HIV-associated changes in the enteric microbial community: potential role in loss of homeostasis and development of systemic inflammation

REVIEW

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HIV-associated changes in the enteric microbial community: potential role in loss of homeostasis and development of systemic inflammation

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Purpose of review
Despite HIV therapy advances, average life expectancy in HIV-infected individuals on effective treatment is significantly decreased relative to uninfected persons, largely because of increased incidence of inflammation-related diseases, such as cardiovascular disease and renal dysfunction. The enteric microbial community could potentially cause this inflammation, as HIV-driven destruction of gastrointestinal $CD4^+$ T cells may disturb the microbiota–mucosal immune system balance, disrupting the stable gut microbiome and leading to further deleterious host outcomes.

Recent findings
Varied enteric microbiome changes have been reported during HIV infection, but unifying patterns have emerged. Community diversity is decreased, similar to pathologies such as inflammatory bowel disease, obesity, and *Clostridium difficile* infection. Many taxa frequently enriched in HIV-infected individuals, such as Enterobacteriaceae and Erysipelotrichaceae, have pathogenic potential, whereas depleted taxa, such as Bacteroidaceae and Ruminococcaceae, are more linked with anti-inflammatory properties and maintenance of gut homeostasis. The gut viral community in HIV has been found to contain a greater abundance of pathogenesis-associated *Adenoviridae* and *Anelloviridae*. These bacterial and viral changes correlate with increased systemic inflammatory markers, such as serum sCD14, sCD163, and IL-6.

Summary
Enteric microbial community changes may contribute to chronic HIV pathogenesis, but more investigation is necessary, especially in the developing world population with the greatest HIV burden (Video, Supplemental Digital Content 1, http://links.lww.com/COID/A15, which includes the authors' summary of the importance of the work).

Keywords
developing world, HIV, enteric, microbiome, systemic inflammation, virome

INTRODUCTION

The enteric 'microbiome' consists of a diverse collection of trillions of Bacteria, Archaea, Eukarya, and viruses [1–5], with a large aggregate genome, referred to as the 'metagenome', that contributes to normal immune development [6] and a number of pathological processes [7–9]. The host immune system acts as an essential curator for this luminal enteric microbial community, serving to shape and control the structure and function of this diverse collection of organisms [10–12]. HIV infection leads to the widespread destruction of host immune function [13,14], including the rapid and profound depletion of $CD4^+$ T cells within gut-associated lymphoid tissue [15,16]. As could be predicted from the loss of mucosal

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KEY POINTS

- HIV-driven destruction of gastrointestinal $CD4^+$ T cells may disturb the microbiota–mucosal immune system balance, disrupting the stable gut microbiome and leading to systemic inflammation and chronic HIV pathogenesis manifested as NCD such as CVD.
- Comparative enteric microbiota studies between HIV-infected individuals and uninfected controls have differed in methods and patient populations studied and found a wide spectrum of microbial community differences associated with HIV infection.
- Several overarching themes have emerged from HIV-enteric microbiome research, including decreased bacterial community diversity similar to that found in pathologies such as IBD, obesity, and *C. difficile* infection, increases in potential pathogens such as Enterobacteriaceae and Erysipelotrichaceae, decreases in commensals such as Bacteroidaceae and Ruminococcaceae, and increased systemic inflammatory markers, such as serum sCD14, sCD163, and IL-6.
- Enteric viral communities also have been found to be changed in HIV infection, with increased abundance of pathogenesis-associated *Adenoviridae* and *Anelloviridae*.
- Despite the disproportionate HIV disease burden in the developing world, the vast majority of HIV-enteric microbiome research has occurred in developed countries, potentially impeding the application of these findings to the population of greatest need.

immune cells, a wide range of changes in the enteric microbial community have been reported during HIV infection [17,18▪▪,19, 20▪,21▪▪,22▪,23▪▪,24▪–27▪, 28▪▪–32▪▪,33▪] (Fig. 1 and Table S1, http://links.lww.com/COID/A16). In light of the role of the enteric microbiome in many inflammation-associated pathologies such as diabetes, obesity, and inflammatory bowel disease (IBD) [7–9], it has been proposed that HIV-associated microbiome shifts could contribute to inflammation-related noncommunicable diseases (NCD) that are responsible for a large share of the increased mortality observed during chronic HIV infection [34–39]. Investigation of microbial changes associated with HIV infection has the potential to aid in the development of therapeutic interventions that could improve many of the pathologic consequences of chronic HIV infection.

CHRONIC SYSTEMIC IMMUNE ACTIVATION IN HIV INFECTION

Despite advancements in HIV antiretroviral therapy (ART), average life expectancy in HIV-infected individuals on effective treatment is 14% less than that of uninfected persons [35]. The ART Cohort Collaboration Study found that deaths were largely because of inflammation-related clinical diseases, such as stroke, long-bone fractures, cardiovascular disease (CVD), and renal dysfunction [34,35,37,38]. CVD, which constitutes a large proportion of HIV-associated NCD [40–42], is increased in HIV infection [43–45] and associated with systemic immune activation as measured by markers such as serum IL-6, sCD163, and C-reactive protein [46–51]. In HIV-uninfected individuals, microbiota-induced inflammation has been shown to drive CVD pathogenesis [52–55], suggesting that this disorder could occur in HIV as well.

Further supporting the connection between systemic inflammation and chronic pathogenesis, individuals with the highest degree of persistent elevated immune activation while on suppressive ART experience higher overall mortality, even with $CD4^+$ T-cell reconstitution more than 500 cells/μl [56,57]. Although systemic immune activation declines after initiation of ART, it remains persistently elevated in the majority of study participants even after years of therapy [58–60] and has also been observed in individuals with undetectable viral loads [61]. In a cohort of HIV-infected Ugandans, a 1.6-fold increased hazard of death was associated with each 10% increase in $CD8^+$ T-cell activation following initial viral suppression with ART [62].

POTENTIAL ROLE OF HIV-ASSOCIATED GUT MICROBIAL CHANGES IN HIV DISEASE PROGRESSION

HIV-associated changes to the enteric microbiome may lead to systemic inflammation by disrupting the balance of metabolic functions performed by the microbiota, such as short-chain fatty acid or bile acid metabolism [63], or causing increased translocation of bacterial products into the systemic circulation [64]. Elevated plasma kynurenine, a tryptophan metabolite, has been found to be associated with $CD8^+$ T-cell activation [65] and mortality [66] in HIV-infected individuals and HIV infection was associated with the presence of a gut microbial community with both the genetic capacity to metabolize tryptophan into kynurenine and demonstrable kynurenine production *in vitro* [21▪▪]. In a similar paradigm, independent of HIV, the enteric microbiome can drive CVD pathogenesis by transforming dietary constituents such as phosphatidylcholine and bile acids into reactive intermediates such as trimethylamine N-oxide that can lead to macrophage and platelet activation, thrombosis, and arterial plaque formation [67–71].

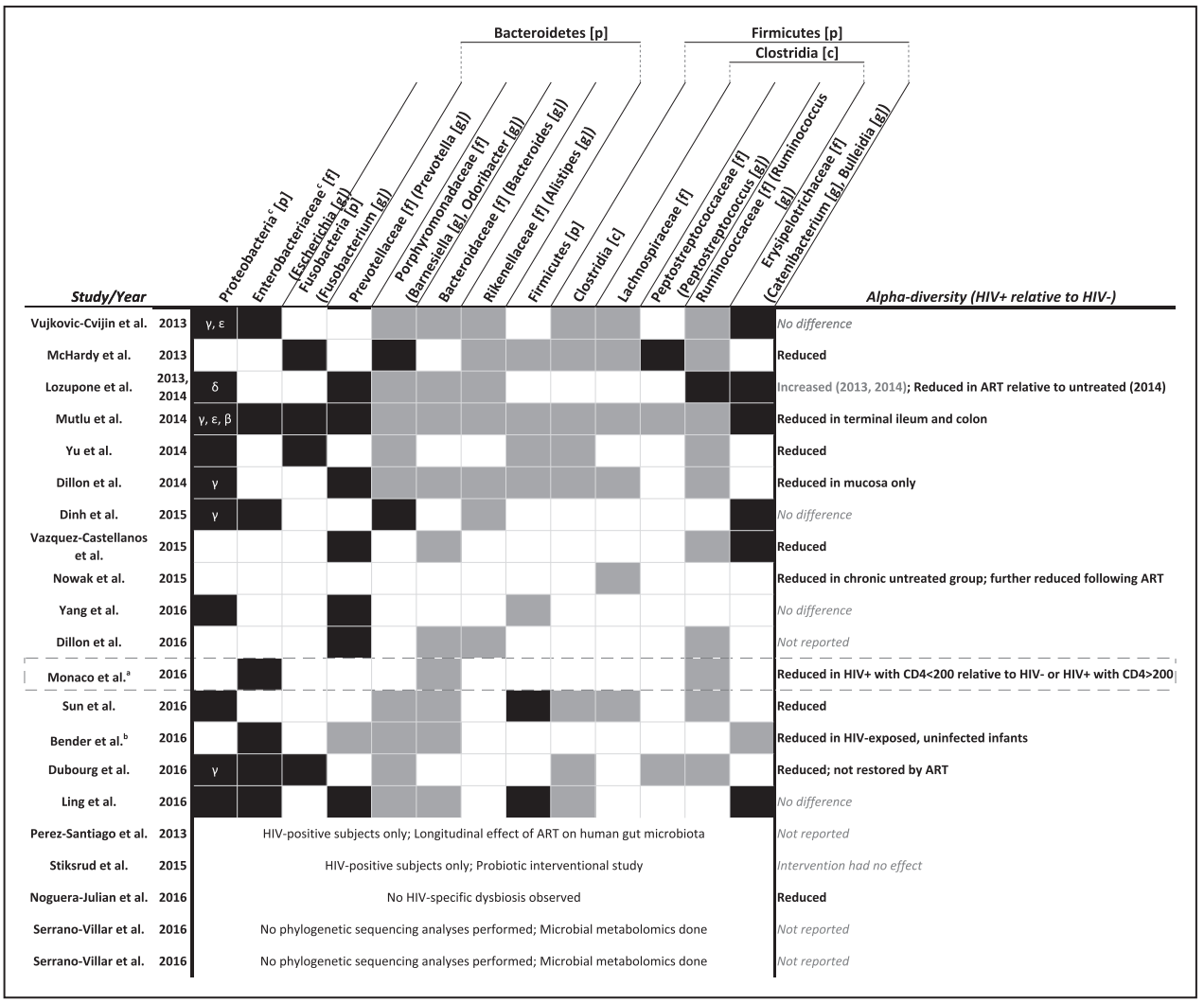


FIGURE 1. Alterations in the gut microbiota reported in HIV microbiome studies. Black and gray boxes, respectively, indicate reported increases and decreases in relative abundance. Bracketed letter indicates taxonomic level of classification (e.g., [p] indicates phylum), parenthetical taxa indicate subtaxa that commonly drive significance of parent taxa. [a]Dysbiosis observed in HIV-positive subjects with less than 200 $CD4^+$ T cells/μL. Black dashed box outlines the only study to date that investigated the relationship between gut microbiota and HIV in a sub-Saharan African cohort. [b]Fecal microbiome data only obtained for HIV seronegative unexposed and exposed infants. [c]Proteobacteria class indicated by corresponding Greek letter (e.g., β for Betaproteobacteria). Enterobacteriaceae are Gammaproteobacteria [c] within Proteobacteria [p]. ART, antiretroviral therapy.

Early in HIV infection the intestinal mucosa is a critical reservoir of viral replication and substantial $CD4^+$ T-cell depletion (80–90%) [72–80]. This depletion is attributed to the widespread surface expression of CCR5 on gastrointestinal T cells, which serves as the coreceptor for HIV entry early on in infection [13,72]. Because certain lymphocyte subsets are important to the maintenance of enteric epithelial integrity (e.g., IL-22-producing ILC3 and Th17 cells [12,81]), it is believed that such a loss of immune surveillance may result in impaired intestinal epithelial barrier function, increased gut permeability, and the translocation of gut bacterial products into systemic circulation [16,64]. These products could trigger persistent systemic immune activation and drive turnover of $CD4^+$ and $CD8^+$ T cells leading to clonal exhaustion and progressive impairment of T-cell function [82]. HIV-associated chronic systemic immune activation, secondary to a loss of gut epithelial homeostasis, may then lead to disease progression in both treated and untreated HIV infection. This model is supported by data showing that circulating levels of lipopolysaccharide (LPS), a bacterial product known to elicit an innate immune response by binding host Toll-like receptors [83], increase significantly as HIV infection progresses [84], though initiation of ART lowers circulating LPS levels [64]. Individuals with both

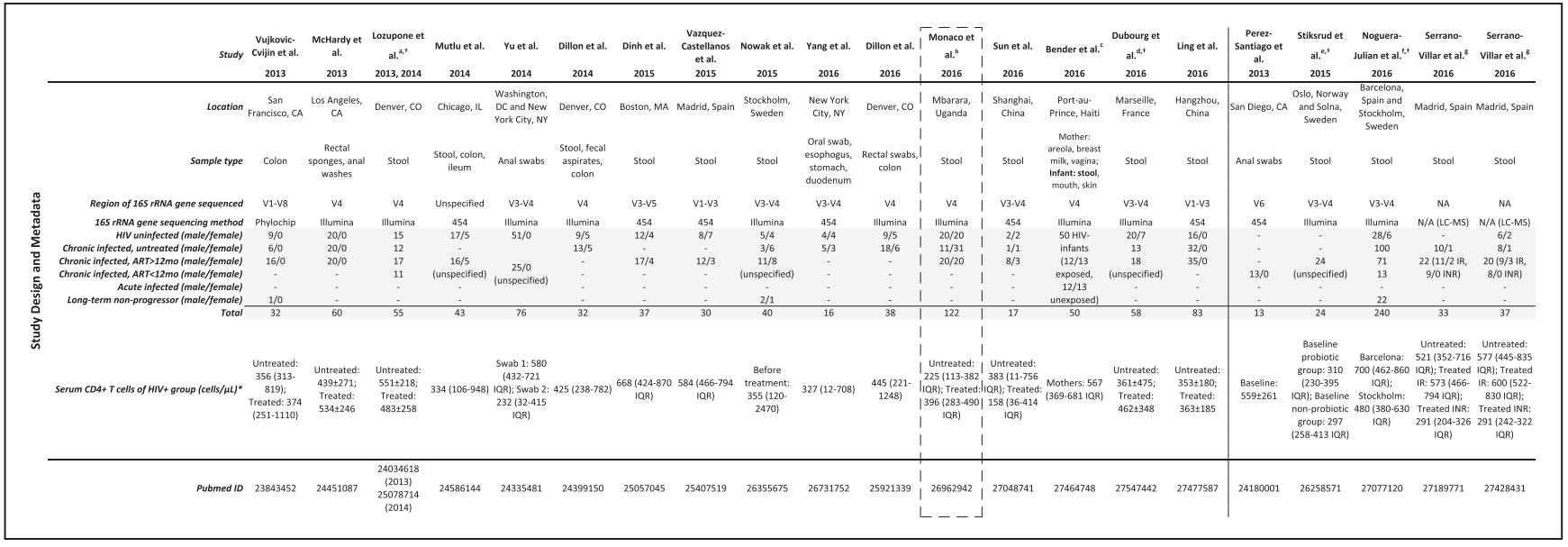
treated and untreated HIV infection, however, exhibit elevated serum levels of bacterial LPS and systemic inflammation relative to uninfected controls [64,85,86].

BACTERIAL MICROBIOME DIFFERENCES IN HIV INFECTION

Changes in the composition of the enteric microbiome that cause it to deviate from what is considered a healthy baseline state are often collectively referred to as 'dysbiosis'. Dysbiotic states are thought to underlie many of the pathologies linked with the microbiota [7–9]. Comparative studies between HIV-infected and uninfected individuals have differed in methods and patient populations studied (Fig. 2 and Table S1, http://links.lww.com/COID/A16) and found a wide spectrum of differences associated with HIV infection (Figs. 1 and S1, http://links.lww.com/COID/A16). However, several overarching themes have emerged. HIV-infected individuals often have reduced diversity of their enteric microbiome, which is also observed in a number of pathologies such as IBD [87–89], type 1 diabetes mellitus [90], obesity [91], and *Clostridium difficile* infection [92,93]. HIV infection also frequently correlates with increased tissue and circulating measures of inflammation (e.g., sCD14, IL-6, $CD38^+HLA\text{-}DR^+CD8^+$ T cells) [64,85,86], as well as increases in traditionally pathogenic bacteria such as Enterobacteriaceae [20▪,21▪▪,24▪,29▪▪,31▪▪,32▪▪,33▪] and decreases in commensals such as Lactobacillaceae, Lachnospiraceae, and Ruminococcaceae [19,20▪,21▪▪,22▪,23▪▪,25▪,26▪,28▪▪–30▪▪,32▪▪,94,95].

Taxa from four bacterial phyla – Proteobacteria, Fusobacteria, Bacteroidetes, and Firmicutes – have been reported in multiple studies to differ between HIV-infected and HIV-uninfected individuals. Proteobacteria were more abundant in HIV-infected individuals in 10 of the 16 published studies whereas others reported no change [17,18▪▪,19,20▪,21▪▪,22▪,23▪▪,24▪,27▪,30▪▪,32▪▪,33▪]. The phylum Proteobacteria includes numerous pathogens, such as *Shigella, Salmonella,* and *Helicobacter*. Many specific Proteobacteria genera have been shown to be enriched in HIV-infected individuals and are capable of potentially pathogenic activities in this context [96]: *Pseudomonas* [21▪▪,95] is an opportunistic pathogen that is capable of impairing host mucus production [97,98]; *Desulfovirbrio* [17] can produce hydrogen sulfide compounds and inflame the host epithelium [99]; *Acinetobacter* [23▪▪] can produce LPS [100] and *in vitro* is able to induce IL-8 production and neutrophil recruitment that could lead to inflammatory tissue damage [101,102]; and *Campylobacter* [20▪] produces multiple toxins [103] that can induce mucosal inflammation [104]. The Proteobacterial family Enterobacteriaceae is associated with inflammation [105,106] and was enriched in HIV-infected individuals in seven of the 16 studies surveyed [20▪,21▪▪,24▪,29▪▪,31▪▪,32▪▪,33▪] (most frequently driven by its constituent genus *Escherichia*, which is capable of pathogenic bile acid transformations and degradation of host mucus [98,107]). The phylum Fusobacteria, which is of particular interest because of its previous associations with intestinal inflammation and colorectal cancer [108–110], was enriched (most frequently driven by its constituent genus *Fusobacterium*) in HIV-infected individuals in four of the 16 previously published studies [19,20▪,22▪,32▪▪].

Taxa in the phylum Bacteroidetes, including the families Prevotellaceae, Porphyromonadaceae, Bacteroidaceae, and Rikenellaceae, exhibited a more heterogeneous pattern of changes in HIV-infected individuals. The family Prevotellaceae (most frequently driven by its constituent genus *Prevotella*) was enriched in HIV-infected individuals in seven of 16 studies [17,18▪▪,20▪,23▪▪,26▪,27▪,28▪▪,33▪] and depleted in one study [31▪▪]. Taxa within the family Prevotellaceae have been associated with inflammation (particularly in the context of autoinflammatory disease [111,112]) and activation of gut dendritic cells [28▪▪], but a greater abundance of Prevotellaceae is also characteristic of the baseline enteric microbial community of healthy individuals in developing world countries such as Burkina Faso, Venezuela, Malawi, or Papua New Guinea [17,113–117]. Taxa from the family Porphyromonadaceae (most frequently driven by the genera *Barnesiella* or *Odoribacter*) were generally depleted in HIV-infected individuals, exhibiting a decrease in nine of 16 studies [17,18▪▪,20▪,21▪▪,22▪,23▪▪,30▪▪–32▪▪,33▪] and an increase in two studies [19,24▪]. Independent of HIV, Porphyromonadaceae exhibit a diverse and complex array of functions, with both positive [110,118,119] and negative [119] associations with colorectal cancer, and negative associations with *C. difficile* [120–122], *Salmonella* [123], vancomycin-resistant *Enterococcus* [124], and *Citrobacter rodentium* [125,126] infection that imply a putative protective role. The family Bacteroidaceae (mostly driven by the abundance of the genus *Bacteroides*) is overall depleted in HIV infection, showing a reduced HIV-associated abundance in 10 of 16 studies [17,18▪▪,21▪▪,23▪▪,26▪,28▪▪–31▪▪,33▪]. This family is generally considered to play an anti-inflammatory role [127–131], with the species *Bacteroides fragilis* promoting regulatory T-cell differentiation and IL-10 production via secreted bacterial products [127–129]. The family Rikenellaceae (mostly driven



Study Design and Metadata	Study	Vujkovic-Cvijin et al.	McHardy et al.	Lozupone et al.[a,†]	Mutlu et al.	Yu et al.	Dillon et al.	Dinh et al.	Vazquez-Castellanos et al.	Nowak et al.	Yang et al.	Dillon et al.	Monaco et al.[b]	Sun et al.	Bender et al.[c]	Dubourg et al.[d,†]	Ling et al.	Perez-Santiago et al.	Stiksrud et al.[e,†]	Noguera-Julian et al.[f,†]	Serrano-Villar et al.[g]	Serrano-Villar et al.[g]
		2013	2013	2013, 2014	2014	2014	2014	2015	2015	2015	2016	2016	2016	2016	2016	2016	2016	2013	2015	2016	2016	2016
	Location	San Francisco, CA	Los Angeles, CA	Denver, CO	Chicago, IL	Washington, DC and New York City, NY	Denver, CO	Boston, MA	Madrid, Spain	Stockholm, Sweden	New York City, NY	Denver, CO	Mbarara, Uganda	Shanghai, China	Port-au-Prince, Haiti	Marseille, France	Hangzhou, China	San Diego, CA	Oslo, Norway and Solna, Sweden	Barcelona, Spain and Stockholm, Sweden	Madrid, Spain	Madrid, Spain
	Sample type	Colon	Rectal sponges, anal washes	Stool	Stool, colon, ileum	Anal swabs	Stool, fecal aspirates, colon	Stool	Stool	Stool	Oral swab, esophogus, stomach, duodenum	Rectal swabs, colon	Stool	Stool	Mother: areola, breast milk, vagina; **Infant: stool**, mouth, skin	Stool	Stool	Anal swabs	Stool	Stool	Stool	Stool
	Region of 16S rRNA gene sequenced	V1-V8	V4	V4	Unspecified	V3-V4	V4	V3-V5	V1-V3	V3-V4	V3-V4	V4	V4	V3-V4	V4	V3-V4	V1-V3	V6	V3-V4	V3-V4	NA	NA
	16S rRNA gene sequencing method	Phylochip	Illumina	Illumina	454	Illumina	Illumina	454	454	Illumina	454	Illumina	Illumina	454	Illumina	Illumina	454	454	Illumina	Illumina	N/A (LC-MS)	N/A (LC-MS)
	HIV uninfected (male/female)	9/0	20/0	15	17/5	51/0	9/5	12/4	8/7	5/4	4/4	9/5	20/20	2/2	50 HIV-infants (12/13 exposed, 12/13 unexposed)	20/7 (unspecified)	16/0	-	-	28/6	-	6/2
	Chronic infected, untreated (male/female)	6/0	20/0	12	-		13/5	-	-	3/6	5/3	18/6	11/31	1/1		13	32/0	-	-	100	10/1	8/1
	Chronic infected, ART>12mo (male/female)	16/0	20/0	17	16/5 (unspecified)	25/0 (unspecified)	-	17/4	12/3	11/8 (unspecified)	-	-	20/20	8/3		18	35/0	-	24	71	22 (11/2 IR, 9/0 INR)	20 (9/3 IR, 8/0 INR)
	Chronic infected, ART<12mo (male/female)	-	-	11			-	-	-		-	-	-	-			-	13/0	(unspecified)	13		
	Acute infected (male/female)	-	-	-	-		-	-	-	-	-	-	-	-		-	-	-	-	-	-	-
	Long-term non-progressor (male/female)	1/0	-	-	-		-	-	-	2/1	-	-	-	-		-	-	-	-	22	-	-
	Total	32	60	55	43	76	32	37	30	40	16	38	122	17	50	58	83	13	24	240	33	37
	Serum CD4+ T cells of HIV+ group (cells/μL)*	Untreated: 356 (313-819); Treated: 374 (251-1110)	Untreated: 439±271; Treated: 534±246	Untreated: 551±218; Treated: 483±258	334 (106-948)	Swab 1: 580 (432-721 IQR); Swab 2: 232 (32-415 IQR)	425 (238-782)	668 (424-870 IQR)	584 (466-794 IQR)	Before treatment: 355 (120-2470)	327 (12-708)	445 (221-1248)	Untreated: 225 (113-382 IQR); Treated: 396 (283-490 IQR)	Untreated: 383 (11-756 IQR); Treated: 158 (36-414 IQR)	Mothers: 567 (369-681 IQR)	Untreated: 361±475; Treated: 462±348	Untreated: 353±180; Treated: 363±185	Baseline: 559±261	Baseline probiotic group: 310 (230-395 IQR); Baseline non-probiotic group: 297 (258-413 IQR)	Barcelona: 700 (462-860 IQR); Stockholm: 480 (380-630 IQR)	Untreated: 521 (352-716 IQR); Treated IR: 573 (466-794 IQR); Treated INR: 291 (204-326 IQR)	Untreated: 577 (445-835 IQR); Treated IR: 600 (522-830 IQR); Treated INR: 291 (242-322 IQR)
	Pubmed ID	23843452	24451087	24034618 (2013) 25078714 (2014)	24586144	24335481	24399150	25057045	25407519	26355675	26731752	25921339	26962942	27048741	27464748	27547442	27477587	24180001	26258571	27077120	27189771	27428431

FIGURE 2. Study design and patient metadata in HIV microbiome studies. *CD4 cell counts (cells/μL) displayed as either median [range (not notated in table)] median (IQR), or average ± SD. †Sex composition of clinical study participant groups not specified. [a]The same patient cohort was used for both Lozupone *et al.* 2013 and 2014. Displayed is patient information from Lozupone *et al.* 2014, which included 17 additional subjects. Proportion of males versus females in each clinical group is only described in Lozupone *et al.* 2013 (male/female: 8/5 seronegative; 11/0 HIV+ untreated; 7/1 HIV+ treated). [b]The black dashed box outlines the only study to date that investigated the relationship between gut microbiota and HIV in a sub-Saharan African cohort. [c]Fecal microbiome data only obtained for HIV seronegative unexposed and exposed infants. [d]The HIV-infected group has a total of 31 individuals, including 22 males and 9 females, specific clinical group not specified. [e]Thirty study participants (22 males, 8 females) originally enrolled but only 24 study participants completed the study, specific clinical group not specified. [f]The HIV-infected groups of the Barcelona and Stockholm cohorts, respectively, included 101 males and 28 females, and 46 males and 31 females, specific clinical group not specified. [g]Immunological responders (IR) and nonresponders (INR) respectively defined as having at least 350 and less than 350 $CD4^+$ T-cell counts/μl after more than 2 years of ART. ART, antiretroviral therapy.

by the abundance of the genus *Alistipes*) is also depleted in HIV infection, with decreased abundance in seven studies [17,18▪▪,19,20▪,21▪▪,23▪▪, 24▪,28▪▪] and this bile-tolerant family [132] displays protective properties against *C. difficile* infection [133] and a negative association with obesity [134] as well as positive associations with both type 1 [135] and type 2 [136] diabetes mellitus.

Similar to the phylum Bacteroidetes, bacterial families within the phylum Firmicutes were in general reduced in abundance in HIV-infected individuals, though this pattern did not hold true for every family within this phylum. The phylum overall behaved in this manner, with decreased abundance in five of 16 studies [19,20▪,22▪,23▪▪,27▪] and increased abundance in two studies [30▪▪,33▪]. The Firmicutes phylum is quite diverse, but broadly can be characterized as associated with developed world individuals [113] as well as obesity and increased energy harvest from diet [137,138]. Within the Firmicutes, the class Clostridia, which was overall depleted in HIV infection with decreased abundance in eight of 16 studies [19,20▪,21▪▪,22▪,23▪▪,30▪▪, 32▪▪,33▪], is characterized by taxa that often function in anti-inflammatory roles by producing butyrate and other short-chain fatty acids (SCFA) [107,139] and shifting T-cell differentiation toward regulatory T cells [140–143]. Within the class Clostridia, the family Lachnospiraceae, which was decreased in abundance in HIV-infected individuals in six of 16 studies [19,20▪,21▪▪,23▪▪,25▪,30▪▪], includes members that are commonly found to be uniquely effective metabolizers of complex polysaccharides [144,145] and characterized by the production of SCFA such as butyrate [146] and acetate [147] that are thought to be anti-inflammatory. Also within the class Clostridia, the family Peptostreptococcaceae varied in its HIV-associated shifts, with two of 16 studies [20▪,32▪▪] showing a relative decrease in abundance in HIV-infected individuals and one study [19] showing a relative increase. Peptostreptococcaceae have been found to function in mostly a proinflammatory role, with positive associations with *C. difficile* infection [121,148], viral diarrhea [149], intestinal inflammation [150], and the mucosal [151] and fecal [152] communities of individuals with colorectal cancer. In contrast to the family Peptostreptococcaceae, the Clostridia family Ruminococcaceae was in general decreased in HIV infection, with 10 of 16 studies [19,20▪,21▪▪,22▪,23▪▪,26▪,28▪▪–30▪▪,32▪▪] reporting decreased abundance in HIV-infected individuals and only one study [17,18▪▪] reporting increased abundance. Ruminococcaceae have been associated with both protective and disruptive roles within the gut microbial community, such as the production of anti-inflammatory SCFA [144] or the degradation of host mucus and potential proinflammatory role in IBD [153], and functional effects within this family have been found to be highly species dependent [132,154–156]. The bacterial family Erysipelotrichaceae, which is contained within the separate class Erysipelotrichia, was on the whole found to be increased in association with HIV infection with a greater abundance demonstrated in six of 16 studies [17,18▪▪,20▪,21▪▪,24▪, 26▪,33▪] and decreased abundance in only one study [31▪▪]. Erysipelotrichaceae are described as adhesive and potentially pathogenic [157], and have been found to be positively associated with obesity [158,159] and luminal microbial communities in colorectal cancer [151,160]. Interestingly, this family is also found to be enriched in the enteric communities of the Hadza hunter-gatherers of Tanzania [157].

MICROBIOME DIFFERENCES AND SAMPLING SITE

Some of the variation in the findings among these studies may be attributed to the differences in body site sampled and sampling methodology. The predominant collection method was stool sampling [17,18▪▪,20▪,23▪▪,24▪–26▪,28▪▪–32▪▪, 33▪,161▪–164▪] which is most representative of the luminal microbial community, though anal swabs and washings [19,22▪,165] or mucosal biopsies [20▪,21▪▪,23▪▪,27▪,28▪▪] were also used. Independent of HIV, mucosal and luminal microbial communities have been shown to differ to varying degrees [166–171], though in some contexts, the mucosal and luminal communities correlate strongly and are representative of one another [170]. With regard to functional differences, facultative anaerobes have been found to be more abundant in mucosal-associated environments, whereas obligate anaerobes are more prevalent in the gut lumen [170]. Studies of the HIV-associated microbiota that used both mucosal and luminal-targeted sampling techniques [20▪,23▪▪,28▪▪] found a variety of differences between these techniques. In the most concordant finding, the two sampling sites produced similar conclusions, with most taxa showing the same patterns of HIV-associated enrichment or depletion at both sampling sites (Fig. 1 and Table S1, http://links.lww.com/COID/A16) [20▪]. However, the HIV-associated reduction in diversity was more pronounced in mucosa than stool samples. Other studies found greater variation in the HIV-associated differences by body site. For instance, Dillon *et al.* [28▪▪] detected an HIV-associated increase in abundance of Prevotellaceae at both sampling sites, but

only observed HIV-associated decreases in taxa in the phyla Bacteroidetes and Firmicutes and increases in Proteobacteria in the mucosal samples. The study with the greatest discordance between mucosal and luminal findings observed many more HIV-associated differences in mucosal-associated communities than luminal communities [23▪▪]. In addition, mucosal community composition changes were more closely associated with mucosal cellular immune activation. Mucosal findings may be more sensitive or representative of the causative community, as these microorganisms are in the closest contact with epithelial cells and immune cells. These advantages, however, must be weighed against the relative difficulty of obtaining mucosal samples.

GEOGRAPHICAL CONTEXT FOR BACTERIAL MICROBIOTA DIFFERENCES

Most current work investigating HIV and the enteric microbiome has focused on populations in the developed world (Fig. 3), as opposed to the developing world where HIV burden is greatest [172]. As the burden of NCD in chronic HIV is growing rapidly in the HIV-infected population in sub-Saharan Africa [173–176], this region could potentially benefit from the deployment of microbiota-directed therapeutics. However, geographic differences in the gut microbiome may make it difficult to translate data derived from developed world subjects to target populations in the developing world.

The microbiota differences observed between HIV-infected and uninfected individuals as a whole [17,18▪▪] mirror some differences seen at baseline between populations in the developing and developed world [113,115,117]. It is currently thought that the differences between developed and developing world microbiota are primarily a result of the corresponding dietary differences, with greater consumption of fat and simple carbohydrates in the developed world and greater consumption of more complex carbohydrates in the developing world [114,132,177]. The observations that a Prevotellaceae-rich community is frequently observed in healthy individuals in developing nations such as Burkina Faso, Venezuela, Malawi, or Papua New Guinea [17,113–117] argue against the simple conclusion that defined HIV-associated taxa changes in the gut microbiota (e.g., an increase in Prevotellaceae and a decrease in Firmicutes) alone are responsible for chronic inflammation and disorder in HIV-infected individuals. Rather, these potentially conflicting observations suggest a more complex relationship wherein a mismatch between the extant taxa and their host context causes

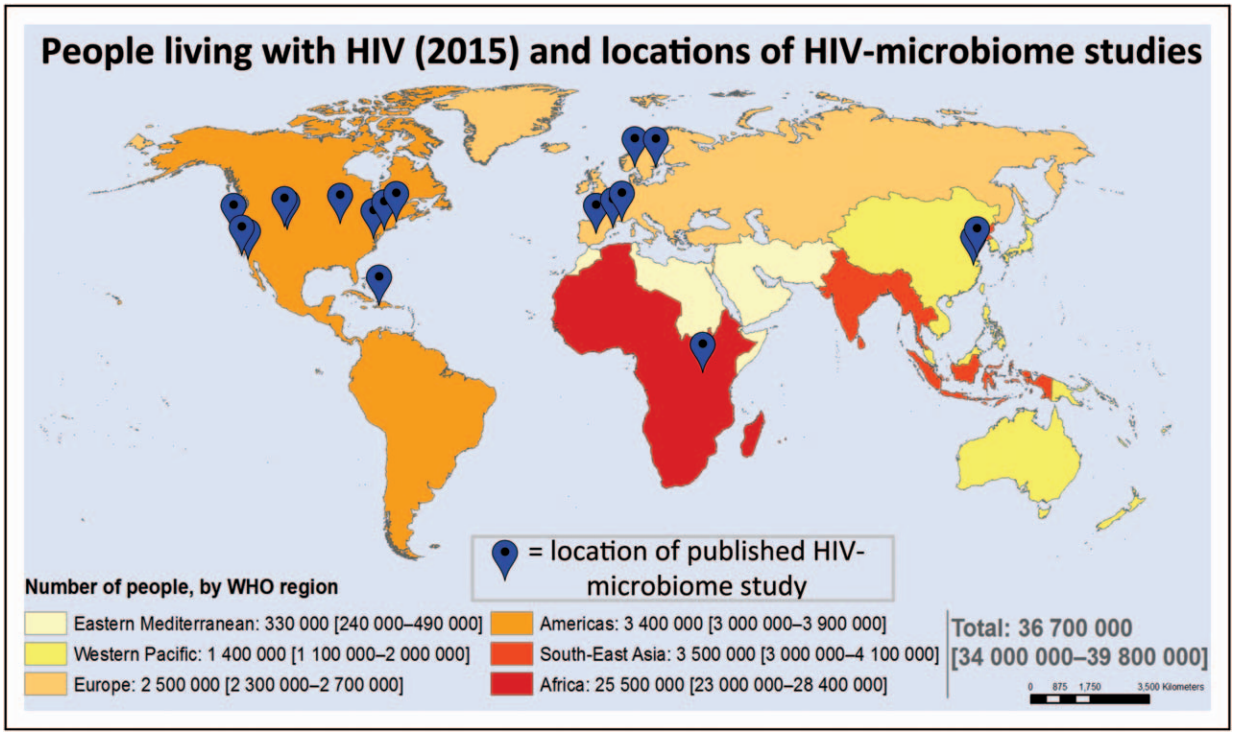


FIGURE 3. People living with HIV and locations of HIV-microbiome studies. Locations of HIV-microbiome cohorts overlaid on world map of HIV prevalence. The vast majority of HIV-microbiome studies have been conducted in developed world settings. Map source: Adults and children estimated to be living with HIV 2015, WHO/UNAIDS/UNICEF.

inflammation [18▪▪]. One possible example of this mismatch might be a microbial community that is inappropriate for the host diet and as a result produces inflammatory metabolites from these dietary constituents. This 'context-dependent' model of microbial-driven systemic inflammation would further heighten the need to study HIV-associated microbial differences in appropriate populations, as therapeutic interventions constructed from data originating from one population may be poorly suited for application in a population with a different microbial and environmental milieu.

VIROME DIFFERENCES IN HIV INFECTION

The diverse human enteric virome includes a wide array of eukaryotic viruses, bacteriophages, and endogenous retroviruses [178–181] and is largely unexplored, with some estimates that only 1% of the virome has been sequenced [182]. To date, only a handful of studies have examined alterations in the virome during lentiviral infection [29▪▪,183–186]. New sequencing technologies offer a unique opportunity for unbiased examination of the virome including discovery of potentially novel unculturable viruses [187]. Enteric eukaryotic viruses can drive host pathology that directly causes gastroenteritis, enteritis, or colitis. Bacteriophages, which are the most abundant enteric viruses, can initiate changes in the bacterial community that influence gut health and may also be able to directly interact with the host immune system [178–190]. In IBD, diversity of the bacteriophage virome increases whereas diversity of the bacterial microbiome decreases, suggesting a potential competitive relationship between bacteria and bacteriophages during enteric inflammation [191]. In light of the emerging recognition of the potential role of the enteric virome in gastrointestinal pathology, there is now a growing focus on characterizing the gut virome associated with HIV infection.

Nonhuman primate simian immunodeficiency virus models of HIV infection have shown expansion of the enteric virome, with significant increases in *Picornaviridae*, *Adenoviridae*, and *Parvoviridae* abundance in pathologic simian immunodeficiency virus infection of rhesus macaques [183,184]. In this model, *Adenoviridae* were associated with development of severe gastrointestinal disease [183,184] and enteric viruses spread to other tissue compartments, with *Parvoviridae* detected in the serum and *Adenoviridae* found in the enteric mucosa [184].

HIV-associated differences in the virome have also been observed in HIV-infected individuals. In a Ugandan cohort, $CD4^+$ T-cell counts less than 200 cells/μl were associated with a significant increase in enteric *Adenoviridae* and *Anelloviridae* [29▪▪]. *Anelloviridae* are small, nonenveloped viruses with circular negative-sense ssDNA genomes often found in human serum [192]. *Anelloviridae* have not yet been identified as causative disease agents, but have been shown to be increased in the serum of immunosuppressed solid organ transplant patients [193] and (not using modern sequencing methods) HIV-infected study participants [194,195]. Similar alterations to the plasma virome were observed in HIV-infected individuals in the United States and Uganda, with an increase in *Anelloviridae* [185]. In the United States but not the Ugandan cohort, there was also a significant increase in total plasma viral sequences, mainly attributed to bacteriophages, in HIV-infected individuals with low (<20 cells/μl) $CD4^+$ T-cell counts as compared with individuals with high (>700 cells/μl) $CD4^+$ T-cell counts [185].

CONCLUSION

The role of enteric microbial changes in HIV disease progression has been the focus of increasing investigation. Models regarding the connections between gut microbiome changes and chronic HIV pathogenesis hypothesize a role for gut epithelial damage and systemic immune activation as an intermediate mechanism. Investigations into HIV-associated differences in the gut microbial community have found varied changes, but a few overall consistent patterns have emerged. In general, HIV infection is associated with decreases in many bacterial families within the phyla Bacteroidetes and Firmicutes as well as increases in the family Prevotellaceae and families within the phyla Proteobacteria and Fusobacteria. This community shift implies an overall pathogenic or proinflammatory outcome based on the functions of the differentially abundant microorganisms, but this causative relationship has not been conclusively shown and bacterial behavior can vary widely based on context. The viral component of the gut microbial community has received relatively little attention, but findings have generally shown an increase in the family *Anelloviridae*, which is frequently found in immunocompromised hosts, and in potentially pathogenic viruses such as the family *Adenoviridae*.

The heterogeneity of the conclusions drawn to date within this field may be in part because of the variation in study populations and methods employed (Fig. 2 and Table S1, http://links.lww.com/COID/A16). Greater coordination of methodologies would allow more robust analysis of multiple studies and potentially reconcile conflicting conclusions. There is also a need to more

finely examine the taxa differentially abundant in HIV infection, as meaningful functional variation can often occur at the species or strain level rather than the family or genera level [196–198]. 16S rRNA gene sequencing cannot provide this taxonomic resolution, creating a role for techniques such as shotgun metagenomic sequencing, which could detect strain or gene content variation. In light of the current findings of HIV-associated Prevotellaceae enrichment and the great abundance of this taxa in developing world populations that constitute the majority of HIV-infected individuals, there is a dire need for further examination of HIV-associated gut microbial differences in developing world populations. It is possible that therapeutic strategies that consider Prevotellaceae enrichment a pathogenic state would be ill suited for HIV-infected individuals in the developing world. In addition, microbiota-targeted probiotic interventions have produced mixed results, with some therapeutics reducing inflammatory markers and others lacking efficacy [162▪,199–208]. Further understanding of the enteric microbial changes associated with HIV infection, especially among developing world populations that bear the greatest burden of HIV infection, is therefore necessary to design therapeutic strategies that could alleviate the sequelae of systemic inflammation and NCD in chronic HIV infection.

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Conflicts of interest

There are no conflicts of interest.

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The study was the first to show that dysbiosis and reduced alpha diversity occur in the terminal ileum and colon in HIV infection. This study observed reduced alpha diversity and increased ratio of Prevotella/Bacteroides in the HIV-infected group.

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The study revealed an increased ratio of Proteobacteria/Bacteroides in viremic, untreated HIV-infected study participants and an intermediate dysbiosis in the ART group. This study found that the degree of dysbiosis was strongly correlated with IP-10, the kynurenine pathway of tryptophan metabolism, and T-cell activation in both the colon and peripheral blood.

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Longitudinal microbiome analyses in this study showed that alpha diversity decreases with advanced HIV infection.

23. ▪▪ Dillon SM, Lee EJ, Kotter CV, *et al.* An altered intestinal mucosal microbiome in HIV-1 infection is associated with mucosal and systemic immune activation and endotoxemia. Mucosal Immunol 2014; 7:983–994.

The study demonstrated an increased ratio of Prevotella/Bacteroides in HIV-infected group, whereas other features of dysbiosis were inconsistent across sample types, such as mucosa-specific increases in Proteobacteria and alpha diversity. In this study, the degree of dysbiosis correlated with plasma LPS levels, peripheral blood CD4 and CD8 activation, and colonic T cell and myeloid dendritic cell activation.

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In this study, Gammaproteobacteria, Enterobacteriales, and Enterobacteriaceae abundance positively correlated with levels of markers of systemic immune activation such as sCD14, IFNγ, and IL-1β.

25. ▪ Nowak P, Troseid M, Avershina E, *et al.* Gut microbiota diversity predicts immune status in HIV-1 infection. AIDS (London, England) 2015; 29:2409–2418.

The study suggested that Prevotella abundance and alpha diversity are further reduced following ART, and that alpha diversity inversely correlates with CD4 cell count and positively correlated with plasma LPS, LBP, sCD14, and sCD163. In this study, elite controllers were comparable to HIV-uninfected study participants at the phylum level, and had a higher abundance of Bacteroidetes than viremic study participants.

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The study revealed an increased ratio of Prevotella/Bacteroides and depletion of Coprococcus in the HIV-infected group. Shotgun metagenomic data in this study demonstrated functional differences in the microbiota of HIV-infected study participants, including enrichment in pathogenic processes, LPS biosynthesis, bacterial translocation, and other inflammatory pathways, as well as the depletion of amino acid metabolism and energy processes.

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This was the first study to suggest that HIV impairs resistance of the duodenum to colonization of environmental bacteria such as Burkholderia fungorum and Bradyrhizobium pachyrhizi, whose abundance was inversely correlated with CD4 cell count but not viral load. The study also observed significant clustering of microbiota based on HIV phenotype in the duodenum but not in other compartments of the proximal gut, characterized by an enrichment of Proteobacteria and depletion of Firmicutes and Lactobacillus.

28. ■■ Dillon SM, Lee EJ, Kotter CV, *et al.* Gut dendritic cell activation links an altered colonic microbiome to mucosal and systemic T-cell activation in untreated HIV-1 infection. Mucosal Immunol 2016; 9:24–37.

The study found that Prevotella positively correlated with colonic myeloid dendritic cell activation *in vivo* and induced proinflammatory cytokine production by colonic mDCs in vitro. These findings led them to propose a model describing myeloid dendritic cells and the gut microbiota as drivers of mucosal immune activation and chronic inflammation in HIV.

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In this first study investigating the gut microbiota in HIV in sub-Saharan Africa, low CD4 T-cell levels correlated with alterations in gut bacterial communities independent of ART treatment, including reduced phylogenetic diversity and enrichment in Enterobacteriaceae. This was also the first study to examine the enteric virome in HIV disease progression, demonstrating an expansion of enteric adenovirus sequences in HIV-infected study participants with low CD4 cell counts.

30. ■■ Sun Y, Ma Y, Lin P, *et al.* Fecal bacterial microbiome diversity in chronic HIV-infected patients in China. Emerg Microbes Infect 2016; 5:e31.

In this first study investigating the gut microbiota in HIV in an Asian cohort, infected individuals had decreased alpha diversity, were enriched for Firmicutes and Proteobacteria at the phylum level, and were depleted in the families Ruminococcaceae and Lachnospiraceae and the class Clostridia.

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The study demonstrated that human breast milk oligosaccharides correlated with the abundance of specific gut bacteria in high-risk infants (increases in HIV-infected mothers' N-fucopentaose-1 in breast milk correlated with increases in Bifidobacteriaceae in infant's stool). In this study, HIV exposed, uninfected infants had less diverse microbiota with greater abundances of Prevotella and Psuedomonas. Maternal CD4 cell count positively correlated with the diversity of infant gut microbiota. Trending but insignificant proportion of HIV exposed, uninfected infant stool microbiota resembled HIV-infected mother's breast millk and areolar skin, suggesting direct seeding of infant gut microbiome via breasfeeding in HIV-infected mothers. HIV-exposed infants had 'younger/immature' gut microbiota.

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The study showed that the microbiota in HIV-positive study participants are enrichment in aerotolerant taxa such as Enterobacteriaceae and Enterococcaceae, and depleted in anaerobic taxa such as Ruminococcus. Reduced diversity in HIV individuals not restored by ART. The increased ratio of aerotolerant to anaerobic taxa in HIV-infected study participants was inversely correlated with inflammation and immune activation markers (IP10, CD14, CD163).

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