# Intestinal Damage and Inflammation In Perinatally HIV-1-Infected African Infants

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## INTRODUCTION

- Increased inflammation and immune activation are features of HIV-1 infection, for which impaired intestinal integrity with microbial translocation are implicated. In HIV-1-infected adults, this is supported by correlations between plasma concentrations of biomarkers of inflammation (IL-6), monocyte activation (sCD14) and intestinal damage (intestinal fatty acid binding protein, iFABP).
- The interaction between inflammation, immune activation and intestinal integrity in perinatal HIV-1-infection is unknown.

## OBJECTIVE

- Measure levels of intestinal integrity markers at two time points (study entry and post-vaccine dose 3, PD3) in early treated, perinatally HIV-1-infected (HIV+) African infants who were enrolled in a randomized, double-blind, placebo-controlled clinical trial (IMPAACT P1072) of the safety and immunogenicity of live, attenuated rotavirus vaccine (RotaTeq™), in whom we previously characterized inflammation and immune activation profiles.
- Correlate intestinal integrity marker levels with differences in cytokine profiles observed in P1072 between HIV+ and HIV-1-exposed uninfected (HEU) infants.

## METHODS

- Plasma levels of intestinal integrity markers, iFABP and zonulin, were measured in HIV+ and HEU infants, using commercially available ELISA's.
- Intestinal integrity markers were correlated with previously measured levels of cytokines, sCD14 and serum anti-rotavirus IgA.
- Categorical variables were compared using Fisher's exact test and continuous variables by Wilcoxon rank sum tests.
- Spearman correlations and multivariate linear regression ($log_{10}$ scale) were used to compare levels by HIV-1, breastfeeding and vaccine received.
- $p<0.05$ indicated statistical significance.

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## RESULTS

**Table 1. Characteristics of participants at study entry**

| Characteristic | HIV-1-infected (n = 56) | HIV-1-exposed, uninfected (n = 53) | p-value |
|---|---|---|---|
| Female, n (%) | 34 (61%) | 28 (53%) | 0.44 |
| Age (days) at randomization, Median (Q1,Q3) | 93 (89, 96) | 92 (79, 96) | 0.29 |
| Received ARV prophylaxis for PMTCT, n (%) | 39 (70%) | 49 (92%) | 0.003 |
| Received vaccine, n (%) | 29 (52%) | 26 (49%) | 0.85 |
| Ever breast-fed prior to entry, n (%) | 37 (66%) | 36 (68%) | <0.99 |
| Oral polio vaccine receipt with 1st vaccination, n (%) | 44 (79%) | 43 (81%) | 0.81 |
| CD4% at screening, Median (Q1, Q3) | 30 (23, 37) | 36 (32, 41) | <0.001 |
| On ART at randomization, n (%) | 51 (91%) | 0 (0%) | NA |
| Duration (days) of ART at randomization, Median (Q1,Q3) | 6 (0,11) | NA | NA |
| HIV-1 RNA >400 copies/mL, n (%) | 49 (92%) | NA | NA |
| WHO Weight-for-age Z-score (WAZ), Median (Q1,Q3) | -1.4 (-2.4, -0.2) | -0.6 (-1.2, -0.1) | 0.005 |
| WHO Height-for-age Z-score, Median Z (Q1,Q3) | -1.0 (-1.8, -0.2) | -0.5 (-1.6, -0.1) | 0.50 |

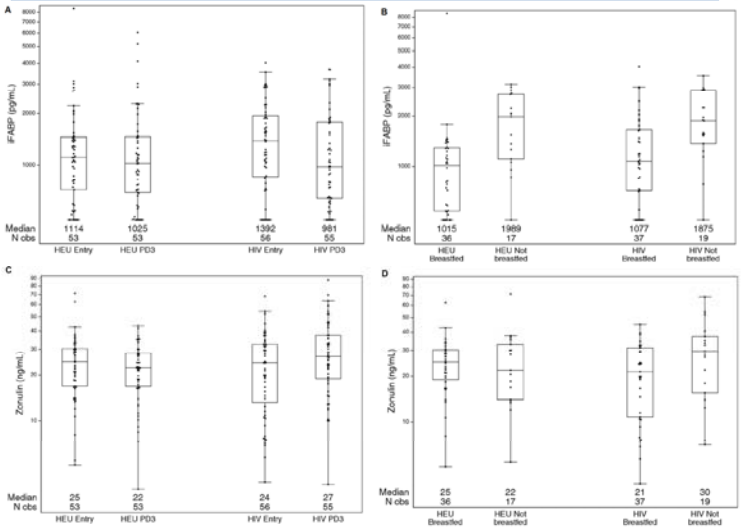


**Figure 1. iFABP and zonulin levels by HIV-1 status (at entry and PD3), and at entry by breastfeeding status.** A: Boxplots of iFABP levels at entry and PD3 by HIV-1 status. B: Boxplots of entry iFABP levels by HIV-1 and breastfeeding status. C: Boxplots of zonulin levels at entry and PD3 levels by HIV-1 status. D: Boxplots of entry zonulin levels by HIV-1 and breastfeeding status.

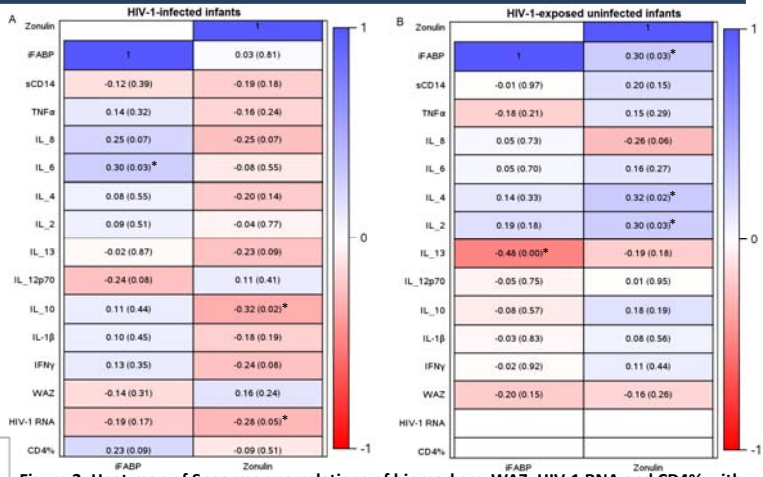


**Figure 2. Heat map of Spearman correlations of biomarkers, WAZ, HIV-1 RNA and CD4% with iFABP and zonulin levels at study entry in (A) HIV+ and (B) HEU infants.** Shades of red and blue indicate the strength of the negative and positive correlations, respectively. P≤0.05 noted with an asterisk.

**Intestinal integrity markers and RotaTeq™ vaccine responses:**

- No significant correlations were found between PD3 iFABP levels and serum anti-rotavirus IgA in HIV+ (r=0.11, p=0.58) or HEU (r=0.23, p=0.28) vaccine recipients.
- Zonulin levels PD3 were not significantly associated with serum anti-rotavirus IgA (r=-0.23, p=0.24) in HIV+, but were positively correlated (r=0.48, p=0.014) in HEU.

## CONCLUSIONS

- Overall, there were no strong correlations between markers of inflammation, immune activation and intestinal integrity at study entry.
- Markers of intestinal integrity did not differ between HIV+ and HEU at age 3 months despite differences in inflammation, immune activation, CD4% and WAZ scores.
- Changes in zonulin in HIV+ over time suggest ongoing intestinal damage in the form of loss of tight junction regulation in perinatal HIV-1 infection independent of viral suppression, but with no overt effects on rotavirus vaccine responses.

## REFERENCES

1. Brenchley JM, Schacker TV, Ruff LE, *et al*. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med 2004; 200: 749-59.
2. Hunt PW, Sinclair E, Rodriguez B, *et al*. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. J Infect Dis 2014; 210: 1228-38.
3. Uprety P, Lindsey JC, Levin MJ, *et al*. Inflammation and Immune Activation in Antiretroviral-Treated HIV-1-Infected African Infants and Rotavirus Vaccine Responses. J Infect Dis. 2017; 215: 928-32.