

Alteration of Gut microbiota during HIV infection

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Abstract

Gut flora is the community of microbial populations that live in the intestine. Approximately 30% of this population is shared by all humans, but the remaining 70% is unique to each individual, hence gut microbiota serves as an identity card. Gut microbiota play numerous functions in the body's defense against invasion, the synthesis of important vitamins, the regulation of immunological marker production, and others. Researchers observed several data when analyzing bacteria species present in HIV-infected individuals using the 16S rRNA sequencing approach, concluding that HIV-infected people had a high number of *Prevotella* species, while *Lachnospiraceae*, *Christensenellaceae*, *Ruminococcaceae*, and *Bacteroidaceae* were all less. Those microbiota shifts may help explain how gut-related disorders interact with HIV. Researchers have discovered various methods for altering the composition of the gut microbiota in order to achieve a healthy gut. This review will focus on and highlight recent discoveries in Gut microbiota shifts during HIV infection and emphasize the immune response and treatment options.

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1. Introduction

Microbial population living in human intestine is called gut microbiota or gut flora. According to research population of gut microbiota contains tens of trillions of microorganisms which means a thousand different species are present in gut and this diversity proves human microbiome contain more than 3 million genes that is a hundred times more than human genes. Human microbiome analysis showed that 1/3 microbial population is common but 2/3 microbial population is specific for each individual [1]. Those analyses also showed that population of gut microbiota generally is anaerobes that means they do not require oxygen to grow up. Five phyla of bacteria present. While *Bacteroidetes* and *Firmicutes* are mostly found in intestine, *Proteobacteria*, *Verrumicrobia*, *Actinobacteria*, *Fusobacteria* and *Cyanobacteria* are in minor amount. It was also observed *Enterococcus spp.* in muscular layer and epithelial crypts of intestine [1,2]. Colonization of human gut microbiota begins at birth so diversity of gut microbiota is individual identity card. Microbes are passing through birth canal to new born. It was showed that vaginal microbiota similar with infant's gut microbiota but infants who are born with caesarean have different microbial composition. This is the first step causing different microbial composition among individuals. Changing of microbial composition also depends on time. After 1 year of age microbial composition stabilizes initial gut microbiota and take new shaping through adulthood [1].



Gut microbiota has essential roles such as regulating gut motility, producing vitamins, transforming bile acid and steroids, metabolizing xenobiotic substances, absorbing minerals and activating and destroying toxins, genotoxins and mutagens. Murine studies showed that gut microbiota intensely influences local and systemic inflammatory diseases [3]. Morbidity and mortality of Human Immunodeficiency Virus (HIV) infected patient is believed mainly affected by systemic inflammation [4]. Therefore, correlation between gut microbiota and HIV draw attention by many researchers. To understand effect of microbiota shifts on HIV disease progression many data found while analysing bacteria species in HIV infected patients and healthy subjects. These alterations can display interaction of gut related diseases and prevalent with HIV.

2. Gut bacteria role in immune system

Invasion of pathogenic bacteria is prevented through two barriers of gut. Mechanical barrier has single layer of polarized intestinal epithelial cells, mucus and enterocytes. The immune barrier consists secreted immunoglobulin A (IgA), intraepithelial lymphocytes, macrophages, natural killers and neutrophils. Presence of excess commensal bacteria in those gut barriers help development of host immune system. The competition between commensal and pathogens decreases capability of invasion by attaching site where pathogenic bacteria attach and microbiota absorbing all nutrients which is needed for pathogens [5]. Invasion is also prevented by decreasing pH level of intestine by production of lactate and short-chain fatty acids [6]. Production of toxic that can be produced by proteolytic fermentation in distal colon and carcinogenic metabolites such as bacteriocins, ammonia, indoles, phenols etc. prevent growth of pathogens. Volatile fatty acids which are produced by microbiota inhibit the colonization of pathogens [7]. Structure of bacterial cell wall consists lipopolysaccharides and peptidoglycan that can activate nuclear factor kB effector causing production of inflammatory cytokines such as tumour necrosis factor a (TNF-a), interleukin 1beta (IL-1beta) which are defender against pathogens. Peptidoglycan stimulates pattern recognition receptors (PRRs) also decreases excessive tissue injury by induced intestinal antigen presenting cells [8]. Gut-associated lymphoid tissue (GALT) is a main part of gut immune system consisting of Peyer's Patches, lamina propria lymphocytes, intra-epithelial lymphocytes and mesenteric lymph nodes. One of gut flora species *L. plantarum* regulates human gut epithelial tight-junction proteins and protect epithelial barriers from chemical-induced disruption [9] and others such as *Bacteroides fragilis* and *Bacillus* is needed to development of GALT and mucosal immunity and required for somatic diversification of immunoglobulin genes such as IgA that regulates bacteria communities in gut [10]. To understand importance of effect of microbiota in immune system it was showed that germ-free animals have abnormal functions such as reduced vascularity, digestive enzyme activity, muscle wall thickness, cytokine production, serum immunoglobulin levels, few Peyer' patches and few intra-epithelial lymphocytes [11]. Another study showed that germ free animals developed early stage of colitis that cannot treated by CD4+CD62L- cells [12].

3. Gut Microbiota in HIV Infection

Gastrointestinal tract is major organ in pathogenesis of HIV infection. Intestinal mucosa is rich in nutrients suitable for HIV replication in early infection. In chronic stage of HIV infection gut associated lymphoid tissues (GALT) is the most importance site of persistence of viral load [13,14]. Gut CD4+ T cells control of promoting T- helper 17 cells or inhibiting T-regulatory Cells during absorption of dietary antigens and foreign microorganism through intestinal epithelial tissue. Those number of T cells located in the intestine exceed the number of T cells in the rest of body. Therefore, intestinal epithelial cells are HIV target cells needed for viral expansion and persistence, which are primary focused of immunologic investigations. [13, 15]. Gut CD4+ T cells play major role in intestinal mucosal homeostasis and in defence mechanism against microbial invasion. Any damage to this immune homeostasis by HIV infection induces depletion of CD4+ T cells that cause alteration in immune system to antigens and change in commensal intestinal bacteria [16].

Early HIV infection is the stage 3-5 days after infection. In that stage rapid viral replication, intense immune response, viral diversification and CD4+T cells are observed greater than 200 cells/ μ L [17, 18]. Atypical microbiota population are also observed in early HIV infection stage that can consider as a detection of microbial

alteration [19]. During HIV infections, mucosal thickness and integrity is related to disease progression. Changing of integrity of mucosa affect microbial composition because gut bacteria are exposed to surrounding environment [20]. Therefore, HIV infection would have to corrupt both gut bacteria flora and intestinal barriers to propagate infection. In the early infection stage impaired of GALT are observed. GALT which is the major defence mechanism which include many metabolomics functions and pathways plays important role in association of mucosal microbiota in HIV infection and progression. GALT also harbors over %60 of CD4+ T cells [21-19]. A study showed high levels of *Enterobacteriales* and *Bacterioidales* were observed in HIV patients. High levels of *Enterobacteriales* and *Bacterioidales* are correlated to depletion of CD4+ T cells and levels of immune activation [22]. Another species that is *Bacteroides fragilis* was depleted in mucosa of HIV infected patients. In normal condition *B.fragilis* interacts with polysaccharide A (PSA) which is CD4+ T cell-interacting coat [21]. Systemic activation is better predictor of disease progression than viral load or level of blood CD4+ T cells [22]. HIV results persistent immune activation cause AIDS development systemic immune activation may be result in immunologic decline and AIDS. Systemic activation in HIV patients is characterized by proliferation of T cell targets supportive of continued viral replication [23, 24]. High levels of immune activation and decrease level of B and T cell clones, increased frequencies of apoptotic T cells [25,26], increased production of pro-inflammatory and pro-apoptotic cytokines describe systemic activation in HIV patients [27]. These results of studies may prove that systemic activation may be result of increased damage of intestinal barriers and lymphoid tissue, may increase permeability of intestinal barrier. Loss of intestinal epithelial cells and disruption of tight junctions between cells lead to increase villous atrophy, malabsorption, diarrhea, increased intestinal permeability, microbial translocation and change gut microbiota composition [28]. Increased permeability of intestinal barriers is observed in HIV infected patients causing gut microbiota and microbial products pass through intestinal barriers which is called microbial translocation. Translocation of microbiome is proven while observing levels of systemic lipopolysaccharides in circulation of HIV infected patients. Lipopolysaccharides are part of bacterial cell wall that stimulates activity of monocytes provides innate and adaptive immunity [29].

The increased prevalence of gut-resident bacteria capable of triggering host inflammation indicates a probable molecular link between HIV-associated microbiota alterations and enhanced systemic immune activation [30]. It was observed effects of abundance of gut bacteria may affect mucosal T cells and dendritic cell (DC) frequency and their activation. They used 16S DNA sequencing technique to take fecal samples from colon of HIV infected patients and HIV negative individuals. 18 untreated on chronic HIV infected and 14 HIV control individuals were analysed. They first determined if there were any differences in abundance of colonic mucosa adherent phylum, genera taxonomic levels between HIV negative controls and HIV positive infected patients. They analysed diet and body mass index (BMI) associations of samples were taken from colonic biopsies. Three dominant phyla detected within biopsies of both HIV positive and HIV negative individuals. Three phyla were *Firmicutes*, *Bacteroidetes* and *Proteobacteria* found on HIV positive subjects while there was no any significant difference at phylum level on HIV negative individuals. Low levels of *Firmicutes* found on HIV infected patients whereas *Proteobacteria* level was significantly higher on HIV positive. *Prevotella* was higher in HIV infected subjects whereas *Lachnospiraceae*, *Christensenellaceae*, *Ruminococcaceae* and *Bacteroidaceae* were all less [31]. The microbial composition of HIV-positive individuals is primarily aerotolerant. In chronic individuals, the *Prevotellaceae*, *Villonellaceae*, *Erysipelotrichaceae*, and *Clostridia* Family are overrepresented. *Proteobacteria*, *Gammaproteobacteria*, *Enterobacteriales*, *Enterobacteriaceae*, *Erysipelotrichi*, *Erysipelotrichales*, *Enterococcaceae*, *Erysipelotrichaceae*, and *Barnesiella* are abundant in HIV patients. *Ruminococcaceae*, *Lachnospiraceae*, *Christensenellaceae*, *Ruminococcaceae*, and *Bacteroidaceae*. *Rikenellaceae* and *Alistipes* decline in HIV-infected people [32,33,34]. The involvement of the *Erysipelotrichaceae* family in inflammatory processes is unknown, possibly due to limited availability of isolation and cultivation methods. Among the limited research that have investigated the link between *Erysipelotrichaceae* members and their hosts, some have discovered that *Erysipelotrichaceae* members capable of generating inflammatory disease in the gut [35,36]. It was also analysed that any difference on gut bacteria composition that is taken from mucosa or stool because some studies showed microbial structure of human fecal

samples can be different than microbiota of colonic mucosa. Although high level of abundance of *Proteobacteria* found in mucosal samples of HIV infected subjects, *Proteobacteria* was not observed in fecal aspirates. They suggested abundance of *Proteobacteria* was restricted to colonic mucosal tissue microbial community. Low level of *Firmicutes* was observed in colonic mucosal tissue and also found in fecal aspirates within HIV infected patients. *Prevotella* also was found in both fecal aspirates and mucosal samples. This research indicates abundance of species which found in either fecal aspirates or mucosal tissue can be different or similar [37].

4. Treatment options

The recovery of gut microbiota could lead the way for future HIV targeted therapy, as well as minimize HIV's impact on the immune system. As previously stated, microbial translocation activates inflammatory markers [8]; however, if gut microbiota modification is structured, these signals are minimized. Various ways for modifying the composition of the gut microbiota in order to create a healthy gut have been found by researchers.

4.1.1. Antiretroviral Therapy

The effect of antiretroviral therapy (ART) on gut microbiota is debatable because some research found no effect of ART on recovery gut microbiota composition while others found that ART combined with probiotics had a positive effect on recovery gut microbiota community [38]. Antiretroviral Therapy (ART) is a broad treatment for HIV infections, which benefits HIV patients by lowering mortality and viral load. The recovery of CD4+ T cells is nearly complete, and the mucus immune system has been restored. Aside from that, long-term ART reduces HIV viral load. After a long period of ART, the *Bacteroides* and *Prevotella* ratios are similar to HIV negative. The impact of ART on gut flora should be studied further [39].

4.1.2. Probiotics

In meta-analyses of randomized controlled studies, probiotics have been proven to aid in the alleviation of symptoms of traveler's and antibiotic-associated diarrhea, as well as irritable bowel syndrome. Probiotics are a common and effective technique to modify the gut microbiota, preventing harmful microorganisms from passing past the intestinal barrier while increasing intestinal barrier consolidation. Probiotics also control IgA, defensin, and antimicrobial agent synthesis. Probiotics arrange ecological stability while altering microbial community [40]. Probiotics influence commensal gut bacteria growth. *Lactococcus lactis*, for example, raises the level of the *Bifidobacteria* community while decreasing the number of *Enterococci* spp. [41]. It has been discovered that the benefits of probiotics on HIV patients boost CD4 count and minimize diarrhoea caused by infections and medicines. Probiotics have no dangerous adverse effects on patients in general, although some HIV positive people get sepsis [42]. Probiotics can delay the progression of AIDS while also reducing inflammation and microbial translocation. It also regulates the formation of short chain fatty acids and glutamine, which helps patients avoid malabsorption and diarrhea. The first probiotics which administered to HIV positive patients was *Lactobacillus reuteri* [43]. Lactobacilli strains aid in the reduction of intestinal inflammation. One study showed that 30 HIV-positive males were drinking one bottle of fermented milk with probiotics that reducing inflammation in the stomach and reducing microbial translocation increased T lymphocytes [44]. *Ruminococcaceae* and *Lachnospiraceae* families have been shown to restore saccharolytic fermentation of carbohydrates and immunological tone of the mucosal barrier in HIV patients. Probiotics also reduce pain of stomach of HIV patients who take ART [45].

4.1.3. Fecal microbiome transplantation (FMT)

Fecal microbiome transplantation (FMT) is a new approach that involves taking fecal microbiota samples from a healthy donor and transplanting them into the colon of another infected person. A pilot human trial using one-time FMT treatment revealed modest changes in the microbiota, implying that techniques to increase the efficacy of FMT to allow donor microbe engraftment are needed [46]. For example, donor fecal material

processed anaerobically demonstrated promise efficacy in ulcerative colitis when compared to multi-dose material from a single donor processed routinely. Despite variations in the microbiota of HIV-infected subjects, the gut microbial community identified in HIV infection is more diverse than that seen in ulcerative colitis and may resist the colonization of exogenously supplied bacteria such as those in FMT. There were no notable negative effects from FMT, and transplanted microbiota samples were altered but not identical to donor samples. It was also revealed that there was no reduction in stomach inflammation [47,30].

5. Conclusion

Because of essential functions such as avoiding pathogenic microbe invasion, manufacturing antibacterial compounds and necessary vitamins, maintaining intestine pH level, and biological transformation of bile acids and steroids, the gut microbiota can be considered a supplementary organ. The increasing recognition of the gut microbiota's influence on host immunological systems is proper for requiring additional research in the context of HIV infection. Microbial translocation occurs in HIV infection, and microbial compounds enter the circulation and trigger immunological inflammatory markers. All of this renders an HIV-infected person defenceless to other external influences such as harmful germs or viruses. Investigation the impact of lifestyle and environmental factors on the gut microbiota in the context of HIV infection are all important areas for future research.

Declaration of competing interest

The authors declare that they have no known financial or non-financial competing interests in any material discussed in this paper.

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