HHS Public Access

Author manuscript

Curr Opin HIV AIDS. Author manuscript; available in PMC 2021 March 01.

Published in final edited form as:

Curr Opin HIV AIDS. 2020 March ; 15(2): 94–100. doi:10.1097/COH.0000000000000611.

What is the collective effect of aging and HIV on the gut microbiome?

Stephanie M. Dillon, **Cara C. Wilson**

University of Colorado Anschutz Medical Campus.

Abstract

Purpose of review: Aging and HIV share features of intestinal damage and alterations in the communities of enteric bacteria, termed dysbiosis. The purpose of this review is to highlight the various features of the gut microbiome in 1) aging and in 2) people with HIV (PWH) and to discuss how aging and HIV converge to impact the gut microbiome. The term microbiome reflects the combined genetic material of micro-organisms present including bacteria, viruses, bacteriophages and fungi. To date, the majority of studies investigating the impact of aging and HIV on the gut microbiome have focused on bacteria and therefore, for the purposes of this review, the term "microbiome" is used to reflect enteric bacterial communities.

Recent Findings: Aging is associated with alterations in the gut bacterial microbiome. Although changes vary by the age of the population, lifestyle (diet, physical activity) and geographic location, the age-associated dysbiosis is typically characterized by an increase in facultative anaerobes with inflammatory properties and a decrease in obligate anaerobes that play critical roles in maintaining intestinal homeostasis and in regulating host immunity. PWH also have dysbiotic gut microbiomes, many features of which reflect those observed in elderly persons. In one study, the age effect on the gut microbiome differed based on HIV serostatus in older adults.

Summary: HIV and age may interact to shape the gut microbiome. Future studies should investigate relationships between the gut microbiome and age-associated co-morbidities in older PWH populations. Identifying these links will provide new avenues for treatments and interventions to improve the healthspan and lifespan of older PWH.\

Keywords

HIV; Aging; Microbiome

Introduction.

The human gut is home to hundreds of different species of bacteria which have co-evolved with the human body and have symbiotic (mutually beneficial) or commensal (of benefit to

Corresponding Author: Cara C. Wilson, University of Colorado Anschutz Medical Campus, 12700 E. 19th Avenue, Division of Infectious Diseases, P15-11011, B168. Aurora, CO 80045, Tel. 303 724 4601, cara.wilson@cuanschutz.edu.

Conflict of Interests.

None.

one without harming the other) relationships with their host (1). A large proportion of enteric bacteria are obligate anaerobes primarily belonging to the Bacteroidetes and Firmicutes phyla. Species within these phyla are known to serve critical roles in host physiology either by interacting directly with host immune cells or providing essential metabolites through digestion of diet-related complex carbohydrates, proteins and fats (2–4). For example, species of Bacteroides directly induce regulatory T cells (5) while several Firmicutes species produce the metabolite butyrate, a short chain fatty acid (SCFA) produced following fermentation of dietary fiber (6). Butyrate not only regulates host immune cell function to dampen inflammation, but also serves as a critical energy source for epithelial cells, regulates the epithelial immune response (e.g., production of anti-microbial peptides) and maintains a low oxygen environment favorable to obligate anaerobes (7).

Given the mutualistic and complex nature of the microbiome-host interactions, it is not surprising that a loss of control of this delicate balance leads to changes in the microbial community, termed dysbiosis. For example, a number of elegant mouse studies have implicated the loss of butyrate-producing bacteria (BPB) and therefore lower butyrate levels in increasing levels of luminal oxygen, thus providing an ideal environment for the expansion of less common species of facultative anaerobes (i.e., anaerobes that can survive in oxygen) (8–10). Despite their commensal nature, many of these bacteria have the potential to induce inflammatory responses and exert pathogenic effects on host immunity and are termed pathobionts (11, 12). Host mucosal inflammatory immune responses may also lead to increases in luminal oxygen, thus further exacerbating dysbiosis (13, 14).

Both HIV and aging are associated with a chronic low-level inflammatory state which has been linked to increased risk of co-morbidities (recently reviewed in (15, 16)). Although there are multiple drivers of chronic inflammation, a breakdown in intestinal homeostasis and the associated ‘leaky gut’ and increased microbial translocation have been linked to systemic inflammation in both HIV (17–20) and aging (21, 22). Given the importance of the enteric bacterial community in maintaining a healthy homeostatic gut microenvironment, understanding the composition and function of the enteric microbiomes associated with physiologic aging and HIV infection have therefore become areas of great scientific interest.

Enteric microbial communities are altered in elderly persons.

The first extensive study to investigate the impact of aging on the gut microbiome utilized a panel of group- and species-specific bacterial 16S ribosomal RNA (rRNA)-targeted oligonucleotides to probe the bacterial taxonomic composition of fecal samples from younger (25–49 years) and older (61–100 years) persons at four European locations (23). Older people, irrespective of geographical location, had higher proportions of the genus *Enterobacteria*, a facultative anaerobe, belong to the Enterobacteriaceae family. Conversely, aging was associated with lower amounts of the butyrate-producing species *Faecalibacterium prausnitzii*, but only in elderly persons from Italy and Sweden and not France or Germany. Thus, while differences in aging-associated microbial communities were identified, they differed between study location, highlighting that aging-associated microbial profiles are likely influenced by factors associated with geographical location such as genetic, dietary and environmental conditions (24). These initial observations are now

supported by a number of subsequent studies that primarily used high-throughput bacterial 16S rRNA gene sequencing approaches. Despite varying by location (primarily Europe and Asia) and differences in participant age ranges and health status (e.g., institutionalized, adjustments for polypharmacy), generally similar aging-associated changes in fecal enteric microbiomes were noted (recently reviewed in (25)). The dysbiotic profiles typically reflected a greater abundance of facultative anaerobes (e.g., Enterobacteriaceae species) and lower abundances of obligate anaerobes with immune-regulatory and/or anti-inflammatory potential including butyrate-producing species (e.g., *Roseburia*) and probiotic species such as *Bifidobacterium*. Other groups have gone beyond taxa identification to highlight potential differences in functional capability of fecal bacteria in older persons. Fecal samples from elderly persons (mean age 86 years) had fewer bacterial genes associated with butyrate production versus younger persons (26). Rampelli and colleagues utilized a metagenomics approach and applied shotgun sequencing to total fecal bacterial DNA (27). In this small study, the aging human fecal bacterial functional profile was characterized by a loss of genes utilized in SCFA production, in starch and sucrose metabolism, and in essential amino acid metabolism, and associated with an enrichment in genes reflective of pathobiont taxa.

A number of recent cross-sectional clinical studies have investigated microbiome profiles associated with extreme aging including super-centenarians (>105 years) (28–35). Although increases in some pathobiont species (e.g., Proteobacteria spp.) and lower abundances of some butyrate-producing bacteria (e.g., *Faecalibacterium*) were noted in centenarians, increased abundances of other potentially health-promoting bacterial groups (e.g., *Akkermansia*, *Bifidobacterium*) were common in extreme aging. Importantly, as noted by Biagi *et al.*, these cross-sectional studies do not delineate whether these health-associated communities are maintained with age and contribute to longevity or are lost and reacquired as new relationships are established between microbiota and host (28). Interestingly, a recent large scale study in China that investigated microbiome changes across the age spectrum (3–100 years) utilizing a compositional data analysis approach with age as a continuous variable (versus other common measures such as Bray-Curtis dissimilarity measures) found only minor variations in taxa between healthy older versus younger persons, even in centenarians (36). This highlights that, in addition to geographical location, the type of analyses undertaken may also be a critical component in how we ultimately define an age-associated dysbiotic profile.

While studies on extreme aging may aid in understanding what constitutes a ‘healthy’ microbiome, investigations into relationships between the gut microbiome and age-associated inflammation and comorbidities may shed light on potentially ‘unhealthy’ microbiome profiles. Alterations in microbiome profiles have been linked to indicators of systemic inflammation. In one study, Proteobacteria species (enriched with age) correlated positively with increased inflammatory cytokine levels (IL-6, IL-8), whereas butyrate-producing bacterial taxa (depleted with age) were inversely associated with these cytokines (29). Numerous studies of aging cohorts (age ranges 42 to >100 years) have observed potential links between gut microbial communities and a decline in physical function with age. Specifically, indicators of frailty have been associated with higher abundance of bacterial taxa in several phyla, including Enterobacteriaceae (Proteobacteria), *Eggerthella* sp. (Actinobacteria) and *Rumminococcus* (Firmicutes) and lower abundance of butyrate-

producing bacteria (e.g., *F. prausnitzii*) (37–41). Metagenomic analyses revealed that frailty was associated with genes responsible for bacterial persistence and with Gram-negative cell wall component Lipopolysacchride (LPS) biosynthesis (38, 40). Production of SCFAs, measured in fecal water, were lower in frail persons (37), reflecting the lower abundance of SCFA-producing bacteria. A recent study provided the first causal evidence of a gut-muscle axis whereby transfer of human fecal samples from high-functioning adults led to greater grip-strength in recipient germ-free mice relative to transfer of fecal samples from low-functioning persons (42).

Potential links between the microbiome and other age-associated co-morbidities such as dementia and cardiovascular disease (CVD) have also been suggested. In elderly Italians with cognitive impairment and brain amyloidosis, higher abundances of fecal *Escherichia* were observed, and *Escherichia* abundance positively correlated with blood levels of the inflammatory cytokine IL-1β. Conversely, lower abundance of the butyrate-producing bacteria *Eubacterium rectale* was linked to cognitive impairment and brain amyloidosis, and abundance of this organism inversely correlated with IL-1β (43). In an elderly Japanese cohort, lower prevalence of *Bacteroides* was strongly associated with dementia (44). In a USA-based cohort of elderly patients with and without Alzheimer's disease, Alzheimer's disease was associated with lower abundance of families of bacteria belonging to Firmicutes (e.g., Rumincoccaceae, Clostridiaceae) and Actinobacteria (e.g., Bifidobacteriaceae), but with higher abundance of Bacteroidetes (e.g., Bacteroidaceae, Rikenellaceae) and Proteobacteria (e.g., *Bilophila*) (45). Production of the bacterial metabolite trimethylamine-N-oxide (TMAO) has been mechanistically linked to atherosclerosis (46, 47), and enteric dysbiosis has been associated with known risk factors for CVD such as hypertension, obesity, metabolic syndrome and diabetes (48).

Enteric microbial communities are altered in PWH.

Recent studies, including our own, have documented that enteric bacterial communities in PWH are different when compared to individuals without HIV infection (recently reviewed in (49)). In both ART-treated and in treatment-naïve PWH, initial studies described a dysbiotic fecal microbiome in PWH characterized by greater abundance of Prevotella with concurrent depletion of some Bacteroides species, higher abundance of Proteobacteria (including the family Enterobacteriaceae), and lower abundance of obligate anaerobes including butyrate-producing bacteria (49). Of note, a number of subsequent studies have highlighted that certain dysbiotic features, in particular high abundance of *Prevotella* sp., were likely attributable to sexual practices rather than to HIV infection *per se* (50–52). Studies suggest that antiretroviral drugs themselves may also contribute to dysbiosis, although studies directly investigating interactions between orally-administered ART drugs and gut microbiota have not been undertaken (reviewed in (53)).

Bacterial taxonomic profiling of gut tissue rather than of fecal samples may provide a better approximation of the communities of bacteria closest to the intestinal epithelium and the underlying immune cells and thus have the greatest potential to directly impact gut health and immunity. In general, profiles in gut tissue samples from PWH reflected those observed in fecal samples from independent studies, with the exception that tissue profiles were

notable for observing greater abundance of a greater variety of Proteobacteria genera (e.g., *Escherichia*, *Acinetobacter*, *Klebsiella*) and lower abundances of genera associated with butyrate production (e.g., *Roseburia* and *Faecalibacterium*) in PWH (54–58). Of note, our study demonstrated that the total summed abundance of known butyrate-producing bacterial species was significantly lower in colonic tissue of untreated PWH compared to uninfected controls, but this difference was not observed in subject-matched fecal samples (59). Variances between fecal and mucosal tissue taxa profiles, as also noted in studies of healthy individuals (60), may reflect differences in the local environment being conducive to growth of one bacteria over another (e.g., an oxygen gradient from tissue to luminal content) and/or that the fecal samples may contain both luminal bacteria as well as those that are poorly adherent to or shed from the mucosa. Different collection procedures may also be a contributing factor. Clinic-based endoscopic collection of tissue samples likely results in the immediate appropriate storage of tissue samples whereas there is likely more variability in storage of fecal samples collected “at home” by study participants.

Both fecal and tissue-associated dysbiotic profiles have been variably linked to indicators of HIV-1 pathogenesis. Dysbiotic microbial communities in PWH positively associated with blood T cell activation and indicators of systemic inflammation and microbial translocation (54, 56, 57, 61). At an individual taxa level, numerous genera containing butyrate-producing bacteria inversely associated with microbial translocation and immune activation (54, 56, 61, 62).

A number of recent studies have begun to probe the metabolic profiles of enteric bacteria in PWH and to look for bacteria-associated functional pathways involved in HIV pathogenesis and inflammation-related comorbidities. In one study, fecal butyrate levels were significantly lower in untreated PWH with no differences noted in the other major gut-associated SCFAs (acetate or propionate) (63). By contrast, butyrate levels in ART-treated person were not found to be significantly different versus controls in another study (64). Compared to uninfected persons with infectious diarrhea caused by toxigenic *Clostridioides difficile*, another infection known to induce gut damage, HIV infection uniquely altered the composition of fecal bacterial metabolites (65). Among these PWH, the impact on gut bacterial metabolism was most notable for the apparent inability of gut bacteria to metabolize the amino acids proline, phenylalanine and lysine, which may be a contributing factor to nutritional deficits observed in PWH (65). Characterization of the functional gene content of the fecal microbiota in PWH either via imputed metagenomics (e.g., PICRUSt) or metagenomic sequencing noted enrichment of genes associated with LPS biosynthesis, bacterial translocation and oxidative stress resistance with depletion of genes associated with anti-inflammatory pathways (e.g., butanoate), amino acid metabolism and energy processes (61, 66–68). Other groups have reported alterations in abundances of enteric bacteria capable of tryptophan catabolism and in metabolites associated with this pathway, suggesting that increased bacteria-produced tryptophan catabolites may be a contributing factor to HIV-associated immunosuppression (57, 65). A recent study noted plasma TMAO levels correlated inversely with fecal Bacteroidetes and positively with Firmicutes, but notably, not with any known TMA-producing genera (69).

HIV and age interact to shape the gut microbiome.

Although many similarities exist in the microbiomes of people as they age and among PWH, few studies have directly investigated the collective effect in an individual aging with HIV. We recently undertook a pilot cross-sectional study based in the USA, comparing the fecal microbiome profiles of PWH aged 50–75 years on ART (≥2 years) and viral suppression to those of uninfected age-matched controls using 16S rRNA gene sequencing (70). Our analysis revealed that among older adults, HIV and age were independently associated with distinct changes in the fecal microbial communities. For example, microbiomes of older PWH were characterized by increased abundances of *Enterobacter*, *Paraprevotella* and *Howardella* genera and decreased abundances of *Eggerthella*, *Alistipes*, *Barnesiella* and *Roseburia*. Evaluation of the impact of age on microbiome profiles independent of HIV serostatus revealed a different profile with increased abundance of *Parabacteroides*, *Lactobacillus*, *Sneathia* and *Desulfovibrio* with decreased abundance of *Butyricimonas*, *Howardella*, *Fusobacterium* and *Enterobacter*. Critically, we demonstrated that the age effect on the fecal microbiome differed based on HIV serostatus: the abundance of certain genera (e.g., *Bifidobacterium*, *Bacteroides*, *Alistipes*) increased to a significantly greater extent with age in PWH than in controls. Other genera (e.g., *Escherichia*, *Butyricimonas*, *Oxalobacter*) significantly increased with age in PWH but decreased in controls. No significant differences were observed in fecal SCFA levels (butyrate, acetate, propionate) between the two cohorts. Associations between the top 25 genera based on all study participants and systemic inflammatory biomarkers also revealed different patterns between the two cohorts. As an example, *Escherichia*, *Subdoligranulum* and *Bifidobacterium* positively associated with levels of soluble TNF receptor (sTNFR) in PWH but not in controls. Our study highlights that the age effect on the gut microbiome and associations between microbiota and systemic biomarkers in an older population differ based on HIV serostatus. However, this study was limited by the small sample size preventing adjustment for a number of confounders including differences in sexual behaviors.

In another recent study, the fecal microbiomes of USA-based older (≥55 years) men who have sex with other men (MSM) with long-term controlled HIV (>10 years ART) versus age-matched MSM without HIV were evaluated by Rhoades and colleagues using 16S rRNA gene sequencing (71). The fecal microbiomes of PWH with long-term controlled HIV were enriched in *Sneathia*, *Fusobacterium*, *Lactobacillus*, *Helicobater* and *Atopbium*, but had lower abundance of *Oxalobacter*, *Eggerthella* and *Streptococcus* versus controls. *Atopbium* and *Streptococcus* are commonly found in the oral cavity, thus the authors conclude that, despite long-term adherence and undetectable viral loads, older PWH with long-term controlled HIV still have alterations in fecal microbial communities in part reflective of a loss of compartmentalization. A cross-sectional study of ART-treated (≥2 years) PWH aged >50 years versus uninfected controls aged >65 years from Mexico quantified specific fecal taxa using qPCR (72). The differences in the lower age limit for recruitment of PWH was explained by the authors as a way to account for the potential “early aging” of the immune system in PWH. In this study, the authors reported a significant increase in Proteobacteria and depletion in Firmicutes in PWH versus controls as well as increased levels of fecal propionate, but decreased butyrate and acetate levels.

Several studies have investigated fecal microbial communities in PWH with age-associated co-morbidities. In a China-based study, gut microbial dysbiosis was not independently associated with neurocognitive impairment in younger (mean age 33 years), untreated PWH with and without HIV-associated neurological diseases (HAND) after adjusting for gender, age, education level and CD4 T cell count (73). In a German-based study, no specific bacterial taxa were found to associate with coronary heart disease (CHD) in PWH (mean age 53 years), but co-occurrence of clusters of bacteria were different between PWH with and without CHD suggesting that networks of bacteria may be more pertinent in determining potential links between the gut microbiome and CHD in PWH (74). Of note, to the best of our knowledge, no studies have directly investigated potential relationships between the gut microbiome and frailty in older PWH.

Acknowledgements.

We would like to acknowledge and thank all the study participants who have generously contributed their time and biological samples.

Financial Support.

SMD and CCW are supported by funding from NIH (R01AI118983; R01AI134220; R21AG062932). Previous studies mentioned in this review were supported by R01DK088663.

REFERENCES

1. Hooper LV, Gordon JI. Commensal host-bacterial relationships in the gut. Science 2001; 292:1115–1118. [PubMed: 11352068]
2. Oliphant K, Allen-Vercoe E. Macronutrient metabolism by the human gut microbiome: major fermentation by-products and their impact on host health. Microbiome 2019; 7:91. [PubMed: 31196177]
3. Pandiyan P, Bhaskaran N, Zou M, et al. Microbiome Dependent Regulation of Tregs and Th17 Cells in Mucosa. Front Immunol 2019; 10:426. [PubMed: 30906299]
4. Zhao Q, Elson CO. Adaptive immune education by gut microbiota antigens. Immunology 2018; 154:28–37. [PubMed: 29338074]
5. Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci U S A 2010; 107:12204–12209.
6. Koh A, De Vadder F, Kovatcheva-Datchary P, Backhed F. From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. Cell 2016; 165:1332–1345. [PubMed: 27259147]
7. Parada Venegas D, De la Fuente MK, Landskron G, et al. Short Chain Fatty Acids (SCFAs)-Mediated Gut Epithelial and Immune Regulation and Its Relevance for Inflammatory Bowel Diseases. Front Immunol 2019; 10:277. [PubMed: 30915065]
8. Byndloss MX, Olsan EE, Rivera-Chavez F, et al. Microbiota-activated PPAR-gamma signaling inhibits dysbiotic Enterobacteriaceae expansion. Science 2017; 357:570–575. [PubMed: 28798125] ** Murine study demonstrating butyrate-producing microbiota-activated PPAR-g signaling is a critical homeostatic pathway that prevents dysbiotic expansion of Enterobacteriaceae.
9. Litvak Y, Byndloss MX, Baumler AJ. Colonocyte metabolism shapes the gut microbiota. Science 2018; 362.
10. Rivera-Chavez F, Zhang LF, Faber F, et al. Depletion of Butyrate-Producing Clostridia from the Gut Microbiota Drives an Aerobic Luminal Expansion of Salmonella. Cell Host Microbe 2016; 19:443–454. [PubMed: 27078066]
11. Chow J, Tang H, Mazmanian SK. Pathobionts of the gastrointestinal microbiota and inflammatory disease. Curr Opin Immunol 2011; 23:473–480. [PubMed: 21856139]

12. Pathogens Hornef M., Commensal Symbionts, and Pathobionts: Discovery and Functional Effects on the Host. ILAR J 2015; 56:159–162. [PubMed: 26323625]
13. Winter SE, Winter MG, Xavier MN, et al. Host-derived nitrate boosts growth of E. coli in the inflamed gut. Science 2013; 339:708–711. [PubMed: 23393266]
14. Zeng MY, Inohara N, Nunez G. Mechanisms of inflammation-driven bacterial dysbiosis in the gut. Mucosal Immunol 2017; 10:18–26. [PubMed: 27554295]
15. Ferrucci L, Fabbri E. Inflammageing: chronic inflammation in ageing, cardiovascular disease, and frailty. Nat Rev Cardiol 2018; 15:505–522. [PubMed: 30065258]
16. Peterson TE, Baker JV. Assessing inflammation and its role in comorbidities among persons living with HIV. Curr Opin Infect Dis 2019; 32:8–15. [PubMed: 30461454]
17. Brenchley JM, Price DA, Schacker TW et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med 2006; 12:1365–1371. [PubMed: 17115046]
18. Hunt PW, Sinclair E, Rodriguez B, et al. Gut epithelial barrier dysfunction and innate immune activation predict mortality in treated HIV infection. J Infect Dis 2014; 210:1228–1238. [PubMed: 24755434]
19. Marchetti G, Tincati C, Silvestri G: Microbial translocation in the pathogenesis of HIV infection and AIDS. Clin Microbiol Rev 2013; 26:2–18. [PubMed: 23297256]
20. Somsouk M, Estes JD, Deleage C, et al. Gut epithelial barrier and systemic inflammation during chronic HIV infection. AIDS 2015; 29:43–51. [PubMed: 25387317]
21. Man AL, Bertelli E, Rentini S, et al. Age-associated modifications of intestinal permeability and innate immunity in human small intestine. Clin Sci (Lond) 2015; 129:515–527. [PubMed: 25948052]
22. Steele AK, Lee EJ, Vestal B et al. Contribution of intestinal barrier damage, microbial translocation and HIV-1 infection status to an inflammaging signature. PLoS One 2014; 9:e97171.
23. Mueller S, Saunier K, Hanisch C et al. Differences in fecal microbiota in different European study populations in relation to age, gender, and country: a cross-sectional study. Appl Environ Microbiol 2006; 72:1027–1033. [PubMed: 16461645]
24. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. Nature 2012; 486:222–227. [PubMed: 22699611]
25. Buford TW: (Dis)Trust your gut: the gut microbiome in age-related inflammation, health, and disease. Microbiome 2017; 5:80. [PubMed: 28709450]
26. Hippe B, Zwielehner J, Liszt K, et al. Quantification of butyryl CoA:acetate CoA-transferase genes reveals different butyrate production capacity in individuals according to diet and age. FEMS Microbiol Lett 2011; 316:130–135. [PubMed: 21204931]
27. Rampelli S, Candela M, Turroni S et al. Functional metagenomic profiling of intestinal microbiome in extreme ageing. Aging 2013; 5:902–912. [PubMed: 24334635]
28. Biagi E, Franceschi C, Rampelli S, et al. Gut Microbiota and Extreme Longevity. Curr Biol 2016; 26:1480–1485. [PubMed: 27185560]
29. Biagi E, Nylund L, Candela M, et al. Through ageing, and beyond: gut microbiota and inflammatory status in seniors and centenarians. PLoS One 2010; 5:e10667.
30. Kong F, Deng F, Li Y, Zhao J. Identification of gut microbiome signatures associated with longevity provides a promising modulation target for healthy aging. Gut Microbes 2019; 10:210–215. [PubMed: 30142010]
31. Kong F, Hua Y, Zeng B, et al. Gut microbiota signatures of longevity. Curr Biol 2016; 26:R832–R833. [PubMed: 27676296]
32. Odamaki T, Kato K, Sugahara H, et al. Age-related changes in gut microbiota composition from newborn to centenarian: a cross-sectional study. BMC Microbiol 2016; 16:90. [PubMed: 27220822]
33. Santoro A, Ostan R, Candela M et al. Gut microbiota changes in the extreme decades of human life: a focus on centenarians. Cell Mol Life Sci 2018; 75:129–148. [PubMed: 29032502] * Review highlighting the recent studies conducted in Europe and Asia investigating microbiome features associated with extreme longevity.

34. Wang F, Yu T, Huang G et al. Gut Microbiota Community and Its Assembly Associated with Age and Diet in Chinese Centenarians. J Microbiol Biotechnol 2015; 25:1195–1204. [PubMed: 25839332]

35. Wu L, Zeng T, Zinellu A, et al. A Cross-Sectional Study of Compositional and Functional Profiles of Gut Microbiota in Sardinian Centenarians. mSystems 2019; 4.

36. Bian G, Gloor GB, Gong A, et al. The Gut Microbiota of Healthy Aged Chinese Is Similar to That of the Healthy Young. mSphere 2017; 2.

37. Claesson MJ, Jeffery IB, Conde S, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature 2012; 488:178–184. [PubMed: 22797518]

38. Haran JP, Bucci V, Dutta P, et al. The nursing home elder microbiome stability and associations with age, frailty, nutrition and physical location. J Med Microbiol 2018; 67:40–51. [PubMed: 29134939]

39. Jackson MA, Jeffery IB, Beaumont M, et al. Signatures of early frailty in the gut microbiota. Genome Med 2016; 8:8. [PubMed: 26822992]

40. Maffei VJ, Kim S, Blanchard Et, et al. Biological Aging and the Human Gut Microbiota. J Gerontol A Biol Sci Med Sci 2017; 72:1474–1482. [PubMed: 28444190]

41. van Tongeren SP, Slaets JP, Harmsen HJ, Welling GW. Fecal microbiota composition and frailty. Appl Environ Microbiol 2005; 71:6438–6442. [PubMed: 16204576]

42. Fielding RA, Reeves AR, Jasuja R, et al. Muscle strength is increased in mice that are colonized with microbiota from high-functioning older adults. Exp Gerontol 2019; 127:110722.** First study to provide direct evidence of link between human gut microbiota and muscle. Transfer of fecal samples from high-functioning human adults into germ-free mice resulted in increased grip strength when compared to low-functioning-colonized mice.

43. Cattaneo A, Cattane N, Galluzzi S, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 2017; 49:60–68. [PubMed: 27776263]

44. Saji N, Niida S, Murotani K, et al. Analysis of the relationship between the gut microbiome and dementia: a cross-sectional study conducted in Japan. Sci Rep 2019; 9:1008. [PubMed: 30700769]

45. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. Sci Rep 2017; 7:13537.

46. Wang Z, Klipfell E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011; 472:57–63. [PubMed: 21475195]

47. Zhu W, Wang Z, Tang WHW, Hazen SL. Gut Microbe-Generated Trimethylamine N-Oxide From Dietary Choline Is Prothrombotic in Subjects. Circulation 2017; 135:1671–1673. [PubMed: 28438808]

48. Ahmadmehrabi S, Tang WHW: Gut microbiome and its role in cardiovascular diseases. Curr Opin Cardiol 2017; 32:761–766. [PubMed: 29023288]

49. Vujkovic-Cvijin I, Somsouk M: HIV and the Gut Microbiota: Composition, Consequences, and Avenues for Amelioration. Curr HIV/AIDS Rep 2019; 16:204–213. [PubMed: 31037552] ** Excellent review summarizing the numerous studies investigating the impact of HIV infection on the gut microbiome.

50. Armstrong AJS, Shaffer M, Nusbacher NM, Griesmer C, et al. An exploration of Prevotella-rich microbiomes in HIV and men who have sex with men. Microbiome 2018; 6:198. [PubMed: 30396369]

51. Kelley CF, Kraft CS, de Man TJ, et al. The rectal mucosa and condomless receptive anal intercourse in HIV-negative MSM: implications for HIV transmission and prevention. Mucosal Immunol 2017; 10:996–1007. [PubMed: 27848950]

52. Noguera-Julian M, Rocafort M, Guillén Y, et al. Gut Microbiota Linked to Sexual Preference and HIV Infection. EBioMedicine 2016; 5:135–146. [PubMed: 27077120]

53. Pinto-Cardoso S, Klatt NR, Reyes-Teran G. Impact of antiretroviral drugs on the microbiome: unknown answers to important questions. Curr Opin HIV AIDS 2018; 13:53–60. [PubMed: 29028667]

54. 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. [PubMed: 24399150]
55. McHardy IH, Li X, Tong M et al. HIV infection is associated with compositional and functional shifts in the rectal mucosal microbiota. Microbiome 2013; 1:26. [PubMed: 24451087]
56. Mutlu EA, Keshavarzian A, Losurdo J, et al. A compositional look at the human gastrointestinal microbiome and immune activation parameters in HIV infected subjects. PLoS Pathog 2014; 10:e1003829.
57. Vujkovic-Cvijin I, Dunham RM, Iwai S, et al. Dysbiosis of the Gut Microbiota Is Associated with HIV Disease Progression and Tryptophan Catabolism. Sci Transl Med 2013; 5:193ra191.
58. Yang L, Poles MA, Fisch GS, et al. HIV-induced immunosuppression is associated with colonization of the proximal gut by environmental bacteria. AIDS 2016; 30:19–29. [PubMed: 26731752]
59. Dillon SM, Kibbie J, Lee EJ, et al. Low abundance of colonic butyrate-producing bacteria in HIV infection is associated with microbial translocation and immune activation. AIDS 2017; 31:511–521. [PubMed: 28002063]
60. Durban A, Abellan JJ, Jimenez-Hernandez N, et al. Assessing gut microbial diversity from feces and rectal mucosa. Microbial Ecology. 2011; 61:123–33. [PubMed: 20734040]
61. Vazquez-Castellanos JF, Serrano-Villar S, Latorre A, et al. Altered metabolism of gut microbiota contributes to chronic immune activation in HIV-infected individuals. Mucosal Immunol 2015; 8:760–72. [PubMed: 25407519]
62. Dubourg G, Lagier JC, Hue S, et al. Gut microbiota associated with HIV infection is significantly enriched in bacteria tolerant to oxygen. BMJ Open Gastroenterol 2016; 3:e000080.
63. Qing Y, Xie H, Su C, et al. Gut Microbiome, Short-Chain Fatty Acids, and Mucosa Injury in Young Adults with Human Immunodeficiency Virus Infection. Dig Dis Sci 2019; 64:1830–1843. [PubMed: 30560340]
64. Serrano-Villar S, Vazquez-Castellanos JF, Vallejo A, et al. The effects of prebiotics on microbial dysbiosis, butyrate production and immunity in HIV-infected subjects. Mucosal Immunol 2017; 10:1279–1293. [PubMed: 28000678]
65. Serrano-Villar S, Rojo D, Martinez-Martinez M, et al. HIV infection results in metabolic alterations in the gut microbiota different from those induced by other diseases. Sci Rep 2016; 6:26192.
66. Guillen Y, Noguera-Julian M, Rivera J, et al. Low nadir CD4+ T-cell counts predict gut dysbiosis in HIV-1 infection. Mucosal Immunol 2019; 12:232–246. [PubMed: 30171206] * Study using shotgun metagenomics to highlight compositional and functional shifts associated with gene richness across various HIV-1 transmission groups. These shifts were similar to those found in other diseases featuring gut inflammation.
67. Serrano-Villar S, Rojo D, Martinez-Martinez M, et al. Gut Bacteria Metabolism Impacts Immune Recovery in HIV-infected Individuals. EBioMedicine 2016; 8:203–216. [PubMed: 27428431]
68. Vazquez-Castellanos JF, Serrano-Villar S, Jimenez-Hernandez N, et al. Interplay between gut microbiota metabolism and inflammation in HIV infection. ISME J 2018; 12:1964–1976. [PubMed: 29789624]
69. Missailidis C, Neogi U, Stenvinkel P, et al. The microbial metabolite trimethylamine-N-oxide in association with inflammation and microbial dysregulation in three HIV cohorts at various disease stages. AIDS 2018; 32:1589–1598. [PubMed: 29620717]
70. Liu J, Johnson R, Dillon S, et al. Among older adults, age-related changes in the stool microbiome differ by HIV-1 serostatus. EBioMedicine 2019; 40:583–594. [PubMed: 30685386] * One of the first studies to investigate the combined effect of age and HIV on gut microbiome. Highlighted that age and HIV interact to shape the fecal microbiome in ART-treated, older adults.
71. Rhoades N, Mendoza N, Jankeel A, et al. Altered Immunity and Microbial Dysbiosis in Aged Individuals With Long-Term Controlled HIV Infection. Front Immunol 2019; 10:463. [PubMed: 30915086] * Additional study investigating the fecal microbiome of older people with HIV on long-term treatment. Observations suggest a loss of compartmentalization of bacteria.

72. Gonzalez-Hernandez LA, Ruiz-Briseno MDR, Sanchez-Reyes K et al. Alterations in bacterial communities, SCFA and biomarkers in an elderly HIV-positive and HIV-negative population in western Mexico. BMC Infect Dis 2019; 19:234. [PubMed: 30845929] * Study from Mexico demonstrating alterations in fecal microbiome of older PWH including higher levels of propionate, but lower levels of butyrate and acetate versus controls.

73. Zhang F, Yang J, Ji Y, et al. Gut Microbiota Dysbiosis Is Not Independently Associated With Neurocognitive Impairment in People Living With HIV. Front Microbiol 2018; 9:3352. [PubMed: 30761121]

74. Kehrmann J, Menzel J, Saeedghalati M, et al. Gut Microbiota in Human Immunodeficiency Virus-Infected Individuals Linked to Coronary Heart Disease. J Infect Dis 2019; 219:497–508. [PubMed: 30202890]

75. Li XV, Leonardi I, Iliev ID. Gut Mycobiota in Immunity and Inflammatory Disease. Immunity 2019; 50:1365–1379. [PubMed: 31216461]

76. Neil JA, Cadwell K. The Intestinal Virome and Immunity. J Immunol 2018; 201:1615–1624. [PubMed: 30181300]

77. Handley SA, Thackray LB, Zhao G, Presti R, et al. Pathogenic simian immunodeficiency virus infection is associated with expansion of the enteric virome. Cell 2012; 151:253–266. [PubMed: 23063120]

78. Monaco CL, Gootenberg DB, Zhao G, et al. Altered Virome and Bacterial Microbiome in Human Immunodeficiency Virus-Associated Acquired Immunodeficiency Syndrome. Cell Host Microbe 2016; 19:311–322. [PubMed: 26962942]

79. Rocafort M, Noguera-Julian M, Rivera J, et al. Evolution of the gut microbiome following acute HIV-1 infection. Microbiome 2019; 7:73. [PubMed: 31078141]

80. Esebelahie NO, Enweani IB, Omoregie R. Candida colonisation in asymptomatic HIV patients attending a tertiary hospital in Benin City, Nigeria. Libyan J Med 2013; 8:20322.

81. Ramendra R, Isnard S, Mehraj V, et al. Circulating LPS and (1-->3)-beta-D-Glucan: A Folie a Deux Contributing to HIV-Associated Immune Activation. Front Immunol 2019; 10:465. [PubMed: 30967860]

82. Bandera A, De Benedetto I, Bozzi G, Gori A. Altered gut microbiome composition in HIV infection: causes, effects and potential intervention. Curr Opin HIV AIDS 2018; 13:73–80. [PubMed: 29045252]

Key questions that remain.

The above studies provide the first insights into how aging and HIV converge to impact the microbiome and suggest that HIV may influence age-associated effects on the gut microbiome. However, a number of questions remain.

1. How does the enteric microbiome contribute to age-associated co-morbidities such as frailty, dementia and CVD in older PWH?

   Additional well-controlled studies that identify both age and HIV effects on gut bacterial communities and their metabolic products in the setting of co-morbidities will help to identify functional pathways that may be modifiable by interventions that alter the existing microbiome (e.g., pre/probiotics, fecal transplant, dietary manipulation, exercise) to supplement current treatment strategies and improve clinical outcomes. Critical to the effectiveness of these studies in contributing to our understanding of the microbiome in HIV and aging will be the undertaking of well-controlled studies accounting for the multitude of confounders that impact the gut microbiome (e.g., diet, gender, sexual behavior, ART) and investigations into microbial communities and function at the tissue level.

2. How do age and HIV impact the virome and mycobiome in older PWH?

   Although techniques for characterizing the viral, bacteriophage and fungal populations that inhabit the human body may be less well established than those used for bacteria, both the virome (viruses, bacteriophages) and mycobiome (fungal) communities influence host physiology in both positive and negative ways (reviewed in (75, 76)) and therefore may impact gut health in older PWH. Indeed, alterations in the fecal virome of PWH (aged <50 years) were linked to features of HIV-associated pathogenesis (77–79). The prevalence of fecal *Candida* colonization significantly increased with age in ART-treated PWH, (80) and systemic levels of fungal β-D-glucan are known to associate with inflammatory and immune activation markers (reviewed in (81)). Treating or modulating the entire gut microbial community may dramatically improve gut health in aging PWH over simply treating bacterial dysbiosis.

3. How can the mechanisms that drive dysbiosis be elucidated in order to further improve treatment options?

   A number of clinical studies have attempted to durably alter the microbiome or block microbial translocation but thus far have met with limited success (reviewed in (82)). These types of treatments will be drastically improved by a better understanding of mechanisms by which HIV-associated mucosal damage drives dysbiosis as well as how dysbiotic microbial and metabolic profiles influence gut health and host immunity in persons aging with HIV infection.

Key Points:

- A breakdown in intestinal homeostasis and the associated leaky gut and increased microbial translocation are linked to systemic inflammation in both HIV and aging.
- Aging is associated with alterations in the gut bacterial microbiome, typically characterized by an increase in facultative anaerobes with pathogenic or inflammatory properties and a decrease in obligate anaerobes that play critical roles in maintaining intestinal homeostasis and in regulating host immunity.
- People with HIV also have dysbiotic gut microbiomes, many features of which reflect those observed in elderly persons.
- The age effect on the gut microbiome and associations between microbiota and systemic biomarkers in an older population differ based on HIV serostatus.
- Additional well-controlled studies that identify both HIV and age effects on gut bacterial communities and their metabolic products in the setting of co-morbidities will help to identify functional pathways that may be modifiable by interventions that alter the existing microbiome to supplement current treatment strategies and improve clinical outcomes.