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Growth Faltering is Associated with Infant Gut Bifidobacterium in Children Exposed to HIV

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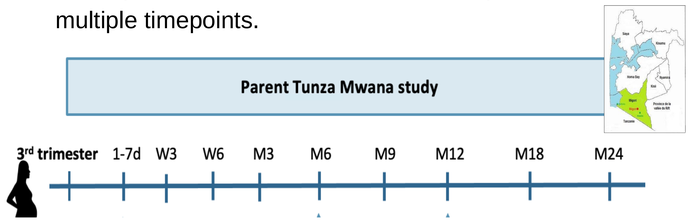
BACKGROUND

- We aimed to determine if children who are exposed, but not infected with HIV (CHEU) continue to experience differences in growth/growth faltering in the setting of highly efficacious maternal antiretroviral therapy.
- If so, are alterations in the infant gut microbiome of CHEU associated with these differential outcomes?

CHEU are at increased risk of growth faltering compared to children unexposed to HIV (CHU). Decreased abundance of Bifidobacterium has been associated with growth faltering in CHEU. We examined the gut microbiota of CHEU versus CHU to determine if specific microbes may influence growth outcomes.

METHODS

- A cohort 350 pregnant women with and without HIV (WWH and WWoH) were enrolled in an observational cohort in Migori County, Kenya.
- Women and infants were followed prospectively with anthropometric measurements and sample collection at multiple timepoints.



- 16S rRNA sequencing of the V4 region was performed on available Infant rectal swabs (319 of 333 pairs).
- Linear mixed effects models were used to identify differentially abundant bacterial taxa.
- An interaction model was used to test if associations between growth outcomes and bacterial abundances differed by HIV exposure.
- All results were significant after correction for multiple comparisons unless stated.

Infant gut Bifidobacterium abundance is associated with weight gain in Children Exposed to HIV.

RESULTS

- 90% of WWH on dolutegravir-based ART
  - 75% started ART prior to pregnancy, and >92% HIV RNA <1000 copies/mL, 65% on TMP/SMX prophylaxis
- Weight-for-Age Z-score (WAZ) differed significantly between CHEU and CHU at 3, 6, and 9 months **(Fig. 1)**
- No differences in the 3-month bacterial abundances between CHEU and CHU (**Fig. 2A**)
- No associations between growth outcomes and bacterial abundance overall (**Fig. 2A**)

TABLE 1

	WWH/ CHEU	WWoH/ CHU	P-value
N	164	155	
Completed 1º education or below	126 (77%)	78 (50%)	<0.001
Overweight/obese	32 (20%)	27 (17%)	0.06
Anemia	64 (39%)	33 (21%)	<0.001
Multiparous	150 (92%)	103 (67%)	<0.001
Cesarean delivery	19 (12%)	28 (18%)	0.14
Preterm (<37 wks)	16 (10%)	15 (10%)	1.0
BW 1st 7 days (kg)	3.21	3.25	0.40
Infant ARV#	135 (82%)		
Infant TMP/SMX*	98%		
EBF for 6 months	97 (59%)	76 (49%)	0.18

WWH: Women with HIV; WWoH: Women without HIV; CHEU: Children with HIV expose; CHU: Children without HIV exposure; 1º: Primary; wks: weeks; BW: Birth weight; ARV: antiretrovirals; TMP/SMX: trimethoprim/sulfamethoxazole; EBF: Exclusively Breastfed.
Nevirapine + Zidovudine = 78.7%; NVP alone = 3%; ZDV alone 1%
*Infant TMP/SMX prophylaxis was started at 6 weeks of age.

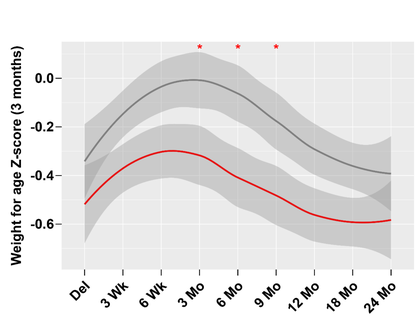


Figure 1. Weight for Z-score over the first two years of life in CHEU versus CHU. Solid lines indicate loess regression curves and shaded areas denote 95% confidence intervals. Red asterisks show significant differences at the 3, 6 and 9-month visits.

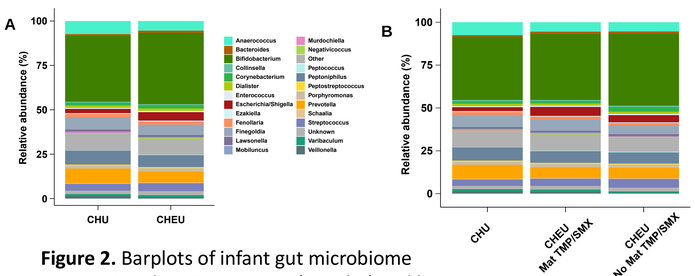


Figure 2. Barplots of infant gut microbiome composition by HIV exposure (panel A) and by HIV exposure and by maternal (mat) HIV TMP/SMX prophylaxis (panel B) show no difference in relative abundance by group.

RESULTS continued . . .

- However, Bifidobacterium relative abundance was associated with WAZ specifically in CHEU (**Fig. 3A**).
- The association between Bifidobacterium relative abundance and weight gain was driven by maternal TMP/SMX in the CHEU (**Fig. 3B**).
- There was no difference in relative abundance in CHEU by maternal TMP/SMX or in WAZ (**Fig. 2B**).
- There was no difference in WAZ in CHEU by maternal TMP/SMX prophylaxis (**Fig. 3C**).

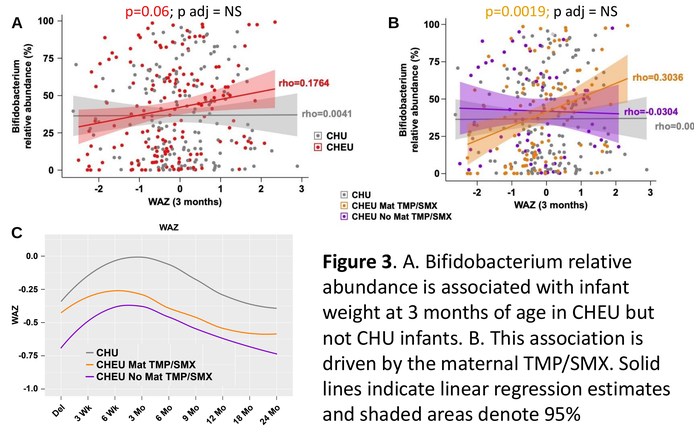


Figure 3. A. Bifidobacterium relative abundance is associated with infant weight at 3 months of age in CHEU but not CHU infants. B. This association is driven by the maternal TMP/SMX. Solid lines indicate linear regression estimates and shaded areas denote 95% confidence intervals. C. No difference in WAZ by maternal TMP/SMX.

CONCLUSIONS

- CHEU continue to experience growth differences even in the setting of highly effective antiretroviral therapy.
- We found that weight gain in CHEU is associated with infant gut Bifidobacterium abundance at 3 months.
- The difference in weight gain in CHEU is driven by maternal TMP/SMX prophylaxis.

Further studies planned include sequencing of 6-week infant samples prior to infant TMP/SMX, HMO analyses, and Bifidobacterium quantification.

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