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Maraviroc Does Not Induce Changes in the Gut Microbiome of HIV Infected Individuals

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Background

- The gut associated lymphoid tissue is a crucial part of the immunological network that maintains the integrity of the gastrointestinal tract against gut microbes. [1]
- HIV preferentially depletes gut CD4+ T cells, likely associated with high levels of CCR5 expression, and consequently the gut integrity is compromised. [2]
- Maraviroc blocks HIV entry by binding CCR5, but its effects on the gut microbiome have not been characterized.[3]

Objective

To determine the impact of maraviroc intensification in the gut microbiome of HIV-infected individuals

Methods

- We evaluated the gut microbiota of recently HIV-infected men (n=13) who were participating in a randomized, double-blind controlled trial of combination ART (tenofovir, emtricitabine, and ritonavir-boosted atazanavir) plus maraviroc (MVC) versus placebo and who were followed for 48 weeks (**Table 1**).
- Bacterial populations were pyrosequenced (Roche 454 FLX Titanium) from anal swabs collected before and longitudinally after the initiation of ART.
- We classified bacterial sequences at the order level and evaluated microbiome profile differences cross-sectionally and longitudinally between MVC+ (n=6) and MVC- (n=7) individuals.
- Statistical tests and principal component analysis were performed in R statistical software.

References

1. Shulzhenko et al. Nat. Medicine. 2011.
2. Brenchley et al. Muc. Immunology. 2008.
3. Dorr et al. Am. Soc. Microbiol. 2005.

Table 1. Participant characteristics at enrollment

PID	Race[1]	Ethnicity[2]	Age	EDI (weeks)	Viral Load (log_{10} copies/mL)	CD4 Absolute (cells/μL)	CD4 %	CD8 Absolute (cells/μL)	CD8 %	CD4/CD8 Ratio
A	A	NH	23	2	5.78	276	10	1890	70	0.15
B	A	NH	28	2	3.10	493	24	856	45	0.58
C	W	NH	35	3	6.78	525	9	5216	85	0.1
D	W	H	22	3	6.99	91	9	728	70	0.13
E	A/W	NH	39	3	4.15	692	29	1387	55	0.5
F	W	NH	52	3	5.36	374	28	732	53	0.51
G	W	NH	21	3	5.93	916	37	1082	44	0.85
H	W	NH	28	4	7.00	520	11	3334	71	0.16
I	W	H	28	10	3.89	501	33	775	51	0.65
J	W	NH	26	11	5.25	614	33	776	42	0.79
K	W	H	33	12	4.40	971	34	1086	38	0.89
L	W	NH	40	14	4.15	383	30	558	42	0.69
M	W	NH	55	14	3.77	913	40	714	31	1.28
Average			33.1	6.46	5.12	559.15	25.15	1471.85	53.62	0.56

Legend: [1]W=White and A=Asian. [2]H=Hispanic and NH=non-Hispanic. Participants are ordered according to estimated duration of infection (EDI) at baseline.

Results

Table 2. Levels of bacteria are not affected by MVC intensification

A.

Order of Bacteria	Maraviroc Week 4	Maraviroc Week 24	Maraviroc Week 48	Placebo Week 4	Placebo Week 24	Placebo Week 48
Actinomycetales	0.16	0.84	0.06	0.38	0.22	0.30
Aeromonadales	0.84	0.31	0.84	0.22	0.81	0.58
Bacteroidales	0.56	0.84	0.44	0.11	0.94	0.22
Campylobacterales	0.56	0.44	0.56	0.38	0.08	0.69
Clostridiales	0.44	0.44	1.00	0.47	0.05	0.22
Enterobacteriales	1.00	0.56	0.84	0.16	0.94	0.38
Erysipelotrichales	0.31	0.56	0.84	0.16	0.02	0.05
Lactobacillales	0.31	0.69	0.44	0.47	0.81	0.30
Myxococcales	0.69	0.84	0.69	0.58	0.81	0.58
Neisseriales	1.00	1.00	0.69	0.58	0.16	0.47
Pseudomonadales	0.56	0.44	0.69	0.11	0.81	0.30
Rhizobiales	0.69	1.00	0.44	0.94	0.69	1.00
Xanthomonadales	0.69	0.69	0.84	0.30	0.81	0.16
Other	0.16	0.56	0.09	0.38	0.16	0.81

Table 2 (A): P-values indicate that the relative abundance of each order of bacteria was similar to baseline at all time points (Wilcoxon Rank Sum Test) after initiation of ART in both groups.

B.

Order of Bacteria	Week 4	Week 24	Week 48
Actinomycetales	0.84	0.63	0.07
Aeromonadales	0.63	0.53	0.18
Bacteroidales	0.29	0.53	0.23
Campylobacterales	0.84	0.63	0.95
Clostridiales	0.95	0.53	0.95
Enterobacteriales	0.63	0.73	0.29
Erysipelotrichales	1.00	0.95	0.84
Lactobacillales	0.63	0.63	0.37
Myxococcales	0.18	0.53	0.84
Neisseriales	0.63	0.45	0.53
Pseudomonadales	0.29	0.63	0.37
Rhizobiales	0.84	0.53	0.29
Xanthomonadales	0.23	1.00	0.23
Other	0.63	0.45	1.00

Table 2 (B): Provided p-values denote that there was no statistical difference in the levels of each order of bacteria between groups (MVC+ vs. MVC-) after initiation of ART (Mann-Whitney test).

Figure 1. Maraviroc intensification is not associated with changes in the gut microbiome

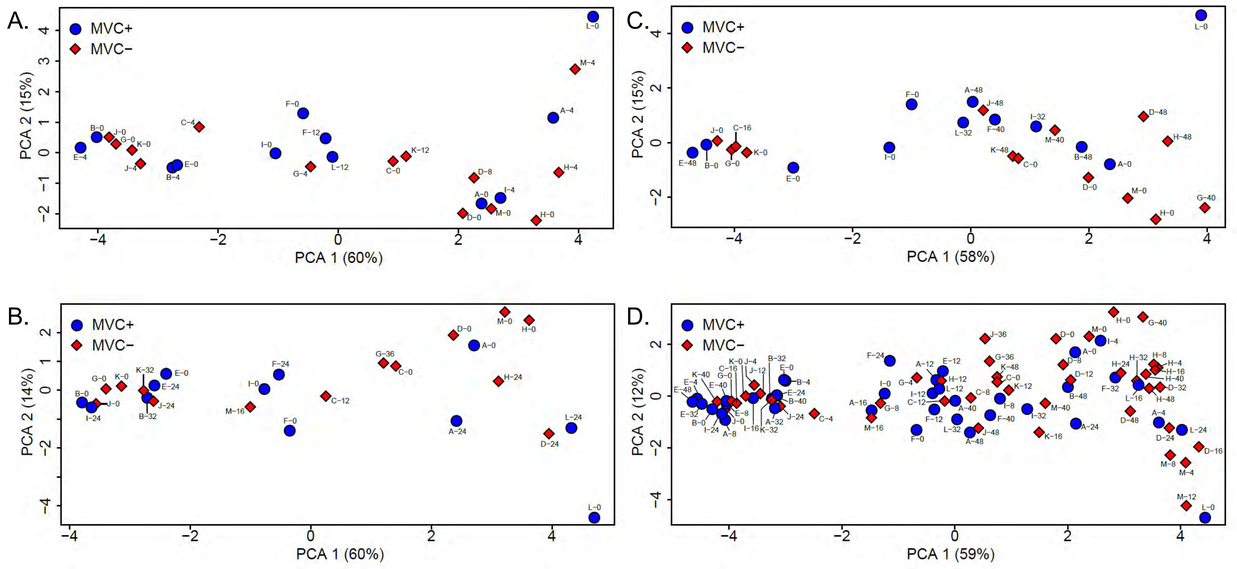


Figure 1: Principal component analysis of the gut microbiome from HIV-infected individuals at various timepoints of the intervention: **(A)** before and at the beginning of the intervention (first time point), **(B)** before and at the middle of the intervention (~week 24), **(C)** before and at the end of the intervention (~week 48), and **(D)** all time points together. Individuals with maraviroc intensification (MVC+) are represented by blue circles and individuals without maraviroc intensification (MVC-) by red diamonds. Letters represent patients and numbers represent weeks on ART. There is no clustering associated with MVC intensification at any time point.

Conclusions

- The abundance of the distinct orders of bacteria was not different at any time point when compared to baseline levels in any group (**Table 2a**).
- There was no statistical difference in the abundance of any order of bacteria between MVC+ and MVC- groups at any time point (**Table 2b**).
- There was not an association in the overall changes of the gut microbiome with maraviroc intensification (**Figure 1**).
- While CCR5 blockade with maraviroc might be a potent antiviral strategy to protect CD4 lymphocytes in the gut, it does not significantly impact the gut microbiome.

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