HIV and Probiotics

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Introduction

HIV is one of the most important medical and social problems in the world. In 2015, around 36.7 million people lived with HIV-1, 2.1 millions became newly infected and 1.1 millions died from AIDS-related diseases. In the twenty-first century, 17 million HIV-1 infected patients have been accessing the Antiretroviral Therapy (ART). [1] Although this number is growing, there are still many infected subjects who do not have access to the therapy. ART has led to dramatic improvements in the lives of HIV-infected people. However, residual immune activation, which persists despite ART, is associated with increased risk of non-AIDS morbidities. Accumulating evidence shows that disruption of the gut mucosal epithelium during Simian Immunodeficiency Virus (SIV) and HIV infections allows translocation of microbial products into the circulation, triggering immune activation. This disruption is due to immune, structural and microbial alterations. [2] Here we highlight key findings of HIV-1 pathogenesis, roles of HIV and SIV in gastrointestinal disorders, the probiotic, and evidences available on the clinical effect of probiotic in current therapeutic regimens for HIV/SIV infections.

HIV-1 pathogenesis

HIV-1 directly infects and kills cells that are critical for effective immune responses. Through direct interaction between the viral envelope and its cellular receptor, CD4 and the chemokine coreceptor, CCR5 or CXCR4, this virus infects key cells of the adaptive immune response, accounting for the clinical manifestations of disease being profound immune suppression. The course of disease varies enormously among infected persons. The time from acute infection to the development of AIDS, defined by a CD4 cell count of less than 200 cells/μL or the appearance of AIDS defining opportunistic infections or cancers, can be as rapid as 6 months. Other persons have been known to be infected for more than 25 years and to maintain normal CD4 cell levels and exhibit no evidence of CD4-cell decline or immune deficiency, despite never having been treated with anti-HIV medications. [3]

The HIV-1 life cycle is complex and its duration and outcome is dependent on target cell type and cell activation. In the early steps, HIV-1 gains access to cells without causing immediate lethal damages but the entry process can stimulate intracellular signal cascades, which in turn might facilitate viral replication. The two molecules on the HIV-1 envelope, the external glycoprotein (gp120) and the transmembrane protein (gp41) and the interaction with CD4 cells are the first step of the virus cycle. On the surface of the CD4 cells the co-receptors (CCR5, CXCR4) interact with virus and let it enter in the host cell. It follows, actually, a fusion of viral envelope and cell membrane with the release of the viral core into the cell cytoplasm. Once the core is disassembled, the enzyme reverse transcriptase activates the reverse transcription of the viral genome into DNA. This process has an error rate of 1 in 1700 (highly error prone step) and that is why there are numerous and related but distinct viral variants. In the core, viral enzyme integrase inserts viral genome into the host cell to form a provirus able to replicate or revert to latency. When the virus is ready for replication, it is transcribed into mRNA that will be transferred into the cytoplasm, then translated into regulatory and structure proteins and packaged into new virus particles.

The principal target of HIV is the CD4 positive T lymphocytes, 70 to 80% of which are located in the gut. A consistent depletion of these CD4+ T cells occurs especially in the gut, associating a compromised epithelial integrity and microbial translocation in the bloodstream. Despite CD4+T lymphocytes in the peripheral blood retrocede to normal level after antiretroviral treatment, those CD4+ T cells in mucosal lymphoid tissues continue depleting even after years of treatment. [4, 5, 6]

SIV and GUT

There are many findings in both humans and nonhuman primates (NHPs) that the intestinal immune system is substantially involved in the course of human (HIV) or simian (SIV) immunodeficiency virus infection [7]. Studies indicate fundamental relations between the gut epithelium and the mucosal immune system [8]. SIV natural hosts include African NHPs (such as sooty mangabeys, African green monkey, mandrill, and many others) who develop non-pathogenic SIV infection in the wild without progression to AIDS. Key features of SIV infection of natural hosts include: high viral loads, normal peripheral CD4+ T-cell counts, lack of microbial translocation despite significant loss of mucosal CD4+ T cells, and lack of immune activation during chronic infection. The lack of disease progression in natural hosts could be due to a lack of chronic immune activation. Interestingly, SIV-infected sooty mangabey

infants do not have increased morbidity or mortality, indicating that the infection is nonpathogenic even when acquired early in life [9]. Studies have indicated that following successful oral SIV infection, the innate immune system including anti-viral (IFN-α) and proinflammatory (IL6, IL12, CXCL10) genes respond rapidly to the virus, which can be detected at both mucosal sites and lymph nodes within just a few days post-infection. [10] Findings from NHP models have proven consistent with the idea that T helper-17 (Th17) cells may play a key role of resistance to disease progression. Although CD4 T cells are massively depleted from the GI tracts of progressively SIV-infected hosts, CD4 T cells that produce the effector cytokine IL-17 are preferentially depleted. [11]

Favre *et al*. demonstrated that SIV infection of the pig-tailed macaques (PT), but not the African green monkeys (AGM), results in T cell activation and generalized CD4+ T cell depletion, and that Th17 cells are lost after SIV infection of the PT but not of the AGM. [12]

Furthermore, Th17 cells depletion was found to be selective in pig-tailed macaques, outpacing any depletion of Th1 and Th2 cells due to overall CD4+ T cell loss. In this model, Th17 cells depletion predicted systemic and sustained T cell immune activation. Th17 cells and CD4+ T cell counts were both independent predictors of T cell immune activation. [13]

According to the roles of IL-17 and IL-22 in maintenance of mucosal barriers, preferential loss of Th17 cells was hypothesized to provide mechanistic insights into damage to the structural barrier of the GI tract observed in chronically SIV-infected animals. [14]

The causes of damage to the integrity of the epithelial barrier of the GI tract are likely to be multifaceted, but in the chronic stages of SIV infection seem unlikely to be due to direct virotoxic effects, given the lack of association with very low levels of demonstrable local viral replication in the lamina propria (LP) relative to the extensive epithelial damage. One possible mechanism may be related to the preferential loss of Th17 cells in the GI tract in progressive immunodeficiency lentiviral infections, because Th17 cells produce cytokines important for enterocyte proliferation and antibacterial defensins and IL-17 has recently been shown to suppress Th1-mediated damage to gut epithelium. [15,16]

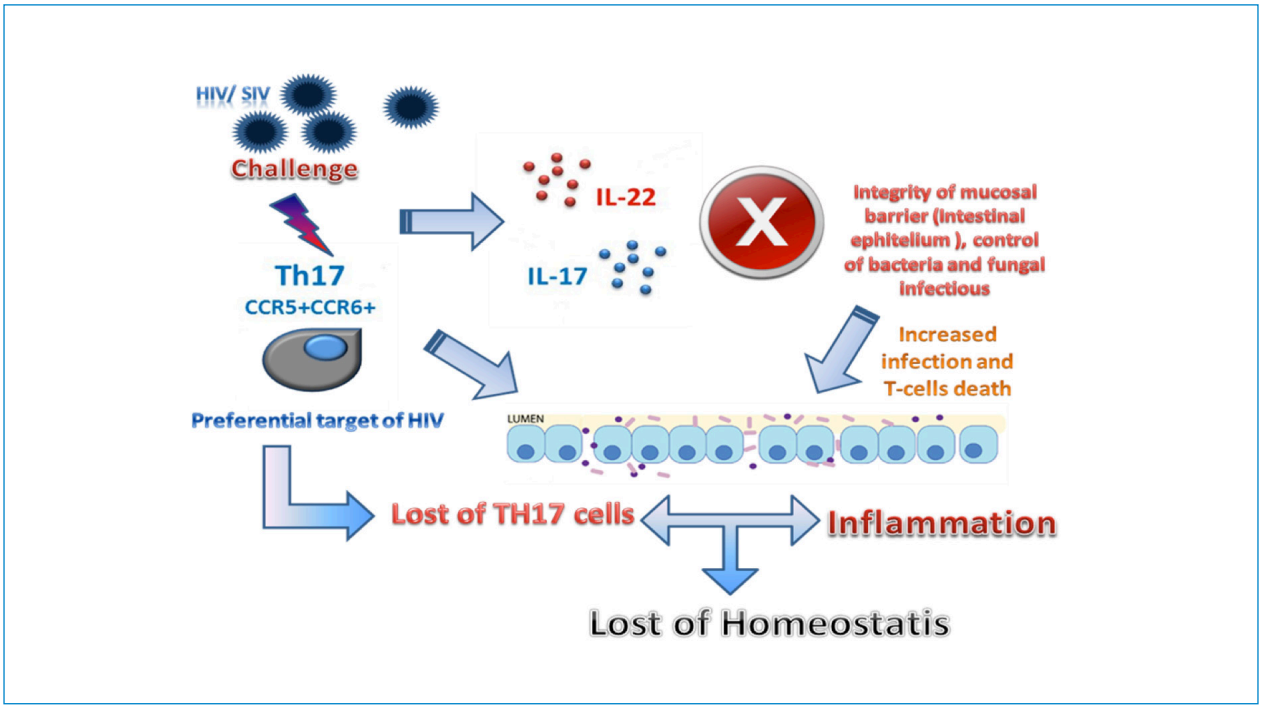

Figure 1: The HIV infection causes less IL-17 and IL-22 production by Th17 cells, because these cells are preferential target of the virus. After loss of the Th17, consequences and disorders such as the change in microbiome composition, microbial translocation and immune activation occur.

HIV and GUT

The role of HIV in the GI tract of humans have been studying since 1984. Kotler and colleagues observed that HIV-infected individuals had histologic abnormalities of the gastrointestinal mucosa, malabsorption, and lymphocyte depletion following with diarrhea, increased gastrointestinal inflammation, increased intestinal permeability and malabsorption of bile acid. Consequently they observed inflammatory infiltrates of lymphocytes and damage to the gastrointestinal epithelial layer, including villous atrophy, crypt hyperplasia, and villous blunting. [17]

Indeed, there are evidences of HIV-related damages to the epithelial barriers in HIV infected individuals. Disruption of the gut barrier is the principle way for microbial translocation and subsequent immune activation. [18]

The factors that contribute to gastrointestinal discomfort or dysfunction include opportunistic infections (usually with <100 CD4+ T cells/mL), medication reaction, fat malabsorption, bacterial overgrowth, functional bowel disease (diarrhea predominantly), bile salt excess, and direct HIV-driven mucosal inflammation, which is a form of inflammatory bowel disease (IBD). [19, 20]

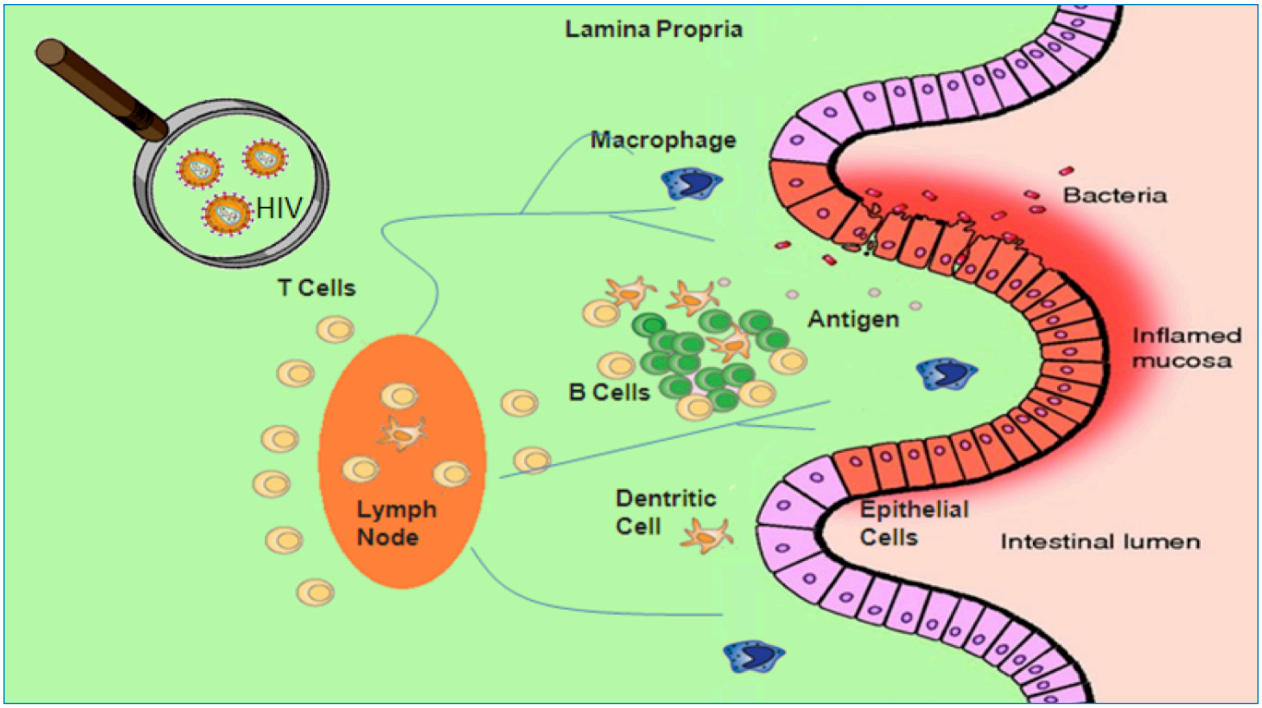

Figure 2: Intestinal inflamed mucosa in HIV-1+ subjects. The inflammation of the intestinal mucosa leads to bacterial translocation and activation of the immune system.

Pathological changes to the gastrointestinal tract have long been known to be a characteristic feature of HIV infection. Some studies have provided mechanistic insights into the underlying causes of HIV enteropathy and CD4 T-cell depletion, but additional studies are certainly warranted to increase our understanding of the long-term consequences of the assault on the GI tract. [21]

Although the structural and immunological damage to the mucosa occurs rapidly during the acute phase of infection, HIV-infected individuals do not surrender to opportunistic infections until peripheral blood CD4 T cells are decreased under 200 CD4 T cells per microliter and mucosal CD4 T cells drop below an undefined threshold. Several studies have shown that the devastation of the GI tract leads to microbial translocation, which is associated with immune activation, and disease progression; however, the relative contribution of microbial translocation and other factors of immune activation is not completely understood. [22]

The GI tract is a site of massive viral infection, CD4 T-cell depletion, enterocyte apoptosis, epithelial tight junction's disruption, and lymphoid tissue fibrosis. Therefore HIV infection could quite reasonably

be considered a disease of the GI tract. One of the most important factors in order to evaluate the mucosal immunity in HIV-1 infection is the number of CD4+ T-cells in the gut.

Studies have shown that mucosal CD4+ T-cells expressing CCR5 as well as peripheral HIV-specific CD4+ cells expressing gut homing markers, integrin-β7 and CCR6, are depleted in both acute and chronic phases of HIV infection. [23] Also the protective roles of gut mucosal Th17 cells in HIV infection is very important, but during the disease the Th17 cells depletion has been linked to lose of mucosal epithelial integrity, and results in multiple deleterious consequences, including microbial translocation and gut inflammation. [24,25]

A big percentage of Th17 cells are lost during acute phase of the infection. In part, functional mucosal immune responses are necessary for maintaining the integrity of the intestinal epithelium. In addition to their protective role, Th17 cells support enterocyte homeostasis by secreting interleukin IL-17 and IL-22 and by recruiting NK cells. [26] During HIV infection, CCR5+CCR6+ Th17 cells are depleted in the gut due to direct targeting of CCR5 receptors by HIV-1 virions. Moreover, bacterial lipopolysaccharide (LPS) may also cause the depletion of CD4+ T cells, since LPS stimulation is known to up regulate CCR5 expression on these cells. Furthermore, In HIV-infected individuals, the reduction of Th17 cells seem to be concomitant with an increase in the number of regulatory CD4+ T (Treg) cells. Low Th17/Treg ratio was correlated with high plasma 16S rDNA levels, which suggest microbial translocation. [27] A fundamental part of the gut mucosal barrier function is orchestrated by the intestinal microbiota that coexist with the host in a mutually beneficial symbiosis. The genomes of these microbiota act together as a living system known as the microbiome. [28] Some advantages of these bacteria in the GI tract include digestion aids, promoting development of the gut immune system, and providing competitive barriers for pathogens invasion. The host, in return, provides safe habitats and nutrients for them. [29]

The host immune system has to balance permissive, tolerogenic responses to food antigens and commensal microbes with potentially damaging, and inflammatory responses to overcome pathogens. This balance is maintained by the constant interplay among the microbiome, the intestinal barrier, and the mucosal immune system, which is essential for normal gut homeostasis. Imbalance of this system may lead to autoimmune inflammation or infectious pathology. [30] Currently available evidences suggest that the gut microbiome is involved in development of inflammation and systemic immune activation due to microbial translocation in HIV-infected individuals. This immune activation may play a fundamental role for virus persistency, the major obstacle to find a cure for HIV infection. Despite new and effective drugs, ART has not resolved the problems related to immune activation and the inflammatory conditions of the people with HIV-1 and, however, searching to find safe and well-tolerated approaches, to prevent or control these problems seem to be essential. [31, 32]

Probiotics

As described by the World Health Organization (WHO), probiotics are “live microorganisms which when administered in adequate amounts, confers a health benefit on the host”. Historically, the concept of probiotics began around 1900 by the Nobel laureate, Elie Metchnikoff, who discovered that the consumption of live bacteria (Lactobacillus bulgaricus) in yogurt or fermented milk improves the biological features of the gastrointestinal tract. [33]

Recent studies have indicated that probiotics can be used for treatment and prevention of necrotizing enterocolitis in premature infants, crying time reduction in colicky babies, reduction in acute pediatric diarrhea duration, and symptoms management in irritable bowel syndrome, prevention of antibiotic-associated diarrhea, gastric ulcer, and many other kinds of diseases.

However, food supplements are now widely available to consumers generally in the form of cultured dairy products which have added probiotic bacteria. Also more recently within the consumer market, ‘probiotic shots’ have developed whereby they can be consumed as capsules. Contained within these food supplements there can be many different strains of bacteria; however, the most common strains belong to the *Lactobacillus* and *Bifidobacterium* species, which have demonstrated health benefits on the human body. In this sense, both of these mentioned bacterial species are known to be involved in essential physiological functions like stimulation of immune response, prevention of pathogenic and opportunistic microbial/bacterial colonization, production of short chain fatty acids, metabolism of carcinogenic substances and synthesis of vitamins such as B and K. [34, 35]

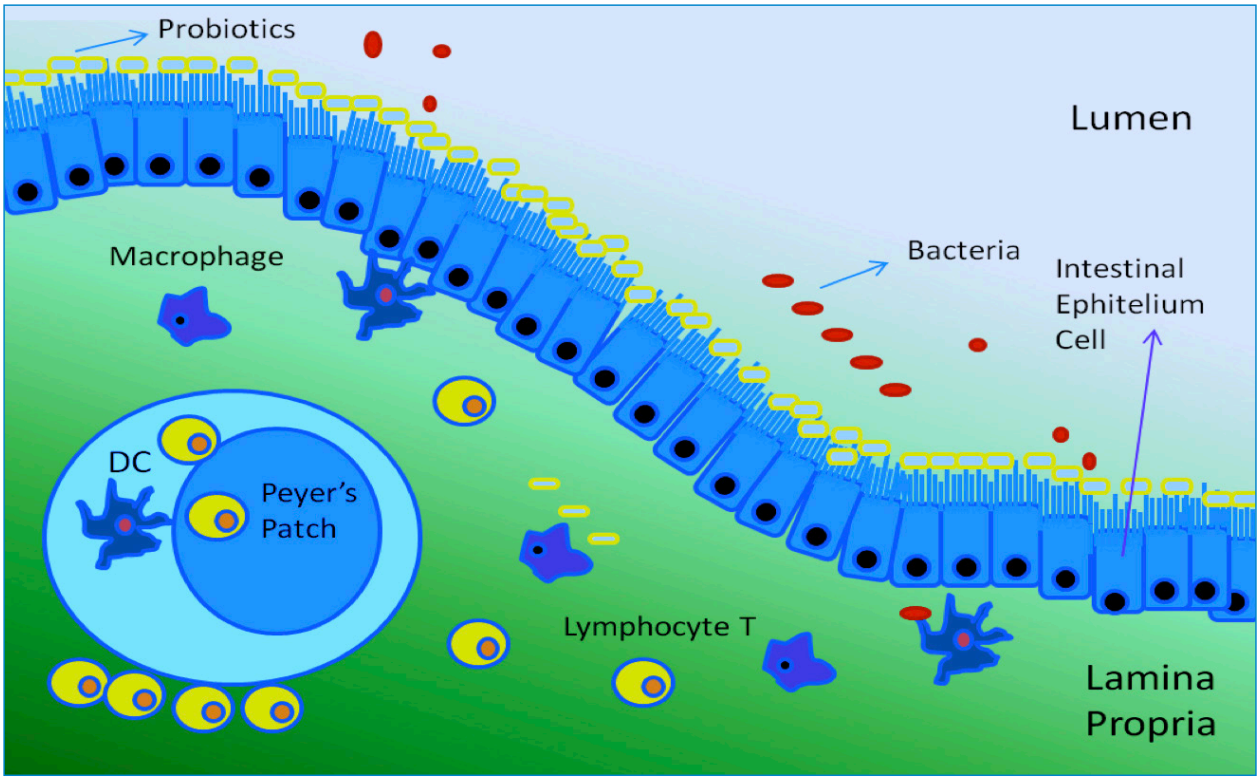

Figure 3: Intestinal mucosa after probiotics supplementation. As shown in the picture, probiotics can cover the surface of gut epithelium and protect them from harmful microbes.

Probiotics and SIV

Acute infection with SIV in animal models is associated with a dysbiosis characterized by increased abundance of pathogenic bacterial strains, such as Pasteurellaceae, Aggregatibacter etc., and a decrease in the abundance of gut-resident Lactobacillus [35,36,37,38]. This dysbiosis is associated with impaired pattern recognition receptor expression, increased immunomodulatory indoleamine 2, 3 dioxygenase (IDO) activity, which is the main enzyme involved in tryptophan catabolism and in the deregulation of Th17/Treg cells ratio that occurs in the gut mucosa after the infection. One possible method to enhance the mucosal immune response is through modulation of the microbiota in the GI tract through probiotic supplementation. Probiotic supplementation is generally a safe and well-tolerated approach to enhance mucosal and overall health [39]. Probiotic supplements have improved outcomes in several diseases characterized by GI tract inflammation. [40]

Few studies have demonstrated that the specific combination of the strains *Streptococcus thermophilus DSM24731, Bifidobacterium breve DSM24732, Bifidobacterium longum DSM24736, Bifidobacterium infantis DSM24737, Lactobacillus acidophilus DSM24735, Lactobacillus plantarum DSM24730, Lactobacillus paracasei DSM24733, Lactobacillus delbrueckii ssp. bulgaricus DSM24734 (De Simone Formulation or DSF)* can induce several beneficial alterations in ART–treated SIV infected macaques. [41] During acute phase of SIV infection, the loss of Th17 cells, and decreased fecal Lactobacillus occur, while the IDO activity is increased. It has been shown that using probiotics containing lactobacilli in this model causes a partial improvement in Th17 frequencies and modulates IDO activity. [38] Furthermore, it has been shown that DSF probiotic supplementation in healthy macaques increases the number of T follicular helper (Tfh) cells in Lymph nodes. [39] Tfh cells can be induced by IL-23. IL-23 is produced mostly by Antigen Presenting Cells (APCs) and is essential for induction of many CD4+ T cell subsets, such as Tfh and Th17 cells. [42] These data suggest that probiotics could improve Th17 frequencies in SIV-infected macaques. Indeed, a recent study on SIV-infected macaques indicates that DSF probiotic supplementation and IL-21 on ART–treated SIV infected macaques promotes the recovery of intestinal TH17 cells, tempers some markers of immune activation and results in better clinical outcomes. [43]

Furthermore, DSF probiotic supplementation showed an almost 2-fold increase in the frequency of CD4+ T cells in the colon of Probiotic/Prebiotic-treated pigtail macaques (PTM) (average 46.13%) compared with PTM treated with ART alone (average 26.12%). [41] This increased reconstitution is very

important and could be useful for humans too, considering that long-term ART-treated HIV-infected individuals rarely reconstitute GI CD4+ T cells to healthy levels. [44] Five months of probiotic treatment in SIV infected animals on ART, substantially reconstituted colonic CD4+ T cells around normal levels. [41] Th17 recovery is associated with decreased microbial translocation. It has been shown that probiotic supplementation with IL-21 in SIV infected macaques is associated with a decreasing trend in Escherichia Coli antigens, a marker of microbial translocation, in lamina propria, and liver tissue followed by altered composition of microbial communities. [41] Klatt *et al* showed a significantly lower frequency of Bifidobacterium as compared to probiotic supplemented animals at day 154 post infection.

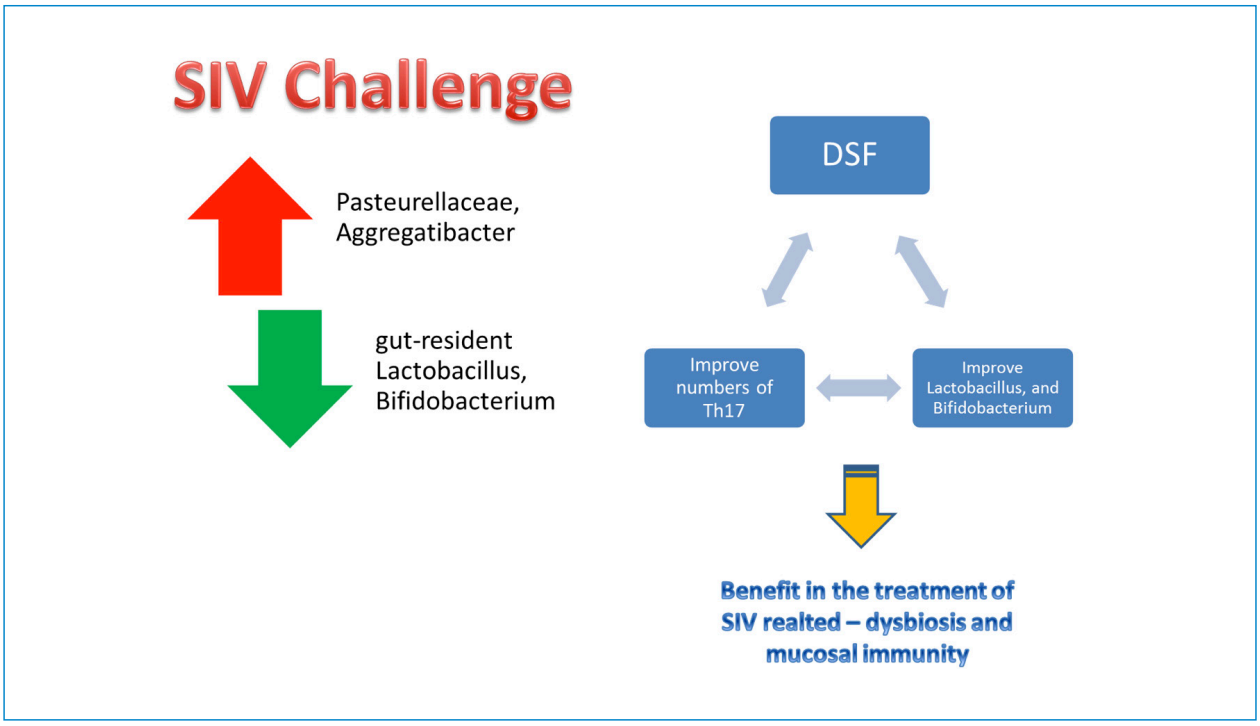

Figure 4: After SIV challenge, probiotic is able to reduce the dysbiosis and improve the gut immune system.

Probiotic and HIV

Few studies have examined the use of probiotics in HIV infection so far. Gastrointestinal discomforts such as constipation, diarrhea, and bloating are very common during HIV-1 infection. [45] Recently, a few studies have used probiotics as a therapeutic approach in inflammatory bowel disease (IBD) to inhibit pathogenic bacteria, protect the intestinal epithelium and produce anti-inflammatory cytokines. [46] Moreover, in this context, an increased IgA production, decreased dendritic cells activation, and less non-specific stimulation of immune cells has been observed too. [47]

A number of studies have administered different kinds of probiotic formulations to evaluate their impact on HIV-1 infection, and in particular on some outcomes like: diarrhea, CD4 count and microbial translocations.

Three studies have reported benefits of probiotics in HIV-1 associated diarrhea. One study using Lactobacillus rhamnosus [48], and two studies using Saccharomyces boulardii reported symptoms alleviation and beneficial effects. [49,50] In contrast a study using Lactobacillus rhamnosus and another study using a mixture of Bifidobacterium bifidum and Streptococcus thermophilus showed no benefits in HIV-1 associated diarrhea. [51,52] These results are inconclusive and more studies are needed to evaluate the effects of different kinds of probiotics in HIV-1 related diarrhea.

Recently the investigators have evaluated the effects of different probiotic formulations on CD4+ cells count. Two studies using Lactobacillus rhamnosus [51,53] and one study using Lactobacillus casei sp. Shirota [54] reported no effects on CD4+ cells count. Interestingly, on the other hand, improvement in

CD4+ cells count was observed in other studies using a mixture of different bacteria species. For example, studies using Lactobacillus and/or Bifidus bacteria showed an increasing trend in CD4+ cell frequencies. [54,55] Moreover, a mix of more than two bacterial strains seem to have better results. For instance, in a study, when a mixture of probiotic bacteria containing Lactobacillus (casei, acidophilus, plantarum, delbrueckii), Bifidobacteria (breve, infantis, longum), and Streptococcus (salivarius, faecium) [56] supplemented, the results showed an increase in the number of CD4+ cells. These findings suggest that some specific types of probiotics could be more useful to improve CD4+ cell counts. The assessment of microbial translocation after probiotic supplementation is another interesting aspect in HIV-1 infection. Some studies have shown a decrease in pro-inflammatory cytokines such as IL-6, IL-12, TGF-beta, hsCRP after using a mix of Lactobacillus rhamnosus, Bifidobacteria lactis [57], Saccharomyces boulardii [58], and Lactobacillus casei sp. Shirota [54] probiotic bacteria.

Furthermore, together with the reduction of inflammation, a couple of these studies showed a reduction in certain microbial translocation markers, such as LPS-binding protein [58] and the bacterial DNA (16S rDNA) levels in plasma. [57]

Conclusion

Studies of SIV infected natural hosts have helped scientists to have a better understanding of the role of gastrointestinal damage in HIV pathogenesis. Persistent chronic HIV infection induces serious damages in lymphoid, myeloid, and stromal cells in the gut that causes the loss of gut barrier integrity, microbial translocation, inflammation, and chronic immune activation, which persists despite effective ART, and increases the risk of non-AIDS morbidities. [6,7,8,9,10]

During HIV infection, however, interactions between host and microbiota are perturbed, with microbial translocation of potentially pathogens linked to a variety of different HIV complications, including more rapid progression of disease. The use of probiotics as potential treatment to alleviate symptoms for a variety of conditions has been investigated and is now being proposed for the treatment of symptoms associated with HIV. [59]

In addition to early ART initiation in HIV-1 infected patients, modulation of the microbiota with probiotics is a promising therapeutic strategy to prevent or alleviate disorders (such as gut damage, inflammation, and immune activation) correlated with imbalances in the intestinal microbiota.

New clinical studies are ongoing with the DSF and data are being published to support this hypothesis and will be the object of a next document for HCPs.

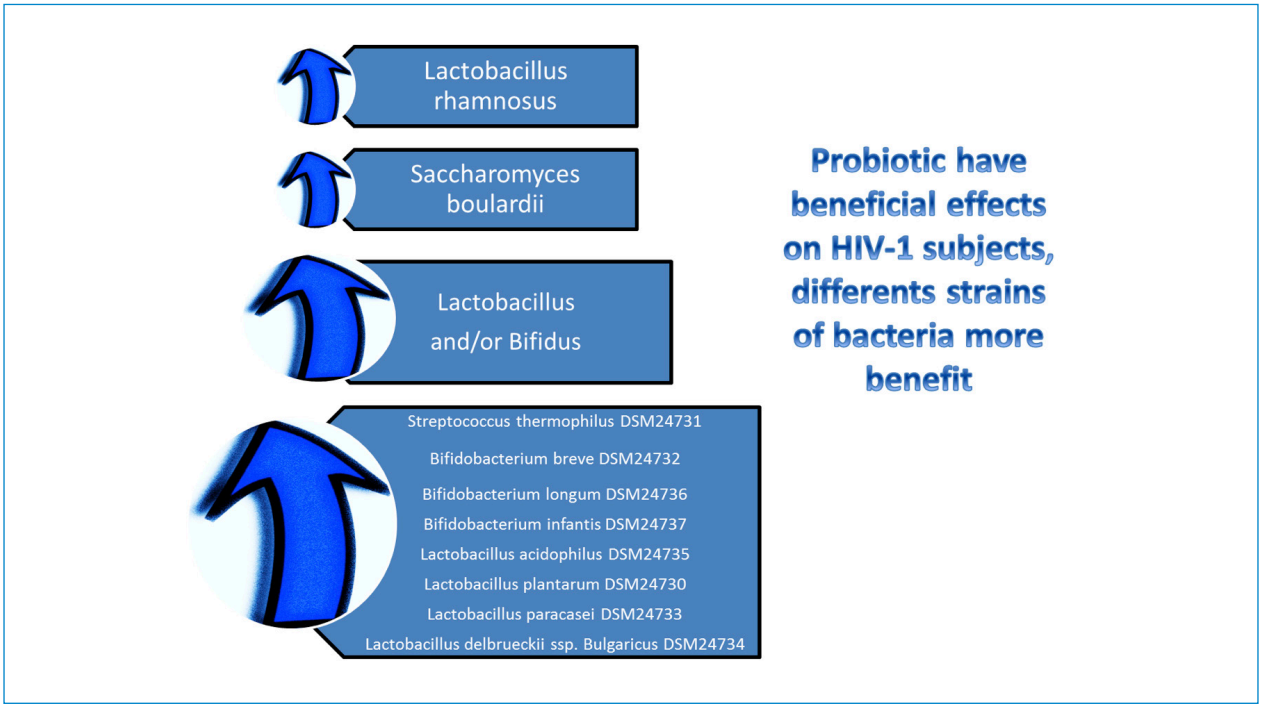

Figure 5: Beneficial effects of different strains of bacteria.

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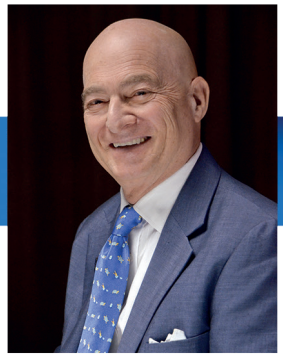

A member of the American College of Gastroenterology, Claudio De Simone is a retired Professor of Infectious Diseases of the University of L'Aquila (Italy), specialized in Gastroenterology, Allergology and Clinical Immunology. His interest in the human microbiota goes back more than 25 years when the understanding of the importance of the role of the intestinal flora was in its infancy.

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The Letter of probiotics

THE BLOG OF A PIONEER IN PROBIOTICS

The Letter of probiotics (probiotixx.info) is the blog of Prof. Claudio De Simone, a pioneer in the intestinal microbiotal and inventor of a probiotic mixture (8 strains, 450 billion bacteria) known as the De Simone Formulation.

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