Investigating Therapeutic Intervention on the Gut Microbiome of Patients with HIV/AIDS

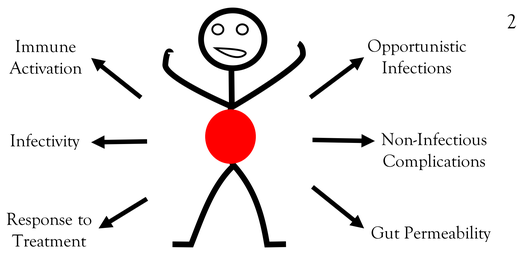
Bryn C. Taylor[1], David Asmuth[3], Rob Knight[1,2]

1. Department of Biomedical Sciences, 2. Departments of Pediatrics and Computer Science, University of California San Diego, La Jolla CA 92093 United States

3. Internal Medicine, University of California Davis Health, Sacramento CA 95817 United States

HIV Decimates the Gut Microbiome

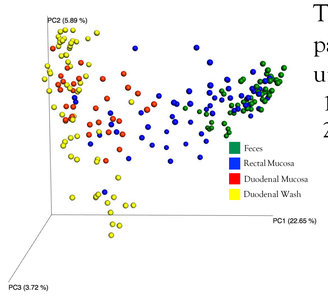
- Dysbiosis of the gut microbiome contributes to sustained systemic immune activation that may cause poor immune reconstitution.
- Many HIV/AIDS patients experience delayed immune reconstitution after successful HIV/AIDS treatment. [1]



[2]

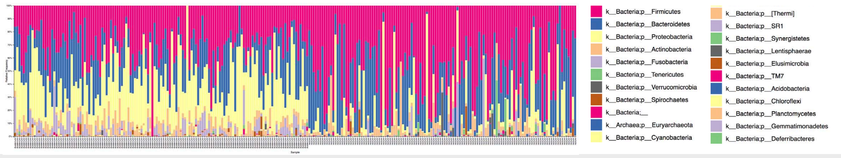
Can we restore proper immune function by **mitigating inflammatory microbial communities** in the gut?

Studying the Gut Microbiome: Duodenal, Rectal, and Fecal Samples



To understand the impact of different therapeutic cocktails on the gut microbiome of patients with HIV/AIDS, and to compare the effect of anti-retroviral therapy (ART) on unique areas of the gastrointestinal tract, we performed:

1. 16S rRNA sequencing on fecal samples, rectal mucosa, duodenal mucosa, and duodenal washes.
2. Metabolomics analysis on fecal samples to determine the functional output of the microbiome.



There is a Significant Difference in all Samples between HIV- and HIV+

Duodenal Samples

HIV Neg

HIV Pos

FDR Corrected
$p \leq 0.05$
$p \geq 0.05$

p-wise permanova
999 perm.,
unweighted unifrac

Fecal & Rectal Samples

HIV Neg

HIV Pos

Summary

- The microbiome of patients with HIV/AIDS is distinct from the microbiome of healthy subjects
- The microbiome of *only* the duodenal samples of patients with HIV/AIDS changes in response to therapeutic intervention, more closely resembling the healthy controls.
- Despite CCR5 blockade, there is no difference between the effect of MVC versus NNRTI on the microbiome.

Future Directions

- Identification of microbes and metabolites that drive the changes we see in the microbiome after treatment (ANCOM, etc.).
- Correlation of clinical markers and taxonomic shifts pre- and post- treatment.
- Correlation of changes in immunologic or inflammatory parameters with shifts in microbial communities.
- Targeted therapies?
- Metabolomics analysis to compare the functional profiles of all subjects.

Randomized Clinical Trial

Entry	9 Months
26 HIV +	
6 HIV -	
Duodenal Biopsy Duodenal Wash Rectal Biopsy Fecal Sample	Duodenal Biopsy Duodenal Wash Rectal Biopsy Fecal Sample

26 HIV positive patients treated with tenofovir disoproxil fumarate/emtricitabine, plus:

- Maraviroc (MVC) or MVC plus raltegravir, n=18
- Non-nucleoside reverse transcriptase inhibitor (NNRTI), n=8

Key Questions:

- Does treatment with anti-retroviral therapy (ART) rescue community structure in the gut? Duodenum? Rectum?
- Is one therapeutic cocktail better than another for microbiome recovery and/or immune reconstitution?

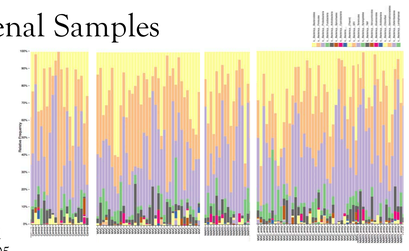
Only Duodenal Microbial Communities Change After Treatment

Duodenal Samples

Entry

Control

9 Month



FDR Corrected
$p \leq 0.05$
$p \geq 0.05$

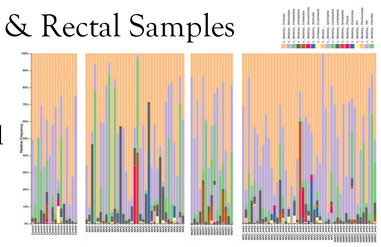
p-wise permanova
999 perm.,
unweighted unifrac

Fecal & Rectal Samples

Entry

Control

9 Month



What microbes or microbial products are driving this change?

There Is No Difference Between Therapeutic Cocktails

There is not a significant difference in the effect of MVC on the microbiome when compared to NNRTIs.

Entry

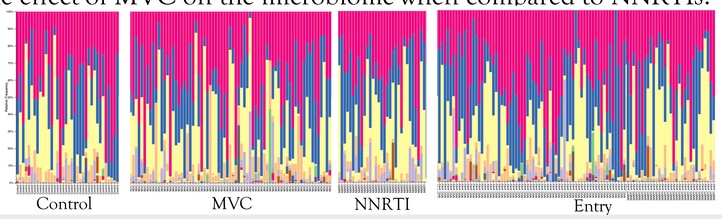
Control

MVC treated

NNRTI treated

FDR Corrected
$p \leq 0.05$
$p \geq 0.05$

p-wise permanova
999 perm.,
unweighted unifrac



References

1. Siddiqui U, Bini EJ, Chandarana K, et al. Prevalence and Impact of Diarrhea on Health-relate d Quality of Life in HIV-infected Patients in the Era of Highly Active Antiretroviral Therapy. J Clin Gastroenterol 2007;41:484–490)
2. Zilberman-Schapira, G., Zmora, N., Itav, S. *et al.* The gut microbiome in human immunodefici ency virus infection. BMC Medicine, 2016.

Acknowledgements

This study was funded through an investigator-initiated grant provided by ViiV Healthcare.

Graduate student funding from the San Diego Diversity Fellowship