

# EARLY ANTIRETROVIRAL THERAPY IN NEONATES AND MATURATION OF THE GUT MICROBIOME

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## BACKGROUND

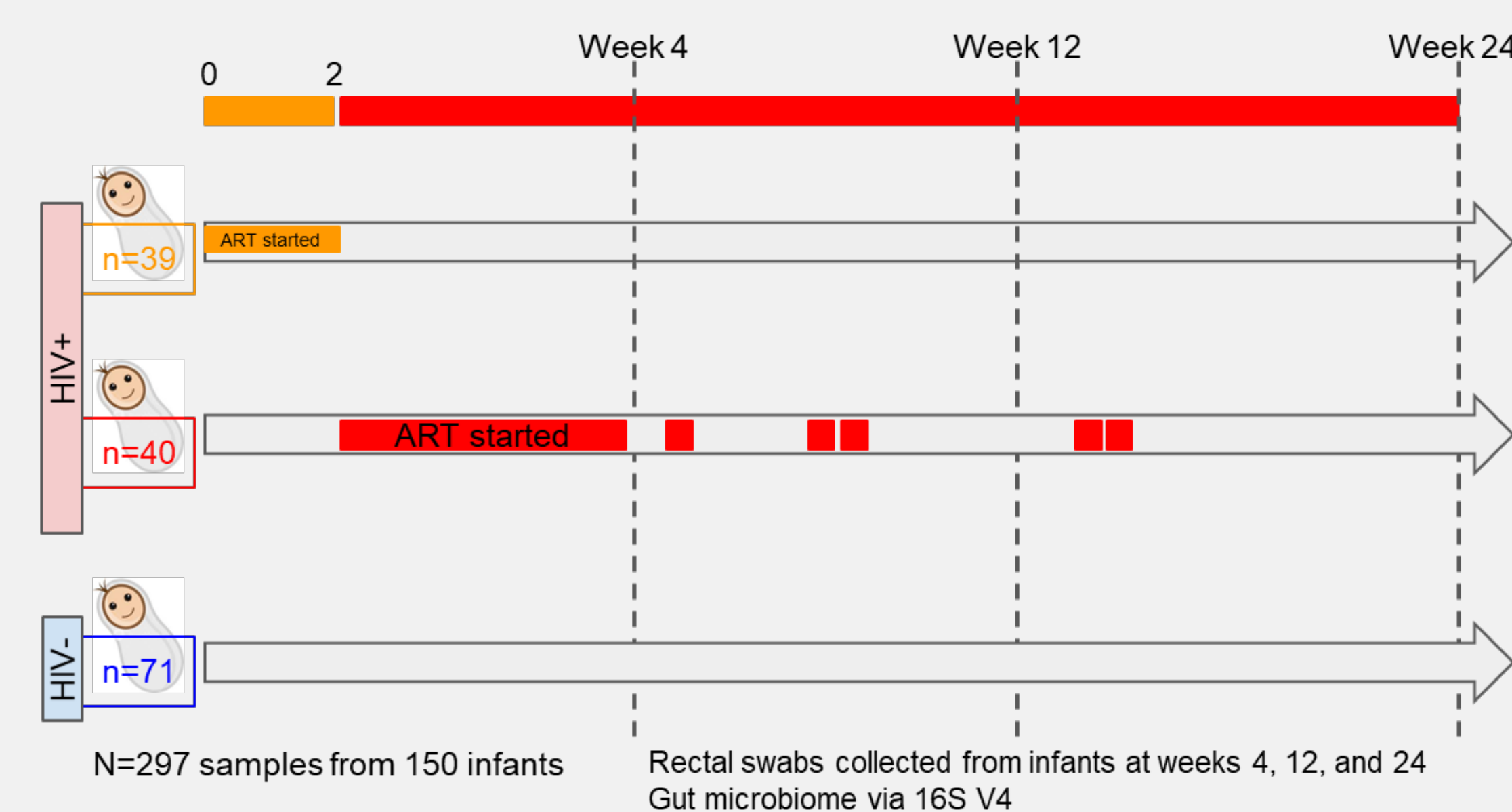
- In the pre-antiretroviral therapy (ART) era, breastfeeding has been associated with improved survival outcomes among infants with perinatally-acquired HIV infection.
- Breastfeeding is known to support optimal establishment of a healthy gut microbiome.

## OBJECTIVES

- Here we investigated whether breastfeeding and early ART mitigate harmful influences of intrauterine HIV infection on the developing infant microbiome.

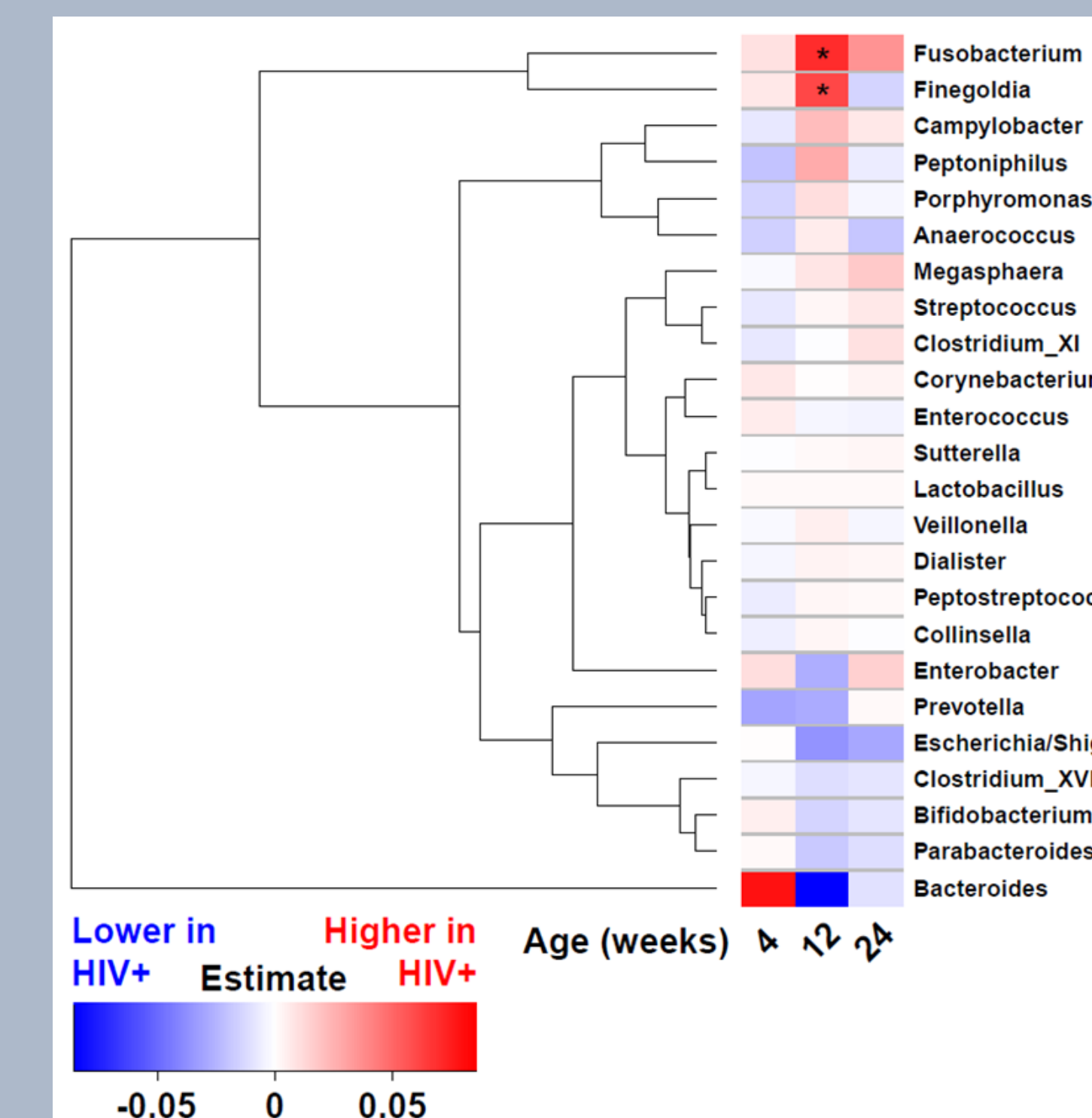
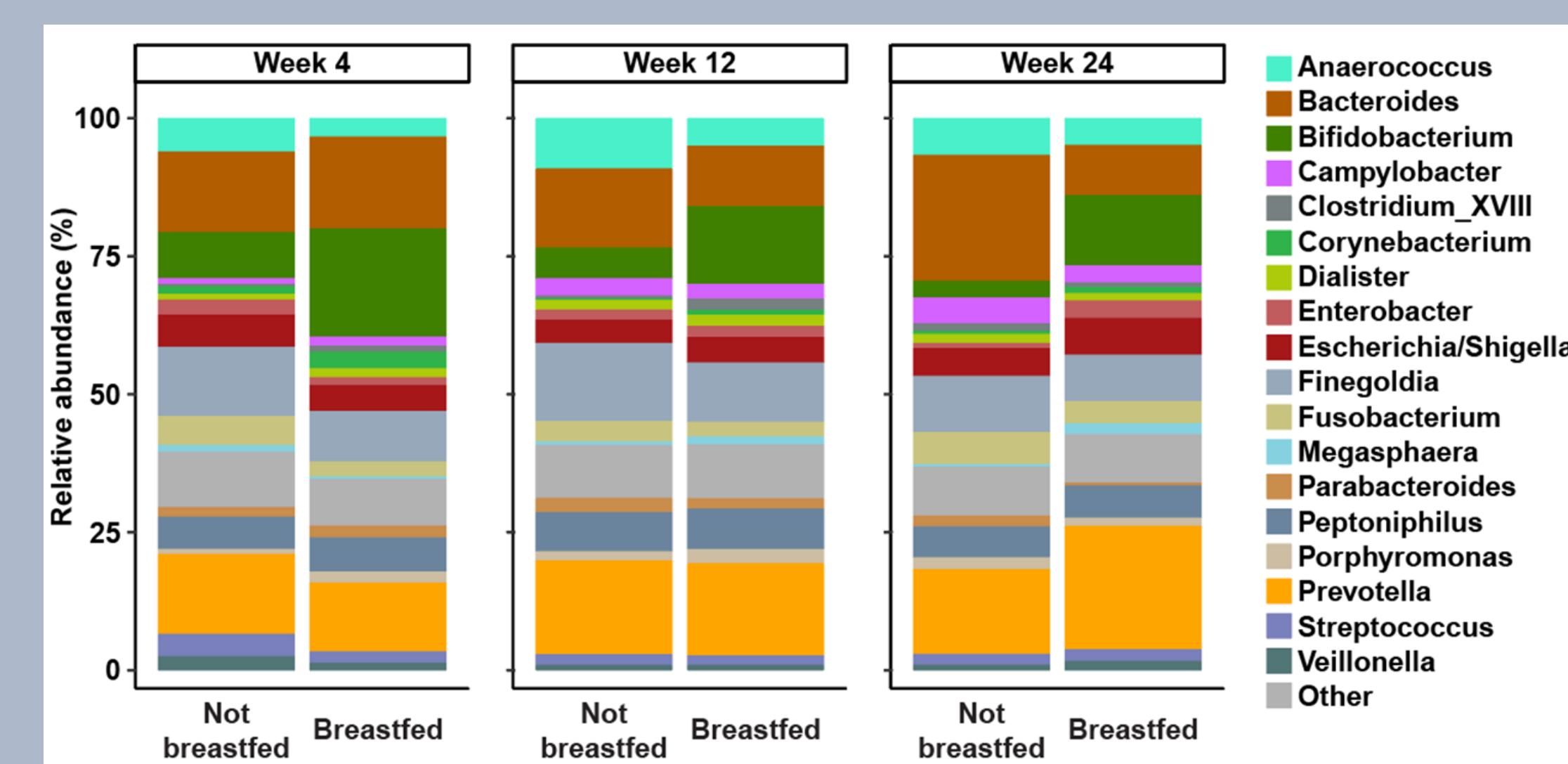
## METHODS

- At one site in Johannesburg, South Africa, 79 infants (39 female) with intrauterine HIV infection diagnosed <48 hours of birth and 71 uninfected infants (37 female) born to women living with HIV were recruited.
- Infants with HIV were started on ART as soon as possible, half <48 hours of birth and the other half a median of 6 days of age.
- Uninfected infants received standard of care prophylaxis.
- Rectal swab samples were collected at 4, 12 and 24 weeks of age.
- Microbiome profiling was performed by sequencing of the V4 region of the 16S rRNA gene, followed by denoising and exact sequence inference using DADA2.
- Statistical comparisons were performed using linear mixed effects models with independent probability of treatment weighting to control for potential confounding variables.



## MAIN FINDINGS

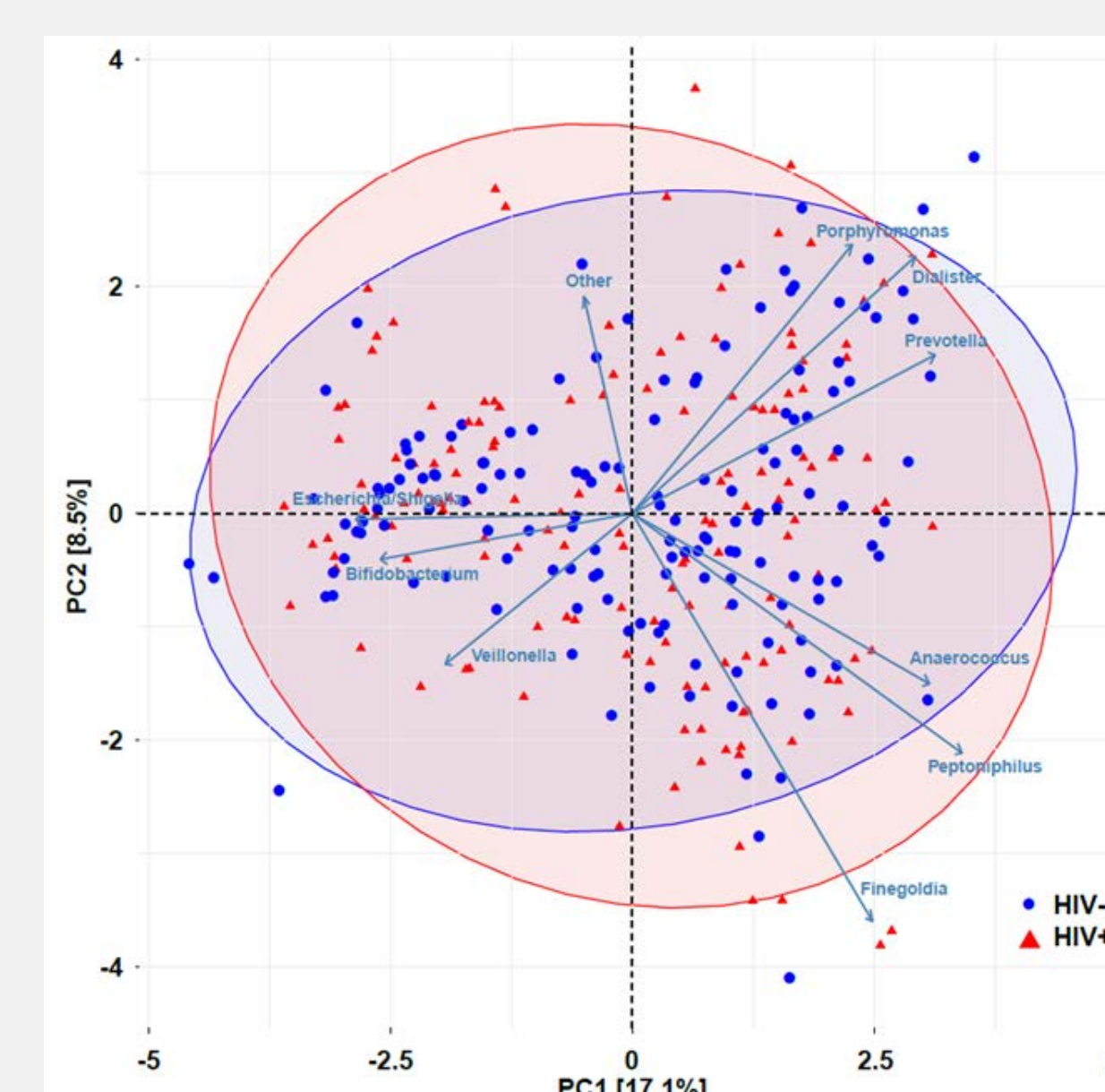
**HIV infection** was associated with significant shifts in taxa including increases in *Bacteroides*, *Fusobacterium* and *Finigoldia* abundances after adjusting for other covariates. Permutational multivariate analysis of variance (PERMANOVA) using weighted UniFrac distances revealed HIV status, age at sampling, mode of delivery, breastfeeding, and sex as significant drivers of overall variation in the developing infant microbiome.



**Breastfeeding** helps maintain *Bifidobacterium* in the early infant microbiome and potentially buffers against *Bacteroides* expansion at later time points. Breastfeeding during the early weeks of life may be especially critical for infants with HIV to maintain a “normal” *Bifidobacterium*-rich microbiome.

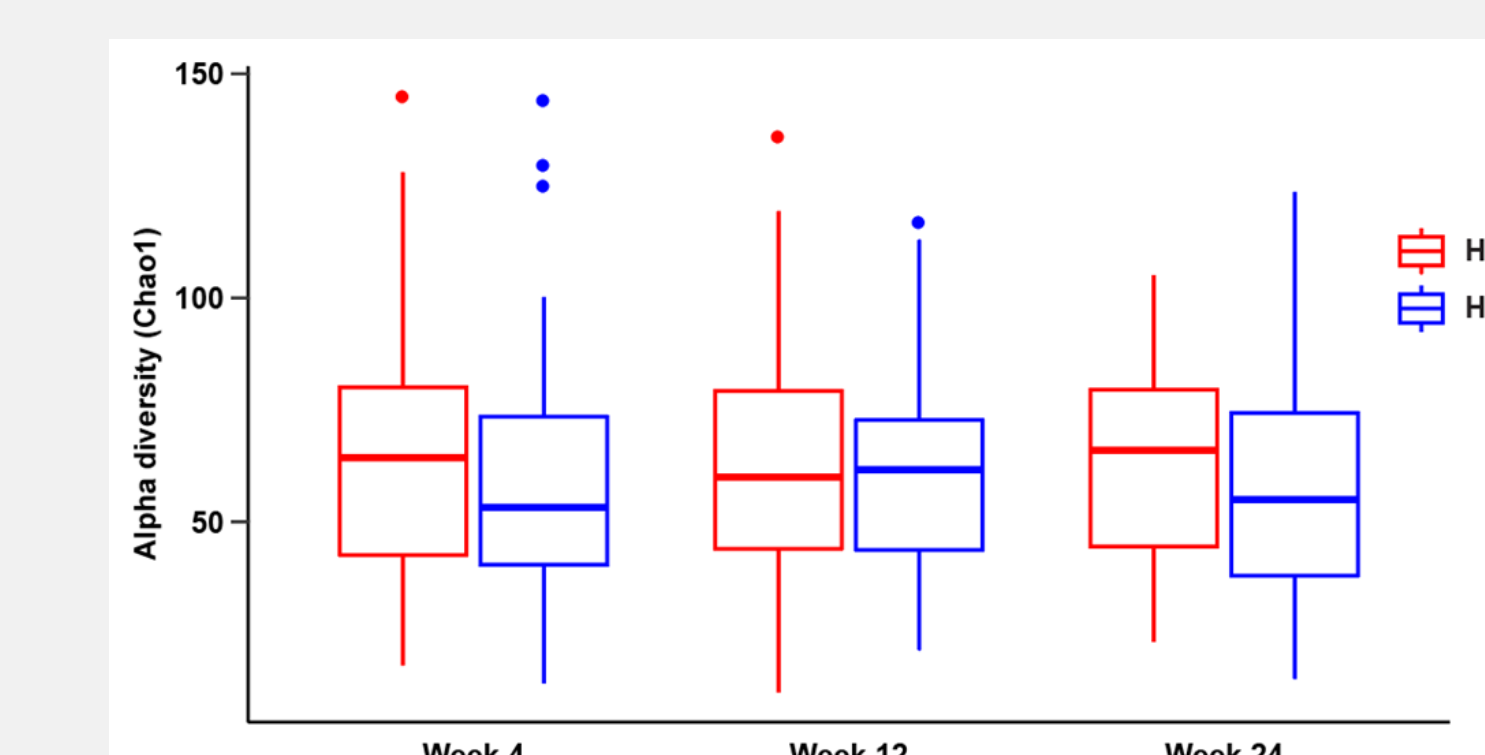
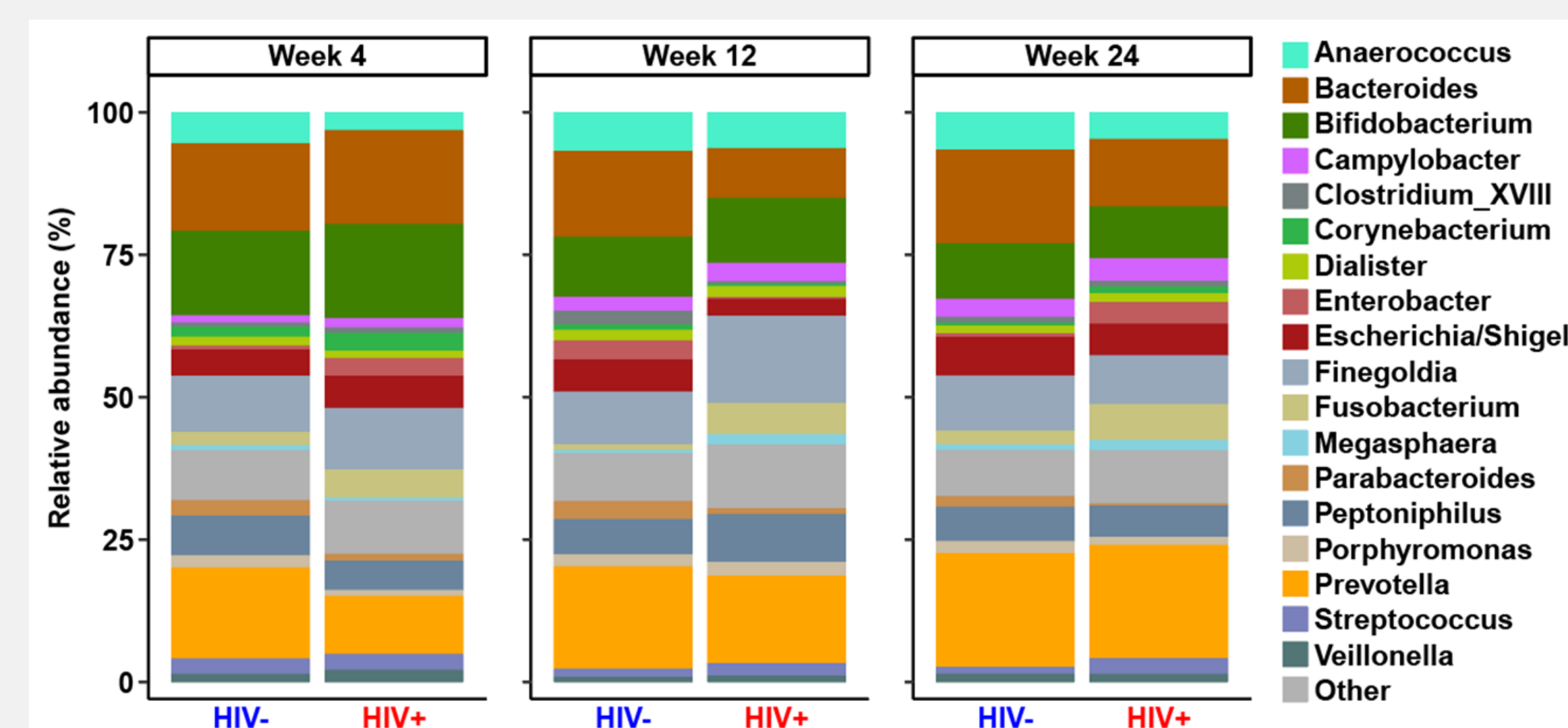
## CHARACTERISTICS OF PARTICIPANTS

	Uninfected infant	Infant with HIV Early ART <48 hours	Infant with HIV Later ART >48 hours	P-value
N	71	39	40	
Infant sex Female	37 (52.1%)	19 (48.7%)	20 (50.0%)	0.939
Delivery mode Cesarean	3 (4.2%)	7 (17.9%)	17 (42.5%)	<0.001
Preterm	4 (5.6%)	2 (5.1%)	10 (25.0%)	0.003
Low birthweight <2.5kg	17 (23.9%)	4 (10.3%)	11 (27.5%)	0.132
Ever breastfed	45 (63.4%)	34 (87.2%)	28 (70.0%)	0.03
Mother's VL >1000	13 (18.3%)	31 (79.5%)	28 (70.0%)	<0.001
Mother's CD4 count <350	15 (21.1%)	22 (56.4%)	18 (45.0%)	0.001
Mother took ART during pregnancy	69 (97.2%)	30 (76.9%)	31 (77.5%)	0.002



Principal components analysis (PCA) biplot showing samples by HIV status. Vectors show loadings of the specified taxa on each of the first two components.

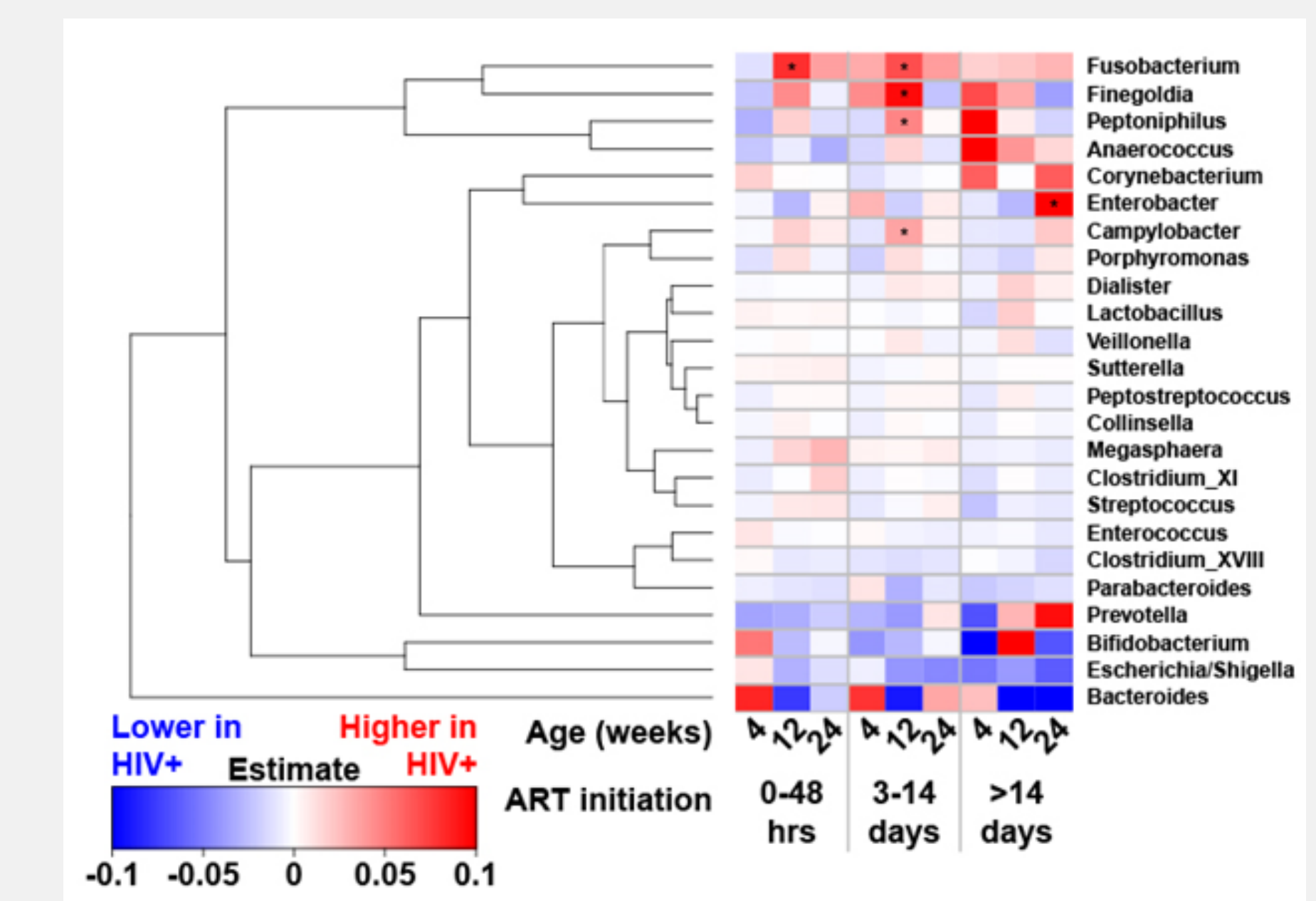
Taxa bar plots show significant increases in abundance of *Bacteroides* at 4 weeks and *Fusobacterium* and *Finigoldia* at 12 weeks associated with HIV infection



Alpha diversity did not differ by HIV status

## EFFECTS OF TIMING OF ART INITIATION

If ART was started later than 14 days of age, the shifts in taxa associated with HIV infection were exacerbated with decrease in *Bifidobacterium* abundance at 4 weeks, and increase in *Fusobacterium* and *Enterobacter* abundances at later time points. Although early ART, like breastfeeding, buffered against *Bacteroides* expansion, increases in *Fusobacterium* abundances persisted regardless compared to uninfected infants born to mothers living with HIV.



## CONCLUSIONS

- There are detectable benefits associated with breastfeeding in conjunction with early ART in maintaining a more *Bifidobacteria*-rich microbiota profile in infants with HIV.
- However, persisting shifts in the microbiota profile despite early ART, even among breast-fed infants, support the need for complementary interventions to strengthen early ART and improve outcomes.

## ACKNOWLEDGEMENTS

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