Decreased diversity of gut microbiota is associated with immune dysfunction and microbial translocation in HIV-1 infection.

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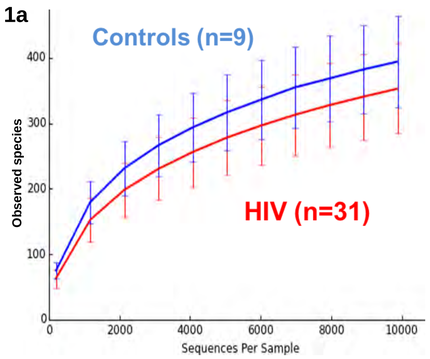
Background

Progressive HIV infection is characterized by dysregulation of the intestinal barrier, translocation of microbial products such as lipopolysaccharide (LPS) and subsequent chronic systemic inflammation.

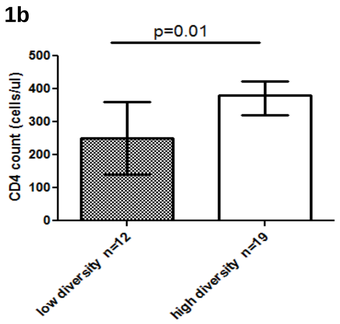
Aim

We hypothesized that the gut microbiota would be altered in HIV-infected individuals, and that the changes would be associated with markers of HIV-progression, microbial translocation and monocyte activation. Additionally, we aimed to assess the potential impact of ART on gut microbiota composition.

1a



1b



1c

Marker	Observed Species	Diversity (Shannon)
CD4	0.59, p=0.009	0.40, p=0.02
CD4/CD8-ratio	0.53, p=0.003	0.48, p=0.01
sCD14	-0.42, p=0.02	-0.42, p=0.02
LPS	-0.51, p=0.007	-0.35, p=0.07
LBP	-0.45, p=0.01	-0.37, p=0.09
sCD163	-0.48, p=0.02	-0.25, p=0.2
Years since diagnosis	0.44, p=0.01	0.47, p=0.01

Figure 1. Number of observed bacterial species in HIV infected patients and controls (a). Stratification of viremic patients (based on median Shannon alpha diversity) into those with high and low diversity at baseline (b). Spearman's correlations between observed species, Shannon diversity index and markers of immune dysfunction/microbial translocation (c).

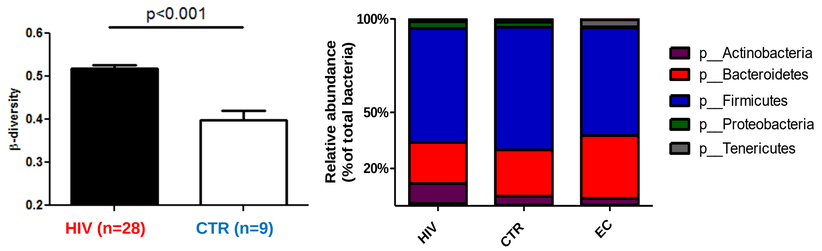


Figure 2. Baseline beta diversity (a) and composition of microbiota at phylum level (b) in viremic patients (HIV, n=28), healthy controls (CTR, n=9) and elite controlers (EC, n=3).

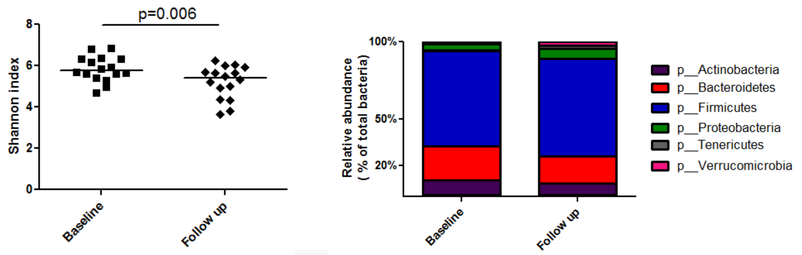


Figure 3. Changes of alpha diversity (a) and composition (b) of microbiota (phylum level) at follow up. Presented figure is based on data from patients (n=16) who received ART.

Methods

Prospective, observational study including 32 patients (median CD4 T cell count 355 cells/μl (120-2470) and 9 controls. Fecal and plasma samples were collected at baseline, and for 19 patients at follow up (median: 10 months [4-15]) after ART introduction. Samples from three elite controllers (EC) were included at baseline. Microbiota composition was initially evaluated by deep sequencing of 16S rRNA gene with 150 bp Illumina chemistry, and then replicated with the latest 300 bp platform. The two methods showed good correlation (r=0.81, p<0.001), and results presented are based on the 300 bp sequencing. Additionally, soluble markers of microbial translocation and monocyte activation were analyzed. Non-parametric statistics were applied.

Results

- The number of observed bacterial species, as well as the alpha diversity (Shannon and Simpson index) was reduced in HIV infected patients as compared to controls.
- CD4, CD4/CD8 ratio and markers of microbial translocations correlated to number of observed species and Shannon alpha diversity, at baseline.
- Microbiota of EC resembled that of uninfected healthy controls, with an increased relative abundance of Bacteroidetes compared to viremic patients. Actinobacteria were enriched in viremic patients compared to controls and EC.
- After introduction of ART, the gut flora changes were still present, with further reduction in alpha diversity compared to baseline.

Conclusions

- The gut microbiota was altered in HIV infected patients, with reduced richness (number of observed species) and alpha diversity as compared to controls.
- Reduced richness and diversity of the microbiota correlated with markers of microbial translocation, monocyte activation and immune dysfunction.
- Introduction of ART did not restore alpha diversity.
- Our data implicate that re-shaping the microbiota may be an adjuvant therapy in HIV-1 infection.

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