Gut microbial diversity in HIV infection post combined antiretroviral therapy: a key target for prevention of cardiovascular disease

Mohamed El-Far and Cécile L. Tremblay

Purpose of review
Although the HIV-infected population is living longer and getting older under current treatment regimens, significant challenges arise for health management as the infection is associated with various premature aging phenotypes, particularly increased incidence of cardiovascular diseases (CVDs). Here we review the current understanding of HIV-related gut dysbiosis in association with CVD and advances in clinical trials aiming to restore gut microbial diversity.

Recent finding
Identification of a unique signature for gut dysbiosis in HIV infection between different cohorts remains challenging. However, low diversity of microbiota combined with the outgrowth of pathogenic bacterial species together with dysregulated metabolic pathways have been linked to compromised gut immunity, bacterial translocation and systemic inflammation, hence higher CVD risk among different cohorts. Data from recent clinical trials aiming to evaluate the tolerability and efficacy of probiotics in treated HIVþ patients are promising and support a significant increase in microbiota diversity and reduction of systemic inflammation. However, the impact of these microbial and immunological corrections on the prevalence of CVD in HIVþ patients remains unclear.

Summary
Positive immunological outcomes following enrichment of the gut microbial diversity have been documented, and further trials are in progress to evaluate the range of patients, with different immunological backgrounds, who might benefit from these treatments.

Keywords
cardiovascular diseases, HIV, metabolic pathways, microbiota, probiotic

INTRODUCTION
In the modern combined antiretroviral therapy (cART) era, vascular diseases remain a leading cause of mortality in HIV infection [1]. Increasing number of observational studies on cohorts of HIV-infected and treated patients, including ours [2], clearly show that acute myocardial infarction and other vascular diseases such as coronary heart diseases are significantly increased among the infected population [3,4,5*]. A recent meta-analysis on 44 cohorts of HIVþ patients showed increased cardiac morbidities in the infected population and further suggested to consider HIV infection, per se, as a vascular risk [6**]. Significantly, the same meta-analysis of studies done on 334,417 HIVþ individuals from both United States America and Europe demonstrated significant geographical disparities as to the incidence rates of cardiac diseases and mortality. Both HIVþ and HIV− populations in United States of America were found to have a poorer vascular health compared with their counterparts in Europe, a risk that is clearly accentuated by HIV infection. Although a multitude of risk factors may underlie the impact of these geographical disparities on cardiovascular diseases (CVDs), environmental exposure and more
KEY POINTS

- Gut dysbiosis in HIV infection continues to represent a health complication in the post combined antiretroviral therapy era and is highly associated with persistent inflammation and CVDs in HIV+ patients.

- Identification of bacterial signatures for both health and disease remains challenging and combination of metagenomics with metabolomics analyses from the same biological sample holds promise for a better understanding and better therapeutic targeting.

- Recent clinical trials aiming to promote wider diversities of gut microbiota in HIV+ patients are encouraging and efforts are ongoing to address whether all patients, immune responders and immune nonresponders, would benefit from these treatments.

GUT MICROBIOTA AND HEALTH: FROM BIRTH TO DEATH

Human cells are largely outnumbered with resident bacteria (estimated to be >100 trillion bacteria) that live on or within the human body [10,11]. Although it may seem odd, at first glance, to imagine that the human body is submerged with a such tremendous numbers of microbes, body microbiota, especially the commensal gut residents that represent more than 99% of the total body-associated bacteria [12*], are in many ways beneficial for human’s health. In addition to its vital role in energy homeostasis, through the impact on host metabolism [13,14], gut microbiota is significantly involved in educating and shaping the two arms of the immune system; both innate and adaptive responses [15]. The importance of these biological processes is reflected by the very early transmission of the mothers’ microbiota to their newborns during delivery [16,17]. Composition of the gut microbiota of newborn babies during the first week of age is similar to that of their mothers and depends on the mode of delivery [18,19]. At the adult stage, composition of the GIT microbiota varies between individuals but remains relatively stable over time within single individuals [20,21]. This composition includes bacteria belonging to different abundant phyla; Actinobacteria, Bacteroidetes, Firmicutes and Proteobacteria, but also contains less diverse bacterial phyla such as Verrucomicrobia, Lentisphaerae, Synergistetes, Planctomycetes, Tenericutes and the Deinococcus-Thermus group [22]. Accumulating evidence points to this diversity as a key element for a better health as it provides functional redundancy, whereas lower diversity is associated with poorer health, particularly associated with inflammatory diseases [23]. The importance of this diversity is particularly interesting when it comes to aging, frailty and longevity. Recent work on female twins from the TwinsUK cohort showed an inverse correlation between diversity of the gut microbiota and frailty [24**]. The Eubacterium dolichum (phylum Firmicutes) and Eggerthella lenta (phylum Actinobacteria) species were among the most abundant species that positively associated with frailty, whereas lower Faecalibacterium prausnitzii (an anti-inflammatory commensal bacterium [25]) showed an inverse correlation [24**]. Significantly, in an effort to identify microbial signatures that differentiate long-living and younger groups on two cohorts of aging centenarian patients from Italy and China, data on gut microbiota showed common greater bacterial community richness [26**,27**]. In the two cohorts, members of the Clostridium cluster XIVa (butyrate-producing bacteria), Ruminococcaceae, Akkermansia and Christensenellaceae were enriched in the long-living groups. As all of these bacterial species are potentially beneficial, there is likely a link between longevity and microbiota. However, cause–effect studies in either a clinical setting or in appropriate animal model are still needed to mechanistically confirm these conclusions.

HIV INFECTION AND DIVERSITY OF GUT MICROBIOTA

To better understand the gut bacterial imbalance under HIV infection and its impact on the overall immune responses, it is first important to recognize the nature of the reference or ‘normal’ gut microbial composition under steady state healthy conditions. Meanwhile, it is obvious that defining a healthy microbiome is difficult as it is challenging to define
the healthy conditions per se. Yet, the Human Microbiome Project (HMP) has defined a set of inclusion and exclusion criteria based on age, overt disease history, use of immunomodulatory drugs or probiotics to define a healthy unbiased cohort of patients that might present minimally perturbed conditions to meet the requirement of the normal microbiome studies [28]. By using these criteria, the HMP reported that the healthy gut microbiota shows a large degree of communities’ diversity and a progression between individuals, from a dominant Bacteroides to dominant Firmicutes diversities [21]. This diversity is dynamic as interindividual variations are influenced by a variety of environmental, physical, genetic or immunological factors [29]. Therefore, the healthy microbiome might not only be defined by its composition but also by its resilience following insult by either exposure to environmental changes/stresses or following a given host illness [23]. Significantly, an ecological model was proposed by Costello et al. [30] suggesting three scenarios for human microbiome assembly; these include development in infants, assembly in the context of invasive pathogenic species and recovery from antibiotics. The last two scenarios typically apply to patients infected with HIV with the exception that this infection remains persistent, even under treatment, and therefore impairment of microbiota diversity is likely to also persist. As HIV targets CD4 T cells, the virus can technically impact all body lymphoid, mucosal and nonlymphoid organs in which these cells can reach and so impacts the associated microbiome. Although true, yet HIV infection is mainly considered as a gut disease as it significantly depletes CD4 T cells from mucosal sites, particularly from gut-associated lymphoid tissues [31]. HIV also induces apoptosis of gut enterocytes, local inflammation (increased TNFα) and promotes dysregulated gut permeability, all of which significantly alters the GIT epithelium structure/function and the overall intestinal immunity [32–35]. In addition, HIV infection depletes mucosal Th17 cells that play a critical role in the antimicrobial defense [36–39]. Together, these alterations are likely to impact the composition of the gut microbial communities leading to dysbiosis. Vujkovic-Cvijin et al. [40] showed that gut microbiota from HIV-infected patients is enriched with genera from the Enterobacteriaceae family that includes members known to be associated with chronic inflammation such as Salmonella, Escherichia, Serratia, Shigella and Klebsiella species. Mutlu et al. [41] also showed that the lower GIT of HIV-infected patients is enriched with a number of potentially pathogenic bacteria such as Prevotella and, in contrast, has poor content of the commensal Bacteroides. This was also associated with increased systemic inflammatory cytokines such as IL-6 and TNFα. Significantly, HIV+ elite controllers, a subgroup of

COMPOSITION OF GUT MICROBIOTA AND ALTERATION OF METABOLIC PATHWAYS

HIV-induced changes in the composition of gut microbial communities is associated with metabolic alteration that, on their turn, would lead to adverse clinical outcomes. Recent data comparing progressor patients with elite controllers, showed that elite controllers have a distinct microbiota metabolic profile that favors fatty acid metabolism, peroxisome proliferator-activated receptors-signaling and lipid biosynthesis protein pathways combined with a decrease in carbohydrate metabolism and secondary bile acid synthesis [42**]. Furthermore, other studies showed that progressive patients are enriched with bacterial communities that catabolise the essential amino acid tryptophan through their capacity to produce the rate-limiting enzyme indoleamine 2,3-dioxygenase 1 [40]. The rate of tryptophan catabolism is known to be increased in HIV infection and is associated with disease progression [43]. Increased levels of tryptophan catabolites, particularly 3-hydroxyanthranilic acid is directly involved in the biased balance of Th17 to Treg cells which further contributes to immune suppression, bacterial translocation and systemic inflammation [43]. More recently, Serrano-Villar et al. [44**] showed viral-induced quantifiable metabolic changes specific to HIV. Using liquid chromatography coupled with mass spectrometry, this study reported a metabolic deficit in the gut microbiota of HIV-infected patients with impaired capacity to produce three amino acids: proline, phenylalanine and lysine. In contrast, but in agreement with the study of Vujkovic-Cvijin et al. [40], there was an accumulation of the tryptophan metabolite 3-hydroxyanthranilate. Significantly, tryptophan catabolism and the kynurenine pathway are inversely correlated with microbiota richness [42**] and thus highlighting the importance of the microbial metabolic pathways in the overall immune status as summarized in Fig. 1.

MICROBIOTA AND METABOLOMICS STUDIES IN HIV AND CARDIOVASCULAR DISEASE

Diet metabolism by gut microbiota produces small-molecule metabolites that interfere with gut
physiology. Measuring these metabolites by metabolomic profiling, although not novel, has gained significant interest over the past decade due to major advances in the high-throughput technologies that permit identification of a large number of metabolites from a single biological sample [50–52]. Using these technologies, Wang et al. [53] identified three metabolites of the dietary lipid phosphatidylcholine, choline, trimethylamine-N-oxide (TMAO), and betaine, that promote and predict risk for CVD. At the mechanistic level, TMAO alters calcium signaling, cholesterol and bile acid metabolism, fosters activation of inflammatory pathways and promotes foam cell formation, all of which are linked with atherosclerosis [54]. TMAO also increases platelet hyper-reactivity, which is associated with cardiometabolic diseases and potential risks of thrombosis [49*]. Of note, TMAO production was shown to vary between men groups based on individual’s diversity of the gut microbiota [55*]. Patients with higher Firmicutes to Bacteroidetes enrichment had higher TMAO production. More recently, Rath et al. [48*] established databases for the key genes of the main trimethylamine (a precursor of TMAO) synthesis pathways that permitted the identification of bacterial producing communities, Clostridium XIVa strains and Eubacterium sp. strain AB3007 among others. Significantly, a meta-analysis on 19 prospective studies showed that blood TMAO and its precursors are associated with elevated risk of major adverse cardiovascular events and a higher all-cause mortality independently of traditional risk factors [56*]. However, a recent study in HIV infection failed to show any association between TMAO levels and platelet-hyperactivity in both treated and untreated patients [57*], although TMAO levels were elevated. Rather, the study showed a significant association between TMAO and sCD14 and a higher ratio of TMAO to its precursors carnitine and betaine in treated patients. The lack of direct association with platelet hyperactivation in this study may in part be explained by the multitude

---

**FIGURE 1.** Lower microbial diversity and dysregulated bacterial metabolic pathways accentuate systemic inflammation in HIV infection. Panel (a) under steady state conditions, gut lumen contains a significant diversity of bacterial communities that differ between individuals but remain relatively stable within single individual. Intact gut epithelium together with normal innate responses mediated by macrophages and dendritic cells, as well as with the Th17 normal T-cell functions (production of IL-17A and IL-17F, IL22 and induction of antimicrobial proteins such as defensins), protects against microbial translocation and further inflammation. Panel (b) under HIV infection, gut epithelium integrity is compromised by epithelial cell death through apoptosis [45] and weakened tight junctions between cells [46] thus leading to enhanced translocation of microbes and microbial products. Together with the HIV-mediated depletion of Th17 cells [37] and enhanced expression of cytokines such as IL-32 [47] that amplifies the inflammatory process, this induces a persistent activation of immune cells and high levels of inflammatory cytokines in circulation. The compromised gut immune response is associated with a decrease in the diversity of microbiota composition and a dysregulated metabolism (lower production of certain amino acids such as proline, phenylalanine and lysine and accelerated catabolism of others such as tryptophan) [44*]. Accelerated tryptophan catabolism leads to increase in the kynurenine pathway, which is involved in the decrease of Th17 cell levels, thus further promoting a biased mucosal immunity. Dysregulated microbial metabolism also leads to increase in the trimethylamine [48*], a precursor for trimethylamine-N-oxide, a molecule involved in thrombosis risk [49*]. Ag, antigen; DC, dendritic cells; EC, epithelial cells.
of HIV-associated factors that may interfere with platelet activation. This may also explain earlier reports showing an inverted U-shaped association between TMAO levels and the presence of coronary artery stenosis among HIV-infected men [58]. In this last study, it was only the middle subpopulation within the second and third TMAO quartiles, compared with the first and fourth quartile, that showed an association with coronary stenosis, which suggests the involvement of other pathways. In this regard, Haissman et al. [57] suggested a role for cART in TMAO metabolism. This observation together with the fact that not all patients with high TMAO levels will experience a cardiac complication limits the role of TMAO as a strong predictor of CVD. However, further studies are needed to dissect the TMAO metabolic pathways to investigate whether there are other compensatory mechanisms that counteract TMAO functions under significantly higher levels of this small molecule. In addition, profound metabolomic studies coupled with microbiota diversity in HIV-infected and treated patients are still needed to uncover other metabolites that may better predict CVD.

RESILIENCE OF MICROBIOTA ASSEMBLY BY CLINICAL INTERVENTION

Administration of a single or multiple biological components of microorganisms (probiotics) into HIV-infected patients to attain resilience of gut microbiota assembly and hence recovery of important metabolic pathways seems to be clinically feasible. A number of successful clinical trials show a clinical benefit from administrating probiotics. For instance, the ProBio-HIV Clinical Trial administered a 1-g packet containing a mixture of different species of bacteria belonging to Lactobacillus and Streptococcus to cART-treated HIV+ patients twice a day for 48 weeks, leading to a decrease in CD4 T-cell activation, lower levels of sCD14 and Lipopolysaccharide-binding protein (LBP) as well as C-reactive protein (CRP) (a biomarker for CVD risk) [59]. Significantly, in the ProGut clinical trial (a double-blind study on 32 patients receiving cART but having CD4 counts below 500), daily self-administration of fermented skimmed milk supplemented with different Lactobacillus and Bifidobacterium subsp. for 8 weeks leads to a significant decrease in CRP, IL-6 and D-dimer, all of which are considered as inflammatory risk markers for CVD [60]. Similarly, studies on probiotics supplementation with Saccharomyces boulardii in HIV-1-infected patients with virologic suppression showed decreased systemic inflammation (lower IL-6) and microbial translocation (lower LBP) [61]. Furthermore, S. boulardii treatment significantly decreased bacterial species within the Clostridiales family, which were correlated with systemic levels of bacterial translocation and inflammation markers at baseline prior to treatment [62].

Fecal microbial transplantation (FMT) is another clinical intervention to promote gut microbial diversity and healthier metabolic environment through the transfer of the bacterial communities in stool isolated from a healthy donor. This type of transfer although shows significant results in the treatment of Clostridium difficile infection (CDI) [63] does not normalize gut microbiota of HIV infected and treated patients [64]. The microbiota taxa remained restrained with no significant impact on the inflammatory markers monitored in this study. Indeed, in a study to treat CDI, fecal transplantation promoted complete resolution of symptoms in patients with CDI alone but failed in patients with inflammatory bowel diseases (IBD) [65]. As HIV and IBD are both considered as inflammatory gut diseases, the lack of success of FMT treatment in both cases may reflect a common pathway of failure that might be linked to the significant level of intestinal insult and inflammation in these patients. Further studies will likely address these questions. Of interest, pilot clinical trials (PROOV IT I and PROOV IT II) to study the impact of probiotics on the gut microbiota in HIV-infected, cART-naïve or cART-treated with poor CD4 recovery, are currently in progress and results from these studies will likely guide future avenues for microbiota studies in patients with marked gut inflammation [66].

CONCLUSION

Gut microbiota is now acknowledged as a potential target for biotherapies to dampen inflammation and risks to develop CVD. However, due to the large diversities between individuals in terms of microbial composition, it remains challenging to identify a signature for the optimal microbial make-up that might protect against these serious health complications. Coupling the microbiota metagenomics with high-throughput metabolomics technologies in the same study represents an opportunity to understand not only the individual’s diversities but also the functional microbiota in terms of microbe–microbe and microbe–host interactions. Finally, whether or not a single regimen of microbial supplementation or a combined therapy targeting a particular metabolic pathway would be necessary to promote recovery of a healthier gut and lower CVD risk is not yet clear and still waiting for larger clinical trials on different populations that should consider geographical disparities.
Acknowledgements

Thanks to Ms Sonia Deschênes for her careful reading of the article.

Financial support and sponsorship
M.E.-F. and C.L.T.’s research is funded through National Institutes of Health in the United States, NIH (1R01AG054324-01) and the Canadian Institutes of Health Research, CIHR (PJT 148482).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

● of special interest
●● of outstanding interest

1. Sackoff JE, Hanna DB, Pfeiffer MR, Torian LV. Causes of death among persons with AIDS in the era of highly active antiretroviral therapy: New York City, Ann Intern Med 2006; 145:397–406.

2. Durand M, Sheehy O, Baril JG, et al. Association between HIV infection, antiretroviral therapy, and risk of acute myocardial infection: a cohort and nested case-control study using Quebec’s public health insurance database. J Acquir Immune Defic Syndr 2011; 57:245–253.

3. Triant VA, Lee H, Hadigan C, Grinspoon SK. Increased acute myocardial infarction rates and cardiovascular risk factors among patients with human immunodeficiency virus disease. J Clin Endocrin Metab 2007; 92:2906–2912.

4. Lang S, Mary-Krause M, Cotte L, et al. Increased risk of myocardial infarction in HIV-infected patients in France, relative to the general population. AIDS Circ 2010; 24:1228–1230.

5. Drozd DR, Kitahata MM, Althoff KN, et al. Increased risk of myocardial infarction in HIV-infected individuals in North America compared to the general population. J Acquir Immune Defic Syndr 2017; 75:568–576.

6. Gutierrez J, Albuquerque ALA, Falcon L. HIV infection as vascular risk: a systematic review of the literature and meta-analysis. PLoS One 2017; 12:e0176686.

A meta-analysis clearly showing geographical disparities as to cerebral complications associated with unsuppressed HIV infection and cardiac outcomes associated with combined antiretroviral therapy (cART) treatment. The study suggests that HIV infection, per se, should be considered as a vascular risk and that reducing vascular burden represents an urgent medical need.

7. Yang J, Faroli A, Korre M, Kales SN. Modified Mediterranean diet score and cardiovascular risk in a North American working population. PLoS One 2014; 9:e87539.

8. Rowland J, Gibson G, Heinken A, et al. Gut microbiota functions: metabolism of nutrients and other food components, Eur J Nutr 2017; 17:1445–1449.

9. Nowak P, Troseid M, Avershina E, et al. Gut microbiota diversity predicts immune status in HIV-1 infection. AIDS 2015; 29:2409–2418.

The study shows that alterations in gut microbiota in HIV infection persist even after receiving cART and suggests to use the intervention of reshaping the microbiota upon commencing therapy as an adjuvant.

10. Luckey TD. Introduction to intestinal microecology. Am J Clin Nutr 1972; 19:252–1294.

11. Bianconi E, Piovesan A, Facchin F, et al. An estimation of the number of cells in the human body, Ann Hum Biol 2013; 40:463–471.

12. Sender R, Fuchs S, Milo R. Revised estimates for the number of human and bacteria cells in the body, PLoS Biol 2016; 14:e1002533.

A novel estimate for the total number of human-body-associated bacteria suggesting equal numbers with human cells.

13. Nicholson JK, Holmes E, Kinross J, et al. Host-gut microbiota metabolic interactions. Science 2012; 336:1262–1267.

14. Tumbee PE, Mahowald MA, et al. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006; 444:1027–1031.

15. Rasko EA, Bajgulov S, Pagliino J, Eslami-Vasarneh F, et al. Recognition of common mesofilic bacteria by toll-like receptors is required for intestinal homeostasis. Cell 2004; 118:229–241.

16. Aagaard K, Ma J, Antony KM, et al. The plasma harbora a unique microbiome. Sci Transl Med 2014; 6:237ra65.

17. Bearfield C, Davenport ES, Sivasathasundaram V, Alkaker RP. Possible association between amniotic fluid micro-organism infection and microflora in the mouth. BJOG 2002; 109:527–533.

18. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proc Natl Acad Sci U S A 2010; 107:11971–11975.

19. Hesla HM, Stienius F, Jaderlund L, et al. Impact of lifestyle on the gut microbiota of healthy infants and their mothers—the ALADDIN birth cohort. FEMS Microbiol Ecol 2014; 90:791–801.

20. Costello EK, Lauber CL, Hamady M, et al. Bacterial community variation in human body habitats across space and time. Science 2009; 326:1694–1697.

21. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. Nature 2012; 486:207–214.

22. Rajilic-Stojanovic M, de Vos WM. The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbiol Rev 2014; 38:966–1047.

23. Lloyd-Price J, Abu-Ali G, Hutterton C. The healthy human microbiome. Genome Med 2016; 8:51.

24. Jackson MA, Jeffery IB, Beaumont M, et al. Signatures of early frailty in the gut microbiota, Genome Med 2016; 8:88.

Using 16S rRNA gene sequence data derived from fecal samples, this study shows a striking negative association between frailty and gut microbiota diversity. The study also identify particular bacteria species that are associated with frailty such as Eubacterium dolichum and Eggerthella lenta.

25. Sokol H, Pigneur B, Watterlot L, et al. Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci U S A 2008; 105:16731–16736.

26. Biagi E, Franceschi C, Rampelli S, et al. Gut microbiota and extreme longevity. Cell 2018; 26:1480–1486.

A study showing for the first time a phylogenetic microbiota analysis of semisupcentenarian humans (105–109 years old). The study shows that some bacteria such as Akkermansia, Bifidobacterium and Christensenellaceae may improve health maintenance during aging.

27. Kong F, Hua Y, Zeng B, et al. Gut microbiota signatures of longevity. Curr Biol 2016; 26:RB932–RB933.

28. Kong F, Hua Y, Zeng B, et al. Comparing gut microbiota from Chinese long-living centenarians to those from the Italian cohort. The study shows some similarities of gut microbiota signatures between the two cohorts.

29. Aagaard K, Petrosino J, Ketel W, et al. The Human Microbiome Project strategy for comprehensive sampling of the human microbiome and why it matters. FASEB J 2013; 27:1012–1022.

30. Quercia S, Candela M, Giulian C, et al. From lifetime to evolution: timescales of human gut microbiota adaptation. Front Microbiol 2014; 5:587.

31. Costello EK, Stagaman K, Dethlefsen L, et al. The application of ecological theory toward an understanding of the human microbiome. Science 2012; 336:1255–1262.

32. Brenchley JM, Schacker TW, Ruff LE, et al. CD4+ T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. J Exp Med 2004; 200:748–759.

33. Kapemba MS, Fleming SC, Sewankambo N, et al. Altered small-intestinal permeability associated with diarrhoea in human-immunodeficiency-virus-in-infected subjects compared with uninfected African subjects. Clin Sci (Lond) 1991; 81:327–334.

34. Cramp ME, Hing MC, Marrott DJ, et al. Bile acid malabsorption in HIV infected patients with chronic diarrhoea. Aust N Z J Med 1996; 26:368–371.

35. Sharpe D, Neilid P, Crane R, et al. Small intestinal transit, absorption, and permeability in patients with AIDS with and without diarrhea. Gut 1999; 45:70–76.

36. Koster DP. HIV infection and the gastrointestinal tract. AIDS 2005; 19:107–117.

37. Liang SC, Tan YH, Luxenberg DP, et al. Interleukin (IL)-22 and IL-17 are coexpressed by Th17 cells and cooperatively enhance expression of anti-microbial peptides. J Exp Med 2006; 203:2271–2279.

38. Brenchley JM, Paiardini M, Knox KS, et al. Differential Th17 CD4+ T cell depletion in pathogenic and nonpathogenic lentiviral infections. Blood 2008; 112:2826–2835.

39. Elhed A, Unutmaz D. Th17 cells and HIV infection. Curr Opin HIV AIDS 2010; 5:146–150.

40. Da Fonseca S, Niesls J, Poureaux S, et al. Impaired Th17 polarization of phenotypically naive CD4+ T cells during chronic HIV-1 infection and potential restoration with early ART. Retrovirology 2015; 12:38.

41. Vukovic-Gijvin I, Dunham RM, Heise S, et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. Sci Transl Med 2013; 5:193ra91.

42. Mufia EF, 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.

43. Vesterbacka J, Rivera J, Noyan K, et al. Metabolic profile in HIV infected elite controllers. Sci Rep 2017; 7:6269.
The microbiome in HIV

43. Favre D, Mold J, Hunt PW, et al. Tryptophan catabolism by indoleamine 2,3-dioxygenase 1 alters the balance of TH17 to regulatory T cells in HIV disease. Sci Transl Med 2010; 2:32ra36.

44. 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.

The study shows a metabolic signature of gut microbiota metabolism associated with metabolic deficits specific for HIV infection.

45. Li Q, Estes JD, Duan L, et al. Sigmoid immunodeficiency virus-induced intestinal cell apoptosis is the underlying mechanism of the regenerative enteropathy of early infection. J Infect Dis 2008; 197:420–429.

46. Applel HJ, Schneider T, Troeger H, et al. Impairment of the intestinal barrier is evident in untreated but absent in suppressively treated HIV-infected patients. Gut 2009; 58:220–227.

47. El-Far M, Kouassi P, Sylf M, et al. Proinflammatory isoforms of IL-32 as novel and robust biomarkers for control failure in HIV-infected slow progressors. Sci Rep 2016; 6:22902.

48. Rath S, Hedin B, Pieper DH, Vital M. Uncovering the trimethylamine-producing bacteria of the human gut microbiota. Microbiome 2017; 5:54.

A study that developed a diagnostic framework enabling comprehensive characterization of the bacterial producers of trimethylamine (a precursor of trimethylamine-N-oxide, TMAO), a cardiovascular diseases (CVD) marker in human fecal samples.

49. Zhu W, Gregory JC, Org E, et al. Gut microbial metabolism TMAO enhances platelet hyperreactivity and thrombosis risk. Cell 2016; 165:111–124.

Important study providing a mechanistic link between diet-microbes-mediated modulation of platelet functions and thrombosis risk.

50. De Preter V. Metabolomics in the clinical diagnosis of inflammatory bowel disease. Dig Dis 2015; 33(Suppl 1):2–10.

51. Zampieri M, Sekar K, Zamboni N, Sauer U. Frontiers of high-throughput metabolomics. Curr Opin Chem Biol 2017; 36:15–23.

52. Li Q, Estes JD, Duan L, et al. Trimming of gut microbiota metabolism associated with proinflammatory isoforms of IL-32 as novel and robust biomarkers for control failure in HIV-infected slow progressors. Sci Rep 2016; 6:26192.

53. Wang Z, Kieplott E, Bennett BJ, et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011; 472:57–63.

54. Velasquez MT, Ramezani A, Manal A, Raj DS. Trimethylamine-N-oxide: the good, the bad and the unknown. Toxins (Basel) 2016; 8:326.

55. Cho CE, Taesuwan S, Malycheva OV, et al. Trimethylamine-N-oxide (TMAO) response to animal source foods varies among healthy young men and is influenced by their gut microbiota composition: a randomized controlled trial. Mol Nutr Food Res 2017; 61:324.

The study shows that the dietary source of precursors of TMAO (predictive risk factor for heart disease in cardiac patients) and individual differences in the gut microbiome impact circulating TMAO concentrations.

56. Heianza Y, Ma W, Manson JE, et al. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: a systematic review and meta-analysis of prospective studies. J Am Heart Assoc 2017; 6:e005447.

A meta-analysis showing that high levels of TMAO are associated with significant major adverse cardiovascular events and also all-cause mortality even after excluding traditional risk factors.

57. Haissman JM, Haugaard AK, Ostrowski SR, et al. Microbiota-dependent metabolite and cardiovascular disease marker trimethylamine-N-oxide (TMAO) is associated with monocyte activation but not platelet function in untreated HIV infection. BMC Infect Dis 2017; 17:445.

A study that argues against the role of TMAO in platelet functions but suggesting a role for cART in TMAO metabolism.

58. Miller PE, Haberlen SA, Brown TT, et al. Brief report: intestinal microbiota produced trimethylamine-N-oxide and its association with coronary stenosis and HIV serostatus. J Acquir Immune Defic Syndr 2016; 72:114–118.

Work highlighting the need for prospective and longitudinal studies to understand the relationship between TMAO and CVD as there was a U-shaped association between these factors in their studied cohort.

59. d’Ettorre Q, Ceccarelli G, Giustini N, et al. Probiotics reduce inflammation in antiretroviral treated, HIV-infected individuals: results of the ‘probio-HIV’ clinical trial. PLoS One 2015; 10:e0137200.

The study highlights the potential of probiotics as a supplemental treatment in HIV-infection to reduce inflammation and its associated complications.

60. Stikendorf B, Nowak P, Nswou FC, et al. Reduced levels of t-dimer and changes in gut microbiota composition after probiotic intervention in HIV-infected individuals on stable ART. J Acquir Immune Defic Syndr 2015; 70:329–337.

The study shows an important reduction in typical CVD risk factors following probiotic intervention.

61. Villar-Garcia J, Hernandez JJ, Guerin-Fernandez R, et al. Effect of probiotics (Saccharomyces boulardii) on microbial translocation and inflammation in HIV-treated patients: a double-blind, randomised, placebo-controlled trial. J Acquir Immune Defic Syndr 2015; 68:256–263.

62. Villar-Garcia J, Guerin-Fernandez R, Maya A, et al. Impact of probiotic Saccharomyces boulardii on the gut microbiome composition in HIV-treated patients: a double-blind, randomised, placebo-controlled trial. PLoS One 2017; 12:e0173802.

The study proposes the use of specific probiotic treatments (herein Saccharomyces boulardii) to reduce the numbers of gut microbiota associated with bacterial translocation and systemic inflammation.

63. Gianotti RU, Moss AC. Fecal microbiota transplantation: from Clostridium difficile to inflammatory bowel disease. Gastroenterol Hepatol (N Y) 2017; 13:209–213.

64. Vujkovic-Cvijin I, Rutishauser RL, Pao M, et al. Limited engraftment of donor microbiome via one-time fecal microbial transplantation in treated HIV-infected individuals. Gut Microbes 2017; 8:440–450.

The study shows that fecal microbial transplantation is well tolerated in HIV-infected patients but demonstrated no significant impact on systemic inflammation.

65. Khanna S, Vazquez-Baeza Y, Gonzalez A, et al. Changes in microbial ecology after fecal microbiota transplantation for recurrent C. difficile infection affected by underlying inflammatory bowel disease. Microbiome 2017; 5:55.

66. Kim CJ, Walmsley SL, Raboud JM, et al. Can probiotics reduce inflammation and enhance gut immune health in people living with HIV? study designs for the Probiotic Viabloom for Inflammation and Translocation (PROOV IT) pilot trials. HIV Clin Trials 2016; 17:147–157.