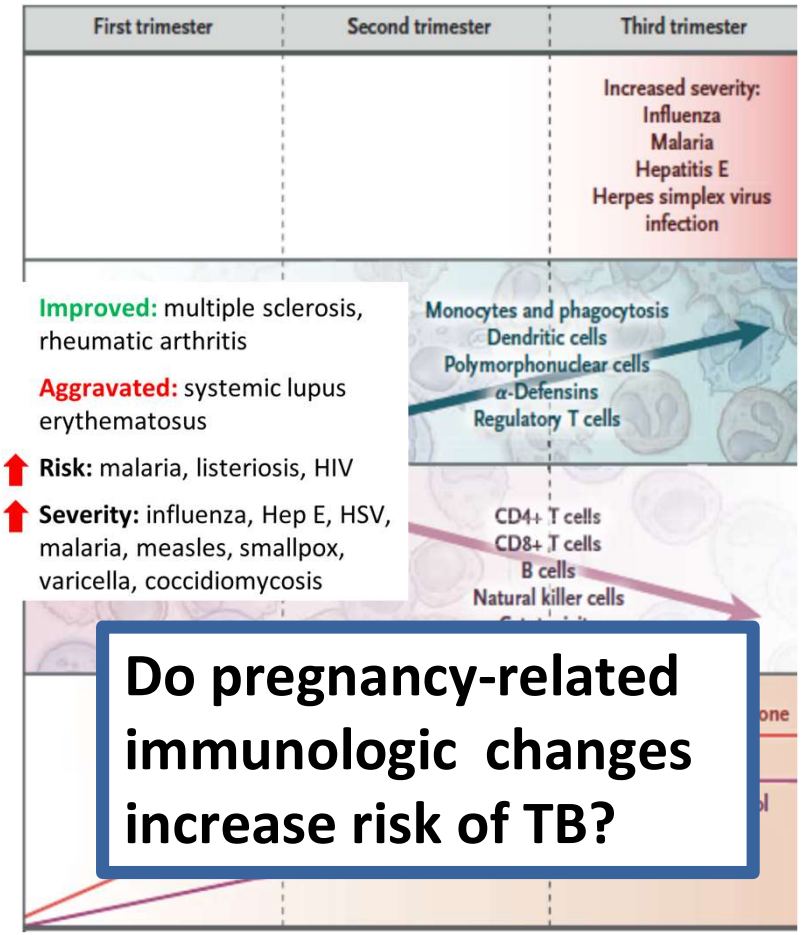
Mother to child transmission of TB

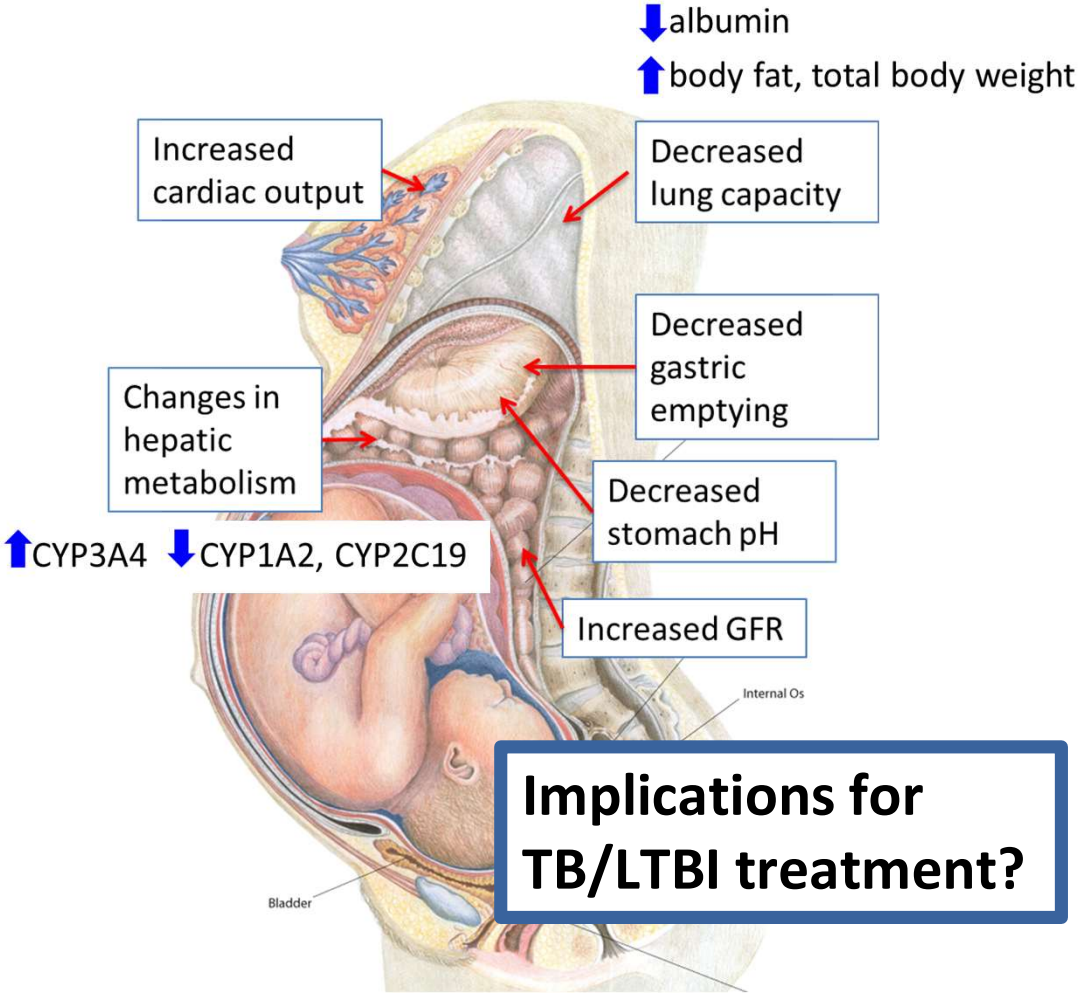
- In utero
  - Hematogenous dissemination via the umbilical vein
  - Aspiration/ingestion of infected amniotic fluid
- Intrapartum
  - Aspiration/ingestion of infected amniotic fluid or genital secretions
- Postpartum
  - Inhalation/ingestion of respiratory droplets from the mother
  - Ingestion of infected breast milk

Does pregnancy or the postpartum period increase the risk of TB acquisition? reactivation? severity?

Pregnancy-related immunologic and physiologic changes



Do pregnancy-related immunologic changes increase risk of TB?



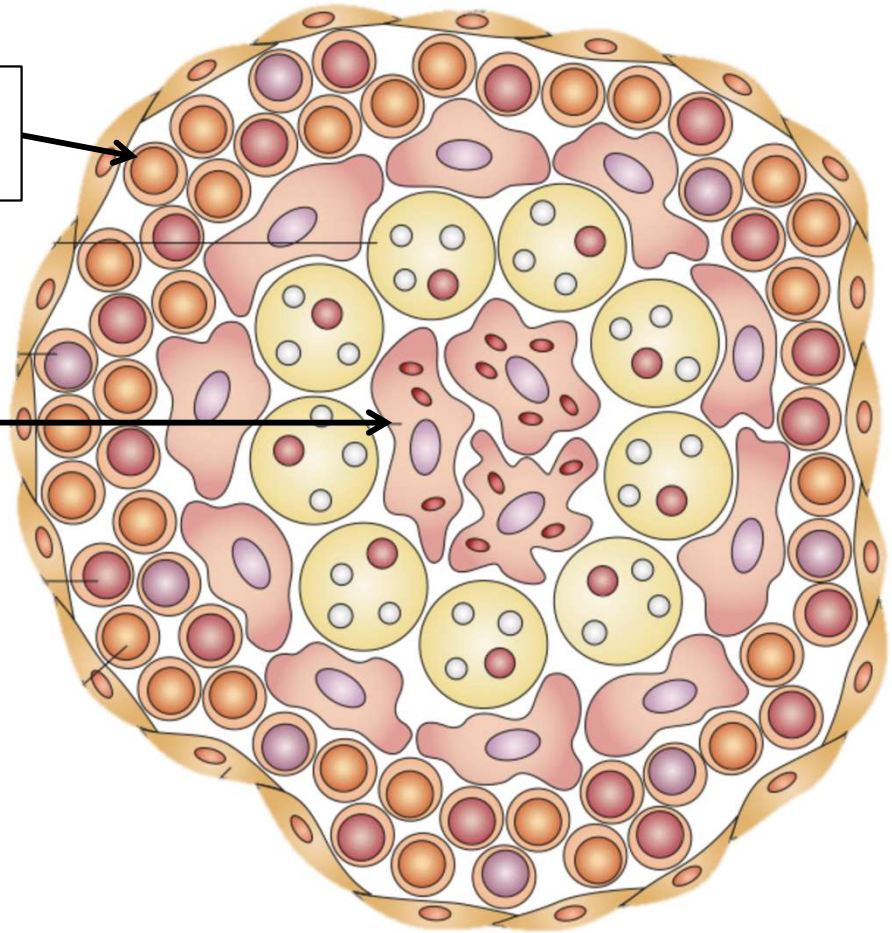
Implications for TB/LTBI treatment?

Kourtis NEJM 2014
Frederiksen Sem Perinatol 2001
Anderson Clin PK 2005

Immune control of TB needs Th1 cytokines

CD4+ T cells release IFN-γ, TNF-α

IFN-γ, TNF-α stimulate macrophages



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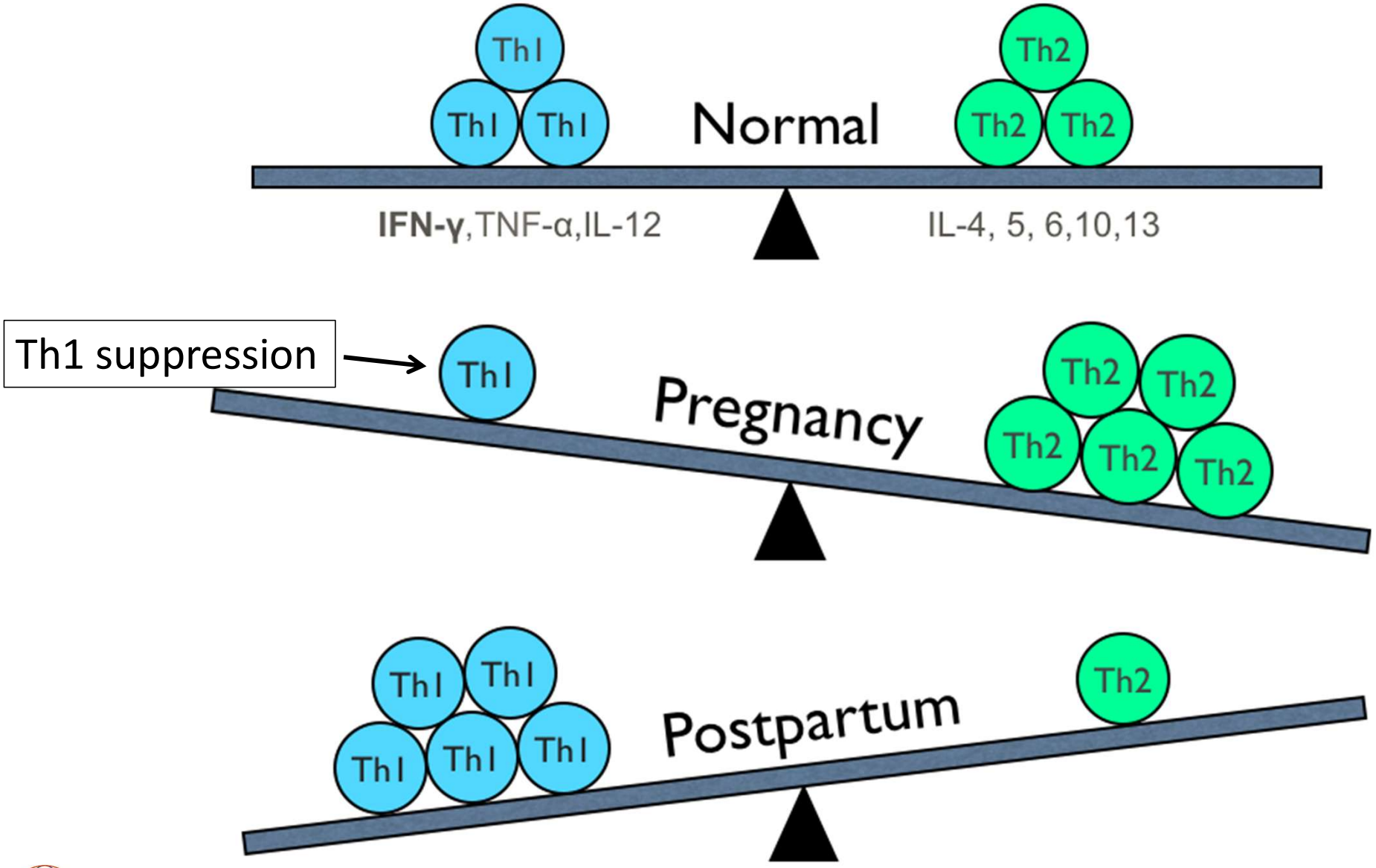
Adapted from Griffiths, Nat Med Review 2010

Biological plausibility?
Immunology of pregnancy & TB



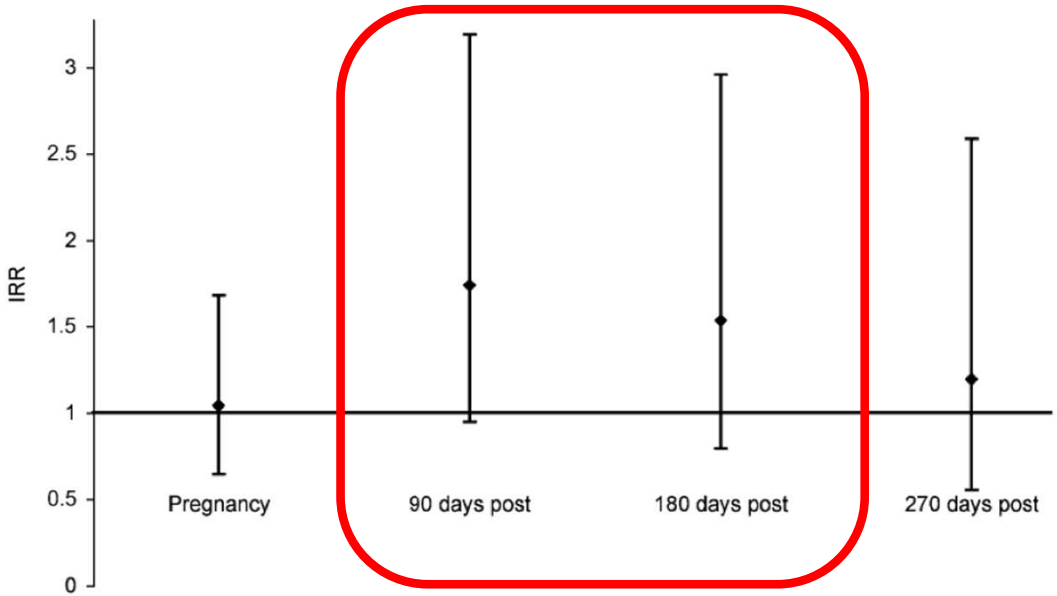
Adapted from Sykes, Mediators Inflamm 2012

Risk of TB in Pregnancy

Impact on TB reactivation and severity debated

Clinical data limited and were not consistent or convincing
(*Good Am. J. Obstet. Gynecol 1981, Carter Chest 1994, Espinal 1996;Sterling 2007)*

	TB Events (n)	Person-Years	IR	95% CI (IR)	IRR	95% CI (IRR)	*P* Value
Outside of pregnancy*	133	1,459,203	9.11	7.63–10.8	1.00	Reference category	
During pregnancy	22	171,765	12.81	8.03–19.39	1.29	0.82–2.03	0.3
6 mo postpregnancy	22	114,866	19.15	12–29	1.95	1.24–3.07	0.004



UK cohort: TB incidence 2x higher postpartum vs non-pregnancy times

India HIV-infected cohort of women

<10% on combination ART

Majority of cases occurred within 120 days postpartum

Postpartum Tuberculosis Incidence and Mortality among HIV-Infected Women and Their Infants in Pune, India, 2002–2005

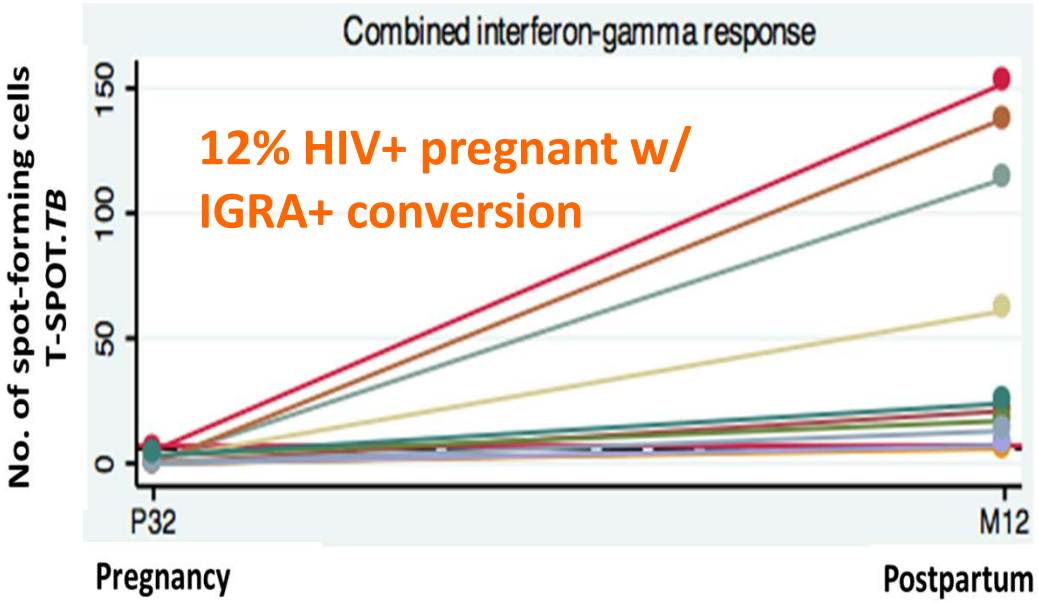
Amita Gupta,[1] Uma Nayak,[2] Malathi Ram,[2] Ramesh Bhosale,[3] Sandesh Patil,[3] Anita Basavraj,[3] Arjun Kakrani,[3] Sheeja Philip,[4] Dipali Desai,[3] Jayagowri Sastry,[4] and Robert C. Bollinger,[1,2] for the Byramjee Jeejeebhoy Medical College–Johns Hopkins University Study Group

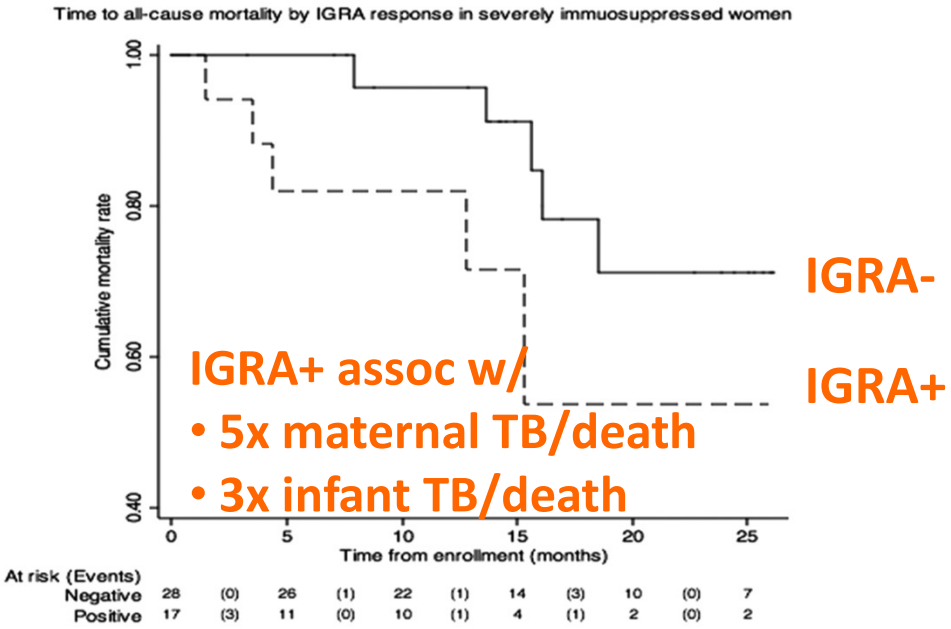
[1]Infectious Diseases, Johns Hopkins University School of Medicine, and [2]Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland; and [3]Byramjee Jeejeebhoy Medical College and [4]Byramjee Jeejeebhoy Medical College–Johns Hopkins University Maternal Infant Transmission Study, Pune, India

(See the editorial commentary by Mofenson and Laughon on pages 250–3)

Peripartum risk of MTB infection and disease progression

- **Cohort Kenyan pregnant HIV+ women pre-ART roll-out**



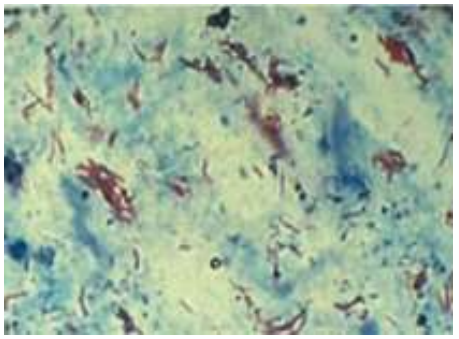


Jonnalagadda IJTLD 2015
Jonnalagadda JID 2010

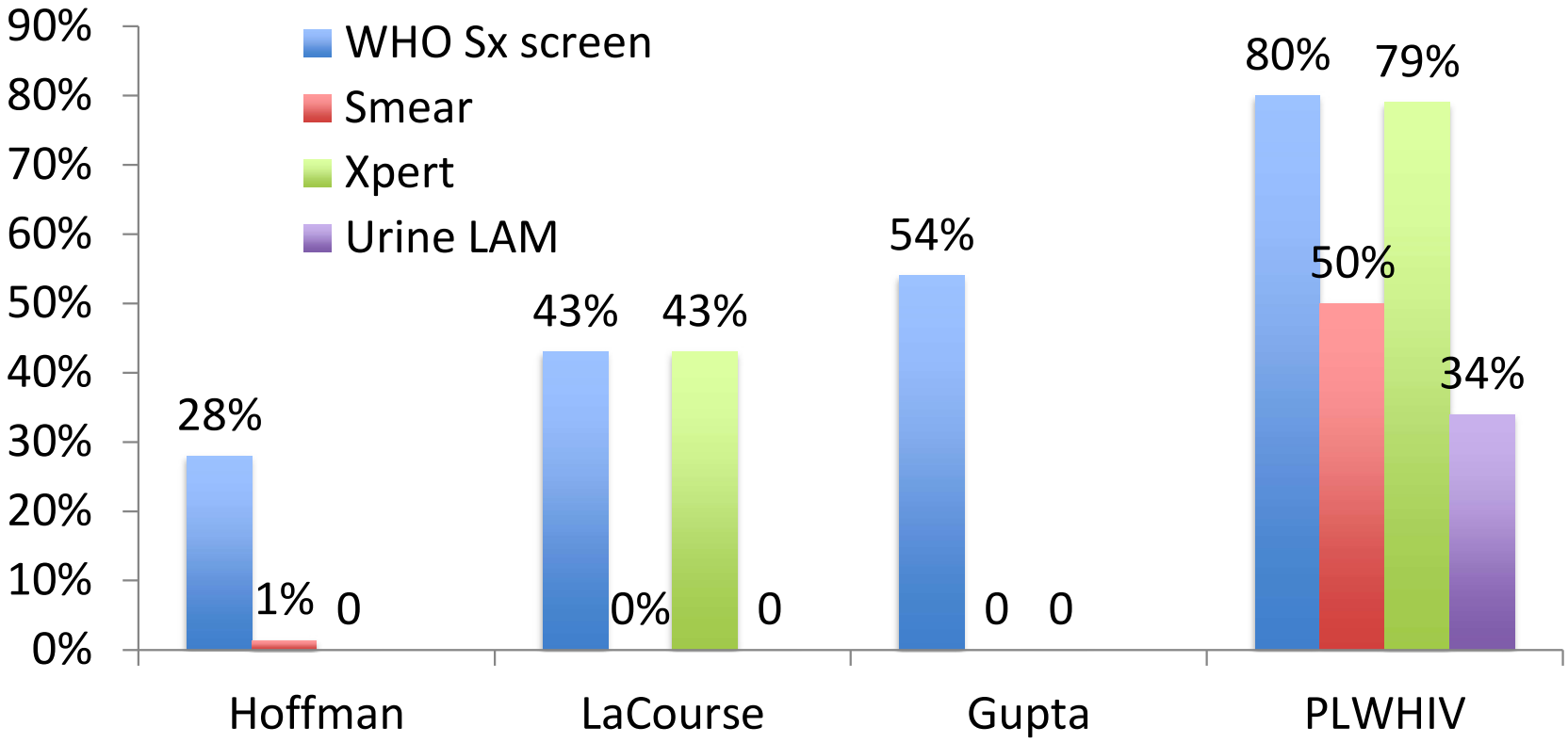
Peripartum increased risk of Mtb infection?

Peripartum increased risk of TB progression?

Does pregnancy impact performance of screening for active disease or TB infection?



TB diagnostic sensitivity of WHO 4-symptom screen in pregnancy



At least one WHO 4-symptom in 9-19% of women

Compared to non-pregnant HIV-infected adults

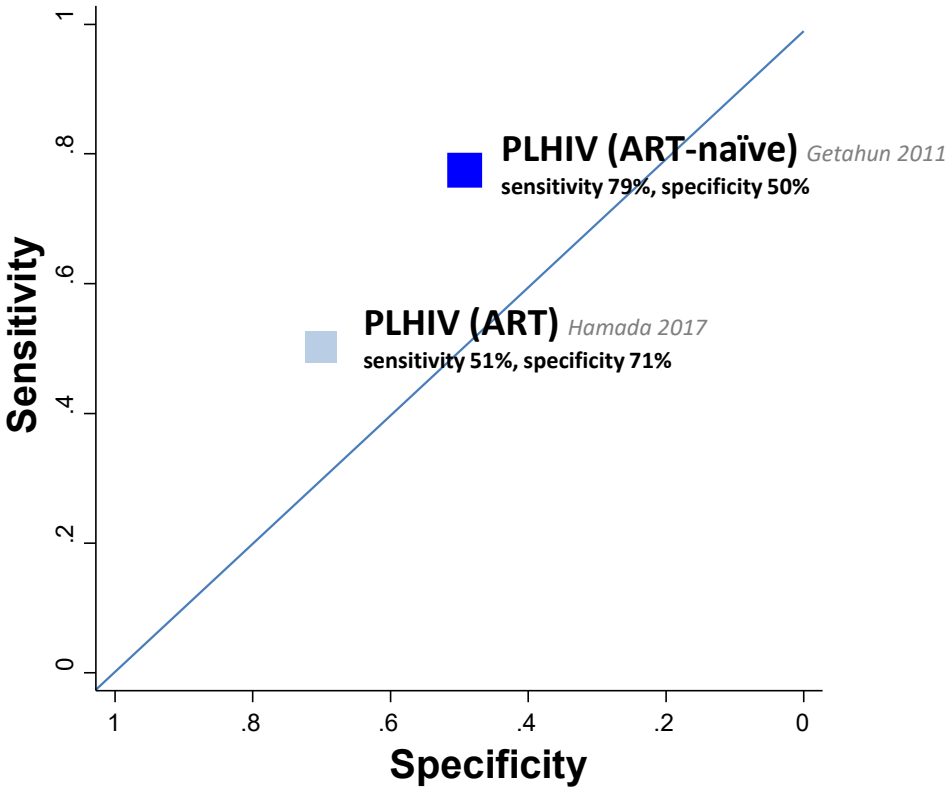
- **Lower sensitivity observed but not clear if that is due to pregnancy alone**
- **High negative predictive value (NPV) BUT**
- **In some settings, high prevalence of undiagnosed asymptomatic TB**

Gupta CID 2011:Hoffmann. PLOS One 2013: LaCourse. JAIDS 2015: Getahun PLOS Med 2011

TB symptom screening in pregnant PLHIV

WHO recommends routine TB screening for PLHIV (including pregnant women)

- Four-symptom screen: cough, fever, night sweats, weight loss



LaCourse Cochrane (Protocol) 2018

TB symptom screening in pregnant PLHIV

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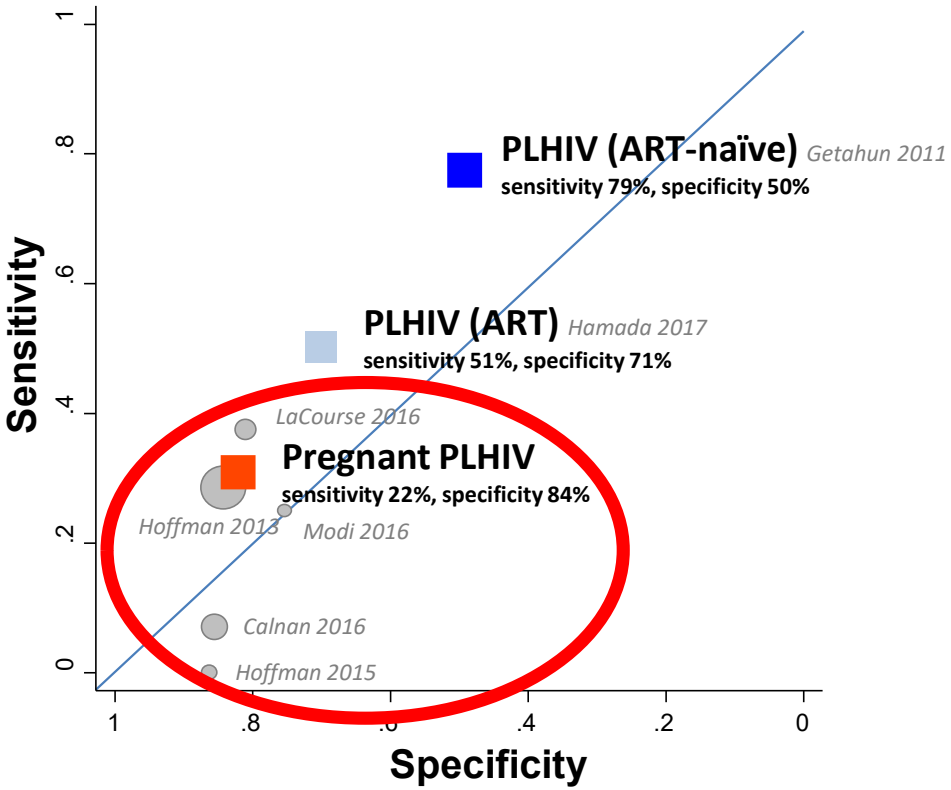


How to improve TB screening in pregnant PLHIV?

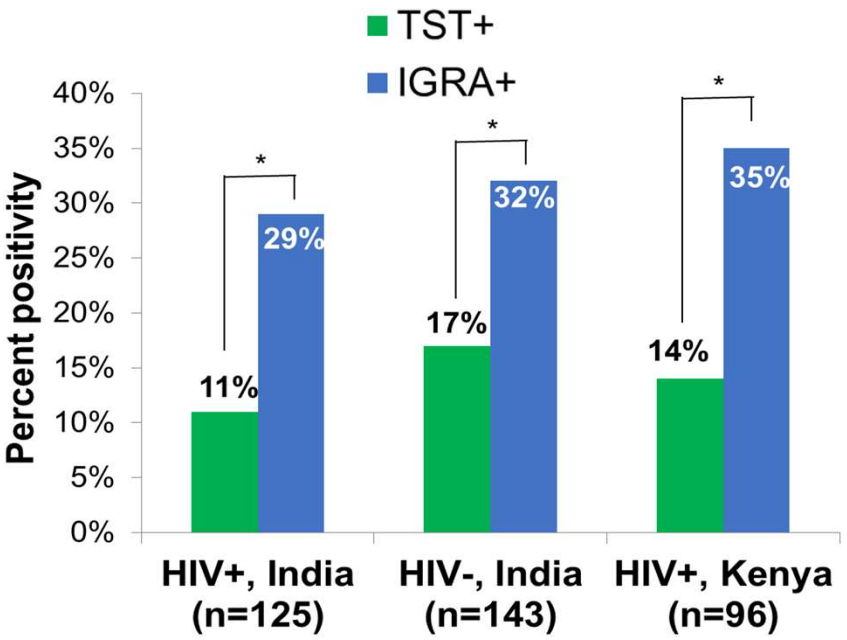
HOW ARE PERIPARTUM PLHIV SCREENED FOR TB IN YOUR SETTING?

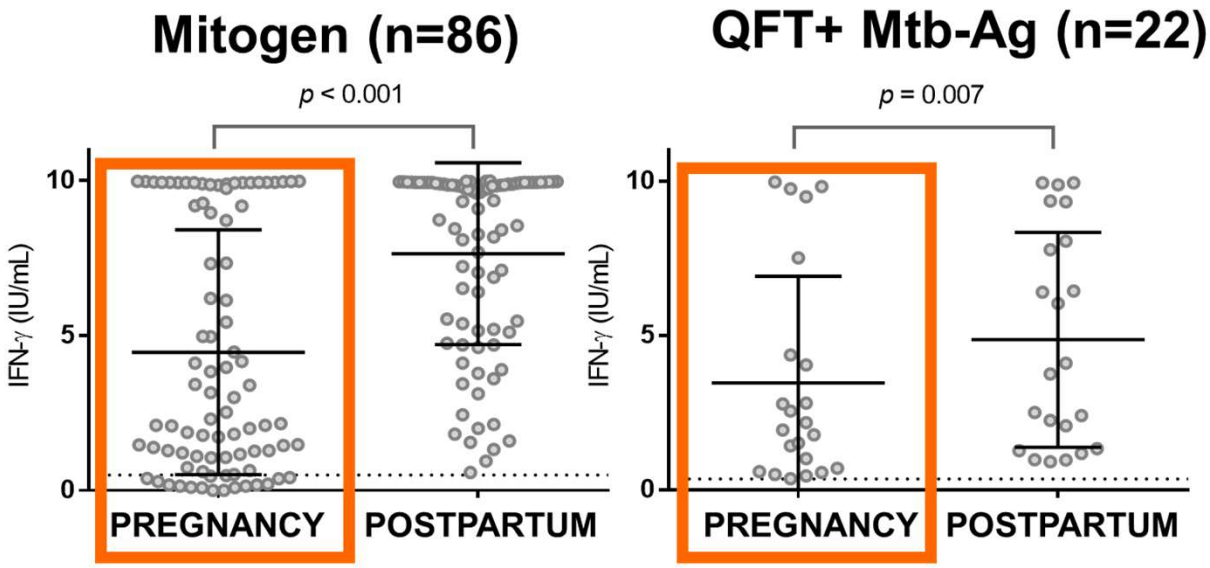
LaCourse Cochrane 2019

TB Infection (TBI) Screening

- Goal of TB Infection (TBI) screening
  - Identify those at highest risk for reactivation disease
  - Target preventive therapy
- Implementation challenges
- Little attention paid to performance of TB diagnostics in pregnant/postpartum women
  - Tuberculin skin test (TST) and Interferon Gamma Release Assay (IGRA)
- Mixed data
  - Two US studies of IGRA (Quantiferon) test positivity was lower than TST (older age, foreign birth associated with positivity) *(Worjohol et al Obstet Gynecol 2011; Chebab Kansas J Med 2010)*
  - India, more IGRA positive than TST and discordance QGIT+/TST- was higher *(Mathad, PLOS One 2014, Mathad AJRCMM 2016)*
- Positive IGRA predictive of active TB postpartum *(Jonalagadda JID 2010, IJTLD*

Pregnancy impact on TBI test results?



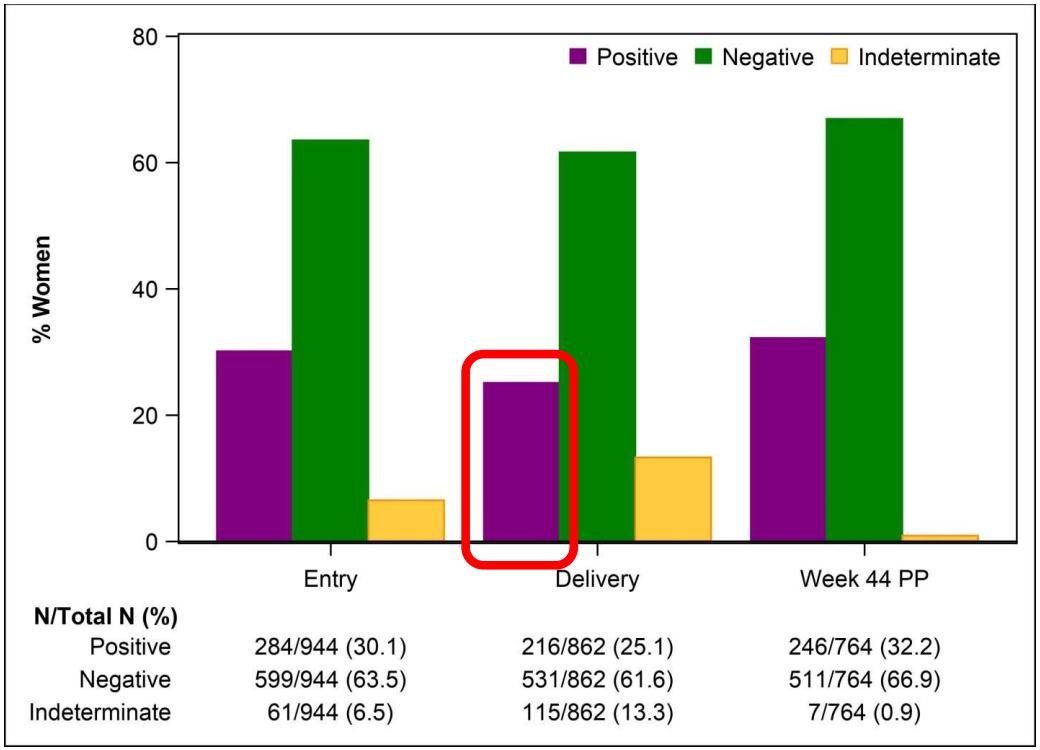


QFT identified 2x more pregnant women with LTBI vs. TST

Mean Mitogen and Mtb antigen lower in pregnancy vs. postpartum

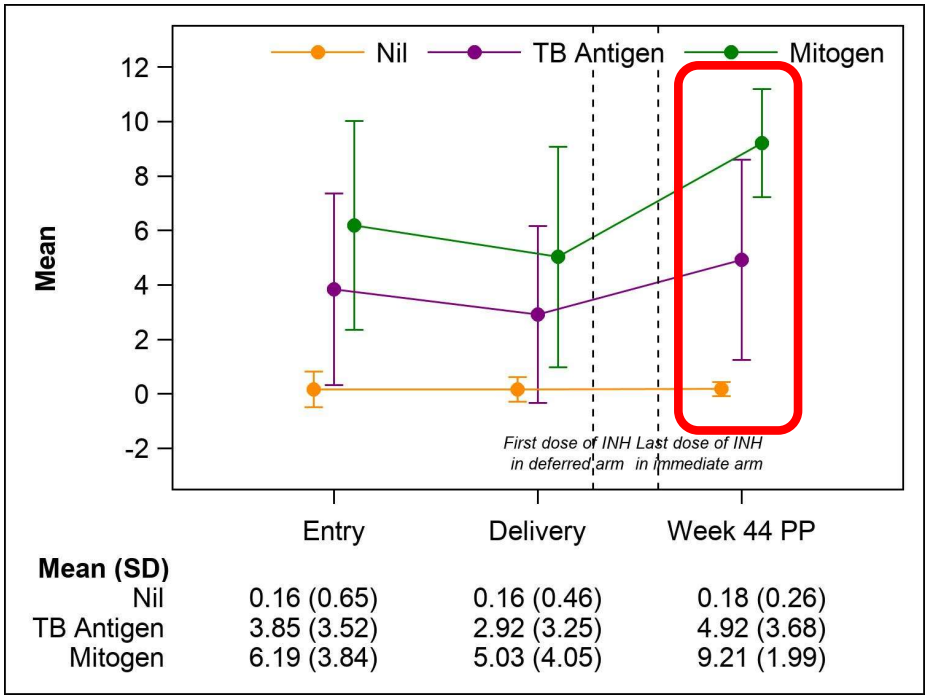
Mathad AJRCCM 2016
Mathad PLOS One 2014
LaCourse JAIDS 2017

Pregnancy impact on TBI test results?



N/Total N (%)	Entry	Delivery	Week 44 PP
Positive	284/944 (30.1)	216/862 (25.1)	246/764 (32.2)
Negative	599/944 (63.5)	531/862 (61.6)	511/764 (66.9)
Indeterminate	61/944 (6.5)	115/862 (13.3)	7/764 (0.9)

QFT-positivity significantly lower at delivery vs pregnancy ($p<0.001$) and higher postpartum ($p=0.04$)

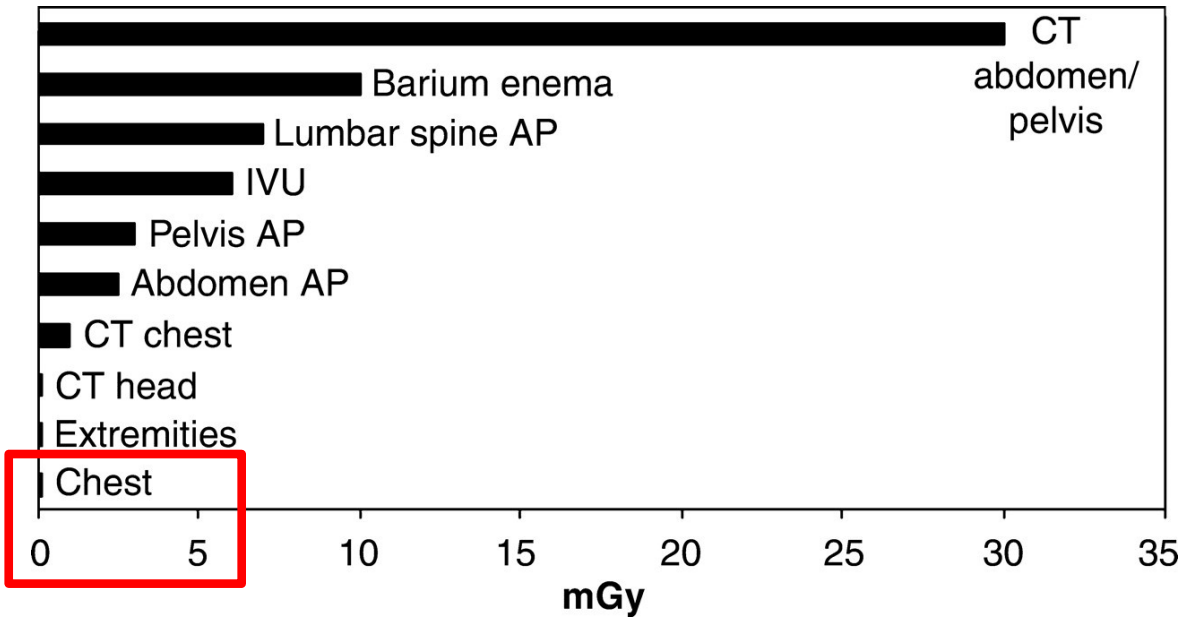


Mean (SD)	Entry	Delivery	Week 44 PP
Nil	0.16 (0.65)	0.16 (0.46)	0.18 (0.26)
TB Antigen	3.85 (3.52)	2.92 (3.25)	4.92 (3.68)
Mitogen	6.19 (3.84)	5.03 (4.05)	9.21 (1.99)

IFNγ production in response to TB antigens and mitogen significantly increased postpartum vs pregnancy and/or delivery ($p<0.001$)

Weinberg IDWeek 2019, CID 2020

Shielded Chest Xray in Pregnancy?



Comparison of the estimated mean fetal absorbed dose from various radiographic and computed tomographic (CT) procedures[1]

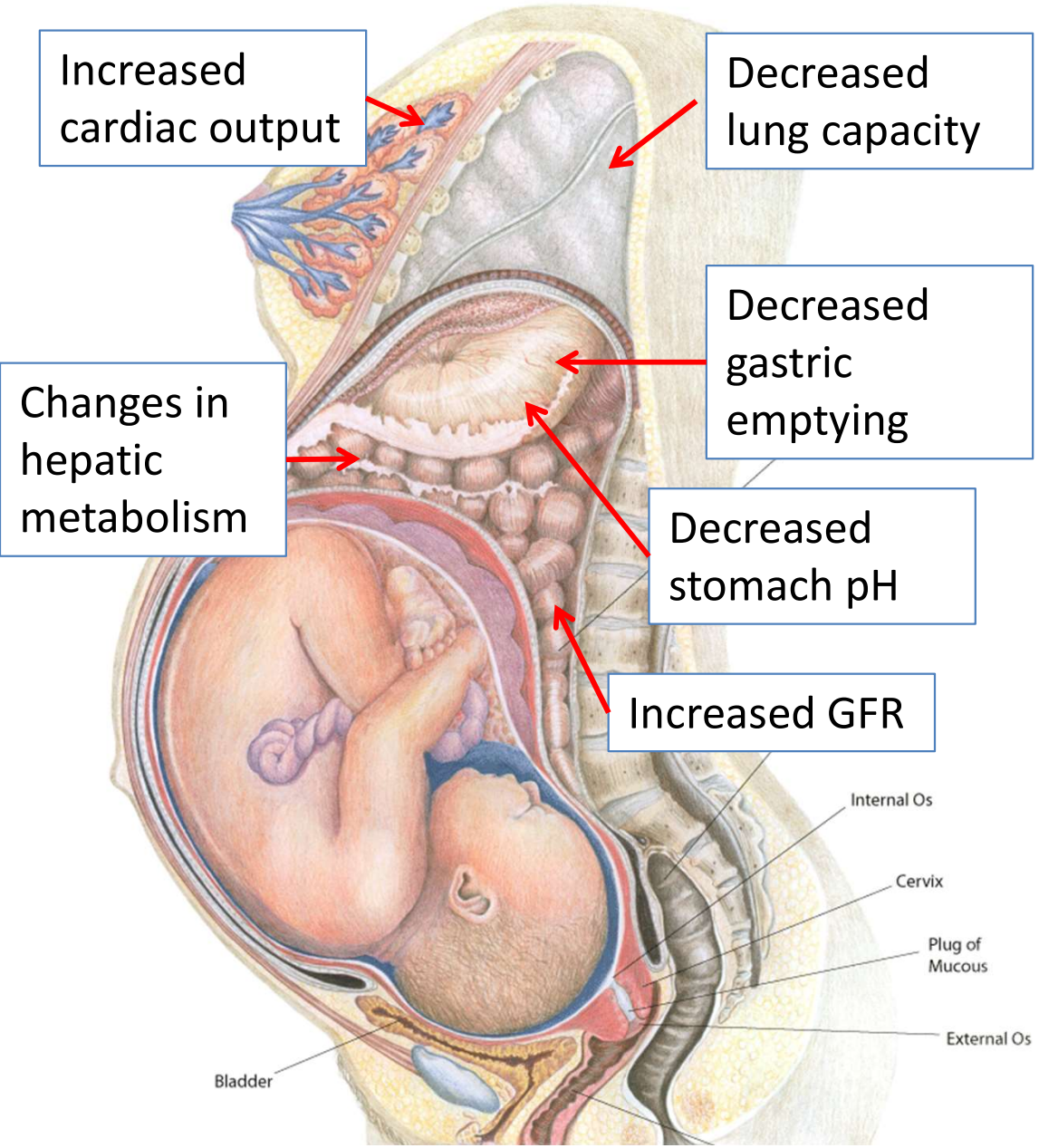
- ACOG[2]

  Xray exposure <5 rad (50 mGy) has not been associated with pregnancy loss or fetal anomalies

[1]Patel, S. J. et al. Radiographics 2007;27:1705-1722; [2]ACOG Committee Opinion No.299, Obstet Gynecol 2004

Does pregnancy impact TB treatment and prevention?

Physiology Changes of Pregnancy Can Significantly Impact Drug Metabolism, Safety and Efficacy



- Increased body fat
- Increased total body weight
- Decreased albumin
- Hepatic metabolism
  - Increased CYP3A4
  - Decreased CYP1A2 and CYP2C19

Frederiksen, Sem Perinatol 2001; Anderson, Clin Pharmacokinetics 2005

FDA Pharmaceutical Pregnancy Categories	
Category A	Adequate and well-controlled human studies demonstrate no risk.
Category B	Animal studies demonstrate no risk, but no human studies have been performed. OR Animal studies demonstrate a risk, but human studies have demonstrated no risk.
Category C	Animal studies demonstrate a risk, but no human studies have been performed. Potential benefits may outweigh the risks.
Category D	Human studies demonstrate a risk. Potential benefits may outweigh the risks.
Category X	Animal or human studies demonstrate a risk. The risks outweigh the potential benefits.

**Historical categorization*

First line drugs for TB in pregnancy

Drug	FDA	Crosses placenta	Breast-feeding	Issues in pregnant women
INH	C	Yes	Yes	Hepatotoxicity
Rifampin	C	Yes	Yes	Drug interactions with NVP, PIs, INSTIs, OCPs; may require Vit K
Rifabutin	B	Unknown	Unknown	Drug interactions with PIs, limited experience
EMB	B	Yes	Yes	
PZA	C	Unknown	Unknown	Different guidance

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Brost Obstet Gyn Clin 1997;Bothamley Drug Safety 2001;Shin CID 2003; Micromedex; Mathad & Gupta CID 2012

Treatment of Pulmonary TB in Pregnancy

	Low Burden[1]	High Burden[2]
HIV negative	INH 5mg/kg/d x 9 mo RIF 10mg/kg/d x 9mo EMB wt-based x 2 mo B6 25mg/d x 9 mo	INH 5 mg/kg/d × 6 mo RIF 10 mg/kg/d × 6 mo EMB 15mg/kg/d x 2 mo PZA 25mg/kg/d x 2 mo B6 10-25mg/d x 6 mo
HIV positive	INH 300 mg/d × 6 mo RIF 600 mg/d × 6 mo EMB wt-based x 2mo PZA wt-based × 2 mo B6 25mg/d x 6 mo	INH 5 mg/kg/d × 6 mo RIF 10 mg/kg/d × 6 mo EMB 15mg/kg/d x 2 mo PZA 25mg/kg/d x 2 mo B6 10-25mg/d x 6 mo

DIFFERENCE IN PZA guidance

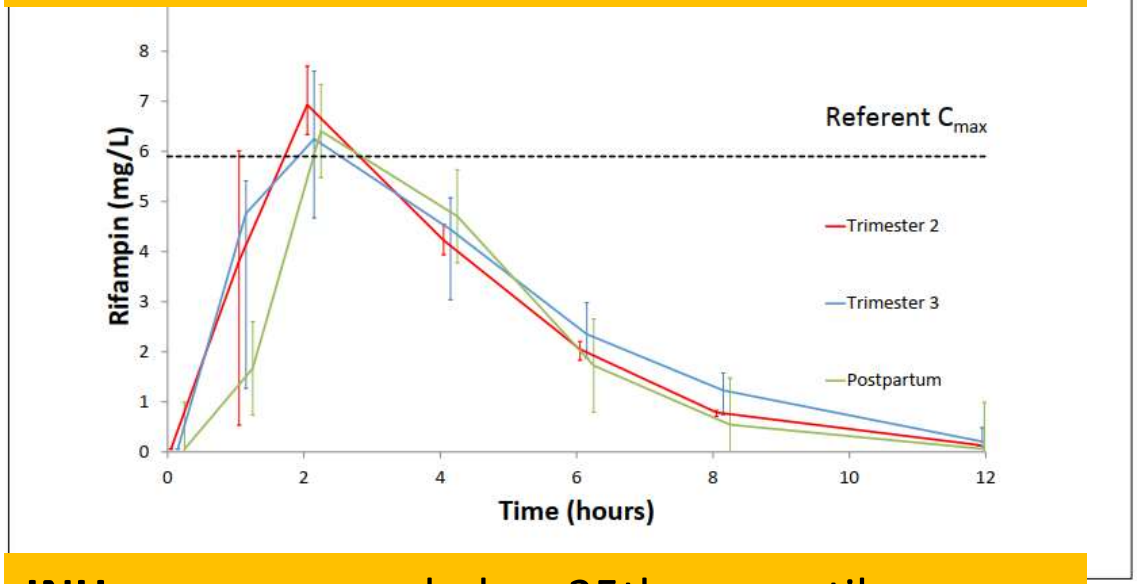
LACTATION

CDC encourages breastfeeding if no longer infectious; WHO once smear negative

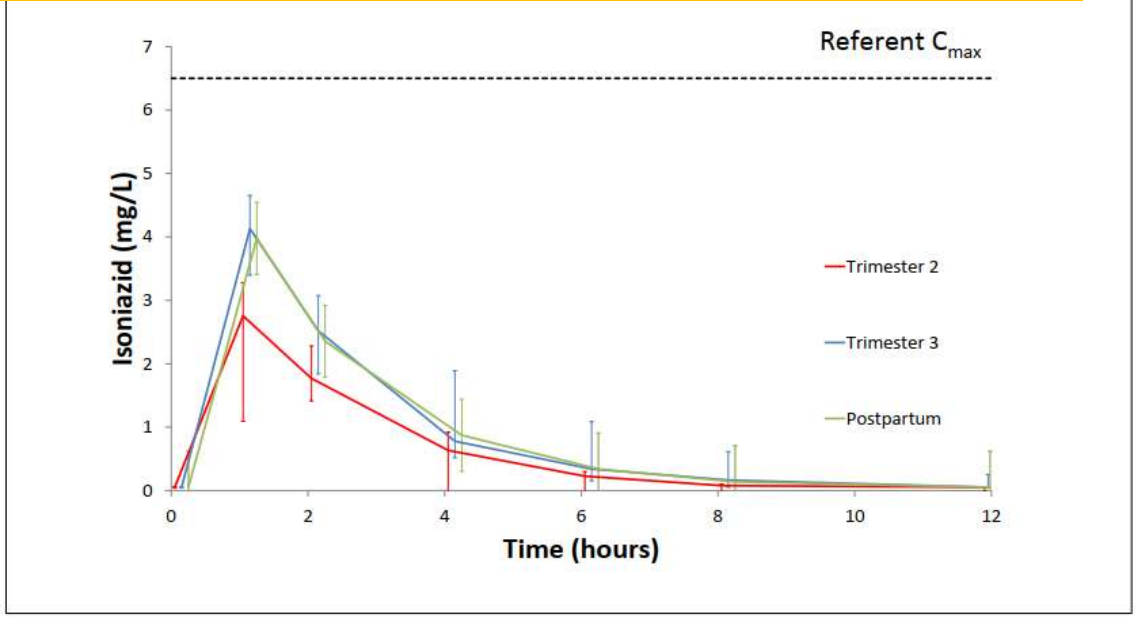
1 CDC, ATS, IDSA guidelines
2 WHO, British thoracic Society, RNTCP and IUATLD guidelines

Treatment of EPTB involves same drugs but most experts recommend 9-12 mo for TBM (but include PZA plus steroids) or bone/joint

Rifampin concentrations in pregnancy compared well to non-pregnant concentrations.



INH exposure was <u>below</u> 25th percentile across all stages of pregnancy.



Intensive PK study in IMPAACT P1026s n=11 women

"More data are needed on isoniazid and rifampin in pregnancy to make dosing recommendations"

Other first line TB drugs

- Sparse PK at >36 weeks GA and 7 weeks postpartum
- N=21 prepartum/birth with 16 postpartum for INH
- N=15 prepartum/birth with 4 postpartum for EMB, PZA

TABLE 3 Model-estimated secondary pharmacokinetic parameters[a]

	C_{max} (mg/liter) for:			AUC_{0-24} (mg · h/liter) for:		
Time period	Isoniazid	Pyrazinamide	Ethambutol	Isoniazid	Pyrazinamide	Ethambutol
Prepartum	1.39 (1.13–1.60)	35.9 (32.7–38.1)	1.82 (1.61–2.14)	6.88 (3.63–10.40)	419 (370–541)	16.5 (14.3–20.6)
Postpartum	1.43 (1.09–1.86)	34.5 (29.9–41.3)	2.11 (1.85–2.46)	5.01 (2.89–8.03)	407 (336–514)	19.0 (16.5–21.6)

[a]Data are given as medians (interquartile ranges). For INH, there were 21 (3 at birth) prepartum and 16 postpartum women; for PZA and EMB, there were 15 (2 at birth) prepartum and 4 postpartum women.

Very low INH levels in pregnancy and postpartum observed
PZA, EMB no relevant changes in pregnancy
SPARSE PK AND SMALL NUMBERS

Abdelwahab AAC 2020

MDR TB Drugs and Pregnancy

Drug Name	FDA[a]	WHO Grouping[b]	Crosses Placenta (Cord: Maternal Ratio)	Fetal Toxicity	Breastfeeding Compatible[b]	Teratogenic in Reproductive Toxicity Studies	Additional Concerns in Pregnancy and Postpartum
Aminoglycosides							
Capreomycin	C	Not A–C	Yes	–	UD	Yes	–
Streptomycin	D	C	Yes	Ototoxicity, thrush, diarrhea	Yes (minimal passage)	No	–
Kanamycin	D	Not A–C	Yes	Ototoxicity	Yes (minimal passage)	No	–
Amikacin	D	C	Yes	Ototoxicity	UD	UD	–
Levofloxacin	C	A	Yes	Possible bone	Yes	No	–
Moxifloxacin	C	A	Yes	Possible bone	UD	No	–
Gatifloxacin	C	Not A–C	UD	Possible bone	UD	No	–
Ethionamide/ prothionamide	C	C	UD	Developmental anomalies	UD	Yes	Developmental abnormalities in human case series
P-aminosalicylic acid	C	C	UD	Diarrhea	No	No	–
Cycloserine	C	B	UD	–	Yes	UD	Congenital sideroblastic anemia
Terizidone	–	B	UD	–	Yes	UD	–
Thioacetazone	–	Not A–C	UD	–	UD	UD	–
Clofazimine	C	B	UD	Reversible skin pigmentation	UD	No	–
Clarithromycin	C	Not A–C	Yes (0.15)	–	UD	No	–
Amoxicillin-clavulanic acid	B	Not A–C	Yes (0.56)	Necrotizing enterocolitis, transaminitis	UD	No	–
Linezolid	C	A	UD	–	UD	No	Case report of reduced PK in pregnancy
Imipenem/ meropenem	C	C	UD	–	UD	No	–
High-dose isoniazid	C	Not A–C	Yes (0.73)	CNS defects	UD	No	Possible hepatotoxicity
Bedaquiline	B	A	UD	–	UD	No	Drug accumulation in tissues
Delamanid	Not approved[c]	C	UD	–	UD	Yes	Embryofetal toxicity at maternally toxic doses in rabbits; breast milk concentration 4× higher than blood in rats

UD= Undetermined

Gupta A et al. PLOS Med 2019

MDR TB in pregnancy

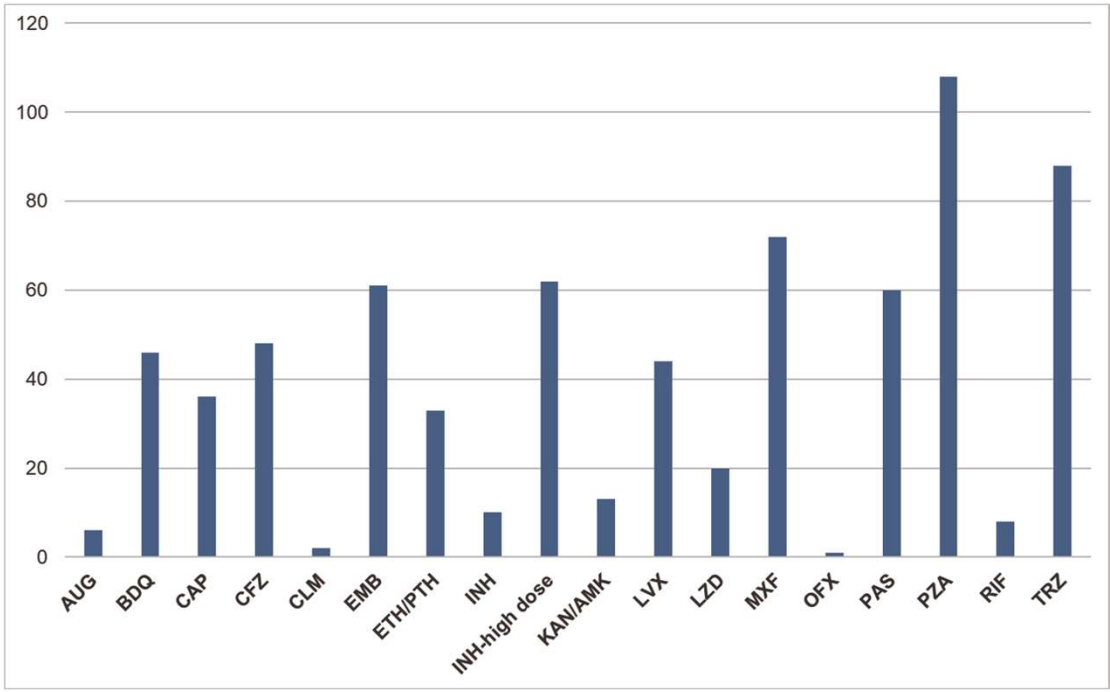
- Treatment guidelines similar to non-pregnant adults
  - Individualized treatment vs public health approach
  - At least 5 active agents
  - Favor injectable after delivery
  - Lactation little to no data so often not recommended
- >60 published case reports *(Gach 1999;Shin 2003; Nitta 1999;Lessnau 2003;Tabarsi 2007; Khan 2007; Palacios 2009; Toro 2011, Rohilla 2016)*
  - 3 case series describes 4 cases HIV+ *(Khan 2007; Palacios 2009, Toro 2011)*
  - US, Italy, Peru, Iran, South Africa
  - 1 case in France: bedaqualline and linezolid in XDR *(Jaspard EID 2017)*
- Regimens: variable
- Outcomes: case series suggest treatment success possible

Maternal and infant outcomes in pregnant women with MDR/RR-TB in South Africa (2013 – 2018)

Methods: Descriptive cohort analysis

- A record review to document treatment & pregnancy outcomes;
- An observational clinical assessment at 2, 6 and 12 months, to document infant outcomes.

	N=108
Pre-XDR/XDR	25 (23%)
HIV+ CD4, median	88 (81%) 353
MDR TB Rx initiation pre-comception 1st trimester 2nd trimester 3rd trimester	 20 (18%) 19 (18%) 42 (39%) 28 (26%)



Loveday CID 2020

MDR/RR TB in Pregnancy Outcomes

Outcome	N (%)
Unfavorable maternal treatment outcome, n=108	36 (33%)
Unfavorable pregnancy outcomes, n=109 Fetal deaths Preterm Low Birth weight	52 (48%) 10 (9%) 28 (28%) 33 (35%)
Unfavorable infant outcome, n=86	14 (16%)

	BDQ, n=58	No BDQ, n=50
Unfavorable treatment outcome	17 (29%)	19 (38%)
Fetal death	4 (8%)	6 (10%)
Preterm birth	13 (29%)	15 (28%)
Low birth weight	**20 (45%)**	**13 (26%), p=0/03**
Unfavorable infant outcome at 12 months	5 (12%)	9 (20%)

Loveday CID 2020

Breastfeeding during TB treatment in pregnancy

- Breastfeeding encouraged once non-infectious on first-line agents
- Concentration of TB meds in breastmilk typically found in small concentrations
  - Non-toxic to infant
  - Not effective treatment for infant

Treatment as Prevention:
The Case for TB Infection (TBI) Treatment in Pregnancy

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PROPHYLACTIC ISONIAZID

PROTECTION OF INFANTS IN A TUBERCULOSIS HOSPITAL

B. A. DORMER
M.D. Durh., D.P.H., T.D.D.
MEDICAL SUPERINTENDENT

I. HARRISON
M.B. Cape Town
MEDICAL OFFICER

J. A. SWART
M.B. Cape Town
MEDICAL OFFICER

S. R. VIDOR
M.B. Cape Town
MEDICAL OFFICER

KING GEORGE V HOSPITAL, DURBAN, SOUTH AFRICA

Some of our mothers with their babies.

Faced with this appalling mortality-rate and encouraged by reports on isoniazid as a prophylactic against tuberculosis in guineapigs, we decided to keep all babies born in hospital with their mothers and to give them isoniazid as prophylactic.

Treatment

The child is kept in a crib by the mother's bedside, and from birth to six months is given 25 mg. of isoniazid in a syrup twice daily. After six months the dose is increased

The Mothers

53 of the mothers had been treated for six to nine months before they were delivered. 22 of them had had less than three months' treatment; 36 of them had advanced disease at the time of the confinement, and 49 of them had positive sputum. 1 woman with very little functioning lung tissue died of cor pulmonale four weeks after delivery. 1, who had hæmoptysis before labour, died of hæmorrhage three weeks later.

Apart from these 2 deaths, there was no evidence of deterioration after pregnancy or during lactation. The disease appeared to behave as would have been expected in women who were not pregnant. Nearly all continued to improve. A few of the chronic cases remained unchanged.

All but 6 of these women breast-fed their children. 3 of those with chronic extensive disease had not enough milk, but begged to be allowed to feed with complements of dried milk. 4 children were weaned because the mothers did not wish to feed. 1 woman had had severe toxæmia of pregnancy, and 1 had puerperal psychosis.

Discussion

While it is always desirable, where possible, to keep a mother and child together, in a backward community this is life-saving. The mothers who have their children with them are the most contented among our patients, and the babies are beautiful thriving children.

From our three years' experience it seems that isoniazid

TBI testing and treatment in pregnancy

- Pregnancy itself not indication for TBI testing
- A decision to test, is a decision to treat… but timing of treatment depends on risk
  - Women **at risk** for progression from TBI -> TB (HIV+, recent converter, recent TB contact)
    - Recommend to treat now even in first trimester
  - Women with **lower risk** of TB
    - Recommend to wait until after delivery or 3 months postpartum due to concerns for hepatotoxicity
- TBI diagnostic cut-offs are same for non-pregnant

ATS AJRCCM 2000

Hepatotoxicity and INH in pregnancy

- 3681 women who initiated INH *Franks Public Health Reports 1989*
  - 5 pregnant women developed hepatitis, 2 died
- 20 INH-associated deaths in California *Moulding Am Rev Resp Disease 1989*
  - 4 initiated INH in pregnancy

Concern initially based primarily on US-based retrospective studies

- IPT implementation in HIV+ pregnant women in Lesotho *Tiam JAIDS 2014*
  - 124 women who initiated IPT, none reported side effects
  - 3/99 mildly elev ALT--> 0/20 repeat LFT testing without significant elevation

In implementation studies in pregnant PLHIV appeared safe

Guidelines for Preventive TB Treatment in Pregnant Women

	Low Burden (US CDC)	High Burden (WHO)
Regimen *Preferred*	INH 300mg/daily x 9 mo *OR* INH 900mg twice weekly x 9 mo **Administer INH w/ pyroxidine (vit B6) 10-25mg to pregnant women and their breastfeeding infants**	INH 300mg/d x 6 or 36 mo B6 10-25mg/d x 6 or 36 mo
Alternative	Rifampin 600mg daily x 4 months	Rifampin 600mg daily x 4 months
HIV-negative	Defer for TST+ or IGRA+ until 2-3 mo postpartum unless known recent TB contact	No recommendations
		ent for all HIV+ without TB

Monitoring:

- ***Baseline LFTs***
- ***Routine monitoring for signs/ symptoms of possible adverse effects***

Selected Planned, On-going, and Recently Completed Randomized Clinical Trials for DS and DR TB

Prepared for the CDC Tuberculosis Trials Consortium *revised 24 April 2013*

Drug(s)	Trial Name	NCT Number	Arms	Ph	N	Group	Comments
High-dose Rifapentine - P - RPT							
	RIFAQUIN	ISRCTN44153044	2MRZE/2M_2P_2 900 v. 2MRZE/4M_1P_1 1200 v. 2HRZE/4RH	III	1095	MRC/UK, EDCTP	Results CROI Mar 2013
	EDA Cape Town Trial	NCT00814671	2P_2 (600 v. 450 mg) HZE v. 2HRZE	II	153	JHU (Dorman)	Results May 2013

>40 trials listed here that are planned, ongoing or recently completed

At least 8 are Phase III trials

All exclude pregnant women

More than 13 trials of preventive therapy in HIV-infected adults

INH for 6, 9, 12, 36 months

INH+ rifampin

INH+ rifapentine

INH+ ART

All excluded pregnant women

Akolo Cochrane metanalysis 2010; Sterling NEJM 2011; Martinson NEJM 2011; Samandari Lancet 2011; Rangaka Lancet ID 2014

AZD-5847 (Astra Zeneca)							
	n/a	NCT01516203	2 wk EBA 500 qd, 500 bid, 1200 qd, 800 bid v. RHZE	EBA	75	NIAID/DMID (Diacon)	Enrolling

Ethical and Scientific Foundation of Inclusion of Pregnant Women Into Clinical Trials of TB Therapeutics

- Women need effective treatment during pregnancy
- Most compelling reason: gather evidence under rigorous scientific conditions
- Safety signals can be more readily interpreted when detected in study setting
- Fetal safety
  - need data on fetal safety
  - inadequately treated mother compromises fetal well being
- Reticence to prescribe needed medications: the cost of uncertainty
- Issues of justice and access to the benefits of research participation

Lyerly AD, Little MO, Faden R. The second wave: Towards responsible inclusion of pregnant women in research. Int J Fem Approaches Bioeth, 2008. Slide adapted from Karen Feibus and Sara Goldkind, US FDA

NIH and WHO sponsored workshops

Clinical Infectious Diseases
VIEWPOINTS

Toward Earlier Inclusion of Pregnant and Postpartum Women in Tuberculosis Drug Trials: Consensus Statements From an International Expert Panel

Amita Gupta,[1,a] Jyoti S. Mathad,[8,a] Susan M. Abdel-Rahman,[9] Jessica D. Albano,[10] Radu Botgros,[18] Vikki Brown,[11] Renee S. Browning,[3] Liza Dawson,[3] Kelly E. Dooley,[2] Devasena Gnanashanmugam,[3] Beatriz Grinsztejn,[19] Sonia Hernandez-Diaz,[13] Patrick Jean-Philippe,[4] Peter Kim,[3] Anne D. Lyerly,[12] Mark Mirochnick,[15] Lynne M. Mofenson,[5] Grace Montepiedra,[14] Jeanna Piper,[3] Leyla Sahin,[7] Radojka Savic,[16] Betsy Smith,[3] Hans Spiegel,[4] Soumya Swaminathan,[20] D. Heather Watts,[17] and Amina White[6]

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CID 2016

Summary of Expert Consensus Statements

- Pregnant/postpartum women should be eligible for Phase III MDR TB trials unless there is a compelling reason for exclusion
- Drug companies should be encouraged to complete reproductive toxicity studies before beginning Phase III
- Trials of shortened treatment regimens for LTBI should be designed to improve completion rates, reduce risk of progression in pregnancy/postpartum
- Targeted PK studies should be nested in all studies when evidence is lacking
- Pregnancy registry should be created to accumulate data on maternal-infant outcomes

Gupta, Mathad et al *Clinical Infectious Diseases, 2016*

Pregnancy and Infant Outcomes in TBI Tx Trials

TB prevention in PLHIV (3HP vs. 3HR vs. 6H) *Martinson NEJM 2011*

- 235 pregnancies during treatment or f/u
- 26 women became pregnant on INH
- 10 chose to continue, no toxicities

LTBI tx exposure in pregnancy not assoc with toxicity

PREVENT TB or iAdhere trials (3H *...nals ATS 2018*

- 126 pregnancies during treat
- 87 exposed to study dr
- Fetal loss similar 3 ...) (all <20 weeks)
- Congenital a ... (3%) vs 9H (4%)

Fetal loss/congenital anom similar between arms and baseline US estimates

All secondary analyses of LTBI treatment trials

BOTUSA (6 vs. *...OBGYN 2013*

- 196 pregnancie ...ng treatment or f/u
- 103 exposed to INH during pregnancy
- IPT exposure during pregnancy not assoc with adverse pregnancy outcomes aOR 0.6 95%CI 0.3-1.1

Long-term INH + ART not assoc with adverse pregnancy outcomes

Inclusion of Peripartum Women in Clinical Trials

Clinical Infectious Diseases
VIEWPOINTS

Toward Earlier Inclusi
Women in Tuberculosi
Statements From an In

Pharmacologic
— Time to Get

Ahizechukwu C. Eke, M.D.,

IDSA hivma

Clinical Infectious Diseases
VIEWPOINTS

TAG
Treatment Action Group

HOME HIV CURE HCV TB

ARE YOU INCLUDING PERIPARTUM WOMEN IN YOUR RESEARCH?

Webinar: It's Time to Deliver - Including Pregnant and Lactating Women in Clinical Research

N ENG

http://www.treatmentactiongroup.org

IDSA hivma

RESEARCH Open Access

Fair inclusion of pregnant women in clinical trials: an integrated scientific and ethical approach

van der Graaf *et al. Trials* (2018) 19:78
DOI 10.1186/s13063-017-2402-9

The American College of Obstetricians and Gynecologists
WOMEN'S HEALTH CARE PHYSICIANS

COMMITTEE OPINION

Number 646 • No
(Reaffirmed 2018)

Committee on Et

"Pregnant women in research trials should be defined as "scientifically complex" rather than a "vulnerable" population."

Ethical Considerations for Including Women as Research Participants

NIH *Eunice Kennedy Shriver* National Institute of Child Health and Human Development
Health research throughout the lifespan

Task Force on Research Specific to Pregnant Women and Lactating Women (PRGLAC)

The 21st Century Cures Act established PRGLAC to advise the Secretary of Health and Human Services (HHS) regarding gaps in knowledge and research on safe and effective therapies for pregnant women and lactating women. PRGLAC was tasked with identifying these gaps and reporting its findings back to the Secretary.

https://www.nichd.nih.gov/About/Advisory/PRGLAC

VIEWPOINT

Increasing the Participation of Pregnant Women in Clinical Trials

JAMA November 27, 2018 Volume 320, Number 20

Katrina Heyrana, MD, PhD
National Institutes of Health, Bethesda, Maryland; and now with Department of Obstetrics and Gynecology, University of Rochester, Rochester, New York.

Preventing pregnant women from participating in clinical trials is well intentioned but misguided. Pregnant women are a "vulnerable" population in research due to their parti terve mini sent insti

evaluation demonstrated a 67.5% reduction in vertical transmission in the zidovudine group compared with the placebo group, without increasing long-term sequelae in

"Of 213 new pharmaceuticals receiving FDA approval 2003-2012, only 5% included any data from pregnant women."

TBI/TB treatment in pregnancy trials

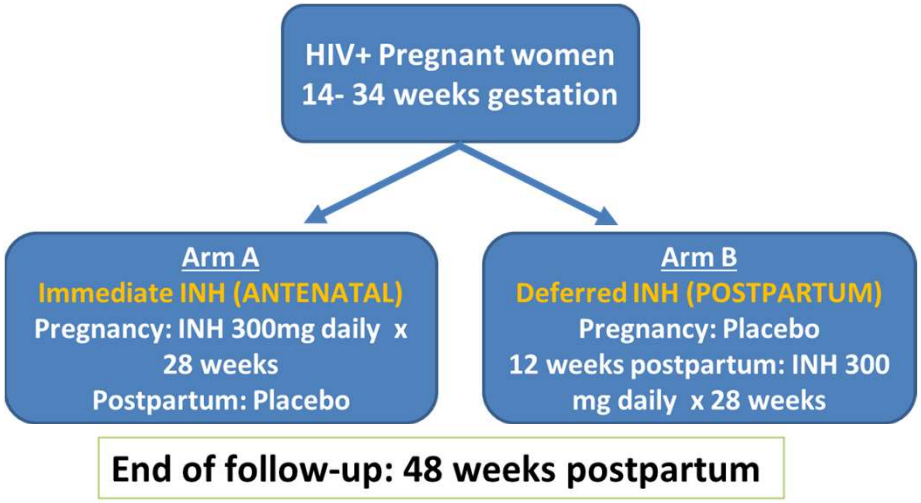
- P1078: phase IV RCT to evaluate the safety of **antepartum versus postpartum 6H** among HIV-infected women COMPLETED
- P2001: Phase I/II PK and tolerability of **3HP** in HIV-infected and HIV-uninfected pregnant and postpartum women COMPLETED
- P2026: Phase IV prospective PK study of **1st line ARVs and TB drugs** in HIV-infected pregnant and postpartum women ONGOING
- **1HP vs 3HP** in pregnancy UNITAID protocol IN DEVELOPMENT

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

TB APPRISE (P1078) Antenatal vs. Postpartum 6H in PLHIV

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

1st trial to evaluate safety of TB preventive therapy in pregnant PLHIV



Primary Endpoints: Maternal Grade ≥ 3 AE, drug discontinuation 2° toxicity

Secondary Endpoints:

Maternal: hepatotoxicity, TB, death

Infant: Grade ≥ 3 AE, TB, death

Pregnancy outcomes

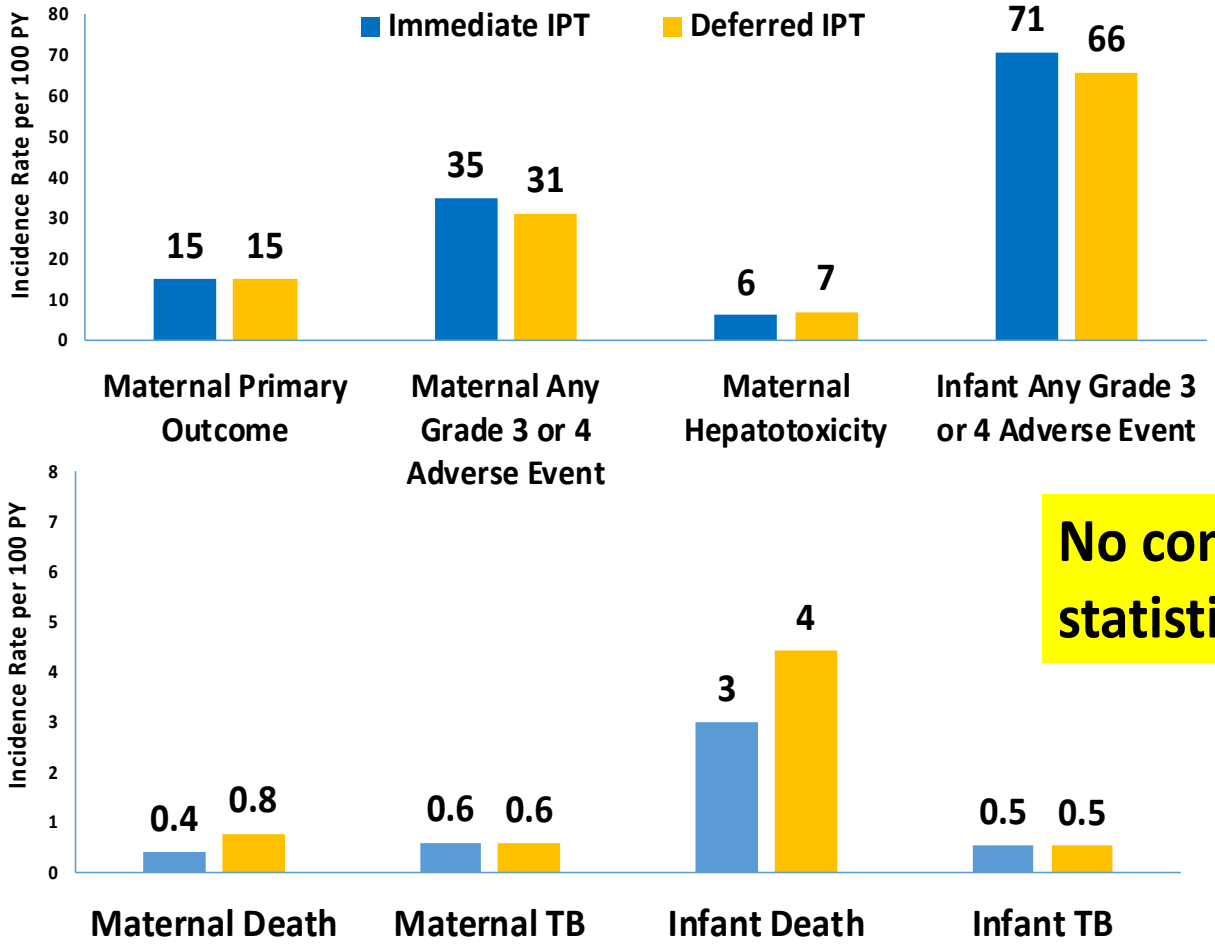
Safety antenatal INH non-inferior to postpartum

Postpartum hepatotoxicity higher than expected (but similar) in both arms

Antenatal INH: increased adverse pregnancy outcomes (fetal demise, LBW)
Signal with earlier gestation initiation

Gupta NEJM 2019

No differences in Maternal or Live-born Infant Safety, TB or Death Rates by Study Arm

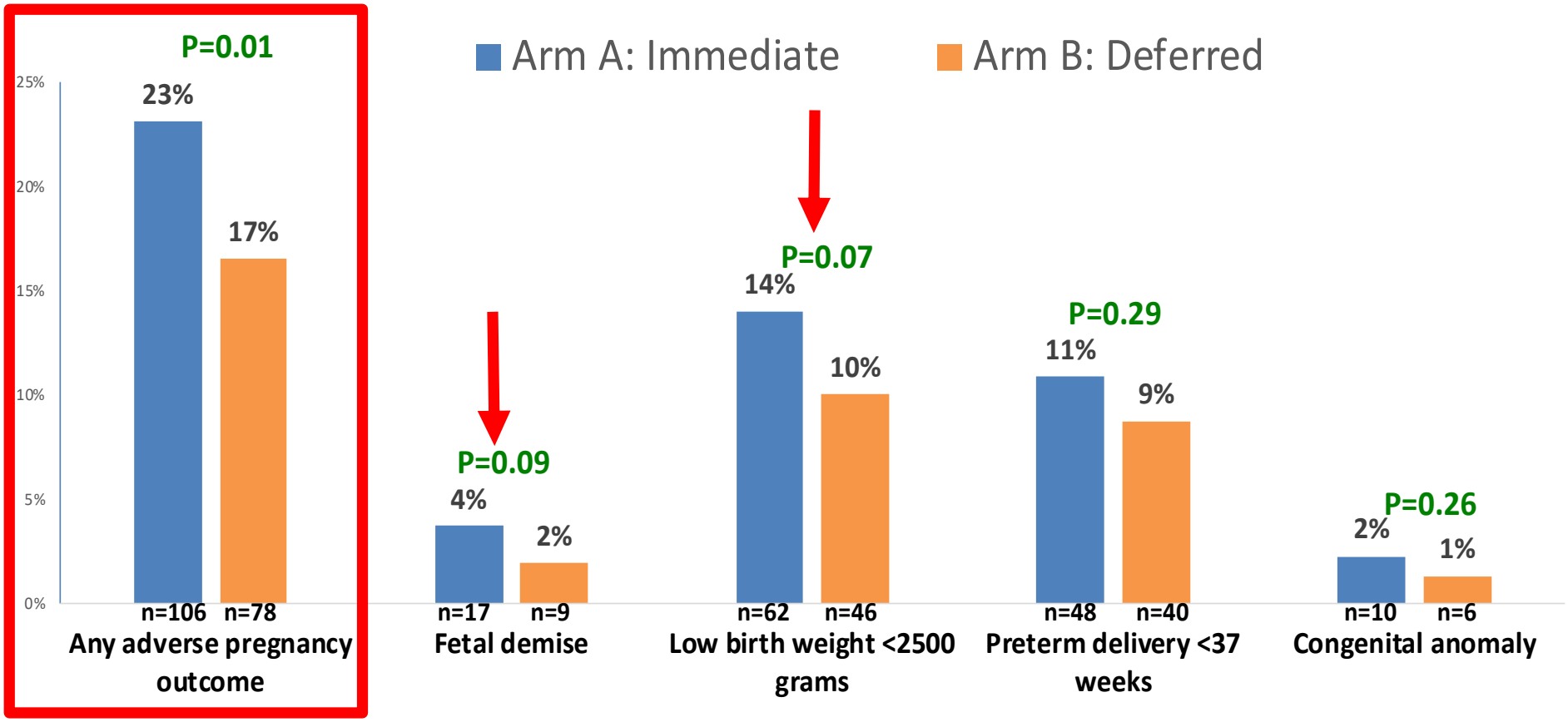


No comparison was statistically different

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Gupta et al NEJM 2019

But there were more Adverse Pregnancy Outcomes in the Immediate IPT arm

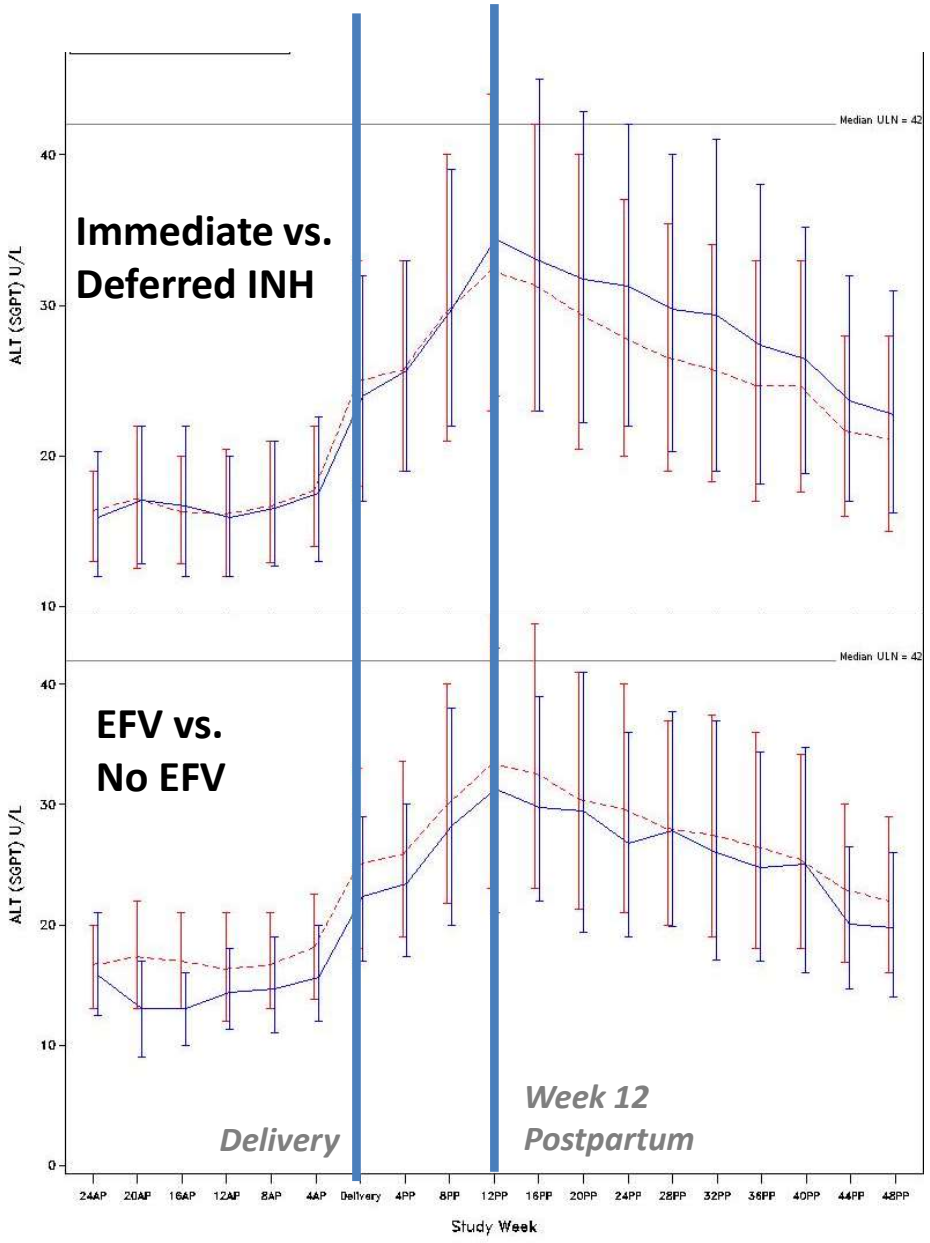


IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Gupta et al NEJM 2019

Median ALT by INH Arm and EFV Regimens

Higher LFTs after delivery in both arms
No difference by INH arm or ART regimen



Gupta NEJM 2019

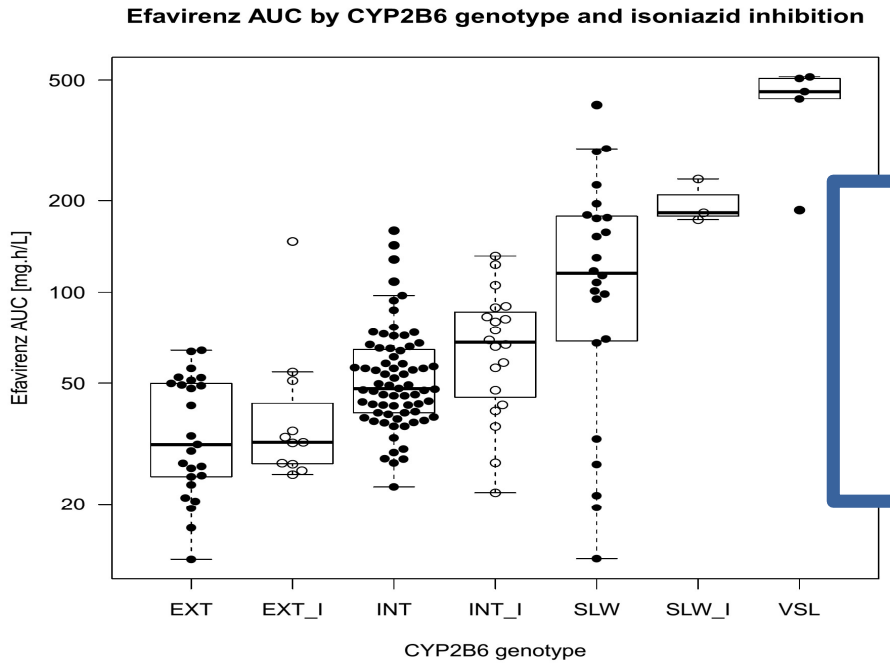
Maternal Deaths, n=6

4 deaths due to hepatotoxicity, 2 deaths related to INH and 2 not (? Efavirenz or other culprit)

	Immediate IPT		Deferred IPT			
	1	2	3	4	5	6
Location	Zimbabwe	Botswana	Zimbabwe	Tanzania	Tanzania	Tanzania
Age (yrs)	34	38	27	35	24	33
CD4	459	469	402	609	431	553
GA at entry (weeks)	33	21	31	26	26	30
Postpartum (PP) week at death	12 weeks	40 weeks	5 weeks	19 weeks	7.5 weeks	5.5 weeks
Time on INH	13 weeks (4 AP & 9 PP)	28 weeks (20 AP, 8 PP)	Never started	1 week PP	Never started	Never started
ART regimen initiated	TDF/3TC/EFV Started 1 week prior to entry	TDF/FTC/EFV Started 2.5 years prior to entry	TDF/3TC/EFV for 4 months prior to entry	DF/3TC/EFV+ OT 14 months rior to entry	TDF/3TC/EFV started 3 weeks before entry	TDF/3TC/EFV started 1 month before entry
Death cause	Fulminant hepatitis Related	Bacterial sepsis Not related	Fulminant hepatitis Not related	Fulminant hepatitis Related	Hepatitis Not related	Pneumonia Not related

Gupta NEJM 2019

PK: EFV AUC by CYP2B6 Genotype and INH Exposure in HIV+ Pregnant Women



CYP2B6 type	Extensive		Intermediate		Slow		Very Slow
INH exposure	-	+	-	+	-	+	-

More data to come: PK ART + TB treatment/preventive therapy in pregnancy

Among slow CYP2B6 metabolizers INH associated with higher EFV Cmin values especially among those with slow NAT 2 genotypes

Gausi 2020

The safety of isoniazid tuberculosis preventive treatment in pregnant and postpartum women: systematic review and meta-analysis

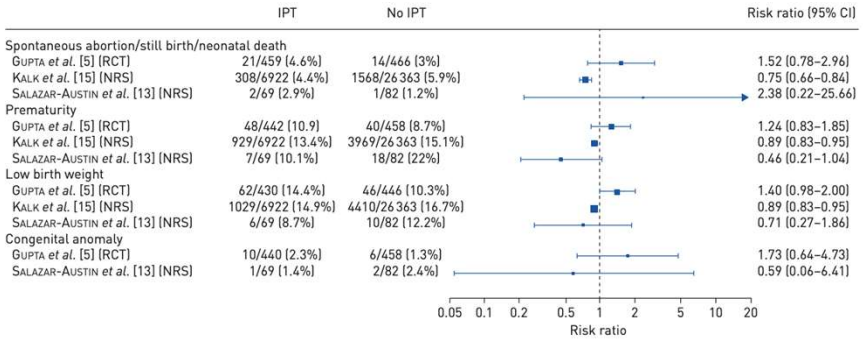
Hamada et al ERJ 2020

TABLE 3 Maternal deaths in pregnant women living with HIV

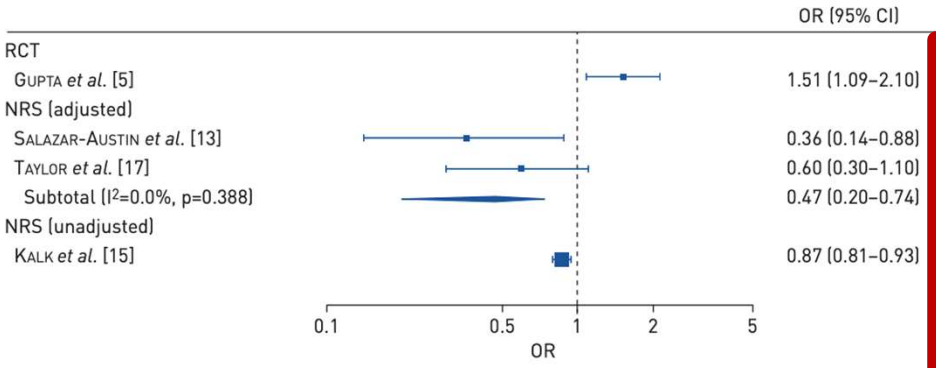
Study	IPT	Control	Risk ratio (95% CI)
Gupta *et al.* [5]	1 out of 477 (0.2%)	Placebo 3 out of 479 (0.6%)	0.33 (0.03–3.21)
Kalk *et al.* [15]	18 out of 10715 (0.2%)	No treatment 103 out of 41227 (0.3%)	0.67 (0.41–1.11)
Salazar-Austin *et al.* [13]	0 out of 71 (0%)	No isoniazid exposure 2 out of 84 (2%)	0.24 (0.01–4.84)
Tiam *et al.* [16]	2 out of 124 (1.6%)	NA	NA
Taylor *et al.* [17]	0 out of 103 (0%)	No isoniazid exposure 0 out of 93 (0%)	NA

IPT: isoniazid preventive therapy; CI: confidence interval; NA: not available.

Individual pregnancy outcomes

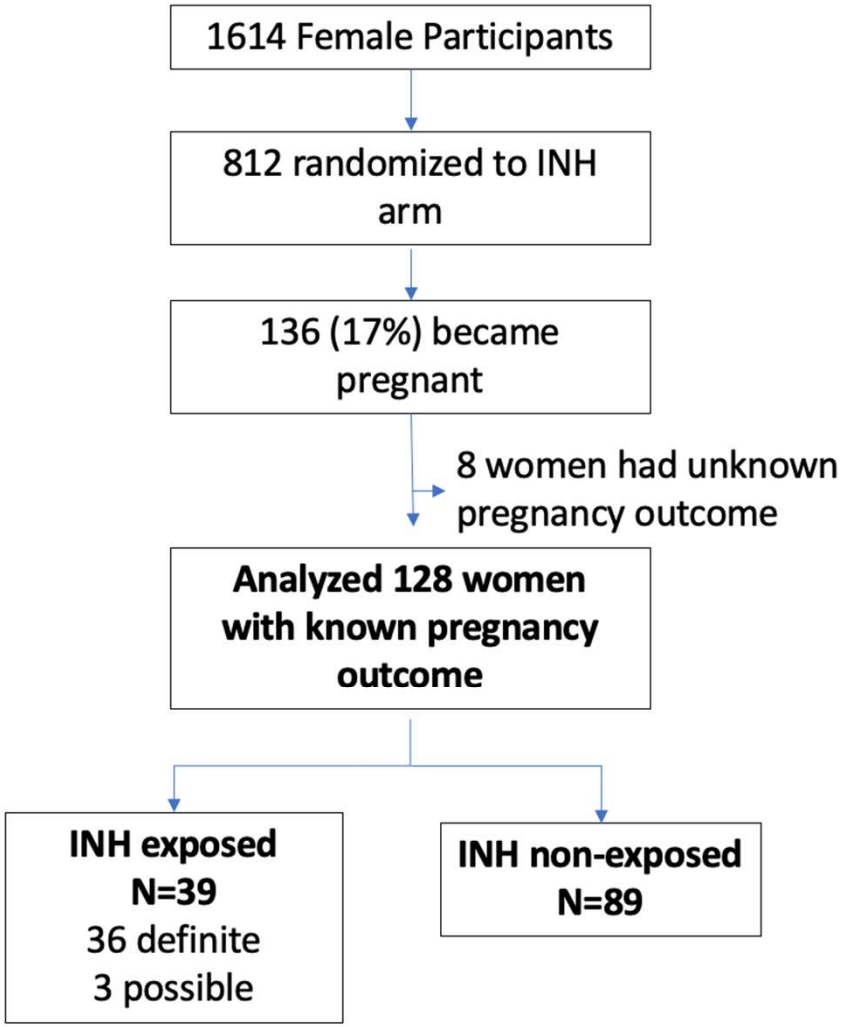


Composite pregnancy outcomes



"We found inconsistent associations between IPT and adverse pregnancy outcomes. Considering the grave consequences of active TB in pregnancy, current evidence does not support systematic deferral of IPT until postpartum. Research on safety is needed"

New data on 1st trimester exposure: Results from BRIEF TB trial INH arm

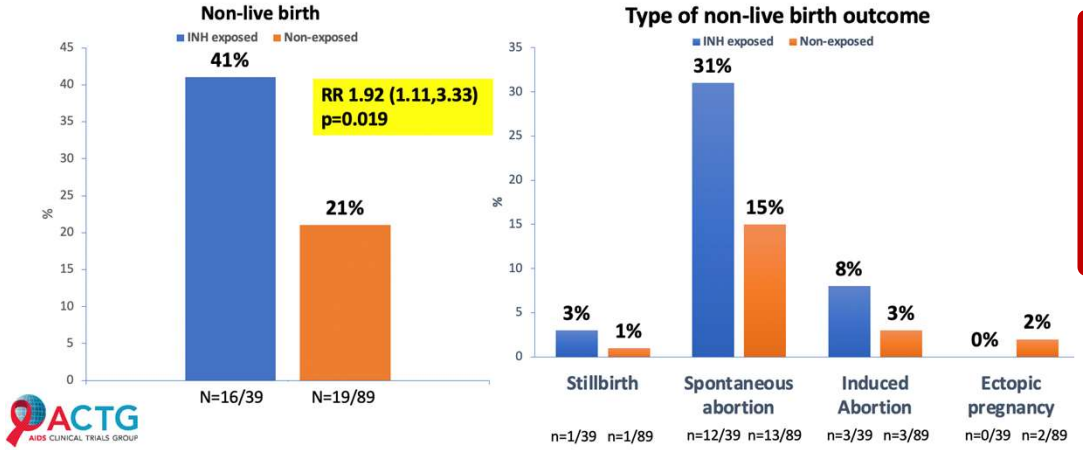


	INH-exposed N=39	Non-exposed N=89	P-value
Median Age (IQR), years (at pregnancy outcome)	30.0 (26.4,36.3)	31.7 (27.2,36.0)	0.538
CD4 count at entry, cells/mm3	527	538	0.541
CD4 closest to pregnancy, cells/mm3	522	555	0.608
ART at study entry	15 (38%)	30 (34%)	0.688
ART at pregnancy outcome EFV-based Non-EFV based	**31 (79%)** **25 (64%)** **6 (15%)**	**85 (96%)** **77 (87%)** **8 (9%)**	**0.007** **0.006**
LTBI positive	10 (26%)	16 (18%)	0.346
INH exposure duration* Completed 36 weeks Partial treatment Ongoing treatment Possible early exposure	 19 (49%) 9 (23%) 8 (20%) 3 (8%)	 NA	

Gupta, CROI 2021

New data on 1st trimester exposure: Results from BRIEF TB trial INH arm

Non-live Birth Outcome More Likely in INH-exposed Pregnancies



INH exposure, which was mainly during the first trimester of pregnancy, was associated with an increased proportion of non-live births

Outcome	Proportion Exposed vs Unexposed	Unadjusted RR (95% CI)	P	Adjusted RR (95% CI)	P	2nd Adjusted Model RR (95% CI)	P
Non-live birth	16 (41%) vs 19 (21%)	1.92 (1.11, 3.33)	0.02	**1.98 (1.15, 3.41)**	**0.01**	1. 47 (0.84, 2.55)	0.18
Adverse Pregnancy Outcome (induced abortions excluded)	13 (36%) vs 16 (19%)	1.94 (1.04, 3.61)	0.04	**1.98 (1.08, 3.65)**	**0.03**	1.52 (0.83, 2.81)	0.18

Adverse pregnancy outcome: spontaneous abortions, still birth, ectopic pregnancy
Primary model adjusted for maternal age, CD4, LTBI status, ART at entry
2nd Adjusted model: proximate to pregnancy variables, maternal age, last CD4, LTBI status, **ART status at pregnancy outcome**. Analysis sensitive to numbers of women on ART.

What about shorter regimens for TPT in pregnancy?

3HP?

1HP?

Rifapentine Pharmacokinetics and Safety of 3HP in Pregnant Women with and without HIV (IMPAACT 2001)

Study design:

Cohort 1: 14 to <28 weeks

Cohort 2: 28 to <34 weeks

TBI+ or recent contact

If HIV+ on EFV-based regimen

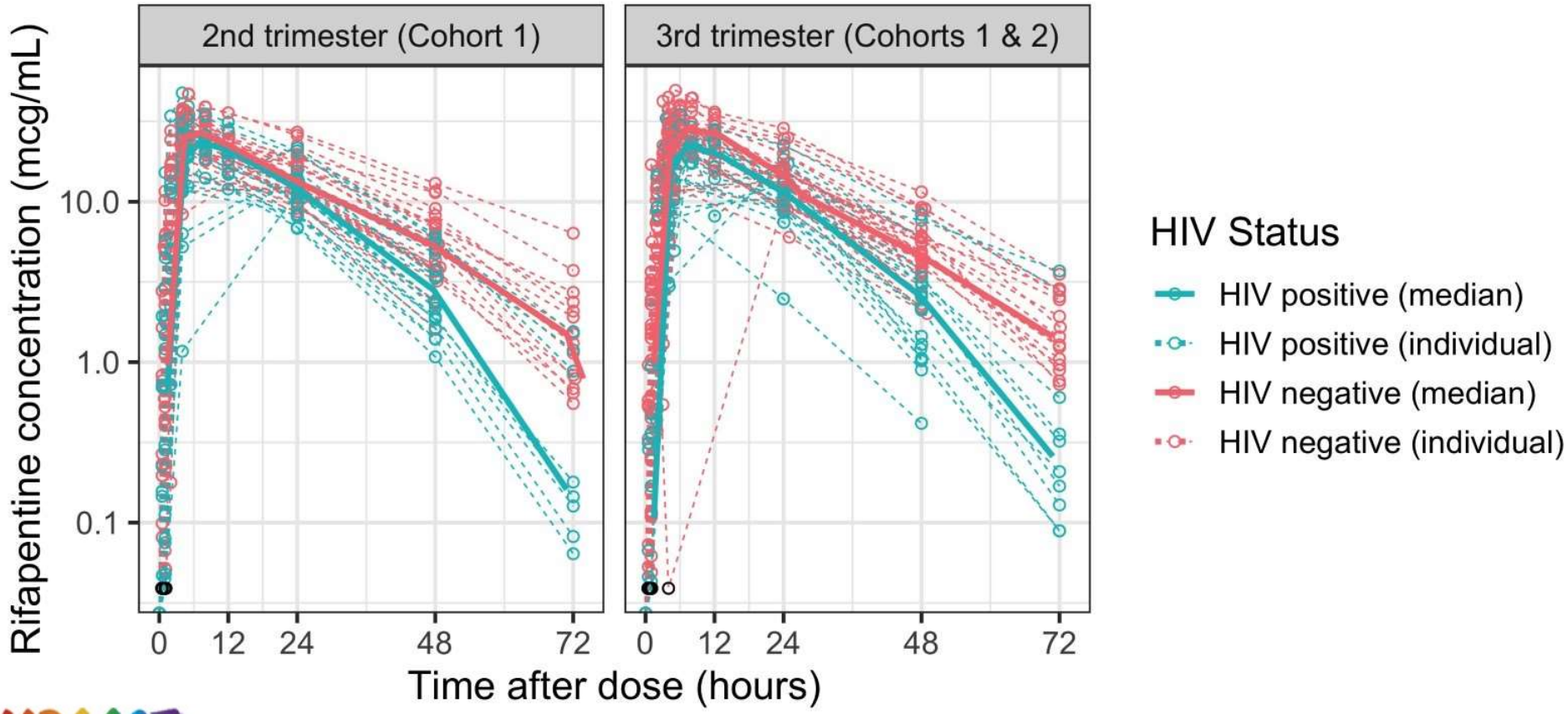
Enrolled 50 pregnant women, 20 HIV+

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Mathad et al CROI LB 2020 Abst. #4428, CID 2021

3HP in pregnancy P2001 trial results
Effect of HIV on clearance of RPT in 2nd and 3rd trimester

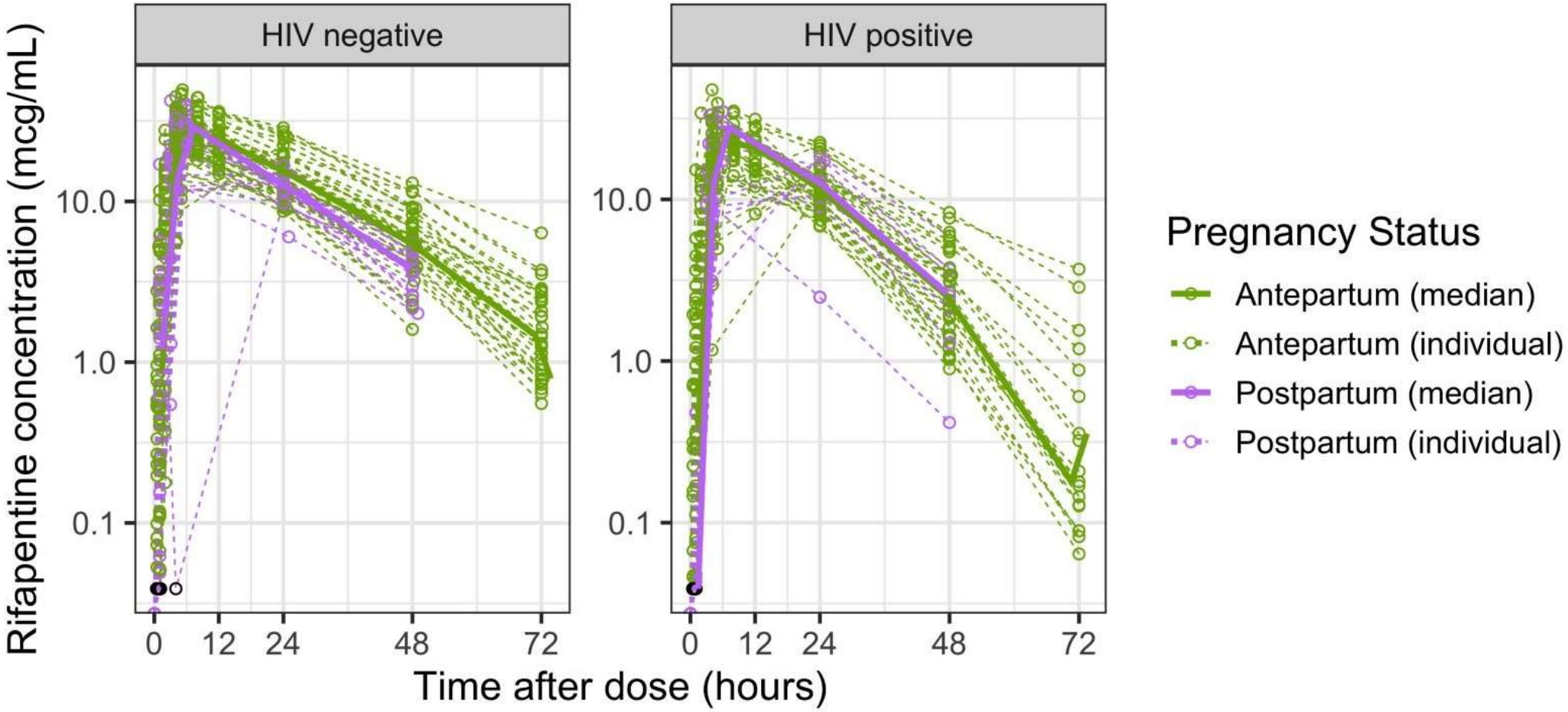
Parameter	HIV-positive	HIV-negative	% change vs. HIV-
Clearance, L/hr (RSE)	1.56 (7%)	1.20 (6%)	↑30%
AUC_{ss}, mg/L*hr (IQR)	522 (359-803)	786 (549-1171)	↓34%



IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

Mathad CID 2021

P2001: Effect of pregnancy on RPT



Status	Antepartum	Postpartum	% change vs. pregnancy
HIV-positive clearance, L/hr (RSE)	1.56 (7%)	1.60 (11%)	↑ 2%
HIV-negative clearance, L/hr (RSE)	1.20 (6%)	1.53 (8%)	↑28%

IMPAACT
International Maternal Pediatric Adolescent AIDS Clinical Trials Network

P2001: Key finding for 3HP in pregnancy

1. There is no dose adjustment of RPT required in pregnancy.
2. In women with HIV on EFV, clearance of RPT was higher than expected during pregnancy.
   - Exposures remained in the therapeutic range
   - Need studies of RPT and other ART options (e.g. DTG) in pregnancy to see if effect is from HIV or EFV, specifically
3. Safety and tolerability data for 3HP in pregnancy are encouraging
   - BUT NOT POWERED FOR SAFETY SO Need larger studies to definitively characterize safety
4. PK data from infants and breast milk coming soon

Filling the gaps for maternal TB

Implementation Science
-PMTCT/TB screening &IPT

Epidemiology of latent and active TB

ARVs /ATT drug interactions

Immunology and pathogenesis of TB

PK, safety, and outcome studies of:
-short course TBI regimens
-1st and 2nd line TB medications

Cost-effectiveness studies for TB screening/treatment

Summary

- Peak incidence of TB during reproductive age
- Maternal TB associated with adverse pregnancy outcomes, maternal mortality and infant TB and mortality
- Immune and physiological changes may be of importance to screening diagnostic yield, TB drug disposition, toxicity
- Difference in PZA guidance between CDC and WHO guidelines
- Need to include pregnant women in trials of diagnostics and drugs whenever feasible
- Safety of INH in pregnancy a concern
- Several studies now ongoing that will help to fill in the knowledge gap

"Each year, millions of women and children die from preventable causes. These are not mere statistics. They are people with names and faces. Their suffering is unacceptable in the 21st century"

Ban Ki-moon,
United Nations Secretary-General,
Global Strategy for Women's and
Children's Health, September 2010

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