Connecting the Dots: Could Microbial Translocation Explain Commonly Reported Symptoms in HIV Disease?

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Microbial translocation within the context of HIV disease has been described as one of the contributing causes of inflammation and disease progression in HIV infection. HIV-associated symptoms have been related to inflammatory markers and sCD14, a surrogate marker for microbial translocation, suggesting a plausible link between microbial translocation and symptom burden in HIV disease. Similar pathophysiological responses and symptoms have been reported in inflammatory bowel disease. We provide a comprehensive review of microbial translocation, HIV-associated symptoms, and symptoms connected with inflammation. We identify studies showing a relationship among inflammatory markers, sCD14, and symptoms reported in HIV disease. A conceptual framework and rationale to investigate the link between microbial translocation and symptoms is presented. The impact of inflammation on symptoms supports recommendations to reduce inflammation as part of HIV symptom management. Research in reducing microbial translocation-induced inflammation is limited, but needed, to further promote positive health outcomes among HIV-infected patients.

(Journal of the Association of Nurses in AIDS Care, 25, *483-495*) *Published by Elsevier Inc. on behalf of Association of Nurses in AIDS Care*

Key words: *HIV, inflammation, microbial translocation, sCD14, symptom management, symptoms*

Insights into the pathogenesis of HIV infection have implicated microbial translocation as one of the key drivers of HIV disease progression and inflammation

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JOURNAL OF THE ASSOCIATION OF NURSES IN AIDS CARE, Vol. 25, No. 6, November/December 2014, 483-495
http://dx.doi.org/10.1016/j.jana.2014.07.004
Published by Elsevier Inc. on behalf of Association of Nurses in AIDS Care

(Brenchley & Douek, 2008; Brenchley et al., 2006; Marchetti et al., 2011; Sandler et al., 2011). Microbial translocation is the movement of bacteria and/or microbial products from the gut to the bloodstream. Commonly reported gastrointestinal (GI) and systemic symptoms may have a relationship with chronic inflammation induced by circulating microbial products from the GI tract in patients with HIV disease. Even with effective combination antiretroviral therapy (cART) and viral suppression, inflammation from chronic immune activation increases the rates of morbidity and mortality among people living with HIV disease (PLWH; Brenchley et al., 2006; Deeks, 2011; Kamat, Misra, et al., 2012; Marchetti et al., 2011). It is critical for nurses to have a working understanding of the concepts of microbial translocation, inflammation, and symptom management in the clinical management of HIV disease.

Background and Significance

Chronic inflammation has been identified as a key predictor in the development of comorbidities and mortality in HIV disease. One source of inflammation – the inflammation of the GI epithelial barrier – ultimately leads to dysfunction of the protective lining of the gut. Consequently, microbes naturally residing in the gut are able to pass through the gut-associated lymph tissue (GALT) into the blood circulation (Estes et al., 2010; see Table 1 for definitions). The immune system responds to circulating microbes with systemic and often chronic inflammation (Brenchley et al., 2006).

Inflammation of the GI epithelial barrier in HIV disease resembles inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Inflammation of the GI epithelial barrier leads to symptoms including diarrhea, bloating, and abdominal pain (Berkes, Viswanathan, Savkovic, & Hecht, 2003; Epple & Zeitz, 2012). In IBD/IBS, inflammation leads to the translocation of microbes naturally residing in the gut into the bloodstream, as seen in HIV disease where microbial products residing in the gut translocate through the GALT into the bloodstream (Brenchley et al., 2006; Epple & Zeitz, 2012).

Systemic inflammation experienced chronically has been associated with systemic symptoms and conditions. Symptoms are often adverse experiences perceived from underlying changes in the biopsychosocial function of an individual. Signs and symptoms provide key assessment information to support the formulation of diagnostic pathways for clinicians. Symptoms are usually measured by self-report as opposed to a sign, which is an abnormality that can be detected by the individual and by others observing the individual (Dodd et al., 2001). PLWH often experience and report symptoms to their providers. However, the subjectivity of symptoms can limit objective assessment by another individual, creating huge challenges for clinicians and scientific investigators, as symptoms may not be objectively measured by another human being unless people report what they are experiencing.

Symptoms are often attributed to side effects of treatment with cART (Johnson, Stallworth, & Neilands, 2003). Patients initiating antiretroviral therapy in the early era of the HIV epidemic were at risk for serious adverse events and major side effects, but current cART regimens are simpler, better tolerated, more effective, and offer lower side-effect profiles than earlier regimens used in the treatment of HIV disease (Katlama et al., 2009; Lennox et al., 2009; Madruga et al., 2007). And yet, many symptoms persist in some individuals. In addition, the symptom burden experienced by PLWH has been associated with poor medication adherence, such as when people want to avoid symptoms, forget to take scheduled doses, and/or sleep through medications due to fatigue (Gay et al., 2011). Symptom burden is the summation of disease expression and/or the product of the treatment of that disease, usually referred to as the side effects of treatment (Cleeland & Reyes-Gibby, 2002).

Our purpose was to review how inflammation from HIV disease may lead to symptoms experienced by PLWH in the context of microbial translocation, as well as how this event may lead to treatment failure. We describe the process and consequences of microbial translocation and inflammation, and how this inflammatory process may be related to symptoms experienced (Figure 1). Furthermore, we address the gaps in knowledge and challenges in demonstrating a valid hypothesis linking microbial translocation and symptoms.

Table 1. Key Definitions on Topic-Specific Abbreviations

Topic-specific definitions	
Gut-associated lymph tissue (GALT)	The GALT is a large lymphatic area clustered behind the gut epithelial tissue that forms the mucosal lining of the gastrointestinal tract. It is organized into the lamina propria, Peyer's patches, and isolated lymphoid follicles. It is rich in Th17 cells (Estes et al., 2010).
T-helper 17 (Th17)	Th17 white blood cells are a type of CD4+ T cell rich in the GALT. They express a CCR5 receptor on their surface and are a prime target for HIV attack once activated in response to HIV (Klatt & Brenchley, 2010).
Chemokine receptor 5 (CCR5)	This gene is a receptor that is present on macrophages and T cells, like the CD4+ cell. HIV can attach to this receptor. (Klatt & Brenchley, 2010)
Commensal bacteria	Friendly bacteria living in the gut. These bacteria help to digest food, regulate immune function, and defend the gut barrier from harmful bacteria. Some strains can be ingested in the form of probiotics (Wilson, Moneyham, & Alexandrov, 2013).
Microbial translocation and epithelial barrier dysfunction	
Lipopolysaccharide (LPS)	Cell wall component of gram negative bacteria. Plasma LPS is directly associated with microbial translocation. Reduced by long term cART but not to health control levels (Kitchens & Thompson, 2005)
LPS binding protein (LBP)	LBP binds to LPS to form the LPS-LBP complex and presents to cells that produce sCD14, which is able to bind to this complex and present to lipoproteins that clear the LPS (Kitchens & Thompson, 2005).
Soluble CD14 (sCD14)	Released by monocytes and macrophages during immune activation in a pro-inflammatory innate response to circulating microbes in an LPS-LBP complex. sCD14 is a more accurate and relevant measure of microbial translocation (Sandler et al., 2011). It is recommended as a surrogate biomarker of microbial translocation and epithelial barrier dysfunction (Stehle et al., 2012).
Endotoxin core antibodies (EndoCab)	Released in response to LBP-LPS complex to clear LPS. Lower levels are found in HIV. Mechanism not fully understood but may be partially due to HIV-1 Tat protein downregulation impairment of immune responses to LPS (Yim, Li, Lau, & Lau, 2009).
Proinflammatory cytokines	
Interleukin (IL)	A type of cytokine, a protein substance released from activated white blood cells that communicates with other cells to stimulate or regulate responses.
Interleukin-1 (IL-1)	A family of pro-inflammatory cytokines secreted by epithelial cells and leukocytes to induce an acute response and neutrophil production. Increased in HIV disease (Deeks, 2011).
Interleukin-6 (IL-6)	Classic marker of inflammation in HIV. Associated with CVD, advanced HIV disease, and non-AIDS events. Correlation with higher plasma viral loads especially with lower CD4+ T cell counts. Associated with immune senescence and the inflammation associated with aging. Positively correlated with sCD14 (El-Sadr et al., 2006).
Interleukin-8 (IL-8)	Secreted by some epithelial and white blood cells in response to HIV-1 exposure (Nazli et al., 2010).
Interleukin-10 (IL-10)	Anti-inflammatory immune modulation inhibiting IFN-γ and IL-2 production. Associated with IBD. Produced by programmed death (PD-1) triggered monocytes (Said et al., 2010).
Interleukin-17 (IL-17)	Promotes a pro-inflammatory effect and recruitment of neutrophils. Produced by a subset of Th17 cells (Brenchley et al., 2008).
Interleukin-21 (IL-21)	Cytokine with crucial role of B cell differentiation; decreased in HIV infection (Ruffin, Thang, Rethi, Nilsson, & Chiodi, 2012).
Interleukin-22 (IL-22)	Secreted by Th17 cells to promote epithelial healing and proliferation caused by inflammation. Can also act synergistically, amplifying other pro-inflammatory cytokines such as IL-17 and cause hyperplastic tissue remodeling as seen in acanthosis (Kitchens & Thompson, 2005; Zheng et al., 2007).
Interleukin-23 (IL-23)	Stimulates production of IL-22 and/or IL-17 by Th17 cells in the GALT. Plays a key role in IBD (Weaver, Elson, Fouser, & Kolls, 2013).
TNFα	Response of enterocytes in response to HIV gp120. Induces inflammation and contributes to the breakdown of tight gap junctions disrupting barrier function (Nazli et al., 2010).
C-reactive protein (CRP)	An inflammatory biomarker elevated in HIV disease. Associated with increased risk of CVD, all-cause mortality, AIDS and non-AIDS events, and with detectable HIV viral loads (El-Sadr et al., 2006).
Coagulation	
D-dimer	Coagulation biomarker also associated with higher levels of sCD14 (El-Sadr et al., 2006).

Note: cART = combination antiretroviral therapy; IBD = irritable bowel disease; CVD = cardiovascular disease.

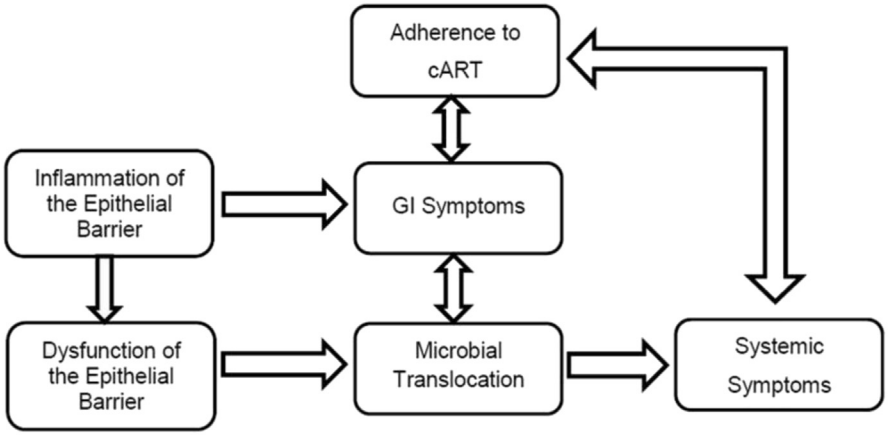

Figure 1. Conceptual framework: symptomatic consequences of inflammation. Inflammation of the epithelial barrier leads to possible gastrointestinal (GI) symptoms and dysfunction of the epithelial barrier. Dysfunction of the epithelial barrier leads to microbial translocation. While microbial translocation has not been associated with GI symptoms, the double arrow signifies a possible association, as outlined in this review. Microbial translocation and inflammation have been associated with some systemic symptoms. Symptom burden has been associated with adherence to combination antiretroviral therapy (cART).

Inflammation of the Epithelial Barrier

HIV has an affinity for Th17 type CD4+ T cells in the GALT. These specific cells, once activated, are prime targets for HIV because of chemokine receptor 5 (CCR5) receptors that HIV can bind to when entering CD4+ T cells. Th17 type CD4+ T cells are rapidly depleted during HIV infection, resulting in the release of signaling proteins called cytokines, which initiate the inflammatory process. Under natural physiological conditions, these cells would release cytokines that would regulate and control the inflammatory process. However, due to the rapid depletion of the Th17 type CD4+ T cells and ongoing replication of HIV, inflammation continues and becomes chronic (Klatt et al., 2010; Pandrea et al., 2007).

Chronic inflammation eventually leads to damage of the tight gap junctions between the epithelial cells of the GI monolayer protective barrier. Under natural physiological circumstances, Th17 cells release a cytokine that can initiate the repair of these junctions. However, due to the depletion of Th17 cells in GALT, repair of the epithelial barrier is impaired (Estes et al., 2010; Klatt et al., 2010; Verhoeven, Sankaran, Silvey, & Dandekar, 2008).

Dysfunction of the Epithelial Barrier

GI barrier dysfunction has many consequences. Alterations to the cellular cytoskeleton and the function of tight gap junctions lead to disruption in epithelial permeability. Disruption of epithelial permeability may lead to malabsorption of nutrients and possibly even medications. In addition, alterations in fluid and electrolyte secretion, which may cause symptoms such as diarrhea, bloating, and constipation, may also lead to abdominal pain and functional symptoms (Berkes et al., 2003). GI symptoms are common in IBD/IBS disease as well as in HIV disease. Clinicians and PLWH have often attributed these symptoms to medication toxicities.

The microbial environment of the gut mucosal epithelium has an extraordinary ability to maintain protection against pathogenic invasion of harmful bacteria (Berkes et al., 2003). The microbiome competes for space and nutrients, while also providing a protective layer of mucous. The microbial environment maintains balance for the gut and interacts well with the immune system; the commensal flora operates synergistically with the human immune system. However, once the barrier becomes dysfunctional, microbes are able to invade and pass through

the barrier, evade immune intervention, and egress into circulation (Berkes et al., 2003). The pathway of microbial translocation is complex, with the main outcome being that microbial products are able to translocate from the gut to the bloodstream.

Microbial Translocation

Microbial translocation is not an exclusive feature of HIV disease. It has been well described in IBD/IBS (Spiller, 2009), graft-versus-host disease (Eriguchi et al., 2012), abdominal postoperative conditions (Sista et al., 2013), and liver disease (Wiest & Garcia-Tsao, 2005). Nonhuman primates are often used as models to understand the extent of damage caused by the immunodeficiency virus in humans because of similar pathology between nonhuman primates and humans. Simian models have similar structural and immunological responses to that of the human model and can be infected with the virus for investigation, and results can be translated to understand the pathogenesis in humans (Klatt et al., 2010).

Brenchley et al. (2006) described microbial translocation as part of the pathogenic process in simian immunodeficiency virus (SIV) and HIV infection by detecting differences in microbial translocation in animal models using African Green Monkeys versus Rhesus macaques, with higher levels of microbial translocation in the pathogenically infected Rhesus macaques. Prior to these findings, the inflammatory process and marked dysfunction of the immune response was attributed to HIV infection within GALT and of the GI epithelial barrier. Stein et al. (1997) described the chronic passage of bacteria leaking across a compromised epithelial wall in HIV disease.

GALT houses a rich supply of Th17 and memory CD4+ T cells, which express high levels of CCR5 receptors, which facilitate entry into cells and result in rapid depletion of these immune cells during the acute phase of HIV/SIV infection (Estes et al., 2010; Pandrea et al., 2007). Immune activation in response to HIV/SIV begins an inflammatory process, secreting proinflammatory cytokines, such as tumor necrosis factor-α, interleukin (IL)-1, IL-6, IL-17, IL-21, and IL-22, that ultimately impair the epithelial barrier (Estes et al., 2010; Klatt et al., 2010; see Table 2). The immune system, which is essential to survival, is subverted by HIV infection and, due to the inflammatory response, continues as a result of dysfunctional regulation. Although treatment with cART is unable to prevent acute loss of CD4+ T cells in GALT, it does support CD4+ T cells by suppressing HIV replication and allowing the body to restore these immune cells. In SIV models, preservation of memory CD4+ T cells, as well as the reduction and suppression of inflammation, promotes repair and regeneration of the mucosal epithelial barrier (Verhoeven et al., 2008).

Without successful cART, HIV infection goes on to deplete CD4+ T cells in the peripheral blood,

Table 2. Inflammatory Symptoms and Their Association with IL-6 and sCD14 Increase

Symptoms Frequently Reported by PLWH	Early ART	sCD14	IL-6
Abdominal pain			
Anxiety			X
Changes in body weight/fat	X	X	X
Cognitive decline	X	X	X
Diarrhea	X		X
Fatigue	X		X
Fever or night sweats	X		X
Headaches	X		
Insomnia	X		X
Joint pain/stiffness			X
Loss of strength		X	X
Muscle pain			X
Nausea/vomiting	X		
Peripheral neuropathy	X		X
Reduction in appetite			
Sadness	X		X
Sexual problems			
Shortness of breath/cough	X		X
Skin problems	X		

Note: PLWH = people living with HIV infection; sCD14 = soluble CD14; IL-6 = interleukin-6; ART = antiretroviral therapy; IL = interleukin.

The symptoms listed are common symptoms currently reported in HIV disease as referenced in the section of this article: "Symptoms in HIV Disease." The column labeled "Early ART" indicates symptoms, which were often attributed to side effects of early era ART, including highly toxic antiretroviral drugs (e.g., zidovudine monotherapy, stavudine, didanosine, indinavir, nelfinavir). The column labeled "sCD14" indicates symptoms with established associations with sCD14. The column labeled "IL-6" indicates symptoms with established associations with IL-6. Blank cells indicate frequently reported HIV-associated symptoms without reported associations with early ART or IL-6 and sCD14.

lymph nodes, and effector tissues leading to AIDS (Klatt & Brenchley, 2010), and the continuous loss of CD4+ T memory cells inhibits reconstitution in spite of treatment (Mehandru et al., 2006). Additionally, cART fails to restore CD4+ T memory cells back to preinfection levels and persistent immune activation continues in response to low levels of viremia in GALT, leading to chronic mucosal inflammation and microbial translocation (Estes et al., 2010). Even with undetectable levels of viral RNA, viral DNA can persist and contribute to ongoing immune activation (Chun et al., 2008), resulting in continued structural and immunologic damage (Brenchley & Douek, 2008).

Damage to the integrity of the mucosal epithelial barrier and loss of phagocytic protection in GALT set the stage for microbial products to translocate to the lymph nodes and then to the plasma through the chronic phase of HIV disease. In addition, levels of lymphatic microbial products and circulating microbial products are associated with the extent of damage to the GI tract (Estes et al., 2010). Once in circulation, these products contribute to and amplify immune activation resulting in chronic inflammation (Klatt, Canary, et al., 2013; Klatt, Chomont, Douek, & Deeks, 2013). Even with long-term suppression of HIV replication in the blood, the epithelial barrier is only partially restored (Epple & Zeitz, 2012). The lack of restoration may be partially due to ongoing residual replication triggering the inflammatory process in the gut and, as a result, contributing to microbial translocation (Baroncelli et al., 2009; Reus et al., 2013). This inflammatory process can lead to systemic symptom development (Figure 1).

Microbial Translocation and Immune Activation

Circulating microbial products from the gut result in immune inflammatory processes. Brenchley et al. (2006) reported microbial translocation as a hallmark predictor of immune activation and disease progression, describing the differences in pathogenic progressive HIV/SIV infections, long-term nonprogressors, and nonpathogenic SIV models. The study established that the source of circulating microbial products, which were commensal and pathogenic bacteria, had passed through the damaged gut epithelial barrier. Levels of microbial products measured by the bacterial lipopolysaccharide (LPS) outer coat increased after the acute/early phase of HIV infection. Levels of LPS were linked to elevated levels of soluble CD14 (sCD14) ($r = 0.3$, $p = .001$) and lower levels of naturally occurring endotoxin core antibodies (EndoCAb) to LPS ($r = -0.319$, $p = .0005$), which clear LPS from the system. In fact, significantly lower levels of EndoCAb were detected in HIV/SIV-infected chronic progressors than in early/acute progressors ($p < .0001$) and those who were uninfected ($p = .0002$), meaning that over time the mechanism to remove circulating microbes decreases. HIV/SIV-infected nonprogressors exhibit higher levels of LPS and sCD14 than uninfected participants, meaning that even elite controllers and long-term nonprogressors with HIV disease have evidence of microbial translocation, which contributes to immune activation (Brenchley et al., 2006).

Microbial translocation has been well documented in the IBD/IBS literature. In fact, there are multiple similarities in the pathogenesis of IBD/IBS and HIV infection and its impact on the function of the GI system, including depletion of Th17 cells in GALT leading to inflammation and subsequent dysfunction of the epithelial barrier (Brenchley & Douek, 2008; McGuckin, Eri, Simms, Florin, & Radford-Smith, 2009). While the underlying reasons for low levels of EndoCAb in HIV disease are not clearly understood, the effect of HIV infection on the dysregulation of monocytes allows continuing circulation of microbial products, which results in chronic monocyte immune activation with sCD14 and a proinflammatory response (Yim, Li, Lau, & Lau, 2009). Even in the presence of high CD4+ T cell counts and suppressed viral loads, chronic inflammation exists with stable levels of sCD14 (Hattab et al., 2014).

Overall, LPS and the sCD14-LPS complex can stimulate the inflammatory pathway. In addition, the LPS–LPS binding protein-bound complex stimulates sCD14, which initiates the inflammatory pathway. The LPS-sCD14 complex induces the production of IL-6; activation of the immune system by circulating microbes is a signature process in the inflammatory cycle (Brenchley et al., 2006; Cassol, Rossouw, Seebregts, & Cassol, 2011; Kamat, Misra, et al., 2012). Therefore, sCD14 is a more reliable surrogate marker for microbial translocation than directly measuring bacterial LPS.

Symptoms in HIV Disease

Symptoms and symptom management are critical in HIV care. While symptom burden is an important issue for patients and providers, symptoms often go under-recognized. Edelman, Gordon, and Justice (2011) conducted a secondary data analysis of the Veterans Aging Cohort Study and found that providers demonstrated poor sensitivity to the report of symptoms, even with a symptom checklist completed by patients. Providers failed to recognize symptoms associated with disease progression. Symptoms reported were fatigue/loss of energy, cognitive decline, shortness of breath, loss of appetite, muscle aches/pain, and problems with weight loss (Edelman et al., 2011; Justice, Chang, Rabeneck, & Zackin, 2001). Among these symptoms, functional decline (Erlandson et al., 2013; Stehle et al., 2012), cognitive decline (Ancuta et al., 2008; Kamat, Lyons, et al., 2012), obesity (Koethe et al., 2013), anxiety, and sadness (Liebregts et al., 2007) have been associated with microbial translocation, indicated by elevated levels of sCD14 and/or Gram-negative bacterial LPS along with other inflammatory cytokines. Fatigue (Klimas, Broderick, & Fletcher, 2012), muscle aches, joint pain (Eriksson, Andersson, Ekerfelt, Ernerudh, & Skogh, 2004), poor sleep (Grandner, Sands-Lincoln, Pak, & Garland, 2013), fever/chills/sweats (Holtzclaw, 2013), night sweats (Mold, Holtzclaw, & McCarthy, 2012), peripheral neuropathy (Harezlak et al., 2011; Zheng et al., 2011), diarrhea (Liebregts et al., 2007), anxiety, depression (Camacho, 2013), and weight loss/wasting (Stein et al., 1997) have been associated with chronic inflammation as indicated by the elevation of proinflammatory cytokines. Table 2 provides a list of HIV-associated symptoms consistently reported by PLWH and displays the gaps in knowledge in regard to whether each has been associated with inflammation. Abdominal pain, reduction in appetite, and sexual problems are commonly reported symptoms in HIV disease, however, there are no relevant data or publications citing an association or lack of one with inflammation. Therefore, because of the prevalence of these symptoms in HIV disease, it is worth an investigation to gain insight into the possible underlying problems contributing to their development.

While there are similarities in pathology and symptoms between IBD/IBS and HIV disease, some of the symptoms have not been widely investigated in the context of microbial translocation in HIV disease. For example, bloating and abdominal pain are commonly reported in both HIV disease and in IBD/IBS, but have not been investigated in the context of inflammation and microbial translocation in HIV disease. Given the emphasis on patient-centered care over the past decade, it is important to understand and seek ways to validate patient symptoms and to work toward a model of care that is tuned in to the symptomatic experience of patients. Symptoms that may be associated with inflammation and disease progression in HIV disease warrant thorough investigation to support providers as they deliver symptom-focused interventions and care.

Inflammation, Immune Activation, and Disease Progression

The inflammatory process helps the host fight off foreign antigens. However, when unregulated inflammation causes damage, inflammation can also be harmful. In the same way, many strains of bacteria serve to protect and maintain functional abilities in a symbiotic relationship with the host. Killing all bacteria or even altering the normal flora is harmful. Some bacterial strains serve to boost and regulate the immune response. However, when bacteria and inflammation become unregulated, disease develops in the body (Antoni, Nuding, Wehkamp, & Stange, 2014).

Immune activation is multifactorial and complex. In numerous clinical trials, mortality, disease progression, and opportunistic infections have been associated with elevations in inflammatory biomarkers, IL-6, C-reactive protein (CRP), and D-dimer (Nixon & Landay, 2010). One important study was conducted by the Strategies for Management of Antiretroviral Therapy (SMART) study group. This large, multicenter, randomized clinical trial examined interruption and late initiation of cART based on CD4+ T cell count with a primary endpoint of new or recurrent opportunistic infection or all causes of death. Secondary endpoints were (a) a potentially life-threatening symptomatic event requiring medical intervention or (b) death (El-Sadr et al., 2006). In this study, participants with higher versus lower levels of

IL-6 were 2.4 (95% confidence interval [CI] 2.1 to 8.8) times more likely to develop opportunistic infections; participants with higher versus lower levels of CRP were 7.6 (95% CI 2.0 to 28.5) times more likely to develop opportunistic disease. Baseline and latest IL-6 levels, and latest CRP were predictive of disease development (Rodger et al., 2009). Elevation of D-dimer was predictive of the development of cardiovascular disease but not opportunistic infection (Rodger et al., 2009). The adjusted risk of mortality was shown to be eight times greater among participants with high sCD14 levels (95% CI 1.2 to 13.9; $p = .02$) versus low levels of sCD14. Participants with higher levels of sCD14 in the SMART study had increased enterocyte damage in comparison to participants with low levels of sCD14, even after treatment and adjusting for age (Sandler et al., 2011). Likewise, sCD14 has been shown to be a surrogate biomarker for immune activation in controlled and uncontrolled patients on cART (Brenchley et al., 2006; Kamat, Misra, et al., 2012).

HIV-associated inflammation processes, as described above, have been shown to cause the early onset of non-AIDS-related complications and early aging. Conditions normally associated with aging in uninfected populations manifest themselves prematurely in patients living with HIV disease (Deeks, 2011; Vance, McDougall, Wilson, Debiasi, & Cody, 2014). As such, aging is associated with cognitive decline, cardiovascular disease, cancer, bone disease, immunosenescence, and frailty (Deeks, 2011), which may be due to chronic inflammation caused by microbial translocation. Microbial translocation measured by sCD14 and LPS is associated with progression of the thickening of carotid arteries or subclinical atherosclerosis in HIV disease (Kelesidis, Kendall, Yang, Hodis, & Currier, 2012). Patients may experience symptoms such as shortness of breath, fatigue, lack of energy, and pain, due to hardened and thickened arterial walls. Atherosclerosis is normally associated with older patients, and clinicians may not look for it in younger patients, especially if symptoms are attributed to medications, HIV, or depression.

Chronic inflammation has been associated with an array of symptoms, which have been commonly reported by PLWH (Edelman et al., 2011; Gay et al., 2011; Johnson et al., 2003). Because inflammation leads to epithelial barrier dysfunction and epithelial barrier dysfunction leads to microbial translocation, which results in inflammation, it is plausible that some symptoms can be linked to microbial translocation. In light of the association between inflammation and symptoms, we need to examine which HIV disease symptoms have an association with GI epithelial barrier dysfunction and which symptoms have an association with inflammation induced by microbial products circulating in the blood. If we can understand the relationship of microbial translocation and symptoms reported by HIV-infected patients, we should be able to develop intervention studies to reduce the symptom burden in PLWH (Wilson, Moneyham, & Alexandrov, 2013).

Discussion

It is important for nurses to educate patients about the significance of discussing symptoms with their providers and not assuming the extent of their symptoms is related to cART. It is also important for nurses to familiarize themselves with microbial translocation, to encourage patients to ask their providers about microbial translocation, and/or to make recommendations on interventions to improve gut health. For example, various nutrition strategies can be discussed to support reduction of inflammation in the gut through dietary choices, such as decreasing sugar and alcohol intake, or taking over-the-counter probiotics.

Inflammatory-related symptoms may create a significant barrier to successful implementation of clinical care by affecting adherence to cART and engagement in care. Chronic inflammation from immune activation and elevated levels of soluble CD14 (sCD14) and IL-6 have been linked to early aging, decline in cognitive function, metabolic disease, cardiovascular disease, decline in renal function, cancer, bone disease, and other end-organ diseases (Deeks, 2011; Duprez et al., 2012; Erlandson et al., 2013; Kamat, Misra, et al., 2012; Marks et al., 2013; Pedersen et al., 2013; Vance et al., 2014). As noted in Table 2, many inflammatory-related symptoms are reported in HIV disease and there are even a few symptoms without any correlation data. Research studies should be conducted to determine

if these symptoms are an indication of underlying inflammation in HIV disease. If there is a correlation between various symptoms and inflammation, microbial translocation may be a target for interventions to prevent HIV disease progression and reduce symptoms experienced in chronic HIV disease.

Knowledge based on the association between epithelial barrier inflammation and GI symptoms, and the association between subsequent microbial translocation and systemic symptoms is limited. Interventions targeted toward improving gut health and microbial translocation still require rigorous research in PLWH. Research designs that address both the quality of life and the association and predictive perspectives of microbial translocation are warranted. Primary steps to improve symptom management strategies would be to conduct studies investigating the association between symptoms and microbial translocation. This would include examining the association between microbial translocation and reported GI and systemic symptoms commonly experienced in HIV disease. Characterizing the overall symptom experience in HIV disease in terms of prevalence and the underlying influence of inflammation caused by immune activation in response to microbial translocation would support clinical trials to develop new treatment strategies.

We have addressed the relationship between symptoms of inflammation and microbial translocation in PLWH. As symptom burden has been associated with poor adherence to HIV medications, a possible target to improving symptoms may be to reduce symptom burden. If there is an association between symptom burden and microbial translocation, the reduction of microbial translocation may support adherence strategies. In addition, reducing inflammation of the epithelial barrier may reduce GI symptoms and microbial translocation, as seen in the IBD/IBS disease model with probiotic use (Wilson et al., 2013).

There are many challenges to symptom research, including numerous confounders and the subjective nature of the symptom experience. Strategies targeting microbial translocation may become an objective supplement to measure improvement of outcomes with symptom management. Given the complexity of symptoms in HIV disease, an interdisciplinary approach from the perspectives of nursing, medicine, nutrition, clinical, and scientific communities would support a more holistic patient-centered model to symptom management. Adjunct treatment strategies designed to heal and reduce inflammation of the epithelial barrier have the potential to reduce the symptom experience, thereby improving adherence. New treatment strategies may also slow disease progression by reducing microbial translocation, one of the key predictors of HIV-associated morbidity and mortality.

Key Considerations

- Nurses need to have a working understanding of the key drivers of disease progression, such as microbial translocation, to support patient understanding of the HIV disease process.
- Symptoms should be regarded as important and addressed by providers in HIV disease.
- Nurses have the opportunity to educate patients about discussing symptoms with their providers and not assuming the symptoms are directly related to HIV medications.
- Nurses should educate patients on interventions to reduce inflammation.
- Symptom management research should begin to target microbial translocation.
- Nurses are in a critical position to make symptom management recommendations.

Disclosures

The authors report no real or perceived vested interests that relate to this article that could be construed as a conflict of interest.

Acknowledgments

Dr. Wilson is a fellow in the VA National Quality Scholars program. The Department of Veterans Affairs Quality Scholars Fellowship (VAQS) is funded by the Department of Veterans Affairs Office of

Academic Affiliations (OAA). The opinions expressed in this article are those of the authors alone and do not reflect the views of the Department of Veterans Affairs. Dr. Wilson also wishes to thank Laura Graham and Patricia Patrician for their technical assistance in the development and production of this manuscript.

References

Ancuta, P., Kamat, A., Kunstman, K. J., Kim, E. Y., Autissier, P., Wurcel, A., … Gabuzda, D. (2008). Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. *PLoS One*, *3*(6), e2516. http://dx.doi.org/10.1371/journal.pone.0002516

Antoni, L., Nuding, S., Wehkamp, J., & Stange, E. F. (2014). Intestinal barrier in inflammatory bowel disease. *World Journal of Gastroenterology*, *20*(5), 1165-1179. http://dx.doi.org/10.3748/wjg.v20.i5.1165

Baroncelli, S., Galluzzo, C. M., Pirillo, M. F., Mancini, M. G., Weimer, L. E., Andreotti, M., … Palmisano, L. (2009). Microbial translocation is associated with residual viral replication in HAART-treated HIV+ subjects with <50 copies/ml HIV-1 RNA. *Journal of Clinical Virology*, *46*(4), 367-370. http://dx.doi.org/10.1016/j.jcv.2009.09.011

Berkes, J., Viswanathan, V. K., Savkovic, S. D., & Hecht, G. (2003). Intestinal epithelial responses to enteric pathogens: Effects on the tight junction barrier, ion transport, and inflammation. *Gut*, *52*(3), 439-451.

Brenchley, J. M., & Douek, D. C. (2008). The mucosal barrier and immune activation in HIV pathogenesis. *Current Opinion in HIV and AIDS*, *3*(3), 356-361. http://dx.doi.org/10.1097/COH.0b013e3282f9ae9c

Brenchley, J. M., Paiardini, M., Knox, K. S., Asher, A. I., Cervasi, B., Asher, T. E., … Douek, D. C. (2008). Differential Th17 CD4 T-cell depletion in pathogenic and nonpathogenic lentiviral infections. *Blood*, *112*(7), 2826-2835. http://dx.doi.org/10.1182/blood-2008-05-159301

Brenchley, J. M., Price, D. A., Schacker, T. W., Asher, T. E., Silvestri, G., Rao, S., … Douek, D. C. (2006). Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nature Medicine*, *12*(12), 1365-1371. http://dx.doi.org/10.1038/nm1511

Camacho, A. (2013). Is anxious-depression an inflammatory state? *Medical Hypotheses*, *81*(4), 577-581. http://dx.doi.org/10.1016/j.mehy.2013.07.006

Cassol, E., Rossouw, T., Seebregts, C., & Cassol, S. (2011). Microbial translocation: A marker of advanced HIV-1 infection and a predictor of treatment failure? *Journal of Infectious Diseases*, *203*(5), 747-748. http://dx.doi.org/10.1093/infdis/jiq109

Chun, T. W., Nickle, D. C., Justement, J. S., Meyers, J. H., Roby, G., Hallahan, C. W., … Fauci, A. S. (2008). Persistence of HIV in gut-associated lymphoid tissue despite long-term antiretroviral therapy. *Journal of Infectious Diseases*, *197*(5), 714-720. http://dx.doi.org/10.1086/527324

Cleeland, C. S., & Reyes-Gibby, C. C. (2002). When is it justified to treat symptoms? Measuring symptom burden. *Oncology*, *16*(9 Suppl. 10), 64-70.

Deeks, S. G. (2011). HIV infection, inflammation, immunosenescence, and aging. *Annual Review in Medicine*, *62*, 141-155. http://dx.doi.org/10.1146/annurev-med-042909-093756

Dodd, M., Janson, S., Facione, N., Faucett, J., Froelicher, E. S., Humphreys, J., … Taylor, D. (2001). Advancing the science of symptom management. *Journal of Nursing Scholarship*, *33*(5), 668-676.

Duprez, D. A., Neuhaus, J., Kuller, L. H., Tracy, R., Belloso, W., De Wit, S., … Neaton, J. D. (2012). Inflammation, coagulation and cardiovascular disease in HIV-infected individuals. *PLoS One*, *7*(9), e44454. http://dx.doi.org/10.1371/journal.pone.0044454

Edelman, E. J., Gordon, K., & Justice, A. C. (2011). Patient and provider-reported symptoms in the post-cART era. *AIDS and Behavior*, *15*(4), 853-861. http://dx.doi.org/10.1007/s10461-010-9706-z

El-Sadr, W. M., Lundgren, J. D., Neaton, J. D., Gordin, F., Abrams, D., Arduino, R. C., … Rappoport, C. (2006). CD4+ count-guided interruption of antiretroviral treatment. *New England Journal of Medicine*, *355*(22), 2283-2296. http://dx.doi.org/10.1056/NEJMoa062360

Epple, H. J., & Zeitz, M. (2012). HIV infection and the intestinal mucosal barrier. *Annals of the New York Academy of Sciences*, *1258*, 19-24. http://dx.doi.org/10.1111/j.1749-6632.2012.06512.x

Eriguchi, Y., Takashima, S., Oka, H., Shimoji, S., Nakamura, K., Uryu, H., … Teshima, T. (2012). Graft-versus-host disease disrupts intestinal microbial ecology by inhibiting Paneth cell production of alpha-defensins. *Blood*, *120*(1), 223-231. http://dx.doi.org/10.1182/blood-2011-12-401166

Eriksson, P., Andersson, C., Ekerfelt, C., Ernerudh, J., & Skogh, T. (2004). Sjogren's syndrome with myalgia is associated with subnormal secretion of cytokines by peripheral blood mononuclear cells. *Journal of Rheumatology*, *31*(4), 729-735.

Erlandson, K. M., Allshouse, A. A., Jankowski, C. M., Lee, E. J., Rufner, K. M., Palmer, B. E., … Campbell, T. B. (2013). Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. *Journal of Infectious Diseases*, *208*(2), 249-259. http://dx.doi.org/10.1093/infdis/jit147

Estes, J. D., Harris, L. D., Klatt, N. R., Tabb, B., Pittaluga, S., Paiardini, M., … Brenchley, J. M. (2010). Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathogens*, *6*(8), e1001052. http://dx.doi.org/10.1371/journal.ppat.1001052

Gay, C., Portillo, C. J., Kelly, R., Coggins, T., Davis, H., Aouizerat, B. E., … Lee, K. A. (2011). Self-reported

medication adherence and symptom experience in adults with HIV. *Journal of the Association of Nurses in AIDS Care*, *22*(4), 257-268. http://dx.doi.org/10.1016/j.jana.2010.11.004

Grandner, M. A., Sands-Lincoln, M. R., Pak, V. M., & Garland, S. N. (2013). Sleep duration, cardiovascular disease, and proinflammatory biomarkers. *Nature and Science of Sleep*, *5*, 93-107. http://dx.doi.org/10.2147/NSS.S31063

Harezlak, J., Buchthal, S., Taylor, M., Schifitto, G., Zhong, J., Daar, E., … Navia, B. (2011). Persistence of HIV-associated cognitive impairment, inflammation, and neuronal injury in era of highly active antiretroviral treatment. *AIDS*, *25*(5), 625-633. http://dx.doi.org/10.1097/QAD.0b013e3283427da7

Hattab, S., Guihot, A., Guiguet, M., Fourati, S., Carcelain, G., Caby, F., … Katlama, C. (2014). Comparative impact of antiretroviral drugs on markers of inflammation and immune activation during the first two years of effective therapy for HIV-1 infection: An observational study. *BMC Infectious Diseases*, *14*, 122. http://dx.doi.org/10.1186/1471-2334-14-122

Holtzclaw, B. J. (2013). Managing fever and febrile symptoms in HIV: Evidence-based approaches. *Journal of the Association of Nurses in AIDS Care*, *24*(1 Suppl), S86-S102. http://dx.doi.org/10.1016/j.jana.2012.07.002

Johnson, M. O., Stallworth, T., & Neilands, T. B. (2003). The drugs or the disease? Causal attributions of symptoms held by HIV-positive adults on HAART. *AIDS and Behavior*, *7*(2), 109-117. http://dx.doi.org/10.1023/A:1023938023005

Justice, A. C., Chang, C. H., Rabeneck, L., & Zackin, R. (2001). Clinical importance of provider-reported HIV symptoms compared with patient-report. *Medical Care*, *39*(4), 397-408.

Kamat, A., Lyons, J. L., Misra, V., Uno, H., Morgello, S., Singer, E. J., & Gabuzda, D. (2012). Monocyte activation markers in cerebrospinal fluid associated with impaired neurocognitive testing in advanced HIV infection. *Journal of Acquired Immune Deficiency Syndromes*, *60*(3), 234-243. http://dx.doi.org/10.1097/QAI.0b013e318256f3bc

Kamat, A., Misra, V., Cassol, E., Ancuta, P., Yan, Z., Li, C., … Gabuzda, D. (2012). A plasma biomarker signature of immune activation in HIV patients on antiretroviral therapy. *PLoS One*, *7*(2), e30881. http://dx.doi.org/10.1371/journal.pone.0030881

Katlama, C., Haubrich, R., Lalezari, J., Lazzarin, A., Madruga, J. V., Molina, J. M., … DeSmedt, G. (2009). Efficacy and safety of etravirine in treatment-experienced, HIV-1 patients: Pooled 48 week analysis of two randomized, controlled trials. *AIDS*, *23*(17), 2289-2300. http://dx.doi.org/10.1097/QAD.0b013e3283316a5e

Kelesidis, T., Kendall, M. A., Yang, O. O., Hodis, H. N., & Currier, J. S. (2012). Biomarkers of microbial translocation and macrophage activation: Association with progression of subclinical atherosclerosis in HIV-1 infection. *Journal of Infectious Diseases*, *206*(10), 1558-1567. http://dx.doi.org/10.1093/infdis/jis545

Kitchens, R. L., & Thompson, P. A. (2005). Modulatory effects of sCD14 and LBP on LPS-host cell interactions. *Journal of Endotoxin Research*, *11*(4), 225-229. http://dx.doi.org/10.1179/096805105X46565

Klatt, N. R., & Brenchley, J. M. (2010). Th17 cell dynamics in HIV infection. *Current Opinion in HIV and AIDS*, *5*(2), 135-140. http://dx.doi.org/10.1097/COH.0b013e3283364846

Klatt, N. R., Canary, L. A., Sun, X., Vinton, C. L., Funderburg, N. T., Morcock, D. R., … Brenchley, J. M. (2013). Probiotic/prebiotic supplementation of antiretrovirals improves gastrointestinal immunity in SIV-infected macaques. *The Journal of Clinical Investigation*, *123*(2), 903-907. http://dx.doi.org/10.1172/JCI66227

Klatt, N. R., Chomont, N., Douek, D. C., & Deeks, S. G. (2013). Immune activation and HIV persistence: implications for curative approaches to HIV infection. *Immunological Reviews*, *254*(1), 326-342. http://dx.doi.org/10.1111/imr.12065

Klatt, N. R., Harris, L. D., Vinton, C. L., Sung, H., Briant, J. A., Tabb, B., … Brenchley, J. M. (2010). Compromised gastrointestinal integrity in pigtail macaques is associated with increased microbial translocation, immune activation, and IL-17 production in the absence of SIV infection. *Mucosal Immunology*, *3*(4), 387-398. http://dx.doi.org/10.1038/mi.2010.14

Klimas, N. G., Broderick, G., & Fletcher, M. A. (2012). Biomarkers for chronic fatigue. *Brain, Behavior, and Immunity*, *26*(8), 1202-1210. http://dx.doi.org/10.1016/j.bbi.2012.06.006

Koethe, J. R., Dee, K., Bian, A., Shintani, A., Turner, M., Bebawy, S., … Hulgan, T. (2013). Circulating interleukin-6, soluble CD14, and other inflammation biomarker levels differ between obese and nonobese HIV-infected adults on antiretroviral therapy. *AIDS Research and Human Retroviruses*, *29*(7), 1019-1025. http://dx.doi.org/10.1089/AID.2013.0016

Lennox, J. L., DeJesus, E., Lazzarin, A., Pollard, R. B., Madruga, J. V., Berger, D. S., … Sklar, P. (2009). Safety and efficacy of raltegravir-based versus efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: A multicentre, double-blind randomised controlled trial. *Lancet*, *374*(9692), 796-806. http://dx.doi.org/10.1016/S0140-6736(09)60918-1

Liebregts, T., Adam, B., Bredack, C., Roth, A., Heinzel, S., Lester, S., … Holtmann, G. (2007). Immune activation in patients with irritable bowel syndrome. *Gastroenterology*, *132*(3), 913-920. http://dx.doi.org/10.1053/j.gastro.2007.01.046

Madruga, J. R., Berger, D., McMurchie, M., Suter, F., Banhegyi, D., Ruxrungtham, K., … Spinoza-Guzman, S. (2007). Efficacy and safety of darunavir-ritonavir compared with that of lopinavir-ritonavir at 48 weeks in treatment-experienced, HIV-infected patients in TITAN: A randomised controlled phase III trial. *Lancet*, *370*(9581), 49-58. http://dx.doi.org/10.1016/S0140-6736(07)61049-6

Marchetti, G., Cozzi-Lepri, A., Merlini, E., Bellistri, G. M., Castagna, A., Galli, M., … Monforte, A. D. (2011). Microbial translocation predicts disease progression of HIV-infected antiretroviral-naive patients with high CD4+ cell count.

AIDS, *25*(11), 1385-1394. http://dx.doi.org/10.1097/QAD.0b013e3283471d10

Marks, M. A., Rabkin, C. S., Engels, E. A., Busch, E., Kopp, W., Rager, H., … Chaturvedi, A. K. (2013). Markers of microbial translocation and risk of AIDS-related lymphoma. *AIDS*, *27*(3), 469-474. http://dx.doi.org/10.1097/QAD.0b013e32835c1333

McGuckin, M. A., Eri, R., Simms, L. A., Florin, T. H., & Radford-Smith, G. (2009). Intestinal barrier dysfunction in inflammatory bowel diseases. *Inflammatory Bowel Diseases*, *15*(1), 100-113. http://dx.doi.org/10.1002/ibd.20539

Mehandru, S., Poles, M. A., Tenner-Racz, K., Jean-Pierre, P., Manuelli, V., Lopez, P., … Markowitz, M. (2006). Lack of mucosal immune reconstitution during prolonged treatment of acute and early HIV-1 infection. *PLoS Medicine*, *3*(12), 2335-2348. http://dx.doi.org/10.1371/journal.pmed.0030484.t003

Mold, J. W., Holtzclaw, B. J., & McCarthy, L. (2012). Night sweats: A systematic review of the literature. *Journal of the American Board of Family Medicine*, *25*(6), 878-893. http://dx.doi.org/10.3122/jabfm.2012.06.120033

Nazli, A., Chan, O., Dobson-Belaire, W. N., Ouellet, M., Tremblay, M. J., Gray-Owen, S. D., … Kaushic, C. (2010). Exposure to HIV-1 directly impairs mucosal epithelial barrier integrity allowing microbial translocation. *PLoS Pathogens*, *6*(4), e1000852. http://dx.doi.org/10.1371/journal.ppat.1000852

Nixon, D. E., & Landay, A. L. (2010). Biomarkers of immune dysfunction in HIV. *Current Opinion in HIV/AIDS*, *5*(6), 498-503. http://dx.doi.org/10.1097/COH.0b013e32833ed6f4

Pandrea, I., Apetrei, C., Gordon, S., Barbercheck, J., Dufour, J., Bohm, R., … Silvestri, G. (2007). Paucity of CD4+CCR5+ T cells is a typical feature of natural SIV hosts. *Blood*, *109*(3), 1069-1076. http://dx.doi.org/10.1182/blood-2006-05-024364

Pedersen, K. K., Pedersen, M., Troseid, M., Gaardbo, J. C., Lund, T. T., Thomsen, C., … Nielsen, S. D. (2013). Microbial translocation in HIV infection is Associated with dyslipidemia, insulin resistance, and risk of myocardial infarction. *Journal of Acquired Immune Deficiency Syndromes*, *64*(5), 425-433. http://dx.doi.org/10.1097/QAI.0b013e31829f919d

Reus, S., Portilla, J., Sánchez-Payá, J., Giner, L., Francés, R., Such, J., … Gimeno, A. (2013). Low-level HIV viremia is associated with microbial translocation and inflammation. *Journal of Acquired Immune Deficiency Syndromes*, *62*(2), 129-134. http://dx.doi.org/10.1097/QAI.0b013e3182745ab0

Rodger, A. J., Fox, Z., Lundgren, J. D., Kuller, L. H., Boesecke, C., Gey, D., … Phillips, A. N. (2009). Activation and coagulation biomarkers are independent predictors of the development of opportunistic disease in patients with HIV infection. *Journal of Infectious Diseases*, *200*(6), 973-983. http://dx.doi.org/10.1086/605447

Ruffin, N., Thang, P. H., Rethi, B., Nilsson, A., & Chiodi, F. (2012). The impact of inflammation and immune activation on B cell differentiation during HIV-1 infection. *Frontiers in Immunology*, *2*, 90. http://dx.doi.org/10.3389/fimmu.2011.00090 eCollection 2011.

Said, E. A., Dupuy, F. P., Trautmann, L., Zhang, Y., Shi, Y., El-Far, M., … Sekaly, R. P. (2010). Programmed death-1-induced interleukin-10 production by monocytes impairs CD4+ T cell activation during HIV infection. *Nature Medicine*, *16*(4), 452-459. http://dx.doi.org/10.1038/nm.2106

Sandler, N. G., Wand, H., Roque, A., Law, M., Nason, M. C., Nixon, D. E., … Douek, D. C. (2011). Plasma levels of soluble CD14 independently predict mortality in HIV infection. *Journal of Infectious Diseases*, *203*(6), 780-790. http://dx.doi.org/10.1093/infdis/jiq118

Sista, F., Schietroma, M., Santis, G. D., Mattei, A., Cecilia, E. M., Piccione, F., … Amicucci, G. (2013). Systemic inflammation and immune response after laparotomy vs laparoscopy in patients with acute cholecystitis, complicated by peritonitis. *World Journal of Gastrointestinal Surgery*, *5*(4), 73-82. http://dx.doi.org/10.4240/wjgs.v5.i4.73

Spiller, R. C. (2009). Overlap between irritable bowel syndrome and inflammatory bowel disease. *Digestive Diseases*, *27*(Suppl. 1), 48-54. http://dx.doi.org/10.1159/000268121

Stehle, J. R., Jr., Leng, X., Kitzman, D. W., Nicklas, B. J., Kritchevsky, S. B., & High, K. P. (2012). Lipopolysaccharide-binding protein, a surrogate marker of microbial translocation, is associated with physical function in healthy older adults. *The Journals of Gerontology. Series A: Biological Sciences and Medical Sciences*, *67*(11), 1212-1218. http://dx.doi.org/10.1093/gerona/gls178

Stein, T. P., Koerner, B., Schluter, M. D., Leskiw, M. J., Gaprindachvilli, T., Richards, E. W., … Condolucci, D. (1997). Weight loss, the gut and the inflammatory response in AIDS patients. *Cytokine*, *9*(2), 143-147. http://dx.doi.org/10.1006/cyto.1996.0148

Vance, D. E., McDougall, G. J., Wilson, N. L., Debiasi, M. O., & Cody, S. L. (2014). Cognitive consequences of aging with HIV: Implications for neuroplasticity and rehabilitation. *Topics in Geriatric Rehabilitation*, *30*(1), 35-45. http://dx.doi.org/10.1097/TGR.0000000000000002

Verhoeven, D., Sankaran, S., Silvey, M., & Dandekar, S. (2008). Antiviral therapy during primary simian immunodeficiency virus infection fails to prevent acute loss of CD4+ T cells in gut mucosa but enhances their rapid restoration through central memory T cells. *Journal of Virology*, *82*(8), 4016-4027. http://dx.doi.org/10.1128/JVI.02164-07

Weaver, C. T., Elson, C. O., Fouser, L. A., & Kolls, J. K. (2013). The th17 pathway and inflammatory diseases of the intestines, lungs, and skin. *Annual Review of Pathology*, *8*, 477-512. http://dx.doi.org/10.1146/annurev-pathol-011110-130318

. Wiest, R., & Garcia-Tsao, G. (2005). Bacterial translocation (BT) in cirrhosis. *Hepatology*, *41*(3), 422-433. http://dx.doi.org/10.1002/hep.20632

Wilson, N. L., Moneyham, L. D., & Alexandrov, A. W. (2013). A systematic review of probiotics as a potential intervention to restore gut health in HIV infection. *Journal of Association*

of Nurses in AIDS Care, *24*(2), 98-111. http://dx.doi.org/10.1016/j.jana.2012.04.004

Yim, H. C., Li, J. C., Lau, J. S., & Lau, A. S. (2009). HIV-1 Tat dysregulation of lipopolysaccharide-induced cytokine responses: Microbial interactions in HIV infection. *AIDS*, *23*(12), 1473-1484. http://dx.doi.org/10.1097/QAD.0b013e32832d7abe

Zheng, W., Ouyang, H., Zheng, X., Liu, S., Mata, M., Fink, D. J., & Hao, S. (2011). Glial TNFalpha in the spinal cord regulates neuropathic pain induced by HIV gp120 application in rats. *Molecular Pain*, *7*, 40. http://dx.doi.org/10.1186/1744-8069-7-40

Zheng, Y., Danilenko, D. M., Valdez, P., Kasman, I., Eastham-Anderson, J., Wu, J., & Ouyang, W. (2007). Interleukin-22, a T(H)17 cytokine, mediates IL-23-induced dermal inflammation and acanthosis. *Nature*, *445*(7128), 648-651. http://dx.doi.org/10.1038/nature05505