# Glycomic Determinants of Gut Microbial Dysbiosis and Translocation During Suppressed HIV Infection

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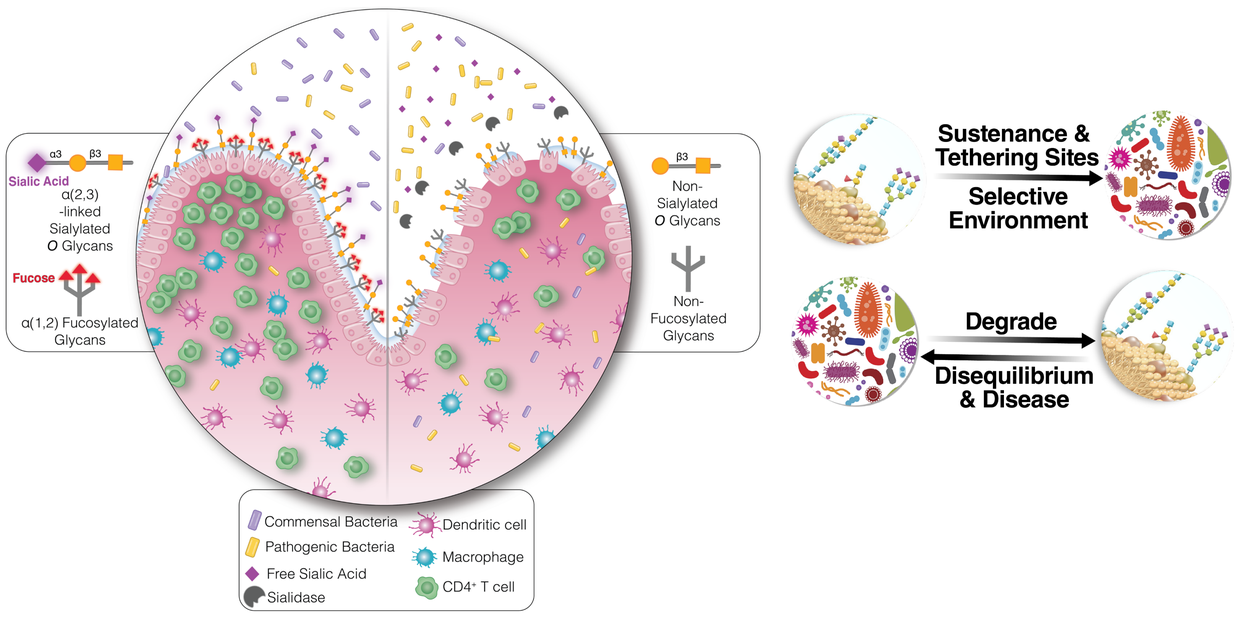
## Introduction



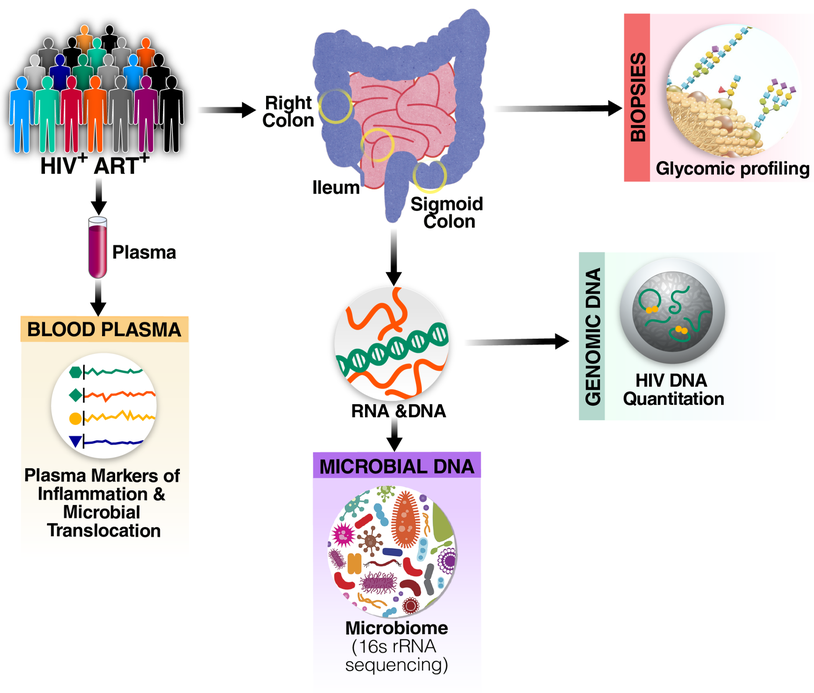




- An emerging paradigm suggests that gut glycosylation is a key force in maintaining a homeostatic relationship between the gut and its microbiota. In the general population, changes in the gut glycome can alter the gut microbial composition, leading to microbial dysbiosis and gut inflammation.
- In HIV-infected individuals, microbial dysbiosis and translocation contribute to the vicious cycle between HIV and immune activation/ inflammation. This cycle likely contributes to the development of non-AIDS inflammatory-related illnesses and HIV persistence. However, how gut glycosylation machinery contributes to this cycle is yet to be characterized.
- Here we investigated the role of altered gut glycans in modulating the gut microbiome and mediating HIV-associated gut inflammation.

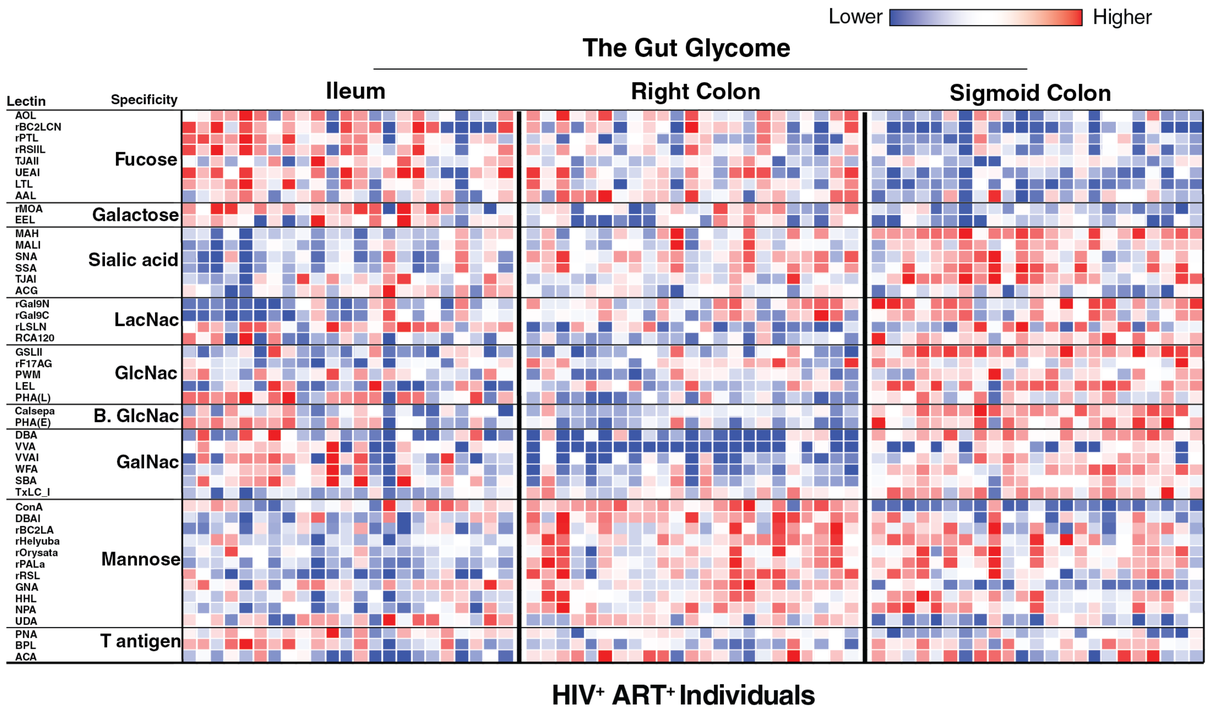
## Methods

| n | 20 |
|---|---|
| Gender (% male) | 75 |
| Ethnicity | 75% AA, 15% HA, 10% CAU |
| Age Mean yrs (SD) | 51.7 (4.9) |
| HIV Viral Load (copies/ml) | <40 |
| CD4 Count Mean cells/mm$^3$ (SD) | 500 (261.3) |
| BMI Mean (SD) | 25.7 (3.9) |

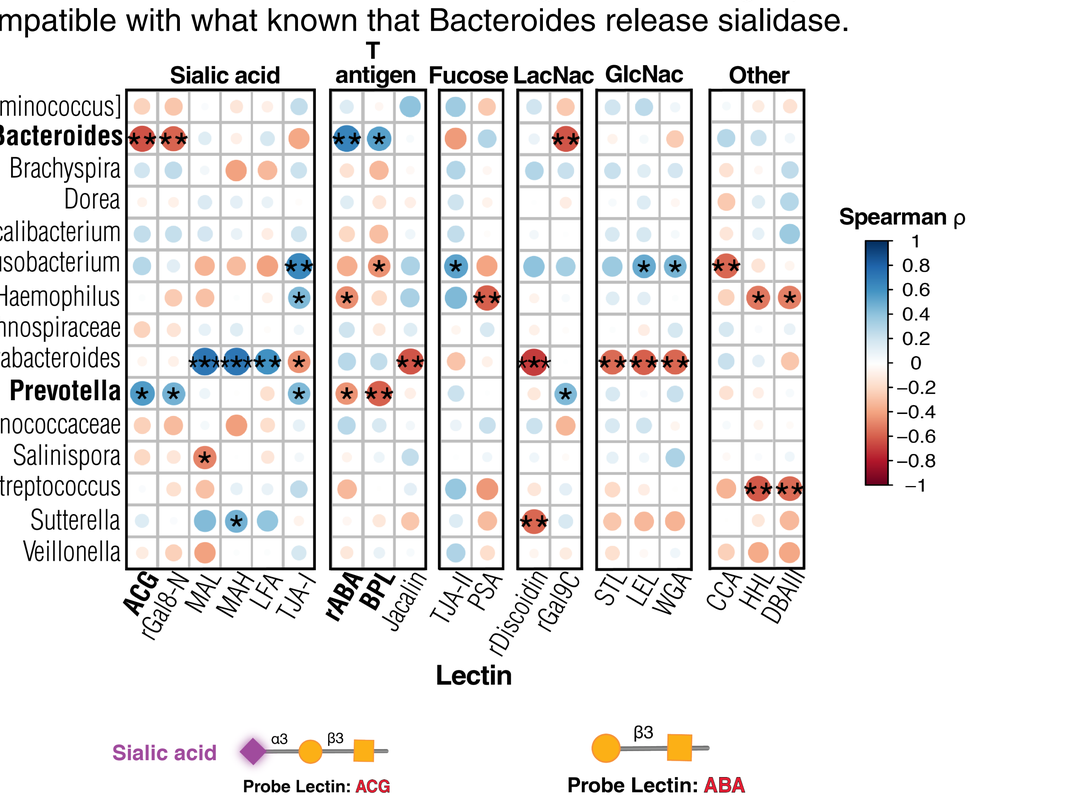



## Results

**1) The gut glycome is compartmentalized between Ileum, right colon, and sigmoid colon.** A decrease in fucose, an increase of sialic acid, and an increase of mannose when going from the ileum to the colon. *FDR*<0.05. Permanova test on euclidean distances <0.05




**2) Mucosal glycosylation may play a role in microbial composition shift during ART-suppressed HIV infection.** Increasing levels of Bacteroides genus correlate with lower sialylated glycans and higher hypo-sialylated glycans (in particular, Gal-GalNAc, also known as T-antigen or TF-antigen). These correlations are compatible with what known that Bacteroides release sialidase.







**3) Mucosal sialic-acid catabolism and gut fucosylation associate with markers of microbial diversity and dysbiosis during ART-suppressed HIV infection. (A)** Correlations with alpha diversity (decreased in HIV infection; the higher the better) and with **(B)** Bacteriodetes/Firmicutes (increased in HIV infection; the higher the worse)

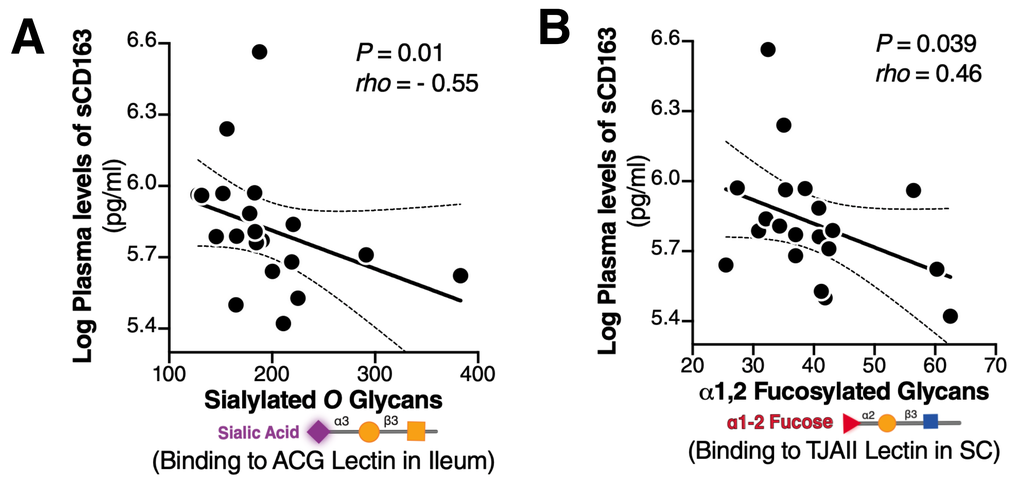
**A**

| *P* | r | Glycan | Lectin | Metric | Tissue Type |
|---|---|---|---|---|---|
| 0.013 | 0.55 | Sialylated *O* glycans | ACG | Shannon | Ileum |
| 0.016 | 0.53 | LacNac, Sialic acid | rGal8N | Shannon | Ileum |
| 0.001 | -0.68 | T Antigen, Mostly Hypo-Sialylated | rABA | Shannon | Ileum |
| 0.005 | -0.6 | T Antigen, Mostly Hypo-Sialylated | DBA | Shannon | Ileum |
| 0.032 | 0.48 | α1,2 Fucose | TJAII | Richness | Ileum |

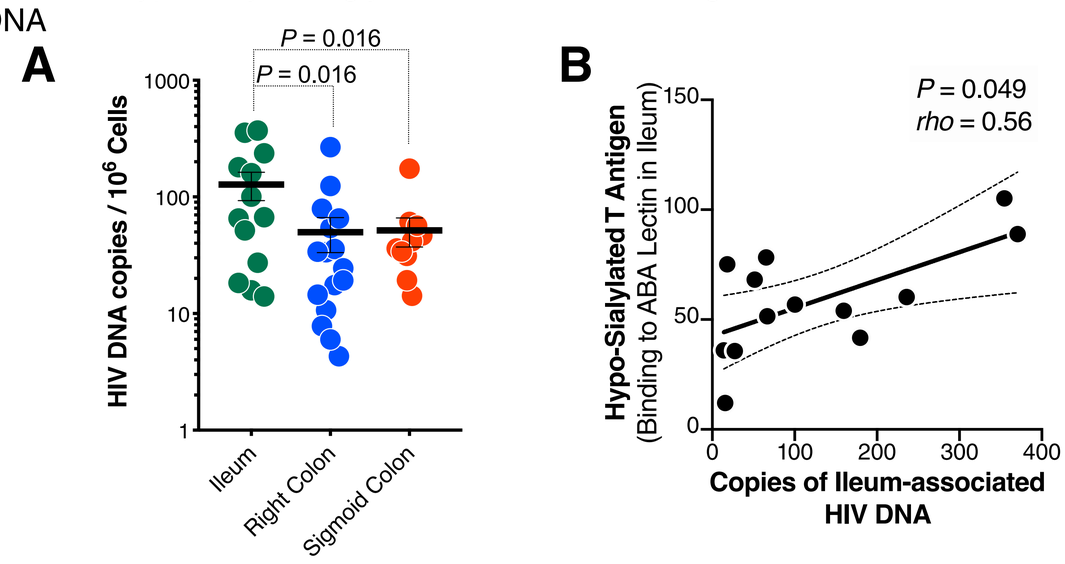
**B**

| *P* | r | Glycan | Lectin | Tissue Type |
|---|---|---|---|---|
| 0.049 | -0.45 | Sialylated *O* glycans | ACG | Ileum |
| 0.003 | 0.64 | T Antigen, Mostly Hypo-Sialylated | rABA | Ileum |
| 0.006 | 0.6 | T Antigen, Mostly Hypo-Sialylated | DBA | Ileum |
| 0.01 | 0.56 | T Antigen, Mostly Hypo-Sialylated | HPA | Ileum |
| 0.009 | -0.57 | α1,2 Fucose | TJAII | Ileum |

**4) Mucosal sialic-acid catabolism and gut fucosylation associate with markers of inflammation during ART-suppressed HIV infection. (A)** Levels of sialylated O-glycans in the illeum correlated with lower levels of sCD163. **(B)** Mucosal-associated α 1-2 fucose correlated with lower plasma levels of sCD163 in sigmoid colon.




**5) Glycomic T antigen correlates with ileum-associated HIV DNA during ART-suppressed HIV infection. (A)** Total HIV DNA distribution between tissues. **(B)** Levels of hypo-sialylated glycans correlated with higher Ileum-associated total HIV DNA




## Conclusions

- Our pilot study provides the first proof-of-concept evidence that differential gut glycomic patterns (mainly sialylated and fucosylated glycans) support distinct microbiome compositions that predispose to microbial translocation, inflammation, and HIV persistence.
- Our data are consistent with previous general population reports which demonstrated that sialic acid catabolism drives microbial dysbiosis and intestinal inflammation and that gut fucosylation sustains host-commensal symbiosis and prevents gut inflammation.
- Exploiting gut glycosylation machinery may allow the design of strategies to manipulate it to prevent/delay the development of HIV-associated co-morbidities.

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