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HIV PATHOGENESIS AND TREATMENT (AL LANDAY AND NS UTAY, SECTION EDITORS)

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

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 HIV-uninfected subjects, how these differences may influence host immune states, and methods that have emerged as promising strategies for precision microbiome editing.

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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 in 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 [38–47, 48••, 49, 50, 51•, 52–57]. Results of these studies share several common patterns among the HIV-infected sample population: an enrichment of *Erysipelotrichaceae*, *Enterobacteriaceae*, *Desulfovibrionaceae*, and *Fusobacteria* and a depletion of *Lachnospiraceae*, *Ruminococceae*, *Bacteroides*, and *Rikenellaceae* (Fig. 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 to tryptophan ratios [50, 58], IL-6 [47, 50], sCD14 [40, 45, 47], IL-1β [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 [59, 60], 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 [61], 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 [62–64], providing another avenue by which these bacteria may contribute

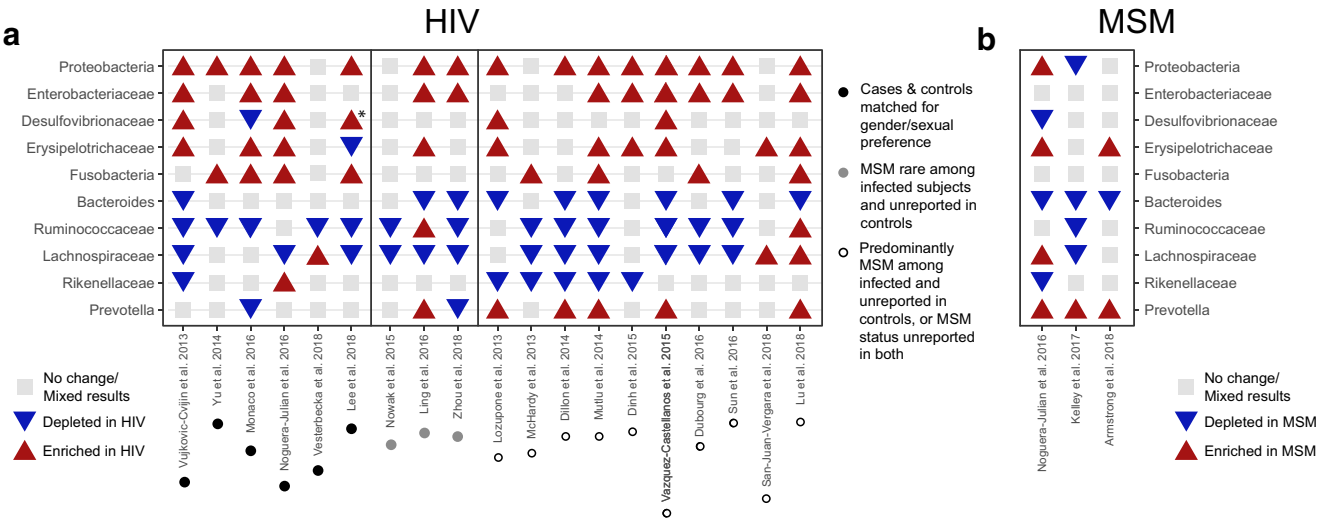

Fig. 1 **a** Trends among surveys comparing HIV-infected subject microbiota profiles to those of uninfected subjects are shown. Clades were considered enriched or depleted for each study if any taxa within those clades were reported as such. In the case of multiple taxa within a clade exhibiting mixed trends (some being depleted in HIV and others being enriched), 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

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 [65]. 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 utilized sim ultaneously decreased *Erysipelotrichaceae* (a clade enriched in HIV infection) while increasing *Proteobacteria* (also enriched 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 [66–68], and given that a durable shift in the gut microbiota is not observed in macaques upon chronic infection with SIV [69–71] 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 [72, 73]. 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 [74, 75], 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. [76]. 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, 58], and HIV-infected subject gut microbiota communities exhibit an increased capacity to catabolize tryptophan to kynurenine [77], highlighting a potential contribution of HIV-associated gut bacteria to increased local and systemic levels of these

catabolites [50, 75]. Several structurally similar tryptophan-derived AhR agonists have been found to be produced by gut microbiota constituents and to modulate severity of inflammatory disease [78–80], 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 [81]. Loss of such fiber fermentation in murine models causes reduced gut barrier integrity [82•] and colonic inflammation due to an expansion of pro-inflammatory gut bacteria [83•].

Finally, *Desulfovibrio* bacteria are known producers of hydrogen sulfide (H_2S) [84], 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 [85, 86]. Thus, in the context of HIV infection, this combination of increased gut microbial-derived kynurenine and H_2S, 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 [87]. 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. [88••], 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 USA 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 HIV-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 (Fig. 1a). 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••, 88••], suggesting that MSM status alone is unlikely to explain the shifts in abundance of these clades in HIV microbiota surveys (Fig. 1b). Furthermore, several studies in which HIV-infected and HIV-uninfected subjects were matched for MSM status, or where MSM constituted a minority of subjects sampled, revealed enrichment of the same aforementioned clades of bacteria (Fig. 1a). There remains a need for well-powered studies examining differences in the gut microbiota of HIV-infected and HIV-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 [89]. 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 [90]—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% [90–92]. This procedure appears safe, with few reported adverse effects even in patients who may be immunocompromised, such as HIV-infected and post-transplant patients [93, 94]. 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 [95] 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 [95], 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 [96•] compared to multi-dose material from single donor with routine processing [97, 98]. 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 [99]. 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 [100, 101] are enriched in subjects consuming a meat diet while *Ruminococcaceae* and *Lachnospiraceae* exhibit a relative increase in those consuming high plant-fiber diets [100, 102, 103]. 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 [104•]. In the setting of HIV infection, despite ART treatment, the incidence of cardiovascular disease is increased compared to the general population [105], though TMAO levels do not differ between these populations [106], 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 [107•], 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 twentieth century, experimental and clinical usage of phages to combat infectious diseases was taking place broadly in the USA, Western Europe, and Eastern Europe. Conflicting studies interrogating bacteriophage efficacy stymied enthusiasm, however, and the advent of highly efficacious chemical antibiotics in the 1930s 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 [108, 109].

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 [110, 111], to kill foodborne pathogens in agricultural products (*Listeria monocytogenes,*

Enterobacteriaceae spp.*)* [112], and to eliminate plant pathogens [113]. 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 [114, 115], 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 [116] and irritable bowel syndrome [117] 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 [118•], a strategy currently advancing through clinical trials [119]. 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 [120], 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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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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