Danno di barriera, traslocazione microbica e composizione microbica in pazienti pediatrici nati da madre HIV-positiva

«HIV e COVID: quali nuove sfide?»

7-8 giugno 2021

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Outcomes of maternal HIV infection

Depending on timing of and adherence to cART:

- HIV-exposed, infected (HEI)
- HIV-exposed, uninfected (HEU)

Comparison with HIV-unexposed, uninfected (HUU) counterparts

HIV-exposed, infected (HEI)

- Increased long-term morbidity and mortality due to infectious and non-infectious disorders (both virus- and cART-related)
- Profound HIV-mediated disruption of mucosal immunity, barrier integrity and microbiome
- Gut dysbiosis (↓ alpha- and beta-diversity, relative abundance) correlates with chronic immune activation and may be associated with non-communicable comorbidities (cardiovascular)
- ↓ *Faecalibacterium* and *Lachnospira;* ↑ *Prevotella, Akkermansia* and *Coprobacillus*
- Prolonged cART (>10 years) may revert microbiota alterations; however, a negative effect of cART on microbiome has also been hypothesized

Kaur et al., Sci Rep, 2018;8(1):1–16. Sessa L et al., Aids. 2019;33(6):1001–11. Flygel TT et al., J Infect Dis. 2020;221(3):483–92. Sainz T et al., 2020;12(7):1–13. Gootenberg DB et al., Curr Opin Infect Dis. 2017;30(1):31–43. Claassen-Weitz S et al., Sci Rep. 2018;8(1):1–15.

Focus on HIV-exposed, uninfected (HEU)

Increased burden of infectious and non-infectious morbidity compared to HUU counterparts:

- Same spectrum of diseases (pneumonia, diarrheal disease, bacterial sepsis) but greater severity (↑ hospitalizations and mortality)
- ↑ risk for streptococcal infections (group B, S. pneumoniae)
- ↑ risk for vertical infections (TORCH, CMV in particular)
- ↓ growth and neurodevelopment

This difference in M&M reaches its peak beyond the neonatal period, during mid-infancy, and seems to wane by the 2° year of life.

Slogrove AL et al., Front Immunol. 2016;7(MAY):1–8. Amenyogbe N et al., J Immunol. 2020;205(10):2618–28.

Focus on HIV-exposed, uninfected (HEU)

Underlying mechanisms are ill-defined and likely multifactorial:

- Prematurity/SGA
- No/suboptimal breastfeeding
- Maternal health status and immune compromise (correlation with CD4 count at delivery)
- Exposure to HIV (viral components) and other infectious agents, **pro-inflammatory environment**
- Exposure to cART and other medications (in utero, breastfeeding)
- Socioeconomic conditions
- **Alterations of innate immunity and fecal microbiome**

Slogrove AL et al., Front Immunol. 2016;7(MAY):1–8. Amenyogbe N et al., J Immunol. 2020;205(10):2618–28.

HEU vs HUU

Innate and adaptive immunity:

- Fewer circulating immune cells
- T cell maturation abnormalities
- Tendency to mount higher proinflammatory responses (↑ IL-6 and IL-8 production in response to LPS and PGN)
- Lower antiviral responses

Microbiome (dysbiosis):

- Correlation with breastfeeding (altered HMO composition)
- ↑ Pseudomonas and Prevotella spp., ↓ SCFA-producing bacteria
- Population-specific differences → importance of local factors
- No macroscopic differences in alpha- and beta-diversity, but differences in relative abundance

Amenyogbe N et al., J Immunol. 2020;205(10):2618–28. Bender JM et al., Sci Transl Med. 2016 Jul 27;8(349):349ra100. Machiavelli A et al, Gut Microbes. 2019;10(5):599–614.

Open research questions

- Persistence of gut and immune alterations in the long term
- Comparison with HEI counterparts

Study design

Study population:

subjects born from HIV-infected mothers

Multicentric study (Modena, Milano, Napoli, Torino, Brescia)

Two groups:

- HEU
- HEI

Exclusion criteria:

- Antibiotics and/or prebiotics 2 weeks prior to enrollment
- Intestinal disorders
- Chronic infections other than HIV (TB, HCV, HBV/HDV)
- Vegan, vegetarian or high-protein diets
- Age <1 yo (physiological immaturity of gut microbiota)

Materials and methods

- Fecal microbiome composition analysis (MiSeq technology):
  - alpha-diversity
  - beta-diversity
  - relative abundance (LEfSe algorithm)
- Soluble markers of gut damage, microbial translocation, immune activation and inflammation (plasma, ELISA):
  - Intestinal Fatty Acid Binding Protein (I-FABP)
  - E-Cadherin
  - soluble CD14 (sCD14)
  - Endotoxin Core Antibodies (EndoCab)
  - IL-6

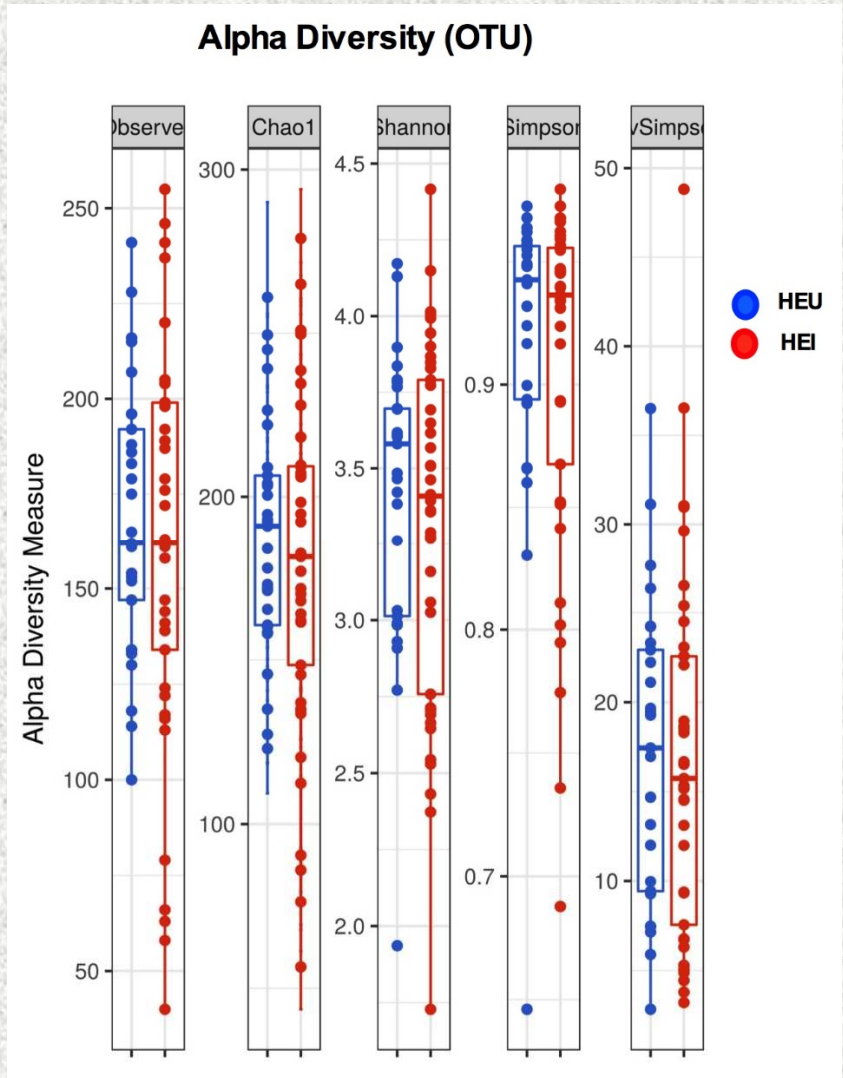
Results

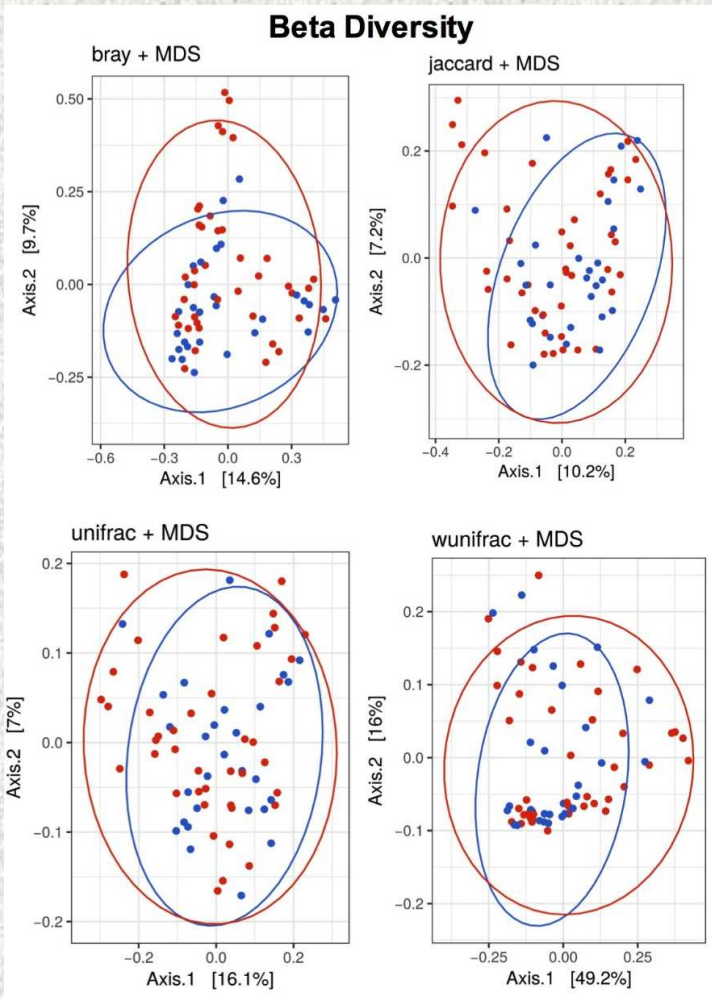
Demographic and epidemiological characteristics of subjects born from HIV+ mothers

Characteristics	Total (n=80)	HEI (n=47)	HEU (n=33)	p values
Sex, female (%)	36 (45)	19 (40)	17 (51)	0.367
Country of Birth, n (%)				0.073
Africa	21 (26)	16 (34)	5 (15)	
Europe	59 (73)	31 (66)	28 (85)	
Age, years (IQR)	13 (8-16)	14 (9-16)	12 (4.5-14.5)	0.062
Breastfeeding, yes (%)	22 (27)	21 (45)	1 (3)	**<0.0001**
Pre-Term delivery, yes (%)	12 (15)	7 (15)	5 (15)	1
Delivery mode, n (%)				**0.0005**
Vaginal delivery	26 (33)	23 (49)	3 (9)	
Cesarean delivery	44 (55)	18 (38)	26 (79)	
Unknown	10 (12)	6 (13)	4 (12)	
BMI, n (%)				**0.0001**
Normal (-1.86; + 1.86 SD)	53 (66)	39 (83)	14 (42)	
Low (< -1.86 SD)	0	0	0	
High (> +1.86 SD)	12 (15)	6 (13)	6 (18)	
Unknown	15 (19)	2 (4)	13 (40)	
CD4 T-cell count, cell/mmc (IQR)	728 (532-945)	728 (532-945)	n/a	n/a
CD4 T-cell count, % (IQR)	34 (30-39)	34 (30-39)	n/a	n/a
CD8 T-cell count, cell/mmc (IQR)	621 (461-892)	621 (461-892)	n/a	n/a
CD8 T-cell count, % (IQR)	32 (25-39)	32 (25-39)	n/a	n/a
CD4/CD8 ratio (IQR)	1.12 (0.79-1.32)	1.12 (0.79-1.32)	n/a	n/a
Detectable viral load, n (%)	3 (4)	3 (6)	n/a	n/a
On cART, n (%)	47 (59)	47 (100)	n/a	n/a
Mothers on cART during pregnancy, n (%)	34 (43)	5 (11)	29 (88)	**<0.0001**

Results

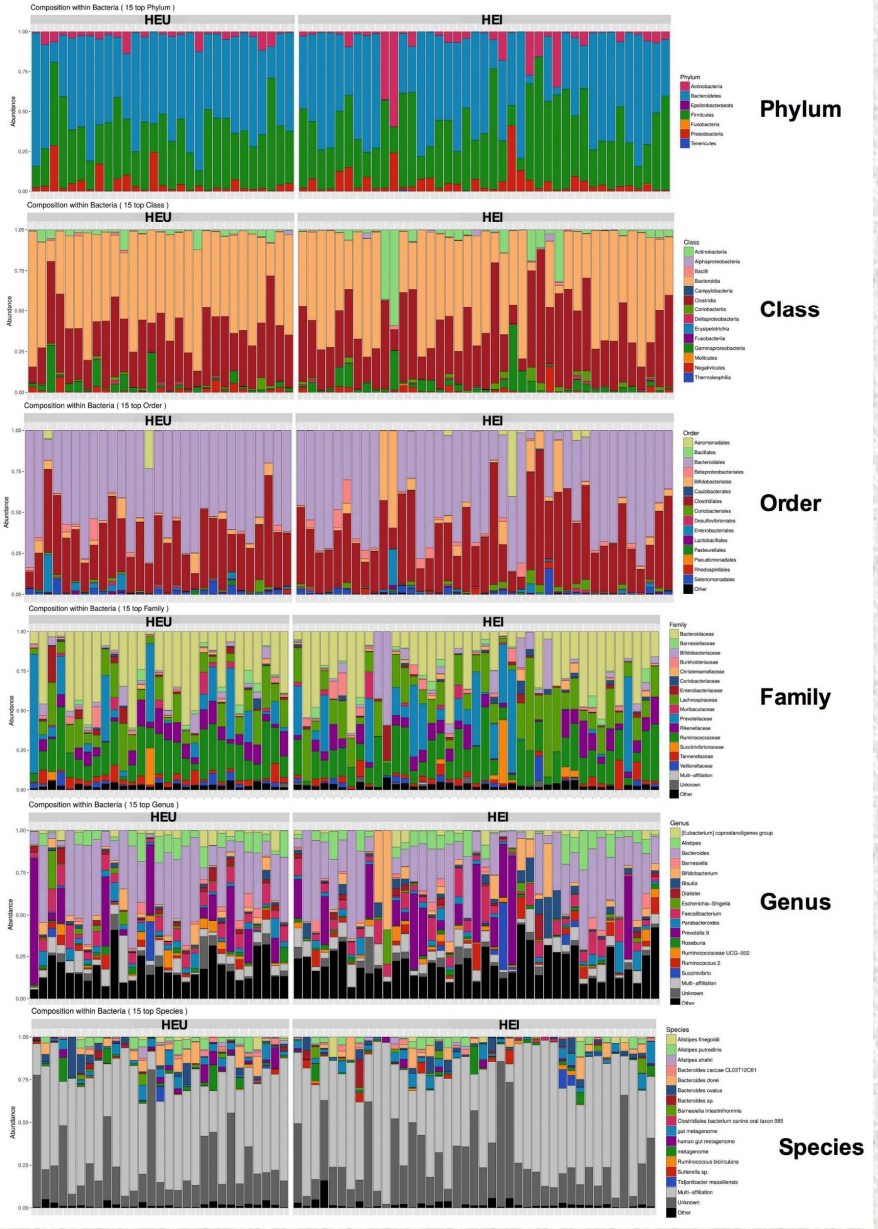
Fecal microbiome analysis

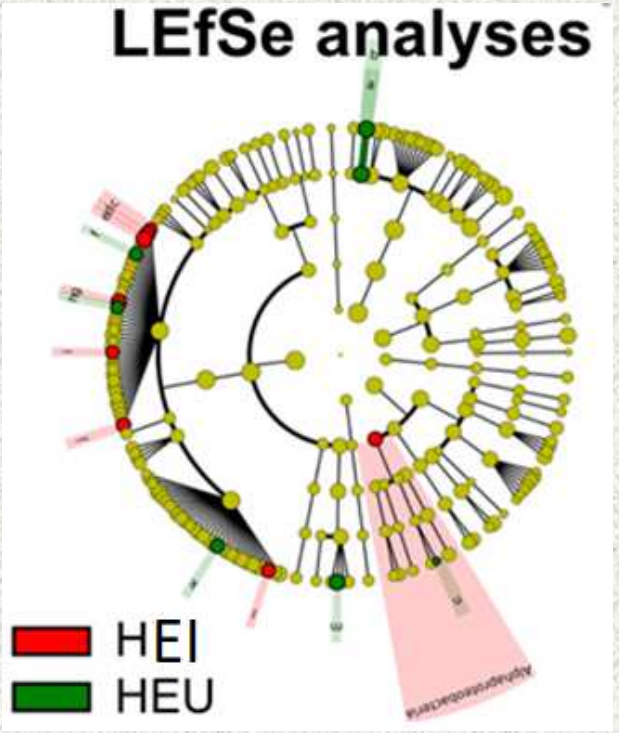




Results

Fecal microbiome analysis

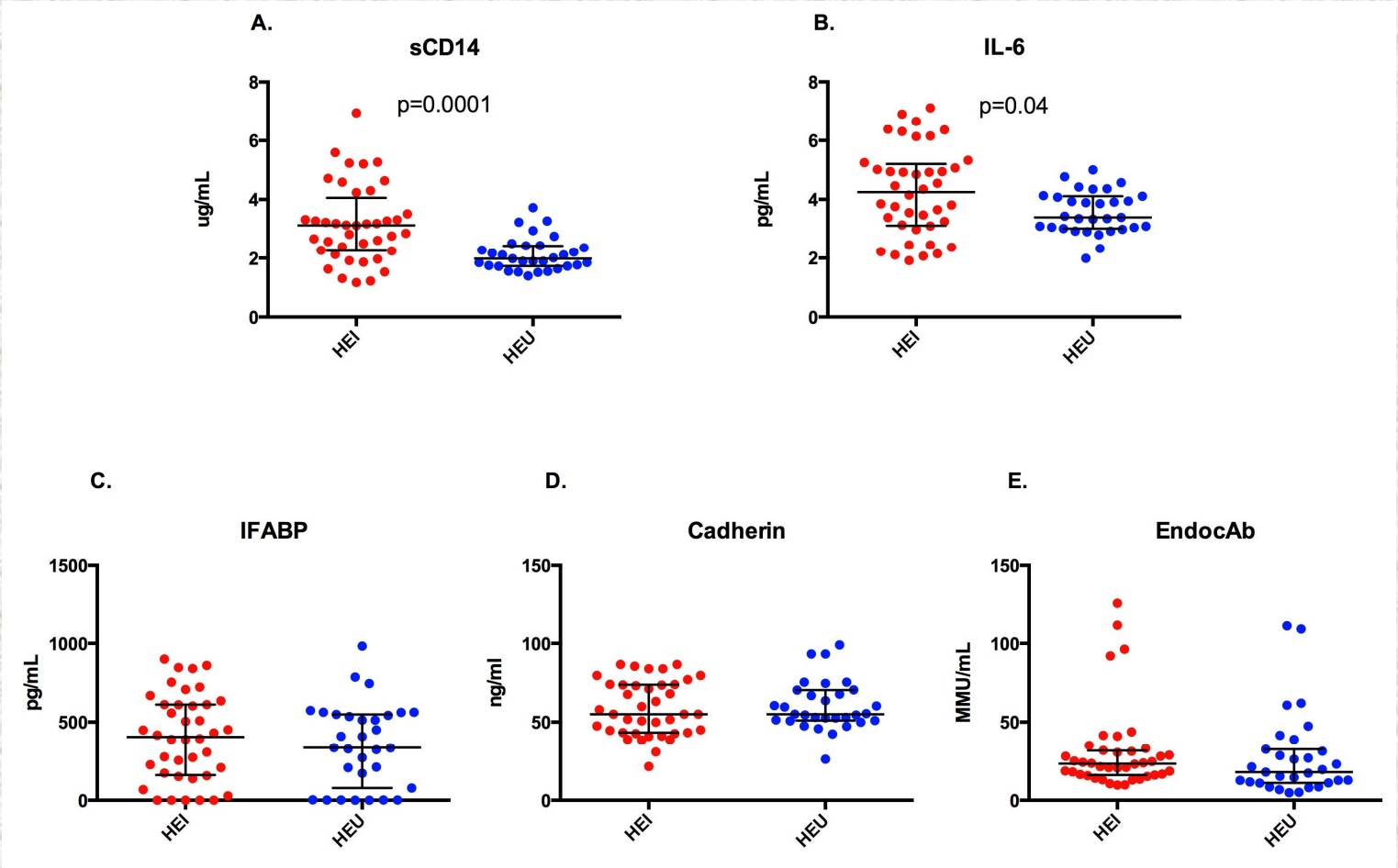




- a: Parabacteroides
- b: Tannerellaceae
- c: Agathobacter
- d: Anaerostipes
- e: Blautia
- f: Coprococcus2
- g: Lachnoclostridium
- h: Lachnospira
- i: Sellimonas
- j: _Ruminococcus_torquesgroup
- k: RuminococcaceaeUCG_003
- l: UBA1819
- m: Dialister
- n: Rhodobacter

Results

Marker of gut damage, microbial translocation, immune activation and inflammation



Discussion and conclusions

Our findings:

- NO significant differences in fecal microbiome composition between infected (HEI) and uninfected (HEU) subjects
- Higher monocyte activation and inflammation in HEI subjects compared to HEU (residual inflammation), BUT comparable intestinal integrity and microbial translocation parameters in the two groups

Possible interpretations:

- Protective role of long-term cART in HEI subjects (reverting alteration)
- Maternal HIV infection is independently associated with differences in both innate immunity and the stool microbiome

Amenyogbe N et al., J Immunol. 2020;205(10):2618–28.

Discussion and conclusions

Novelty of our study:

- Comparison between HEU vs HEI
- Older pediatric subjects (beyond infancy)

Interestingly, we found comparable microbiome characteristics between HEI and HEU despite significant differences in feeding practices and delivery mode.

Heightened clinical risk in HEU subjects → need for long-term follow-up

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