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

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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.**

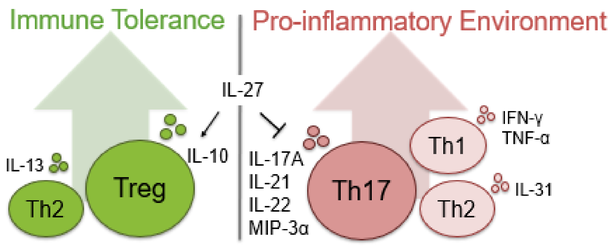


Figure 1. Th17 and Treg Paradigm

OBJECTIVE

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

METHOD

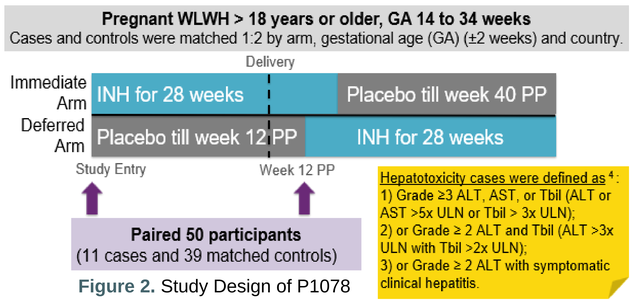


Figure 2. Study Design of P1078

- 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)

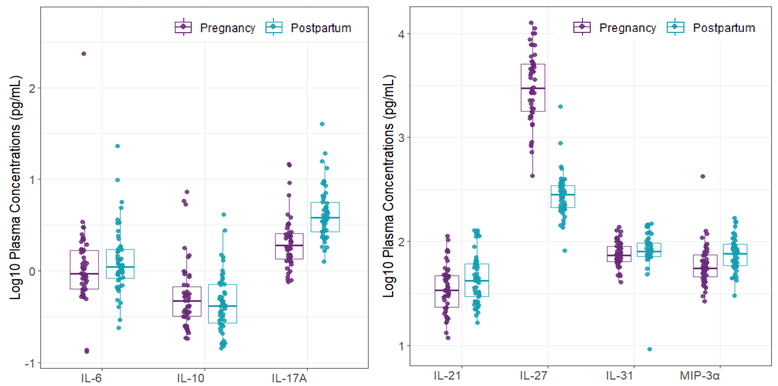
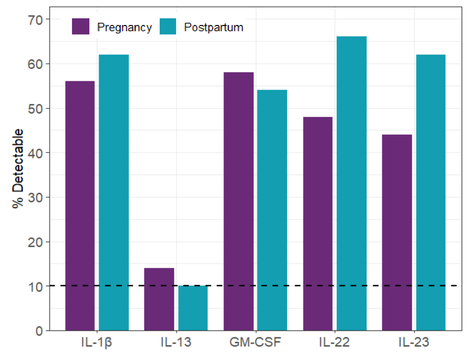


Figure 4. Detectability of Cytokines by Pregnancy Status where BLQ >30% (Unadjusted)



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)

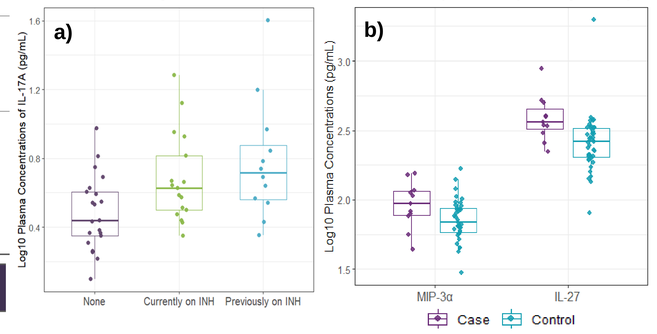


Table 1. Demographics & Clinical Characteristics

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.

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REFERENCE

(1) Gupta A, et al. N Engl J Med. 2019 Oct 3;381(14):1333-1346; (2) Uetrecht J. Semin Liver Dis. 2009 Nov;29(4):383-92; (3) Figueiredo AS, et al. Immunology. 2016;148(1):13-21; (4) Division of AIDS (DAIDS) Grading Criteria. Version 2. November 2014

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