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# Gut Mucosal Barrier Dysfunction, Microbial Dysbiosis, and Their Role in HIV-1 Disease Progression

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Distinct pathological events occur within the gastrointestinal (GI) tract of Asian macaques with progressive simian immunodeficiency virus (SIV) infection and humans with human immunodeficiency virus type 1 (HIV-1) infection that are critical in shaping disease course. These events include depletion and functional alteration of GI-resident $CD4^+$ T cells, loss of antigen-presenting cells, loss of innate lymphocytes, and possible alterations to the composition of the gut microbiota. These contribute to structural damage to the GI tract and systemic translocation of GI tract microbial products. These translocated microbial products directly stimulate the immune system, and there is now overwhelming evidence that this drives chronic immune activation in HIV-1 and SIV infection. While combined antiretroviral therapy (cART) in HIV-1–infected subjects generally allows for immune reconstitution in peripheral blood, reconstitution of the GI tract occurs at a much slower pace, and both immunological and structural abnormalities persist in the GI tract. Importantly, studies of large cohorts of individuals have linked suboptimal GI reconstitution to residual inflammation and heightened morbidities in HIV-1–infected cART recipients. As a result, current era treatments aimed at augmenting restoration of the GI tract hold promise in returning cART recipients to full health.

**Keywords.** HIV-1 pathogenesis; gastrointestinal tract; microbiome; Th17; cART; residual inflammation; probiotics.

Human immunodeficiency virus type 1 (HIV-1) and simian immunodeficiency virus (SIV) preferentially target and kill $CD4^+$ leukocytes. Thus, it is not surprising that loss of $CD4^+$ T cells and eventual development of AIDS are hallmarks of the infection [1–3]. However, viral replication within $CD4^+$ T cells does not encompass the entire breadth of disease pathogenesis, given that immunological abnormalities in HIV-1 and SIV infection extend well beyond the $CD4^+$ T-cell compartment and the pathology of HIV-1 infection is not completely reversed upon combined antiretroviral therapy (cART) administration [4]. Indeed, the pathogenesis of HIV-1 infection is multifaceted, and it is now widely accepted that chronic immune activation drives disease pathogenesis [1, 4]. Understanding the determinants of HIV-1-associated inflammation is an important step in mitigating some of the barriers that prevent HIV-1–infected subjects from returning fully to health.

Damage to the gastrointestinal (GI) tract occurs early and irreversibly in progressive HIV-1 and SIV infections and is closely linked to systemic inflammation [5–8]. In health, the GI tract serves as an important structural and immunological barrier against the trillions of microbial cells within the GI tract and also provides a microenvironment for their survival and their largely beneficial interactions with the host. Here, we discuss the numerous alterations observed within the GI tract in both human and simian immunodeficiency lentiviral infections and discuss novel therapeutic strategies to reduce intestinal inflammation and restore GI tract anatomy and physiology.

## HEALTHY INTERACTIONS AMONG GUT COMMENSAL BACTERIA, INTESTINAL EPITHELIAL CELLS, AND IMMUNE CELLS

The GI tract is colonized by trillions of microorganisms, including bacteria, viruses, and fungi. Their interactions with the host, locally, are important in maintaining gut homeostasis [9–11]. In humans, large-scale metagenomic studies based predominantly on bacterial composition of the colonic (or fecal) biota suggest that the intestinal microbiota is enormously diverse and shaped by a number of host-genetic and environmental factors. While interindividual variation in the gut microbiome is apparent at the genus and species level, composition at the phylum level is relatively consistent among individuals. In healthy adults, gram-negative Bacteroidetes and gram-positive Firmicutes constitute a large majority of the colonic biota, with Proteobacteria, Tenericutes, and Fusobacteria represented with lower abundance [12].

Commensal bacteria of the gut are separated from the host by a single layer of epithelial cells, forming a barrier that is both physical and chemical in nature. This is accomplished in part by E-cadherin and claudins, which reinforce barrier integrity by forming tight junctions between epithelial cells [13]. Additionally, the mucosal layer of the gut separates the host from luminal bacteria through the action of antimicrobial peptides such as defensins, while also providing a nutrient-rich source to promote commensal bacteria colonization [13].

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Gut barrier integrity is further maintained by specialized lymphocyte subsets that reside within GI tract tissues. Epithelial cells within the GI tract express receptors for the cytokines interleukin 17 (IL-17) and interleukin 22 (IL-22). $CD4^+$, $CD8^+$, and innate lymphoid subsets residing within the lamina propria of the gut are important sources of these cytokines [14–16], and they promote gut integrity through induction of epithelial cell proliferation and inducing expression of claudins, defensins, and mucin [16, 17]. Taken together, the net effect of these interactions among epithelial cells, immune cells, and the gut commensal microbiota promote a healthy GI tract.

## IMMUNOLOGICAL DAMAGE TO THE GI TRACT IN HIV-1 INFECTION

Damage to the gut occurs very early after viral acquisition and is a sentinel manifestation of HIV-1 pathology. There is now overwhelming evidence that $CD4^+$ T cells in the GI tract are lost disproportionately when compared to $CD4^+$ T cells in peripheral blood and lymphoid tissues of humans with acute HIV-1 infection and Asian macaques with acute SIV infection [5, 18, 19]. The mechanisms underlying this loss are likely multifactorial, but it is thought that direct viral replication plays a significant role [20]. Unlike $CD4^+$ T cells in peripheral blood, the majority of gut-resident $CD4^+$ T cells possess an effector memory phenotype and express high levels of the HIV-1 coreceptor CCR5 [5]. Indeed, several studies in SIV-infected rhesus macaques have shown that CCR5-expressing $CD4^+$ T cells are almost completely lost in the GI tract, and in situ hybridization has shown significant viral replication in the lamina propria of rhesus macaques with acute SIV infection [5, 19]. While a large majority of gut-resident $CD4^+$ T cells are lost by direct viral cytopathic effects, some $CD4^+$ T cells in the gut go on to become latently infected. Careful kinetic studies in hosts with progressive SIV infection have found abundant levels of SIV DNA in GI tissues as early as 3 days after infection [21, 22]. Importantly, the initial detection of viral DNA in gut tissues occurs within the eclipse phase of the SIV disease course and precedes systemic viremia.

While profound loss of $CD4^+$ T cells in gut tissues is a salient event of the HIV-1 disease course, it is important to point out that these events alone cannot fully explain progression to AIDS or the broad dysfunction that exists in the GI tract. During nonprogressive SIV infection of natural hosts, moderate $CD4^+$ T-cell depletion also occurs yet does not result in disease progression [23]. Furthermore, uninfected humans with idiopathic $CD4^+$ lymphopenia exhibit very low numbers of $CD4^+$ T cells in the GI tract without any evidence of systemic inflammation [24], indicating that there are other pathological phenomena that must contribute to HIV-1 pathogenesis.

Dysfunction that occurs within the GI tract during HIV-1 infection and progressive SIV infection is also associated with a number of functional alterations in resident leukocytes. Cells expressing IL-17 and/or IL-22 are significantly depleted from the GI tract and mesenteric lymph nodes as early as 10–14 days after infection and remain so throughout disease course [25, 26]. Importantly, only administration of cART during very early stages of acute HIV-1 infection is sufficient to restore frequencies of IL-17–producing cells in the GI tract [25, 27]. Given the importance of IL-17/IL-22–producing cells on GI barrier maintenance, a number of groups have hypothesized that a preferential depletion of these cells underlies gut barrier dysfunction in HIV-1 infection and progressive SIV infection [28–30]. While $CD4^+$ T cells in the GI tract, termed T-helper type 17 (Th17) cells, are a predominant source of IL-17 in the gut, and while these cells are preferentially lost from the overall $CD4^+$ T-cell pool, other groups of leukocytes are capable of producing IL-17 and IL-22 in the gut, and functional defects exist in these subsets as well during HIV-1 infection and progressive SIV infection. Considerable interest has recently been given to innate lymphoid cells (ILCs), particularly the ILC type 3 (ILC3) subset that provides an innate source of IL-17. Initial reports in SIV-infected rhesus macaques have found that ILC3s are depleted proportionally in gut tissues very early in the disease course and remain so throughout the chronic phase [31, 32]. Reports in HIV-1–infected humans have supported these findings, as early and sustained ILC depletion in blood has also been observed [33]. In addition, IL-17–producing $CD8^+$ mucosal-associated invariant T (MAIT) cells, which uniformly express the semi-invariant Vα7.2 T-cell receptor, follow similar dynamics of early and nonreversible loss in SIV/HIV-1-infected subjects [34, 35], implicating a dysfunction of IL-17–producing leukocytes well beyond the Th17 subset in HIV-1 infection.

Given that the loss of IL-17–producing gut leukocytes is linked to GI damage, the mechanisms underlying the loss of these cells are thus of considerable interest. The surface chemokine receptor CCR6 marks Th17 polarization, and some studies have noted a preferential infection of the CCR6-expressing $CD4^+$ T cells in vitro [28, 30]. Yet it is likely that characterizing Th17 cells on the basis of this phenotype overestimates Th17 cell frequency in comparison to functional Th17 assessment. Indeed, we have previously mitogenically stimulated $CD4^+$ T cells from SIV-infected rhesus macaques and flow cytometrically sorted Th1 and Th17 cells to determine levels of SIV DNA and found equal frequencies of SIV infection among Th1 and Th17 cells [36], indicating that preferential infection of Th17 cells may not occur systemically in vivo.

Intriguingly, ILC3s and MAIT cells do not express HIV-1 receptors and are not permissive to SIV or HIV-1 infection, yet they are depleted concurrently with Th17 cells in HIV-1 or SIV infection [32, 34]. Precise mechanisms behind the loss of these cells are just beginning to be explored, although inflammatory mediators may play a role, as a recent report in humanized-mouse models of HIV-1 infection have implicated interferon α as a potential determinant of ILC3 loss in this setting [37]. Additionally, several groups have investigated cell

types that are known to maintain IL-17–producing cells, such as gut-resident dendritic cells (DCs), and have found that they too are altered both functionally and proportionally in SIV or HIV-1 infection. The enzyme indoleamine 2,3-dioxegenase 1 (IDO1) catabolizes the amino acid tryptophan and suppresses T-cell function in a number of disease states [38, 39]. IDO also suppresses Th17 cell function in vitro, and in HIV-1 infection upregulation of IDO activity in DCs is associated with lower frequencies of Th17 cells [39]. Moreover, we have shown in SIV-infected rhesus macaques that increased IDO activity is associated with loss of $CD103^+$ DCs in the gut, which are a source of factors important for Th17 polarization [16]. Taken together, alterations in the landscape of gut-resident APCs may also be important in IL-17–producing cell dysfunction during HIV-1 or SIV infection.

## STRUCTURAL DAMAGE TO THE GI TRACT IN HIV-1 INFECTION

Both inflammation and immunological abnormalities that occur in the gut during the HIV-1 or SIV disease course are tightly linked to structural damage to the GI tract. Even in the early days of the HIV-1 epidemic, several structural abnormalities were observed at the tissue level in the GI tract of subjects with chronic HIV-1 infection, such as focal epithelial cell degeneration, malabsorption, and crypt hyperplasia [40]. As histological techniques have advanced, several groups have corroborated these findings at the cellular level, observing massive enterocyte apoptosis, decreased expression of tight junction proteins, and increased intestinal permeability in both chronic HIV-1 and SIV infection [7, 26, 41]. The net effect of these abnormalities results in focal breaches to the gut epithelial barrier, and this is associated directly with the degree of microbial translocation both locally and systemically (discussed below) [42, 43].

HIV-1 and SIV-associated structural damage that occurs to the gut is likely due to a variety of mechanisms. As barrier integrity of the GI epithelium is progressively compromised, sterile anatomical niches of the gut become exposed to lumenal bacterial products. Translocation of bacterial products regulate inflammatory processes locally within the gut, and it is believed that inflammation is, at least in part, a key initiator of GI barrier dysfunction in HIV-1 and SIV infection. Indeed, levels of transcripts encoding inflammatory cytokines such as tumor necrosis factor (TNF), interleukin 6 (IL-6), interleukin 10, and interferon γ (IFN-γ) are significantly elevated in the colonic mucosa of HIV-1–infected patients and remain so after suppressive cART [44]. Additionally, given that the amount of damage to the GI tract in HIV-1 and SIV infection is inversely related to frequencies of IL-17–producing lymphocytes in the gut [16], it is also likely that, after initial inflammatory processes occur, damage is further perpetuated by alterations in lymphocyte subsets involved in maintenance and repair of the GI tract.

## CONSEQUENCES OF GI BARRIER DYSFUNCTION IN HIV-1 AND SIV INFECTIONS

Immunological and structural damage to the GI tract promote translocation of commensal bacteria locally and systemically. In both HIV-1 and progressive SIV infection, focal breaches of the epithelial barrier can be found in spatial juxtaposition to infiltrating microbial products in vivo [7, 42]. There is overwhelming evidence of persistent endotoxemia during chronic HIV-1 and SIV infection. Since the first description of this phenomenon in 2006 [6], >50 groups have corroborated the existence of microbial products in plasma from HIV-1-infected humans and Asian macaques with progressively SIV infection [2, 22]. Importantly, there is clear indication that these microbial products are bioactive in vivo and exacerbate immune activation. For example, monocyte subsets that directly respond to microbial products through Toll-like receptors (TLRs) are systemically activated in HIV-1-infected humans and SIV-infected Asian macaques [45, 46], and while microbial products may stimulate the adaptive immune system more indirectly, higher levels of lipopolysaccharide (LPS) have been linked with elevated indices of immune activation on $CD8^+$ T cells in HIV-1-infected subjects [2, 6].

While it is clear that translocated microbial products contribute to HIV-1-associated immune activation, the degree to which they contribute is less certain. Because HIV-1 and SIV replication alone each induce inflammation and chronic immune stimulation, researchers have turned to settings that uncouple these factors, to assess how GI damage and resulting microbial translocation independently influence HIV-1 and SIV disease pathology. This has been highlighted recently in work by Hao et al, in which gut damage induced by dextran-sodium sulfate administration to healthy, SIV-uninfected, rhesus macaques recapitulated many pathologic features of HIV-1 and SIV infection [47]. Given that microbial translocation in patients with inflammatory bowel diseases is also associated with systemic inflammation and immune activation [48, 49], these data provide evidence that microbial translocation independently contributes to HIV-1 and SIV disease pathology.

The degree to which microbial translocation, as opposed to HIV-1 and SIV replication, influences immune activation can be further understood in HIV-1–infected cART recipients. In the current era of treatment, cART is highly successful at suppressing viremia to undetectable levels over prolonged periods [50]. Nevertheless, treated HIV-1–infected individuals exhibit higher incidences of non–AIDS-related morbidities and mortalities when compared to the general population. These morbidities include cardiovascular disease, cancer, osteoporosis, and neurocognitive dysfunction [4]. Importantly, several studies point to residual inflammation as an independent predictor of these morbidities [4]. Indeed, levels inflammatory proteins such as IL-6, C-reactive protein, and the coagulation marker D-dimer remain elevated in plasma of virally suppressed HIV-1-infected

subjects, and they are particularly elevated in a subset of patients who display suboptimal $CD4^+$ T-cell reconstitution in response to cART [51, 52].

As cART recipients are, for the most part, virally suppressed, it is important to consider mechanisms other than viral replication that may contribute to residual inflammation in treated HIV-1-infected subjects. Much effort has focused on assessing immune reconstitution in mucosal and lymphoid tissues after ART administration. Shortly after the first description of microbial translocation in HIV-1 and SIV infection, in 2006, it was found that significant $CD4^+$ T-cell depletion remained in the GI tract of cART-treated patients, some of whom had had virological suppression for up to 7 years [8]. Several follow-up studies have corroborated these results, and it is now known that despite immune reconstitution in peripheral blood, reconstitution of $CD4^+$ T cells in the GI tract occurs at a much slower pace [53, 54]. Defects in structural components of the GI tract persist as well in HIV-1–infected subjects who received long-term cART, as one study reported that expression of tight junction proteins remained significantly lower in colonic tissue of HIV-1–infected patients receiving cART [55]. Interestingly, these defects were not observed in the terminal ileum, indicating that cART may be more effective at reconstituting some anatomical sites of the GI tract than at others, with immunological improvements more pronounced in the duodenum as compared to the rectum [56]. While gut reconstitution may be compartmentalized, it remains clear that, overall, the GI tract of cART recipients does not completely normalize despite a general improvement in the health of these subjects. Moreover, GI damage, residual inflammation, microbial translocation, and non–AIDS-related morbidities all appear to be linked to one another. This link is most significantly illustrated in the findings of multiple groups, showing that levels of soluble CD14, a molecule cleaved from the cell surface of monocytes in response to activation by LPS, are elevated in plasma of HIV-1–infected cART recipients and predict earlier mortality [57–60]. These associations are also seen with surrogate plasma markers of gut epithelial integrity, such as zonulin-1 and intestinal fatty-acid binding protein, which independently predict mortality in cART recipients with a diagnosis of AIDS [58].

Exactly why reconstitution of the GI tract is suboptimal following cART is uncertain, although an altered immunological microenvironment in the GI tract that persists long after cART administration is likely a contributing factor. Indeed, levels of inflammatory cytokines such as TNF, IL-6, and IFN-γ remain elevated in gut tissues of cART recipients [44]. Local inflammation within the gut promotes collagen deposition and damage to the architecture of gut-associated lymphoid tissues (GALT) that support a large majority of GI tract–resident $CD4^+$ T cells [61]. Importantly, the degree of collagen deposition has shown to be inversely related to the extent of $CD4^+$ T-cell depletion in the GALT and of GALT $CD4^+$ T-cell reconstitution after cART [62]. While cART can successfully reconstitute $CD4^+$ T cells in the peripheral blood of many HIV-1–infected subjects, functional abnormalities in gut-resident $CD4^+$ T cells oftentimes persist as well, particularly in the Th17 cell subset [27, 55, 63]. Although the mechanisms are unclear, it appears that immunological abnormalities in the gut influence the size of the viral reservoir. $CD4^+$ T cells harboring viral DNA are enriched in gut tissues of HIV-1–infected cART recipients, compared with $CD4^+$ T cells in peripheral blood [64], and in SIV-infected rhesus macaques receiving ART regimens, functional defects in Th17 cells correlate inversely with levels of viral DNA in gut tissues of these animals [27], suggesting a link between residual GI dysfunction and persistence of the viral reservoir.

## DYSBIOSIS IN LENTIVIRAL IMMUNODEFICIENCY INFECTIONS

Diseases associated with GI inflammation are not limited to HIV-1 and SIV infection, as inflammatory bowel diseases have several similarities [65]. In these settings, significant shifts in the gut microflora composition (or dysbiosis) occur, and these are linked to inflammation [66]. Because chronic gut inflammation is also characteristic of HIV-1 and SIV infection, researchers have begun to examine whether dysbiosis occurs in HIV-1 and SIV infection and how this influences disease pathology. Indeed, significant dysbiosis is clearly evident in both the rectal and fecal biota of untreated HIV-1–infected subjects as compared to uninfected individuals [67–69]. While it is important to note that the composition of the microbiome is not uniform across the GI tract, significant dysbiosis is clearly evident in both the rectal and fecal biota of untreated HIV-1–infected subjects as compared to uninfected individuals [67–69]. Moreover, cART might alter the microbiota composition, but the resulting composition bears more resemblance to the microbiome of untreated HIV-1–infected subjects than that of healthy uninfected individuals [69, 70]. The microbiota of HIV-1–infected subjects are profoundly depleted of *Bacteroides* (which are associated with limiting inflammation) and enriched for Proteobacteria (which promote inflammation) [67–69]. While it is clear that the studies noted above have uncovered potential common features of HIV-1-associated dysbiosis, some inconsistencies exist, highlighting a growing need to identify non–HIV-1-related variables that may affect the microbiome. For example, contradictory findings have been reported in associations between HIV-1 serostatus and shifts in the fecal composition of the *Prevotella* genus. While some studies observed a significant enrichment of *Prevotella* in chronic HIV-1 infection [70, 71], these findings are contradicted by studies controlling for HIV-1 risk groups [67, 72]. Intriguingly, a recent report stratified sexual preference and studied the fecal microbial composition among HIV-1–infected and uninfected control subjects, finding that same-sex-attracted men had microbiomes

enriched for *Prevotella* [73]. Moreover, no specific signature of dysbiosis at the genera level was apparent in the HIV-1–infected group when controlling for sexual preference, with the only HIV-1-infected difference being decreased microbiome richness [74, 75]. In line with these findings, lower bacterial richness has reported to be more pronounced in immunological nonresponders displaying suboptimal $CD4^+$ T-cell reconstitution during cART [76].

Nonhuman primate SIV models of HIV-1 infection have allowed researchers to longitudinally assess the GI tract microbiome relative to SIV infection while also controlling for factors such as diet. In 3 initial reports, all animals infected with SIV progressed to AIDS, yet disease progression was not associated with any significant changes to composition of the bacterial flora [77–79]. While bacterial community composition may remain relatively stable during SIV infection, disease course may be associated with emergence of specific groups of bacteria, as bacterial families that frequently harbor enteropathogens are expanded in SIV-infected animals with low blood $CD4^+$ T-cell percentages [78]. Notably, these findings appear to be concordant with those from studies in HIV-1–infected humans, as well [80]. It is unclear why other aspects of microbial dysbiosis in HIV-1–infected infected humans are not recapitulated in nonhuman primate models of HIV-1 infection. However, it is clear that, in both species, HIV-1 and progressive SIV infection are associated with a significant increase in both abundance and diversity of the enteric virome [78]. In SIV-infected Asian macaques, those viruses that were expanded included potentially pathogenic adenoviruses, which were found to be in close proximity to lesions in the intestinal epithelium [78]. Separate studies in a cohort of HIV-1–infected Ugandan patients similarly found an expansion of the fecal virome [80], and this was particularly apparent in subjects with low peripheral $CD4^+$ T-cell counts and was independent of cART [80].

Unraveling the precise host-microbiota interactions that drive pathogenic features of HIV-1 and SIV infection has proved difficult to date, given that many microbial species of the gut are anaerobic and difficult to culture in vitro. Nevertheless, some researchers have used metagenomic approaches to uncover metabolic gene pathways enriched in gut microbial communities of HIV-1–infected subjects, with one study noting an increase in pathways involved in synthesis of molecules such as LPS [71]. We also have examined metabolic properties of the GI tract microbiome, finding that Proteobacteria, while constituting only a small component of the microbiome, are the most metabolically active and preferentially translocate in SIV-infected Asian macaques [81]. While these studies begin to shed light on the functional properties of potentially pathogenic bacteria, a better indication of the role of dysbiosis in HIV-1 and SIV pathogenesis has come from correlative studies that link dysbiosis to important features of HIV-1 and SIV disease progression. For example, 2 studies have found that the overall microbial composition in rectosigmoid biopsy specimens correlates directly with $CD4^+$ and $CD8^+$ T-cell activation in the blood and gut mucosa of HIV-1–infected subjects [67–69]. A greater and more reliable predictor of gut microbial health may be an overall measurement of species diversity, and 2 groups have found that decreased diversity is associated with low $CD4^+$ T-cell counts in HIV-1–infected subjects [76, 80]. Interestingly, 2 groups have reported that overall bacterial diversity in the stool of cART recipients is decreased when compared to both untreated HIV-1–infected and healthy control subjects [69, 70]. Given that up to 40% of ART recipients experience mild-to-severe diarrhea [82], these results raise the possibility that antiretroviral drugs alone may affect the gut microbiota. In line with this hypothesis, we have also seen that administration of ART is marked by transient dysbiosis in the stool of SIV-infected rhesus macaques [81]. Taken together, these studies outline the increasing importance of the microbiome in shaping HIV-1 pathogenesis and leave open the possibility of therapeutic strategies aimed at targeting the microbiome to improve the health of HIV-1–infected subjects.

## TREATMENTS

GI dysfunction and resultant inflammation clearly persist in HIV-1–infected subjects despite long-term suppressive cART. Importantly, when cART is given in the first 10–20 days after HIV-1 transmission, mucosal and systemic inflammation tend to be fully reversed (or prevented) [25, 83]. Because HIV-1 diagnosis and treatment at such early stages in the disease course is challenging, supplementation of cART with therapies aimed at augmenting gut mucosal reconstitution and reducing microbial translocation have been considered. Two studies have focused on interfering with translocating microbial products directly through administration of the LPS-sequestering, phosphate-binding drug sevelamer, and these have had conflicting results. While sevelamer drastically reduced indices of immune activation and inflammation systemically in untreated SIVagm-infected pigtail macaques [84], the drug had no effect on any of these parameters in cART-naive HIV-1–infected humans [85]. Other approaches to cART supplementation, one involving rifaximin, a nonabsorbable antibiotic that decreases microbial translocation in cirrhotics, and another involving mesalamine, an antiinflammatory drug used in treatment of inflammatory bowel disease, have yielded negligible improvements in inflammatory or immune parameters in treated HIV-1–infected subjects [86, 87]. It is notable that rifaximin treatment with the addition of sulfasalazine (an antiinflammatory agent) in pigtail macaques with acute SIV infection transiently reduced inflammation and coagulation markers [88], suggesting that combinatorial approaches blocking inflammation/microbial translocation could warrant more-promising results when compared to the monotherapy studies in HIV-1–infected humans noted above.

While the studies described have centered on blockade of microbial translocation, a therapeutic strategy gaining recent

attention has been dietary supplementation with probiotic bacteria. Probiotic bacteria are thought to confer benefit to the host via a variety of mechanisms, such as production of short-chain fatty acids and competition with potentially pathogenic bacteria, all of which promote an antiinflammatory state. Given the importance of the microbiome in gut homeostasis and that many immune abnormalities in the treatment era appear to be related to residual gut damage, a number of recent studies have investigated supplementation of cART with probiotics. Each of these studies found some reduction in indices of inflammation, coagulation, or immune activation associated with probiotics when compared to cART alone [89–91]. In related approaches, unique oligosaccharide mixtures thought to stimulate the growth of probiotic species (prebiotics) have been used alone or in combination with probiotic supplementation (synbiotics). In these studies, prebiotic or synbiotic therapy in HIV-1–infected subjects was associated with reductions in markers of inflammation and marginally significant increases in $CD4^+$ T-cell counts [92, 93]. Thus, most of these studies show that probiotic supplementation was associated with some degree of immunological improvement. It is important to note, however, that the mechanisms by which probiotics exert these effects are unclear. There is also some uncertainty as to which formulations of probiotic species are the most beneficial in HIV-1–infected cART recipients or whether the same probiotic or prebiotic mixtures would work for HIV-1–infected individuals across all demographic characteristics. Two of the most widely used probiotic formulations, Lactobacillus GG and VSL-3, were recently shown to confer an immunological benefit in SIV-infected Asian macaques receiving cART, reducing fibrosis of GI tract lymphoid follicles and reconstituting gut $CD4^+$ T cells to near healthy levels [79]. These results suggest that the largest effects of probiotic treatment may be within the GI tract itself and that some of the systemic benefits conferred by probiotics in the human studies noted above may be related to GI tract reconstitution. It is notable that all of these studies relied on relatively small sample sizes and thus will need to be confirmed within larger cohorts. Yet, given the relative safety of probiotics when compared to that of other therapies, these studies may warrant probiotics as promising supplements to cART in HIV-1–infected subjects.

Fecal microbiota transplantation (FMT), which involves the transfer of microbial flora from a recipient to a donor, has

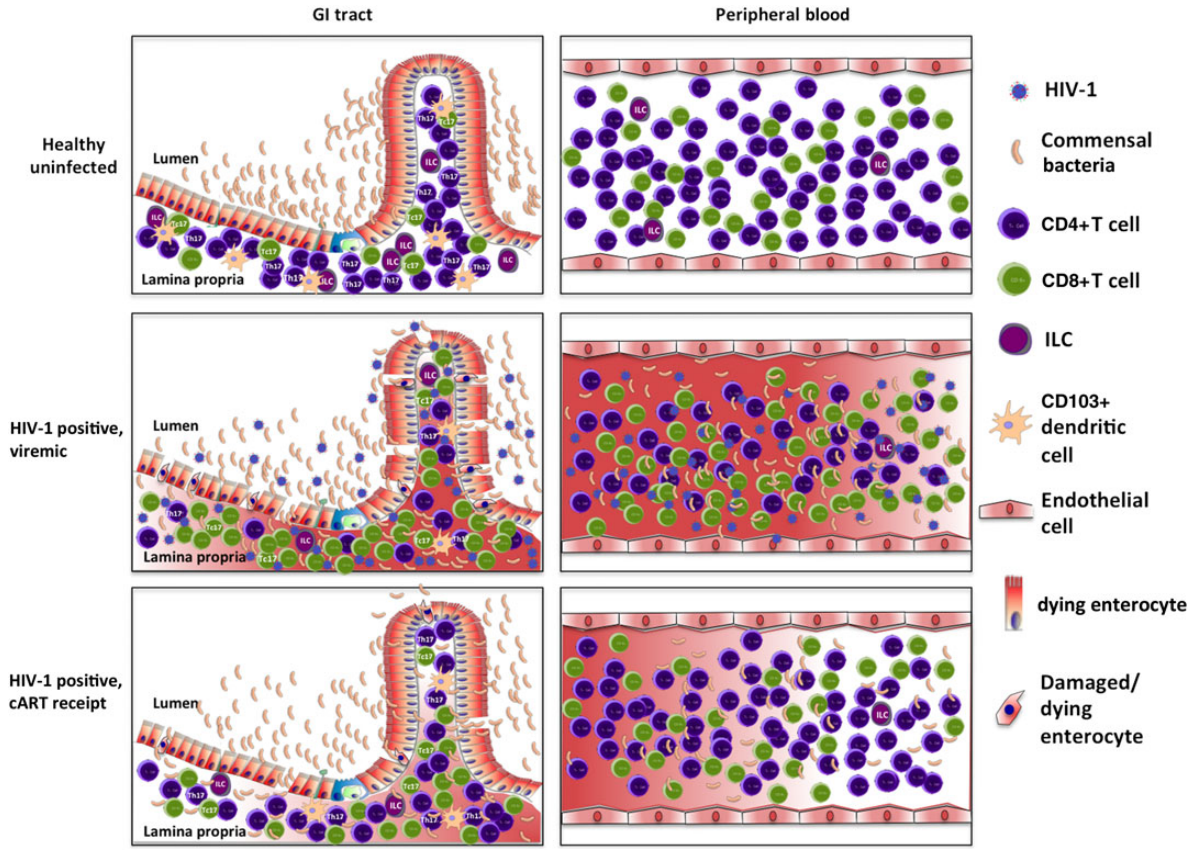


**Figure 1.** Gastrointestinal (GI) damage is not fully reversed during human immunodeficiency virus type 1 (HIV-1) infection, despite immune reconstitution in peripheral blood. Viral replication, chronic inflammation, and loss of interleukin 17 (IL-17)–producing cells (Th17/Tc17) cause irreparable damage to the GI tract, inducing the translocation of commensal microbes from the lumen into the systemic circulation. The GI microenvironment does not fully normalize with combined antiretroviral therapy (cART), despite apparent immune reconstitution in peripheral blood. Abbreviation: ILC, innate lymphoid cell.

recently been considered as a potential therapy in HIV-1–infected subjects. In comparison to probiotics, the fecal microbiota is more diverse and tailored to the colonic niche, thus having the potential to mediate more-durable effects. Indeed, a recent study found that a single transfer of donor microbial strains persisted within the recipient for up to 3 months [94]. One FMT trial is currently underway in HIV-1–infected cART recipients. While clinical end points have yet to be reported, FMT appeared to be safe and engraftment of donor microbial flora was seen in all 6 subjects enrolled in the study [95]. FMT has recently been performed in SIV-infected Asian macaques receiving cART [96]. Treatment was well tolerated and reduced indices of immune activation after FMT.

Last, several approaches have sought to boost immune reconstitution in HIV-1–infected cART recipients with exogenous homeostatic cytokines. For example, interleukin 21 (IL-21) is a pleiotropic cytokine that can promote gut homeostasis through enhancement of Th17 cell function. Recombinant IL-21 has recently been given to SIV-infected Asian macaques receiving cART, where it improved Th17 restoration and promoted more-effective reduction of immune activation in blood and gut mucosal tissues when compared to cART alone [97]. In line with a model whereby incomplete gut reconstitution can promote persistence of the HIV-1 reservoir, cART-recipient animals receiving IL-21 in this study also exhibited lower levels of proviral DNA in gut tissues [97], thus potentially providing a rational for clinical studies of IL-21 therapy in HIV-1–infected cART recipients. In other studies, encouraging results have been obtained with a separate homeostatic cytokine, interleukin 7 (IL-7), which is currently in phase 2 clinical trials in HIV-1–infected cART recipients [98]. IL-7 is important in promoting homeostatic division of naive T cells and enhancing T-cell homing to the gut. When compared to cART alone, IL-7 therapy achieved more-sustained $CD4^+$ T-cell restoration in the majority of participants [98]. Taken together, the novel therapeutic strategies outlined above may promote effective immune reconstitution by restoring structural and immunological components of the GI tract.

## CONCLUDING REMARKS

Structural and immunological damage to the GI tract have become salient features of HIV-1 and SIV disease (Figure 1). There have been significant strides in understanding the mechanisms underlying damage to the GI tract, although significant questions remain. These include the following: (1) how early after infection do these begin? (2) what mechanisms underlie microbial dysbiosis, and is this an important consideration for HIV-1-infected individuals? (3) are particular bacterial taxa actually mediating pathology in HIV-1 and SIV infection? and (4) will cART recipients benefit from therapies aimed at restoring GI tract health? The therapeutic strategies outlined above not only provide promising directions for research, but also underscore proof-of-principle observations that reconstitution of the gut mucosa will likely be important in returning HIV-1–infected subjects fully to health.

## Notes

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