

Review

Microbiome and Probiotics in health and HIV infection

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Abstract: Microbiota plays a key role in various body functions, as well as in physiological, metabolic and immunological processes, through different mechanisms, such as the regulation of the development and/or functions of different types of immune cells in the intestines. Several evidences indicate that alteration in the gut microbiota can influence infectious and non-infectious diseases. Bacteria that resides on the mucosal surface or within the mucus layer interact with the host immune system, thus a healthy gut microbiota is essential for the development of mucosal immunity. The immunomodulatory activity of probiotics has been proposed in several bowel disorders or in aging-related dysfunctions. In HIV infected patients, the intestinal immune system is affected and inflammation persists during ART therapy, too. Several studies are in progress to investigate the ability of probiotics to modulate epithelial barrier functions, microbiota composition and microbial translocation in HIV infection. This mini-review aims to suggest how the use of probiotics is beneficial not only in maintaining a healthy status but also in improving HIV subjects conditions.

Keywords: microbiome; probiotics; dietary supplements; nutrition; HIV; inflammation

1. Introduction

Over the past 20 years, the increasing interest on probiotics use in healthy subjects has sprung in researches both in food and pharmaceuticals companies, thanks to probiotics effects on cell proliferation and activity [1], homeostasis of the immune system [2], modulation of host's microbiota and related improvement of host's health by limiting pathogens colonization and controlling inflammatory gut disorders [3,4], and on metabolic disorders [5].

Probiotics benefits are not a recent discovery: they were already present a long time ago, in traditional foods, such as cheese, yogurt, milk and salty fishes, and their use was related to their ability of interaction and modulation of the indigenous microflora of the host. The total human body surface and the gastrointestinal (GI) tract host over 10^{14} microorganisms – starting from the birth - which form the microbiota. It is known that a healthy gut flora is largely responsible of the overall health of the host, while gut microbiota alteration was associated with several human diseases such as bowel diseases, metabolic and allergic diseases or neurodevelopmental illnesses [6,7].

The gut microbiota is a complex microbial ecosystem that, in healthy conditions, includes more than 400 species of bacteria, each of which contains many functionally different strains with significant genetic diversity. The majority of strains are strictly anaerobes, even if facultative anaerobes and aerobes are present [8,9]. Some bacterial strains are prevalent: fermenting bacteria (such as *Lactobacillus* and *Bifidobacteria*) represent 80% of the gut microbiota, while the remaining 20% includes *Escherichia*, *Bacteroides*, *Eubacteria* and *Clostridium* [10,11]. Lactic acid bacteria (LAB) are considered a major group of probiotic bacteria and have been isolated directly from humans. To date different bacterial genera are known, including *Bifidobacterium* and *Lactobacillus*:

they survive to stomach acid pH and to intestinal bile salts, reach sites of action, and their ingestion does not cause any risk for the host [12].

Fermented foods, drinks, vegetables, and fruit juices represent an unconventional source of microorganisms [13]. Probiotics, though deriving from different sources, must be non-pathogenic bacteria, must have acid and bile tolerance, ability to adhere to gut epithelial cells and be able to combat pathogens in the GI tract.

For the Food and Agriculture Organization/World Health Organization (FAO/WHO), the term probiotic defines “live microorganisms which when administered in adequate amounts confer a health benefit on the host”. The improvement of our health status would help us protect from different types of sickness. The effectiveness of probiotics has been demonstrated in several disorders, such as inflammatory bowel diseases (IBD), diarrhea, allergies and prevention of upper respiratory tract infections. Furthermore, probiotics may exert their beneficial properties also in unbalanced conditions of intestinal flora induced by stress, genetic disorders, antibiotic therapy, inadequate food and exposure to environmental toxins. Thus, thanks to their healthy features, probiotics use became part of human diet [14,15,16,17,18].

One of the pathologies characterized by gut microbiota dysbiosis, altered intestinal barrier and systemic inflammation, is the Human Immunodeficiency Virus (HIV) infection [19]. The mucosal immune system can be modulated by gut-resident bacteria and alteration of mucosal innate immune system can result in the outgrowth of a dysbiotic pro-inflammatory group accountable for chronic inflammation in the mucosa and the periphery. Progressive HIV infection is characterized by dysregulation of intestinal immunity that may persist also during highly active antiretroviral therapy, and the extent of dysbiosis correlates with markers of disease progression [20,21]. In HIV positive subjects, the use of probiotics could restore gut microbiota and gut barrier functions, as well as modulate the immune system, during short-term antiretroviral therapy (ART).

Mechanisms by which probiotics may exert their effects are strain-related and include host's microbiota modulation, improvement of mucosal barrier functions, and modulation of immune system [22,23]. As all the implicated mechanisms are not completely known, probiotics clinical use needs to be related to probiotic strain and dosage, in order to identify their efficacy in specific conditions. Many studies are in progress, with the aim of understanding probiotic-specific mechanisms and selecting probiotic strains in relation to target patient's specific pathogenic and clinical defects [24].

2. The intestinal microbiota functions

2.1 Function and preservation of the mechanical intestinal barrier

The GI mucosal surface is the biggest area of the body in contact with the external environment; it plays a key role in blocking the access of potentially harmful substances. The epithelium and the mucus layer, lining the gut, represent the first host's defence and the essential mechanical barrier that avoids the contact between the internal and the external environments by blocking the passage of antigens, toxins and microbial products.

In a normal gut, the epithelial barrier consists of a layer of enterocytes tight junctions, anchoring junctions and desmosomes - which hinder microbes passage - goblet cells producing mucus, and Paneth cells producing antimicrobial peptides, a natural alternative to chemical antibiotics [25,26]. In the mucosal tissue, a layer of epithelial cells establish a barrier between external and internal environment and play a key role in the discrimination between pathogenic and non-pathogenic bacteria. Breaks of the epithelial barrier or a bacterial invasion give a signal to the epithelial cells that initiate inflammatory responses. GI infections may be responsible of altered nutrient absorption, depleted levels of micronutrients and waste secretion.

Many factors can alter intestinal permeability, including gut microbiota modifications. As a consequence of microbes activity and release of soluble peptides or toxins, there are alterations in enterocytes components and their metabolism, leading to a breakdown of the epithelial barrier and to microbial translocation to the gut [27,28,29]. Moreover, lifestyle and dietetic factors, including

alcohol and energy-dense food, can increase intestinal permeability [30]. The resulting increased permeability does facilitate chronic intestinal inflammation, strictly connected to the immune system, as observed in the existing association between inflammation and barrier dysfunction in several GI diseases. This suggests that the impaired permeability is the result of a chronic inflammation in the gut that finally leads to structural proteins change, including the claudins proteins, which are essential for the formation and the integrity of tight junctions which regulate the flow of water ions and small molecules [31]. The significance of intact epithelial tight junctions is showed in IBD [32] and inflammatory joint diseases [33].

The proper defence activity of the epithelial barrier is supported by the microbiota, which influences cell metabolism and proliferation, maintenance and repair of barrier integrity, nutrient acquisition and energy regulation, inflammatory response and angiogenesis [34,35].

In several human diseases, including the celiac disease and IBD, as well as in older people and in antibiotic treated individuals, biodiversity of beneficial or protective anaerobes, such as *Lactobacillus* and *Bifidobacteria*, is reduced and the increasing presence of pathogenic microbes can predominate on the resident microflora. The intake of probiotics can reduce the risk of diseases associated with intestinal barrier dysfunction. The exact mechanisms by which probiotics can influence barrier function are not fully understood. It is known that certain lactobacilli adhere to mucosal surfaces, inhibit attachment of pathogenic bacteria, and enhance secretion of mucin. Probiotics reinforce the various lines of gut defence: immune exclusion, immune elimination, and immune regulation. Probiotics also stimulate non-specific host resistance to microbial pathogens and thereby aid in their eradication. These actions may depend on specific strain characteristics, and on host's age and immunological state. It is likely that some probiotic strains adhere better to the small intestine, while other bind specifically to different parts of the large intestine, as well as different strains adhere differently in healthy or injured mucosa. Strictly related probiotics have shown different *in vitro* properties, which may mirror differences in clinical effects. The application of probiotics currently lies in reducing the risk of diseases associated with gut barrier dysfunction.

2.2 Resistance to pathogenic colonization

One of the major functions of the intestinal microbiota is the protection of the host from colonization and overgrowth of ingested invading bacteria, a phenomenon known as resistance to colonization [36]. Endogenous microbial populations act by several mechanisms, including the modification of the pH in the environment and ecological niches, the release of antimicrobial substances and the direct competition for the adhesion sites on the epithelium and for nutritive substrates.

After ingestion, pathogens penetrate the highly colonized mucus layer, where they compete with the resident microbiota for adhesion to the intestinal epithelial cells receptors. In healthy subjects, the direct competition for nutrients limits the possibilities for exogenous pathogenic microbes to colonize and replicate within the gut lumen and invading deeper tissues [37,38]. Also the production of pathogen growth inhibitors or the resistance to colonization, due to the induction of immune responses and to metabolic products of beneficial bacterial, makes the host resistant to pathogenic infections. In addition, in the GI tract, the microbiota affects biosynthesis and availability of neurotransmitters that modulate peristalsis, the flow of blood and the secretion of ions [39,40].

Patients with HIV infection exhibit numerous GI tract pathologies, are susceptible to gastric hypoacidity that may be responsible of a greater risk of opportunistic infection. Delayed gastric emptying may also contribute to the increased bacterial colonization of upper digestive tract in Acquired Immune Deficiency Syndrome (AIDS) patients, playing a key role in chronic diarrhea and weight loss, frequently observed in HIV infected subjects. In HIV, malabsorption and GI infections are common conditions that are further impaired as HIV disease progresses [41,42].

2.3 Development and stimulation of the GALT

The presence of the microbiota is crucial for the normal development of GALT (Gut-Associated Lymphoid Tissue). Already from birth, the presence of intestinal microorganisms stimulates the GALT to the recognition of conserved microbial structures, ensuring an appropriate immune activity. GALT composition is modified immediately after microbial colonization of the GI tract, with number of intraepithelial lymphocytes and immunoglobulin-producing cells in follicles and in the *lamina propria*. Bacterial antigen detection is performed by the resident cells of innate and adaptive immune system. Signals from bacteria can be transmitted to macrophages, dendritic cells (DCs) and lymphocytes through molecules expressed on the epithelial cell surface, such as molecules of the major histocompatibility complex I and II, Toll-like receptors (TLRs) and nucleotide oligomerization domain (NOD)-like receptors or nucleotide-binding domain leucine-rich repeat containing (NLRs) proteins [43,44]. Antigen-presenting cells (APCs) provide processed antigens to naïve lymphocytes within distinct T- and B-cells zones. TLRs detect various conserved microbial structures, while DCs, the main APCs, interact with T and B-lymphocytes to induce immune responses [45].

The CD4⁺ T lymphocytes, that can differentiate into Th1, Th2, Th17 and regulatory T (Treg) cells, represent another key component of the mucosal immune defence against pathogens. Mucosal effector sites consist of T lymphocytes, primarily CD8⁺, located in the epithelium and in the *lamina propria*, and CD4⁺ T cells and plasmacells that heavily populate the large and small intestines, beneath the *lamina propria*. At the same time, the presence of commensal bacteria, with their antigens in the gut, induces the expansion of cytotoxic lymphocytes and T-helper CD4⁺ lymphocytes producing IL-17 (Th17) [46,47,48,49,50].

Humoral immune response represents the main mechanism of protection given by the GALT, mediated also by B cells secreting IgA, of which the intestinal DCs are potent inducers. It has anti-pathogenic effects and prevents commensal bacteria penetration in the host [51].

Epithelial cells, APCs and lymphocytes can secrete cytokines, chemokines, and other factors that can be tuned to promote tolerance, inflammation or specific immunity.

The dualistic effect that the microbiota exerts on the GALT consists in maintaining tolerance and preventing inflammation through β -defensins and IgA production in the epithelium, whose integrity is enhanced through TLRs signalling and Treg induction [52]. The equilibrium between microbiota, immune response and tolerance mechanisms is important for a healthy intestine, and an aberrant colonization that breaks the balance may drive feeding intolerance in early postnatal life and GI disease in childhood.

The constant interplay between the microbiota, the intestinal barrier and the mucosal immune system ensures the balance between permissive or tolerogenic responses to pathogens or food antigens [53]. Probiotics may induce a tolerogenic situation by modulating anti-inflammatory/regulatory cytokines, such as IL-10 and TGF- β , and DCs functionality and T-helper differentiation/effector function towards a regulatory/suppressive phenotype [54].

In the GALT, the absence of bacteria leads to an inadequate development of Peyer's patches, decreased B-cell activation and IgA production, lower numbers and turnover of intestinal epithelial cells and mucus production. Thus, intestinal microbioma and immune system influence each other

2.4 Modulation of the Th17/Treg ratio to induce inflammation or tolerance

CD4⁺ Th17 cells share differentiation pathways and a reciprocal relationship with antigen-induced cells and CD4⁺ Treg cells, which are both able to maintain the balance between inflammation and tolerance. Th17 cells, a newly identified subtype of CD4⁺ T-cells, constitute a distinct lineage from Th1 and Th2, characterized by the production of peculiar cytokines IL-17A, IL-17F, IL-22 which have their receptors on epithelial cells [55,56].

Th17 cells are localized at mucosa tissue level in the intestinal *lamina propria*, and are specialized in maintaining mucosal integrity, stimulating proliferation of epithelial cells, producing tight junction proteins (claudins) and producing a robust antimicrobial inflammatory response by neutrophils and macrophages recruitment via chemokine, antimicrobial defensins and mucin

production, which are vital for mucosal integrity [57,58,59,60]. Th17 cells are considered active especially against bacteria and fungi infections.

Treg cells, maintaining immune homeostasis, have anti-inflammatory activity and prevent autoimmunity, inducing tolerance against self-antigens. Without an inflammatory stimulus, commensal microorganisms induce tolerogenic maturation of DCs, leading to the induction of various types of Treg or hypo responsive T-cells [61,62]. Th17 and Treg cells CD4⁺ differentiation pathway results unbalanced in aberrant immune disorders related to host–pathogen interactions, inflammatory syndromes, autoimmune diseases, and primary immune deficiencies.

Probiotics consumption, through balancing the gut microbiota, can restore the Th17/Treg ratio and the mechanical barrier, thanks to a lower local inflammation: the microbial translocation is thus limited, which leads to a reduction of systemic inflammation [63,64].

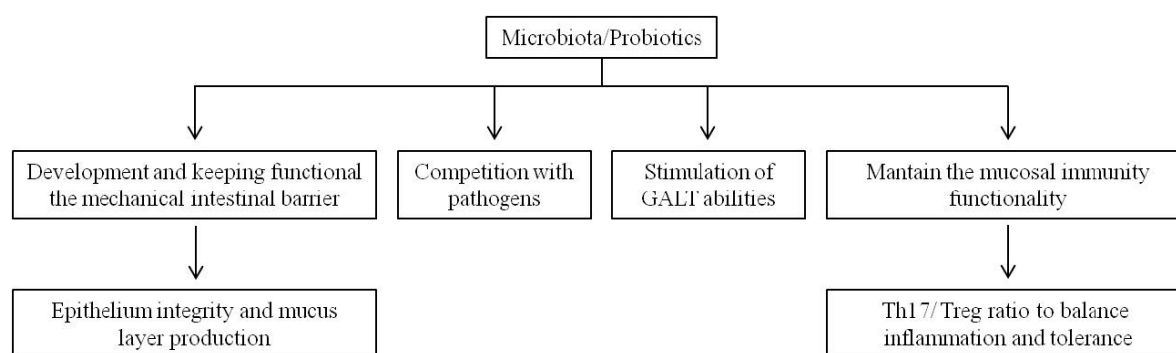
3. How can probiotics help maintaining health?

Many studies are focused on investigating the possible link between microbiota changes and diseases development. In fact, the presence of different microbial populations and temporary changes in microbiota microbial composition has been observed.

An unbalanced microbiota composition, with a reduced species diversity, few beneficial bacteria and/or presence of pathogens, is associated to intestinal mucosa diseases as well as to other systemic diseases [65,66,67].

Probiotics consumption can confer health benefits by rebalancing the microbiota in the large intestine, and restoring the colonization resistance capability. Different probiotics may differ in terms of safety, and different species or strains have different physiological effects and different health benefits. The most common probiotics belong to *Lactobacillus* and *Bifidobacterium* genera: they can support a rich and complex microbiota and compete for nutrients, making the intestinal habitat hostile for detrimental bacteria, such as Clostridia, Enterobacteria and Eubacteria [68] (Figure 1).

Figure 1: Microbiota and Probiotics activities in the gut.



Antibiotics represent the most usual therapeutic strategy to treat bacterial infections, but they are responsible of changes in gut microbiota composition, host susceptibility to enteric infection and effects on intestinal absorption. The health benefits of probiotics are also helpful during antibiotics administration - reducing antibiotic-associated diarrhea - and to restore normal gut permeability, mechanical integrity, and homeostasis [69,70].

Probiotics modulatory action on the immune system focuses mainly on the activation of cells in the innate immune system, such as phagocytes and natural killer (NK) cells, and on the inhibition of excessive or abnormal immune responses. Different probiotic strains show a different ability to stimulate the production of various cytokines and, thus, to induce the differentiation of T-cells that is mainly regulated by cytokines in the microenvironment [1,71]. Thus, the supplementation with specific probiotics can promote the restoration of intestinal CD4⁺ T-cell population in many immunological diseases, while the anti-inflammatory effects of probiotics in Th17-related diseases might be a consequence of the downregulation of pro-inflammatory IL-17 production (Figure 1).

In vivo and *in vitro* studies have shown that *Bifidobacterium longum* inhibits IL-17 production with a shift towards Treg. Two recent investigations showed, in mouse models of autoimmune disease, a Tregs upregulation achieved with a combination of probiotics. Lavasani et al. administered five different *Lactobacillus* strains to C57BL/6 mice before immunizing them with a synthetic peptide of myelin oligodendrocyte glycoprotein known to induce experimental autoimmune encephalomyelitis (EAE). Combining three *Lactobacillus* active strains in a mixture (*L. paracasei* DSM 13434, *L. plantarum* DSM 15312, DSM 15313) and feeding this to established EAE mice, suppression of EAE disease was observed with a reduced production of pro inflammatory Th1 cytokines, such as TNF and IFN γ , and an increased level of Th2 cytokines, such as IL-4, IL-10, and TGF- β [72].

It has also been shown that the administration of a combination of *L. acidophilus*, *L. casei*, *L. reuteri*, *Bifidobacterium bifidum* and *Streptococcus thermophilus* in experimental mouse models of IBD, atopic dermatitis and rheumatoid arthritis, induces hyporesponsiveness of both T-cells and B-cells, downregulation of Th1, Th2, and Th17 cytokines without apoptosis and migration of Tregs to inflammatory regions [73].

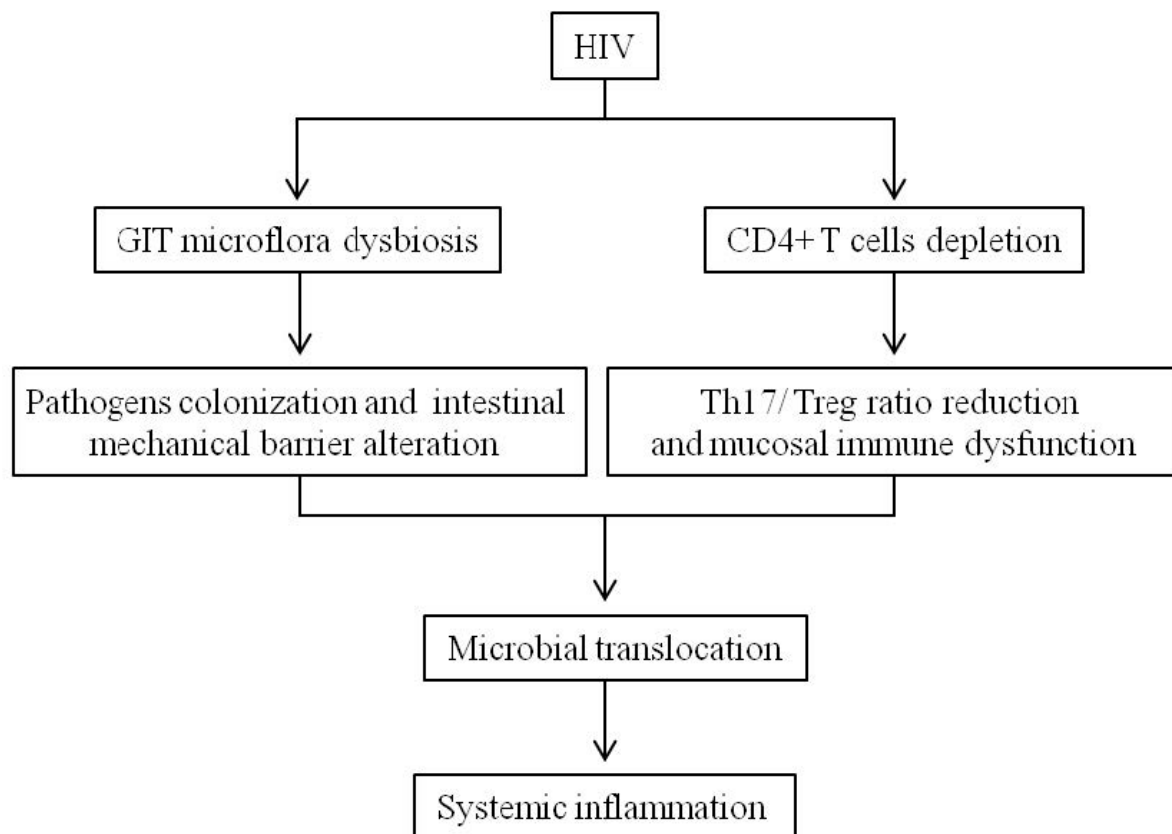
Several probiotic strains can promote Th1 responses by inducing the production of IFN- γ , IL-12, TNF α and IL-2, which are involved in cellular immunity against intracellular pathogens. On the contrary, other strains can induce the differentiation of Th2 profile resulting in the production of high amounts of anti-inflammatory cytokine such as IL-10, IL-4 and TGF β that is essential for the development of Th17 subpopulation [74].

Probiotics intake sustains the indigenous microflora in modulating gut immune system through interaction with gut epithelial cells and immune cells by TLRs; it can increase IgA and modulate the production of cytokines involved in the regulation, activation, growth and differentiation of immune cells. Probiotics may have an inhibitory effect against infections, cancer cells and abnormal immune responses, limiting IBDs, allergies, and autoimmune diseases [75].

4. Bowel condition in people living with HIV

GI disorders are among the most frequent complaints in patients with HIV infection. Diarrhea, dysphagia and odynophagia, nausea, vomiting, weight loss and abdominal pain are the most frequent symptoms. During HIV infection, progressive immune-decline is associated with increasing GI symptoms. The GI tract is a major site of HIV replication and, although the mechanisms responsible of GI dysfunction are not completely understood, it has been proposed that HIV causes disruption of gut microbiota and massive loss of *lamina propria* CD4⁺ T-cells. High levels of pro-inflammatory chemokines and cytokines are determined in the colon *lamina propria* of HIV infected patients. Moreover, the degree of inflammation within the GI tract correlates with viral replication.

In people with HIV infection or AIDS, the wall of the small intestine is impaired, the crypts are enlarged and the atrophy of the microvilli decreases their surface area. These modifications are responsible of malabsorption, digestive discomfort, or decreased intake of nutrients. The homeostatic balance between GI bacteria and gut immunity breaks down, so commensal bacteria and their products can cross the intestinal barrier reaching the systemic circulation, bacteria in the small intestine begin to overgrow and other pathogenic bacteria may also infect the intestine [76,77,78] (Figure 2). Although ART has markedly improved survival in HIV infected individuals, microbial translocation is still not under a full control and remains associated with systemic immune activation and inflammation, characterized by elevated pro-inflammatory cytokine levels, as well as T and B cells activation.

Figure 2: Gastrointestinal tract dysfunctions in HIV infected patients.

4.1 Microbiota alteration, CD4⁺ T-cells depletion and unbalanced Th17/Treg ratio

HIV infection causes breakdown of the GI barrier and an altered composition of the gut microbiome [79], leading to the reduction of *Bifidobacteria* levels and *Lactobacillus* species with damage and loss of mucosal barrier functions. Thus, in the gut, a greater presence of potential pathogens such as *Pseudomonas aeruginosa* and *Candida albicans* was observed, together with increased mucosal inflammation and co-receptor expression on intestinal T-cells [80,81].

Throughout the initial stage of HIV infection, the immune system is unprepared to the attack of the virus, which therefore reproduces at very high levels in the *lamina propria*, spreading throughout the body. HIV induces CD4⁺ T cells destruction by a combination of mechanisms including direct infection, apoptosis (perhaps after contact with viral proteins) and direct killing of infected cells by NK cells or cytotoxic T cells. The combination of these mechanisms may contribute to CD4⁺ T cells loss, mucosal barrier damage and chronic systemic inflammation.

Usually, with <100 CD4⁺ T cells/mL, opportunistic infections of pathogenic bacteria and/or fungi drive GI dysfunctions, and HIV-1 directly drives mucosal inflammation, causing HIV related enteropathies such as IBD.

During HIV infection, the CD4⁺ T cells depletion in the GALT is observed, in association to inflammation of the mucosal tissues; Th17 cells, the CD4⁺ T cells expressing both CCR5 and CCR6 markers, are preferentially lost from the GI tract of HIV infected individuals. High levels of viremia are associated with a more important Th17 reduction; as suggested by several studies, Th17 cells may have a double effect on HIV infection, due to their functionality in the mucosal tissue. In the inflammatory environment of the acute phase of infection, Th17 cells could promote cell migration into the gut and create conditions for viral replication, while since Th17 cells produce IL-22, which enhances epithelial regeneration, the reduced number of Th17 cells may be related to a decrease in mucosal restoration and increase of microbial translocation and immune hyperactivation, contributing to exacerbation of the infection and to opportunistic infections [82].

The loss of Th17 cells was accompanied by a concomitant rise of Treg cells, resulting in an imbalanced Th17/Treg ratio during the HIV progression. Tregs cells may have both a beneficial and a detrimental role; the first one by limiting immune activation, while the second one is based on the ability of Treg cells to suppress virus-specific immune responses. Thus, the role of Treg cells in regulating T cell activation in HIV infection is still debated. The effects can be beneficial or detrimental depending on the balance between attenuating HIV induced immune hyperactivation and raising an immune response to HIV and opportunistic pathogens [83,84,85,86]. A low Th17/Treg ratio, in HIV infected individuals, correlates with microbial translocation and with a higher frequency of activated CD8⁺ T cells, which is one of the strongest predictors of mortality. Th17 cells loss leads to an increased microbial translocation, and systemic immune activation may further perpetuate bacterial overgrowth. The increase of Treg cells drives further Th17 cells depletion and a lower production of IL-17 and IL-22 by NK cells.

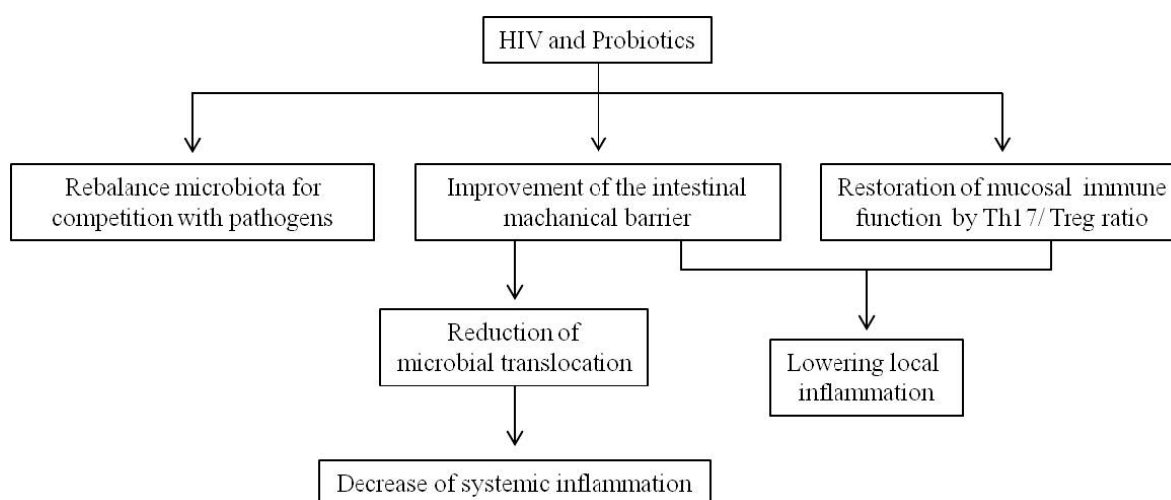
4.2 Microbial translocation and systemic immune activation

In order to understand how the intestinal mucosa damage can influence the activation of immune cells in periphery, it is important to consider that the mucosal integrity requires the interaction of a variety of cells in a complex network, involving cell surface, soluble cytokines, growth factors and hormones. Acute HIV infection is accompanied by an increased production of pro-inflammatory cytokines and an altered expression of genes related to mucosal repair and regeneration [87,88]. These changes, together with the loss of T cells subsets, may lead to impaired barrier function and intestinal permeability with leakage of bacterial products, such as lipopolysaccharide (LPS) into plasma. HIV infected individuals produce high levels of TNF and IFN α , and increased TNF production may also lead to tight junctions destruction.

Circulating microbial products have been appointed as a possible cause of HIV related systemic immune activation, HIV progression promotion and suboptimal response to therapy and comorbidity. This process is known as microbial translocation. Brenchley et al. [89] reported that plasma LPS levels and bacterial ribosomal DNA were elevated in patients with HIV infection compared with healthy controls. Chronic TLRs activation in HIV disease, through recognition of translocated bacterial products and/or viral products, can cause dysregulation of immune responses. A mechanism that can further contribute to the barrier damage is the loss of IL-17 and IL-22 producing cells in the GI tract; moreover, HIV replication can itself drive epithelial damage by producing pro-inflammatory cytokines, which can directly induce apoptosis of epithelial cells.

5. Probiotics as a new therapeutic approach that might improve life in HIV positive subjects

Several HIV affected patients may be effectively managed by controlling HIV infection with high-efficacy and improved ART, while others HIV positive patients require more complex approaches [90,91]. Unfortunately, although ART and other pharmacological therapies are life-saving in HIV positives subjects, due to the suppression of plasma viremia, they have many side effects, such as diarrhea and other GI symptoms associated with a worse quality of life, leading to a discontinuation of treatment. HIV infection has an unfavourable effect on the interaction between the commensal microbiota and the immune system, with inefficient epithelial repair and enhanced epithelial permeability, accountable of GI disorders. In HIV infection, the increased translocation of microbes and bacterial products from the intestinal tract, may induce a systemic immune activation, that causes further damage to the gut barrier function, augmenting bacterial translocation and subsequently increasing systemic inflammation and in turn HIV progression [92]. The intestinal microbiota of HIV patients appears to contain higher levels of pathogens, such as *Pseudomonas aeruginosa* and *Candida albicans* and reduced levels of LAB species. Thus, gut reconditioning through probiotic administration could be protective for the gut surface and delay the progression to AIDS [93,94] (Figure 3). In young HIV infected subjects, elevated inflammation levels, persistent immune activation and dysfunction will be observed for many years. The ART itself leads to a persistent low-level inflammation that may affect many tissues, leading to a multi-organ dysfunction.

Figure 3: Probiotics use and beneficial effects in gastrointestinal tract of HIV-1 infected patients

In HIV infected individuals, ART may cause adverse lipid profiles and increased risk for cardiovascular events, diabetes, neurocognitive impairment, osteoporosis and malignancies, also contributing to increased mortality during the treatment [95,96,97]. The hypothesis that probiotics administration protects the gut surface and can delay progression of HIV infection to AIDS was proposed some years ago. Several studies have shown that probiotics supplementation could be useful in the reduction of risk factors for cardiovascular diseases such as hypercholesterolemia [98].

The effectiveness of diet supplementation with different probiotic strains has been shown in people with HIV and, especially, as an additional strategy in patients on ART, in order to improve antioxidant defences and reconstitution of the immune function. Probiotics, by altering intestinal flora, may induce epithelial healing, and by preventing decline in CD4⁺ cells count may lower the risk of virus transmission and reduce hospitalization for co-infections. In 2010, Irvine et al. run an observational retrospective study to assess the effect of a *Lactobacillus rhamnosus* Fiti yogurt on the CD4⁺ cells count in HIV subjects; the study has shown an increased CD4⁺ cells average count, over a period of 3 years, in yogurt consumers [99]. Combination of probiotic bacteria upregulates Treg cells activation and suppresses pro-inflammatory immune response in models of autoimmunity, including IBD, thus providing a rationale for the use of probiotics in HIV infection.

In addition to the ability of probiotics to improve barrier function and intestinal homeostasis, specific probiotic strains may be able to revert the HIV induced Th-2 polarization [100]. In Caucasian HIV positive patients on ART, the supplementation of a fermented dairy drink with *Lactobacillus casei* Shirota for 4 weeks led to increased levels of CD56⁺ cells and to a reduction of inflammatory status with significantly increased IL-23 serum levels [101]. These results are in accordance with a study carried out by d'Ettorre et al. in 2015, where HIV infected patients on ART have been supplemented with probiotics for 48 weeks. In the treatment group, it has been observed a significant reduction in the levels of immune activation on CD4⁺ and CD8⁺ T lymphocytes for both markers CD38 and HLA-DR, and of their simultaneous expression, and lower microbial products, LPS and C-reactive protein plasma levels, with values comparable to control group (HIV seronegative subjects) [23]. Thus, in HIV infected subjects, the *Lactobacillus casei* Shirota would be beneficial immunologically, virologically, and bacteriologically.

Also, chronic immune activation, inflammation and immune dysfunction persistence are likely to have important effects on the size and distribution of the viral reservoir [88,98,102]. There is a growing recognition that probiotics supplementation in HIV positive patients improves quality of life by improving the nutritional status, alleviating GI manifestations, and stimulating mucosal immune function [103].

6. Conclusions

Helpful effects of probiotics to maintain our body in good health are well known, and several clinical and *in vitro* studies have shown a large field of application for probiotics supplementation, related to benefits that occurred in infections and diseases.

Lactobacilli are the best studied probiotics, and may represent a potential therapeutic adjuvant also in HIV clinical treatment. There are many possible mechanisms by which probiotics may interfere with HIV: they can compete for nutrients and epithelial and mucosal adherence, inhibit epithelial invasion, counteract the inflammatory process by stabilizing and strengthening the gut microbiota responsible of the intestinal barrier integrity, and prevent the microbial translocation, lower mucosal and systemic inflammation, stimulate production of antimicrobial substances. Instead of promoting a non immunological defence barrier of the gut, probiotics can promote intestinal immunoglobulin A responses, thus improving the immunological barrier function.

However, the functional properties and the mechanisms underlying probiotics actions are very different between the different strains and distinct regulatory effects have been detected in healthy subjects and in patients. Thus, immunomodulatory properties of all probiotic bacteria should be characterized in order to develop clinical applications in different target populations. Additional investigations are necessary to provide a full clarification of the mechanism of action by which probiotics can be used as innovative tools to alleviate intestinal inflammation, normalize gut mucosal dysfunction, downregulate hypersensitivity reactions, with the aim of helping to live better during HIV infection, and underlining the economic advantages of probiotics diet supplementation.

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