Th17 and Treg Cytokines in Pregnant and Postpartum Women With HIV on Isoniazid in IMPAACT P1078

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Zixuan Wei,[1] Mary Morrow,[1] Samantha MaWhinney,[1] Amita Gupta,[2] Adriana Weinberg,[1] Grace Montepiedra,[3] Avy Violari,[4] Gerhard Theron,[5] Ponego L Ponatshego,[6] Gaerolwe Masheto,[6] Anneke C. Hesseling,[7] Peter L. Anderson,[1] Kristina M. Brooks,[1] on behalf of the IMPAACT P1078 Study Team

[1] University of Colorado Anschutz Medical Campus, Aurora, CO, USA; [2] Johns Hopkins School of Medicine, Baltimore, MD, USA; [3]Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA
[4] Perinatal HIV Research Unit, University of Witwatersrand, South Africa; [5]Department of Obstetrics and Gynaecology, Faculty and Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; [6]Botswana Harvard Health Partnership, Gaborone, Botswana; [7]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty and Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa

BACKGROUND

- IMPAACT P1078 showed high rates of hepatotoxicity (~6-7%) in women with HIV (WWH) receiving daily isoniazid (INH) preventive therapy (IPT), regardless of when INH was initiated and most commonly during postpartum (PP).[1]
- T helper 17 cells (Th17) promote a pro-inflammatory environment that can drive progressive liver injury, and regulatory T cells (Treg) mediate immune tolerance. [2]
- These pathways are also altered during pregnancy (Treg dominates) and PP (shift towards Th17),[3] **but the overlap in cytokine changes in pregnant and PP WWH on IPT have not been well characterized.**

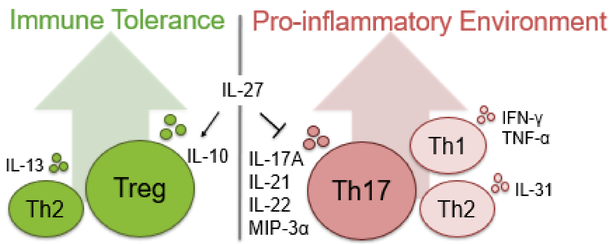


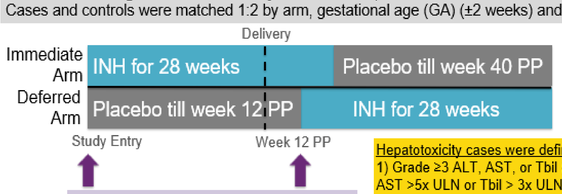
Figure 1. Th17 and Treg Paradigm

OBJECTIVE

To identify factors associated with Th17 and Treg cytokine concentrations in pregnant and PP WWH receiving IPT.

METHOD

Pregnant WLWH > 18 years or older, GA 14 to 34 weeks
Cases and controls were matched 1:2 by arm, gestational age (GA) (±2 weeks) and country.



Paired 50 participants
(11 cases and 39 matched controls)

Figure 2. Study Design of P1078

Hepatotoxicity cases were defined as [4]:
1) Grade ≥3 ALT, AST, or Tbil (ALT or AST >5x ULN or Tbil > 3x ULN);
2) or Grade ≥ 2 ALT and Tbil (ALT >3x ULN with Tbil >2x ULN);
3) or Grade ≥ 2 ALT with symptomatic clinical hepatitis.

- Cytokines were quantified using mesoscale V-PLEX multiplex assays during pregnancy (entry) and week 12 PP.
- **Regression models evaluated whether PP cytokines (n=12) were associated with concentrations during pregnancy, by GA, case vs. control, and INH exposure**.
- Linear models with log_{10}-transformed values were performed if <30% of samples were BLQ, and logistic regressions where >30% were BLQ. P<0.05 was considered significant due to the exploratory nature of the analyses.
- All statistical analyses and figures were generated in R (version 4.5.1) and RStudio (version 2025.05.1).

Proinflammatory cytokines during the postpartum period were associated with concentrations measured during pregnancy. Elevations in IL-17A occurred with current/recent INH exposure and IL-27/MIP-3a (marginal) in those with liver toxicity.

Th17 and Treg Cytokine Concentrations & Detectability During Pregnancy vs. Postpartum

Figure 3. Log_{10}-transformed Cytokines by Pregnancy Status (Unadjusted)

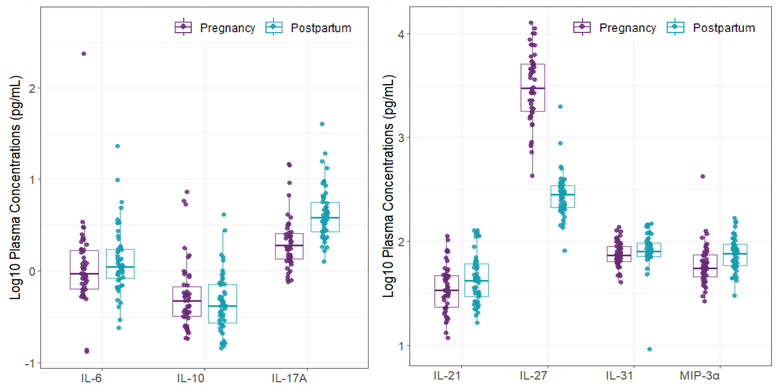
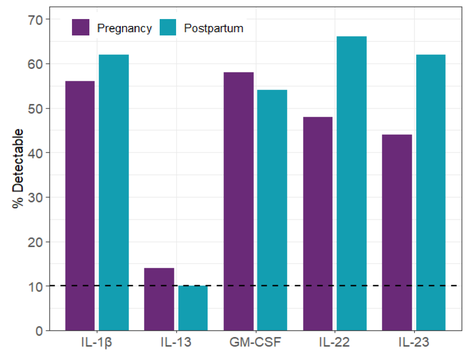


Figure 4. Detectability of Cytokines by Pregnancy Status where BLQ >30% (Unadjusted)



Multivariable Model Results

Table 2. Factors Associated with Week 12 PP Cytokine Concentrations

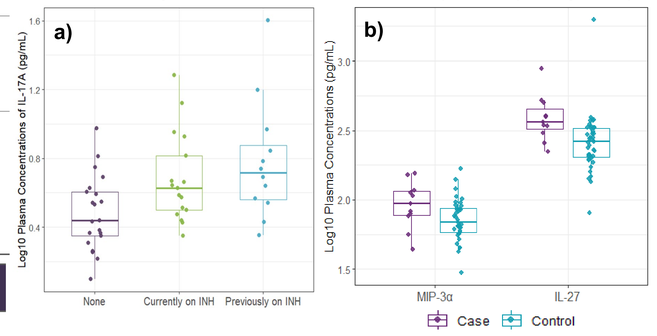
Cytokine	Factor at Week 12 (Postpartum)		Estimate (95% CI)* P-value
IL-17A	INH exposure (% difference)	Current vs. none	65.1% (8.7%, 150.9%) P=0.020
		Previous vs. none	89.7% (15.6%, 211.4%) P=0.012
IL-27	Cases vs. controls (% difference)		44% (5%, 99%) P=0.026
MIP-3α			27.8% (-0.3%, 63.9%) P=0.053
IL-10	Pregnancy (Per 1 log_{10} increase in cytokine concentrations during pregnancy [entry visit])		0.39 (0.14, 0.63) P=0.003
IL-21			0.63 (0.38, 0.88) P<0.001
IL-31			0.55 (0.13, 0.97) P=0.01

Cytokine	Factor at Week 12 (Postpartum)	Odds Ratios (95% CI)** P-value
IL-13	Pregnancy (Detectable cytokine during pregnancy [entry visit])	78.6 (5.7, 6105.3) P=0.008
IL-22		8.2 (1.5, 74.8) P=0.029
GM-CSF		23.4 (4.3, 224.1) P<0.001

*Point estimate (95% CI) reflects the log_{10} increase in week 12 for every one log_{10} increase at entry.
**Odds ratio (95% CI) reflects the odds of being detectable at week 12 vs. the odds of being detectable at entry

- Estimates and ORs reflect significant factors identified from fully adjusted models for each cytokine.
- No factors were significantly associated with IL-1β, IL-6, or IL-23.

Figure 5. Log_{10}-transformed **a)** IL-17A by INH exposure and **b)** MIP-3α /IL-27 by case status at week 12 Postpartum (Unadjusted)



ACKNOWLEDGEMENTS

The IMPAACT P1078/TB APPRISE Protocol Team gratefully acknowledges the dedication and commitment of the 956 mother-infant pairs, their communities, and CAB representatives, without whom this study would not have been possible. The authors also wish to acknowledge the IMPAACT P1078/TB APPRISE Protocol team, NIAID, NICHD, and NIMH, and the thirteen IMPAACT sites and staff.
Funded by K08 AI152942 (KMB). | **Author contact:** kristina.brooks@cuanschutz.edu

Table 1. Demographics & Clinical Characteristics

Characteristics	Case (n=11)	Control (n=39)
GA at Entry (wks)	28 (20-31)	21 (18-29)
Time Post-Delivery (wks)	12 (12-13)	12 (12-12)
Age (years) [a]	29 (27-34)	32 (27-35)
Weight (kg) [a]	63 (58-79)	66 (59-79)
Black, Non-Hispanic (n, %)	11 (100%)	39 (100%)
Country (n, %)		
Botswana	6 (55%)	13 (33%)
South Africa	5 (45%)	26 (67%)
HIV VL <200 copies/mL [a]	8 (73%)	27 (69%)
CD4 count (cells/mm3) [a]	469 (341-734)	566 (377-740)
LFTs at Entry		
ALT (U/L)	13 (10-20)	13 (12-16)
AST (U/L)	22 (17-25)	21 (29-23)
Total bilirubin (mg/dL)	0.16 (0.13-0.21)	0.2 (0.16-0.23)
LFTs at wk 12 PP		
ALT (U/L)	74 (45-157)	31 (21-39)
AST (U/L)	57 (33-78)	24 (21-31)
Total bilirubin (mg/dL)	0.23 (0.2-0.28)	0.2 (0.18-0.25)
INH exposure at wk 12 PP		
None	4 (36%)	17 (44%)
Currently Exposed	5 (45%)	12 (31%)
Previously Exposed[b]	2 (18%)	10 (26%)
Concomitant ARVs		
Efavirenz	9 (82%)	37 (95%)
Nevirapine	2 (18%)	2 (5%)

Results presented as n (%) for categorical or median (IQR) for continuous.
All entry samples were pre-INH.
[a]Measured at study entry. [b]Median [range] 40 [21-89] days since last dose.

CONCLUSIONS

- Cytokines at week 12 PP were associated with increases in IL-17A with current/prior INH exposure, higher IL-27 and MIP-3α (marginal) in cases, and higher or detectable cytokines during pregnancy.
- Elevations in IL-17A, IL-27, and MIP-3α overlap with those some markers associated with hepatotoxicity.
- These findings suggest a shift towards a proinflammatory Th17 environment during PP, but further mechanistic studies are needed.

Plain Language summary:
Some immune signals in postpartum women were higher when taking isoniazid or in those with liver toxicity. Multiple immune signals were also associate with pregnancy.

REFERENCE

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Overall support for the International Maternal Pediatric Adolescent AIDS Clinical Trials Network (IMPAACT) was provided by the National Institute of Allergy and Infectious Diseases (NIAID) with co-funding from the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) and the National Institute of Mental Health (NIMH), all components of the National Institutes of Health (NIH), under Award Numbers UM1AI068632 (IMPAACT LOC), UM1AI068616 (IMPAACT SDMC), and UM1AI106716 (IMPAACT LC), and by NICHD contract number HHSN275201800001I. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Presented at the
2026 Conference on Retroviruses
and Opportunistic Infections (CROI)
22-25 February 2026
Denver, Colorado, USA