



TB infection in pregnancy:

Novel insights into immunology and prevention

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Weill Cornell Medicine
Center for Global Health

Objectives

Epidemiology

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graph TD; A[Epidemiology] --> B[Immunology of TB and pregnancy]; B --> C[TB prevention in pregnancy];
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Immunology of TB and pregnancy

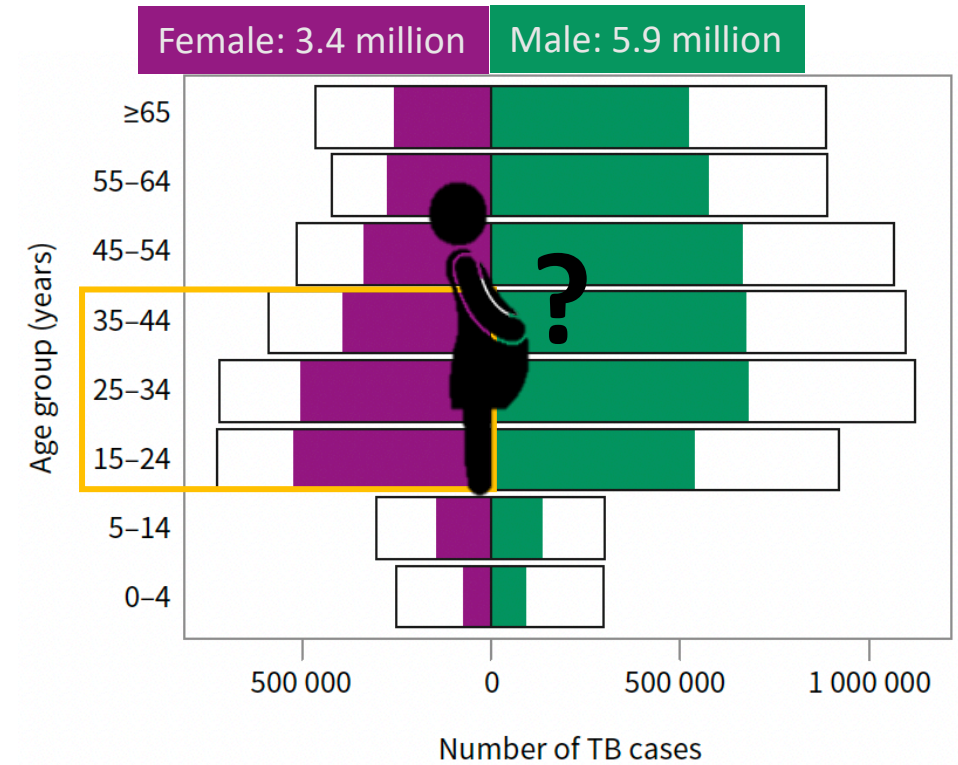
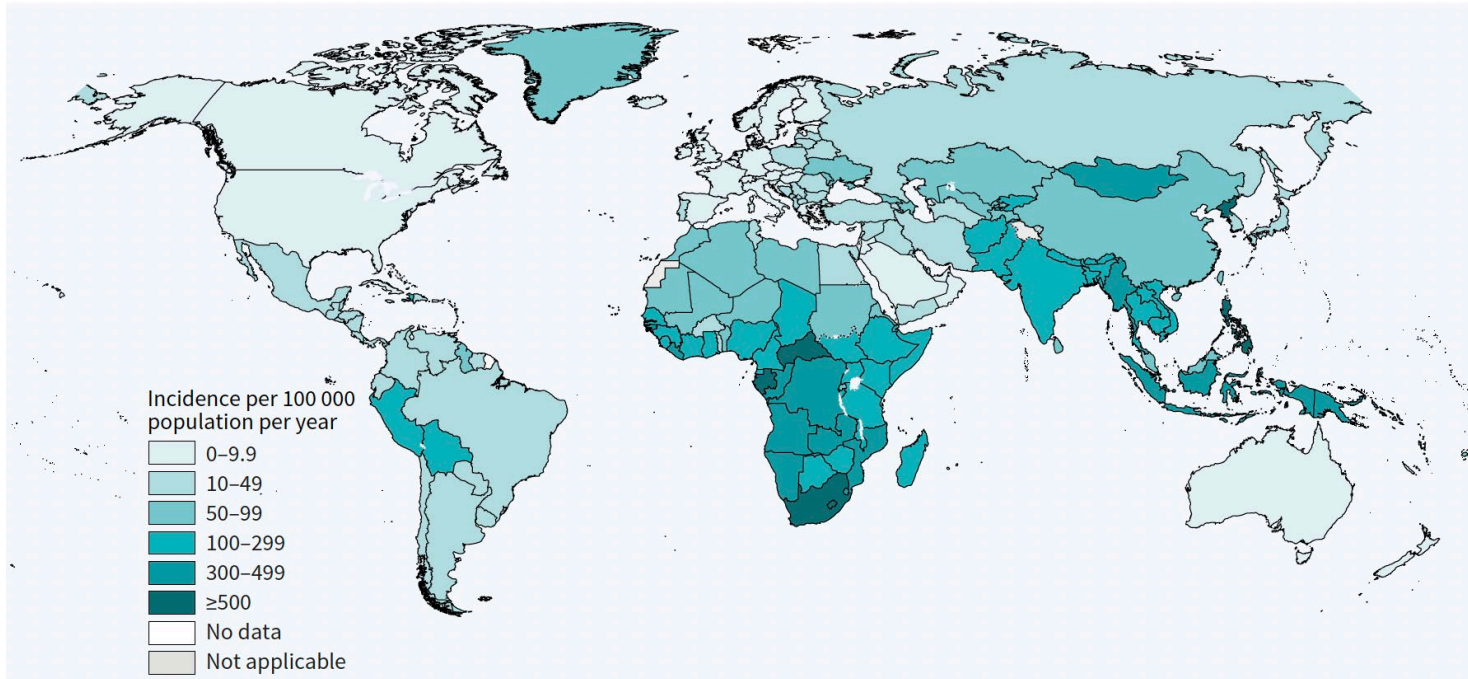
TB prevention in pregnancy



What is the burden
of TB in pregnancy?



Global TB incidence by sex, 2021



Global estimate of TB in pregnancy

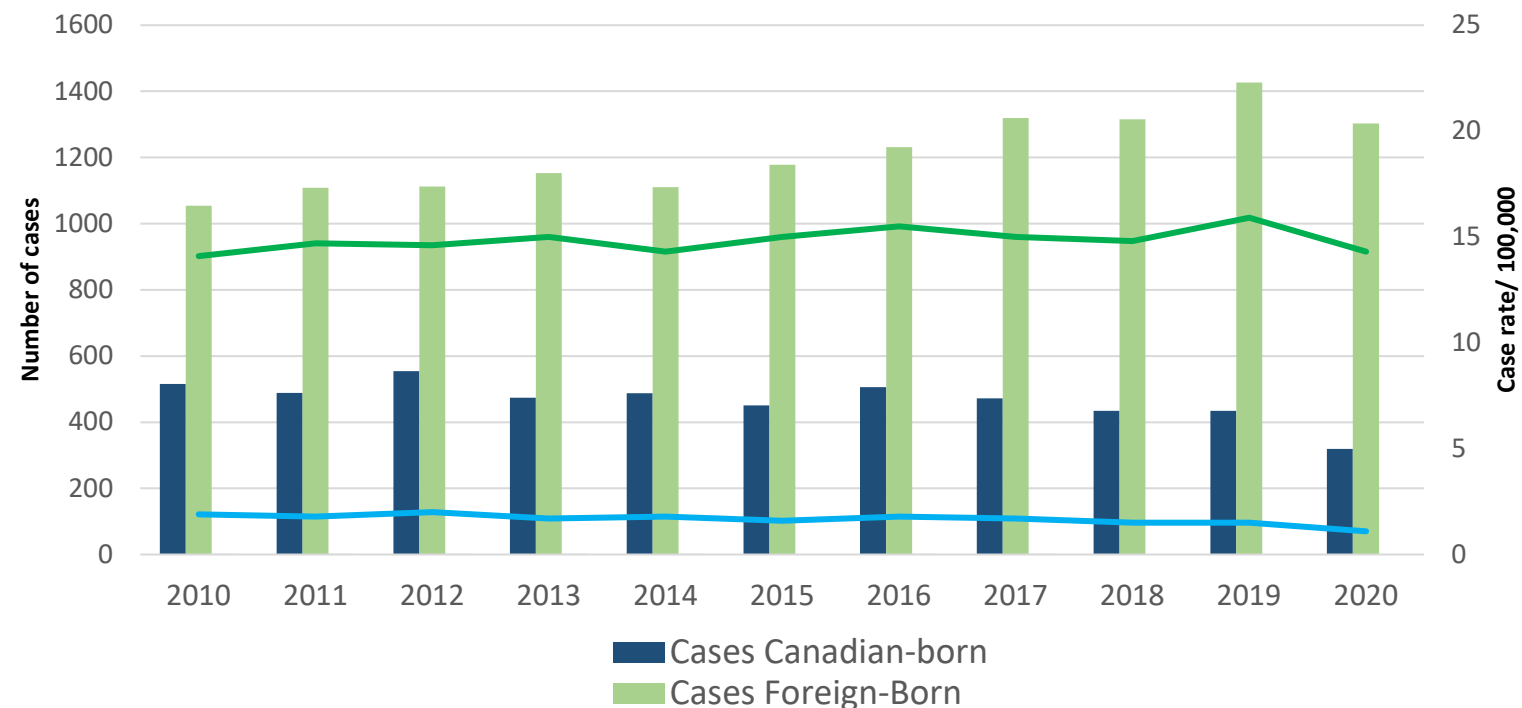
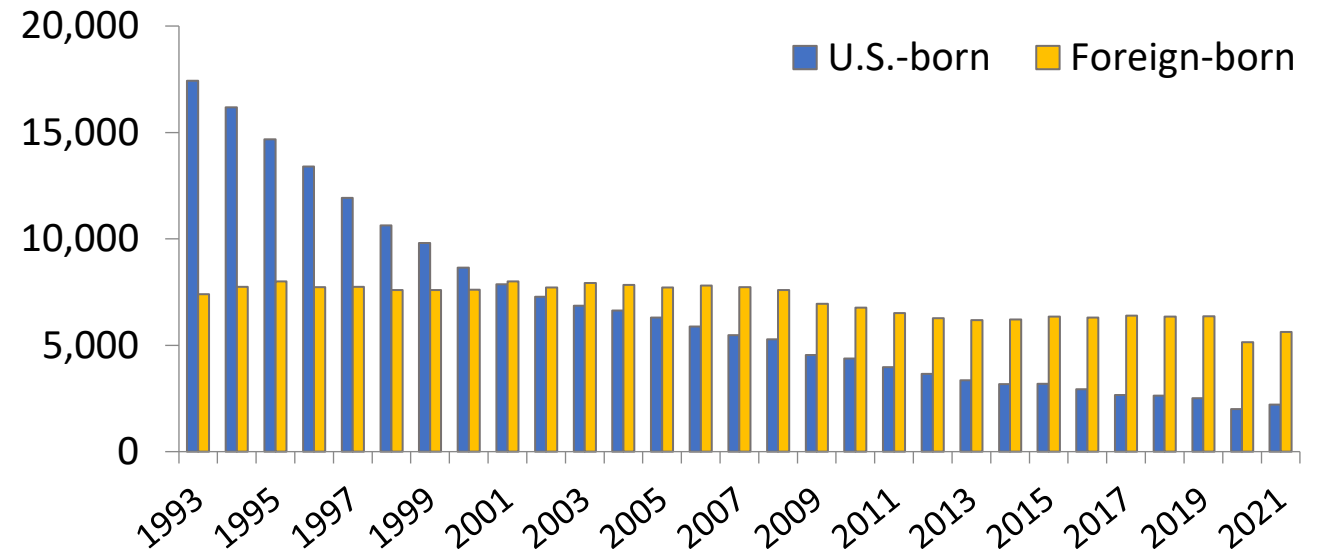
	Mean (95% uncertainty range)	Rate per 1000 pregnant women (95% uncertainty range)	Percentage of global burden
All countries combined	216 500 (192 100–247 000)	2.1 (1.8–2.4)	..
African Region	89 400 (74 200–110 500)	3.6 (3.0–4.5)	41%
Region of the Americas	4800 (3900–6000)	0.4 (0.3–0.5)	2%
Eastern Mediterranean 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

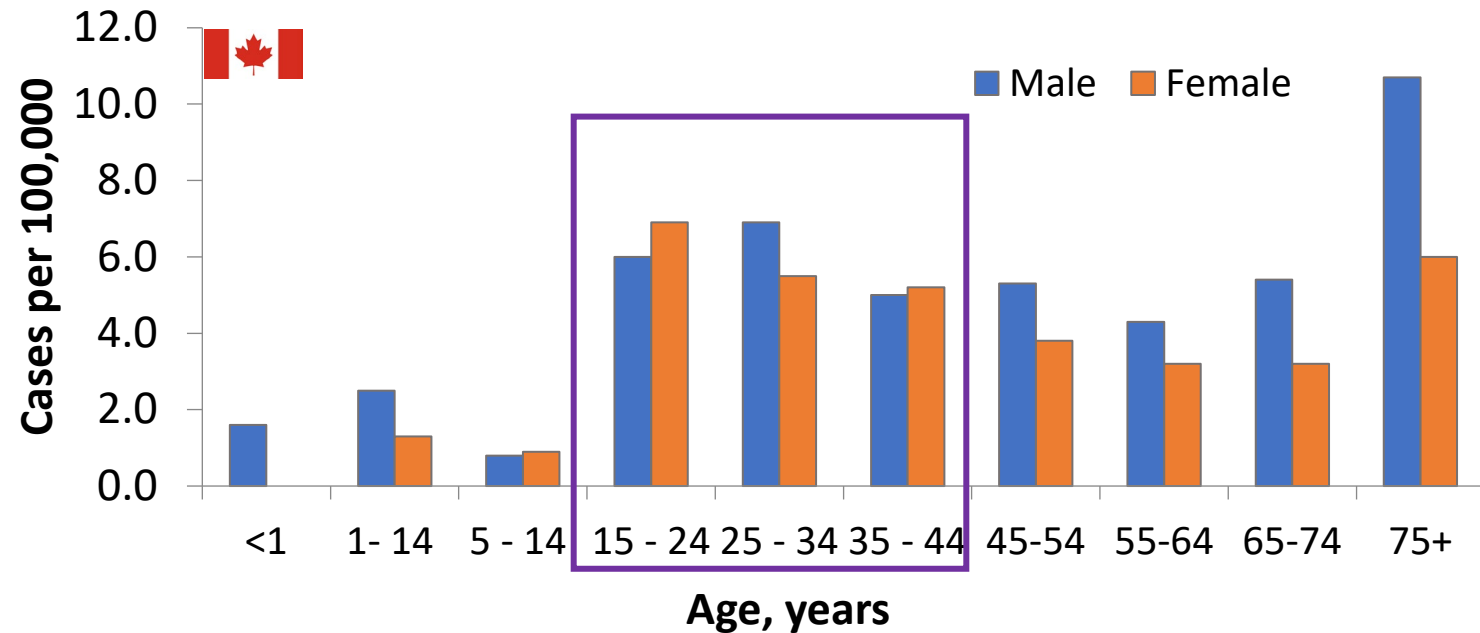
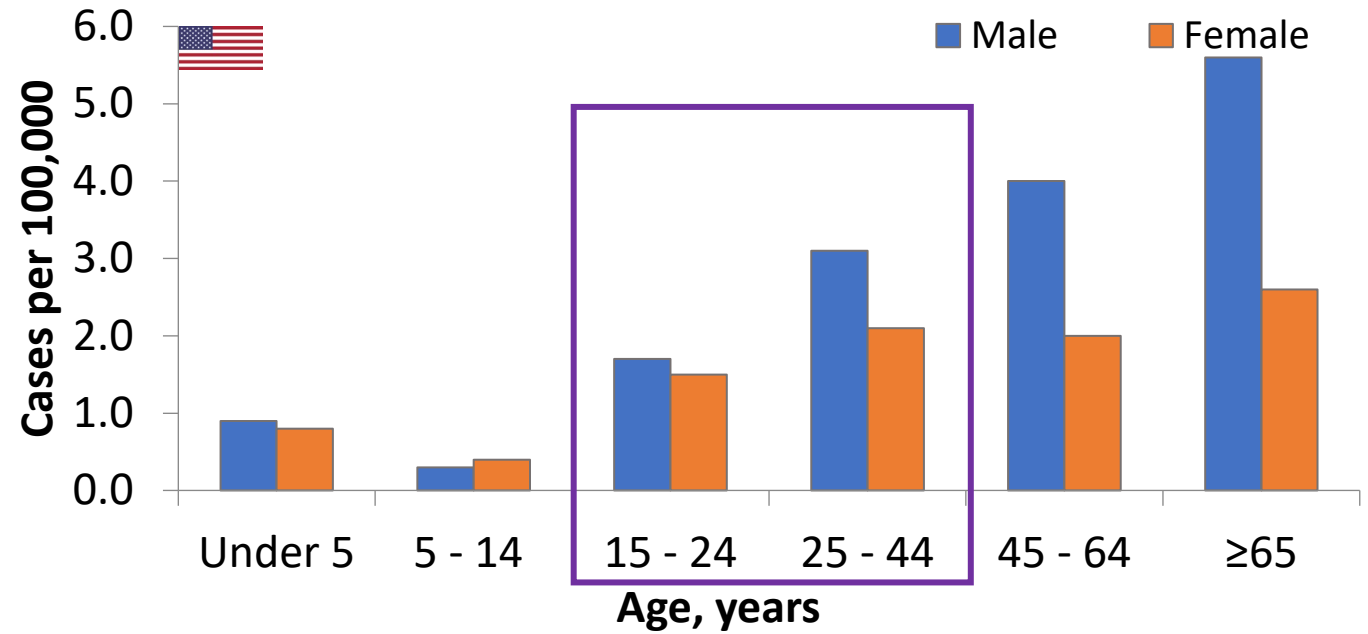
TB Incidence in US- or Canadian- vs. foreign-born persons, 1993-2021

- *US CDC TB Report, 2022*
- *Tuberculosis Surveillance in Canada Summary Report, 2010-2020*



TB Rates, by Age and Sex: United States, 2022 Canada, 2020

- *US CDC TB Report, 2022*
- *Tuberculosis Surveillance in Canada Summary Report, 2020*



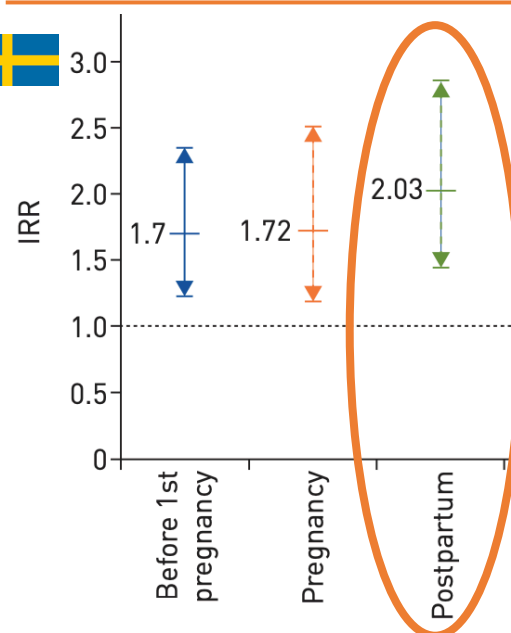
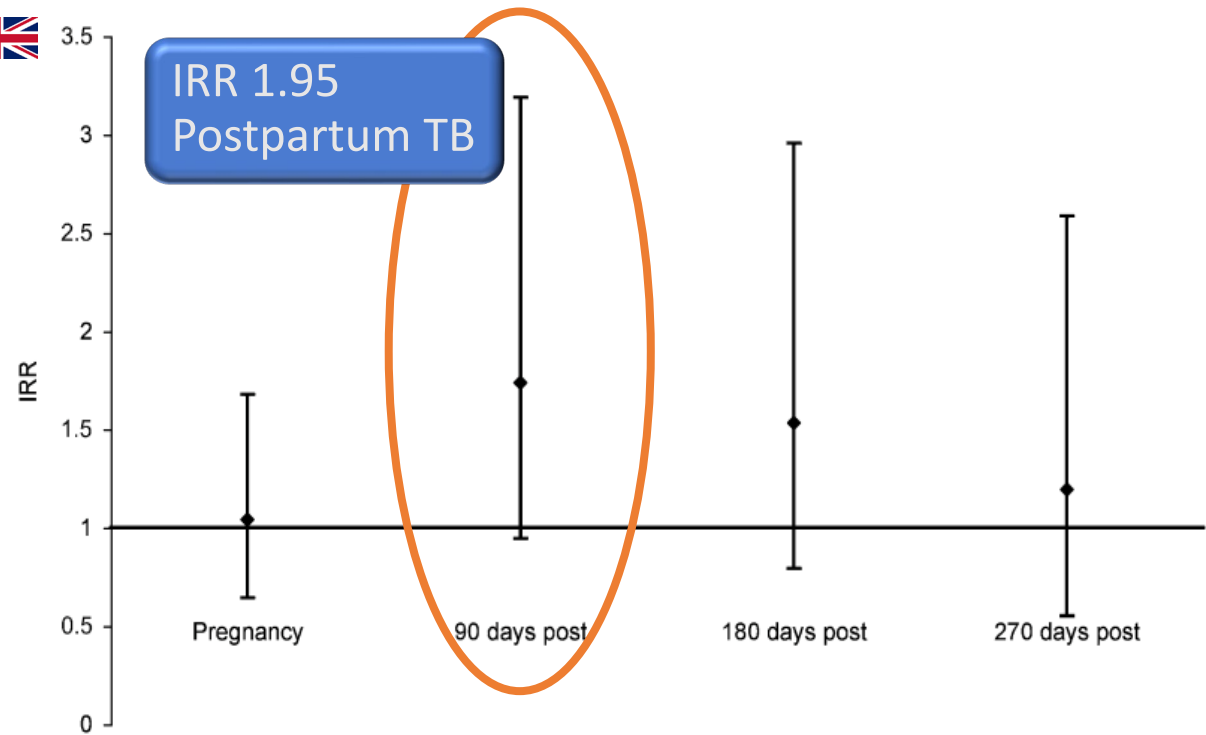
Risk of TB in Pregnancy

UK Cohort: 1996-2008

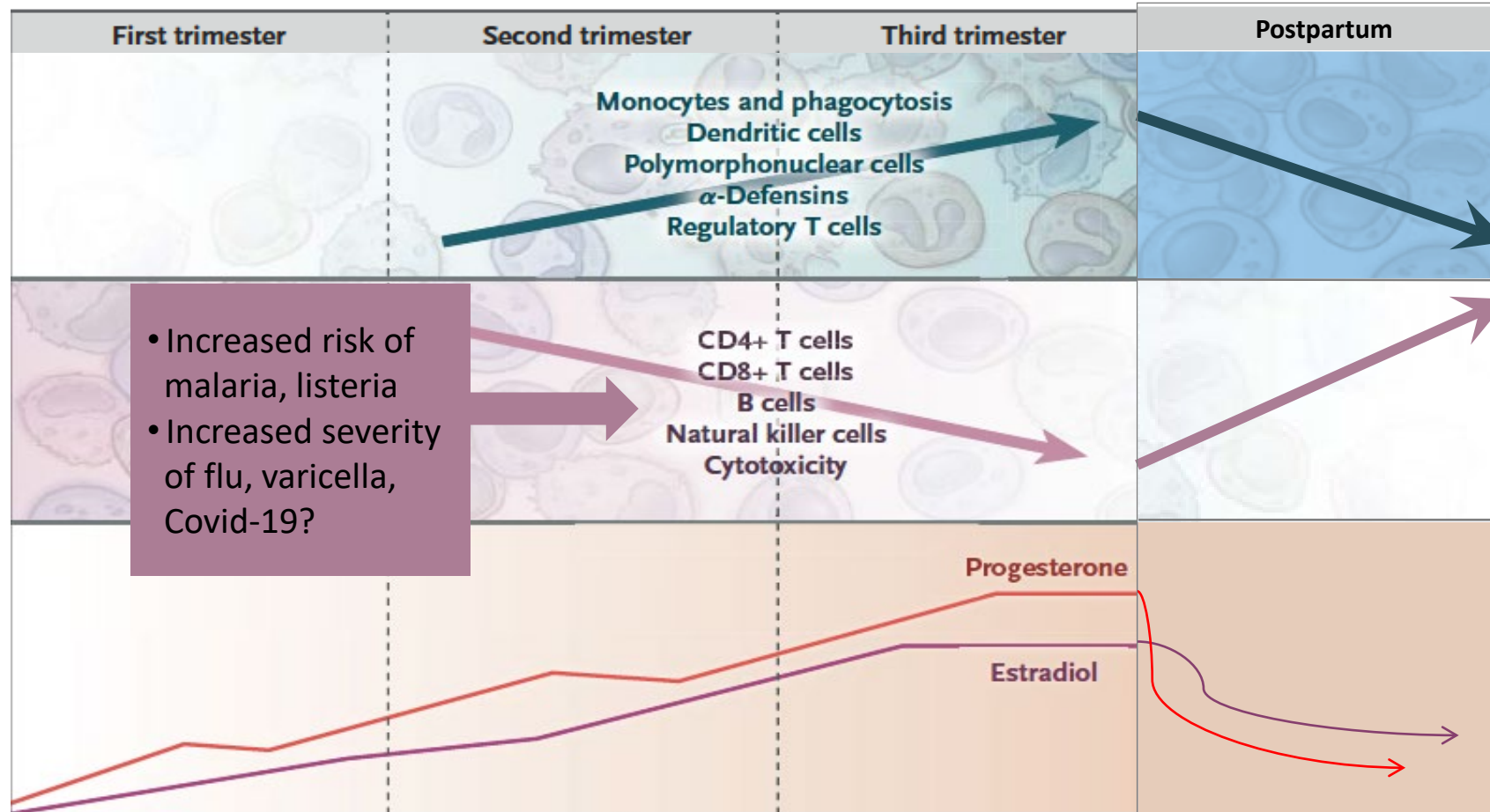
- 192, 801 women
- 177 TB events:
 - **Postpartum 15.4 vs. 9.1 per 100,000 PY**

Swedish cohort: 2005-2013

- 649, 342 women
- 553 TB events:
 - **Postpartum: 17 vs. 9 per 100,000 PY**



Immune changes during pregnancy increase risk of disease

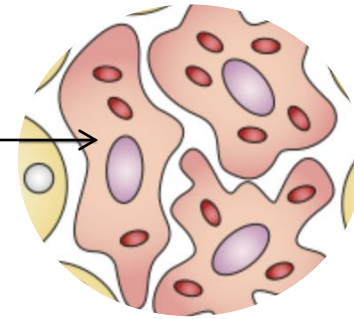
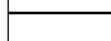


Immunology of TB infection

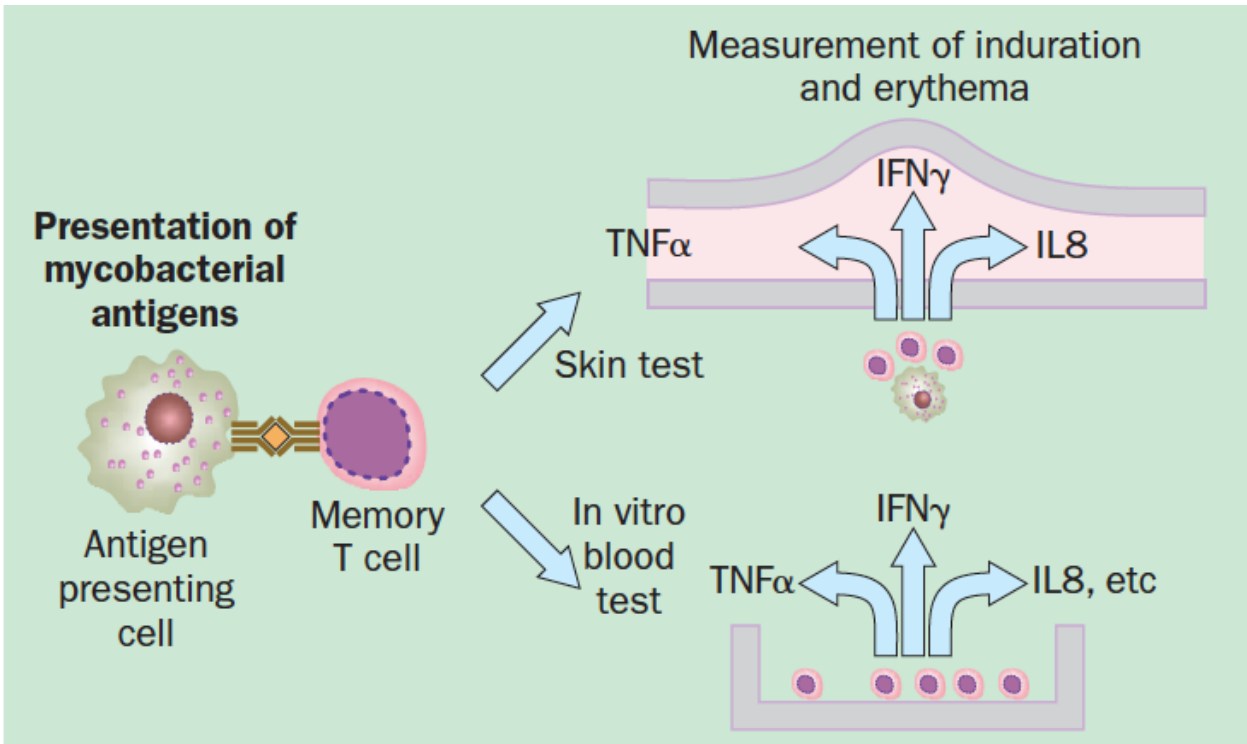
CD4⁺ T cells release
IFN- γ , TNF- α



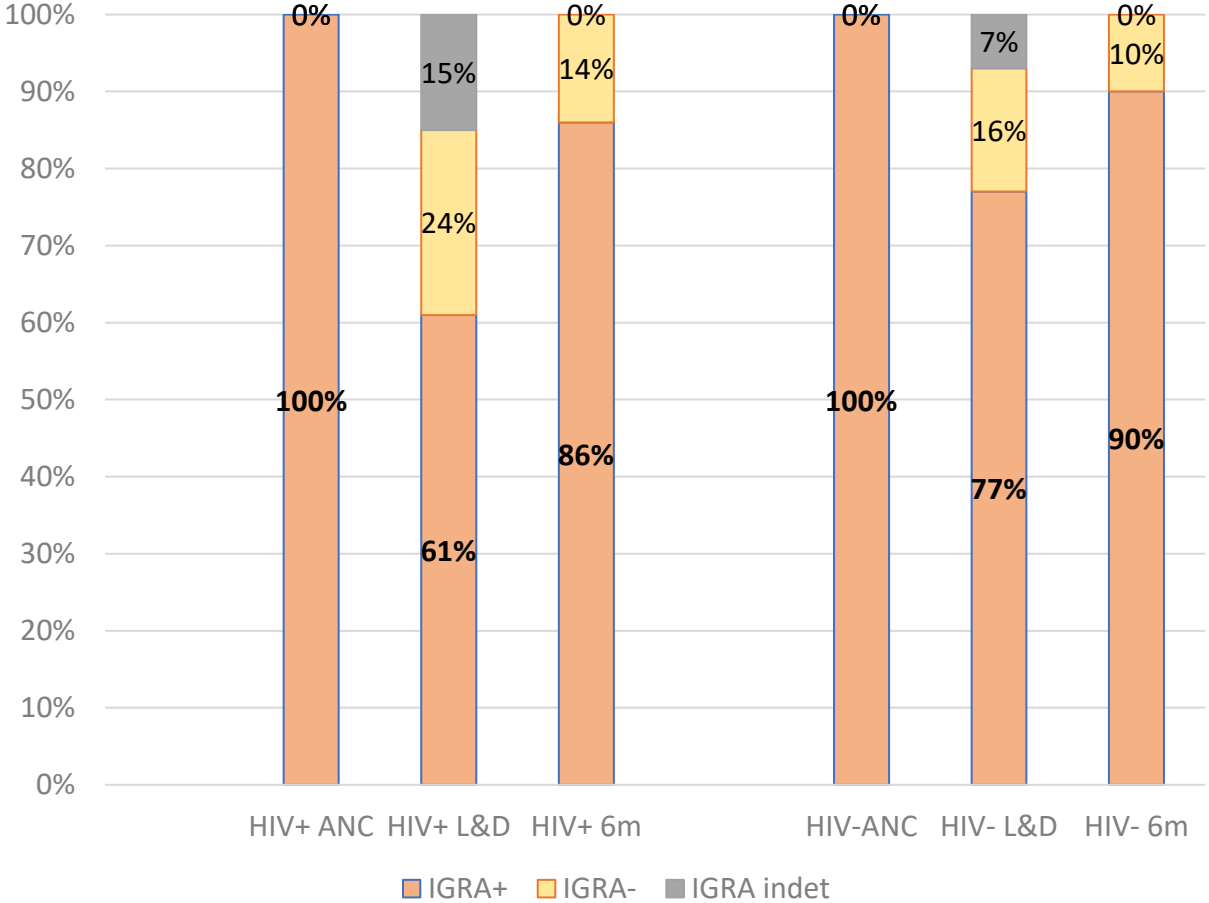
IFN- γ , TNF- α
stimulate
macrophages



Clue #1: Latent TB tests perform differently during pregnancy

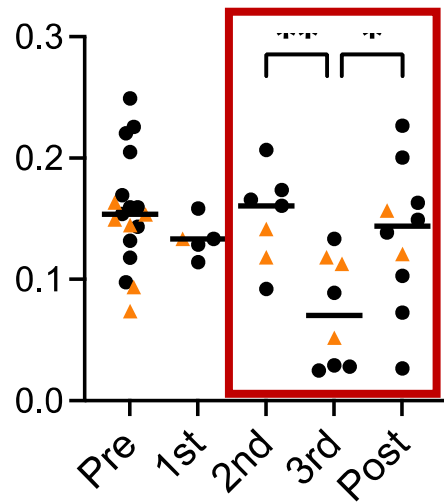


Clue #2: IGRA and IFN- γ responses change with stages of pregnancy

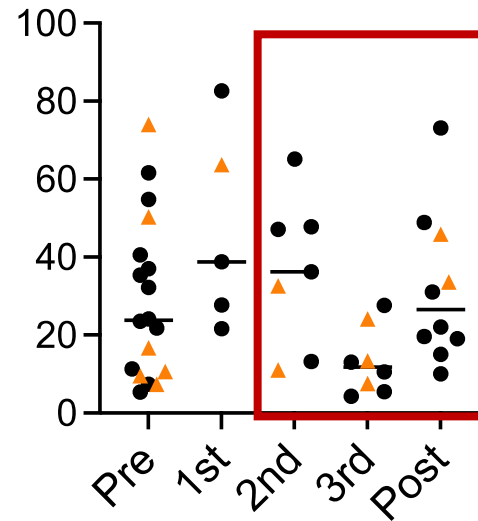


Clue #3: Cellular responses change in the 3rd trimester

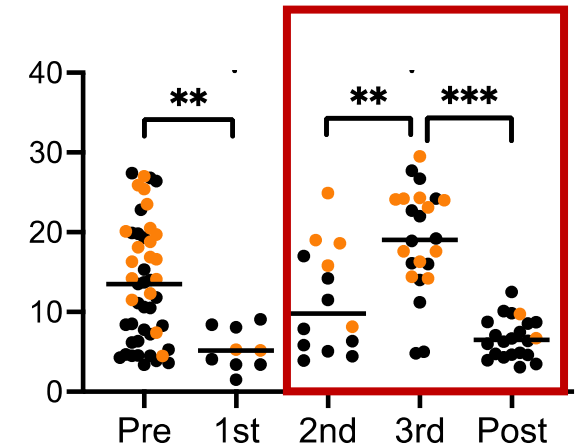
1. Mtb-specific CD4+ T-cell responses diminish third trimester



2. Mtb-specific T Effector memory cells diminish third trimester



3. Non-specific CD4+ T-cell activation increases third trimester



● Black circle: HIV-
▲ Gold triangle or circle: PLHIV

Putting it all
together

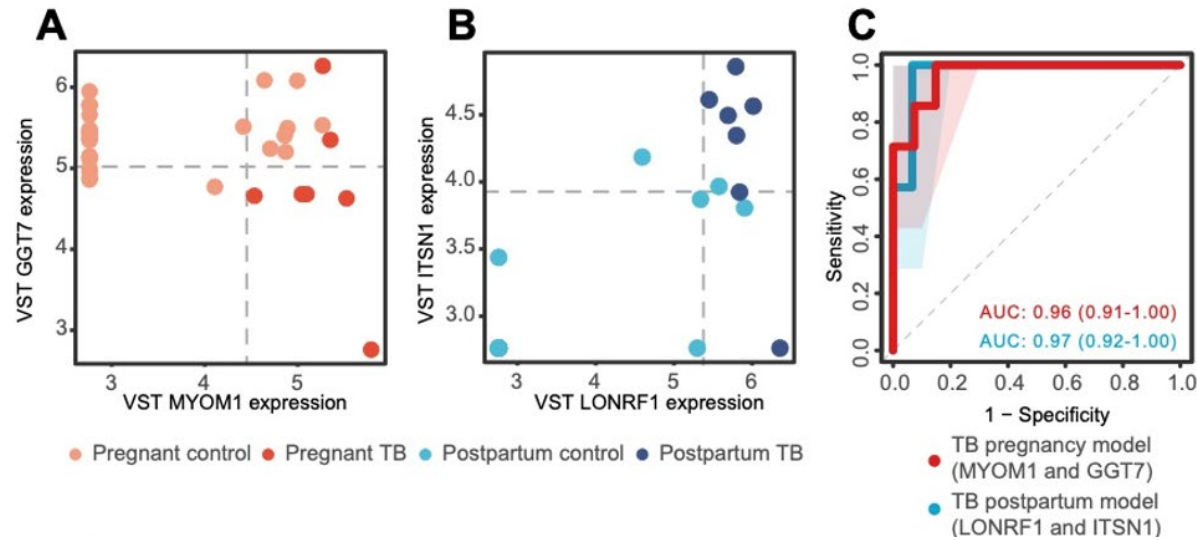
The **frequency of MTB-specific T-cell subtypes decreases** as pregnancy progresses.

Non-specific CD4+ T-cell activation increases in 3rd trimester; this has been associated with progression in other populations.

Cellular and cytokine changes correlate with the longitudinal changes in IGRA responses during pregnancy.

But does this result in TB progression?

Unique gene sets diagnose and predict postpartum TB



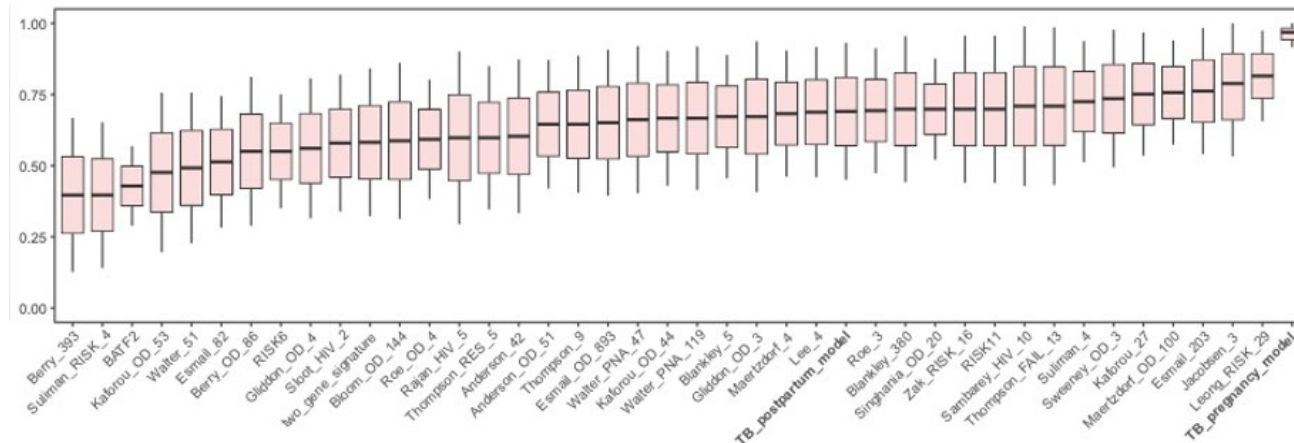
Diagnostic model:
ITSN1 and LONRF1

- Involved in adaptive *and* innate immunity

Predictive model:
MYOM2 and GGT7

- Glutathione metabolism

Neither involve IFN pathways.



The background features a dark grey gradient with several overlapping, wavy, translucent purple shapes that create a sense of movement and depth. A thin white rectangular border is centered on the page, framing the text.

TB prevention in pregnancy



Case presentation

35 yo pregnant female
with HIV from India
presenting for first
antenatal visit.
IGRA is positive.

How would you manage
this patient?

Recommendations for TB prevention regimens

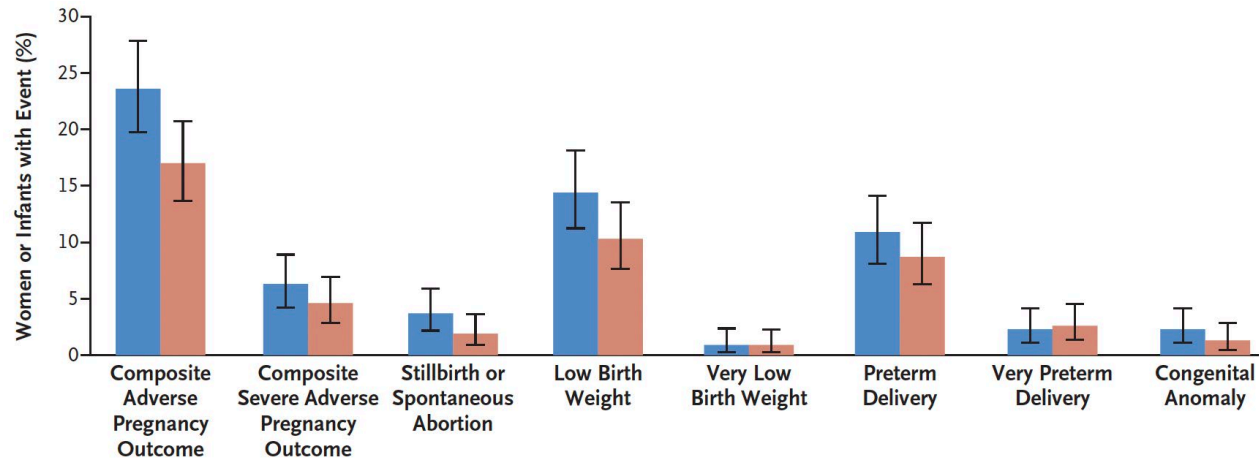
Priority	Regimen	Recommendation	Evidence
Preferred	3 months of weekly INH + RPT (3HP)	Strong	Moderate
Preferred	4 months daily RIF (4R)	Strong	Moderate (HIV negative)
Preferred	3 months daily INH + RIF (3HR)	Conditional	Very low (HIV negative)
Alternative	6 months daily INH (6H)	Strong Conditional	Moderate (HIV negative) Moderate (HIV positive)
Alternative	9 months daily INH (9H)	Strong	Moderate

Is IPT safe in pregnancy?

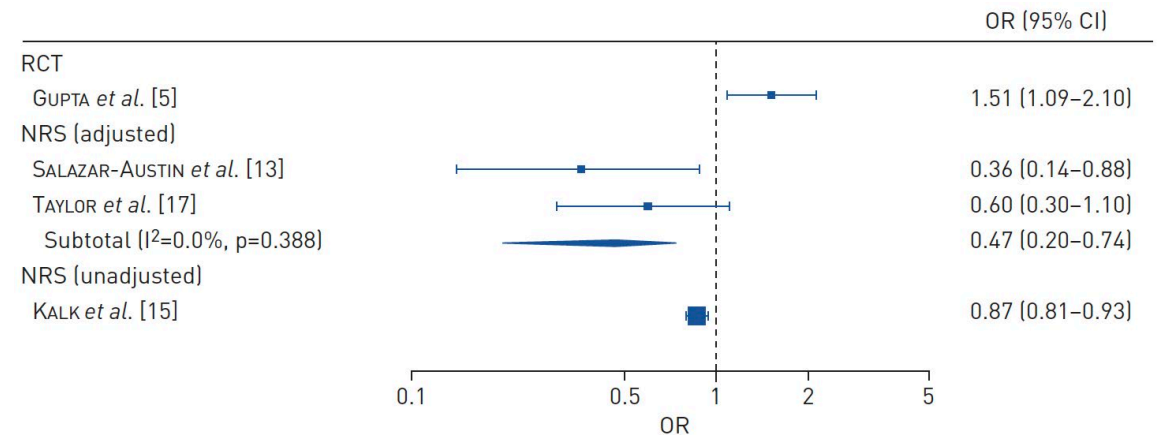
HIV+ pregnant women:
14-34 weeks gestation

Arm A:
Immediate IPT

Arm B:
Deferred IPT



Systematic Review

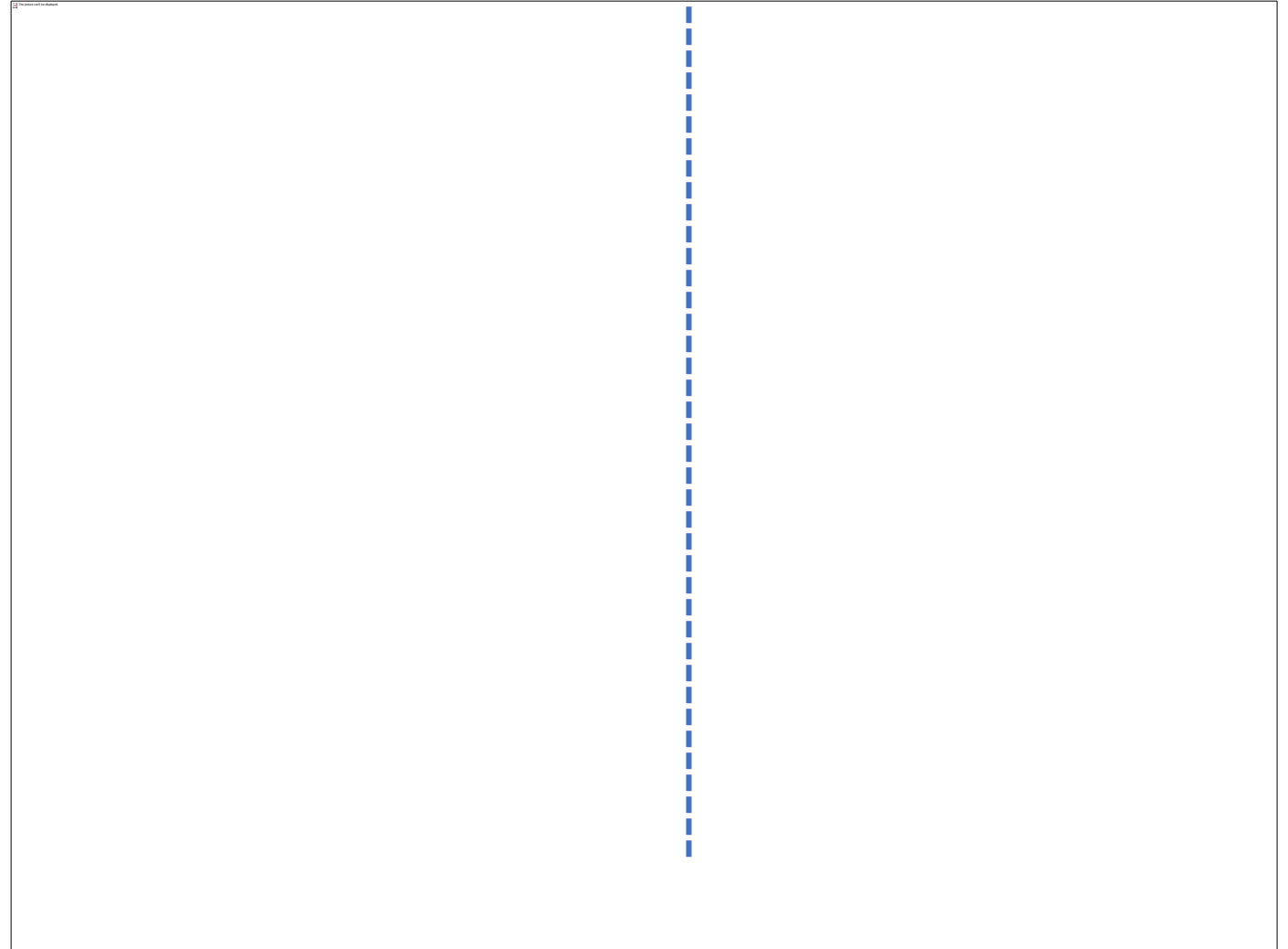


Which one do you believe?

Is IPT safe postpartum?

TB APPRISE:

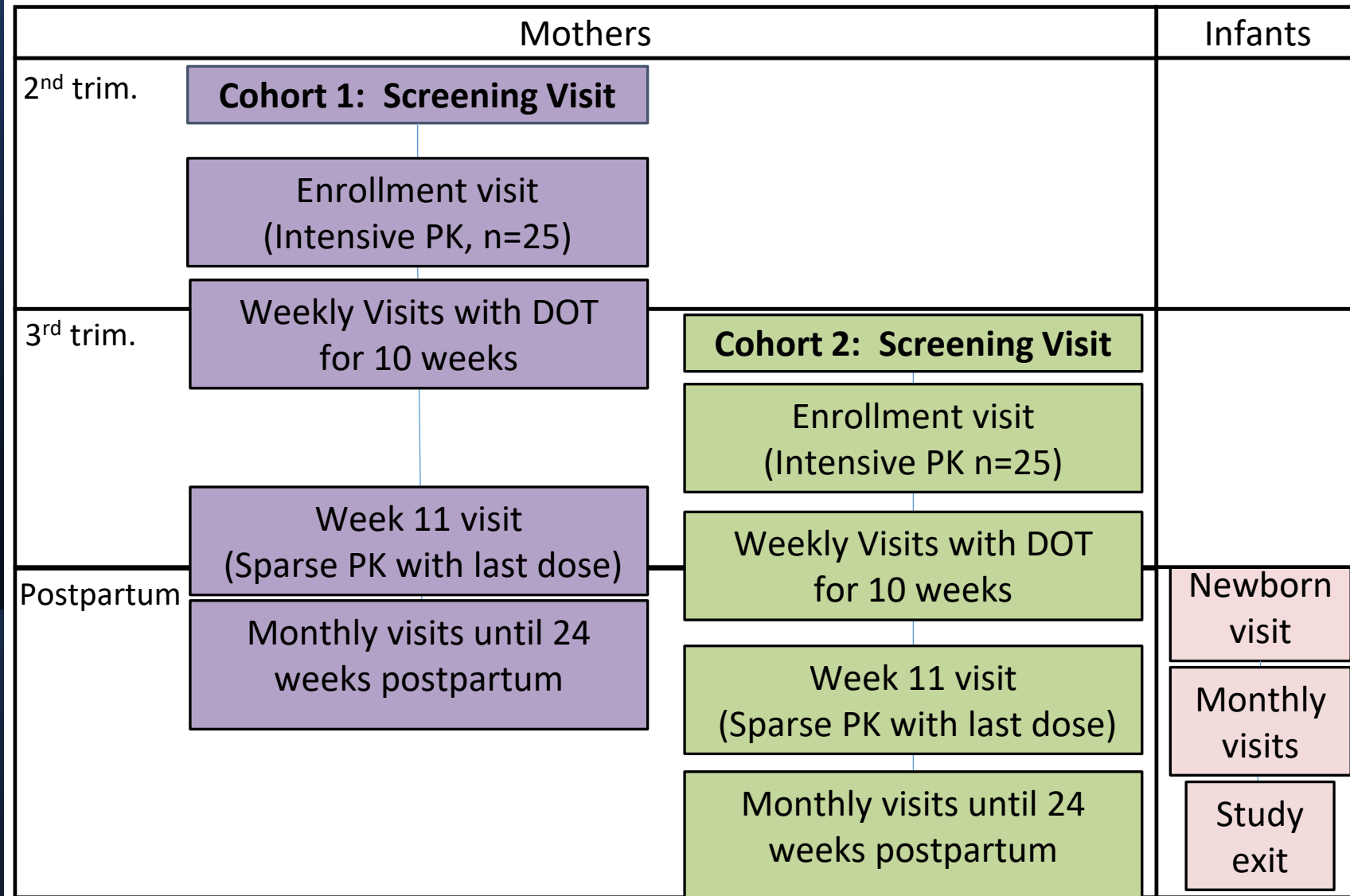
- Increased hepatotoxicity postpartum (7.2% vs. 6.2%, $p=0.56$)
- Increased ALT in both arms at 12 weeks postpartum

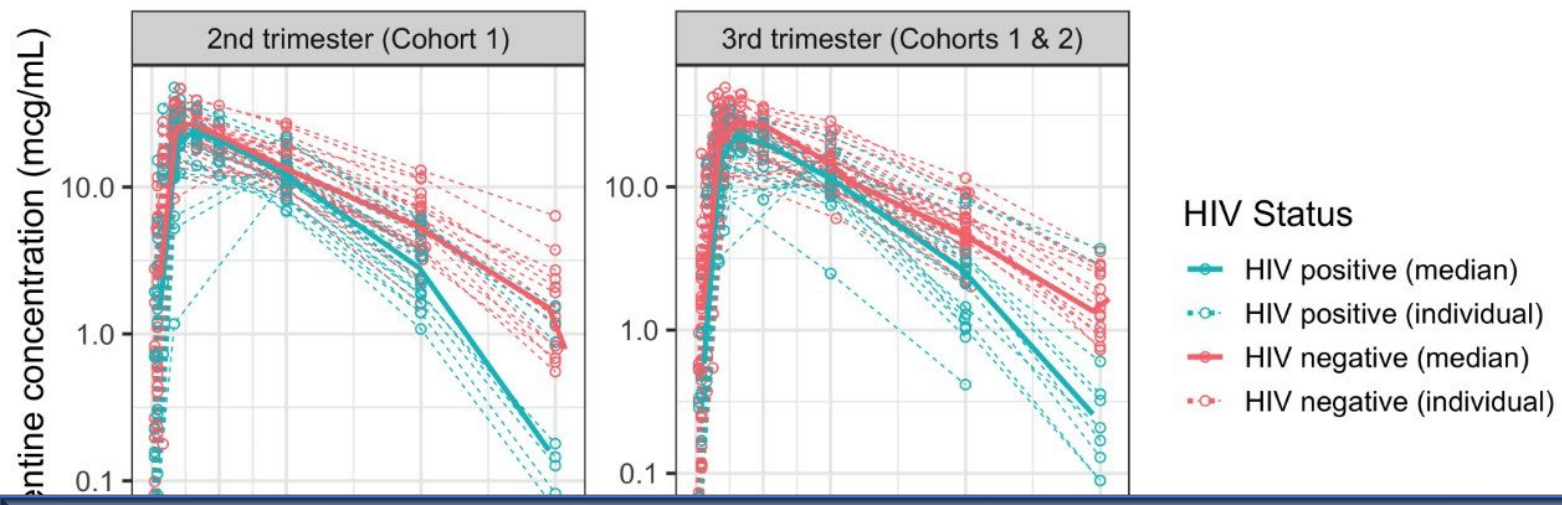


What about 3HP?

Outcome	Pregnancies Exposed to Study Drugs			All Reported Pregnancies		
	3HP (<i>n</i> = 31)	9H (<i>n</i> = 56)	Total (<i>n</i> = 87)	3HP (<i>n</i> = 54)	9H (<i>n</i> = 72)	Total (<i>n</i> = 126)
Pregnancy outcomes						
Live birth, <i>n</i> (%)	20 (65)	41 (73)	61 (70)	37 (69)	56 (78)	93 (74)
Elective abortion, <i>n</i> (%)	7 (23)	7 (13)	14 (16)	9 (17)	7 (10)	16 (13)
Fetal loss (all are spontaneous abortion <20 wk), <i>n</i> (%)	4 (13)*	8 (14)*	12 (14) [†]	8 (15) [‡]	9 (13) [‡]	17 (13) [§]
Fetal loss, <i>n</i> (%) 95% CI of individual proportion	4/31 (13) (4–30)	8/56 (14) (6–26)	12/87 (14) (7–23)	8/54 (15) (7–27)	9/72 (13) (6–22)	17/126 (13) (8–21)
Infant outcomes						
Congenital anomalies, <i>n</i> (%)	0	2 (5)	2 (3) ^{**}	1 (3) ^{††}	2 (4) ^{††}	3 (3) ^{††}
Congenital anomalies, <i>n</i> (%) 95% CI of individual proportion	0/20 (0) (0–17)	2/41 (5) (1–17)	2/61 (3) (0–11)	1/37 (3) (0–14)	2/56 (4) (0–12)	3/93 (3) (1–9)

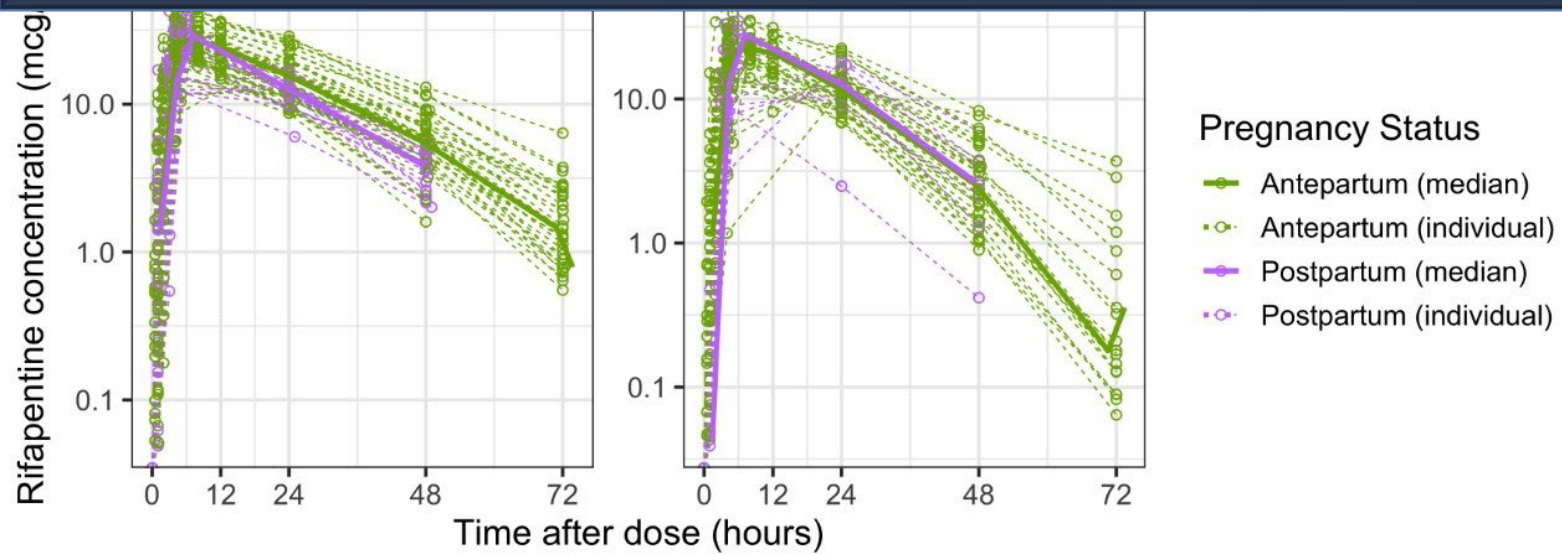
IMPAACT 2001: Safety and PK of 3HP in pregnancy





Clearance in pregnant people with HIV was **30% HIGHER** than without HIV

NO dose change required for RPT in pregnant or postpartum women

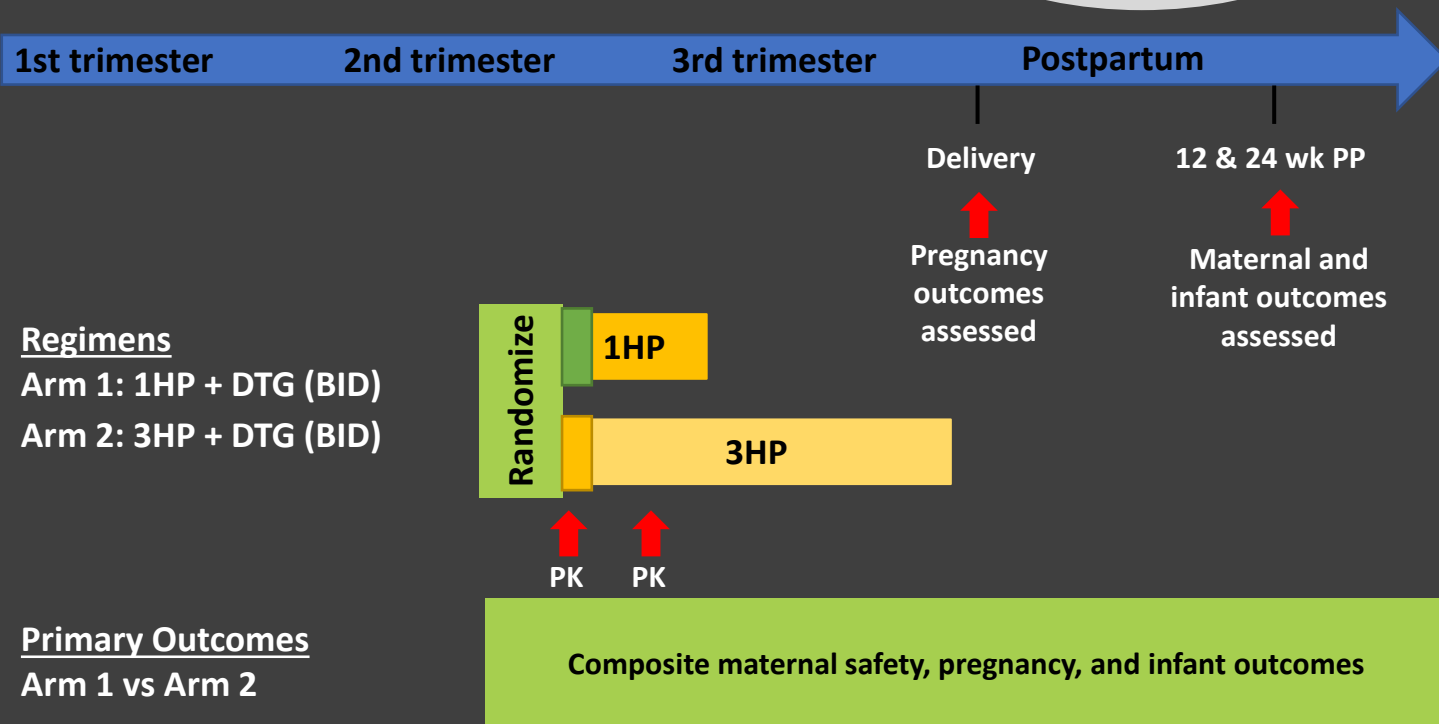


Postpartum clearance was **28% HIGHER** in participants without, but *not* with HIV



DOLPHIN Moms

Safety and tolerability of 1HP and 3HP with pharmacokinetics of dolutegravir in pregnant people with HIV



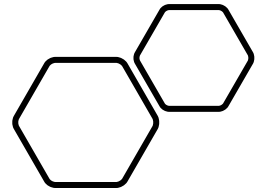
Conclusions

4R remains the safest option for TB prevention in pregnancy except for:

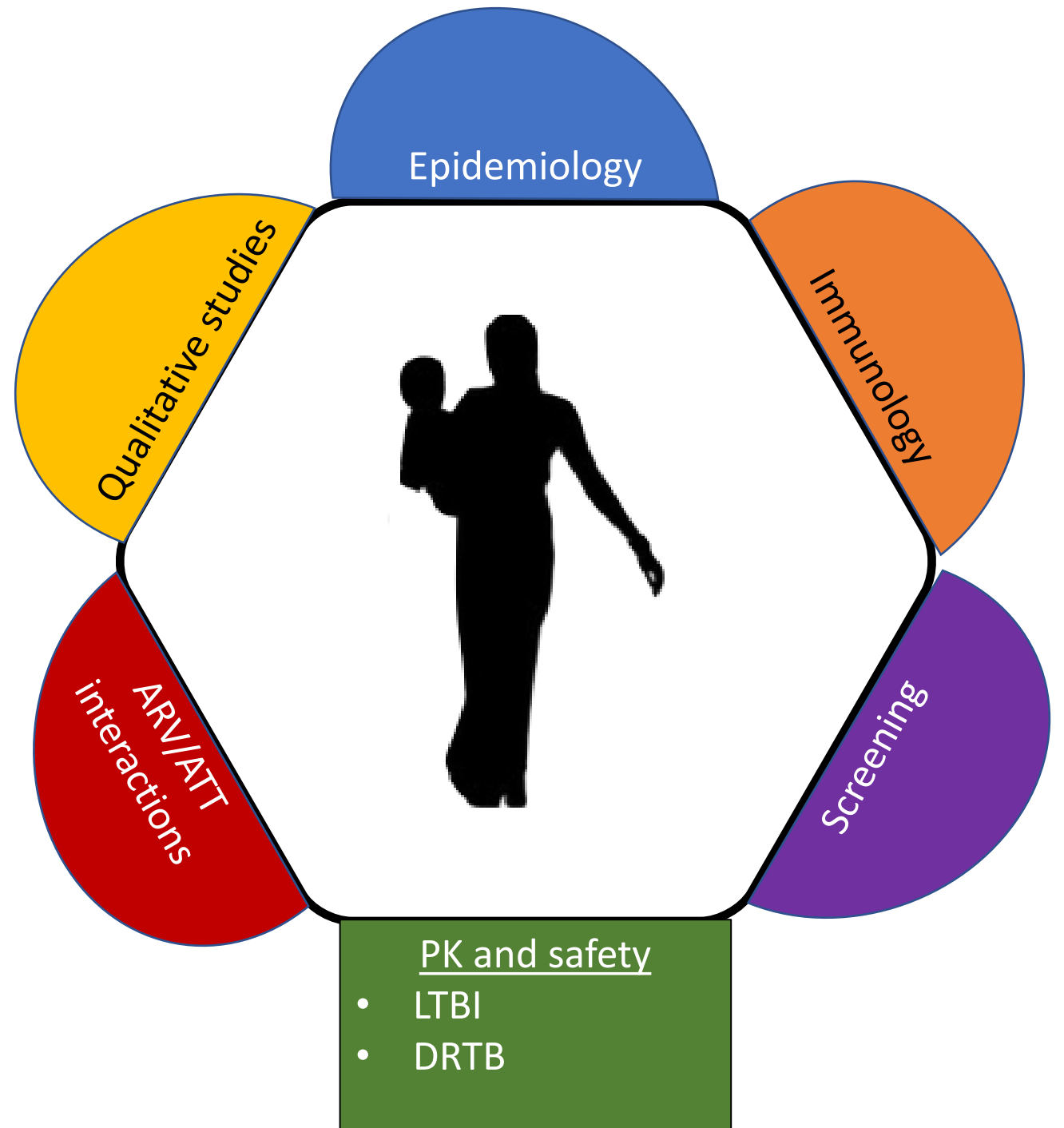
- People with HIV or on other medications that interact with rifampin
- People with liver abnormalities or bleeding risks

Best options for TB prevention in pregnant people with HIV remain unknown.

- INH may increase risk of adverse pregnancy outcomes
- 3HP has promising but inadequate safety data



What are the gaps?



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Puja Chebrolu
Arthi Vaidyanathan

IMPAACT

Amita Gupta
Anneke Hesseling
Sharon Nachman
Kelly Dooley
Rada Savic
Paula Britto
Grace Montepiedra
IMPAACT 2001 team

DOLPHIN-Moms

Sylvia LaCourse
Soyeon Kim
Ethel Weld
Dick Chaisson
Gavin Churchyard



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NIAID K23 AI129854, 1R21 HD099000
NICHD UM1AI068632 (IMPAACT)
Foundations: Ujala, Wyncote, Gilead

The women, children and families who participate in our studies!