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HIV and the gut microbiota: composition, consequences, and avenues for amelioration

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Abstract

Purpose of review: We discuss recent advances in understanding of gut bacterial microbiota composition in HIV-infected subjects and comment on controversies. We discuss the putative effects of microbiota shifts on systemic inflammation and HIV disease progression and potential mechanisms, as well as ongoing strategies being developed to modulate the gut microbiota in humans for amelioration of infectious and inflammatory diseases.

Recent findings: Lifestyle and behavioral factors relevant to HIV infection studies have independent effects on the microbiota. Microbial metabolism of immunomodulatory compounds and direct immune stimulation by translocation of microbes are putative mechanisms contributing to HIV disease. Fecal microbiota transplantation, microbial enzyme inhibition, phage therapy, and rationally selected probiotic cocktails have emerged as promising strategies for microbiota modulation.

Summary: Numerous surveys of the HIV gut microbiota matched for lifestyle factors suggest consistent shifts in gut microbiota composition among HIV-infected subjects. Evidence exists for a complex pathogenic role of the gut microbiota in HIV disease progression, warranting further study.

Keywords

gut microbiota; fecal transplant; engraftment; HIV; inflammation

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Conflict of Interest

The authors declare no conflicts of interest

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Introduction

The past decade has seen a rapid expansion in knowledge of how the gut microbiota – the community of bacteria, viruses, fungi, and symbiotic protozoa that inhabit metazoan body surfaces – profoundly influences immune development and function(1-3). Importantly, murine studies have revealed an important causative role of specific communities of gut microbes to local and systemic inflammatory diseases in animal models(4). As systemic inflammation is thought to be one of the primary contributors to morbidity and mortality in both untreated and antiretroviral-treated HIV-infected subjects(5), the role of the gut microbiota in HIV infection has garnered great interest. Herein, we discuss recent advances in understanding of differences in the gut microbiota among HIV-infected and uninfected subjects, how these differences may influence host immune states, and methods that have emerged as promising strategies for precision microbiome editing.

Inflammatory consequences of HIV infection

Evidence from numerous studies supports the broad notion that chronic immune activation is a major driver of HIV disease progression and mortality among HIV-infected individuals. (6-11) Early in the treatment era, CD4 and CD8 T cell activation were among the strongest independent predictors of time to AIDS(9). While antiretroviral therapy (ART) has proven successful in the modern era, a substantial proportion of individuals on suppressive ART do not exhibit resolution of systemic inflammation(12). Importantly, persistent inflammation is strongly associated with increased cardiovascular events(13, 14), accelerated liver disease(15), impaired immunologic recovery (e.g. low CD4 count, low CD4 to CD8 ratio) (16), and mortality(6, 17). Therefore, understanding and reversing persistent inflammation remains a major goal toward restoring health and lifespan in HIV-infected individuals.

The etiology of this persistent inflammation during antiretroviral therapy, as well as the pathologic inflammation during untreated HIV infection, has been the subject of intense study. In treated subjects, associations have been noted between measures of the remaining viral reservoir and T cell activation(18), though these have been noted to have weak effect sizes (Spearman rho < 0.3), suggesting that factors other than HIV itself may contribute to immune activation during antiretroviral therapy. Non-human primate models utilizing the closely-related simian immunodeficiency virus (SIV) have revealed that among the salient events of primary untreated infection is the massive depletion of CD4 T cells of the gastrointestinal tract(19). Furthermore, among those CD4 T cells remaining the gut, the subset producing IL-17 and IL-22 (known as Th17 cells) were especially depleted(20-22). These cells and the cytokines they produce fortify mucosal barrier function via induction of antimicrobial peptides, mucus production, and wound repair(23). The observed loss of these cells coincides with markers of immune activation(24), and such observations led to the hypothesis that an impaired gut barrier may contribute to inflammation and disease progression by permitting the translocation of bacterial products from the gut lumen into systemic circulation(25, 26).

Several additional components of the gastrointestinal barrier are affected during HIV infection and the closely-related non-human primate model of simian immunodeficiency virus (SIV) infection. Diminution of the gut mucosal CD4 T cell population as a whole

occurs early in infection(19) and is not completely restored during antiretroviral therapy(27). Disruption of the epithelial cell layer of the gastrointestinal barrier is observed in both SIV and HIV infection(28-30). A loss of Th17-inducing CD103+ dendritic cells also occurs in SIV infection(31). Additionally, the specialized epithelial cells responsible for the production of antimicrobial peptides at the gastrointestinal surface, known as Paneth cells, exhibit increased production of antimicrobial peptides(32). Gut mucosal macrophages also exhibit impaired phagocytosis and impaired clearance of microbial products in HIV(33) and SIV infection(29).

Microbiota perturbations in HIV infection

Many of the disturbances to the gastrointestinal immune barrier during HIV infection comprise dysfunction of cell types responsible for regulating the composition of the microbiota. The effector cytokine IL-17 induces expression of a variety of antimicrobial peptides that shape microbiota composition(34), and its loss in mice leads to an altered microbiota that exacerbates systemic inflammation(35). Furthermore, disruptions to macrophage function can engender an altered microbiota that is sufficient to cause local and systemic inflammatory pathology(36, 37).

Such observations have spurred investigation into the hypothesis that HIV infection alters the gut microbiota and that this altered composition of microbes may contribute to HIV inflammatory pathology. Numerous survey studies have been performed in human cohorts comparing HIV-infected gut microbiota composition to that of HIV-uninfected control subjects(38-54). Results of these studies share several common patterns among the HIV cohort: an enrichment of *Erysipelotrichaceae*, *Enterobacteriaceae*, *Desulfovibrionaceae*, and *Fusobacteria*, a depletion of *Lachnospiraceae*, *Ruminococceae*, *Bacteroides*, and *Rikenellaceae* (Figure 1A). Several of these gut microbiota survey studies additionally found correlations between some of these perturbations to the gut community and markers of inflammation and HIV disease progression, including kynurenine:tryptophan ratios(50, 55), IL-6(47, 50), sCD14(40, 45, 47), IL-1 β (40), and peripheral T cell activation(39, 44, 50, 51).

Direct inflammatory consequences of microbiota perturbations in HIV

The increased abundance of gut-resident bacteria capable of directly stimulating host inflammation constitutes a plausible mechanistic link between HIV-associated microbiota perturbations and elevated systemic immune activation. This is particularly so in light of the observed increased abundance of various *Proteobacteria* including *Enterobacteriaceae*, a family comprised of numerous pro-inflammatory, flagellated, motile members with the capacity to translocate, including *E. coli*, *Salmonella*, *Pseudomonas*, *Yersinia*, and *Klebsiella*. Members of this family induce host inflammation upon infection and are able to utilize byproducts of this inflammation - namely, reactive oxygen species (ROS) from neutrophils and macrophages - as terminal electron acceptors in their respiratory chain(56, 57), allowing them to uniquely derive cellular energy from a source that endogenous gut microbiota members cannot readily utilize. This trait confers a competitive growth advantage over endogenous bacteria in the setting of host inflammatory processes including neutrophil influx. As neutrophils capable of ROS production are increased in the gut mucosa of both acute and chronically HIV-infected subjects(58), it is thus tenable that ROS

production in the HIV-infected mucosa stimulates an increase of pro-inflammatory *Enterobacteriaceae* and that these bacteria in turn exacerbate gut inflammation. Members of this clade also have a high propensity to translocate across the gut barrier(59-61), providing another avenue by which these bacteria may contribute to the pathologic systemic immune activation of HIV infection.

Efforts to understand the contribution of *Proteobacteria* to HIV-associated inflammation and subsequent disease progression have included antibiotic treatment of SIV-infected non-human primates(62). These animals exhibited an increase of *Proteobacteria* native to the non-human primate gut, but did not experience elevated immune activation or accelerated SIV disease progression. However, the antibiotic regimen used simultaneously depleted *Erysipelotrichaceae* (a clade enriched in HIV infection) while enriching *Proteobacteria* (also increased in HIV infection), which may have balanced the increase of one group of translocators with the depletion of another. Given that substantial differences in gut microbiota composition exist between non-human primates and humans at baseline(63-65), and given that a durable shift in the gut microbiota is not observed in macaques upon chronic infection with SIV(66-68) which appears at odds with observations in HIV-infected humans as discussed above, further development of models for HIV-associated microbiota perturbations (such as gnotobiotic animals) and their effects on host immune states is warranted to delineate the role of the gut microbiota in HIV pathogenesis and inflammatory co-morbidities.

The role of the *Erysipelotrichaceae* family in inflammatory processes is poorly understood, possibly due to their fastidious nature and relative lack of available methods for isolation and cultivation. As a result, few isolates are available for study at present. However, members of this family can be broadly detected in the gut microbiota of numerous mammals, suggesting some degree of co-evolution between this clade and its hosts in the animal kingdom. Among the few studies that experimentally dissect the relationship of *Erysipelotrichaceae* members and their host, some have shown that this clade is capable of promoting inflammatory pathology in the gut(69, 70). Further study into the role of this poorly understood family in HIV-associated inflammation is warranted.

Effects of microbial metabolism in HIV

Another avenue by which the gut microbiota may influence HIV disease progression independently of direct immunostimulation lies in its metabolic capacity. Metabolism of tryptophan through the kynurenine pathway has been implicated in gut barrier disruption in HIV infection. Kynurenine compounds bind the aryl hydrocarbon receptor (AhR) in T cells and cause decreased differentiation of gut barrier-promoting Th17 cells (71, 72), and the activity of the kynurenine pathway (as measured by plasma kynurenine to tryptophan ratios) correlates with Th17 cell loss, inflammation, and disease progression in HIV-infected subjects as reviewed by Routy et al.(73). While it is known that the murine and human enzyme indoleamine 2,3-dioxygenase 1 (IDO1) catabolizes tryptophan down this pathway, the potential for gut bacteria to participate in this metabolic pathway has been examined recently. Indeed, abundance of bacteria encoding kynurenine production enzymes was found to correlate with systemic kynurenine pathway activity(50, 55), and HIV-infected subject gut

microbiota communities exhibit an increased capacity to catabolize tryptophan to kynurenine(74), highlighting a potential contribution of HIV-associated gut bacteria to increased local and systemic levels of these catabolites.(50, 72) Several structurally similar tryptophan-derived AhR agonists have been found to be produced by gut microbiota constituents and to modulate severity of inflammatory disease (75-77), supporting a role for gut microbes in kynurenine pathway metabolism and its possible contribution to HIV pathogenesis.

While enrichment of kynurenine-producing bacteria may produce immunomodulatory metabolites, the depletion of *Ruminococcaceae* and *Lachnospiraceae* taxa, which comprise the primary producers of short-chain fatty acids (SCFA), in HIV-infected subjects may decrease production of a desirable metabolite. SCFA, produced exclusively in the gut by the action of bacterial fermentation of dietary fibers, are the primary energy source for colonic epithelial cells and can induce differentiation of anti-inflammatory T_{reg} cells(78). Loss of such fiber fermentation in murine models causes reduced gut barrier integrity(79) and colonic inflammation due to an expansion of pro-inflammatory gut bacteria(80).

Finally, *Desulfovibrio* bacteria are known producers of hydrogen sulfide (H₂S)(81), a compound toxic to epithelial cells and thought to contribute to the capacity of the microbiome to cause gut epithelial injury and reduced mucus integrity in inflammatory bowel disease(82, 83). Thus, in the context of HIV infection, this combination of increased gut microbial-derived kynurenine and H₂S, and decreased SCFA, may promote a positive feedback cycle that perpetuates depletion of gut barrier-promoting cells producing IL-17 and/or IL-22, a loss of epithelial and mucosal integrity, microbial translocation, and decreased counter-regulation of immune activation even after HIV replication is controlled by ART(84). Given this putative pathogenic cycle, interventions aimed at rehabilitating the gut microbiome have the potential to interrupt gut barrier disruption and chronic immune activation.

Effect of MSM

Several early HIV gut microbiota studies found an enrichment of *Prevotella* in HIV-infected subjects, though subsequent studies revealed mixed results. Studies by Noguera-Julian et al. (48), Kelley et al.(85), and Armstrong et al.(38) all found that *Prevotella* is enriched in men who have sex with men (MSM), and that *Bacteroides* are depleted in MSM. As MSM are most commonly recruited for HIV infection studies due to this population comprising the dominant group infected with HIV in the United States and Western Europe, gut microbiota alterations in this population as compared to heterosexual men may influence gut microbiota surveys that are not balanced in numbers of MSM in their HIV-infected and uninfected subject groups. Indeed, studies in which *Prevotella* was found to be enriched in HIV infected MSM subjects either utilized non-MSM uninfected control subjects or did not deliberately select MSM subjects for their control comparator groups. This raises the possibility that the observed differences in *Prevotella* abundance were due to mismatch of MSM status among cases and controls rather than a result of HIV infection *per se*. However, *Proteobacteria*, *Desulfovibrio*, *Enterobacteriaceae*, *Fusobacteria*, *Ruminococcaceae*, and *Lachnospiraceae* members did not exhibit consistent differences based on MSM status in studies performed to

date(38, 48, 85), suggesting that MSM status alone may not explain the shifts in abundance of these clades in HIV microbiota surveys (Figure 1B). Furthermore, several studies in which HIV-infected and uninfected subjects were matched for MSM status, or where MSM constituted a minority of subjects sampled, revealed enrichment of many of the aforementioned clades of bacteria (Figure 1A). There remains a need for well-powered studies examining differences in the gut microbiota of HIV-infected and uninfected subjects stratified by gender and sexual preference.

Microbial therapeutics to address dysbiosis and inflammation

Efficacy of fecal microbiome transplantation (FMT)

The gut microbe-mediated disease *Clostridium difficile* infection (CDI) is a prevalent nosocomial condition with a high risk of recurrence(86). Patients with recurrent cases of CDI carry a gut microbiome signature that is enriched for *C. difficile* and *Proteobacteria*, depleted for *Lachnospiraceae* and *Ruminococcaceae*, and exhibits a drastically reduced gut bacterial alpha diversity(87) – a measure of the number of different gut-resident taxa and the evenness of their abundance. Given that antibiotic use is one of the main predisposing factors associated with CDI, it has been postulated that a loss of a diverse microbiome reduces colonization resistance – the occupation of a metabolic or spatial niche by one or more microbes that prevents invasion by other microbes. Indeed, infusion of a diverse fecal microbial community from a healthy donor is highly efficacious for resolving CDI and eliminating *C. difficile* from the gut microbiota, with a mean cure rate of 89%(87-89). This procedure appears safe, with few reported adverse effects even in patients who may be immunocompromised, such as HIV-infected and post-transplant patients(90, 91). Given that CDI-associated dysbiosis shares a commonality with HIV infection due to its constituting an enrichment of *Proteobacteria*, the efficacy of FMT underscores that such an approach may be effective in HIV-associated dysbiosis. However, despite differences in the HIV-infected subject microbiota, the gut microbial community observed in HIV infection maintains greater diversity than that seen in CDI(92) and may resist the colonization of exogenously administered microbes as those in FMT. Indeed, minimal shifts were observed in the microbiota by a pilot human trial employing one-time FMT administration(92), suggesting that development of methods to increase engraftment and efficacy for FMT to allow engraftment of donor microbes is warranted. For example, utilizing multi-dose fecal material from pooled donors with anaerobic processing has shown promising efficacy in ulcerative colitis(93) compared to multi-dose material from single donor with routine processing(94, 95). Most effective practices could also be considered in HIV-infected subjects.

Dietary interventions

Diet is among the most significant variables that explain gut microbiota variation in human cohorts(96). Broad dietary classifications such as plant-based vs. animal meat-based diets have been studied in terms of their effects on the gut microbiota and have shown that *Bacteroides*, *Rikenellaceae*, and *Desulfovibrionaceae* members(97, 98) are enriched in subjects consuming a meat diet while *Ruminococcaceae* and *Lachnospiraceae* exhibit a relative increase in those consuming high plant-fiber diets(97, 99, 100). While the microbiome shifts resulting from an animal meat-based diet partially overlap with the shifts

seen in HIV infection, the abundance of *Bacteroides* in HIV-infected subjects does not correlate with meat intake as it does in uninfected subjects(39), and another study in HIV-infected subjects showed few correlations between gut microbial composition and diet(48). These studies thus raise the possibility that gut immune barrier disruptions and inflammation may have a dominant effect on some components of microbiota composition in the setting of HIV infection. However, the potential for success of dietary interventions such as prebiotics – orally administered compounds that engender growth of specific bacterial taxa in the gut community – to restore abundance of gut bacteria lost in HIV infection or engender growth of competitors to pro-inflammatory bacteria remains unknown.

Microbial enzyme inhibition

In the case of microbial kynurenine-producing enzymes, targeted inhibitors of such pathways may ameliorate the immunomodulatory effects of these catabolites. Strategies to curtail microbial metabolism that contributes to human disease have demonstrated potential for success. The microbial metabolite trimethylamine N-oxide (TMAO) has been shown to contribute to atherosclerotic plaque formation in mice and correlates strongly with atherosclerosis in human cohorts. The Hazen group successfully screened a library of natural products to identify non-toxic compounds that inhibit the microbial TMA-lyase enzyme family that drives elevated TMAO levels(101). In the setting of HIV infection, despite ART treatment, the incidence of cardiovascular disease is increased compared to the general population(102), though TMAO levels do not differ between these populations(103), suggesting that inhibition of this microbial metabolic pathway may not alleviate HIV-associated inflammatory cardiovascular co-morbidities. Nevertheless, a similar strategy may be effective for restoring gut Th17 cell-mediated barrier function by inhibition of gut microbial kynurenine pathway metabolic activity or alternative metabolic pathways deemed pro-inflammatory and upregulated during chronic HIV infection.

Modulation of gut microbiota function via inhibition of microbial metabolism has also yielded a way to limit the activity of gut microbes that thrive in the setting of inflammation and themselves exacerbate inflammation. Chemical inhibition of molybdenum-cofactor-dependent microbial respiratory pathways has been shown to prevent blooms of such facultative anaerobes during inflammatory processes(104), preventing such bacteria from establishing an inflammatory cycle that engenders both their growth and inflammatory response from the host. Thus, inhibition of microbial pathways using traditional small molecule inhibitors presents another avenue to mitigate pathologic effects of the gut microbiota, and may comprise a strategy to alleviate potentially pro-inflammatory effects of the HIV-associated gut microbiota.

Targeted deletion of microbiota members

Bacteriophages are viruses that infect bacteria and can result in their lysis and clearance from a community. In the early 20th century, experimental and clinical usage of phages to combat infectious diseases was taking place broadly in the United States, Western Europe, and Eastern Europe. Conflicting studies interrogating bacteriophage efficacy stymied enthusiasm, however, and the advent of highly efficacious chemical antibiotics in the 1930's diminished usage and exploration of phage therapy in Western nations. Phages continued to

be developed and utilized therapeutically to combat human bacterial infections on a large scale in the Soviet Union for several decades until its collapse, with phage preparations being commercially produced on a large scale against *Shigella*, *Pseudomonas*, *Proteus*, and *Staphylococci*, among others(105, 106).

A strength of an antibiotic is the capacity of a single compound to eliminate classes of bacteria with shared molecular features. However, this broad range can be a double-edged sword, in that it eliminates commensal microbes that impart benefits to the host including colonization resistance against harmful pathogens such as *Clostridium difficile*. Furthermore, the rising incidence of antibiotic resistance has stimulated renewed interest in phages as a therapeutic. Phages, with their potential for higher host specificity, may impart greater safety, for they can have a lower capacity for off-target effects on the endogenous commensal community. Their use in Western nations has emerged, and it is now used for treatment of livestock infections(107, 108), to kill foodborne pathogens in agricultural products (*Listeria monocytogenes*, *Enterobacteriaceae spp.*)(109), and to eliminate plant pathogens(110). The capacity for phage to act as tools for precision microbiome editing in humans warrants further study, and is likely to be a major area of research in the future. This strategy holds promise for the elimination of bacteria enriched in HIV, such as *Fusobacteria*, *Proteobacteria*, and *Erysipelotrichaceae*.

Exogenous supplementation of beneficial bacteria

Consensus among studies is that currently commercially available probiotics do not durably colonize human or murine hosts(111, 112), though some studies indicate probiotics can cause transient host transcriptional changes and also have shown benefit in the amelioration of symptoms of traveler's and antibiotic-associated diarrhea(113) and irritable bowel syndrome(114) in meta-analyses of randomized controlled trials. Dramatic improvements in disease, however, are rarely seen across a given study population in the setting of probiotic supplementation. This may be due to the selection of probiotic strains having been biased toward easily cultivable food fermenters (*Lactobacillus* and *Bifidobacterium* are the primary bacteria found in fermented vegetables and yogurts while *Saccharomyces* is the primary fermenter in bread production; these three are the most commonly used over-the-counter probiotics). It is tenable that prevention of food spoilage conferred by these fermentative strains was erroneously conflated with a supposed health benefit, and that consumers of fermented foods experienced better overall health than non-consumers due to a reduced intake of spoiled foods. However, rationally-designed mixtures of gut bacterial isolates for exogenous supplementation hold promise for ameliorating human pathological states. For example, selection of bacterial strains that compete with and confer colonization resistance against *Clostridium difficile* holds promise as a therapeutic strategy for recurrent CDI(115), a strategy currently advancing through clinical trials(116). The identification of pro-inflammatory bacteria in HIV infection will thus open doors to strategies to similarly select gut bacteria that compete with the putative pro-inflammatory gut microbiota members, allowing exogenous supplementation of competitors and clearance of bacteria exacerbating inflammation and associated co-morbidities. Exogenous supplementation of microbes depleted in HIV-infected subjects, such as *Ruminococcaceae* and *Lachnospiraceae* members, also presents an avenue toward restoration of SCFA production and immunological tone of

the mucosal barrier. Consortia of such bacteria are currently being developed for treatment of inflammatory bowel disease(117), and it remains to be tested whether they are capable of improving inflammatory states of the gut in HIV-infected subjects.

Conclusions

The burgeoning understanding of the gut microbiota as it influences host immune states is sufficient to justify further study in the context of HIV infection. Major areas that warrant future study include the development of microbiome-targeted strategies to eliminate or engraft exogenous microbes, development of tools to identify pro-inflammatory gut microbes, and to expand cohort studies that investigate the impact of lifestyle and environmental factors on the gut microbiota in the context of HIV infection.

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REFERENCES

1. Ivanov II, Atarashi K, Manel N, Brodie EL, Shima T, Karaoz U, et al. Induction of intestinal Th17 cells by segmented filamentous bacteria. *Cell*. 2009;139(3):485–98. [PubMed: 19836068]
2. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, Momose Y, et al. Induction of colonic regulatory T cells by indigenous *Clostridium* species. *Science*. 2011;331(6015):337–41. [PubMed: 21205640]
3. Hooper LV, Littman DR, Macpherson AJ. Interactions between the microbiota and the immune system. *Science*. 2012;336(6086):1268–73. [PubMed: 22674334]
4. Kamada N, Seo SU, Chen GY, Nunez G. Role of the gut microbiota in immunity and inflammatory disease. *Nat Rev Immunol*. 2013;13(5):321–35. [PubMed: 23618829]
5. Deeks SG, Tracy R, Douek DC. Systemic effects of inflammation on health during chronic HIV infection. *Immunity*. 2013;39(4):633–45. [PubMed: 24138880]
6. Kuller LH, Tracy R, Belloso W, De Wit S, Drummond F, Lane HC, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med*. 2008;5(10):e203. [PubMed: 18942885]
7. Kalayjian RC, Machekano RN, Rizk N, Robbins GK, Gandhi RT, Rodriguez BA, et al. Pretreatment levels of soluble cellular receptors and interleukin-6 are associated with HIV disease progression in subjects treated with highly active antiretroviral therapy. *J Infect Dis*. 2010;201(12):1796–805. [PubMed: 20446847]
8. Deeks SG, Kitchen CM, Liu L, Guo H, Gascon R, Narváez AB, et al. Immune activation set point during early HIV infection predicts subsequent CD4+ T-cell changes independent of viral load. *Blood*. 2004; 104(4):942–7. [PubMed: 15117761]
9. Giorgi JV, Hultin LE, McKeating JA, Johnson TD, Owens B, Jacobson LP, et al. Shorter survival in advanced human immunodeficiency virus type 1 infection is more closely associated with T lymphocyte activation than with plasma virus burden or virus chemokine coreceptor usage. *J Infect Dis*. 1999; 179(4):859–70. [PubMed: 10068581]
10. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med*. 2006;12(12):1365–71. [PubMed: 17115046]
11. Lohse N, Hansen A-BE, Pedersen G, Kronborg G, Gerstoft J, Sørensen HT, et al. Survival of persons with and without HIV infection in Denmark, 1995–2005. *Annals of Internal Medicine*. 2007;146(2):87–95. [PubMed: 17227932]

12. Neuhaus J, Jacobs DR Jr., Baker JV, Calmy A, Duprez D, La Rosa A, et al. Markers of inflammation, coagulation, and renal function are elevated in adults with HIV infection. *J Infect Dis.* 2010;201(12):1788–95. [PubMed: 20446848]
13. Tang WH, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. *N Engl J Med.* 2013;368(17):1575–84. [PubMed: 23614584]
14. Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nat Med.* 2013;19(5):576–85. [PubMed: 23563705]
15. Alejos B, Hernando V, Lopez-Aldeguer J, Segura F, Oteo JA, Rubio R, et al. Overall and cause-specific mortality in HIV-positive subjects compared to the general population. *J Int AIDS Soc.* 2014;17(4 Suppl 3): 19711. [PubMed: 25397458]
16. Serrano-Villar S, Sainz T, Lee SA, Hunt PW, Sinclair E, Shacklett BL, et al. HIV-infected individuals with low CD4/CD8 ratio despite effective antiretroviral therapy exhibit altered T cell subsets, heightened CD8+ T cell activation, and increased risk of non-AIDS morbidity and mortality. *PLoS Pathog.* 2014;10(5):e1004078. [PubMed: 24831517]
17. Hunt PW, Sinclair E, Rodriguez B, Shive C, Clagett B, Funderburg N, et al. Gut Epithelial Barrier Dysfunction and Innate Immune Activation Predict Mortality in Treated HIV Infection. *J Infect Dis.* 2014.
18. Hatano H, Jain V, Hunt PW, Lee TH, Sinclair E, Do TD, et al. Cell-based measures of viral persistence are associated with immune activation and programmed cell death protein 1 (PD-1)-expressing CD4+ T cells. *J Infect Dis.* 2013;208(1):50–6. [PubMed: 23089590]
19. Li Q, Duan L, Estes JD, Ma ZM, Rourke T, Wang Y, et al. Peak SIV replication in resting memory CD4+ T cells depletes gut lamina propria CD4+ T cells. *Nature.* 2005;434(7037):1148–52. [PubMed: 15793562]
20. Brenchley JM, Paiardini M, Knox KS, Asher AI, Cervasi B, Asher TE, et al. Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. *Blood.* 2008;112(7):2826–35. [PubMed: 18664624]
21. Favre D, Lederer S, Kanwar B, Ma ZM, Proll S, Kasakow Z, et al. Critical loss of the balance between Th17 and T regulatory cell populations in pathogenic SIV infection. *PLoS Pathog.* 2009;5(2):e1000295. [PubMed: 19214220]
22. Kok A, Hocqueloux L, Hocini H, Carriere M, Lefrou L, Guguin A, et al. Early initiation of combined antiretroviral therapy preserves immune function in the gut of HIV-infected patients. *Mucosal Immunol.* 2015;8(1):127–40. [PubMed: 24985081]
23. Eyerich K, Dimartino V, Cavani A. IL-17 and IL-22 in immunity: Driving protection and pathology. *Eur J Immunol.* 2017;47(4):607–14. [PubMed: 28295238]
24. Chevalier MF, Petitjean G, Dunyach-Remy C, Didier C, Girard PM, Manea ME, et al. The Th17/Treg ratio, IL-1RA and sCD14 levels in primary HIV infection predict the T-cell activation set point in the absence of systemic microbial translocation. *PLoS Pathog.* 2013;9(6):e1003453. [PubMed: 23818854]
25. Ryan ES, Micci L, Fromentin R, Paganini S, McGary CS, Easley K, et al. Loss of Function of Intestinal IL-17 and IL-22 Producing Cells Contributes to Inflammation and Viral Persistence in SIV-Infected Rhesus Macaques. *PLoS Pathog.* 2016;12(2):e1005412. [PubMed: 26829644]
26. Marchetti G, Tincati C, Silvestri G. Microbial translocation in the pathogenesis of HIV infection and AIDS. *Clin Microbiol Rev.* 2013;26(1):2–18. [PubMed: 23297256]
27. Shacklett BL, Anton PA. HIV Infection and Gut Mucosal Immune Function: Updates on Pathogenesis with Implications for Management and Intervention. *Curr Infect Dis Rep.* 2010;12(1):19–27. [PubMed: 20174448]
28. Chitre AS, Kattah MG, Rosli YY, Pao M, Deswal M, Deeks SG, et al. A20 upregulation during treated HIV disease is associated with intestinal epithelial cell recovery and function. *PLoS Pathog.* 2018;14(3):e1006806. [PubMed: 29505600]
29. Estes JD, Harris LD, Klatt NR, Tabb B, Pittaluga S, Paiardini M, et al. Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog.* 2010;6(8):e1001052. [PubMed: 20808901]

30. Somsouk M, Estes JD, Deleage C, Dunham RM, Albright R, Inadomi JM, et al. Gut epithelial barrier and systemic inflammation during chronic HIV infection. *AIDS*. 2015;29(1):43–51. [PubMed: 25387317]
31. Klatt NR, Estes JD, Sun X, Ortiz AM, Barber JS, Harris LD, et al. Loss of mucosal CD103+ DCs and IL-17+ and IL-22+ lymphocytes is associated with mucosal damage in SIV infection. *Mucosal Immunol*. 2012;5(6):646–57. [PubMed: 22643849]
32. Zaragoza MM, Sankaran-Walters S, Canfield DR, Hung JK, Martinez E, Ouellette AJ, et al. Persistence of gut mucosal innate immune defenses by enteric alpha-defensin expression in the simian immunodeficiency virus model of AIDS. *J Immunol*. 2011;186(3):1589–97. [PubMed: 21178012]
33. Allers K, Fehr M, Conrad K, Eppe HJ, Schurmann D, Geelhaar-Karsch A, et al. Macrophages accumulate in the gut mucosa of untreated HIV-infected patients. *J Infect Dis*. 2014;209(5):739–48. [PubMed: 24133185]
34. Salzman NH, Hung K, Haribhai D, Chu H, Karlsson-Sjoberg J, Amir E, et al. Enteric defensins are essential regulators of intestinal microbial ecology. *Nat Immunol*. 2010;11(1):76–83. [PubMed: 19855381]
35. Kumar P, Monin L, Castillo P, Elsegeiny W, Horne W, Eddens T, et al. Intestinal Interleukin-17 Receptor Signaling Mediates Reciprocal Control of the Gut Microbiota and Autoimmune Inflammation. *Immunity*. 2016;44(3):659–71. [PubMed: 26982366]
36. Garrett WS, Lord GM, Punit S, Lugo-Villarino G, Mazmanian SK, Ito S, et al. Communicable ulcerative colitis induced by T-bet deficiency in the innate immune system. *Cell*. 2007;131(1):33–45. [PubMed: 17923086]
37. Garrett WS, Gallini CA, Yatsunenko T, Michaud M, DuBois A, Delaney ML, et al. Enterobacteriaceae act in concert with the gut microbiota to induce spontaneous and maternally transmitted colitis. *Cell Host Microbe*. 2010;8(3):292–300. [PubMed: 20833380]
38. Armstrong AJS, Shaffer M, Nusbacher NM, Griesmer C, Fiorillo S, Schneider JM, et al. An exploration of Prevotella-rich microbiomes in HIV and men who have sex with men. *Microbiome*. 2018;6(1):198. [PubMed: 30396369]
39. Dillon SM, Lee EJ, Kotter CV, Austin GL, Dong Z, Hecht DK, et al. An altered intestinal mucosal microbiome in HIV-1 infection is associated with mucosal and systemic immune activation and endotoxemia. *Mucosal Immunol*. 2014;7(4):983–94. [PubMed: 24399150]
40. Dinh DM, Volpe GE, Duffalo C, Bhalchandra S, Tai AK, Kane AV, et al. Intestinal microbiota, microbial translocation, and systemic inflammation in chronic HIV infection. *J Infect Dis*. 2015;211(1):19–27. [PubMed: 25057045]
41. Lu W, Feng Y, Jing F, Han Y, Lyu N, Liu F, et al. Association Between Gut Microbiota and CD4 Recovery in HIV-1 Infected Patients. *Front Microbiol*. 2018;9:1451. [PubMed: 30034377]
42. Lozupone CA, Li M, Campbell TB, Flores SC, Linderman D, Gebert MJ, et al. Alterations in the gut microbiota associated with HIV-1 infection. *Cell Host Microbe*. 2013;14(3):329–39. [PubMed: 24034618]
43. Ling Z, Jin C, Xie T, Cheng Y, Li L, Wu N. Alterations in the Fecal Microbiota of Patients with HIV-1 Infection: An Observational Study in A Chinese Population. *Sci Rep*. 2016;6:30673. [PubMed: 27477587]
44. Lee SC, Chua LL, Yap SH, Khang TF, Leng CY, Raja Azwa RI, et al. Enrichment of gut-derived *Fusobacterium* is associated with suboptimal immune recovery in HIV-infected individuals. *Sci Rep*. 2018;8(1):14277. [PubMed: 30250162]
45. Monaco CL, Gootenberg DB, Zhao G, Handley SA, Ghebremichael MS, Lim ES, et al. Altered Virome and Bacterial Microbiome in Human Immunodeficiency Virus-Associated Acquired Immunodeficiency Syndrome. *Cell Host Microbe*. 2016; 19(3):311–22. [PubMed: 26962942]
46. McHardy IH, Li X, Tong M, Ruegger P, Jacobs J, Borneman J, et al. HIV Infection is associated with compositional and functional shifts in the rectal mucosal microbiota. *Microbiome*. 2013; 1(1):26. [PubMed: 24451087]
47. Mutlu EA, Keshavarzian A, Losurdo J, Swanson G, Siewe B, Forsyth C, et al. A compositional look at the human gastrointestinal microbiome and immune activation parameters in HIV infected subjects. *PLoS Pathog*. 2014; 10(2):e1003829. [PubMed: 24586144]

48. Noguera-Julian M, Rocafort M, Guillen Y, Rivera J, Casadella M, Nowak P, et al. Gut Microbiota Linked to Sexual Preference and HIV Infection. *EBioMedicine*. 2016;5:135–46. [PubMed: 27077120] ••This paper (along with Kelley et al.) demonstrated microbiota differences between MSM and non-MSM, highlighting the importance of matching subject groups by sexual orientation.
49. Nowak P, Troseid M, Avershina E, Barqasho B, Neogi U, Holm K, et al. Gut microbiota diversity predicts immune status in HIV-1 infection. *AIDS*. 2015;29(18):2409–18. [PubMed: 26355675]
50. Vujkovic-Cvijin I, Dunham RM, Iwai S, Maher MC, Albright RG, Broadhurst MJ, et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. *Sci Transl Med*. 2013;5(193): 193ra91.
51. Vazquez-Castellanos JF, Serrano-Villar S, Latorre A, Artacho A, Ferrus ML, Madrid N, et al. Altered metabolism of gut microbiota contributes to chronic immune activation in HIV-infected individuals. *Mucosal Immunol*. 2015;8(4):760–72. [PubMed: 25407519] •This paper investigated stool metabolite profiles of HIV-infected and uninfected subjects, finding that kynurenine pathway enzymatic products were enriched in stool of HIV-infected subjects.
52. San-Juan-Vergara H, Zurek E, Ajami NJ, Mogollon C, Pena M, Portnoy I, et al. A Lachnospiraceae-dominated bacterial signature in the fecal microbiota of HIV-infected individuals from Colombia, South America. *Sci Rep*. 2018;8(1):4479. [PubMed: 29540734]
53. Yu G, Fadrosch D, Ma B, Ravel J, Goedert JJ. Anal microbiota profiles in HIV-positive and HIV-negative MSM. *AIDS*. 2014;28(5):753–60. [PubMed: 24335481]
54. Zhou Y, Ou Z, Tang X, Zhou Y, Xu H, Wang X, et al. Alterations in the gut microbiota of patients with acquired immune deficiency syndrome. *J Cell Mol Med*. 2018;22(4):2263–71. [PubMed: 29411528]
55. Hoel H, Hove-Skovsgaard M, Hov JR, Gaardbo JC, Holm K, Kummen M, et al. Impact of HIV and Type 2 diabetes on Gut Microbiota Diversity, Tryptophan Catabolism and Endothelial Dysfunction. *Sci Rep*. 2018;8(1):6725. [PubMed: 29712976]
56. Winter SE, Winter MG, Xavier MN, Thiennimitr P, Poon V, Keestra AM, et al. Host-derived nitrate boosts growth of *E. coli* in the inflamed gut. *Science*. 2013;339(6120):708–11. [PubMed: 23393266]
57. Winter SE, Thiennimitr P, Winter MG, Butler BP, Huseby DL, Crawford RW, et al. Gut inflammation provides a respiratory electron acceptor for *Salmonella*. *Nature*. 2010;467(7314): 426–9. [PubMed: 20864996]
58. Deleage C, Schuetz A, Alvord WG, Johnston L, Hao XP, Morcock DR, et al. Impact of early cART in the gut during acute HIV infection. *JCI Insight*. 2016; 1 (10).
59. Mahjoub-Messai F, Bidet P, Caro V, Diancourt L, Biran V, Aujard Y, et al. *Escherichia coli* isolates causing bacteremia via gut translocation and urinary tract infection in young infants exhibit different virulence genotypes. *J Infect Dis*. 2011;203(12): 1844–9. [PubMed: 21550999]
60. O'Boyle CJ, MacFie J, Mitchell CJ, Johnstone D, Sagar PM, Sedman PC. Microbiology of bacterial translocation in humans. *Gut*. 1998;42(1):29–35. [PubMed: 9505882]
61. Steffen EK, Berg RD, Deitch EA. Comparison of translocation rates of various indigenous bacteria from the gastrointestinal tract to the mesenteric lymph node. *J Infect Dis*. 1988;157(5):1032–8. [PubMed: 3283254]
62. Ortiz AM, Flynn JK, DiNapoli SR, Vujkovic-Cvijin I, Starke CE, Lai SH, et al. Experimental microbial dysbiosis does not promote disease progression in SIV-infected macaques. *Nat Med*. 2018;24(9):1313–6. [PubMed: 30061696]
63. Amato KR, Yeoman CJ, Cerda G, Schmitt CA, Cramer JD, Miller ME, et al. Variable responses of human and non-human primate gut microbiomes to a Western diet. *Microbiome*. 2015;3:53. [PubMed: 26568112]
64. McKenna P, Hoffmann C, Minkah N, Aye PP, Lackner A, Liu Z, et al. The macaque gut microbiome in health, lentiviral infection, and chronic enterocolitis. *PLoS Pathog*. 2008;4(2):e20. [PubMed: 18248093]
65. Nagpal R, Wang S, Solberg Woods LC, Seshie O, Chung ST, Shively CA, et al. Comparative Microbiome Signatures and Short-Chain Fatty Acids in Mouse, Rat, Non-human Primate, and Human Feces. *Front Microbiol*. 2018;9:2897. [PubMed: 30555441]

66. Glavan TW, Gaulke CA, Santos Rocha C, Sankaran-Walters S, Hirao LA, Raffatellu M, et al. Gut immune dysfunction through impaired innate pattern recognition receptor expression and gut microbiota dysbiosis in chronic SIV infection. *Mucosal Immunol.* 2016;9(3):677–88. [PubMed: 26376368]
67. Klase Z, Ortiz A, Deleage C, Mudd JC, Quinones M, Schwartzman E, et al. Dysbiotic bacteria translocate in progressive SIV infection. *Mucosal Immunol.* 2015;8(5): 1009–20. [PubMed: 25586559]
68. Vujkovic-Cvijin I, Swainson LA, Chu SN, Ortiz AM, Santee CA, Petriello A, et al. Gut-Resident *Lactobacillus* Abundance Associates with IDO1 Inhibition and Th17 Dynamics in SIV-Infected Macaques. *Cell Rep.* 2015; 13(8): 1589–97. [PubMed: 26586432]
69. Chen L, Wilson JE, Koenigsnecht MJ, Chou WC, Montgomery SA, Truax AD, et al. NLRP12 attenuates colon inflammation by maintaining colonic microbial diversity and promoting protective commensal bacterial growth. *Nat Immunol.* 2017; 18(5):541–51. [PubMed: 28288099]
70. Truax AD, Chen L, Tam JW, Cheng N, Guo H, Koblansky AA, et al. The Inhibitory Innate Immune Sensor NLRP12 Maintains a Threshold against Obesity by Regulating Gut Microbiota Homeostasis. *Cell Host Microbe.* 2018;24(3):364–78 e6. [PubMed: 30212649]
71. Desvignes L, Ernst JD. Interferon-gamma-responsive nonhematopoietic cells regulate the immune response to *Mycobacterium tuberculosis*. *Immunity.* 2009;31(6):974–85. [PubMed: 20064452]
72. Favre D, Mold J, Hunt PW, Kanwar B, Loke P, Seu L, et al. Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. *Sci Transl Med.* 2010;2(32):32ra6.
73. Routy JP, Mehraj V, Vyboh K, Cao W, Kema I, Jenabian MA. Clinical Relevance of Kynurenine Pathway in HIV/AIDS: An Immune Checkpoint at the Crossroads of Metabolism and Inflammation. *AIDS Rev.* 2015;17(2):96–106. [PubMed: 26035167]
74. Serrano-Villar S, Rojo D, Martinez-Martinez M, Deusch S, Vazquez-Castellanos JF, Sainz T, et al. HIV infection results in metabolic alterations in the gut microbiota different from those induced by other diseases. *Sci Rep.* 2016;6:26192. [PubMed: 27189771]
75. Lamas B, Richard ML, Leducq V, Pham H-P, Michel M-L, Da Costa G, et al. CARD9 impacts colitis by altering gut microbiota metabolism of tryptophan into aryl hydrocarbon receptor ligands. *Nature Medicine.* 2016;22(6):598–605.
76. Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity.* 2013;39(2):372–85. [PubMed: 23973224]
77. Rothhammer V, Mascalfroni ID, Bunse L, Takenaka MC, Kenison JE, Mayo L, et al. Type I interferons and microbial metabolites of tryptophan modulate astrocyte activity and central nervous system inflammation via the aryl hydrocarbon receptor. *Nat Med.* 2016;22(6):586–97. [PubMed: 27158906]
78. Atarashi K, Tanoue T, Oshima K, Suda W, Nagano Y, Nishikawa H, et al. Treg induction by a rationally selected mixture of *Clostridia* strains from the human microbiota. *Nature.* 2013;500(7461):232–6. [PubMed: 23842501]
79. Desai MS, Seekatz AM, Koropatkin NM, Kamada N, Hickey CA, Wolter M, et al. A Dietary Fiber-Deprived Gut Microbiota Degrades the Colonic Mucus Barrier and Enhances Pathogen Susceptibility. *Cell.* 2016; 167(5): 1339–53 e21. [PubMed: 27863247] •This study demonstrated the importance of dietary fiber fermentation by the gut microbiota (which produces short-chain fatty acids) in preventing gut mucosal inflammation.
80. Rivera-Chavez F, Zhang LF, Faber F, Lopez CA, Byndloss MX, Olsan EE, et al. Depletion of Butyrate-Producing *Clostridia* from the Gut Microbiota Drives an Aerobic Luminal Expansion of *Salmonella*. *Cell Host Microbe.* 2016;19(4):443–54. [PubMed: 27078066] •This study found that loss of SCFA-producing microbes creates a niche for *Enterobacteriaceae* and facilitates their promotion of inflammation.
81. Singh SB, Lin HC. Hydrogen Sulfide in Physiology and Diseases of the Digestive Tract. *Microorganisms.* 2015;3(4):866–89. [PubMed: 27682122]
82. Ijssennagger N, van der Meer R, van Mil SWC. Sulfide as a Mucus Barrier-Breaker in Inflammatory Bowel Disease? *Trends Mol Med.* 2016;22(3): 190–9. [PubMed: 26852376]

83. Guo FF, Yu TC, Hong J, Fang JY. Emerging Roles of Hydrogen Sulfide in Inflammatory and Neoplastic Colonic Diseases. *Front Physiol.* 2016;7:156. [PubMed: 27199771]
84. Hunt PW. Th17, gut, and HIV: therapeutic implications. *Curr Opin HIV AIDS.* 2010;5:189–93. [PubMed: 20543599]
85. Kelley CF, Kraft CS, de Man TJ, Duphare C, Lee HW, Yang J, et al. The rectal mucosa and condomless receptive anal intercourse in HIV-negative MSM: implications for HIV transmission and prevention. *Mucosal Immunol.* 2017;10(4):996–1007. [PubMed: 27848950] ••This study concurrently supported the aforementioned conclusion of Noguera-Julian et al.
86. McFarland LV, Elmer GW, Surawicz CM. Breaking the cycle: treatment strategies for 163 cases of recurrent *Clostridium difficile* disease. *Am J Gastroenterol.* 2002;97(7): 1769–75. [PubMed: 12135033]
87. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent *Clostridium difficile*. *N Engl J Med.* 2013;368(5):407–15. [PubMed: 23323867]
88. Gough E, Shaikh H, Manges AR. Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent *Clostridium difficile* infection. *Clin Infect Dis.* 2011;53(10):994–1002. [PubMed: 22002980]
89. Brandt LJ, Aroniadis OC, Mellow M, Kanatzar A, Kelly C, Park T, et al. Long-term follow-up of colonoscopic fecal microbiota transplant for recurrent *Clostridium difficile* infection. *Am J Gastroenterol.* 2012; 107(7): 1079–87. [PubMed: 22450732]
90. Ihunnah C, Kelly C, Hohmann E, Brandt LJ, Khoruts A, Stollman N, et al. Fecal Microbiota Transplantation (FMT) for Treatment of *Clostridium difficile* Infection (CDI) in Immunocompromised Patients. *Am J Gastroenterol.* 2013(ACG Abstract): 1745628.
91. Elore L, Rodriguez M. Fecal microbiota therapy for recurrent *Clostridium difficile* infection in HIV-infected persons. *Ann Intern Med.* 2013;158(10):779–80. [PubMed: 23689775]
92. Vujkovic-Cvijin I, Rutishauser RL, Pao M, Hunt PW, Lynch SV, McCune JM, et al. Limited engraftment of donor microbiome via one-time fecal microbial transplantation in treated HIV-infected individuals. *Gut Microbes.* 2017;8(5):440–50. [PubMed: 28541799]
93. Costello SP, Hughes PA, Waters O, Bryant RV, Vincent AD, Blatchford P, et al. Effect of Fecal Microbiota Transplantation on 8-Week Remission in Patients With Ulcerative Colitis: A Randomized Clinical Trial. *JAMA.* 2019;321(2): 156–64. [PubMed: 30644982] •This study found that multi-dose anaerobically-prepared healthy donor stool in the context of fecal microbiota transplant effectively induced remission of ulcerative colitis in a subset of subjects.
94. Rossen NG, Fuentes S, van der Spek MJ, Tijssen JG, Hartman JH, Duflou A, et al. Findings From a Randomized Controlled Trial of Fecal Transplantation for Patients With Ulcerative Colitis. *Gastroenterology.* 2015;149(1):110–8 e4. [PubMed: 25836986]
95. Moayyedi P, Surette MG, Kim PT, Libertucci J, Wolfe M, Onischi C, et al. Fecal Microbiota Transplantation Induces Remission in Patients With Active Ulcerative Colitis in a Randomized Controlled Trial. *Gastroenterology.* 2015;149(1):102–9 e6. [PubMed: 25857665]
96. Rothschild D, Weissbrod O, Barkan E, Kurilshikov A, Korem T, Zeevi D, et al. Environment dominates over host genetics in shaping human gut microbiota. *Nature.* 2018;555(7695):210–5. [PubMed: 29489753]
97. David LA, Maurice CF, Carmody RN, Gootenberg DB, Button JE, Wolfe BE, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484):559–63. [PubMed: 24336217]
98. Wu GD, Chen J, Hoffmann C, Bittinger K, Chen YY, Keilbaugh SA, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052): 105–8. [PubMed: 21885731]
99. Duncan SH, Belenguer A, Holtrop G, Johnstone AM, Flint HJ, Lobley GE. Reduced dietary intake of carbohydrates by obese subjects results in decreased concentrations of butyrate and butyrate-producing bacteria in feces. *Appl Environ Microbiol.* 2007;73(4): 1073–8. [PubMed: 17189447]
100. Kim MS, Hwang SS, Park EJ, Bae JW. Strict vegetarian diet improves the risk factors associated with metabolic diseases by modulating gut microbiota and reducing intestinal inflammation. *Environ Microbiol Rep.* 2013;5(5):765–75. [PubMed: 24115628]

101. Wang Z, Roberts AB, Buffa JA, Levison BS, Zhu W, Org E, et al. Non-lethal Inhibition of Gut Microbial Trimethylamine Production for the Treatment of Atherosclerosis. *Cell*. 2015;163(7): 1585–95. [PubMed: 26687352] •This study demonstrated efficacy of targeting microbial enzymes with small molecules to block pathogenic functions of the microbiota, a novel strategy to alter human health by modulating the microbiota.
102. Stein JH, Hsue PY. Inflammation, immune activation, and CVD risk in individuals with HIV infection. *JAMA*. 2012;308(4):405–6. [PubMed: 22820794]
103. Missailidis C, Neogi U, Stenvinkel P, Troseid M, Nowak P, Bergman P. The microbial metabolite trimethylamine-N-oxide in association with inflammation and microbial dysregulation in three HIV cohorts at various disease stages. *AIDS*. 2018;32(12): 1589–98. [PubMed: 29620717]
104. Zhu W, Winter MG, Byndloss MX, Spiga L, Duerkop BA, Hughes ER, et al. Precision editing of the gut microbiota ameliorates colitis. *Nature*. 2018;553(7687):208–11. [PubMed: 29323293] •This study demonstrated efficacy of targeting fundamental microbial metabolic pathways with small molecules to specifically delete pro-inflammatory *Enterobacteriaceae* from the microbiota.
105. Kutter E, De Vos D, Gvasalia G, Alavidze Z, Gogokhia L, Kuhl S, et al. Phage therapy in clinical practice: treatment of human infections. *Curr Pharm Biotechnol*. 2010;11(1):69–86. [PubMed: 20214609]
106. Sulakvelidze A, Alavidze Z, Morris JG Jr. Bacteriophage therapy. *Antimicrob Agents Chemother*. 2001;45(3):649–59. [PubMed: 11181338]
107. Atterbury RJ. Bacteriophage biocontrol in animals and meat products. *Microb Biotechnol*. 2009;2(6):601–12. [PubMed: 21255295]
108. Miller RW, Skinner EJ, Sulakvelidze A, Mathis GF, Hofacre CL. Bacteriophage therapy for control of necrotic enteritis of broiler chickens experimentally infected with *Clostridium perfringens*. *Avian Dis*. 2010;54(1):33–40. [PubMed: 20408396]
109. de Melo AG, Levesque S, Moineau S. Phages as friends and enemies in food processing. *Curr Opin Biotechnol*. 2018;49:185–90. [PubMed: 28987913]
110. Buttner C, McAuliffe O, Ross RP, Hill C, O'Mahony J, Coffey A. Bacteriophages and Bacterial Plant Diseases. *Front Microbiol*. 2017;8:34. [PubMed: 28163700]
111. Kristensen NB, Bryrup T, Allin KH, Nielsen T, Hansen TH, Pedersen O. Alterations in fecal microbiota composition by probiotic supplementation in healthy adults: a systematic review of randomized controlled trials. *Genome Med*. 2016;8(1):52. [PubMed: 27159972]
112. Zmora N, Zilberman-Schapira G, Suez J, Mor U, Dori-Bachash M, Bashariades S, et al. Personalized Gut Mucosal Colonization Resistance to Empiric Probiotics Is Associated with Unique Host and Microbiome Features. *Cell*. 2018; 174(6): 1388–405 e21. [PubMed: 30193112]
113. Hempel S, Newberry SJ, Maher AR, Wang Z, Miles JN, Shanman R, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA*. 2012;307(18): 1959–69. [PubMed: 22570464]
114. Ford AC, Quigley EM, Lacy BE, Lembo AJ, Saito YA, Schiller LR, et al. Efficacy of prebiotics, probiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: systematic review and meta-analysis. *Am J Gastroenterol*. 2014; 109(10): 1547–61; quiz 6, 62. [PubMed: 25070051]
115. Buffie CG, Bucci V, Stein RR, McKenney PT, Ling L, Gobburne A, et al. Precision microbiome reconstitution restores bile acid mediated resistance to *Clostridium difficile*. *Nature*. 2015;517(7533):205–8. [PubMed: 25337874] •This study identified gut bacteria that were anti-correlated with a pro-inflammatory gut bacterium (*C. difficile*), and demonstrated that anti-correlates were competitors and could be used to eliminate the pro-inflammatory bacterium in the context of exogenous supplementation.
116. Seres Therapeutics Announces Initiation of SER-287 Phase 2B ECO-RESET Clinical Study for Ulcerative Colitis [press release]. Seres Therapeutics, Inc.2019.
117. Nature Paper by Team at RIKEN and Vedanta Shows Efficacy of Candidate in Autoimmune Diseases [press release]. Vedanta Biosciences, Inc.2013.

Figure 1:

A) Trends among surveys comparing HIV-infected subject microbiota profiles to those of uninfected subjects are shown. Clades were considered enriched or depleted for each study if any taxa within those clades were reported as such. In the multiple taxa within a clade having mixed results, the clade is shown as enriched or depleted if the majority of taxa followed the same trend and if their combined effect size outweighed that of the opposite trend. *Enriched in suboptimal HIV ART subject with CD4<350 cells/ul as compared to CD4>500 cells/ul. B) Trends among surveys comparing gut microbiota profiles of MSM to non-MSM male subjects.