

## 2016 Hepatitis C Virus: Global view

## Gut epithelial barrier dysfunction in human immunodeficiency virus-hepatitis C virus coinfecting patients: Influence on innate and acquired immunity

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### Abstract

Even in cases where viral replication has been controlled by antiretroviral therapy for long periods of time, human immunodeficiency virus (HIV)-infected patients have several non-acquired immunodeficiency syndrome (AIDS) related co-morbidities, including liver disease, cardiovascular disease and neurocognitive decline, which have a clear impact on survival. It has been considered that persistent innate and acquired immune activation contributes to the pathogenesis of these non-AIDS related diseases. Immune activation has been related with several conditions, remarkably with the bacterial translocation related with the intestinal barrier damage by the HIV or by hepatitis C virus (HCV)-related liver cirrhosis. Consequently, increased morbidity and mortality must be expected in HIV-HCV coinfecting patients. Disrupted gut barrier lead to an increased passage of microbial products and to an activation of the mucosal immune system and secretion of inflammatory mediators, which in turn might increase barrier dysfunction. In the present review, the intestinal barrier structure, measures of intestinal barrier dysfunction and the modifications of them in HIV monoinfection and in HIV-HCV coinfection will be considered. Both pathogenesis and the consequences for the progression of liver disease secondary to gut microbial fragment leakage and immune activation will be assessed.

**Key words:** Human immunodeficiency virus infection; Hepatitis C virus infection; Innate immunity; Acquired immunity; Gut barrier

**Core tip:** Even in patients with a long-term controlled human immunodeficiency virus (HIV) replication by antiretroviral therapy, HIV-infected patients have several non-acquired immunodeficiency virus (AIDS) related co-morbidities, including liver disease. Persistent innate and acquired immune activation contributes to the pathogenesis of these non-AIDS related diseases. Immune activation has been related with bacterial translocation secondary to gut barrier damage by the HIV or the hepatitis C virus (HCV)-related liver cirrhosis. Modifications in gut barrier structure and function and immune activation in HIV-HCV coinfecting patients will be reviewed.

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## INTRODUCTION

Human immunodeficiency virus (HIV) infection has evolved from a relative rapidly fatal disease to a chronic entity as a consequence of antiretroviral treatment (ART). However, even in patients with a long-term controlled disease, HIV-infected patients have several non-acquired immunodeficiency syndrome (AIDS) related co-morbidities, including cardiovascular and liver diseases, malignancy and neurocognitive decline, with a clear impact on survival<sup>[1,2]</sup>. It has been considered that persistent innate and acquired immune activation contributes to the pathogenesis of these non-AIDS related diseases<sup>[3]</sup>.

Immune activation has been related to several situations, such as the persistence of HIV replication in the lymph nodes (even when peripheral blood HIV replication has been controlled)<sup>[4]</sup>, the existence of other coinfections, [such as cytomegalovirus<sup>[5]</sup> and hepatitis C virus (HCV)<sup>[6]</sup> infection] and bacterial translocation which is an effect of the intestinal barrier damage caused by the HIV itself<sup>[7]</sup>. Bacterial translocation is defined as the translocation of bacteria and/or bacterial products from the gut to the mesenteric lymph nodes and other extra-intestinal organs<sup>[8,9]</sup>.

In the present review the intestinal barrier structure, measures of intestinal barrier dysfunction and the modifications of them in HIV monoinfection and HIV-HCV coinfection will be considered.

## GUT EPITHELIAL BARRIER DESCRIPTION

The intestinal mucosa is made up of the epithelium, the lamina propria and the muscularis mucosa<sup>[10]</sup>. Innate and adaptive immune cells are distributed in the intestinal mucosa and submucosa. Effector immune cells are located primarily in the epithelium and lamina propria. The epithelium contains T cells, whereas lamina propria contains T and B lymphocytes and several cellular elements implicated in innate response, such as dendritic cells, macrophages, eosinophils and mast cells. Organized structures of the gut-associated lymphoid tissue (GALT) lie in the mucosa and submucosa<sup>[11]</sup>.

In an expanded sense, we define the intestinal barrier as the sum of commensal intraluminal bacteria, the epithelial lining of intestine and the immune system. There are three barriers against pathological bacterial translocation: firstly, structures and mediators that limit the direct contact between the epithelial surface and the intestinal bacteria; secondly, the integrity of intestinal epithelial lining; finally, immune protection, characterized by the rapid detection and killing of bacteria that manage to penetrate<sup>[12]</sup>.

### Intestinal bacterial flora

In healthy subjects, the composition of the gut microbiome is essential to maintain both local and systemic immunity<sup>[13]</sup>. The microbial density increases from 10<sup>5</sup> colony forming units (CFU)/mL in the jejunum to 10<sup>8</sup> in distal ileum and cecum, up to 10<sup>12</sup> in the colon<sup>[14]</sup>. Most intestinal bacteria belong to two phylogenetic lineages, *Firmicutes* and *Bacteroidetes*, and in minor proportion, *Actinobacteria* and *Proteobacteria*<sup>[15]</sup>.

Small intestinal bacterial overgrowth is defined as > 10<sup>5</sup> CFU/mL and/or the presence of colonic bacteria in upper jejunal aspirate<sup>[16]</sup>.

Anaerobes are 100 times more abundant than aerobes. Anaerobic bacteria do not easily translocate<sup>[17]</sup>. In contrast, gram-negative aerobic bacteria [*Escherichia coli* (*E. coli*), *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* (*P. aeruginosa*)], *Enterococci* and other *Streptococci*, translocate readily, even across a histologically intact intestinal epithelium<sup>[18,19]</sup> and are those mainly implicated in infections in conditions characterized by pathological bacterial translocation, such as liver cirrhosis<sup>[20]</sup>. Alterations in the intestinal ecosystem equilibrium (dysbiosis) has been correlated with several pathologies<sup>[21]</sup>.

### Intestinal epithelial barrier

In the normal individual, the intestinal epithelium absorbs water and nutrients while effectively preventing translocation of intraluminal bacteria<sup>[22]</sup>. Intestinal defensive mechanisms include the following elements: (1) Bile<sup>[23]</sup>; (2) Mucin and antimicrobial peptides, secreted by goblet cells and Paneth cells

respectively<sup>[24-26]</sup>. Intestinal epithelial cells directly transport secretory immunoglobulin A (IgA), synthesized by plasma cells in the lamina propria, across the epithelial barrier; and (3) Intestinal epithelium. The barrier is formed by individual epithelial cell membranes and junction proteins. Intestinal epithelial cells express pattern-recognition receptors (PRRs), such as toll-like receptors (TLRs), cell surface C-type lectin receptors, and intracytoplasmic nucleotide oligomerization domain-like receptors (NLR), that enable them to act as sensors of the microbial flora and as necessary elements to maintain the mutualism<sup>[27-31]</sup>. Pathogen-associated molecular patterns (PAMPs) are conserved molecular patterns that are recognized by these PRRs<sup>[32]</sup>.

Transmembrane adhesion molecules organized into structures called tight junctions, adherens junctions and desmosomes, connected to the actin cytoskeleton, ensure the stability of the epithelial barrier<sup>[33,34]</sup>.

Inflammation and immune-related cytokines might modify the epithelial integrity and the function of the tight junctions: (1) Interferon gamma (IFN- $\gamma$ ) modifies actin-myosin contractility, resulting in intestinal tight junctions disruption and increased paracellular permeability<sup>[35]</sup>; (2) Tumor necrosis factor alpha (TNF- $\alpha$ ) induce an inflammatory response and apoptosis in intestinal epithelial cells<sup>[36]</sup>; (3) Interleukin (IL)-10 antagonizes the cellular functions induced by TNF- $\alpha$  and IFN- $\gamma$ <sup>[37]</sup>; and (4) Likewise, transforming growth factor- $\beta$  (TGF- $\beta$ ) has protective effects on intestinal barrier function<sup>[38]</sup>.

### Intestinal immune system

The peaceful coexistence with the intestinal bacterial flora is demonstrated by the lack of inflammatory responses against commensal bacteria. In healthy people, bacteria present in the autochthonous flora translocate in low numbers, but are killed during their passage through the epithelial barrier or in the mesenteric lymph nodes<sup>[39]</sup>. In fact, mesenteric lymph nodes are normally sterile.

Microbial antigens access to innate system by various routes: (1) Microfold cells (M cells), located within epithelium or in the follicle-associated structures of the GALT, can sample microbial antigens and transport them from the lumen into the dendritic cell-rich region<sup>[40]</sup>; (2) Dendritic cells that underlie the epithelium may open tight junctions, sending processes into the lumen that directly sample microbes and present them to lymphoid cells<sup>[41]</sup>; and (3) When the intestinal integrity failed, dendritic cells recognize the antigenic material in lamina propria<sup>[42]</sup>.

Myeloid and plasmocitoid dendritic cells (DCs) are two subsets of DCs with ability to recognize different PAMPs<sup>[43]</sup>. For instance, *E. coli* lipopolysaccharide (LPS) stimulates myeloid DCs through TLR4<sup>[44]</sup> and induces a Th1 differentiation *via* secretion of IL-12. Viral particles are recognized by plasmocytoid DCs *via* TLR-7, TLR-8 or TLR-9, which secrete interferon-alpha (INF- $\alpha$ ) as response to them<sup>[45]</sup>. Once activated, intestinal DCs

induce mucosal B and T cells<sup>[46]</sup>.

## MEASURES OF INTESTINAL PERMEABILITY

Measures of gut barrier dysfunction has been recently revised<sup>[47]</sup>. They can be classified as histological (structural) or functional measures<sup>[48-52]</sup>.

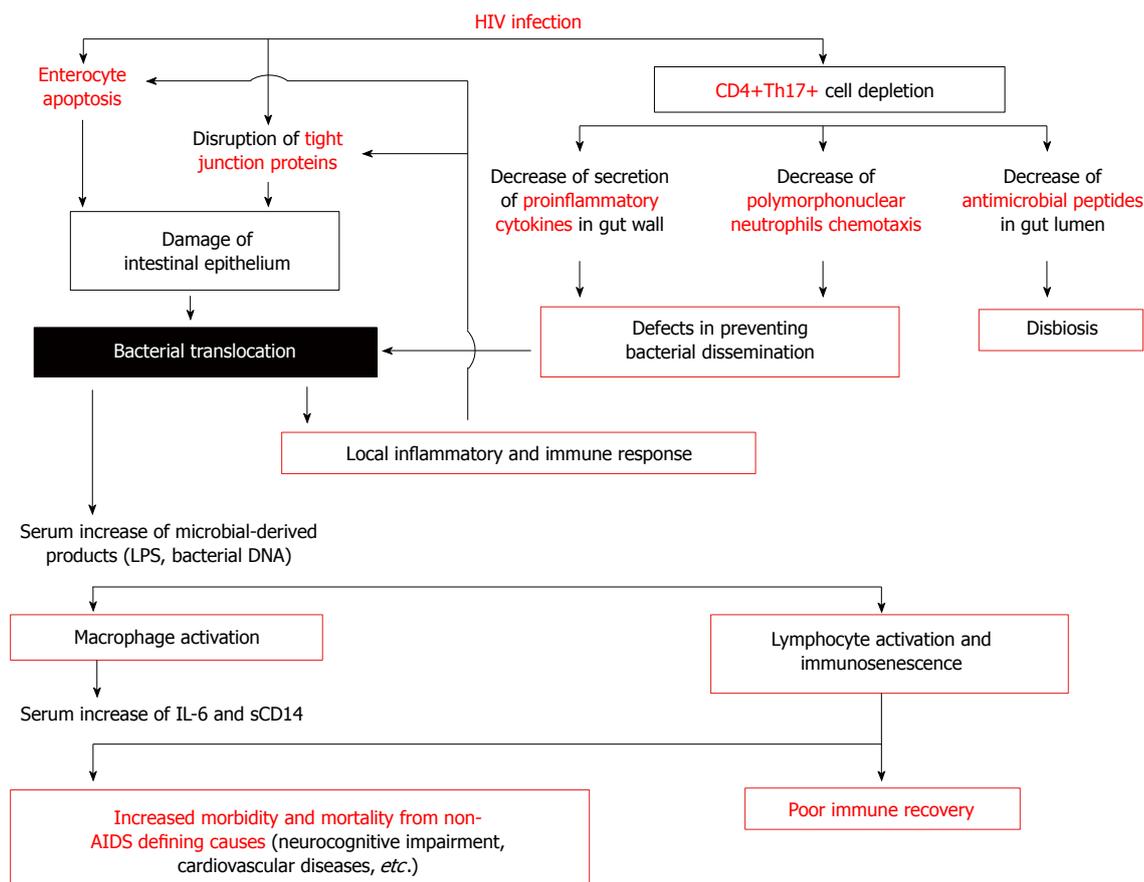
Methods of evaluating the intestinal function *in vivo* can be classified as follows: (1) Intestinal permeability can be assessed analyzing the urinary recovery of orally administered inert test markers (sugars, such as monosaccharides and disaccharides, polyethylene glycols or radiolabeled chelates)<sup>[47,53]</sup>; (2) Intestinal barrier dysfunction can be assessed by measuring intestinal fatty acid binding protein (I-FABP) in plasma or urine<sup>[54,55]</sup>. I-FABP is uniquely located in mature small-intestinal enterocytes. Its leakage into the circulation from enterocytes is detected when intestinal mucosal damage occurs<sup>[56]</sup>. Serum levels of zonulin, a protein linked to tight junctions, have been studied as markers of intestinal permeability, although further analyses are needed; and (3) Another method to analyze barrier permeability is the measurement in extraintestinal fluids, such as the systemic blood, of gut-derived microbial fragments levels: LPS<sup>[57]</sup>, bacterial 16S ribosomal DNA<sup>[58]</sup> or bacterial flagellin<sup>[59]</sup>.

Markers of intestinal inflammation are the following: (1) Fecal calprotectin, a zinc-binding protein complex, is a sensitive marker of intestinal inflammation. It constitutes one of the cytosolic proteins in neutrophil granulocytes and in activated macrophages<sup>[60,61]</sup>; and (2) Alpha-1-antitrypsin is a protease inhibitor, highly resistant to proteolysis in the intestine. Alpha-1-antitrypsin can be extravasated from serum into the gut in the case of increased intestinal permeability, and finally be detected in the faeces<sup>[62]</sup>.

## ALTERATIONS IN INNATE AND ADAPTATIVE IMMUNITY SECONDARY TO GUT EPITHELIAL BARRIER DYSFUNCTION

LPS is a component of the outer membrane of Gram-negative bacteria, considered a major marker of microbial translocation. LPS elicit several responses in the innate immune system, after the interaction with the liver-derived LPS binding protein (LBP), which transfers LPS onto membrane CD14-TLR4 complex. TLR4 transduces the signal to the cell nucleus, leading to transcription factor nuclear factor  $\kappa$ -B (NF- $\kappa$ B) activation and cytokine production<sup>[63]</sup>. CD14 is shed during activation as soluble CD14 (sCD14). Both increased sCD14 and proinflammatory cytokines (TNF- $\alpha$ , IL-6) are considered evidence of this proinflammatory state.

Continuous exposure to antigens is associated



**Figure 1** Effect of bacterial translocation on innate and acquired immune activation in human immunodeficiency virus-infected patients. In the gastrointestinal tract, human immunodeficiency virus (HIV) infection induces a Th17 CD4+ T helper cells depletion and a damage of intestinal epithelium as a consequence of the HIV exposure itself or by immune-induced enterocyte damage. The consequence of the alteration in gut barrier is the bacterial translocation. Increased plasma concentrations of several markers indicative of pathological bacterial translocation [lipopolysaccharide (LPS), bacterial DNA] have been detected in these patients. These molecules induce a monocyte and lymphocyte activation implicated in the increased morbidity and mortality from non-acquired immunodeficiency syndrome (AIDS) defining causes (neurocognitive impairment, cardiovascular diseases, etc.) and in the poor immune recovery. IL: Interleukin; sCD14: Soluble CD14.

with lymphocyte activation<sup>[64]</sup>, increase of “exhausted” cytotoxic populations (CD8+CD45RO+CD57+)<sup>[65]</sup> and an increase of lymphocytes that have evolved close to apoptosis<sup>[66]</sup>. To down-regulate the chronic activation, a modification of lymphocyte co-stimulatory molecules (monocyte CD80 and CD86 and lymphocyte CD28 molecules)<sup>[67]</sup> and an expansion of the population of suppressor or regulatory T lymphocytes (CD4+CD25highFoxP3+)<sup>[68]</sup>, is expected.

## GUT EPITHELIAL BARRIER AND IMMUNE DYSFUNCTION IN HIV PATIENTS

Even in patients with a long-term controlled HIV replication by antiretroviral therapy, HIV-infected patients have several non-AIDS related co-morbidities, including liver disease. Persistent innate and acquired immune activation contributes to the pathogenesis of these non-AIDS related diseases. Immune activation has been related with bacterial translocation secondary to gut barrier damage by the HIV<sup>[68]</sup>.

HIV-associated microbial translocation results from a series of events occurring at the gastrointestinal

mucosa (Figure 1): (1) early mucosal CD4+ depletion; (2) immune hyperactivation/persistent inflammation; (3) damage to the integrity of the intestinal epithelium; and (4) modifications of the gut microbiome<sup>[69]</sup>.

### Mucosal CD4+ T cell depletion

The simian immunodeficiency virus (SIV) model has been very valuable to define host-virus interactions and immunologic consequences in GALT<sup>[70]</sup>. During acute infection of SIV-infected macaques or HIV-infected patients, it has been clearly demonstrated the massive and rapid destruction of memory CD4+ T cells within the gastrointestinal tract<sup>[4,71,72]</sup>, due to both direct virus cytopathicity and CD8+ T-cell-mediated killing of infected CD4+ T cells<sup>[69,73,74]</sup>.

Th17 CD4+ T helper cells generate a rapid response to microbial pathogens at mucosal sites (including the intestinal mucosa), inducing chemokine expression for recruitment of neutrophils, monocytes and lymphocytes<sup>[75]</sup>. Also, Th17 stimulate the production of antimicrobial proteins and peptides<sup>[76-79]</sup>. Moreover, Th17 cells, through the expression of IL-17, regulate the synthesis of tight junction proteins<sup>[80]</sup>.

Th17 cells express the CCR5 receptor and are severely depleted during acute HIV and SIV infections<sup>[81,82]</sup>. The consequences of gut Th17 depletion in SIV and HIV infections are the following: (1) The Th17-derived cytokines IL-17 and IL-22 induce the production of antimicrobial peptides that controls microbial replication at the luminal surface of the intestine. In a HIV or SIV infection, Th17 depletion could favor a dysbiosis in the intestinal flora; (2) During SIV infection, gut Th17 cell depletion impairs the ability to secrete proinflammatory cytokines and to mount local acute inflammatory responses after gram negative bacilli challenge; the impaired Th17 response has been associated with increased bacterial translocation across the epithelial barrier<sup>[83]</sup>; and (3) Th17 depletion results in a reduced number and activity of neutrophils<sup>[84,85]</sup>, which may contribute to defects in preventing bacterial dissemination.

A significant support for the importance of Th17 cell depletion in pathogenic HIV infection comes from investigations of HIV-infected elite controllers (those who maintained CD4+ T cell levels at healthy levels and control HIV replication without ART). Elite controllers retain the gut Th17 subset and do not exhibit systemic immune activation<sup>[86]</sup>.

Regulatory T cells (FoxP3+ Treg) are essential to control inflammation and autoimmunity. The loss of Treg lymphocytes in GALT, demonstrated during primary SIV infection<sup>[87]</sup>, might contribute to chronic immune activation in HIV and SIV infections<sup>[88]</sup>.

Numbers and functions of other gut immune cell subsets are also altered during HIV infection. Increased turnover, cell activation, apoptosis, and altered function in cytotoxic CD8 T cells, natural killer cells, innate lymphoid cells and B cells have been reported<sup>[89,90]</sup>.

### **Mucosal immune hyperactivation/persistent inflammation**

Immunohistochemistry and confocal fluorescence microscopy have detected the presence of LPS in the gut mucosa since the earliest phases of infection, associated with epithelial barrier dysfunction<sup>[91]</sup>, persisting even after ART-induced control of HIV replication<sup>[92]</sup>. The extent of damage to the epithelial barrier is correlated with the degree of microbial translocation<sup>[91]</sup>, and of innate immune activation<sup>[92]</sup>. However, whereas an intense macrophage phagocytosis occurs during acute infection in SIV-infected animals, intestinal macrophages appear free from bacterial cells during chronic infection although accumulation of microbial components persists<sup>[93]</sup>, suggesting a progressive exhaustion of macrophage phagocytic function.

Reciprocal interactions between immune activation and microbial translocation would be hypothesized in HIV infection: the sustained activation induces a cycle whereby new susceptible HIV targets (activated CD4+ T lymphocytes) are created and cytotoxic and inflammatory responses increase damage

to the intestinal gut barrier and stimulate further translocation<sup>[69]</sup>.

### **Damage to the integrity of the intestinal epithelium**

Damage of intestinal epithelium might occur as a consequence of the HIV exposure itself or by immune-induced enterocyte damage.

*In vitro*, a disruption of tight junction proteins has been observed after exposure to HIV glycoprotein gp120<sup>[94]</sup>. In addition, the HIV transactivator factor Tat alters microtubule and actin cytoskeleton and induce apoptosis<sup>[95]</sup>. These data have been supported by immunohistochemical studies of gut mucosa from HIV-infected individuals: an alteration of enterocyte microtubules and increased paracellular permeability has been observed<sup>[96]</sup>.

Immune-induced enterocyte damage is also observed in HIV infection. In acute HIV and SIV infection, a noticeable perforin expression of mucosal CD8+ T cells has been detected and was associated with significant numbers of apoptotic epithelial cells<sup>[97]</sup>. In acute SIV infection, increased expression of Fas-ligand on lamina propria lymphocytes and Fas on enterocytes has been found<sup>[74]</sup>. Furthermore, proinflammatory cytokines, secreted by activated gut macrophages, can induce enterocyte apoptosis<sup>[98]</sup>. Finally, the induction of the kynurenine pathway of tryptophan catabolism by indoleamine 2,3-dioxygenase-1 in infiltrating activated myeloid cells contributes to suppress T-cell proliferation and Th17 development<sup>[99,100]</sup>. Taken together, these data suggest that altered tight junction composition and cellular apoptosis may contribute to the barrier defect.

Antiretroviral therapy improves the immune function in the periphery, but restoration of GALT is only partial<sup>[101,102]</sup>. ART-treated chronic HIV infected patients continue to show increased neutrophil infiltration in the gut compartment and epithelial cell apoptosis<sup>[92]</sup>, as well as persistent pathological microbial translocation<sup>[103]</sup>.

### **Modifications of the gut microbiome**

There is evidence of gastrointestinal dysbiosis in HIV-infected individuals<sup>[104]</sup>. Previous studies demonstrated an abundance of *P. aeruginosa* and *Candida albicans* and a reduction of bifidobacteria and lactobacilli in faecal samples of HIV-infected patients compared with healthy controls<sup>[105]</sup>. More recently, Dillon *et al.* have showed that HIV-infected individuals had increased proportion of *Proteobacteria* and decreased percentages of *Firmicutes* in the colonic mucosa. At the genus level, a significant outgrowth of *Prevotella* and a decrease of *Bacteroides* were detected<sup>[106]</sup>. In these patients, dysbiosis is associated with increased tryptophan catabolism and biomarkers of inflammation<sup>[107]</sup>. Dysbiosis is persistent in ART-treated HIV-infected patients<sup>[104,106]</sup>. It must be noted that those patients with virological response to ART (control of HIV replication) but poor immunological reconstitution (limited increase of peripheral blood CD4+ T cells, maintaining values

lower than 200/mm<sup>3</sup>) exhibit a translocating bacterial microflora enriched in *Enterobacteriaceae* compared with those with a good immunological response<sup>[108]</sup>, suggesting that changes in the intestinal microflora could affect the immune reconstitution *via* continued lymphocyte activation.

### **Systemic consequences of the bacterial translocation in HIV infection**

Increased plasma concentration of several markers indicative of pathological bacterial translocation or systemic inflammation has been detected in HIV-infected patients: LPS<sup>[109]</sup>, bacterial DNA<sup>[110]</sup>, bacterial flagellin<sup>[111]</sup>, LBP<sup>[112]</sup>, sCD14<sup>[113]</sup>, IL-6<sup>[113]</sup> and EndoAb<sup>[114]</sup>.

During acute and chronic HIV-infection, LPS is identified not only in mucosa, but also within systemic lymph nodes, liver and peripheral blood: LPS concentrations in gut mucosa, lymph nodes and liver are positively correlated, therefore supporting the systemic passage of gut-derived microbial fragments<sup>[91]</sup>.

In acute HIV infection, serum levels of LPS are normal but EndoCAB (IgM, IgG and IgA antibodies directed against LPS core antigen) titers are increased, thus suggesting that the translocation of LPS is rapidly counteracted by the host Ig response. In chronic HIV infection, EndoCAB titers decrease progressively and higher plasma levels of LPS are detected<sup>[109]</sup>. Brenchley *et al.*<sup>[109]</sup> reported that increased levels of circulating LPS in chronically HIV-infected individuals positively correlate with measures of immune activation. This finding has been corroborated by other groups<sup>[91,94,115,116]</sup>.

Chronic immune activation is observed in HIV-infected patients. HIV- and SIV-associated chronic immune activation is characterized by high T-cell turnover of both CD4+ and CD8+ T cells, increased surface expression of HLA-DR and CD38 molecules, high levels of circulating proinflammatory cytokines and chemokines and polyclonal B-cell activation<sup>[117,118]</sup>. The HIV-related immunosenescence is another concept characteristic of both HIV infection and aging; it is defined by an expansion of CD28-/CD57+CD8+ T cells, shortened telomeres, reduced IL-2 production, elevated IL-6 levels, and resistance to apoptosis<sup>[119,120]</sup>.

It is accepted that one of the most important forces inducing immunoactivation and immunosenescence in these individuals is gut bacterial translocation. *In vitro* stimulation by microbial TLR ligands induces T-cell activation in ART-naïve and ART-treated, HIV-infected patients<sup>[121]</sup>. In accordance with these findings, the concentration of bacterial-derived fragments has been correlated with systemic immune activation, mainly measured as circulating activated CD8+ lymphocytes (CD8+HLA-DR+CD38+ T cells)<sup>[109,110,122,123]</sup>.

Notably, ART-induced complete suppression of HIV replication is not sufficient to fully turn off

altered intestinal permeability or immune activation: circulating levels of intestinal permeability markers or immune activation parameters decrease after ART, even though they did not return to the levels observed in healthy individuals<sup>[109,110,124-128]</sup>.

The prognostic importance of markers of intestinal permeability and immune activation has been analyzed. Whereas bacterial translocation markers, such as LPS, have been inconsistently associated with the progression of HIV infection<sup>[129,130]</sup>, multiple studies have demonstrated that the main determinant of disease progression is the chronic immune activation, independent of the HIV load<sup>[131,132]</sup>.

Two types of clinical consequences of the maintained intestinal permeability have been described: (1) A poor immune recovery in those patients with higher values of bacterial translocation parameters. An inverse correlation between serum concentrations of barrier damage or immune activation markers and the magnitude of recovery of peripheral blood CD4+ T cell count has been demonstrated in ART-treated individuals<sup>[109,110,126,133]</sup>; and (2) Increased morbidity and mortality from non-AIDS defining causes, such as neurocognitive impairment or cardiovascular diseases, in those patients with a more pathological bacterial translocation and immune activation<sup>[113]</sup>.

In ART-treated patients, causes of death are different of those classically associated with AIDS: most of patients in the Hunt's study<sup>[134]</sup> died by non-AIDS related causes, such as cardiovascular diseases (19%-27%), non-AIDS related cancer (11%-13%) and end-stage liver disease (8%-11%), among others. It has been demonstrated that chronic inflammation markers are independent prognostic factors of non-AIDS related morbidity (myocardial infarction, stroke, non-AIDS-defining cancer, non-AIDS-defining serious bacterial infection) or death in HIV-infected patients<sup>[135]</sup>. However, not every marker has the same prognostic value at each stage of HIV-infection. In a recently published nested case-control study of individuals with ART-suppressed HIV infection, Hunt *et al.*<sup>[134]</sup> have assessed the relationship between intestinal barrier alteration, monocyte activation markers and immunologic factors with mortality. Both gut epithelial barrier function markers (serum levels of I-FABP) and parameters of innate immunity activation (serum levels of sCD14 or IL-6, kynurenine/tryptophan ratio) strongly predicted mortality in individuals with ART-suppressed HIV infection and a history of AIDS. However, T-cell activation (percentages of CD8+CD38+ cells) or T-cell senescence (proportion of CD28-CD57+ lymphocytes) failed to predict mortality in treated patients with an acceptable stage of immunocompetence. Other investigations have demonstrated the importance of T cell activation and senescence in untreated or immunodeficient-treated HIV-infected patients<sup>[131,136]</sup>. Thus, Hunt *et al.*<sup>[134]</sup> stated that T-cell activation may predict mortality in situations

in which persistent T-cell immunodeficiency may play an important role in susceptibility to opportunistic infections and AIDS-related malignancies, but not necessarily in treated patients with less advanced immunodeficiency; in these less advanced phases, gut barrier dysfunction or monocyte activation markers are the predominant prognostic factors.

Several therapeutic interventions aimed at reducing microbial translocation and its downstream effects have been proposed<sup>[137]</sup>:

**Restoring the normal composition of the intestinal microbiome:**

Prebiotics and probiotics can be used to modify the altered intestinal microbioma. In a pilot, placebo-controlled study, untreated HIV-infected individuals received a prebiotic oligosaccharide mixture for 12 wk<sup>[138]</sup>. Microbiota composition improved substantially, increasing the proportion of bifidobacteria; also, there was a significant reduction in sCD14 levels and in activated CD4+ T cell lymphocytes.

In HIV-infected subjects during ART, non-absorbed antibiotics available for oral administration, such as rifaximin, have been also assayed to decrease the intestinal load of aerobic gram-negative bacilli and reduce gut microbial translocation and immune activation levels. However, results showed only minimal effect on serum levels of LPS and sCD14 or on the CD8+ T cell activation<sup>[139]</sup>.

**Decreasing the intestinal concentration of microbial products to be translocated:**

Studies in patients with renal insufficiency have demonstrated that blocking microbial translocation using sevelamer, a LPS-binding resin, decreased both systemic microbial translocation and systemic T cell activation and inflammation<sup>[140]</sup>. Oral sevelamer has been assayed in HIV-infected individuals naïve to antiretrovirals as a proof-of-principle in this strategy. Sevelamer did not significantly change markers of microbial translocation, inflammation, or T-cell activation<sup>[141]</sup>.

**Improving intestinal barrier damage:**

IL-7 is a cytokine produced by non-marrow-derived stromal and epithelial cells, required for the development and persistence of T cells. The administration of recombinant IL-7 to a cohort of subjects with low-level CD4+ T-cell recovery on ART has demonstrated to be efficacious in increase the peripheral and, more importantly, gut T lymphocyte numbers, decreasing the inflammatory infiltrate of the gut lamina propria and reducing plasma levels of sCD14<sup>[142]</sup>.

The anti-inflammatory drug mesalamine has been assayed to reduce the inflammation and consequently the intestinal barrier damage. After 12 wk of treatment, no significant changes in activated T lymphocytes counted at gut mucosa or at peripheral blood, or in the serum levels of sCD14 or IL-6 were observed in mesalamine-treated HIV-infected individuals<sup>[143]</sup>.

**Limiting immune activation:** Chloroquine (which inhibits toll-like receptor signalling) has been also assayed in a pilot study. CD4 and CD8 T-cell counts, T-cell activation, and the kynurenine/tryptophan ratio did not change after 24 wk of chloroquine treatment<sup>[144]</sup>.

Also, statins have been used to decrease the immune activation. After 24 wk of rosuvastatin, significant decreases in plasma levels of sCD14 but not in levels of T-cell activation were detected; these findings were independent of the lipid-lowering effect of rosuvastatin and the use of protease inhibitors<sup>[145]</sup>.

**Antagonizing molecules implicated in lymph node or liver lesions:**

TGF-β1 has been implicated in the lymph node fibrosis (which hinders CD4+ T cell reconstitution)<sup>[146]</sup> and in the progression of liver disease<sup>[147]</sup>. Angiotensin 2 is proinflammatory and induces fibrosis by increasing levels of TGF-β1<sup>[148]</sup>. Angiotensin-converting enzyme inhibitors have consistently proven beneficial in a number of clinical settings, but emerging data suggest that these drugs may also have anti-fibrotic properties<sup>[149,150]</sup>. We are waiting more data in HIV-infected patients.

In brief, some interventions (probiotics, IL-7, statins) have shown beneficial effects on gut barrier damage effects. However, until now these interventions have not been applied to the care of HIV-infected patients.

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## GUT EPITHELIAL BARRIER AND IMMUNE DYSFUNCTION IN HIV-HCV COINFECTED PATIENTS

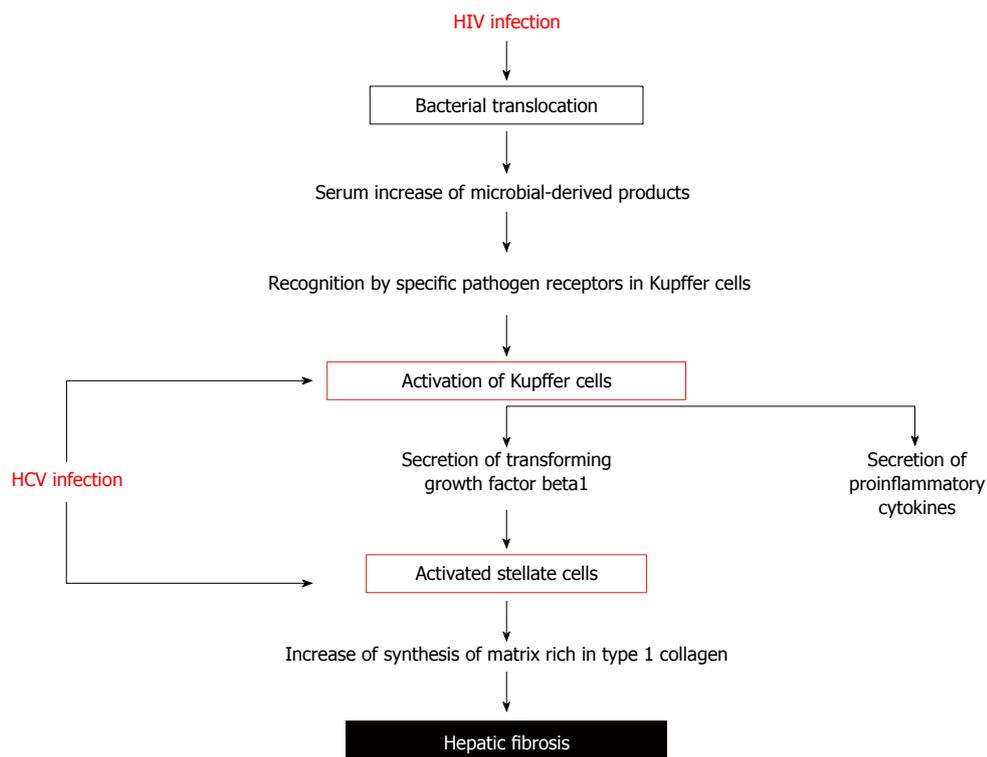
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HCV-related liver cirrhosis is associated with gut barrier defects, thus increasing the bacterial permeability observed in individuals with HIV mono-infection. Also, bacterial translocation contributes to accelerating the process of liver fibrogenesis (Figure 2).

**Bacterial translocation in liver cirrhosis**

It has long been appreciated that liver disease is associated with increased intestinal barrier permeability<sup>[151]</sup>. When classical culture methods are used as measurement of intestinal permeability, the presence of enteric-derived bacteria in mesenteric lymph nodes occurs more frequently in patients with cirrhosis compared with controls, and bacterial translocation is more frequent in Child C compared to Child A and B<sup>[152-155]</sup>. In contrast, if we consider the translocation of non-viable organisms (bacterial DNA), translocation to mesenteric lymph node and to systemic circulation also occurs in non-ascitic cirrhosis and it is independent from the severity of liver disease<sup>[156]</sup>. Liver insufficiency<sup>[157]</sup> and portal hypertension<sup>[158]</sup> are the driving forces for bacterial translocation.

Several excellent reviews have been recently



**Figure 2** Increased fibrogenesis rate in human immunodeficiency virus-hepatitis C virus coinfecting patients. In human immunodeficiency virus (HIV)-hepatitis C virus (HCV) coinfection, translocated bacterial products contribute to liver disease progression by binding to specific pathogen recognition receptors in Kupffer cells. Activated Kupffer cells secrete proinflammatory cytokines and transforming growth factor  $\beta$ 1. Activated stellate cells, stimulated by transforming growth factor  $\beta$ 1, produce a matrix rich in type 1 collagen, increasing the effect of HCV on hepatic fibrosis.

published on this subject<sup>[12,21,28,53,159]</sup>. As a summary, factors influencing pathological intestinal permeability and its consequences in cirrhotic patients include: (1) Advances stages of liver cirrhosis are frequently associated with malnutrition<sup>[160]</sup>, which has been reported to contribute to decreased epithelial cell proliferation and synthesis of mucins and antimicrobial peptides<sup>[161,162]</sup>; (2) Significant decreases in intraluminal concentrations of bile acids<sup>[163,164]</sup>; (3) A deficit of Paneth cell-derived defensins, accompanied by a diminished *in vitro* antibacterial activity against various enterobacteria has been observed in experimental cirrhosis<sup>[165]</sup>. In cirrhosis, a reduced secretion of mucosal IgA into the jejunum have been detected<sup>[159,166]</sup>; (4) Higher gastric pH and autonomic neuropathy-related intestinal hypomotility, seen in patients with cirrhosis and exposition to health care structures and antibiotic therapy, may lead to failure in the control of bacterial intestinal growth with both qualitative (dysbiosis) and quantitative (overgrowth) differences<sup>[167-169]</sup>. A depletion of the beneficial *Lachnospiraceae* and *Bacteroidetes* (mainly the *Bacteroidaceae* family) and enrichment in *Proteobacteria* (mainly *Gammaproteobacteria* class and among those, particularly *Enterobacteriaceae*) has been observed<sup>[169]</sup>, with differences more marked in patients with advanced cirrhosis<sup>[170]</sup>; (5) Alterations in tight junction proteins have been demonstrated<sup>[171]</sup>; (6) A mononuclear cell infiltrate in the lamina propria has been detected in cirrhotic patients<sup>[172,173]</sup>, as well as

increased faecal concentrations of polymorphonuclear elastase<sup>[166]</sup> and calprotectin<sup>[174]</sup>. Activated monocytes in the lamina propria disrupt epithelial tight junctions and perpetuate pathological bacterial translocation<sup>[175]</sup>; (7) Plasma markers of enterocyte necrosis (I-FABP), microbial translocation (LPS), and monocyte activation (sCD14) are increased in subjects with chronic hepatitis B or C infection, with higher values in those with advanced fibrosis<sup>[176]</sup>; (8) Immune activation and immunosenescence has been also demonstrated in cirrhotic patients<sup>[177]</sup>; and (9) Serum levels of inflammation markers are independently associated with cirrhosis complications and with mortality<sup>[178-182]</sup>.

In HIV-HCV coinfecting patients the additive effects of HIV and liver cirrhosis on intestinal permeability have been demonstrated. Increased sCD14 levels have been detected in HIV-HCV coinfecting patients with liver cirrhosis compared with those with minimal or moderate fibrosis<sup>[176,183,184]</sup>. Elevated levels of barrier damage markers and proinflammatory cytokines have been observed in those HIV-HCV coinfecting patients with more advanced forms of liver cirrhosis: significant higher concentrations of plasma LBP, sCD14 or IL-6 levels were observed in HIV-HCV coinfecting patients with decompensated cirrhosis compared with those with compensated cirrhosis<sup>[185]</sup>. However, lymphocyte activation parameters show similar values than those observed in HIV-monoinfecting patients<sup>[6]</sup>, suggesting the existence of a maximal plateau in lymphocyte

activation as result of gut bacterial fragment stimulus.

### **Increased fibrogenesis rate in HIV-HCV coinfecting patients**

It has been demonstrated that the liver fibrosis progression is more rapid in HIV-HCV coinfecting than in HCV-monoinfecting patients, with a lower period of HCV infection being required for the development of liver cirrhosis<sup>[186,187]</sup>. Furthermore, the progression of liver cirrhosis towards death is accelerated in HIV-HCV coinfecting patients, compared with HCV-monoinfecting individuals<sup>[188-190]</sup>. Death occurs in these individuals by causes mainly related with liver disease<sup>[191]</sup>. Liver function indexes (Child-Pugh, MELD score), immunodepression and absence of ART have been considered prognostic factors in HIV-HCV coinfecting patients<sup>[189,191]</sup>.

Microbial translocation has been suggested to exert a major pathogenic role in the worsened liver disease in HIV-infected individuals<sup>[192]</sup>. Translocated bacterial products contribute to liver disease progression by binding to specific pathogen recognition receptors<sup>[193]</sup>. Several cells in the liver express significant levels of multiple Toll like receptors. TLR2, TLR3, and TLR4 are highly expressed in Kupffer cells. Free LPS binds to Kupffer cells *via* interaction with LBP and CD14<sup>[194]</sup>. The LPS-LBP-CD14 complex, *via* TLR4 and NF $\kappa$ B, lead to the rapid production of superoxide, TNF- $\alpha$  and IL-6<sup>[12]</sup>. Also, LPS sensitizes hepatic stellate cells to Kupffer-derived TGF- $\beta$ <sup>[147]</sup>. Activated stellate cells produce a matrix rich in type 1 collagen, leading to liver fibrosis<sup>[195]</sup>. In support of this hypothesis, it has been observed that a polymorphism in the gene encoding TLR4, which attenuates the signaling downstream of the receptor in response to LPS stimulation, has been associated with a decreased risk of developing cirrhosis<sup>[196]</sup>. Furthermore, deficiency in TLR4 signalling reduces hepatic fibrosis after bile duct ligation<sup>[147]</sup>. Likewise, our group has demonstrated that a polymorphism in the TNF- $\alpha$  gene influences the rate of liver cirrhosis, probably due to a decreased synthesis of TGF- $\beta$ <sup>[197]</sup>.

Recently, French *et al.*<sup>[198]</sup>, in a 5-year longitudinal study of HIV-HCV coinfecting patients, demonstrated that those individuals in whom liver disease progresses showed higher levels of intestinal mucosal lesion (I-FABP), macrophage activation (sCD14), and inflammation (IL-6) markers compared with non progressors. In progressors, I-FABP levels increased significantly with time. Studies carried out by our group have demonstrated that in these patients, proinflammatory cytokines levels were correlated with parameters indicative of haemodynamic alterations in cirrhotic patients, such as renin activity or the aldosterone concentration, as well as with the mortality<sup>[185]</sup>.

Modification of the natural history of HCV-related liver disease in HIV-coinfecting patients has been

attempted in two main ways: (1) Treatment of HIV infection down-regulates the accelerated course of liver fibrosis in HIV-HCV coinfecting patients: ART-treated individuals show a progression rate of HCV-related liver fibrosis similar to those patients without HIV coinfection<sup>[191,199]</sup>. As has been previously commented, circulating levels of intestinal permeability markers or immune activation parameters decrease after the initiation of ART, although they did not return to the levels observed in healthy individuals; and (2) Treatment of HCV infection. The attainment of a sustained virological response after HCV treatment is associated with a lower rate of the progression of liver disease<sup>[190]</sup>, and lower mortality due to liver-related causes<sup>[200]</sup> and non-liver and non-AIDS related causes<sup>[201]</sup>. There is only limited data about modifications in gut barrier damage or proinflammatory cytokines related with the HCV treatment<sup>[202]</sup>.

## **CONCLUSION**

Both HIV and HCV infections could modify intestinal permeability, allowing the pass of gut bacterial fragments into the peripheral blood. Both markers of intestinal damage, increased gut permeability and immune activation, have been related to increased morbidity due to neurocognitive, cardiovascular or liver lesions. The combined effect of HIV infection and HCV-derived liver cirrhosis increases even more the levels of proinflammatory molecules and could be implicated in the elevated mortality observed in HIV-HCV coinfecting patients compared with those with HIV- or HCV-monoinfection.

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