INTESTINAL MICROBIOTA AND HIV-1 INFECTION

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ABSTRACT: The intestinal microbiota consists of a qualitatively and quantitatively diverse range of microorganisms dynamically interacting with the host. It is remarkably stable with regard to the presence of microorganisms and their roles which, however, can be altered due to pathological conditions, diet composition, gastrointestinal disturbances and/or drug ingestion. The present review aimed at contributing to the discussion about changes in the intestinal microbiota due to HIV-1 infection, focusing on the triad infection-microbiota-nutrition as factors that promote intestinal bacterial imbalance. Intestinal microbiota alterations can be due to the HIV-1 infection as a primary factor or the pharmacotherapy employed, or they can be one of the consequences of the disease.

CONFLICTS OF INTEREST: There is no conflict.

CORRESPONDENCE TO:

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INTRODUCTION

The immune system integrity is essential for the defense against microorganisms and their toxic products and, therefore, for the survival of all individuals. Defects in one or more components of the immune system can lead to severe and often fatal disturbances such as diseases caused by immunodeficiency (1). Among such notable diseases is AIDS, a transmissible disease characterized by marked immunosuppression, opportunistic infection, malignant disease and degeneration of the central nervous system (2, 11), which can compromise the nutritional status and bring about changes in the normal intestinal microbiota.

Nutrition, metabolic and endocrine activities depend on the gastrointestinal tract functionality, which may affect the host's health, nutritional status and intestinal microbiota composition. The intestinal flora, particularly in the colon, plays a determinant role in the health/disease status of humans, and its relationship with the host has been vastly investigated (38, 61).

Fooks and colleagues (13) reported that the bacterial population in the intestine is quantitatively and qualitatively balanced; each genus has its own growth niche maintaining an "optimal balance" for the physiological performance of the digestive system. However, numerous factors can alter it, either by stimulating beneficial actions through an increase in the number of certain bacteria (bifidobacteria and lactobacilli), or by stimulating the proliferation of bacteria considered pathogenic (clostridia, certain species of bacteroids, etc.).

The aim of the present review is to contribute to the discussion about changes in the intestinal microbiota following HIV-1 infection, focusing on the triad: infection-microbiota-nutrition, as factors that promote intestinal bacterial imbalance.

INTESTINAL MICROBIOTA

The digestive system physiology is extremely complex, consisting of three components that are permanently in contact and interacting with one another: intestinal cells, nutrients, and microflora. Besides the functions of digestion and absorption, the microflora as well as the mucosal barrier and the immune system of the gastrointestinal tract has a defensive action against aggressor agents. (7).

In general terms, the gastrointestinal tract is a large lymphoid organ exposed to a wide spectrum of pathogenic microorganisms (viruses, fungi, bacteria and protozoa)

which may change the cellular and humoral immunity affecting the physiology of the digestive system as well as that of the normal bacterial flora (5, 48).

The bacterial flora of the digestive system consists of a qualitatively and quantitatively diverse range of microorganisms that dynamically interact with the host (6, 17).

Bacteria are present throughout the digestive system. The large intestine shows the highest number of such microorganisms, and in the stomach and in the upper part of the intestine (duodenum and jejunum), the population is approximately 10^5 colony forming units per milliliter (CFU/ml) (17, 44).

In the duodenum and jejunum, the flora is mainly composed of lactobacilli and streptococci (about 10^3–10^4CFU/ml) originated in the oral cavity and resistant to the gastric acidity. The ileac flora is characterized as a zone of transition between a relatively poor flora and the extremely dense flora of the large intestine, where more diverse microorganisms are quantitatively present (about 10^{11}–10^{12}CFU/ml) (6, 17).

The colon (large intestine) presents an extremely rich flora of approximately 400–500 microorganisms species, out of which 99.9% are anaerobic bacteria including, in descending order: bacteroids, bifidobacteria, clostridia, peptostreptococci, fusobacteria, lactobacilli, enterobacteria, enterococci, eubacteria, methanogenic bacteria, and sulfate reducers. Such diversity is probably due to the decreased intestinal motility and the very low potential for oxy-reduction in this region (6, 7, 17, 44).

According to Macfarlane *et al.* (28), the concentrations of bacteroids, bifidobacteria and lactobacilli are markedly increased in the large intestine, as shown in Table 1, below:

Table 1: Concentration of bacteria in the human large intestine.

Bacteria	Concentration (Log$_{10}$/g feces)	
	Mean	**Variation**
Bacteroids	11.3	9.2 – 13.5
Bifidobacteria	10.2	4.9 – 13.4
Lactobacilli	9.6	3.6 – 12.5

The intestinal flora is implanted soon after birth and initially consists of facultative anaerobic bacteria. In exclusively breast-fed children, the fecal flora is predominantly composed of bifidobacteria including 1% enterobacteria. During the weaning period, children exhibit a more complex flora including bifidobacteria, bacteroids, clostridia and streptococci. Thus, the more diversified the diet during childhood, the more similar the flora will be to that of the adult individuals (55, 59).

All microorganisms of the intestinal flora obtain energetic substrates from undigested components of the diet, or from intestinal secretions such as mucus, proteins and enzymes (41).

Carbohydrates not digested in the upper gastrointestinal tract reach the colon at the rate of 10-60g/day. Out of these, 8–40g/day consists of resistant starches; 8–18g/day, non-starch polysaccharides; 2–10g/day, unabsorbed sugars; 2–8g/day, oligosaccharides; and 2–3g/day, endogenous carbohydrates. Carbohydrates constitute the main stimulus to bacterial growth. Proteins can also be used as substrates for growth and approximately 3–9g/day are of dietary origin and 4–6g/day are of endogenous origin such as the pancreatic enzymes (26, 27).

In the colon, sources of nitrogen include urea as well as dietary and endogenous proteins. Colonic fermentation has an important effect on nitrogen metabolism, since it stimulates bacterial proliferation, subsequently decreasing ammonia serum levels (42).

Once established, the flora can have a beneficial or pathogenic effect upon the host. Beneficial effects include inhibition of pathogens growth, stimulation of immune function, reduction in problems due to distension by gases, facilitation of digestion and essential nutrients absorption, and synthesis of vitamins. The most notable deleterious effects are: diarrhea, hepatocytes infection due to the production of toxins, carcinogenesis and intestinal putrefaction (7, 14, 17).

The gastrointestinal tract presents control mechanisms that allow some selectivity in bacterial colonization. Such mechanisms include: the gastric secretion, which reduces pH and has bactericidal effects; the digestive secretions (mucus, bile, pancreatic and enteric secretions); the gastrointestinal motility, which when reduced can lead to chronic bacterial colonization of the small intestine; and the intestinal immune system, which is also activated as a form of defense and control of the intestinal bacterial flora (55).

Besides the above-mentioned mechanisms, the microorganisms of the normal intestinal flora themselves present certain self-regulation over the population density in the colon. This regulation occurs through depletion of energy substrates necessary for the growth of pathogenic bacteria, through the production by the bacterial flora of metabolic products that inhibit the proliferation of bacterial pathogens, or alternatively through the production of bactericidal substances that inhibit the growth of other bacteria (7, 43, 55).

This self-regulation of the microorganisms of the intestinal flora was demonstrated by Gibson and Wang (15), who studied the regulatory effect of bifidobacteria on the growth of other colonic bacteria and observed that they exert an important action in the inhibition of bacterial pathogens growth. The inhibitory mechanism involved probably results from the production of short-chain fatty acids (acetate and lactate) during the fermentation process, as well as from pH reduction, characterizing fermentation as an important process in the protection against gastroenteritis.

Fermentation is the main function of the colonic flora and presents nutritional, metabolic, and immunological implications as well as consequences for physical protection. It ensures bacterial growth and proliferation; epithelial cells differentiation; xenobiotics metabolism and enterohepatic circulation; immunostimulation; pro-anticarcinogenesis and mutagenesis; prevention of bacterial translocation; resistance to infection; control of ions concentration and absorption; and control of motility, transit time and colonic pH (7, 17, 40, 55).

Considering the functional complexity of the intestinal flora, fermentation is one of its most important actions. During this process, oxidases produce short-chain fatty acids (acetic, propionic and butyric acids), lactic acid, hydrogen, carbon dioxide and methane as final products (8, 32).

Besides its final products, which have physiological actions important to the host as they participate in the colonic metabolism, the fermentation process results in the hepatic regulation of fats and sugar and in the production of an energetic substrate for the colonocytes themselves. The fermentation final products also participate in the hydrolysis of lipids and proteins and in the production of vitamins (7).

The normal intestinal bacterial flora is remarkably stable with respect to the presence of microorganisms and its functions; however, it can be altered as a consequence of pathological conditions, diet composition, gastrointestinal disturbances and/or medicines ingestion (6, 7, 34).

ALTERATIONS IN THE INTESTINAL MICROBIOTA

Pathological Conditions

Numerous inflammatory and infectious diseases contribute to quantitative and qualitative changes in the intestinal bacterial flora including diarrhea of varied etiology, inflammatory intestinal diseases, colon cancer, gastroenteritis, and food allergy (31).

Inflammatory and/or infectious processes can alter the normal intestinal bacterial flora either as primary causal factors or as secondary disorders. Among the most notable infectious process are HIV-1 infection and its consequences, which represent possible factors for the alteration of the normal intestinal bacterial flora.

The human immunodeficiency virus (HIV) is considered a member of the Lentivirus family (of animal retroviruses) based on its gene sequence homology, morphology and life cycle. Lentiviruses are capable of causing latent infection of cells in the long term, or cytopathic effects in the short term, slowly inducing progressive and fatal diseases. Two types of virus are intimately related to HIV, designated HIV-1 and HIV-2, which produce similar clinical syndromes but differ in gene structure and antigenicity. HIV-1 is the most common cause of AIDS in the United States as well as in Brazil, while HIV-2 is particularly common in West Africa (1, 2).

A decline in circulating lymphocytes, especially CD_4^+ T helper lymphocytes, lead to the disease progression together with opportunistic infections, which constitute a marker for immunosuppression induced by HIV-1. Levels of CD_4^+ cells between 200 and 400cells/mm^3 favor the following opportunistic infections: herpes simplex and zoster, oropharyngeal candidiasis and tuberculosis. When these levels are lower than 200cells/mm^3, the main infectious agents secondary to the HIV-1 infection are: *Pneumocystis carini*, *Cryptococcus neoformans*, cytomegalovirus and *Mycobacterium avium intracellulare* (10), which add a compromised nutritional status to these alterations.

Due to the complexity of HIV-related infection, the clinical manifestations of the primary condition can vary. For a better understanding, HIV infection can be divided into three phases: acute, latent or asymptomatic, and symptomatic, which are interrelated to the number of CD_4^+ T lymphocytes and the viral load in an inversely proportional manner (1, 36, 37).

Protein-energy malnutrition (PEM) is one of the most frequent consequences in HIV-1-infected individuals, associated with the decline in CD_4^+ T lymphocytes and the

increase in the viral load. It may manifest at various stages over the disease course (29) and is an important factor for the disease progression, the individual survival (3, 52) and the intestinal bacterial flora alterations (3, 34).

There are two broad paradigms related to malnutrition and infection: 1) malnutrition causes a disturbance in the humoral and cellular immunity, increasing the risk of infection in the host; 2) the catabolic state resultant from the infection leads to malnutrition, compromising the immune response and predisposing the host to complications due to infections secondary to PEM (30), characterizing thus a synergic relationship between nutrition, infection and immunity, distinctively evident, as the acquired immunodeficiency syndrome (3, 52).

The etiology of malnutrition in HIV-1 individuals is multifactorial; however, the causal factors can be categorized as: change in food intake, malabsorption and metabolic alterations (4, 18, 47). These factors, therefore, can contribute to changes in the normal intestinal bacterial flora, since the gastrointestinal tract is one of the biggest targets of diseases related to HIV-1 infection, favoring the occurrence of diarrhea and malabsorption (21, 49).

In addition, most of the therapeutic agents employed have side effects including nausea, vomiting and diarrhea (37) and can contribute to changes in the normal intestinal bacterial flora.

Diet Composition

Another important factor that can contribute to changes in the normal intestinal bacterial flora is the diet.

Interactions between nutrition and the normal intestinal bacterial flora are complex. Firstly, the diet can affect the survival and metabolism of bacteria (9). It can cause changes to the intestinal flora and/or its metabolism through two important mechanisms: the presence of undigested dietary components used as energy source, and the host nutritional status, which influences the quantity and type of substances secreted by the intestine (41).

Dietary fiber, defined as "indigestible carbohydrates plus lignin present in vegetables that have a physiological action on humans" (54), can alter the bacterial flora directly through the regulation of its metabolites and indirectly through physical changes to the digestive system (24), contributing, therefore, to the intestinal bacterial population in both quantitative and qualitative terms (55).

According to Woords and Gorbach (58) and Ziegler *et al.* (60), the interaction between dietary fiber and intestinal flora occurs via the following mechanisms:

a) Change in the intestinal pH: a reduced pH favors the increase in bifidobacteria, consequently decreasing pathogens;

b) Production of short-chain fatty acids: their presence contributes to pH reduction together with bactericidal effects, and they can act as substrate for colonic cells;

c) Production of immunostimulants: the metabolic products of bifidobacteria can lead to a decrease in pathogenic bacteria in the intestinal flora; and

d) Change in bacterial enzymes: the bacterial reduction of glucuronidase and/or glucosidase can be considered a positive change due to its association with a reduction in the absorption of cholesterol and other steroids. The reduction of 7-α-hydroxylase can also be considered a positive factor in the decreased formation of bile acids (lithocholic and deoxycholic acids), which are considered co-carcinogenic, through a secondary pathway.

The effect of the diet on the intestinal bacterial flora can be more efficient and efficacious if specific substrates are used for determined bacteria, such as fructooligosaccharides which contribute to an increase in the concentration of bifidobacteria and a decrease in bacteroids (7).

Gibson and Roberfroid (14) defined prebiotics as "compounds present in indigestible food that have beneficial actions on the host by selectively stimulating the growth and/or by activating the metabolism of one or more bacteria in the digestive system".

The participation of dietary components with positive actions on the intestinal bacterial flora encouraged the food industry to develop products that include determined bacteria in their composition; such products have been known as probiotics (Table 2), which consist of "food containing bacteria common in the gastrointestinal tract, resistant to the action of digestive juices and that has beneficial actions on the host, altering the intestinal microbiota composition or metabolic activity, or participating in the modulation of the immune response" (7, 26, 39, 45, 46, 51).

Table 2: Microorganisms considered probiotic.

Lactobacilli	Bifidobacteria	Other lactic-acid bacteria
L. acidophilus	*B. adolescentis*	*Enterococcus faecium*
L. amylovorus	*B. animalis*	*Leuconostoc mesenteroides*
L. casei	*B. bifidum*	
L. crispatus	*B. breve*	
L. gasseri	*B. infantis*	
L. johnsonii	*B. longum*	
L. paracasei		
L. plantarum		
L. reuteri		
L. rhamnosus		

Source: Holzapfel *et al*. (19).

Marteau *et al*. (31) described the positive participation of probiotics in gastrointestinal diseases such as diarrhea associated with antibiotic use, gastroenteritis, irritable bowel syndrome, intestinal inflammatory diseases, and colon cancer.

Differently from the situations mentioned above, there are no reports on the supplementation and effects of prebiotics and probiotics on HIV-1 infection.

The normal intestinal bacterial flora can be altered in infected individuals, particularly in cases of HIV-1 as a result of changes in the food intake, since anorexia is initiated by the infecting virus itself (HIV-1), by the action of cytokines such as interleukin-1 (IL-1) and tumour necrosis factor (TNF), as well as by the side effects of the medication used (50). Furthermore, HIV-1/AIDS individuals can also exhibit a change in food intake due to the presence of secondary diseases in the oral cavity and esophagus (candidiasis, herpes or cytomegalovirus infections) (12, 20, 57).

Gastrointestinal Disturbances

Diarrhea and malabsorption are important gastrointestinal disturbances in HIV-1 infection (21, 49). The causes of diarrhea can be grouped in three broad categories: enteric pathogens, drugs (the most important are dideoxyinosine and antibiotics), and another group of idiopathic origin (46).

The enteric pathogens that contribute to the diarrhea process and/or malabsorption are: *Salmonella*, *Shigella*, *Clostridium difficile*, *Escherichia coli*, *Candida sp.*, *Mycobacterium avium intracellulare*, *Mycobacterium tuberculosis*, *Cryptosporidium*, cytomegalovirus, as well as HIV-1. In general, enteric pathogens can disrupt the anatomo-physiology of the digestive system, causing, for example, atrophy of villi, hyperplasia of crypts, and loss of enzyme activity on the brush border (33, 46).

Diarrhea is accompanied by increase in the fecal pH, reduction in the number of bacteria, production of volatile fatty acids, and increase of opportunistic pathogens (44), which may affect the normal intestinal bacterial flora.

Nutritional Status and Intestinal Microbiota in HIV-1 Infection

The nutritional status is defined by the American Association of Public Health as "the health condition of an individual due to consumption and use of nutrients, identified by combining information obtained from physical, biochemical, clinical and dietetic studies" (35).

Several authors (22, 23, 25, 53) have noticed that changes in the nutritional status together with a reduction in lean mass, weight loss, food intake, serum levels of albumin and proteins of short half-life are important consequences of HIV-1 infection.

Wheler *et al*. (56) studied the weight loss as a predictor of survival and disease progression in HIV-1 infection and concluded that when this was mild (<5%) or moderate (5%–10%) over a period of four months, there was increased risk of developing opportunistic complications and reduced survival.

Changes in the body mass index (BMI) in HIV-1 infected individuals consist of two phases: a phase of relative stability and another phase of rapid decline in the six months that precede AIDS diagnosis. This marked decline has been associated with the rapid progression of the disease.

Gorbach and Goldin (16) reported that individuals presenting moderate to severe PEM showed alterations in the gastrointestinal tract, with reduced secretions (gastric, biliary, pancreatic and intestinal secretions) and motility, contributing to the excessive growth of anaerobic microorganisms in the upper gastrointestinal tract, impeding the absorption of carbohydrates, lipids, vitamin B_{12} and proteins. Therefore, compromising of the nutritional status of HIV-1 infected individuals can contribute to changes in the intestinal bacterial flora.

As outlined at the beginning of this review, the intestinal microbiota is altered by HIV-1 infection, either directly or indirectly, or even by the therapeutic regimen employed. Therefore, different ways of modulating this microbiota must be identified aiming at a positive action for the host.

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