HHS Public Access

Author manuscript

Clin Transl Discov. Author manuscript; available in PMC 2023 June 01.

Published in final edited form as:

Clin Transl Discov. 2022 June ; 2(2): . doi:10.1002/ctd2.58.

HIV-associated dysbiosis and immune recovery during antiretroviral therapy

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Abstract

The microbiomes of people living with HIV (PLWH) are significantly dysregulated with a loss of bacteria diversity and shifts in composition, including increases in pathogenic and decreases in beneficial species. Because of the microbiome's role in modulating health, the effect of this dysbiosis on immune response in PLWH has been a significant concern, mainly because these shifts can persist even after viral suppression during combination antiretroviral therapy (cART). However, due to limitations on sample availability, few studies have been able to provide insights into these microbiome-immune interactions. Recently, Olivas-Martínez, et al. characterized ileum and caecum mucosa-associated microbiomes of PLWH based on their level of peripheral CD4+ T-cell reconstitution following long-term cART. Their analysis revealed distinct microbiome signatures predictive of recovery. Additionally, differences in markers of gut inflammation and damage between response groups were described, further implicating mucosal disruptions with immune reconstitution. These new data demonstrate an interdependence of microbiome and therapy response, and additional studies were urgently required to fully elucidate this crosstalk and microbiome dynamics from before/after infection and finally, long-term viral suppression with cART.

Keywords

Dysbiosis; Antiretroviral Therapy; HIV; microbiome

The sum of all microorganisms residing in or on a person, known as the microbiome, can significantly impact host health, whether ostensibly pathogenic or not. Microbiome diversity and composition differ considerably depending on the tissue sampled and additional factors, including initial exposure to microbes, diet, and interspecies interactions, including mutualism, antagonism, and competition for "real estate" and nutrients. Finally, host immune response from previous exposures, infections, and cross-reactive antibodies,

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Conflict of Interest

The authors declare no conflict of interest.

can influence population structures. Because of the hosts' ability to regulate microbiome composition, it is understandable that many taxa possess immune-modulating capabilities such as immunosuppressive metabolites and the production of virulence factors favoring their survival. Ultimately, these last interactions, the immune-microbiome crosstalk, remain poorly understood in the context of HIV pathogenesis, particularly across infection states such as elite control, early treatment, and CD4+ lymphocyte reconstitution following acute depletion.

HIV and the microbiome

It is well-established that people living with HIV (PLWH) have differences in their gut microbiome compared with healthy individuals. These include substantial decreases in both diversity and richness indicative of dysbiosis. Further, specific compositional changes include expansion of Proteobacteria and the Bacteroidete genus *Prevotella* at the expense of *Bacteroides* and loss of several butyrate-producing Firmicute taxa (1, 2). These compositional shifts seem to be consistent across populations(3) and share many similarities with the commonly-used simian immunodeficiency virus (SIV)-infected macaque models(4). Such changes are anticipated given the rapid gut inflammation-associated damage following initial HIV infection, including loss of CD4+ cells and epithelial barrier dysfunction(5). Additionally, many of these microbiome differences have been linked to markers of disease progression and immune activation like sCD14 and cytokines IL-6 and TNF(2). The butyrate-producing *Roseburia,* in particular, has been correlated with reduced viral loads, immune activation, and plasma lipopolysaccharide(6). Fortunately, in most cases, cART facilitates considerable, although incomplete, CD4+ lymphocyte recovery, including gut lamina propria lymphocytes (LPLs)(7). This immune reconstitution is accompanied by decreased activation markers (CD38 and HLA-DR) in LPLs(7). However, data about the relationship between the microbiome and recovery have been lacking, especially when controlling for population and method of characterization. Further, a knowledge gap exists in whether fecal samples have the same constituent bacterial taxa in proportions representative of the mucosa.

To shed light on the questions above, a recent paper by Olivas-Martínez et al (8) attempts to address the microbiome composition of HIV patients based on their treatment regimen and immunological outcome. Due to differences in populations, local diet, sampling, and analysis techniques, previous assessments according to immune response following infection and combination antiretroviral therapy (cART) have been lacking or challenging to interpret when compared with each other. Additionally, due to relative ease of access, many studies in PLWH have characterized the fecal microbiome, which can differ considerably from the microbial communities in closest contact with tissue. This shortcoming has been overcome by utilizing patient ileum and caecum biopsies in conjunction with assessments of tissue inflammation and damage. These significant improvements in technique and large sample size provide new insights into HIV-associated dysbiosis and pathogenesis following viral suppression in PLWH. Consistent with previous findings, the microbiomes of elite controllers clustered with healthy controls having the highest diversity, richness, and relative abundance of Firmicutes, including *Lachnospira* and *Roseburia* operational taxonomic units (OTUs). Further, both uninfected controls and elite controllers had several

OTUs in Ruminococcaceae, and other Lachnospiraceae were lower in the cART-suppressed groups. Intriguingly, *Prevotella* was highest in the early-treated group, further confounding the debate on its relationship with sexual behavior, given the relatively proximal gut locations compared with previously sampled fecal microbiomes (1). However, perhaps the most important findings relate to the differences in immune reconstitution of lost peripheral CD4+ cells in people first receiving cART late during chronic infection. Both late-treated groups had the lowest Ruminococcaceae and Lachnospiraceae emphasizing the importance of early treatment strategies. The low recovery group had a significantly higher abundance of the pathobiont *Escherichia* and lower *Bacteroides*. These findings are consistent with previous research suggesting that fecal Bacteroidetes are increased in PLWH regardless of CD4+ lymphocyte reconstitution, with *Prevotella* taxa higher in incomplete responders and *Bacteroides* higher in full responders(9). Notably, the group characterized gut inflammation and damage markers, finding that the ileum specifically was associated with increased inflammation score and zonulin-1 levels in the non-responding group compared with those that responded, with early-treated having a range overlapping each group. These findings are consistent with current understandings of HIV pathogenesis but provide further details to help understand how damage markers are associated with distinct dysbiosis signatures(5).

Future Perspectives

These findings suggest a direct relationship between microbiome composition and immune reconstitution in HIV patients. With this relationship so clearly established, further research to determine whether modifying the population structures in the gut is critical. Potential interventions include diet changes, consumption of pre- or pro-biotics, or fecal microbiota transplants to introduce requisite taxa for an improved immunologic response. Indeed, transplantation is already being explored in pilot studies in which Lachnospiraceae and Ruminococcaceae, key taxa depleted during HIV, were robustly and stably engrafted, followed by a significant decline in the intestinal damage marker IFABP(10). Additionally, though currently limited, targeted antibiotics may also be a possibility in the future.
Since immune-microbiome crosstalk is so complex, even if the microbiome differences are present before infection, it remains unclear whether these differences are due only to the microbiome or whether the host has a significant role in determining composition. These remaining uncertainties may necessitate more extensive studies incorporating individuals with high HIV risk to assess the impact of baseline microbiome composition on long-term immunological outcomes. Additionally, animal models such as SIV/SHIV-infected macaques may provide the improved granularity of these dynamics since such models allow more frequent sampling before and during infection and precise documentation of initial infection and resultant viremia and response to cART. Already, oral probiotic administration to SIV-infected macaques, in addition to exogenous IL-21 therapy, was shown to increase Th17 reconstitution better than therapy alone(11). Whether more advanced manipulation of infection-associated dysbiosis, with or without cART-adjunctive therapies, could provide even more significant improvements to incomplete immune reconstitution remains a promising prospect.

Acknowledgments

This work is partially supported by the National Institute of Allergy and Infectious Diseases Grant R01 AI129745 to SNB

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