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REVIEW

The Potential of *Clostridium butyricum* to Preserve Gut Health, and to Mitigate Non-AIDS Comorbidities in People Living with HIV

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Abstract

A dramatic reduction in mortality among people living with HIV (PLWH) has been achieved during the modern antiretroviral therapy (ART) era. However, ART does not restore gut barrier function even after long-term viral suppression, allowing microbial products to enter the systemic blood circulation and induce chronic immune activation. In PLWH, a chronic state of systemic inflammation exists and persists, which increases the risk of development of inflammation-associated non-AIDS comorbidities such as metabolic disorders, cardiovascular diseases, and cancer. *Clostridium butyricum* is a human butyrate-producing symbiont present in the gut microbiome. Convergent evidence has demonstrated favorable effects of *C. butyricum* for gastrointestinal health, including maintenance of the structural and functional integrity of the gut barrier, inhibition of pathogenic bacteria within the intestine, and reduction of microbial translocation. Moreover, *C. butyricum* supplementation has been observed to have a positive effect on various inflammation-related diseases such as diabetes, ulcerative colitis, and cancer, which are also recognized as non-AIDS comorbidities associated with epithelial gut damage. There is currently scant published research in the literature, focusing on the influence of *C. butyricum* in the gut of PLWH. In this hypothesis review, we speculate the use of *C. butyricum* as a probiotic oral supplementation may well emerge as a potential future synergistic adjunctive strategy in PLWH, in tandem with ART, to restore and consolidate intestinal barrier integrity, repair the leaky gut, prevent microbial translocation from the gut, and reduce both gut and systemic inflammation, with the ultimate objective of decreasing the risk for development of non-AIDS comorbidities in PLWH.

Keywords *Clostridium butyricum* · Inflammation · Gut · HIV · Cancer

Introduction

Cumulative evidence has demonstrated that compared to uninfected individuals, people living with HIV (PLWH) experience a significantly increased risk of non-AIDS comorbidities, even in the context of long-term, effective antiretroviral therapy (ART). One recent meta-analysis, which included 236,127 women living with HIV, has shown that this population had a dramatically higher overall pooled risk of cervical cancer, compared to uninfected individuals, with a risk ratio (RR) of 6.07 (95% CI 4.40–8.37) [1]. Chronic systemic inflammation in PLWH has been considered to be the major contributor that facilitates the development of these comorbidities, which include the metabolic syndromes, cardiovascular diseases, cancers, and HIV-associated neurocognitive disorder (HAND) [2–5]. One systematic review of 29 studies has indicated that higher levels of monocyte activation and inflammatory markers in cerebrospinal fluid are consistently associated with

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neurocognitive impairment in PLWH [2]. The fundamental underlying mechanisms linking chronic inflammation to non-AIDS comorbidities are complex, and may include immune exhaustion, premature immune senescence, and direct harm to organs through the release of pro-inflammatory cytokines [3].

The elevated level of microbial translocation associated with the leaky gut in HIV-infected individuals is recognized to be the major source of systemic inflammation in PLWH [6]. In addition to the uptake of nutrients and water, other critical functions of the intestinal barrier are to prevent toxic substances originating from the external environment from entering the portal and systemic circulation, and to preserve intestinal homeostasis. Once this barrier is disrupted, nonviable and viable intraluminal gut microbes and their pro-inflammatory products may translocate from the gut into the systemic circulation, a phenomenon referred to as microbial translocation. During HIV infection, the gastrointestinal tract is the major site of HIV replication, and is considered to be the primary location of the HIV viral reservoir as a result of greater expression of the C–C chemokine receptor (CCR)-5, a vital co-receptor for HIV to entry into the gut epithelial cells, and also the opportune localized presence of a large quantity of gut-associated lymphoid tissue (GALT) [7–10]. As such, among PLWH, rapid loss of gastrointestinal mucosal integrity and heightened gastrointestinal permeability are relatively common, leading to increased microbial translocation and chronic systemic inflammation [11]. Therefore, in addition to modern ART, strategies which ameliorate poor intestinal barrier function and which mitigate the chronic systemic inflammation present in PLWH have emerged as a research priority.

Clostridium butyricum is an anaerobic bacterium existing symbiotically in the human intestine, as well as in various environmental niches, such as soil and vegetables [12]. When used as an oral probiotic supplement, *C. butyricum* could produce an important metabolite short-chain fatty acid (SCFA), namely butyrate by fermentation, and influence other gut flora or the host health in various ways [13]. Encouragingly, *C. butyricum*, as well as butyrate, has been reported to restore and maintain the integrity of the gut barrier, inhibit the proliferation of pathogenic bacteria in the intestine, and reduce microbial translocation and systemic inflammation [14–18]. Moreover, *C. butyricum* supplementation has been shown to exert a beneficial effect on metabolic diseases, non-alcoholic fatty liver disease (NAFLD), ulcerative colitis (UC), tumorigenesis, and neurodegeneration, all of which have been recognized as relatively common comorbidities in PLWH [19–25]. However, there remain very few published research works which focus on the gastrointestinal and other effects of *C. butyricum* in PLWH. The present work is intended to discuss the influences of *C. butyricum* on the gastrointestinal system and systemically, and the implications of *C. butyricum* supplementation for gut health, systemic inflammation, and non-AIDS comorbidities in PLWH.

Based on the known favorable effects of *C. butyricum* on the human body, such as restoration and maintenance of the integrity of the gut barrier, inhibition of the growth of pathogenic bacteria in the intestine, reduction of microbial translocation, and the inherent characteristics of the clinical consequences of HIV infection present in PLWH, we speculate that oral supplementation of *C. butyricum* may serve as a potential mitigative strategy to ameliorate non-AIDS comorbidities in PLWH (Fig. 1).

(1) *C. butyricum* may alleviate inflammation through its interactions with immune cells (macrophages and T-helper cells). As such, *C. butyricum* is capable of inducing the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β. In parallel, *C. butyricum* may drastically reduce the expression of pro-inflammatory cytokines. Within the gut of an HIV-infected individual, gut integrity is compromised, leading to a permanent leaky gut syndrome. (2) *C. butyricum* and its metabolites (butyric acid, butyrate) in addition to IL-10 increase the production of the mucin layer and protectin D1. The combination of anti-inflammatory cytokines, protectin D1, and the mucin layer participates in reducing contact between epithelial cells and pathogenic microbes and, thus, participates in protecting gut integrity. (3) Within the gut, *C. butyricum* has been shown to be capable of repressing the proliferation of pathogenic bacteria such as *C. difficile*, *Helicobacter pylori*, and *Vibrio cholerae*. Furthermore, evidence suggests that *C. butyricum* is important in promoting the growth of beneficial bacteria such as the butyrate-producing bacteria (particularly those carrying the buk and butyryl-CoA genes), *Lactobacillus*, and *Bifidobacterium* spp. In the context of HIV infection where it is known that pathogenic bacteria are augmented while beneficial bacteria are depleted, gut supplementation with *C. butyricum* may potentially help to regulate the overall microbial balance within the gut microbiome. Thus, we believe that *C. butyricum* may help to regulate the gut microbiome, alleviate inflammation, and significantly reduce the leaky gut syndrome and the consequences of the abnormal systemic condition observed in an HIV-infected individual. Indeed, several research teams [3, 26, 27] have demonstrated that the during HIV infection, chronic inflammation, the leaky gut syndrome, and the proliferation of pathogenic bacteria may be responsible for the evolution of non-AIDS conditions.

Profile of *C. butyricum*

Metabolism

C. butyricum is believed to exist symbiotically in the human gastro-intestine [28]. It consumes undigested dietary fiber,

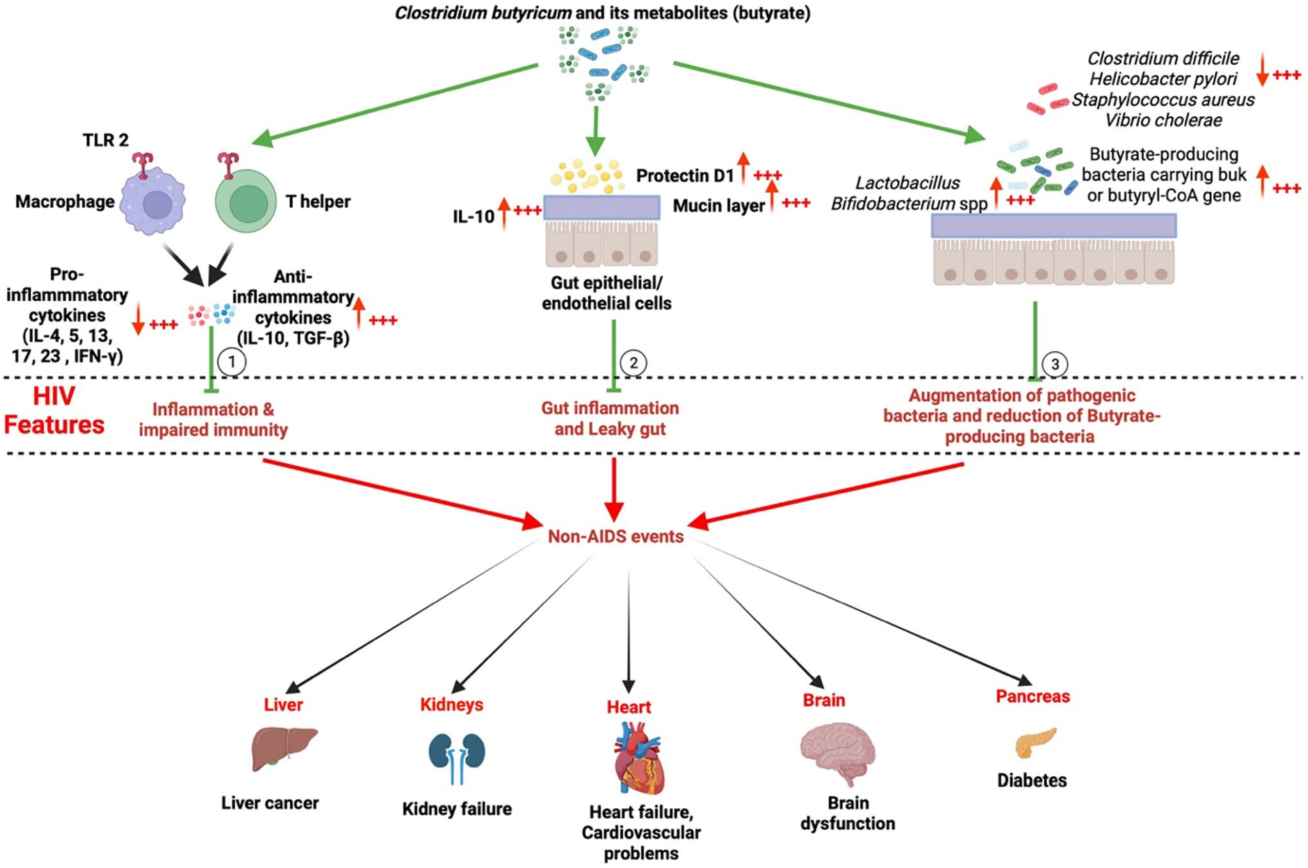

Fig. 1 The potential beneficial roles of *C. butyricum* in an HIV infection context

including indigestible carbohydrate, and generates SCFAs, particularly butyrate and acetate [13, 29]. Among them, butyrate outstands as one of the dominant metabolic end-products and the most multifunctional metabolite. Involved enzymes are quite critical in butyrate production process. *C. butyricum* mainly utilizes the butyrae kinase pathway to release butyrate in intestine. For other bacteria, such as *Coprococcus eutactus*, butyryl-coenzyme A (CoA) transferase pathway is the important metabolic pathway to produce butyrate [30]. There is a strong positive correlation between gene expression levels of butyrate kinase (buk), which codes buk and butyryl-CoA transferase respectively, and the concentrations of butyrate or the content of butyrate-producing bacteria within the intestine [31]. Apart from carbohydrate residues, protein residues such as amino acids may also be regarded as another butyrate source for *C. butyricum* in the human colon [32]. Specifically, lysine could be converted into butyrate and acetate, with aid from the microbial enzyme crotonyl CoA [32]. Butyrate not only plays as the preferred energy source supply for colonic epithelial cells, but also has a role in various metabolic processes, including reducing bile salt solubility by decreased pH, inhibiting ammonia absorption, lowering blood glucose by enhanced colonic glucagon-like peptide-1 (GLP-1) secretion, and regulating hepatic glucose or lipid homeostasis in a phosphoadenosine activated protein kinase dependent pathway [28, 29, 33, 34].

Efficacy in Alleviation of Inflammation

During the metabolic process, *C. butyricum* may influence specific behaviors of immune cells such as macrophages and T-lymphocytes, which may alter the release of inflammatory cytokines from these cells [35–37]. Increased levels of interleukin (IL)-10, an anti-inflammatory cytokine, plays an indispensable role in the protective effects of *C. butyricum* [38, 39]. Gao Q and colleagues have reported that *C. butyricum* may activate toll-like receptor (TLR)-2 within gut macrophages, enhance the release of IL-10, and inhibit cell apoptosis, thus further weakening inflammatory responses in vitro [35]. With the absence of IL-10 in colonic macrophages, the anti-inflammatory benefits of *C. butyricum* may be attenuated in mice with colitis [37]. Moreover, *C. butyricum* and butyrate may directly affect the behavior of helper T (Th) cells as well as their produced cytokines, such as TGF-β and IL-10. In asthmatic mice, *C. butyricum* has been shown to inhibit the secretion of Th2-related cytokines such as IL-4 and IL-13, increase the abundance of anti-inflammatory factors IL-10 and TGF-β, decrease bronchial reactivity, and relieve pulmonary inflammation [36]. Similarly, *C. butyricum* may reduce Th2 cytokines, including IL-5 and IL-13, and alleviate gastrointestinal inflammatory symptoms and diarrhea induced by food allergies in vivo [38]. Treatment with *C. butyricum* in animal models may decrease other pro-inflammatory cytokines, such as IL-17 in diarrhea, IL-23 in colitis, and interferon (IFN)-γ in NAFLD, resulting in improved clinical outcomes for these conditions [38, 40, 41]. In addition, representative metabolites SCFAs, such as butyric and valeric acid, were significantly reduced in HIV-positive patients, compared to normal people [42]. The supplementation of SCFAs contributed to a remarkable decrease in pro-inflammatory cytokines (such as IL-10) and an obvious depletion of effector T-lymphocytes in PLWH, leading to reduced inflammatory immune responses and improved life-quality assessment [43], suggesting that SCFA producer *C. butyricum* may also benefit PLWH. Thus, *C. butyricum* may exert profound anti-inflammatory effects both directly and indirectly.

There may be some possible mechanisms underlying these anti-inflammatory effects. The MyD88 and nuclear factor-kappa B (NF-κB) signaling pathway might be one possibility. MyD88 is a common regulatory element of innate inflammation, which may activate the NF-κB signaling, thus suppressing apoptosis and mediating inflammation [44]. *C. butyricum* has been reported to restrain the proliferation of colorectal cancer (CRC) cells, inhibit the mRNA and protein expression of MyD88 and NF-κB/p65, which is inversely proportional to multiplicities of infection (MOIs) of *C. butyricum*, and improve intestinal inflammation in both cell tests and mice [45]. Toll-like receptor 4 (TLR4)–dependent pathway may also be involved. TLR4, one TLR family member, could recognize lipopolysaccharide and bacterial endotoxins, trigger the production of varied pro-inflammatory factors, and herein mediate inflammatory responses [46]. *C. butyricum* could suppress intestinal inflammation and attenuate bacteria-induced gut damage, through downregulating the TLR4-dependent signal transduction pathways in *Salmonella* enteritidis–infected broiler chickens [18]. Moreover, regulation on the expression of some enzymes does matter during the anti-inflammatory response mentioned earlier. Matrix metalloprotein-9 (MMP-9) is a secretory member of the zinc metallopeptidase family, which can exacerbate airway inflammation by increasing inflammatory cells recruitment and inflammatory cytokines release [47]. In comparison to the negative controls, *C. butyricum* was effective in repressing MMP-9 expression, inhibiting degranulation of mast cells, and reducing respiratory inflammation, in mice with allergic airway inflammation [36].

Modulation of Immune Homeostasis

Along with regulating inflammation, *C. butyricum* may affect the release of inflammatory cell factors by regulating the balance among immune cells in the gut, as well as the homeostasis of the endogenous enteric immunity. To maintain the intestinal steady state, *C. butyricum* may regulate the functionality of various immune cells, typically dendritic cells (DCs) and regulatory T-cells (Tregs) [48, 49]. Compared with controls, *C. butyricum* intervention has been shown to inhibit the activation and proliferation of DCs, and alleviate Th1- or Th17-correlated inflammatory responses in the intestinal mucosa of mouse models with irritable bowel syndrome (IBS) [48]. Further data indicates that *C. butyricum* significantly suppresses the levels of secreted pro-inflammatory cytokines such as IL-1β and IL-6, and reduces the proportion of cells expressing T-cell immunoglobulin and mucin domain 3 (TIM3) in colonic DC clusters in both mice and humans with IBS [48, 50, 51]. *C. butyricum* has been shown to promote the induction of Tregs in the colon and the activity of anti-inflammatory Treg immune responses through enhancement of the secretion of TGF-β [39, 52]. Research data has further indicated that *C. butyricum* increases the expression of TGF-β in a TLR2-dependent manner within DCs, facilitates the differentiation of the Treg population, and establishes the intestinal immune tolerance seen in a murine colitis model [13, 53]. Several murine models have confirmed that *C. butyricum* contributes to the aggregation of Tregs in intestinal lymphatic organs and decreases inflammatory indices in injured organs, e.g., a reduction of the Th1 to Th17 cellular ratio [38, 49, 54]. When there is a lack of Treg cells, the anti-inflammatory effects of *C. butyricum* administration may be weakened in mice with colitis, suggesting that Treg cells may have a partially beneficial role in this process [37].

Reinforcement of the Gut Barrier

The intestinal epithelial barrier, composed of the mucous layer, the epithelial monolayer, and the lamina propria, maintains gut epithelial homeostasis by prevention of the transmigration of intestinal microorganisms, promotion of the absorption of nutrients, and by resisting the invasion of pathogens [55, 56]. In healthy mice, *C. butyricum* supplementation significantly thickens the first layer of the intestinal mucosa [57]. Butyrate, a metabolite of *C. butyricum*, has also been shown to increase the mucin proteins secreted by epithelial goblet cells, with up-regulation in the mucin gene and the involved mitogen-activated protein kinase (MAPK) pathway factors [58, 59], which is likely to be the underlying mechanism whereby *C. butyricum* affects the mucus layer. Similarly, in a murine model of colitis, *C. butyricum* has been seen to raise the production of mucin 2, exaggerate the protective properties of the mucous membrane, and mitigate colonic epithelial injury [60]. The second layer tight junction (TJ) complexes between epithelial cells, composed of claudin, occludin, adhesion junctions, and accessory proteins such as ZO-1, knits epithelial cells together [61]. Ingestion of *C. butyricum* upregulates the expression of different TJ proteins and anti-inflammatory cytokines, which may prevent the increase in intestinal tract permeability, prevent pathogen invasion, and reduce intestinal inflammation [60, 62]. In mouse models of diarrhea or pancreatitis, administration of *C. butyricum* has been seen to enhance the expression of TJ proteins including occludin and ZO-1, thus improving intestinal barrier function and reducing the risk of gut leakage [60, 63]. Similarly in mice with traumatic brain injury (TBI), *C. butyricum* promotes the recovery and expression of occludin in the colon, and protects the integrity of the intestinal mucosal barrier [25]. Moreover, reports have shown that *C. butyricum* may induce γδ T-cells to secrete higher levels of IL-17, which enhances the defensive role of the colonic lamina propria and maintains the expression levels of TJ proteins so as to protect gut barrier defensive functions in vivo [60, 64]. Ingestion of *C. butyricum* by mice with colitis may enrich a representative anti-inflammatory lipid metabolite, i.e., protectin D1 in the colon, thus enhancing the release of the anti-inflammatory factor IL-10, which attenuates gut inflammatory responses and strengthens the intestinal barrier [65].

Inhibition of Pathogenic Bacteria in the Intestine

C. butyricum has been reported to increase the proportion of several beneficial bacteria, such as *Lactobacillus* spp., and to inhibit the proliferation of some harmful bacterial species, thus preventing microbial translocation, improving gastrointestinal infections, and maintaining the dynamic microbial balance inherent to the gut microbiome [66]. Data has suggested that *C. butyricum* may reverse the dramatically decreased growth of butyrate-producing bacteria, and increase levels of SCFA metabolites, particularly butyrate, in the colon of diabetic mice [20]. Butyryl-CoA and buk are top two most commonly used genetic biomarkers for detection of butyrate-producing communities [67]. Normally, *C. butyricum* carries only the buk gene. However, researchers have observed that in diabetic mice, the orally administered *C. butyricum* strain may cause significant enrichment in levels of butyrate-producing bacteria carrying either the buk or the butyryl-CoA gene, which may be related to improvement of metabolic dysfunction and glucose homeostasis [20, 49]. Increases in levels of other beneficial anaerobic bacteria, such as *Lactobacillus* and *Bifidobacterium* spp., have also been observed after *C. butyricum* supplementation in mice [66]. Apart from that, in vitro studies have shown that after contact with *C. butyricum*, proliferation and cytotoxin production of *Clostridium difficile*, a typical pathogen linked to nosocomial diarrhea, are significantly inhibited [68]. Murine models of *C. difficile* infection (CDI) have demonstrated that *C. butyricum* can consume its nutrient source (succinic acid), produce SCFAs to inhibit growth, decrease release tumor necrosis factor (TNF)-α secretion, and reduce intestinal colonization of *C. difficile*, resulting in alleviation of intestinal inflammatory diarrhea [16]. It has been reported that *C. butyricum* and its butyrate product may limit the growth of *Helicobacter pylori* in vitro and in vivo [69]. This may be achieved via inhibition of the bacterial adhesion of *H. pylori* to gastric epithelial cells, thus easing clinical symptoms in patients having gastrointestinal *H. pylori* infection [70]. Similarly, when *C. butyricum* and enterohemorrhagic *E. coli* (EHEC) are co-cultured in vitro, the reproduction and enterotoxin production of EHEC are notably decreased [71]. Administration of *C. butyricum* has been observed to contribute to a 50% reduction in mortality rates of mice infected with EHEC [72]. Inhibitory effects of *C. butyricum* on growth of other enteric pathogens have also been noticed in vitro with respect to pathogens such as on *Staphylococcus aureus*, *Vibrio cholerae*, *Shigella flexneri*, and *Salmonella* species [18, 73, 74]. Possible underlying mechanisms for this effect include upregulation of levels of EGFR and anti-inflammatory elements such as IL-10 [73, 74]. This provides further evidence for amelioration of intestinal injury secondary to bacterial enteritis associated with *C. butyricum* treatment.

Effects of *C. butyricum* in the Context of Disease Spectrum

Regarding these beneficial characteristics of *C. butyricum*, it has been used in various ailments, such as metabolic disorders, cancer, gastrointestinal infection, neurological disorders, cerebrovascular diseases, and aging.

Effects of *C. butyricum* on Metabolic Disorders

C. butyricum inhabiting the gastrointestinal tract may enter the systemic circulatory system by transmigration through the gut barrier, and may interfere with host metabolic signals via endocrine modulation. The metabolite, butyrate, is postulated to be the trigger that enables these processes [40]. A negative correlation exists between enrichment of *C. butyricum* and fat accumulation, and the total number of this particular organism is reduced in murine models of type 2 diabetes [75]. Additional supplementation with *C. butyricum* is likely to benefit diabetic mice in the following metabolic ways: (1) Glucose. *C. butyricum* may increase insulin concentrations, promote glucose catabolism, and decrease levels of fructosamine. *C. butyricum* has also been shown to increase the abundance of peroxisomes and improves insulin sensitivity [19, 76]. (2) Lipids: Administration of *C. butyricum* upregulates the respiratory exchange ratio (RER), enhances mitochondrial function, stimulates ANGPTL4 production to prevent fat build-up, and eventually reduces weight gain [19, 76, 77]. (3) Metabolites: With *C. butyricum* supplementation, butyrate-producing gene expression is enhanced, and the reduction of butyric acid production is improved in obese mice with diabetes [76]. In the disease model of non-obese diabetic (NOD) mice, *C. butyricum* intake may induce intestinal Tregs production, inhibit the accumulation of pro-inflammatory cytokines such as IFN-γ in the pancreas, and decrease the degree of insulitis by reduction of pancreatic autoimmune injury, thus delaying the onset of diabetes [49]. Moreover, the levels of butyrate in feces are also increased with *C. butyricum* treatment [49].

Reports have revealed that in animal NAFLD models, besides the methods described above, treatment with *C. butyricum* may also reduce hepatic lipid accumulation at source and improve hepatic inflammatory indicators [40, 78]. Specifically, this therapy reduces the synthesis of triglycerides, promotes the conversion of cholesterol into bile acid, and boosts excretion of excessive lipids [78]. Also, the presence of *C. butyricum* has a protective effect on acute hepatic injury and raises the activity of anti-oxidant enzymes and their correlated factors, enhances anti-inflammatory reactions and anti-oxidant responses, and repairs the damaged liver to improve survival rates in mice [79]. Diabetic patients may also suffer from NAFLD, which ranges from hepatitis, fibrosis, cirrhosis, and eventually to hepatocellular carcinoma [13, 80]. The combination of *C. butyricum* and statin therapy can effectively improve the intestinal flora dysbiosis, lower blood lipid levels, reduce liver fibrosis and inflammation, and further alleviate liver function damage in patients with NAFLD [21]. One single-blind clinical trial with *C. butyricum* in elderly people revealed that intervention with *C. butyricum* could facilitate SCFA production, increase the probiotics abundance, and accelerate bile acid metabolism, eventually enhancing immunity and nutrition [81]. Dietary fiber could promote SCFA producers in greater abundance and more diversity, leading to increased GLP-1 production, improved hemoglobin A1c levels, and better prognosis in type 2 diabetes population [82].

Effects of *C. butyricum* on Cancer

Intestinal microorganisms, including the *C. butyricum* community, are essential for the maintenance of intra-epithelial homeostasis, while immune homeostasis imbalance, inflammation, and oncogenesis are inextricably linked [83–85].

CRC remains a major cause for cancer-related mortality worldwide [86]. Compared with the healthy population, butyric acid–producing genes in the gut microbiota of CRC patients showed a dramatic reduction, and also a reduction of the amount of butyric-producing bacteria (such as Lachnospiraceae) in their feces [87, 88]. Several CRC murine models have shown that *C. butyricum* restores weight loss, reduces tumor morbidity, lowers intestinal tumor burden, and improves tumor survival rate [24, 89, 90]. Evidence suggests that *C. butyricum* induces the up-regulation of the mir-200c cancer inhibitor at a molecular level, inhibiting colitis-related tumors [89]. It also enhances the expression of the p21 cell cycle inhibitor, suppresses the Wnt cell proliferation signal pathway, arrests the cell cycle, and thus inhibits proliferation of CRC cells [91, 92]. Researchers have also observed the enhancement of apoptosis in CRC cells, consistent with an increase of the Bax pro-apoptosis protein and a decreased level of the Bcl-2 anti-apoptosis protein [24]. *C. butyricum* and its metabolites are able to modify the tumor microenvironment in vitro and to restrain growth and reproduction of the intestinal enterotoxigenic *Bacteroides fragilis* carcinogenic bacterium [93]. In the murine CRC model, supplementation of *C. butyricum* triggers anti-inflammatory immuno-signals, which inhibits NF-κB signal transduction, and reduces the expression of the TLR4 and IL-22 pro-inflammatory elements, decreasing enteric leakage, and maintaining the integrity of the intestinal barrier [24, 90, 94]. Also, in a murine colon tumor model, a synergistic anti-tumor effect has been observed with the combination of *C. butyricum* and the targeting drug, lapatinib [95]. Clinical study suggests that higher fecal SCFA concentrations may indicate a longer progression-free survival and better efficacy when receiving the immune checkpoint blockade (ICB) therapy in solid cancer tumors [96].

Other than colon cancer, *C. butyricum* has also shown advantages for the treatment of other tumors, and may be used as an auxiliary anti-cancer strategy. *C. butyricum* strengthens the function of polymorphonuclear neutrophils, and may migrate into the bladder and release TNF-related apoptosis-inducing ligand (TRAIL) [97–99]. This may significantly inhibit the growth, and specifically induce apoptosis, of bladder cancer cells in a tumor-bearing murine model, and has been shown to be more effective than Bacillus Calmette-Guérin (BCG) therapy [97]. Cancer patients with higher amounts of blood butyrate seemed to exhibit a better chemotherapeutic response with oxaliplatin [100]. Compared with the group with no *C. butyricum* supplements, *C. butyricum* significantly improves the prognosis of non-small cell lung cancer (NSCLC) patients with early ICB treatment [101]. *C. butyricum* may raise overall survival rates, during which microbiota regulation and immunomodulation may be one potential mechanism of action [13, 101]. *C. butyricum* may also assist in neutralizing the more severe adverse effects of anti-cancer drugs used for pulmonary carcinoma, particularly diarrhea [102]. In patients with *H. pylori* infection, *C. butyricum* may prevent gastric cancer by eradicating *H. pylori* [103]. Oral supplement of *C. butyricum* in gastric cancer patients after gastrectomy can significantly reduce pro-inflammatory factors or cells, upregulate intestinal SCFAs, and increase the enrichment of beneficial bacteria such as *Bacteroides*, ultimately decreasing the incidence of postoperative complications [104].

Effects of *C. butyricum* on Gastrointestinal Infection

Gastrointestinal tract infection is caused by disruption of the balance of the originally existing intestinal microbiota by the invasion of different pathogens, and manifests as vomiting, intestinal spasm, diarrhea, and fever [105, 106]. Bacterial infections account for a significant portion of gastrointestinal infections [107]. A comparative study reported that the inflammatory bowel disease (IBD) susceptible population manifested lower fecal bacterial abundance, weaker fiber digestion efficacy, and insufficient SCFA-producing bacteria [108]. In the rat model of bacterial enteropathy, *C. butyricum* significantly relieves intestinal discomfort and reduces the frequency of diarrhea [109]. A number of animal models and clinical investigations have observed that probiotic supplementation may lower the risk of gastrointestinal tract infection and enhance host immunity [110–112]. Among the various probiotic bacterial species, *C. butyricum* is often used as a probiotic supplement to improve the symptoms of gut infections [112]. As has been previously mentioned, *C. butyricum* curbs the reproduction and harmful behavior of the deleterious bacterium, *C. difficile* [68]. The representative fermentation product butyrate exhibits potential antibacterial activities towards *C. difficile*, strengthens the intestinal barrier, and maintains host immune homeostasis [113, 114]. *C. butyricum* also downregulates the concentration of succinic acid in the intestines of mice, preventing the colonization of *C. difficile*, suppresses pro-inflammatory cytokines, such as TNF-α, induces macrophage aggregation in the intestinal lumen, and restores intestinal epithelial damage [112, 115, 116]. Additionally, *C. butyricum* also mobilizes the host immune system to function optimally. The butyrate metabolite has been reported to activate the GPR43/109a signal transduction pathway, induce the production of neutrophils, upregulate the release of pathogen-specific antibodies, and promote Th17 cells to participate in intestinal epithelial barrier reinforcement, which may ultimately weaken the pathogenicity of pathogens to a certain extent, just as for *C. difficile* [16, 112, 117]. Clinical data showed that *C. butyricum* may effectively suppress *H. pylori* to a certain extent in human [103]. When combined with antibiotics in *H. pylori* positive patients, it could help decrease variations in gut microbiota and alleviate the severity of treatment related diarrhea [118, 119]. *C. butyricum* can also be used as a probiotics to ameliorate stool consistency and frequency, and improve quality of life in IBS population [50]. In patients with UC, administration of *C. butyricum* can reduce the risk of postoperative pouchitis occurrence [22]. Therapy with *C. butyricum* to alleviate IBD is currently under study (NCT02614963). Therefore, *C. butyricum* is likely to prevent and treat gastrointestinal tract infection, and may be used as a probiotic for interventional therapeutic purposes.

Effects of *C. butyricum* on Neurological Disorders

Gastrointestinal microbiota may regulate CNS endocrine function, alter the signal transmission of neurotransmitters, and may even activate immune reactions within the nervous system via the microbiota-entero-brain axis that discourages and reduces harmful neuroinflammation [13, 120]. A meta-analysis showed that SCFA-producing bacteria were actually decreased in people with Parkinson's disease [121]. In murine models, *C. butyricum* improves and treats neurodegenerative diseases by activating the Akt pathway and reducing cell apoptosis [25, 122]. *C. butyricum* has been shown to also alleviate or even reverse the hippocampal injury of mice caused by cerebral ischemia, mainly strengthening the spatial learning capacity and improving memory deficiency [122, 123]. H. Li and colleague observed that *C. butyricum* treatment also effectively enhances motor and sensory function, and reduces neurodegeneration in mice afflicted by TBI [25]. Nerve function benefits from increased enrichment of butyrate in the brain via anti-apoptotic mechanisms [124]. Research suggests that GLP-1 may protect the integrity of the blood–brain barrier by up-regulating levels of TJ proteins, and assumes a neuroprotective role in the murine brain injury model [125, 126]. Treatment with *C. butyricum* may increase the expression of the GLP-1 receptor in the intestine and brain, which may mediate intestinal and brain barrier function through GLP-1 signaling, and protecting the blood–brain barrier, alleviating brain edema, and addressing neuronal injury [25]. *C. butyricum* may also be used in the management of multiple sclerosis. Treatment with *C. butyricum* significantly reduces the myelin loss resulting from attack by the immune system and may mitigate neuropathological inflammation at lesional sites in mice [54].

Effects of *C. butyricum* on Cerebrovascular Diseases

Cerebral ischemia/reperfusion (I/R) can lead to severe brain damage [127]. Jing Sun and associates constructed a mice model of cerebral I/R, and observed that *C. butyricum* increases the content of butyrate in the brain, which enhances the activity of the superoxide dismutase (SOD) anti-oxidant, and significantly decreases protein expression of apoptosis-related Caspase-3 and Bax, thus improving neurological deficits present in these patients [124]. Diabetes may also aggravate cerebral injury induced by I/R, leading to an exacerbation of neural functional deficits [128, 129]. *C. butyricum* has been shown to be capable of reversing this situation in mice models. Apart from the mechanism already mentioned, *C. butyricum* may also reduce protein levels of phosphorylated Akt and inhibit the apoptosis of nerve cells. Thus, reconsidering its protective potential, *C. butyricum* may be used as an effective adjuvant therapeutic strategy for the treatment of cerebrovascular disease in diabetics [123]. Additionally, in murine models of vascular dementia or Alzheimer's disease (AD), the therapeutic effects of *C. butyricum* include restoration of butyrate levels in the gut and brain, improvement of cognitive impairment, an increase in levels of Bcl-2, and a reduction of neuronal apoptosis [122, 130]. Clinical results showed that patients with acute ischemic stroke (AIS) usually present less SCFA-producing bacteria and lower fecal SCFAs concentrations, when compared to healthy controls [131]. Several clinical studies also found out that a negative correlation existed between SCFAs levels and stroke severity or disability risk in AIS patients [131–133].

Effects of *C. butyricum* on Aging

The lifespan of organisms may be influenced by *C. butyricum*. Subsequent to being fed with the *C. butyricum* probiotic strain, the lifespan of *Caenorhabditis elegans* (*C. elegans*) is significantly prolonged, locomotive efficiency is enhanced, and the resistance to pathogenic bacterial infection (such as *Staphylococcus aureus*) is enhanced when compared to the control group [134]. This may be attributable to regulation of Nrf2 transcription factor and IGF-1 signal transduction, which are two key factors associated with longevity [134–136].

Typical Non-AIDS Comorbidities in PLWH

Coincidentally, these above diseases are prevalent in PLWH, and are recognized as non-AIDS comorbidities. In developing countries, with the popularization and optimization of modern combined antiretroviral treatment (ART), survival rates of PLWH have been gradually improving over the past three decades [137]. However, with HIV virus replication controlled, non-AIDS comorbidities gradually emerge and increase, resulting in an elevated mortality rate in this population that may even exceed rates of mortality caused by HIV itself [138]. Based on many investigations, typically encountered non-AIDS comorbidities comprise various metabolic and neoplastic diseases, which will be elaborated on in the following sections.

For PLWH, the dysfunctional catabolic state caused by the uncontrollable HIV viremia and ART may induce variations in adipose tissue immunity, which may elevate prevailing obesity rates [139–141]. Excess adiposity may increase the risk of metabolic abnormalities, including diabetes and hepatic disease [142–144]. Compared to the HIV-negative population, obese or overweight PLWH have a higher risk of developing the preceding metabolic diseases [142, 144]. One all-male study observed that the incidence of diabetes in HIV-negative controls was over 4 times lower than that in PLWH [145]. Assuming identical weight gain, the increased risk of diabetes in PLWH is nearly twice as that of HIV-negative patients [144]. For PLWH, the lower the baseline CD4 + T-cell count and the older the protease inhibitors or nucleoside reverse transcriptase inhibitors used, the higher the risk is for the emergence of diabetes [145, 146]. Hepatic disease is the most common non-AIDS associated comorbidity in PLWH [147]. The prevalence of NAFLD in PLWH is higher than that in the general population, and the use of some specific antiretroviral drugs may be one reason for this [148–150]. PLWH are more prone to develop steatohepatitis or hepatic fibrosis than HIV-negative individuals, and this may be related to increased adipogenesis and decreased lipid clearance [151–153]. Lipodystrophy, attributed to the redistribution of human fatty tissue, is another common metabolic abnormality in PLWH, and considered an adverse effect of ART [154]. This could change the external appearance of individuals, affect their personality and life quality, and further increase the risk of diabetes and cardiovascular diseases through hyperlipidemia, insulin resistance, and impaired endothelial function [154–156]. Diabetes, NAFLD, and lipodystrophy constitute the common abnormal metabolic conditions seen in HIV.

Cancer accounts for 10–20% of mortality in PLWH [157, 158]. Compared to healthy individuals, PLWH also exhibit a heightened risk of malignancies, with a higher mortality rate and a poorer prognosis [159, 160]. For PLWH, malignant tumors are classified into two main categories, non-AIDS-defining cancers (NADCs) and traditional AIDS-defining cancers (ADCs); the latter includes Kaposi's sarcoma, invasive cervical cancer, and non-Hodgkin's lymphoma (NHL) [161, 162]. NADCs account for the majority (approximately two-thirds) of all cancers in PLWH [163, 164]. This is likely to be related to the prolongation of the average life expectancy of this population after ART treatment, and is expected to continue growing [165, 166]. Overall, in PLWH, the cumulative incidence rate of NADCs is approximately triple that of ordinary people [164, 167]. Among the NADCs, virus-associated NADCs such as hepatitis B virus–related hepatoma and EBV-related lymphoma have an even higher-than-expected incidence [164]. This may be explained by the uniquely low CD4 + T-cell counts found in PLWH [168]. Smoking may be a factor contributing towards a higher prevalence of ADCs (including laryngeal cancer and lung cancer) in PLWH, when compared to HIV-negative individuals [169, 170]. In people with Hodgkin lymphoma (HL), the 3-year survival rate for the HIV-positive cohort was observed to be statistically lower than that in the negative control cohort [171]. A similar trend was observed in those with cervical cancer and NHL [171, 172]. In fact, the implementation of ART has been observed to reduce the risk of most cancers among HIV-infected patients [173, 174]. This may be secondary to HIV viral suppression and the rejuvenation of cellular immunity among those PLWH using ART [175]. When ART is used in conjunction with anti-cancer therapeutic strategies, such as radiotherapy or chemotherapy, enhanced therapeutic effectiveness is observed for tumors in PLWH, compared to ART alone (albeit with an augmented adverse effect profile) [176, 177]. It is, therefore, particularly critical to weigh and consider the balance between therapeutic efficacy and toxicity when using multiple therapeutic modalities in tandem. Additionally, reduction of principal cancer risk factors such as smoking, alcohol consumption, and obesity should be promoted and implemented as adjunctive cancer prevention strategies in PLWH [162, 163].

Beyond this, the incident rate of a wide variety of disorders such as gastrointestinal infection, neurological disorders, cerebrovascular disease, and aging has also increased in PLWH, when compared with non-HIV-infected populations. The gastrointestinal tract is the principal site for HIV replication, due to high expression of CCR5 and abundant GALT [178]. HIV infection initially leads to disruption of gastrointestinal mucosal integrity, and subsequently to increased gut permeability and enhanced microbial translocation, and ultimately causes chronic intestinal inflammation [179], resulting in the increased incidence and severity of gastrointestinal infections such as enteritis. One primary manifestation of the neurological disorder spectrum in PLWH is the development of cognitive impairment [180]. When compared to healthy controls, approximately half of PLWH show impaired cognitive functioning, such as dementia [180, 181]. PLWH also experience a higher risk (ranging from 40 to 150%) for different cardiovascular diseases (CVDs), including acute myocardial infarction (AMI), heart failure, ischemic stroke, and coronary heart disease when compared to normal controls [182–185]. Also, CVD accounts for 20% of non-AIDS deaths in PLWH, and these patients exhibit a 70% higher mortality rate from CVD-related death than the non-HIV-infected population [186]. ART aims to extend the total lifespan of PLWH. However, in treated PLWH, with the associated prolongation of survival, the age of onset of senility-related complications or syndromes tends to be earlier, and the incident rate of these conditions is correspondingly increased [187]. Even with ART, systemic inflammation and immune disorders prevail, along with chronic persistent HIV infection attributable to the HIV reservoir, ultimately leading to an overall decline in life expectancy [188].

HIV Infection Promotes the Onset of Non-AIDS Comorbidities Through the Leaky Gut Syndrome

HIV-Associated Leaky Gut Syndrome

Gut microbiota strongly participates to gut homeostasis [189]. For example, evidences indicate that commensal bacteria can regulate the balance between pro-inflammatory and anti-inflammatory T-helper subsets (example Th17 and Tregs) involved in host responses [189]. In mice, *Bacteroides fragilis* can inhibit Th17 differentiation and Tregs proliferation. In humans, Th17 differentiation is also inhibited by the YCH46 strain of *Bacteroides fragilis* through the production of propionic acid [190]. In the context of HIV infection, it has been demonstrated that cell cultures of lamina propria with heat-killed *Escherichia coli* favor increased activation, proliferation, and HIV infection of CD4 + T-cells [191]. Concretely, compared to uninfected individuals, greater productions of TNF-α and IL-10 were noted in peripheral cells from HIV-infected patients when exposed to bacterial products of *Prevotella* spp., *Bacteroides* spp., and *Erysipelotrichaceae* [192]. Further ex vivo investigations have shown that altered gut microbiota contributes to enhance HIV replication ex vivo [193]. Altogether, studies in the HIV research field indicate that HIV infection profoundly perturbates the gut homeostasis through a particular feature referred to as HIV-associated gut dysbiosis syndrome. In turn, the gut dysbiosis strongly participates in the onset of the leaky gut syndrome. By definition, the leaky gut syndrome refers to an intestinal condition whereby the intestinal lining allows microorganisms (bacteria, fungi, etc.) and toxins to enter the bloodstream [194, 195]. In other words, during HIV infection, the leaky gut syndrome is a consequence of perturbations seen in the gut homeostasis, particularly changes in the immune system, inflammation, and dysbiosis [196]. This topic has been extensively investigated in previous research [27], and our group even believe that for this reason, the gut microbiota represents an important target to cure incomplete immune reconstitution in HIV infection [27, 197].

It has been shown that gut microbial communities differ significantly from that within the GI tracts of HIV-uninfected individuals [198, 199]. Most past studies [200–202] and one recent meta-analysis [203] uphold the preceding conclusion; however, some research groups have not observed any change in gut microbiota diversity during HIV infection, compared to HIV-negative individuals [192, 204]. It is, however, accepted that HIV infection provokes the onset of a change characterized by a reduction in symbiotic beneficial bacteria, and an elevation in levels of potentially pathogenic bacteria [205, 206], and this significantly impacts gut barrier integrity. Indeed, the diminution of beneficial bacteria (*Akkermansia muciniphila*, *Bacteroides*, *Bacteroides vulvae*, *Diplococcus*, and *Arbuscular roseus*) induces a significant reduction of their protective effects [digestion of carbohydrates into SCFA such as butyrate, acetate, and propionate] [207], which leaves the gut barrier relatively unprotected [208]. Furthermore, bacterial metabolites as butyrate can enhance Tregs differentiation [209], while *Clostridium* spp. are responsible for Tregs accumulation [52]. Conversely, the augmentation of levels of potentially pathogenic bacteria [*Proteus*, *Enterococcus*, *Klebsiella*, *Shigella*, and *Streptococcus* [201, 210]] and their toxins participate in the ultimate weakening and dismantling of the intestinal barrier. Consequently, microorganisms (bacteria, fungi, etc.) and toxins may readily translocate into the bloodstream. In short, gut microbiota and its related metabolites contribute (positively or negatively) in the gut homeostasis which is deteriorated by HIV infection.

In addition to microbial dysbiosis, HIV replication within intestinal cells directly instigates apoptosis and gut epithelial TJ disruption, which subsequently induces the leaky gut syndrome and promotes microbial translocation [211, 212]. Besides the apoptosis, it is also acknowledged that pyroptosis is responsible for the death of HIV-infected cells [213]. Interestingly, one category of HIV-positive individuals, referred to as elite controllers (ECs), do not possess the preceding gastrointestinal profile. It has been observed that HIV infection does not significantly affect the gut microbiome of ECs [214]. Thus, ECs tend to have a relatively analogous microbiomic composition to HIV-uninfected individuals [195, 214], and a conspicuous absence of the enduring leaky gut syndrome ubiquitously seen in HIV-infected individuals who are not ECs. Given that ECs (i) preserve their CD4 + T-cell counts in the gut [215], (ii) have lower levels of immune activation [216], and (iii) display smaller HIV reservoirs [216], it is therefore valid to further explore the association between the leaky gut syndrome and HIV reservoir persistence.

Furthermore, HIV infection induces the depletion of predominantly CD4 + T-cells [217, 218], and the exhaustion of immune cells in general (characterized by the loss of immune and/or secretory functions) [219–221]. However, it has been shown that T-helper 17 (Th17) cytokines, which are secreted by various cells including CD4 + T-cells, CD8 + T-cells, gamma delta T-cells, natural killer T-cells (NKT), and natural killer (NK) cells, are critical for gut barrier integrity. Indeed, Th17 cytokines promote mucosal barrier function through enhancement of the epithelial release of antimicrobial peptides, induction of mucus production, and promotion of wound healing [198, 222]. Thus, in an HIV infection context, both immune cell depletion and exhaustion contribute to the decrease of levels of Th17 cytokines and therefore promotes the leaky gut syndrome. The preceding mechanisms may be summarized as a modulation of the gut microbiome by HIV infection [198, 199, 223, 224], which progressively leads to (i) changes in microbial diversity [205, 206], (ii) damage to the intestinal barrier, (iii) impairment of mucosal immunological function, (iv) augmentation of microbial translocation, and (v) long-term immune activation. Therefore, during HIV infection, the gut microbiota and their metabolites are thought to be essential in contributing to the persistence of inflammation and immune activation, even in ART-treated individuals [225–227]. Nevertheless, it is worth mentioning that ART acts differently on the gut microbiota. Evidence suggests that PLWH receiving integrase inhibitors seem to have a gut microbiota more similar to healthy individuals [228]. In recent publications, Villoslada-Blanco et al. have successively indicated that the administration of integrase inhibitors alleviates both the leaky gut syndrome and the inflammation [229], and partially restores gut dysbiosis at the viral level [230]. These findings represent another area of investigation which may further explain the interesting role played by ART in the composition of gut microbiota. In the following section, we demonstrate how the leaky gut syndrome fosters the onset of non-AIDS comorbidities via inflammation and immune activation.

Leaky Gut Promotes Non-AIDS Comorbidities

Cumulative evidence suggests that the continuing state of inflammation seen in PLWH is primarily driven by the leaky gut syndrome during HIV infection, and is associated with an increased risk of development of non-AIDS comorbidities. Hence, translocated microbial products, which are recognized by the immune system as pathogen-associated molecular patterns (PAMPs), may induce inflammation and thus lead to development of non-AIDS comorbidities. Upon PAMP recognition, pattern recognition receptors (PRRs) present at the cell surface trigger pro-inflammatory and antimicrobial responses by activation of a multitude of intracellular signaling pathways, including adaptor molecules, kinases, and transcription factors [231]. In other words, microbial translocated products recognized by PRRs trigger PRR-mediated signaling and induction of an innate immune response (comprising gene expression and synthesis of a broad range of immune molecules, including cytokines, chemokines, cell adhesion molecules, and immunoreceptors [232], which ultimately sustains the prevailing inflammatory state). These processes, however, have several detrimental consequences as they may promote the onset of non-AIDS comorbidities.

The leaky gut facilitates the translocation of microbial products which in turn may activate monocytes and macrophages via interactions with TLRs (TLR4 for example). This activation is characterized by the increase circulating levels of IL-6, sCD14, and sCD163 [233]. In the context of HIV infection, the inflammation exhibited by monocytes underlies HIV pathology and is associated to age-related comorbidities. To illustrate this, Alzahrani et al. have indicated that monocytes activation is associated with all-risk of mortality in PLWH, particularly those on ART [27]. As such, the preceding immune cells increase glycolysis and lactate production, which ultimately favor immunosenescence and immune cell aging [234]. This context establishes an environment in which HAND, CVD, frailty, and osteoporosis can develop [235–238]. The preceding case represents pieces of evidence towards the major role played by the leaky in the development of non-AIDS comorbidities, and many studies have already reported findings corroborating this [6, 27, 212, 239].

In a past hypothesis review [212], our research team has explored the influence of the leaky gut syndrome on the onset of HBV infection. In that review, we have indicated that once in the portal vein, translocated microbes and their products are able to reach hepatocytes and activate the liver's innate immune system. Consequently, hepatocytes are injured by PAMPs produced by intestinal microbes, and therefore become vulnerable to HBV. Beyond HBV infection, we believe that the leaky gut represents a widely opened gateway via which translocated microbial products may injure the liver and induce liver cancer. Based on published evidence, it has been shown that during HIV infection, gut microbiota enhances the degree of tryptophan catabolism to kynurenine [198]. In the context of the leaky gut syndrome, kynurenine may reach the liver and induce cancer by suppression of liver anti-tumor immunity (e.g., activation of the aryl hydrocarbon receptor and CD39 in tumor-associated immune cells which become dysfunctional). This phenomenon has been observed and reported by several research teams [240–243]. Additionally, secondary bile acids, which are known to be converted from primary bile acids (cholic acid and chenodeoxycholic acid) solely by gut microbial bile acid-inducible operon via the 7-α-dehydroxylation process [244, 245], have been shown to be capable of inducing liver cancer by promotion of the senescence-associated secretory phenotype (secretion of inflammatory cytokines, chemokines, proteases, and growth factors which promote liver cancer progression) in hepatic stellate cells [246]. A complete review of gut-liver axis mechanisms potentially involved in liver cancer development has been published by Yu and Schwabe [247], and subsequently by Ohtani and Hara [248].

Microbial translocation has also been linked to several pathological conditions and/or diseases. Indeed, Morris et al. [249] have observed that HIV-positive individuals displaying a leaky gut syndrome with higher circulating (1−>3)-beta-D-glucan (BDG) levels had a higher frequency of cardiopulmonary abnormalities (including a reduced diffusion capacity for carbon monoxide), a higher pulmonary artery systolic pressure, and an increased tricuspid regurgitant jet velocity. Similarly, Isnard et al. [250] have observed an association between plasma BDG levels and subclinical coronary atherosclerotic plaque formation in ART-treated PLWH. Higher blood BDG levels have also been associated with (i) greater trunk and total body fat accumulation [251] and (ii) poorer cognitive functioning (elevated levels of BDG in cerebrospinal fluid are associated with worse Global Deficit Scores) [252] in PLWH. Furthermore, one cross-sectional study (including 11 years of follow-up after ART commencement) by Hoenigl et al. [253] has observed that soluble urokinase plasminogen activator receptor (a marker for monocyte, T-cell, and plasminogen activation) [254–258] is predictive of non-AIDS medical events, including myocardial infarction, stroke, non-AIDS malignancy, bacterial infection, and death from a non-AIDS-related event.

To date, several animal studies have observed the beneficial effects of the probiotic use of *C. butyricum* on gut microbes, intestinal health, and anti-inflammatory responses [15, 259–263]. In general, results indicate that dietary supplementation with *C. butyricum* may improve the preceding factors and also enhance mucosal barrier functioning. Administered to humans, *C. butyricum* is safe, and improves inflammation and immunity [81, 104, 264]. Intervention with *C. butyricum* administration in HIV-positive individuals may also help to mitigate the effects of HIV-associated gut dysbiosis syndrome. However, to our knowledge and in the particular context of HIV infection, specific clinical trials investigating the benefits of *C. butyricum* supplementation on gut health remain sparse in the literature. Future studies focusing on probiotic *C. butyricum* supplementation in humans will provide more definitive answers with regard to potential adverse effects and safety concerns.

Conclusion

Due to the enduring presence of chronic inflammation, HIV-infected individuals have an elevated incidence of a series of non-AIDS comorbidities, such as metabolic disorders, cancer, gastrointestinal infections, neurological disorders, and cerebrovascular diseases. The presence of *C. butyricum* in the gut has been shown to have multiple beneficial outcomes, such as amelioration of inflammation, regulation of immune homeostasis, maintenance of the structural and functional integrity of the intestinal barrier, and inhibition of intestinal pathogenic bacterial species. An increase in the abundance of *C. butyricum* in the gut helps to prevent and manage various inflammation-associated diseases, including metabolic syndromes, tumors, intestinal infections, and neurological diseases. Additionally, HIV infection may promote the emergence and development of the preceding non-AIDS complications via aggravation of a leaky gut, suggesting that *C. butyricum* may be a fundamental participant in relation to the non-AIDS complications associated with HIV infection. Therefore, it may be possible to inhibit the occurrence and slow down the progress of non-AIDS-related diseases by increasing the concentration of *C. butyricum* or its metabolites in the gut, thereby reducing the chronic inflammatory state and maintaining the dynamic equilibrium of the intestinal microecology. This may have clinical value for the monitoring of disease development and evaluation of the effects of treatment and of prognosis among HIV-infected individuals. However, further studies are warranted to confirm the clinical benefits of an enriched *C. butyricum* presence in HIV-positive patients, and to further explore the mechanisms whereby *C. butyricum* therapeutic utilization as a probiotic supplement exerts its effects on the maintenance and restoration of human intestinal microbiotic ecosystems in HIV-infected patients, and in the mitigation of non-AIDS complications in these individuals. Multidisciplinary research cooperation is necessary and inevitable for this quest, and future research priorities will require a focus on both the known and as yet undiscovered biological properties of *C. butyricum*, and to seamlessly and creatively combine the knowledge gleaned therefrom with the disciplines of metabonomics, microbiology, and oncology. This future research may well reveal whether *C. butyricum* is a potentially viable future therapeutic candidate for PLWH, and is likely to go a long way towards mitigating the persisting gastrointestinal inflammation present in HIV-infected individuals, decreasing non-HIV-related complications, and improving the overall quality of lives of PLWH.

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Declarations

Competing Interest The authors declare no competing interests.

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