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

Wei Li A. Koay1, Jane C. Lindsey2, Priyanka Upotrety3, Mutsa Bwakura-Dangarembizi4, Adriana Weinberg3, Myron J. Levin5, Deborah Persaud6

1 Department of Pediatrics, Johns Hopkins University School of Medicine, Baltimore, MD, USA; 2 Center for Biostatistics in AIDS Research, Harvard T.H. Chan School of Public Health, Boston, MA, USA; 3 Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia, PA, USA; 4 Colleges of Health Sciences, University of Zimbabwe, Harare, Zimbabwe; 5 Division of Infectious Diseases, University of Colorado School of Medicine, Denver, CO, USA

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, fFABP).

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 (RotarTeq™), 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, fFABP and zonulin, were measured in HIV+ and HEU infants, using commercially available ELISAs.

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

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>HIV-1-infected (n = 56)</th>
<th>HIV-1-exposed, uninfected (n = 53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female, n (%)</td>
<td>34 (61%)</td>
<td>28 (53%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Age (days) at randomization, Median (Q1,Q3)</td>
<td>93 (79, 96)</td>
<td>92 (79, 96)</td>
<td>0.29</td>
</tr>
<tr>
<td>Received ART prophylaxis for PMTCT, n (%)</td>
<td>39 (70%)</td>
<td>49 (92%)</td>
<td>0.003</td>
</tr>
<tr>
<td>Received vaccine, n (%)</td>
<td>29 (52%)</td>
<td>26 (49%)</td>
<td>0.85</td>
</tr>
<tr>
<td>Ever breast-fed prior to entry, n (%)</td>
<td>37 (66%)</td>
<td>36 (68%)</td>
<td>&lt;0.99</td>
</tr>
<tr>
<td>Oral polio vaccine receipt with 1st vaccination, n (%)</td>
<td>44 (79%)</td>
<td>43 (81%)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

CD4% at screening, Median (Q1,Q3) 30 (23, 37) 36 (32, 41) <0.001

On ART at randomization, Median (Q1,Q3) 52 (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 Height-for-age Z-score (WAH), Median (Q1,Q3) -1.4 (-2.4,-0.2) -0.6 (-3.2,-0.1) 0.005

WHO Weight-for-age Z-score, Median Z (Q1,Q3) -1.0 (-1.8,-0.2) -0.5 (-1.6,-0.1) 0.50

Figure 1. fFABP and zonulin levels by HIV-1 status (at entry and PD3), and at entry by breastfeeding status. A: Boxplots of fFABP levels at entry and PD3 by HIV-1 status. B: Boxplots of entry fFABP 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, WAH, HIV-1 RNA and CD4% with fFABP and zonulin levels at study entry (A) HIV+ and (B) HEU infants. Shades of red and blue indicate the strength of the positive and negative correlations, respectively. *p<0.05 noted with an asterisk.

Intestinal integrity markers and RotarTeq™ vaccine responses:

- No significant correlations were found between PD3 fFABP 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

