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The Microbiome and HIV Persistence: Implications for Viral Remission and Cure

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Abstract

Purpose of review—This article discusses the interaction between HIV infection, the gut microbiome, inflammation and immune activation, and HIV reservoirs, along with interventions to target the microbiome and their implications for HIV remission and cure.

Recent findings—Most studies show that HIV-infected adults have a gut microbiome associated with decreased bacterial richness and diversity, and associated systemic inflammation and immune activation. A unique set of individuals, elite controllers, who spontaneously control HIV replication, have a similar microbiome to HIV-uninfected individuals. Conversely, exposure to maternal HIV in infants was shown to alter the gut microbiome, even in infants who escaped perinatal infection. Emerging research highlights the importance of the metabolomics and metaproteomics of the gut microbiome, which may have relevance for HIV remission and cure. Together, these studies illustrate the complexity of the relationship between HIV infection, the gut microbiome and its systemic effects.

Summary—Understanding the association of HIV with the microbiome, metabolome and metaproteome, may lead to novel therapies to decrease inflammation and immune activation, and impact HIV reservoir size and vaccine responses. Further research in this area is important to inform HIV remission and cure treatments.

Keywords

HIV/AIDS; gut microbiome; HIV persistence; remission; cure

INTRODUCTION

Life expectancy and health outcomes in persons infected with HIV have improved tremendously with the advent of combination antiretroviral therapy (ART) that controls HIV replication to clinically undetectable levels for years [1]. However, a cure for HIV remains elusive, largely due to the capacity of HIV to establish persistent, quiescent infection in long-lived cells (so-called “viral reservoirs”) in virtually all infected individuals. Latent HIV

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Conflicts of Interest

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infection cannot be targeted with current ART or HIV-specific immune responses, thereby precluding cure. The ability to identify the latent reservoir and target it for destruction, including with therapeutic HIV vaccinations, is crucial for the remission and cure of HIV [2**], as is understanding the processes that contribute to its persistence, such as inflammation and immune activation [3**].

The gut microbiome and its metabolites have been shown to promote inflammation and immune activation in HIV-infected adults, which in turn contributes to the persistence of HIV during ART [3**, 4, 5**]. This inflammation and immune activation is attributed to the disruption of gut mucosal integrity from the direct effects of HIV replication in the gut-associated lymphoid tissue (GALT), which persists even with years of long-term virologic control [6–8]. A number of microbiome studies in HIV-infected adults have found an association between gut dysbiosis, microbial translocation, and increased inflammation and immune activation, further suggesting that changes in the gut are crucial in the pathogenesis of HIV infection [9, 10]. HIV-infected adults treated with ART have a persistent HIV reservoir that is driven by inflammation and immune activation [11]. Infants who have been infected with HIV perinatally also have increased inflammation and immune activation [12*, 13*, 14], yet the contribution of persistent inflammation and immune activation to the maintenance of HIV reservoirs in pediatric populations is not defined. This current opinion piece will discuss the effects of HIV infection on gut dysbiosis, microbial translocation, inflammation and immune activation and HIV reservoirs across the age spectrum from infancy to adulthood, and in elite controllers, their effects on vaccine efficacy, and interventions targeting the microbiome with implications for HIV remission and cure.

The gut as an HIV reservoir

A reservoir for HIV can be defined as an anatomical site or cell type in which there is stable and persistent HIV infection that can produce replication-competent virus under permissive conditions. The gastrointestinal (GI) tract, the most concentrated site of CD4+ T cells in the body, is a vital site for early HIV replication and hence a likely reservoir [15]. Depletion of CD4+ T cells in the gut leads to loss of intestinal integrity, epithelial dysfunction, and loss of Th17 cells [16*]. Th17 cells are quintessential for gut homeostasis to maintain the epithelial barrier and prevent microbial antigens in the gut from entering systemic circulation [16*]. Impairment of the gut's tight junctions is a precursor to microbial translocation, the main driver of inflammation and immune activation [17].

Several studies have found that virally suppressed HIV-infected patients have persistent HIV infection in the gut-associated CD4+ memory T cells, with higher levels of HIV DNA in the gut compared to blood [8, 18], highlighting the importance of the gut as a viral reservoir. Initiating ART early in the course of infection significantly improves inflammation and immune activation and decreases the size of the reservoir, but does not eliminate the gut reservoir [19, 20]. Additionally, the GALT has been shown to refuel rebound viremia after ART discontinuation, providing evidence for the gut as a source of viremic rebound [21]. The role of the gut as a reservoir in perinatal infection is unknown, although the neonatal gut mucosa has been shown to be a compartment enriched for CD4+ CCR5+ T cells, compared with peripheral blood, which can be the prime targets for HIV replication [22].

Importantly, the seminal case of the Berlin patient, the only patient to date who was been cured of HIV as a result of an allogenic hematopoietic stem cell transplant from a donor with the CCR5 $\Delta 32$ deletion, was found to have low-level HIV DNA persisting in the rectum, five years following transplant [23], when other sites were negative. Together these studies emphasize the gut is a significant anatomic reservoir for HIV.

Other tissue reservoirs of HIV and the microbiome with implications for HIV remission and cure

The reproductive system represents potential HIV reservoirs, for which the microbiome influence antiretroviral drug metabolism. Both seminal and cervicovaginal fluid have detectable HIV despite undetectable plasma viremia with the use of ART, suggesting that a separate reservoir exists in the reproductive tract [24, 25]. The recent report of the effect of the vaginal microbiome on lowering antiretroviral drug concentrations in the vaginal tract highlight the importance of the microbiome on HIV treatment effects and viral persistence [26**]. Wong and Yukl (2016) review in detail the other tissues and organs that are potential HIV reservoirs [27].

HIV-associated gut dysbiosis, inflammation and immune activation

In recent years, a growing number of studies have investigated HIV-induced changes in the gut microbiome and its association with systemic inflammation and immune activation [28–30]. Most studies agree that individuals with HIV have distinct changes in the gut microbiome with a decrease in bacterial richness and diversity [16*, 29*, 31, 32]. The decrease in bacterial richness and diversity is consistent with other disease states that have alterations in the gut microbiome such as inflammatory bowel disease and diabetes [33, 34]. Most studies show an increase in *Prevotella* and a decrease in *Bacteroides* in HIV-infected adults compared to uninfected adults [10, 30, 31]. Indeed, some strains of *Prevotella* have been shown to enhance Th17-mediated mucosal inflammation and some strains of *Bacteroides* have been found to diminish pro-inflammatory cytokines [35, 36]. Paquin-Proulx *et al.* (2017) highlights a possibility that inflammation and immune activation can be attenuated with changes in the microbiome in HIV infection by showing that *Bacteroides* genus, which is generally decreased in HIV infection, is associated with the production of invariant natural killer T (iNKT) cells in GALT that decreases immune activation [37**]. Strategies that boost GALT iNKT by increasing *Bacteroides* may reduce persistent immune activation in HIV.

Microbiome studies between HIV-infected and uninfected adults have also found a spectrum of differences associated with HIV [31], identifying additional factors that affect the gut microbiome such as sexual preference [38], ART regimens [32, 39] and treatment status [40]. The findings in these studies are, however limited by the use of different methods of 16S rRNA sequencing analysis to characterize the microbiome and complicated by the presence of multiple factors in patients with HIV that can also influence the microbiome. These include antibiotic and drug use, co-infections and dietary preferences. These factors require consideration for future interventions aimed at manipulating the microbiome in HIV-infected individuals.

Elite controllers (EC) who spontaneously control HIV replication without ART, preserve CD4⁺ T cells in the gut mucosa [41], have lower levels of immune activation and smaller HIV reservoirs [42]. Vesterbacka *et al.* (2017) found that EC's have a richer gut microbiota with a distinct metabolic profile that resembles that of HIV-uninfected adults, and that is vastly unique from ART-treated HIV-infected individuals (Table 1) [43**]. The increased frequency of Th17 cells in the gut mucosa of EC's compared to ART-treated HIV-infected adults [48] may be responsible for their low levels of inflammation and seemingly "normal" gut microbiome. Understanding whether there is a direct interaction between the microbiome and reduced inflammation and immune activation and smaller reservoirs in ECs could inform pathogenesis and treatment of dysbiosis in HIV infection.

A major gap in knowledge in the field of the gut microbiome in perinatal HIV infection exists (Table 1). The gut microbiome plays a major role in the development of effective immune responses to routine childhood vaccines [49]. In a recent study, HIV-exposed and uninfected (HEU) Haitian infants showed a clear difference in their gut microbiome when compared to HIV-unexposed uninfected infants (HUU) (Table 1), highlighting the potential impact of HIV on the gut microbiome [44**]. This study demonstrated that the alterations in the gut microbiome were associated with human breast milk oligosaccharides, which differed by maternal HIV status [44**]. This is the first study to highlight the implications of infant exposure to maternal HIV infection on the infant's gut microbiome, even when the infant has escaped HIV infection.

Table 1 details results of microbiome studies done in populations of particular interest for understanding the gut microbiome and its role in HIV remission and cure [43**, 44**, 45–47].

Potential effects of the bacterial metabolome on HIV

More recently, studies have begun to suggest that the metabolites and proteins produced by gut bacteria may be more relevant than the gut bacteria themselves in the modulation of HIV-induced inflammation and immune activation [50**], which in turn may affect HIV reservoirs. In particular, short chain fatty acids such as propionate, butyrate and acetate are produced by gut microbiota as fermentation products of dietary carbohydrates [51]. Butyrate has been shown to reactivate latent HIV *in-vitro* through its effects of inhibiting histone deacetylase [52]. Acetate has also been shown to impair histone deacetylase activity and increase HIV viral integration into host DNA [53**]. Histone deacetylase inhibitors (HDACi) are being studied in HIV-infected adults as latency reversing agents as a way to eradicate the latent HIV reservoir [54]. To date, HDACi have been shown to upregulate HIV transcription but have not led to reductions in HIV reservoirs when added to standard ART [54].

Serrano-Villar *et al.* (2016) found that the metabolites and proteins produced by gut bacteria are closely associated with immune recovery in HIV-infected individuals [50**]. Bacteria from the *Succinivibrionaceae* family, which was enriched in immunologic responders, may have an anti-inflammatory effect by allowing the pro-inflammatory lipid mediator, leukotriene B₄ (LTB₄), to accumulate within gut bacteria itself instead of being released into the gut environment, thus mitigating inflammation in the intestine [50**]. Interestingly,

Serrano-Villar *et al.* (2017) found that butyrate production correlates with a decrease in monocyte activation and inflammation as measured by soluble CD14 and CRP [55**]. Dillon *et al.* (2017) also showed that exogenous butyrate, in the presence of *Prevotella stercorea*, suppressed immune activation and HIV-1 infection levels *in vitro* [56], suggesting that butyrate-producing-bacteria may reduce immune activation and HIV replication.

These studies suggest a complex interplay between gut bacteria, bacterial metabolome and metaproteome that requires further studies to aid with the management of inflammation and immune activation in HIV.

Impact of microbiome on vaccine responses

There is emerging evidence highlighting the interaction between the gut microbiome and vaccine efficacy, including to HIV vaccines. Of significance for HIV remission and cure, pilot studies of therapeutic HIV vaccines to aid with reservoir clearance are ongoing [2**]. In the RV144 trial of the canarypox vector HIV vaccine, a 31.2% efficacy for prevention of HIV was observed in a Thai population, where a lower concentration of IgG antibody binding to the variable regions 1 and 2 of HIV envelope proteins (Env) were identified as a protective correlate, suggesting that humoral responses might be critical for HIV vaccine efficacy [57**]. In a seminal study, Williams *et al.* (2015), demonstrated that HIV uninfected adults had pre-existing, cross-reactive antibodies to the gp41 subunit of Env that were induced by the gut microbiome, that in the context of a DNA prime vaccine (HIV DNA/rAd5 boost), led to induction of non-neutralizing gp41-reactive antibodies, thereby adversely affecting vaccine efficacy and vaccine response [58]. Han *et al.* (2017) studied the HIV DNA/rAd5 vaccine in adult and infant SIV-infected rhesus macaques (RM), confirming that the intestinal microbiota elicits cross-reacting antibodies to SIV antigens as early as within the first week of infection [59]. These early studies highlight the significance of the microbiome on vaccine-induced immunity.

The strongest evidence for the effects of the gut microbiome on vaccine efficacy is in the field of routine childhood immunization. Malnourished children and those living in areas of poor sanitation have markedly reduced responses to many oral childhood vaccines [60]. A recent study in Ghanaian infants showed that the infant gut microbiome composition correlates significantly with Rotavirus vaccine responses, with vaccine non-responders having increased abundance of several bacterial groups, mainly of the Bacteroidetes phylum including the *Bacteroides* and *Prevotella* genus [61**]. Interestingly, modifications to *Bacteroides* and *Prevotella* seem to be a dominant pattern of gut dysbiosis, as it is also altered in HIV-infected adults [10, 30, 31]. To date, there is no data on the gut microbiome in perinatal HIV infection, which is an important area of investigation. The interaction between the gut microbiota and vaccine responses, including HIV vaccines in infected individuals are unknown and requires further study.

Targeting the Microbiome for HIV Cure

Altering the gut microbiome to affect disease processes is a complex issue that has been attempted in several conditions, most notably in inflammatory bowel disease and *Clostridium difficile* colitis [62]. The general idea is to provide healthy bacteria in order to

reduce inflammation and immune activation, restore intestinal integrity and prevent microbial translocation. Presumably, by restoring the epithelial barrier, microbial translocation can be diminished, and systemic inflammation averted, which together may lead to a decrease in HIV reservoirs.

Several studies in HIV-infected adults have looked at the effects of prebiotics and probiotics on the gut microbiome and inflammation and generally found a decrease in T cell activation and mixed effects on inflammation [55**, 63, 64]. One of the main challenges in using probiotics as an adjunct to HIV treatment is that there are multiple factors affecting the microbiome in HIV, making it challenging to identify a probiotic that would be beneficial for therapy. These recent studies are only pilot studies and further studies are needed to validate the use of prebiotics and probiotics in patients infected with HIV.

Fecal microbiota transplant (FMT) is an emerging therapeutic strategy for the management of patients with *Clostridium difficile* colitis [65]. In one study of FMT from healthy adults to HIV-infected adults, complete engraftment of the donor's microbiome did not occur, nor was there any changes in systemic inflammation [66**]. The lack of change in the microbiome pre- and post- FMT is also seen in SIV-infected macaques [67]. However, in the transplanted macaques, an increase in Th17 and Th22 in the peripheral blood was found after FMT, as well as a reduction in CD4+ T cell activation in the intestinal tissue, suggesting that some protective changes may occur with FMT [67]. Further research is required in this field.

As briefly discussed above, the depletion of CD4+ T cells in HIV infection results in the loss of gut integrity and Th17 cells [16*]. In vitro studies show that HIV infection contributes to dysregulation of regulatory T cells and Th17 cells in the gut mucosa, which in turn may exacerbate inflammation and immune activation in HIV infection [68]. Anti-inflammatory therapeutic strategies using a small molecule (ABX464) to inhibit HIV replication and increase IL-22, a potent anti-inflammatory cytokine known to regulate tissue repair and gut mucosal injury, are being pursued as part of the HIV cure strategy to eliminate viral reservoirs (ABX464-005) [69].

Conclusion

Many areas of HIV research continue, including the search for a cure for HIV and identifying a clear relationship between HIV persistence and the gut microbiome. We have addressed some of the latest findings on the interaction of the gut microbiome with systemic inflammation and immune activation and viral persistence and treatment efforts underway to reduce HIV reservoirs, towards HIV remission and cure. It is clear that the microbiome or its byproducts (metabolome and metaproteome) are associated with inflammation and immune activation, and play important roles in vaccine responses, including to routine childhood vaccines and HIV vaccines. Ultimately, strategies that work as adjuncts to ART towards normalizing the microbiome to decrease inflammation and immune activation may impact HIV reservoir size (Figure 1).

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Key Points

1. HIV latency is established early in infection and cannot be abrogated by early treatment with ART. The inability of current treatment methods to target and deplete the latent reservoir is a major barrier to the cure of HIV.
2. The microbiome is implicated in inflammation and immune activation that enables HIV persistence.
3. While the precise pathogenesis of HIV infection and microbiome changes is unclear, normalizing and altering the microbiome in HIV may reduce inflammation to facilitate a decrease in reservoir size towards HIV remission and cure.
4. The effects of the microbiome on vaccine responses and reducing the size of the viral reservoir have important implications for HIV remission and cure.

Fig. 1.

This schema summarizes methods to restore the gut microbiome in HIV infection to reduce systemic inflammation and immune activation. The normalization of the microbiome through these methods may reduce the HIV reservoir size and improve HIV vaccine responses. Strategies that complement standard ART, including immunotherapeutics and latency reversing agents, may need to be incorporated to achieve HIV remission and cure.

Table 1

Populations of particular interest for understanding the microbiome and its role in HIV remission and cure.

Reference	Year	Location	Sample Size	Population of Interest	Comparison Group	Enriched	Depleted	Summary
HIV-Exposed, Uninfected (HEU) Infants								
Bender <i>et al.</i> [44]	2016	Haiti	25 HEU; 25 HIV-unexposed, uninfected (HUU)	HEU infants	HUU infants	Pseudomonadaceae Oxalobacterae Rhodobacteraceae Thermaceae Bacillaceae Corynebacteriaceae Chloroacidobacteria Alicyclobacillaceae Sphingomonadaceae Enterobacteriaceae	Prevotellaceae Alcaligenaceae Desulfovibrionaceae Tissierellaceae Bacteroidiaceae Paraprevotellaceae Porphyromonadaceae Campylobacteraceae Erysipelotrichaceae Gemellaceae Bacilli (class)	Maternal HIV infection is associated with changes in the microbiome of HEU infants. Human breast milk oligosaccharides differ in mothers depending on their HIV status, and is associated with bacterial species found in the infant's gut microbiome.
Perinatally HIV-Infected Infants								
No Existing Data								
Elite Controllers (EC)								
Vesterbacka <i>et al.</i> [43]	2017	Sweden	16 EC, 32 HIV-infected (HIV+) ART-naïve, 16 HIV-uninfected (HIV-)	EC adults	HIV+ ART naïve, HIV-	EC compared to ART naïve and HIV-; <i>Succinivibrio</i> <i>Sutterella</i> EC compared to ART naïve; <i>Rhizobium</i> <i>Deftia</i> <i>Anaerofilum</i> <i>Oscillospira</i>	EC compared to ART naïve; <i>Blautia</i> <i>Anaerostipes</i>	ECs have a richer gut microbiota than untreated HIV adults, and their microbiome is more similar to HIV-uninfected adults than untreated HIV adults.

Reference	Year	Location	Sample Size	Population of Interest	Comparison Group	Enriched	Depleted	Summary
Nowak <i>et al.</i> [45]	2015	Sweden	28 HIV+, 3 EC, 9 HIV-	EC adults	HIV+, HIV-	EC compared to HIV + Bacteroidetes[45]	EC compared to HIV+ Actinobacteria Proteobacteria	The microbiome of ECs is significantly different from viremic HIV+ individuals. ECs are more similar to healthy controls.
Acute HIV-Infected Adults								
Perez-Santiago <i>et al.</i> [46]	2013	USA	13 HIV+	Acute HIV + adults	Differences noted between those with low CD4% and high VL vs high CD4% and low VL. Compared before and after ART initiation.	Low CD4% compared to high CD4%: <i>Bacteroidales</i> <i>Clostridiales</i>	<i>Lactobacillales</i> <i>Enterobacteriales</i> <i>Pseudomonadales</i> <i>Xanthomonadales</i> <i>Aeromonadales</i> <i>Rhizobiales</i> <i>Neisseriales</i>	Higher <i>Lactobacillales</i> proportions were found to be associated with higher CD4% and lower viral loads before ART initiation, as compared to those with lower CD4% and high viral load.
Hoenigl <i>et al.</i> [47]	2016	USA	11 HIV+	Acute HIV + adults. ART initiated within 2 weeks of enrollment	No HIV- control	No data	No data	This study looked at the relationship between <i>Lactobacillales</i> and (1→3)-β-D-Glucan as a biomarker for microbial translocation. It did not measure other bacteria populations.