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Review

The gut-microbiome contribution to HIV-associated cardiovascular disease and metabolic disorders

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Abstract

During the past decade, there has been a great effort in characterizing the gut microbiome of individuals living with HIV and its influence on HIV-metabolic disorders. Herein, the current understanding of the changes in the composition and function of the gut microbiome in the context of HIV infection, cardiovascular disease, and HIV-associated metabolic disorders is reviewed. A focus is especially given to bacteria gut microbiome and their produced metabolites, including tryptophan, short-chain fatty acids, and trimethylamine-N-oxide, and discuss current literatures that have investigated their role in HIV pathogenesis and HIV metabolic disorders. This review finally calls for future studies to focus on interrogating the mechanism of host-gut microbiome interaction in relation to HIV and HIV comorbidities by using multiomics approaches and on geographically diverse populations.

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Gut microbiome, HIV, Epithelia barrier, Cardiovascular disease, Metabolic disorders.

Introduction

The majority of human resident microbial communities (microbiome) reside in the gut. It is a complex community with highly interacting microbial species that maintain a close mutualistic interplay with the host. The gut microbiome composition of humans includes bacteria from five main phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, *and* Verrucomicrobia. Bacteroidetes and Firmicutes are the most abundant groups of the gut microbiota making up >90% of the total gut bacterial community of healthy adults [1–3]. The human gut microbiome has an impact on a wide range of human physiology, including in sustaining host metabolic pathways and maintenance of the gut epithelial barrier integrity [2–4]. It should, however, be noted that the composition of the human gut microbiome varies depending on a number of factors, including age, diet, socioeconomic status, and geographic location [5]. For example, Schnorr et al. reported a greater bacterial diversity in the gut microbiome of people from Tanzania, a developing nation, compared to those from developed nations [6]. The gut microbiome of Africans may be more diverse than of other populations, possibly due to their interaction with microbes, including helminths, which induce potent immunomodulatory effects but are largely absent in Western populations. Perturbation of the gut microbiome may have major clinical and gut homeostatic implications. In recent years, HIV infection has been shown to induce changes in the gut microbiome, whose consequences will be discussed in this review.

HIV pathogenesis

To comprehend the impact of HIV on the diversity and function of the gut microbiome, and its role in HIV disease progression, it is important to first understand the basic principles of HIV pathogenesis (recommended review [7]). HIV infection is characterized by a progressive loss of CD4 T cells and associated systemic dysfunction of the immune system brought on by persistent HIV viral replication. Majority of CD4 T cell depletion by HIV occurs in the gastrointestinal tract early on during infection [8–10]. HIV disrupts Gut-Associated Lymphoid Tissues (GALT) by primarily depleting GALT-resident Th17 cells that are involved in maintaining the intestinal epithelial homeostasis [9,11–14]. This leads to a 'leaky gut', that subsequently allows translocation of microbes and/or microbial products from the gut to the systemic circulation/blood. It is widely accepted that microbial translocation is a major mechanism for persistent immune activation and inflammation in HIV-infected individuals, even for those on therapy [11,15]. Persistent immune activation is a hallmark of HIV infection and is strongly linked to AIDS and non-AIDS mortality and co-morbidities [16–18].

Despite the importance of antiretroviral therapy (ART) in reducing HIV morbidity and mortality, infected individuals have, even under therapy, increased morbidity and decreased life expectancy [19–21]. Furthermore, compared to the general population, people living with HIV have an accelerated aging process, which is often associated with increased frailty and a high burden of age-related co-morbidities [22,23]. For instance, chronic metabolic disorders such as cardiovascular disease (CVD) and diabetes still burden people living with HIV (PLWH) compared to their uninfected counterparts, even with successful ART. Several publications have reported the observed increased risk of metabolic disorders for HIV-positive persons at a younger age compared to that of their age-matched uninfected counterparts [24–27]. The risk for metabolic disorders in PLWH are multifactorial and include long-term ART exposure and HIV-induced chronic inflammation and immune activation that persists despite the use of ART [24,28,29]. Notably, perturbations on the human gut microbiome have also been associated with an increase in CVD and diabetes [30,31]. In PLWH, gut microbiome alterations have recently been linked to an increased risk of metabolic syndrome driven by hypertriglyceridemia, diabetes, and hypertension, especially in individuals with a previous severe immune dysfunction [32]. This suggests a role of gut microbiome in influencing critical aspects of host metabolism, which when altered can affect the onset of metabolic disorders that occur at higher rates in PLWH.

HIV-induced gut dysbiosis

During the past decade, there has been a substantial body of evidence linking HIV with alterations of the gut microbiome (a term coined as gut dysbiosis). Generally, HIV-induced gut dysbiosis has been characterized by a shift in the composition and function of gut microbiome, including the replacement of commensal bacteria that maintain a healthy gut ecology and function with those that promote chronic inflammation and immune dysfunction (reviewed in Ref. [33]). At the phyla level, PLWH, when compared to HIV uninfected individuals, have reduced relative abundance of Firmicutes and are enriched with relative abundances Actinobacteria Proteobacteria, even under ART [34–41]. Recent metagenomic data has further revealed significant bacterial enrichment in treated PLWH even at a species level [42]. However, a positive impact of long-term ART use in restoring the gut microbiome of PLWH to profiles that are closer in similarity with HIV uninfected people than HIV untreated or short-term treated individuals has been noted * [43,44].

In resource-rich countries where the majority of gut microbiome studies have been performed, several groups have reported a low microbial diversity in HIV infected individuals that is often characterized by the high relative abundance of the genus *Prevotella*, compared to the high relative abundance of the genus *Bacteroides* in non-HIV infected individuals, and found to correlate with poor health outcomes, including immune dysfunction and HIV progression [13,14,34,45–48]. A recent integrated analysis of multiomics from HIV-associated gut microbiome revealed that species of *Prevotella* and other distinct members of the HIV-altered gut microbiome are enriched in genes involved in pro-inflammatory pathways (eg: LPS synthesis) and present a preferential expression of oxidative stress genes and underexpression of genes of anti-inflammatory metabolic pathways * [49]. However, Vujkovic-Cvijin et al. examined the gut microbiome of PLWH on the basis of their sexual practices and did not observe a depletion of *Bacteroides* and enrichment of *Prevotella* taxa in the studied cohort of PLWH ** [41]. *Prevotella* species were rather enriched in men who have sex with men (MSM), implying that the shift from *Bacteroides* to *Prevotella* that was observed in earlier studies may not be an absolute feature of HIV infection but rather a characteristic of MSM associated microbiota. Enrichment of Prevotella in the gut microbiome of HIV + MSM has also been described in recent publications [40,50].

To date, the gut microbiome of PLWH from developing regions, including Africa, remains barely explored. Monaco et al. examined the HIV-induced gut viral and bacterial alterations in a cohort of 82 HIV untreated and treated Ugandans in comparison with 40 HIV uninfected controls and similarly observed a decrease in the diversity of bacterial gut microbiome of people with chronic and advanced HIV infection, with no clear trend in the relative abundance of *Prevotella* versus *Bacteroides* [51]. However, in this cohort, the predominance of *Prevotella* was not dependent on HIV status since the baseline gut microbiome of HIV- Ugandans was also *Prevotella*-predominant, possibly due to dietary differences between Ugandans and western societies. Likewise, a more recent research from a Mozambican cohort of *Prevotella*-rich population could also not observe any substantial changes in the *Prevotella* composition between HIV+ and HIV- individuals ** [52]. Contrary, depletion of *Prevotella* and *Bacteroides* has been reported in the gut microbiome of PLWH from peri-urban Ghanaian communities [48].

Of note, HIV infection has also been associated with fecal adenovirus shedding, as well as enrichment of Adenoviridae and Anelloviridae viral sequences in African cohorts [51,52]. Since evidence exists of the differences in the gutmicrobiome of Africans and Western populations, it is crucial to extensively examine the relationship between the gut microbiome and HIV/AIDS in Africans living with HIV. This will aid in the development of novel/additional approaches for the control of HIV and HIV-related disorders that will also

benefit these individuals that are disproportionately scourged by the HIV epidemic.

HIV gut dysbiosis in relation to host metabolic disorders

HIV gut dysbiosis not only does it affect the composition of the gut microbial community but also results in changes in the metabolism of gut microbiome [53], in turn, having serious consequences on the host metabolism. Moreover, metabolic changes in the gut microbiome that are triggered by HIV are distinct from those induced by other diseases [53].

Chronic HIV infection is specifically associated with altered amino acid metabolism, including the accumulation of amino acid metabolites during tryptophan catabolism [53]. Tryptophan is an essential amino acid involved in protein synthesis, whereby its degradation/catabolism produces a number of biologically active metabolites that are necessary for neurotransmission, regulation of immune responses, and intestinal homeostasis [54]. A major catabolic pathway of tryptophan is the kynurenine pathway (KP), which, in the first step, involves the degradation of tryptophan to kynurenine and other downstream metabolites via the action of indoleamine-2,3- dioxygenase 1 (IDO1), IDO2, or tryptophan-2,3-dioxygenase (TDO2) enzymes [55]. The rate of tryptophan catabolism defined by IDO1 activity and/or kynurenine-to-tryptophan (KYN/TRP) ratio is increased in the plasma of PLWH and is linked to HIV disease progression [56,57]. Importantly, gut microbial communities that are capable of metabolizing tryptophan through the KP are abundant in HIV+ people [13]. These include members of the phylum Proteobacteria with capacity to produce IDO1, where Vujkovic-Cvijin et al. reported 140 genera within this phylum that directly contribute to the catabolism of tryptophan through the KP and a few that encode for enzyme machinery for tryptophan catabolism homologous to that of humans [13].

Of note, Favre et al. reported a direct link between host-derived IDO1 activity and a lower proportion of systemic and gastrointestinal (rectosigmoid) mucosa Th17 T-cells during HIV progression [57]. Since IDO1 is primarily induced by IFN and TLR ligands such as LPS and microbial DNA [57,58], Th17 loss allows more microbial products (including TLR agonists) to enter the circulation through a compromised gut mucosa barrier, in turn, heightening chronic inflammation, immune activation, and potentiating for further induction of IDO1. On the contrary, recent work of V'azquez-Castellanos et al. found no IDO1 gene or gene expression in the gut metagenome and transcriptome of HIV + individuals [49]. This requires further investigation into the changes in tryptophan catabolism brought about by the HIV-induced microbiome.

Higher plasma KYN/TRP ratios have also been associated with CVD in the general population and in PLWH [56,59,60]. The aforementioned ratio strongly correlates with endothelial dysfunction and inflammation, especially in HIV+ individuals with Type 2 diabetes [60,61], implying that a high KYN/TRP ratio may further fuel the onset of metabolic disorders in PLWH. A multicentered cohort study reported a higher incidence of developing carotid artery atherosclerosis in HIV+ participants than in HIV uninfected people after a median follow-up of 7 years [62]. Of note, the increased risk of developing carotid plaque in this cohort correlated with the KYN/TRP ratio [56]. Conversely, a study conducted in Uganda showed an association between decreased plasma KYN/TRP ratio following 6 months of ART and lower measurement of subclinical atherosclerosis taken 7 years later [62]. Nonetheless, data on the contribution of gut microbiome on HIV-induced metabolic disorders is still scarce and, in some cases, controversial. Hoel et al. showed a substantial reduction of gut microbiome (alpha diversity) in HIV+ people with type 2 diabetes compared to individuals with HIV infection alone and HIV uninfected controls [60]. On the contrary, a recent study of women with and without HIV and/or diabetes found no pronounced differences in the gut microbiome composition of the studied groups, probably due to their study design or a long ART use in the studied cohort [61]. Likewise, Villanueva-Millán et al. observed no substantial changes in the gut microbiome when compared HIV+ individuals with and without metabolic disorders, although a decrease in some anti-inflammatory bacteria was noted in individuals with metabolic syndrome * [63]. Further larger studies with multiomics (meta-genomics/transcriptomics/bolomics) data are needed to better understand the mechanistic relationship between gut microbiome, their metabolites, and host metabolic disorders in the context of HIV.

The inverse relationship between KYN/TRP ratio and a butyrate-producing microbe has also been reported [61]. Butyrate, a predominant short-chain fatty acid metabolite of gut microbiome fermentation of host dietary fiber, is involved in anti-inflammatory responses and is important for the regulation of intestinal homeostasis [4]. Butyrate producers include bacteria belonging to phylum Firmicutes such as *Eubacterium rectale*/*Roseburia* spp. and *Faecalibacterium prausnitzii* [64]. Several studies have consistently observed a reduction of butyrate producers in PLWH, which has been linked to increased markers of systemic immune activation and inflammation, potentially reflecting the breach in the intestinal barrier [34,35,46,65–67]. In the general population, reduced butyrate-producing microbes have also been associated with diabetes [30]. In the context of HIV, a recent study observed a depletion of butyrate producers to be associated with diabetes among HIV+ women [61]. Similarly, reduction of butyrate producers microbes

has been observed in HIV+ individuals with metabolic disorders such as hyperglycemia, hypertension, and dyslipidemia * [63].

Trimethylamine-N-oxide and trimethylamine, metabolites of gut microbes, have also been strongly associated with increased risk of CVD and less microbial diversity in the general population and PLWH [68–70]. In HIV infection, blood trimethylamine (TMA) is also significantly and positively associated with coronary plaques [71]. Trimethylamine-N-oxide (TMAO) production is mostly mediated by Firmicutes, Actinobacteria, and Proteobacteria [50,70,72,73] and involves metabolism of host dietary choline to TMA, which upon absorption, it is further converted in the liver to TMAO. Among a few studies that have compared the levels of circulating TMAO and its precursors in HIV uninfected and infected individuals, most studies did not find substantial differences in the levels of this metabolite between the studied groups or any association with HIV progression markers [67,71,74,75]. A small prospective study from the USA, which included HIV+ and HIV- MSM, found comparable levels of plasma TMAO between HIV+ and HIV-men, although an inverted U-shaped association between levels of TMAO and the presence of coronary artery stenosis among HIV+ men was observed [74]. Similarly, three other studies found similar levels of TMAO between HIV-infected and uninfected individuals [67,71,75].

On the other hand, blood TMAO has been reported to positively correlate with monocyte activation [76] and elevation of systemic inflammatory markers such as LPS and sCD14 [71,76] among PLWH, which may, in turn, enhance foam cell formation and atherosclerosis. Consistent with other studies, Haissman et al. similarly observed no association between TMAO and HIV related factors (CD4 T cell count, HIV viral load, and ART use); however, they reported elevated ratios of TMAO to some of its precursors in ART-treated HIV+ individuals suggesting an influence of ART in TMAO metabolism [76]. Nonetheless, the mentioned studies did not investigate the relationship between the gut microbiome and TMAO levels in the context of HIV infection, leaving an avenue for future research.

Concluding remarks

In recent years, there has been a great effort in characterizing the gut microbiome of individuals living with HIV and its influence on HIV-metabolic disorders. However, much still has to be done to determine the direct link and mechanism of HIV gut dysbiosis and metabolic disorders. Larger multiomics studies are needed, that will focus on interrogating the mechanism of host–gut– microbiome interaction in relation to HIV and HIV comorbidities such as CVD and diabetes. Importantly, to have a better understanding of the HIV-induced gut dysbiosis which will be beneficial to global citizens, characterization and consequences of gut microbiome alterations by HIV should not be biased to Western populations as it is now but should also be conducted on developing nations, including Africa, which is home to two-thirds of global PLWH.

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Conflict of interest statement

Nothing declared.

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