The Effects of Prebiotics on Microbial Dysbiosis, Butyrate Production and Immunity in HIV-Infected Subjects


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INTRODUCTION

• A depletion of CD4+ T cells and an altered microbiota in the gut of people living with HIV are likely major drivers of chronic immunovactivation, a predictor of poor prognosis.

• Microbiota modification with prebiotics has previously demonstrated to reduce bacterial translocation and immunovactivation in ART naïve patients. Glutamine has demonstrated to reduce bacterial translocation in previous studies.

• A deep understanding of how these interventions could ameliorate gut dysbiosis and influence health among HIV-infected individuals remain unexplored.

METHODS

• Pilot double-blind randomized placebo-controlled trial.

• Forty-four subjects, including 12 HIV+ viremic untreated (VU), 23 antiretroviral therapy-treated (ART+) virally suppressed (15 immunological responders and 8 non-responders) and 9 HIV- controls (HIV-), were blindly randomized to receive either prebiotics (scGOS/IcFOS/glutamine) or placebo (34/11), during 6 weeks.

• We performed a comprehensive assessment of changes in fecal microbiota composition using 16S rRNA deep sequencing and determination of short chain fatty acid abundance by HPLC and measured in blood a number of immunological and genetic markers involved in HIV immunopathogenesis.

RESULTS

HIV infection alters microbiota structure and introduces depletion of butyrate producers

- The most enriched genus was Prevotella.
- Other genera in the Bacteroidetes phylum: Subcubacterium, Acidaminococcus, Bulleidia.

- Enriched in HIV+ subjects:
  - Bacteroides and Clostridiales.
  - Principal butyrate producers: Faecalibacterium prausnitzii, Lachnospiraceae, Roseburia, Butyricimonas, Caprooccus.

- HIV+ individuals in the active arm and, to a lesser extent, INR individuals, experienced a compositional shift in the gut microbiota.

- Significant differences in acetate and propionate abundance between groups at baseline.

- Significant increases in butyrate production among Viremic Untreated in the active arm.

- Interactions between changes in genera contributing to HIV-associated dysbiosis, SCFAs and peripheral markers of disease progression using generalized linear models are represented in Panel A. We observed statistically significant associations between changes of bacterial taxa and peripheral markers, which differed across groups of HIV+ individuals. Red edges represent negative correlations, and blue edges positive correlations. Gray squares represent the peripheral markers of disease progression and the green rectangles represent the SCFAs. Blue gradient circles correspond to species in the Bacteroidetes phylum, purple gradient circles correspond to the Acidobacteria phylum and gold gradient correspond to the Firmicutes phylum.

- Panel B shows changes in the GLM-based network of all the HIV+ subjects of the cohort and illustrates the interactions between the faecal microbiota. Arrows indicate conditional dependencies between variables in the Bayesian Network plotted in panel B. The network (Panels B and C) highlight the interactions of Faecalibacterium prausnitzii, as well as other known butyrate producers, with butyrate production and the immunological markers high-sensitivity C reactive protein (CRP) and soluble CD14 (sCD14).

CONCLUSIONS

• Increases in the abundance of Faecalibacterium and Lachnospiraceae were observed with the prebiotic intervention and strongly correlated with an increase of butyrate production and amelioration of the inflammatory biomarkers soluble CD14 and high-sensitivity C reactive protein.

• Dietary prebiotic supplementation ameliorates HIV-associated dysbiosis and improves key species responsible for the production of butyrate, ultimately alleviating systemic inflammation.

• Hence, bacterial butyrate synthesis pathway holds promise as a viable target for interventions.

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