Microbial translocation and microbiome dysbiosis in HIV-associated immune activation

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Abstract

\textbf{Purpose of Review}—To describe the mechanisms and consequences of both microbial translocation and microbial dysbiosis in HIV infection.

\textbf{Recent Findings}—Microbes in HIV are likely playing a large role in contributing to HIV pathogenesis, morbidities and mortality. Two major disruptions to microbial systems in HIV infection include microbial translocation and microbiome dysbiosis. Microbial translocation occurs when the bacteria (or bacterial products) that should be in the lumen of the intestine translocate across the tight epithelial barrier into systemic circulation, where they contribute to inflammation and pathogenesis. This is associated with poorer health outcomes in HIV infected individuals. In addition, microbial populations in the GI tract are also altered after HIV infection, resulting in microbiome dysbiosis, which further exacerbates microbial translocation, epithelial barrier disruption, inflammation, and mucosal immune functioning.

\textbf{Summary}—Altered microbial regulation in HIV infection can lead to poor health outcomes, and understanding the mechanisms underlying microbial dysbiosis and translocation may result in novel pathways for therapeutic interventions.

\textbf{Keywords}
Microbiome; microbial translocation; HIV/AIDS; inflammation; mucosal
Introduction

Immune activation is a hallmark of HIV infection and is strongly associated with AIDS and non-AIDS morbidity and mortality. There are several causes of immune activation in HIV infected individuals, however mucosal dysfunction is a major factor contributing to persistent inflammation and immunological dysfunction. Mucosal dysfunction in HIV infection is characterized by drastic immunological alterations, breaches in the epithelial barrier, translocation of microbial products into circulation, and microbiome dysbiosis [1,2]. Thus the mucosal barrier of the gastrointestinal (GI) tract is a central component of HIV. As the GI tract contains the largest source of CD4+ T cells it is not surprising to be a primary site of ongoing viral replication [3,4]. However, despite antiretroviral therapy (ART) that restricts virus replication, complete restoration of barrier function does not occur and mucosal immune dysfunction persists [5,6].

The proper functioning of the mucosal barrier relies on protein structures that maintain epithelial integrity including tight junctions, adherens junctions, or desmosomes. These structures adhere cells to one another [7], which seals the paracellular space between epithelial cells and forms branching networks of strands that help form intact epithelial sheets [8]. Although the complete understanding and the etiology of epithelial disruption during HIV infection remains unclear, it is known that these tight junctions are breached during HIV infection [6], which has been linked to many immunological influences [9]. For example, homeostatic T cell subsets are lost very early in infection, including Th17 cells, which are crucial in responding to bacterial antigens [10,11]. Indeed, Th17 cells in HIV infection are thought to aid in maintenance of the epithelial barrier by amplifying signals of microbial translocation [12]. Also, neutrophils, which are crucial in the immune response to bacterial and fungal pathogens [13], infiltrate into the GI tract in both HIV and the simian immunodeficiency virus (SIV) model of infection [2,14]. This coincides with damage to the epithelial barrier and microbial translocation, suggesting that neutrophils are responding to translocation of bacterial products but are unable to contribute to their containment, but could be releasing inflammatory factors that contribute to barrier damage [15]. However, their contribution to mucosal dysfunction in the GI tissue is unknown [2,14]. Many other effects on local immune cell milieu, epithelial cell responses, virus-cell interactions [16], altered molecular events [17], enhanced proinflammatory soluble products [18,19], and altered microbial regulation have been observed which suggest a multifacotral process [1,20]. While acknowledging there are many immunological contributions to this disruption, this review will focus on the contributing roles of microbial dysbiosis and translocation HIV-related inflammation.

Microbial Translocation in HIV infection

Microbial translocation (MT) is defined as the movement of microbial products from the gut mucosa into circulation. Though recognized in other fields, MT in the context of HIV was first characterized only 10 years ago [21], but the finding has since been replicated in many cohorts and is now accepted as a general phenomenon in HIV. In retrospect, MT in HIV should not be surprising, given that HIV is a gut tropic infection and a site of major and irreversible damage regardless of how infection is acquired [22,23]. In addition the gut
represents one of the body's largest and most influential microbiomes, exerting an impact on a diverse range of human health and immunological conditions [24,25].

MT has been found to be a major driver of morbidity and mortality in HIV infection, likely due to the persistent inflammation it induces and sustains [26-28]. Importantly, the associations between microbial translocation and disease progression and mortality are independent of whether the HIV-infected individual is virally suppressed with ART [29]. A commonly identified translocating microbial product is lipopolysaccharide (LPS) from the surface of Gram-negative bacteria [21]. Several studies have demonstrated direct correlations between plasma LPS levels in HIV-infected individuals residual viremia, cellular activation including CD38+HLA-DR+ CD8+ T cells and activation of monocytes, interferon responsive genes such as MxA, and proinflammatory cytokines including IFN-α, IL-6, TNFα [21,23,30-34]. In addition, LPS levels and/or bacterial DNA levels directly correlate with other markers of microbial translocation and innate immune activation such as soluble CD14 (sCD14; released by monocytes in response to bacterial stimulation), LPS-binding protein (LBP) and endotoxin. While it is unclear how much inflammation during HIV infection is directly attributed to microbial translocation given the many inflammatory mechanisms which occur during HIV infection (including virus replication, opportunistic infections, etc.), studies in the absence of HIV demonstrate relationships between microbial translocation and inflammation. In idiopathic CD4 lymphocytopenia (ICL), LPS is elevated and associated with proliferating CD4+ T cells [35], and colon LPS levels in uninfected pigtail macaques correlate with interferon responsive gene MxA in the GI tract [36], demonstrating that microbial products can directly stimulate inflammatory responses.

Microbial translocation occurs early in infection, and in SIV models has been demonstrated to begin mainly in the post-peak viremia phase, or days 14-28 post-SIV infection [14]. However, prior to infection in the macaque SIV model, the extent of epithelial breaches and MT predicts the kinetics of progression to AIDS [33]. Additionaly, epithelial damage and local inflammation predicts mortality in HIV infection [2**,37**]. Indeed, a major mechanism which drives MT is focal breaches that occur to the epithelial barrier of the GI tract, which physically allows microbial products to translocate [14,36], however it is unclear what induces these breaches. One potential mechanism underlying damage to the epithelial barrier is alterations in the microbial communities of the GI tract. In HIV infection, there is an increased abundance of epithelial-adherent bacteria of the Proteobacteria family [38], and interestingly, it is this increased Proteobacteria that is found to predominantly translocate in SIV infection [39**]. This suggests that interactions between bacteria associated with the mucosa and the epithelium may contribute to MT. However, the relative contribution of various host and microbial factors to barrier damage are not well defined and studies examining these processes promise to provide novel targets for therapeutics designed to restore GI barrier function.

**Microbial dysbiosis in HIV infection**

Microorganisms associated with the GI lumen and mucosa are mostly bacteria but also include Archaea, Fungi, other eukaryotes such as helminthes, and viruses, many of which are bacteriophages [40-43]. It has become exceedingly clear that GI resident microbes and
their associated metabolites are required to maintain proper function of the immune system and general health [40]. Perturbation of these microbial communities can have dramatic impacts on the health of the host and recent studies have demonstrated that shifts in the composition and function of the GI microbiome are associated with many disease states including HIV [38,44**,45].

HIV-induced alterations to the gut microbiota are most commonly characterized by overall decreased diversity [46], with reduced abundances of the genus *Bacteroides* and increased abundances of the genus *Prevotella* [38,44-45, 46**, 47]. Bacteria from these two genera are known to be important drivers of gut ecology and function [48]. Thus, shifts in the abundances of these bacteria can have major consequences for the gut microbiome and host. Indeed, altered abundances of *Bacteroides* and *Prevotella* have been implicated in a number of disease states, such as inflammatory bowel diseases (IBD) [49-52]. Table 1 shows different genera of bacteria found to be altered in HIV infection and possible roles for these bacteria in the context of the disease.

Loss of bacteria from the gut may reduce the ability of HIV-infected individuals to manage gastrointestinal inflammation, and may result in altered T cell subsets shown in HIV infection. For example, in murine models, polysaccharide A (PSA) produced by *Bacteroides fragilis* has been shown to increase the expression of the anti-inflammatory cytokine IL-10 and increase populations of memory CD4+ T cells [67]. Additionally, *Bacteroides* are typically associated with the gut microbiota of individuals that consume a diet rich in animal-derived fats and glycans [74] and reduced abundances of these bacteria may lead to a diet-microbiome mismatch in HIV-infected individuals, which can manifest as metabolic disease [75].

Other bacterial genera that are reduced in abundance in HIV infection are *Lactobacillus*, *Bifidobacterium*, *Coprococcus*, *Eubacterium*, *Blautia*, and *Ruminococcus*. Genera enriched in the gut microbiome of HIV-infected individuals include *Pseudomonas*, *Acinetobacter*, *Campylobacter*, *Escherichia*, and *Desulfovibrio* [38,44-47,54,76**]. *Lactobacillus* spp. and *Bifidobacterium* spp. are generally regarded as beneficial, especially in the context of mucosal immunity and administration of probiotic supplements containing these bacteria have been found to be highly beneficial in the context of GI disease and inflammation [77-80]. These bacteria are also known to provide B and K vitamins to the host which are necessary for a variety of metabolic processes [71]. *Coprococcus* spp., *Eubacterium* spp., *Blautia* spp., and *Ruminococcus* spp. are usually commensal bacteria that are rarely implicated in intestinal infections and ferment dietary polysaccharides to form short chain fatty acids (SCFAs) such as acetate and butyrate, which are important energy sources for intestinal epithelial cells [57,72,81]. The genera *Pseudomonas*, *Acinetobacter*, *Campylobacter*, and *Escherichia* include a variety of opportunistic pathogens [56,60,61,82] while *Desulfovibrio* spp. produce toxic hydrogen sulfide and are closely associated with the mucosa [83,84]. Expansion of these bacteria has been implicated in the pathogenesis of other inflammatory bowel diseases [85]. Thus, HIV-induced dysbiosis appears to be characterized by decreased abundances of bacteria that are generally regarded as commensal, fermentative, or protective accompanied by an expansion of bacteria that are
potentially inflammatory or pathogenic, which agrees with the general phenotype of mucosal inflammation in HIV infection.

In the SIV model, Handley et al. showed that an overall decrease in bacterial populations and an increase in enteric viruses was linked to GI pathology [86]. Interestingly, the authors of this study did not detect significant dysbiosis of the bacterial component of the microbiome. However these studies were performed on fecal samples, which do not exhibit dysbiosis as clearly as tissue samples in HIV or SIV infection. These authors also demonstrated an increase in enteric viruses in viremic macaques, including altered bacteriophages, which could be a potential mechanism underlying altered microbiome in HIV infection, and should be researched further. Another recent study demonstrated shifts in the oral fungal microbiota in ART-treated, HIV-infected individuals characterized by increased Candida colonization, which may cause infection [87**]. Studies examining potential dysbiosis of fungal or Archaeal communities in the gut of HIV-infected individuals are lacking and warrant investigation. Further, given the unclear mechanisms underlying dysbiosis, the interactions between bacteria, viruses, fungi and Archaea should be better elucidated in order to develop a complete understanding of the nature of HIV-induced dysbiosis.

Microbial dysbiosis in immunity and inflammation

The alterations to the microbiome in HIV infection have also been demonstrated to result in direct effects on immunity and increased inflammation (summarized in Figure 1). Vujkovic-Cvijin et al. demonstrated that enrichment of Proteobacteria and loss of Bacteroides in HIV infection results in increased adherent bacteria to the mucosal epithelium, which could be a mechanism for barrier damage, although this has not been directly demonstrated [38]. In addition, the authors of this study found that dysbiosis of the microbiome was associated with increased gut and peripheral T cell activation, and plasma inflammatory soluble factors, which have independently been found to be associated with HIV pathogenesis [38,88,89]. Furthermore, dysbiosis was associated with an increased Kynurenine:Tryptophan ratio (Kyn:Trp) and increased indoleamine-2,3-dioxygenase (IDO) activity, which were previously demonstrated to be associated with loss of mucosal IL-17 producing cells [90], also a pathogenic consequence of HIV infection [91-93].

Dillon et al. recently demonstrated that HIV-altered mucosal bacteria (HAMBs) are associated with inflammatory responses from immune cells. Here the authors found that increased abundance of Prevotella in HIV-infected individuals was associated with increased mucosal T cell and dendritic cell (DC) activation [44]. Furthermore, the co-culturing of HAMBs with colonic lamina propria mononuclear cells, including Prevotella copri and Prevotella stercore, directly stimulated activation of CD1c+ DCs, compared to bacteria lost in HIV including Rumminococcus bromii [94**]. This may affect HIV pathogenesis given that the authors also demonstrated DC activation in mucosal tissues was associated with increased mucosal viral load, increased mucosal and systemic T cell activation, and increased plasma and mucosal cytokine production, including several cytokines associated with mortality in HIV infection IL-6, TNFα, IL-10, IL-1β, and IFNγ [94**]. Thus, there is a clear relationship between microbial dysbiosis on immunity and
inflammation in HIV infection, and preventing or reversing this altered GI microbiome in HIV infection may result in beneficial effects on immunity. However, whether altered immunity after HIV infection drives dysbiosis or vice versa is unclear, and cause and effect of microbe dysregulation relative to immune dysfunction needs to be clarified.

Another role of the microbiome in HIV that is not as clear is the ability of the microbiome to drive IgA responses. It is well established that secretory IgA in the lamina propria is essential for proper management and containment of intestinal microbiota [95]. Indeed, IgA in mucosal tissues can act to protect from pathogens, block microbe-epithelium interactions, clear microbes from lamina propria if translocated, and can itself act to shape the microbiota [95-97]. Given the loss of CD4+ T cells, and specifically T follicular helper (Tfh) cells which induce class switching of B cells, during HIV infection, a potential mechanism underlying altered microbiome could be loss of IgA control in mucosa, but these mechanisms have not been clearly defined. Of interest, recent studies have demonstrated that there is a dual specificity of IgA for the microbiome and HIV [98**,99]. Thus, altered IgA responses in the presence of HIV infection could be an underlying mechanism of microbiome dysbiosis or lack of immune control of the microbiota. Interestingly, a link between IgA and neutrophil responses has recently been demonstrated whereby neutrophils negatively regulated mucosal IgA after vaccination [100**]. Given the accumulation of neutrophils during HIV infection the interactions between neutrophils and IgA depletion in this context may be a novel avenue of exploration.

**Therapeutic approaches to improve microbiome and microbial translocation in HIV infection**

Novel therapies to restore the microbiome and repair damage to the GI epithelial barrier can improve mucosal function and may reduce morbidity and mortality in ART-treated HIV-infected individuals. Oral administration of beneficial microbes in the form of probiotic supplements has attracted attention as a method to enhance mucosal function by increasing mucus production, preventing apoptosis, or stabilizing tight junctions [101]. In a recent study, intake of a probiotic containing several *Lactobacillus*, *Bifidobacterium*, and *Streptococcus* spp. significantly reduced CD4+ and CD8+ T cell activation and plasma concentrations of high-sensitivity C-reactive protein, a biomarker associated with cardiovascular disease risk, in ART treated HIV-infected adults [102**]. Interestingly, these patients also reported fewer episodes of diarrhea and constipation. However, plasma concentrations of sCD14, a biomarker of MT, did not decrease after sustained probiotic intake [102**]. Another study demonstrated that intake of a probiotic yeast, *Saccharomyces boulardii*, reduced plasma concentrations of LBP and IL-6 in ART-treated HIV-infected individuals [103*]. Similarly, intake of prebiotic oligosaccharides significantly increased populations of beneficial *Bifidobacterium* spp., reduced plasma concentrations of sCD14, and reduced CD4+ T cell activation in a cohort of untreated HIV-infected individuals [104]. Probiotic therapy in SIV-infected non-human primates treated with ART results in multiple benefits to mucosal immunity including increased mucosal CD4+ T cell frequency and functionality, which was attributed to decreased fibrosis in the GI tract [70]. In addition, the authors observed improved functionality of antigen presenting cells (APCs) without overt
DC activation, suggesting that innate immunity can also be enhanced by probiotic supplementation [70]. In a follow up study, ART-treated SIV-infected macaques were given a combination of probiotics and IL-21, which also improved frequencies of Th17 cells, potentially due to an observed decrease in Kyn:Trp ratios and decreased IDO activity in plasma [105**].

The drug sevelamer, which sequesters bacterial LPS, has been shown to reduce plasma concentrations of LPS and sCD14 while also decreasing immune activation when administered to macaques during acute SIV infection [106*]. Administration of sevelamer did not reduce plasma LPS concentrations in patients in the chronic stage of HIV infection, but did produce potential cardiovascular benefits [107*]. Similarly, treatment of HIV-infected individuals with hyperimmune bovine colostrum containing anti-LPS antibodies did not reduce plasma LPS concentrations [108]. In SIV-infected macaques, blockade of the immune inhibitory receptor programmed death-1 (PD-1), which plays a critical role in determining the functionality of HIV-specific T cells, improved gut barrier function by increasing expression of tight junction proteins and reduced plasma LPS concentrations. Furthermore, PD-1 blockade enhanced immune responses against potentially pathogenic bacteria [109]. Together, these studies demonstrate that therapies designed to restore the structure and function of the microbiome and reduce microbial translocation can be effective for reducing inflammation in ART-treated HIV-infected individuals. However, further studies are needed to properly assess the efficacy of these approaches and need for combinational approaches, and whether restoration of the GI tract is even possible after the extensive damage that HIV induces in mucosal tissues rapidly after infection.

### Conclusion

It is clear that HIV infection results in damage to the GI mucosa and epithelium leading to translocation of microbes and microbial products into the lamina propria and systemic circulation and that these events are accompanied by dysbiosis of the GI-resident microbes. However, whether this dysbiosis is a cause or a symptom of immune dysregulation in HIV remains unclear. The intestinal microbiome is heavily regulated by the innate and adaptive arms of the immune system and the microbiota contribute to its maintenance [40]. Persistent activation of the immune system may lead to an inability of the host to properly regulate the microbiome. This, in turn, may result in microbial dysbiosis and outgrowth of potentially pathogenic bacteria, which creates an inflammatory cycle. Thus, in order to identify novel targets for therapeutic intervention, it is imperative to better understand the interplay between microbial community changes and mucosal dysfunction in HIV infection.

### Acknowledgments

Financial support and sponsorship: Personnel time and support provided by University of Washington (AZ, NK), CAPRISA (LM) and University of Manitoba (AB).

### References

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39*. Klase Z, Ortiz A, Delage C, Mudd JC, Schwartzman E, Klatt NR, Canary L, Estes JD, Brenchley JM. Dysbiotic bacteria translocate in progressive SIV infection. Mucosal Immunol. 2015 • The authors find that the bacteria which translocate during SIV infection in macaques is predominantly Proteobacteria, which is also associated with dysbiosis of the microbiome in HIV infection.


69*. Perez-Santiago J, Gianella S, Massanella M, Spina CA, Karris MY, Var SR, Patel D, Jordan PS, Young JA, Little SJ, et al. Gut Lactobacillales are associated with higher CD4 and less microbial translocation during HIV infection. AIDS. 2013; 27:1921–1931. • The authors find that levels of Lactobacillales in anal swabs of HIV-infected individuals associated with decreased microbial translocation, higher CD4+ T cell levels and decreased viral load prior to ART. [PubMed: 24180001]


   • The authors characterized the fungal mycobiome in HIV infected vs uninfected individuals and found that the oral mycobiome was altered after HIV infection, and dominated in both groups by Candida species. [PubMed: 24626467]


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Key Points

- HIV infection is associated with persistent inflammation caused by translocation of microbes and/or microbial products from the GI lumen to the lamina propria and circulation; this process remains elevated even with successful antiretroviral treatment.

- HIV is also associated with bacterial dysbiosis characterized by reduced abundances of beneficial bacteria and increased abundances of potentially inflammatory bacteria.

- Both bacterial dysbiosis and translocation have been linked to altered immune function and/or persistent inflammation, and are likely causative contributors.

- Novel therapies to restore gut ecology and function are necessary to reduce inflammation and improve prognosis of ART-treated HIV-infected individuals.
Figure 1.
Microbial dysbiosis in HIV is characterized by decreased abundances of *Bacteroides*, *Lactobacillus*, and beneficial Clostridia with increased abundances of *Prevotella* and pathogenic Proteobacteria, increasing T cell and DC activation. Loss of secretory IgA may help to explain the outgrowth of pathogenic bacteria. Increased neutrophil and macrophage accumulation in the LP, bacterial activity in the mucosa, and other mechanisms destabilize the mucosa and GI epithelium, leading to MT and further accumulation of inflammatory microbial products and cytokines in circulation. Together, these mechanisms perpetuate an inflammatory cycle that leads to chronic immune activation in ART treated HIV-infected individuals.
Table 1
Bacteria altered in HIV infection and potential role on health and disease progression

<table>
<thead>
<tr>
<th>Genus</th>
<th>Compounds produced</th>
<th>Potential Role(s) in HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Prevotella</em> [44,45] (P. copri)</td>
<td>SCFAs</td>
<td>Increase activation of myeloid dendritic cells [53*]</td>
</tr>
<tr>
<td><em>Pseudomonas</em> [38,54] (P. aeruginosa)</td>
<td>Acetate, Lactate, NO₂ [55]</td>
<td>Potential opportunistic pathogen [56], mucolytic [57]</td>
</tr>
<tr>
<td><em>Desalvibrio</em> [45] (D. piger)</td>
<td>H₂S [58]</td>
<td>Colonic inflammation [58]</td>
</tr>
<tr>
<td><em>Acinetobacter</em> [44**] (A. baumannii)</td>
<td>LPS, α-ketoglutarate [59]</td>
<td>Can recruit neutrophils by induction of IL-8 production † [60]</td>
</tr>
<tr>
<td><em>Campylobacter</em> [46**] (C. jejuni)</td>
<td>Enterotoxin, Cytotoxin [61]</td>
<td>Induces mucosal inflammation [62]</td>
</tr>
<tr>
<td><em>Ruminococcus</em> [45] (R. productus)</td>
<td>Soluble oligosaccharides, SCFAS [63]</td>
<td>Mucolytic, Proinflammatory [64]</td>
</tr>
<tr>
<td><em>Escherichia</em> [46**] (E. coli)</td>
<td>Indole derivatives [65]</td>
<td>Mucolytic [57], Increase HIV replication [66]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genus</th>
<th>Compounds produced</th>
<th>Potential Role(s) in HIV</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteroides</em> [44**-46] (B. fragilis)</td>
<td>PSA, SCFAs</td>
<td>Mucolytic [64], induces IL-10 production, protects against inflammation, increases proportion of memory CD4+ T cells † [67,68]</td>
</tr>
<tr>
<td><em>Lactobacillus</em> [54] (L. acidophilus)</td>
<td>Lactate, B, K Vitamins</td>
<td>Support health, increase colonic CD4+ T cells [69*,70]</td>
</tr>
<tr>
<td><em>Bifidobacterium</em> [54] (B. breve)</td>
<td>Lactate, B, K Vitamins [71]</td>
<td>Support health</td>
</tr>
<tr>
<td><em>Eubacterium</em> [47] (E. rectale)</td>
<td>Butyrate, other SCFAs [65,72]</td>
<td>Support colonic health</td>
</tr>
<tr>
<td><em>Coprococcus</em> [44***,46***,47] (C. etactus)</td>
<td>Butyrate, other SCFAs [72]</td>
<td>Support colonic health</td>
</tr>
<tr>
<td><em>Blautia</em> [44***,46***,47] (B. hydrogenotrophicus)</td>
<td>Acetate [73]</td>
<td>Support colonic health</td>
</tr>
<tr>
<td><em>Ruminococcus</em> [46,47] (R. productus)</td>
<td>Soluble oligosaccharides, SCFAS [63]</td>
<td>Mucolytic, Proinflammatory [64]</td>
</tr>
</tbody>
</table>

* Shown in vitro
† Shown in murine models

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