Presented at 15th International Workshop on HIV & Pediatrics, Brisbane, Australia, and virtual 21-22 July 2023; **Poster Number: 93**

IMPAACT International Maternal Pediatric Adolescent AIDS Clinical Trials Network

PROMISE IMPAACT 1077

Promoting Maternal and Infant Survival Everywhere

Systemic inflammation in pregnant women with HIV: relationship with preterm delivery and HIV treatment regimen

Rupak Shivakoti, Mark Giganti, Michael Lederman, Rachel Ketchum, Sean Brummel, Daniela Moisi, Sufia Dadabhai, Daya Moodley, Avy Violari, Lameck Chinula, Maxensia Owor, Amita Gupta, Judith S. Currier, Taha E Taha, Mary Glenn Fowler for the PROMISE study team

Background

- HIV treatment regimen during pregnancy was associated with preterm delivery (PTD) in a large multi-site international perinatal (IMPAACT1077BF/FF PROMISE trial, N=3490 evaluable mother-infant pairs.
- Antenatal zidovudine (ZDV) alone was associated with lower PTD compared to two protease inhibitor (PI)-based ART regimens: 13.1% vs 20.5%, p<0.001.
- Systemic inflammation among pregnant women with HIV could be linked to PTD, and could explain differences in PTD by treatment regimens.

Methods

- 1:1 nested case-control study within PROMISE 1077BF/FF, a randomized trial comparing 3 ART regimens in pregnant women: 1) ZDV alone, and ART with lopinavir/ritonavir and either 2) ZDV or 3) TDF
- Cases: women with PTD; controls: women without PTD
- **Objective 1**: Determine the association of second trimester plasma inflammation markers with PTD
  - Inflammation measured at: W0 pre-ART initiation from women at 13-23 weeks GA and W4 post-ART initiation
  - Soluble markers of inflammation: IL-6, IFNγ, TNFα, sCD14, sCD163, I-FABP
  - Inflammation: as both continuous and categorical variable
    - Persistently high; increasing; decreasing; persistently low
- **Objective 2**: Determine between treatment regimen and biomarkers of inflammation
- **Objective 3:** Investigate whether inflammation was a mediator in the relationship between ART regimens and PTD

Results

- 362 women (n=181 PTD and n=181 no PTD) from 1 Asian and six African countries were studied.
- 176 (49%) on ZDV-based ART, 145 (40%) on ZDV alone and 41 (11%) on TFV-based ART; Median gestational age: 19.1
- HIV characteristics: 351 (97%) WHO clinical stage I; Median CD4 cell count: 530; Median viral load: 4.0 $\log_{10}$copies/mL
- Sociodemographic and clinical characteristics were similar by cases and controls

Table 1: Adjusted odds ratios for preterm delivery by immune marker concentration

	Week 0 Pre-ART initiation		Week 4 post-ART initiation		Change (Week 4-Week 0)	
Immune Marker	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
I-FABP	0.96 (0.40-2.31)	0.92	1.06 (0.50-2.24)	0.88	1.03 (0.45-2.37)	0.95
IFNγ	1.08 (0.58-2.02)	0.81	1.56 (0.86-2.82)	0.15	1.68 (0.88-3.21)	0.11
IL-6	1.61 (0.71-3.64)	0.25	1.85 (0.77-4.44)	0.17	1.75 (0.62-4.98)	0.29
TNFα	2.15 (0.87-5.28)	0.097	2.29 (0.86-6.11)	0.098	1.94 (0.39-9.73)	0.42
sCD14	0.96 (0.14-6.46)	0.96	1.50 (0.25-8.84)	0.65	2.70 (0.19-38.11)	0.46
sCD163	0.90 (0.29-2.85)	0.86	1.87 (0.49-7.15)	0.36	4.40 (0.63-30.91)	0.14

Table 1 Legend: Odds ratios (ORs) greater than 1 indicate a higher odds of PTD for a 1-$\log_{10}$-unit higher immune marker concentration. Units for all cytokines are $\log_{10}$-fg/mL, for monocyte activation biomarkers are $\log_{10}$-ng/mL, and for I-FABP are $\log_{10}$-pg/mL.
Multivariable conditional logistic models stratified by enrollment gestational age and country and adjusted for treatment, age, BMI, parity, previous preterm delivery, hemoglobin, viral load, CD8 count, education level, and CD4 count. A multiple imputation procedure was used to impute missing values for education level and CD8 count.

Table 2: Adjusted odds ratios for PTD by select, categorized marker levels at Week 0 and Week 4

Immune Marker	Categories	OR (95% CI)
I-FABP	Persistently Low	Ref.
	Increasing	1.49 (0.81, 2.77)
	Decreasing	0.73 (0.33, 1.62)
	Persistently High	1.05 (0.50, 2.21)
IFNγ	Persistently Low	Ref.
	Increasing	0.83 (0.42, 1.63)
	Decreasing	0.77 (0.39, 1.54)
	Persistently High	1.72 (0.79, 3.72)
IL-6	Persistently Low	Ref.
	Increasing	0.96 (0.45, 2.05)
	Decreasing	0.96 (0.49, 1.89)
	Persistently High	2.47 (1.16, 5.29)

*Only a subset of analyzed immune markers are being presented.

Figure 1: Forest plot for treatment effect on change in immune marker concentrations

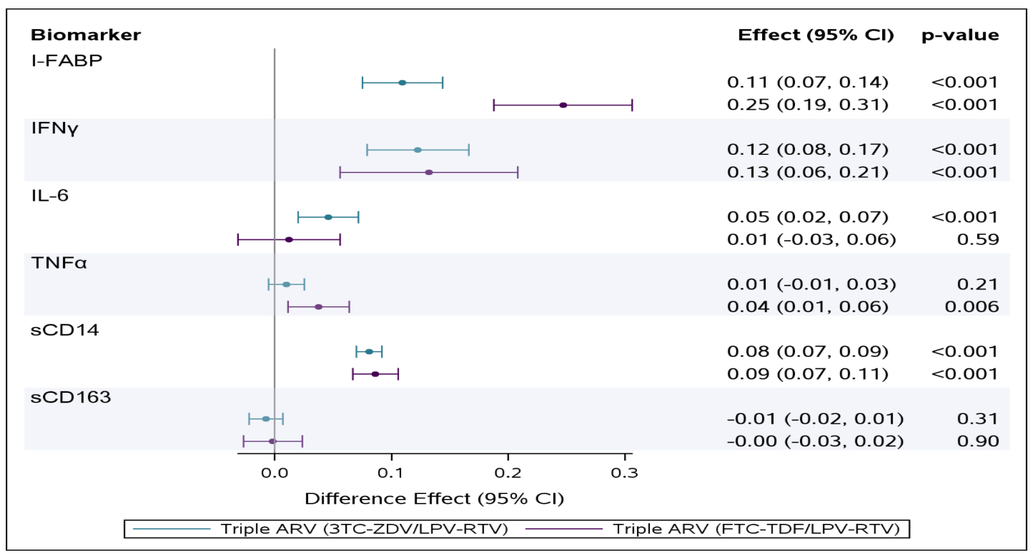

Figure 1 Legend: Forest plot for treatment effect compared to ZDV+sdNVP+TRV on change in immune marker concentration from pre-ART to Week 4 post ART initiationAll estimates use ZDV+sdNVP+TRV tail as reference treatment group. Models additionally adjusted for baseline inflammation, age, BMI, gestational age at entry, country, education level, CD4 and CD8 counts, hemoglobin, and HIV-1 RNA.

The estimated proportion of the ART effect on increased PTD mediated by persistently high levels of inflammation was 5% or lower for all biomarkers (data not shown).

Conclusion

- Persistently high IL-6 during pregnancy was associated with PTD.
- While PI-based ART was associated with increases in inflammation, our results suggest that factors other than inflammation explain the increased PTD in women taking ART-based regimens compared to zidovudine alone in the 1077BF PROMISE trial.

For more information, visit impaactnetwork.org and follow us:
Facebook: IMPAACTNetwork | Twitter: @IMPAACTNetwork | LinkedIn: IMPAACTNetwork

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 UM1AI068632-15 (IMPAACT LOC), UM1AI068616-15 (IMPAACT SDMC) and UM1AI106716-15 (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. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH