HIV Burden is Associated with Specific Bacteriome Profiles Relative to Specific Gut Segments

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Mattia Trunfio[1], Davey Smith[1], Noah Gaitan[1], Mina Awad[1], Magali Porrachia[1], Alan Wells[1], Jesus Rivera-Nieves[1], Elizabeth Hastie[1], Patricia Riggs[1], Sara Gianella[1], Antoine Chaillon[1]
[1]Department of Medicine, University of California San Diego (UCSD), San Diego, CA, USA

BACKGROUND

- The composition and characteristics of the local microbiome[1], immune system[1], and HIV reservoirs[2] vary across different tracts of the human gut.
- Gut microbiome signatures may influence the HIV reservoir and viremia control[3].
- Therapeutic microbiome modulation has failed to significantly impact microbial translocation, systemic inflammation, and HIV-related metrics (e.g., CD4 count)[4].

OBJECTIVE

We examined the gut bacteriome's impact on HIV reservoir size and activity and sought a core bacteriome linked to the reservoir across all gut segments.

METHODS

Samples. Tissue collected from five gut segments (small bowel: duodenum, jejunum, ileum; large bowel: right colon, rectum) ≤6 hours postmortem from 24 people with HIV (PWH) in the *Last Gift* rapid autopsy program.

Microbiome Analysis. Gut bacteriome characterized via 16S rRNA sequencing. α- and β-diversity analyzed using *Phyloseq R* after dimension reduction of taxa.

HIV Reservoir Quantification. Cell-associated total HIV DNA and RNA quantified via digital droplet PCR (ddPCR).

Statistical Analysis. Mixed-effect models assessed associations between the relative abundance (RA) of taxa and HIV DNA/RNA and were adjusted for age, sex, CD4⁺ T cell counts (current, nadir), duration of HIV, last plasma HIV RNA, and antibiotic exposure.

- **Model A**: Gut-level analysis adjusted for gut segment (**Fig.1**).
- **Model B**: Segment-specific analysis.

FIG.2. LARGE HETEROGENEITY IN THE BACTERIOME COMPOSITION ACROSS THE GUT SEGMENTS: THE 20 MOST ABUNDANT BACTERIAL SPECIES ARE SHOWN

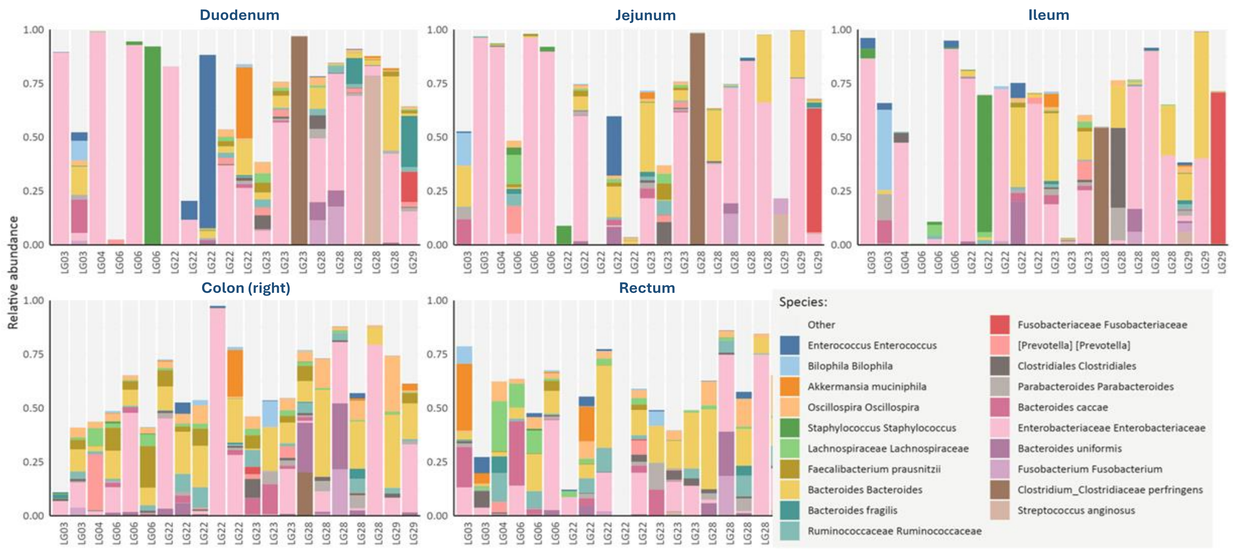


FIG.3 GREATER DIVERSITY IN THE LARGE BOWEL WITH SIGNIFICANT INTRA-BOWEL VARIATION

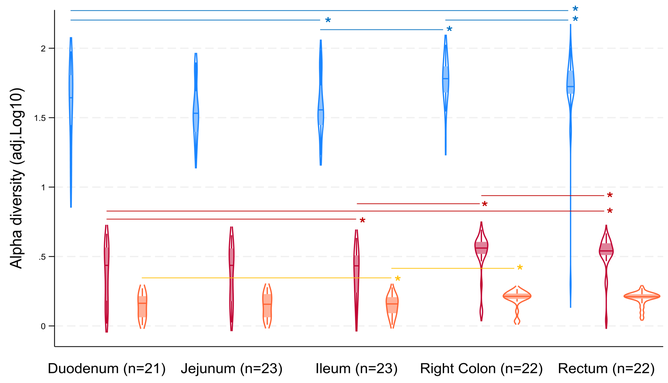


FIG.4 HIGHER TOTAL HIV DNA LEVELS IN THE SMALL BOWEL

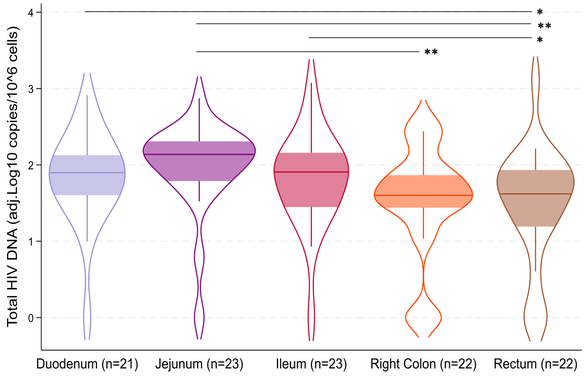


*Fig.3 legend: Blue= number of observed taxa; Red=Shannon index; Orange=Pielou index. Fig.3-4: *Adj.p value<0.05, **Adj.p value<0.01*

FIG.1 A CORE BACTERIOME WAS ASSOCIATED WITH HIV BURDEN IN THE GUT (MODELS A): the RA of 9 bacterial genera was associated with HIV DNA (left) and the RA of 6 bacterial genera with HIV RNA (right)

Phylum	Genus	aβ
Fusobacteriota	*Fusobacteriaceae f*	
Verrucomicrobiota	-	
Bacillota	*Lachnospira*	+35
	Ruminococcus	+20
	Ruminococcaceae f	+5
	Dorea	0
	Lactobacillus	-5
Pseudomonadota	*Pseudomonas*	-20
	Alteromonadales o	-100
Bacteroidota	*Barnesiellaceae f*	-200

Phylum	Genus	aβ
Bacillota	*Clostridium*	+25
	Lachnospira	+20
	Erysipelotrichaceae f	+10
	Coprobacillus	+5
	Acidaminococcus	0
		-5
		-10
Pseudomonadota	*Proteus*	-15
		-20

Increasing RA (relative abundance) of the shown taxa was associated with higher/lower (yellow/green) HIV DNA (left) or HIV RNA in the gut (right). Legend: f/o, attribution at the family/order level for uncertain attribution at the genus level; aβ, adjusted beta coefficient.

STUDY POPULATION	N=24
Age, years	63 ± 13
Male sex at birth, n	21 (87.5%)
Ethnicity, n	
Caucasian	20 (83.3%)
Black	3 (12.5%)
Other	1 (4.2%)
On ART at death, n	21 (87.5%)
Plasma HIV RNA, copies/mL*	48 – 275 – 68.007
CD4⁺ T cell count, cells/μL	194 (97-347)
Nadir CD4⁺ T cell count, cells/μL	77 (38-166)
Est. duration of HIV, years	23 (17-33)
ART regimen, n	
INSTI-including	23 (95.8%)
PI-including	2 (8.4%)
NNRTI-including	5 (20.8%)
Cause of death, n	
Non-GI solid cancer	11 (45.8%)
GI solid cancer	4 (16.7%)
Blood cancer	1 (4.2%)
End stage organ disease	5 (20.8%)
Infections/AIDS	5 (20.8%)
Neurologic disease	2 (8.4%)
Antibiotic exposure, n	14 (58.3%)

*ART, antiretroviral; INSTI, integrase strand-transfer inhibitor; PI, protease inhibitor; NNRTI, nonnucleoside reverse transcriptase inhibitor; GI, gastrointestinal. *In participants with plasma HIV RNA > 20 cp/mL.*

RESULTS

- **Study Population**: *n* = 24; 21 had plasma HIV RNA <20 cp/mL, 22 <200 cp/mL (**Table**).
- **Bacteriome Composition**: Highly heterogeneous, even between adjacent segments (**Fig.2**).
- **α-Diversity**: Highest in the large bowel, with significant differences within both small and large bowel segments (**Fig.3**).
- **β-Diversity**: Bacterial communities differed significantly between the small and large bowel (p = 0.037; not shown).
- **HIV burden**: Total HIV DNA levels were higher in the small bowel than in the large bowel (101 vs. 40 copies/10^6 cells, p = 0.003; **Fig.4**), while HIV RNA showed no significant difference across segments.
- **Associations of Bacteriome with HIV burden:**
  - **Models A**: 9 bacterial genera correlated with HIV DNA levels, and 6 with HIV RNA (**Fig. 1**).
  - **Models B (segment-specific)**: No single taxon was consistently linked to HIV burden across all segments; for instance:
    - *Clostridium* correlated with higher HIV RNA in the duodenum, ileum, and rectum ($p \leq 0.03$) but not in the jejunum or colon.
    - *Lachnospira* was associated with lower HIV DNA in the colon but higher in the ileum ($p \leq 0.01$).
    - *Ruminococcus* correlated with higher HIV RNA in the duodenum but lower in the rectum ($p \leq 0.01$).

CONCLUSIONS

The gut bacteriome influences the size and activity of the HIV reservoir, but its impact varies by gut segment.

The lack of a universal gut bacteriome-HIV relationship suggests that microbiome-based therapies may require region-specific targeting rather than a one-size-fits-all approach.

ADDITIONAL KEY INFORMATION

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Last Gift

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Author Contact Information

mtrunfio@health.ucsd.edu