

Can We Control the Progression of HIV by Monitor Markers of Microbial Translocation?

Wen-jun Zhang, Zhi-hong Guo, Jia-feng Zhang, Jun Jiang and Xiao-hong Pan*

Department of HIV/AIDS & STD control and prevention, Zhejiang Provincial Center for Disease Control and Prevention, Hangzhou, 310051, P.R.China

*Corresponding author: Xiao-hong Pan, Zhejiang Provincial Center for Disease Control and Prevention

No.3399, Binsheng Road, Hangzhou, 310051, P.R.China, Fax: 86-057-87115190; Tel: 86-0571-87115190;

E-mail: Panxh2015_article@163.com

Received date: October 30, 2015, Accepted date: January 02, 2016, Published date: January 10, 2016

Copyright: © 2015 Zhang W, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

This review summarizes microbial translocation in HIV infection. Microbial translocation can be measured by bacterial products in plasma, such as LPS and bacterial DNA or RNA fragments, or indirectly by LBP, sCD14, EndoCAB, and anti-flagellin antibodies. In some study, these markers had contrary results. May be microbial translocation is not the sole driver of HIV progression. Several lines of research indicated that a major contributor to immune activation and disease progression during HIV infection was microbial translocation. Although successful treatment with ART increased GALT CD4⁺ T cells and suppresses HIV RNA, the numbers of these cells did not return to prior levels. There is a negative effect of mucosal immune dysfunction and microbial translocation on HIV disease progression in the presence of ART. The topic of microbial translocation and immune activation in HIV infection still is a research focus.

Keywords Microbial translocation; HIV-1; Immune activation; ART

Introduction

Human immunodeficiency virus (HIV) infection is a chronic illness characterized by progressive CD4⁺ T cell loss and immune system destroys. HIV infection is now controlled by anti-retroviral therapy (ART), resulting in reduced death from opportunistic infections. However, despite successful viral suppression, many HIV patients still have persistent immune activation [1,2].

In fact, the mechanism of immune activation in HIV infected patients is not fully understood in nowadays. Although their viral load is successfully suppressed by ART, some immune activation phenomenon appears at the same time. Several studies suggest that immune activation could be a consequence of gut-triggered systemic inflammation and microbial translocation [3]. Microbial translocation and chronic activation of the immune system are major driving forces of HIV disease progression [6]. It was found that the magnitude of HIV-associated chronic immune activation could predict disease progression [3-5]. Low levels of immune activation were observed in chronically infected natural hosts of simian immunodeficiency virus (SIV), who do not progress to diseases despite high levels of virus replication [6-8]. One study showed that early *in vivo* blockade of microbial translocation in SIV-infected pigtailed macaques would result in the control of chronic immune activation [9]. However, the relationship of microbial translocation, immune activation and HIV infection has not been completely understood. If we can control the extent of microbial translocation in HIV infected patients, it may be helpful for controlling the progression of HIV infection, especially in ART accepted patients.

Microbial translocation is caused by depletion of CD4⁺T cells in the gut mucosa and the gut's increased permeability; it is also observed in idiopathic CD4 lymphocytopenia [10]. Infection with HIV-1 leads to

the depletion of CD4⁺T cells in gut-associated lymphoid tissues (GALT), which is associated with the translocation of microbial products, such as lipopolysaccharide (LPS), across the mucosa of the gastrointestinal tract [11,12]. CD4⁺T cell depletion in GALT occurs within 4-6 weeks of primary HIV infection [13]. In gut, the expression of genes associated with inflammation increased but the expression of genes regulating epithelial barrier and digestive functions decreased [13]. Increased levels of LPS that occurred in patients with chronic progressive HIV infection decreased after 48 weeks of effective ART but this level did not normalize [11]. These increased levels of LPS are associated with persistent immune activation [11]. So study the phenomenon of microbial translocation in HIV infected patients will help to understand persistent immune activation with HIV.

In this review, we discuss microbial translocation markers, immune active and microbial translocation under ART. Some new results show in this paper and we want to illuminate these work in itself aspect.

Microbial translocation markers in HIV infection

The extent of microbial translocation can be assessed either directly through the measurement of bacterial products in plasma, such as LPS and bacterial DNA or RNA fragments, or indirectly by soluble CD14 (sCD14), LBP and EndoCAB [6]. In recent studies, plasma levels of intestinal fatty acid binding protein (IFABP), as a marker of enterocyte damage, have also been used to correlate intestinal impairment and microbial translocation [2,14,15].

sCD14 is secreted by monocytes, dendritic cells and hepatocytes; it binds both LPS and peptoglycan of Gram positive bacteria. sCD14 is a receptor molecule produced primarily by macrophages and hepatocytes as part of the innate immune response to LPS [16-18]. sCD14 functions as a co-factor along with LBP to mediate LPS recognition and response by Toll-like receptor 4 (TLR-4) [18]. So sCD14 is accepted as a marker of immune activation. LPS is a potent

immunogenic component of Gram-negative bacterial cell membranes, and the presence of LPS in the blood stream is a marker of the breakdown in gut-mucosal immune barrier [11,18,20]. Nevertheless, in fact each marker has limitations: sCD14 can be induced by different factors other than LPS in unsuppressed HIV-1 infection [21]; LPS is only present in Gram-negative bacteria and plasmas have to handle with care to prevent contamination. On the other hand, although 16S rDNA is present in both Gram-negative and Gram-positive bacteria, it has been technically hampered due to DNA contamination [4].

sCD14, EndoCab and LBP are measured in the plasma or serum by enzyme-linked immunosorbent assay (ELISA) in the majority of published studies [22]. In particular, sCD14 has been given the relatively easy standardization of its measurement between different laboratories [6]. It must be noted that sCD14 serves as a biomarker of monocyte activation [23], and although it correlates with LPS, it is not a direct and specific marker of microbial translocation per se. Conversely, the commercial *Limulus* amoebocyte lysate (LAL) assay allows for the quantitative determination of LPS in reference to known endotoxin concentrations and is therefore a direct measure of endotoxemia [6]. In a new study, Shive demonstrated that inflammatory cytokines can induce the release of sCD14 in peripheral blood mononuclear cell cultures from healthy donors. So sCD14 is a marker of monocyte activation, not restricted to activation by LPS [24]. An alternative method to assess microbial translocation is the detection and quantification of the universally conserved microbial 16S rRNA gene in plasma by PCR [25,26].

However, contradictory results have been published that link microbial translocation and HIV disease. Recent studies of microbial translocation have also reported consistent associations with sCD14, but inconsistent associations across LPS, LBP, and EndoCab [2,18]. This inconsistent associations across markers of microbial translocation suggested that markers of LPS bio reactivity as opposed to LPS exposure were perhaps more reliable measures for microbial translocation-related outcomes [2,18]. Redd et al. [27] demonstrated no correlation between LPS levels and counts of sCD14, a co-receptor in the recognition of bacterial LPS in systemic circulation. In another study, increased levels of LPS were associated with HIV infection in late stages [36,63]. These contrary findings indicate that microbial translocation is not the sole driver of HIV progression [28]. On the other hand, incongruence among these studies may also result from differences in experimental approaches in determining the levels of LPS and sCD14 [29]. These results told us the markers of microbial translocation in HIV-associated patients may have special situation.

Microbial translocation and immune active in HIV/SIV infection

HIV infection results in chronic immune activation, which is closely associated with progression to acquired immunodeficiency syndrome (AIDS) [30]. Several studies illustrate that a key contributor to immune activation and disease progression during HIV infection is microbial translocation [31-37]. During HIV infection and pathogenic SIV infection of non-human primates, several factors underlie microbial translocation, including injury of the epithelial barrier of the gastrointestinal tract and mucosal immune dysfunction [33,38,39].

In our previous study indicated that complex interactions occur between diverse types of enteroendocrine cells and various immune cells through paracrine mechanisms or via mechanisms dependent on cell-to-cell contact; such interactions might play key roles in

maintaining the gut mucosal barrier integrity of rhesus macaques [40]. Then our another new study revealed that acute simian/human immunodeficiency viruses (SHIV), and by extension HIV infection could affect the expression of gastrointestinal tract epithelial tight junction associated genes, probably through IL-17A and other immune alterations [41]. These two studies talked about integrity of the gut mucosal barrier, which had effect on microbial translocation. Then we will research the relationship between Th17 cell and microbial translocation in HIV-1 infected patients.

In recent years, several researches have focused on the hypothesis that translocation of gut microbe antigens across an injured intestinal epithelial barrier. This phenomenon plays an important role in the chronic immune activation. Brenchley et al. [11] first reported increased circulating LPS in both HIV-infected humans and SIV-infected rhesus macaques during chronic infection. More recently, clinical investigations [42,43] have confirmed that microbial translocation is also a major source of immune activation and may contribute to the rapid disease progression in HIV infected children [44]. But, in another study, Wittkop et al. illuminated that autoimmune response and microbial translocation were not associated with immune activation [45]. So, we should deeply understand the relationship between microbial translocation and immune activation in HIV.

Indeed, many of these investigations have demonstrated that the persistence in translocation was associated with chronic inflammation [46,47] and impaired reconstitution of intestinal CD4⁺T cells [31,48]. Interesting, investigations of nonhuman primates demonstrated that microbial translocation did not occur in nonpathogenic SIV infection of natural hosts such as sooty mangabeys and African green monkeys [6]. Moreno [4] reported the results from 18 elite controllers patients showing that there was a good correlation in the quantification of LPS, sCD14, and LBP levels, but not with bacterial 16S rDNA, and did not exist any significant association between these markers of microbial translocation and immune activation [49]. These findings imply that we should study microbial translocation through treatment naive HIV elite controllers in the future.

SIV infected natural hosts did not progress to AIDS despite high levels of virus replication, and did not have evidence of microbial translocation [3,50]. This may explain the lack of immune activation and disease progression in chronically SIV-infected natural hosts [11,51]. Furthermore, experimental administration of bacterial products in natural hosts induced immune activation [7]. These data supported a role of microbial translocation in immune activation and disease progression during progressive HIV/SIV infection [3]. Microbial translocation can induce immune activation in the absence of HIV or SIV infections. For example, in pigtail macaques, which have increased levels of damage to their gut intestinal tract even in the absence of SIV infection, microbial translocation into the lamina propria of the gut intestinal tract correlates with immune activation, both locally in mucosal tissues and systemically [52].

In nowadays, there are some contrary results in microbial translocation and immune active. So, we should do some research on the relationship between microbial translocation and immune active in HIV infected patients. At the meantime, studying the mechanism of microbial translocation with HIV also has importance.

Microbial translocation and ART

Although successful treatment with ART increased GALT CD4⁺ T cells, the numbers of these cells did not return to prior levels, even when viremia was completely suppressed [11,53]. In fact, advances in the administration of antiretroviral cocktails have dramatically increased the life expectancy of HIV infected patients in the past years [54]. However, reconstruction of GALT structure and function was markedly delayed [50,55]. Moreover, initiation of ART early in infection did not appear to promote significant maintenance of CD4⁺T cells in GALT [44,56]. Available data indicated that restoration of the intestinal mucosal barrier function was possible in patients on suppressive antiretroviral therapy despite persistence of structural and functional abnormalities of the mucosal immune system [57].

The role of microbial translocation in predicting disease progression in the absence of ART as well as the effects of ART have recently been investigated in several studies. For a cohort of HIV infected individuals from Rakai, Redd et al. failed to find significant associations between levels of sCD14, LPS, and endotoxin antibody and HIV disease progression [58]. A nested-control study from the strategies for management of anti-retroviral therapy (SMART) trial by Sandler et al. reported that plasma levels of sCD14 were independent predictors of overall mortality in HIV disease [2]. Gene expression studies showed that multiple biomarkers of mucosal growth remain repressed in GALT during chronic HIV infection despite suppressive therapy [59,60]. More recent evidence suggested that this residual immune dysregulation is most prevalent when ART fails to increase circulating CD4⁺T cells to normal levels [44,61]. Taken together, these data strongly suggest a negative effect of mucosal immune dysfunction and microbial translocation on HIV disease progression under ART.

Persistent immune activation has long been implicated as a factor impairing the immunological response to ART, the question as to whether microbial translocation might affect immune recovery after ART has been investigated by different study groups. Brenchley et al. observed an inverse correlation between CD4⁺T cell reconstitution and microbial translocation [11]. Marchetti revealed that increased plasma levels of LPS in immunological nonresponder (INR) ART-treated HIV-infected individuals compared to levels in subjects with full immunological recovery after ART [48]. Jiang et al. showed that higher levels of bacterial 16S rRNA genes were associated with greater T-cell activation and impaired CD4⁺T cell restoration after ART [12]. In one new study [47], HIV-infected patients with negative HIV viral load (<20 copies/ml) present less frequently microbial translocation and have lower levels of inflammation markers (tumor necrosis factor α and interleukin 6) than patients with low-level HIV viremias (20-200 copies/ml). Inflammation seems to be induced by microbial translocation and not by HIV viremia itself [47]. Toossi et al. supposed that circulating LPS levels in HIV/tuberculosis patients with CD4⁺T cell count $\geq 350/\mu\text{l}$ were unaffected by treatment of tuberculosis with or without ART and changes in circulating sCD14 and LPS are dependent on CD4⁺T cell count [62]. Likewise, successful ART has been associated with decreased levels of microbial products in the plasma, but again, there was failure to normalize to levels seen in HIV-seronegative persons [2,12]. Some studies reported decreased sCD14 levels while others demonstrated lower LPS levels among patients on ART; however, outcomes were not comparable to HIV uninfected individuals [6,63,64]. The possible mechanism by which ART decreased the translocation of microbes could be by partial restoration of Th17 cells and improved clearance of LPS [6,64,65]. ART has also helped in improving number of Kupffer cells, which has been shown to

contribute to intestinal healing [65,66]. Lozupone et al. [67] has shown that the microbiome of HIV infected patients with gastrointestinal inflammation presents a bacterial species profile that is distinct from that of other intestinal inflammatory diseases during ART. A recent study [68] of bacterial communities in the rectal mucosa of untreated and treated HIV-1 infected individuals revealed that dysbiosis was associated with elevated levels of tryptophan catabolism and increases in multiple biomarkers of inflammation and disease progression [44].

In this part, we will do further study on the changes microbial translocation in HIV-1 infected patients. And we would like to discuss the relationship between microbial translocation changes and with or without ART.

Conclusions

In conclusion, HIV infections characteristically cause damage to the gut mucosa, injury the epithelial barrier, compromising gut immunity, and exposing its host to a broad range of microbial bio products that have been implicated in the progression of HIV. Similarly, the gut micro biota is severely impacted and the altered bacterial communities play vital roles, directly or indirectly in HIV progression. ART alone does not may effectively control microbial translocation through the gastrointestinal tract. The contribution of gut microbes in HIV disease progression has been explored but conclusive knowledge is lacking. Therefore, an increased understanding of correlations between the proinflammatory bacteria composition and structure in the human gut and HIV infection status can contribute to an improved and holistic management of HIV progression.

Further investigation is needed to firmly establish microbial translocation as a cause of HIV progression. May be we can control the progression of HIV by monitor markers of microbial translocation. It will therefore be of interest to investigate any direct or indirect links of gut microbes and microbial products in other non-AIDS related disorders such as liver, cardiovascular, central nervous system, and cancer diseases among others.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgement

This study was supported by funds from the Health and Family Planning Commission of Zhejiang Province (grant nos: 2014KYB326).

References

1. Ostrowski SR, Piironen T, Hoyer-Hansen G, Gerstoft J, Pedersen BK, et al. (2005) High plasma levels of intact and cleaved soluble urokinase receptor reflect immune activation and are independent predictors of mortality in HIV-1-infected patients. *J Acquir Immune Defic Syndr* 39: 23-31
2. Sandler NG1, Wand H, Roque A, Law M, Nason MC, et al. (2011) Plasma levels of soluble CD14 independently predict mortality in HIV infection. *J Infect Dis* 203: 780-790.
3. Klatt NR, Funderburg NT, Brenchley JM (2013) Microbial translocation, immune activation, and HIV disease. *Trends Microbiol* 21: 6-13.
4. Abad-Fernandez M, Vallejo A, Hernandez-Novoa B, Diaz L, Gutierrez C, et al. (2013) Correlation between different methods to measure microbial translocation and its association with immune activation in long-term

- suppressed HIV-1-infected individuals. *J Acquir Immune Defic Syndr* 64: 149-153
5. Nasi M, Pinti M, Mussini C, Cossarizza A (2014) Persistent inflammation in HIV infection: established concepts, new perspectives. *Immunol Lett* 161: 184-188.
 6. Marchetti G, Tincati C, Silvestri G (2013) Microbial translocation in the pathogenesis of HIV infection and AIDS. *Clin Microbiol Rev* 26: 2-18.
 7. Pandrea I, Gaufin T, Brenchley JM, Gautam R, Monjure C, et al. (2008) Cutting edge: Experimentally induced immune activation in natural hosts of simian immunodeficiency virus induces significant increases in viral replication and CD4+ T cell depletion. *J Immunol* 181: 6687-6691.
 8. Silvestri G, Sodora DL, Koup RA, Paiardini M, O'Neil SP, et al. (2003) Nonpathogenic SIV infection of sooty mangabeys is characterized by limited bystander immunopathology despite chronic high-level viremia. *Immunity* 18: 441-452
 9. Kristoff J, Haret-Richter G, Ma D, Ribeiro RM, Xu C, et al. (2014) Early microbial translocation blockade reduces SIV-mediated inflammation and viral replication. *J Clin Invest* 124: 2802-2806.
 10. Lee PI, Ciccone EJ, Read SW, Asher A, Pitts R, et al. (2009) Evidence for translocation of microbial products in patients with idiopathic CD4 lymphocytopenia. *J Infect Dis* 199: 1664-1670
 11. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, et al. (2006) Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med* 12: 1365-1371.
 12. Jiang W, Lederman MM, Hunt P, Sieg SF, Haley K, et al. (2009) Plasma levels of bacterial DNA correlate with immune activation and the magnitude of immune restoration in persons with antiretroviral-treated HIV infection. *J Infect Dis* 199: 1177-1185
 13. Sankaran S, George MD, Reay E, Guadalupe M, Flamm J, et al. (2008) Rapid onset of intestinal epithelial barrier dysfunction in primary human immunodeficiency virus infection is driven by an imbalance between immune response and mucosal repair and regeneration. *J Virol* 82: 538-545.
 14. Santos-Oliveira JR, Regis EG, Giacoia-Gripp CB, Valverde JG, Alexandrino-de-Oliveira P, et al. (2013) Microbial translocation induces an intense proinflammatory response in patients with visceral leishmaniasis and HIV type 1 coinfection. *J Infect Dis* 208: 57-66
 15. Thumser AE, Moore JB, Plant NJ (2014) Fatty acid binding proteins: tissue-specific functions in health and disease. *Curr Opin Clin Nutr Metab Care* 17: 124-129
 16. Hailman E, Vasselon T, Kelley M, Busse LA, Hu MC, et al. (1996) Stimulation of macrophages and neutrophils by complexes of lipopolysaccharide and soluble CD14. *J Immunol* 156: 4384-4390.
 17. Landmann R, Knopf HP, Link S, Sansano S, Schumann R, et al. (1996) Human monocyte CD14 is upregulated by lipopolysaccharide. *Infect Immun* 64: 1762-1769.
 18. Marks MA, Rabkin CS, Engels EA, Busch E, Kopp W, et al. (2013) Markers of microbial translocation and risk of AIDS-related lymphoma. *AIDS* 27: 469-474.
 19. Meuleman P, Steyaert S, Libbrecht L, Couvent S, Van Houtte F, et al. (2006) Human hepatocytes secrete soluble CD14, a process not directly influenced by HBV and HCV infection. *Clin Chim Acta* 366: 156-162.
 20. Brenchley JM, Douek DC (2008) The mucosal barrier and immune activation in HIV pathogenesis. *Curr Opin HIV AIDS* 3: 356-361.
 21. Rempel H1, Sun B, Calosing C, Pillai SK, Pulliam L (2010) Interferon-alpha drives monocyte gene expression in chronic unsuppressed HIV-1 infection. *AIDS* 24: 1415-1423.
 22. Nixon DE, Landay AL (2010) Biomarkers of immune dysfunction in HIV. *Curr Opin HIV AIDS* 5: 498-503.
 23. Anderson KV (2000) Toll signaling pathways in the innate immune response. *Curr Opin Immunol* 12: 13-19.
 24. Shive CL, Jiang W, Anthony DD, Lederman MM (2015) Soluble CD14 is a nonspecific marker of monocyte activation. *AIDS* 29: 1263-1265
 25. Drancourt M, Bollet C, Carlouz A, Martelin R, Gayral JP, et al. (2000) 16S ribosomal DNA sequence analysis of a large collection of environmental and clinical unidentifiable bacterial isolates. *J Clin Microbiol* 38: 3623-3630
 26. Mutlu EA, Keshavarzian A, Losurdo J, Swanson G, Siewe B, et al. (2014) A compositional look at the human gastrointestinal microbiome and immune activation parameters in HIV infected subjects. *PLoS Pathog* 10: e1003829
 27. Redd AD, Eaton KP, Kong X, Laeyendecker O, Lutalo T, et al. (2010) C-reactive protein levels increase during HIV-1 disease progression in Rakai, Uganda, despite the absence of microbial translocation. *J Acquir Immune Defic Syndr* 54: 556-559
 28. Nwosu FC, Avershina E, Wilson R, Rudi K (2014) Gut Microbiota in HIV Infection: Implication for Disease Progression and Management. *Gastroenterol Res Pract* 2014: 803185
 29. Redd AD, Gray RH, Quinn TC (2011) Is microbial translocation a cause or consequence of HIV disease progression? *J Infect Dis* 203: 744-745.
 30. Salazar-Gonzalez JF, Martinez-Maza O, Nishanian P, Aziz N, Shen LP, et al. (1998) Increased immune activation precedes the inflection point of CD4 T cells and the increased serum virus load in human immunodeficiency virus infection. *J Infect Dis* 178: 423-430
 31. Ciccone EJ, Read SW, Mannon PJ, Yao MD, Hodge JN, et al. (2010) Cycling of gut mucosal CD4+ T cells decreases after prolonged antiretroviral therapy and is associated with plasma LPS levels. *Mucosal Immunol* 3: 172-181.
 32. d'Ettorre G, Paiardini M, Zaffiri L, Andreotti M, Ceccarelli G, et al. (2011) HIV persistence in the gut mucosa of HIV-infected subjects undergoing antiretroviral therapy correlates with immune activation and increased levels of LPS. *Curr HIV Res* 9: 148-153
 33. Estes JD, Harris LD, Klatt NR, Tabb B, Pittaluga S, et al. (2010) Damaged intestinal epithelial integrity linked to microbial translocation in pathogenic simian immunodeficiency virus infections. *PLoS Pathog* 6: e1001052
 34. Marchetti G, Cozzi-Lepri A, Merlini E, Bellistri GM, Castagna A, et al. (2011) Microbial translocation predicts disease progression of HIV-infected antiretroviral-naive patients with high CD4+ cell count. *AIDS* 25: 1385-1394
 35. Mavigner M, Cazabat M, Dubois M, L'Faqihi FE, Requena M, et al. (2012) Altered CD4+ T cell homing to the gut impairs mucosal immune reconstitution in treated HIV-infected individuals. *J Clin Invest* 122: 62-69.
 36. Nowroozalizadeh S, Månsson F, da Silva Z, Repits J, Dabo B, et al. (2010) Microbial translocation correlates with the severity of both HIV-1 and HIV-2 infections. *J Infect Dis* 201: 1150-1154.
 37. Wallet MA, Rodriguez CA, Yin L, Saporta S, Chinratanapit S, et al. (2010) Microbial translocation induces persistent macrophage activation unrelated to HIV-1 levels or T-cell activation following therapy. *AIDS* 24: 1281-1290.
 38. Nazli A, Chan O, Dobson-Belaire WN, Ouellet M, Tremblay MJ, et al. (2010) Exposure to HIV-1 directly impairs mucosal epithelial barrier integrity allowing microbial translocation. *PLoS Pathog* 6: e1000852.
 39. Wilson NL, Vance DE, Moneyham LD, Raper JL, Mugavero MJ, et al. (2014) Connecting the dots: could microbial translocation explain commonly reported symptoms in HIV disease?. *J Assoc Nurses AIDS Care* 25: 483-495
 40. Zhang WJ, Duan JZ, Lei N, Xing H, Shao Y, et al. (2012) Cellular bases for interactions between immunocytes and enteroendocrine cells in the intestinal mucosal barrier of rhesus macaques. *Cell Tissue Res* 350: 135-141.
 41. Zhang WJ, Wang Y, Yu K, Duan JZ, Yao WR, et al. (2014) Associated changes in the transcription levels of IL-17A and tight junction-associated genes in the duodenal mucosa of rhesus macaques repeatedly exposed to simian/human immunodeficiency virus. *Exp Mol Pathol* 97: 225-233.
 42. Fitzgerald F, Harris K, Doyle R, Alber D, Klein N (2013) Short communication: Evidence that microbial translocation occurs in HIV-infected children in the United Kingdom. *AIDS Res Hum Retroviruses* 29: 1589-1593.

43. Pilakka-Kanthikeel S, Kris A, Selvaraj A, Swaminathan S, Pahwa S (2014) Immune activation is associated with increased gut microbial translocation in treatment-naive, HIV-infected children in a resource-limited setting. *J Acquir Immune Defic Syndr* 66: 16-24
44. George MD, Asmuth DM (2014) Mucosal immunity in HIV infection: what can be done to restore gastrointestinal-associated lymphoid tissue function? *Curr Opin Infect Dis* 27: 275-281.
45. Wittkop L, Bitard J, Lazaro E, Neau D, Bonnet F, et al. (2013) Effect of cytomegalovirus-induced immune response, self antigen-induced immune response, and microbial translocation on chronic immune activation in successfully treated HIV type 1-infected patients: the ANRS CO3 Aquitaine Cohort. *J Infect Dis* 207: 622-627
46. Erlandson KM, Allshouse AA, Jankowski CM, Lee EJ, Rufner KM, et al. (2013) Association of functional impairment with inflammation and immune activation in HIV type 1-infected adults receiving effective antiretroviral therapy. *J Infect Dis* 208: 249-259.
47. Reus S, Portilla J, Sánchez-Payá J, Giner L, Francés R, et al. (2013) Low-level HIV viremia is associated with microbial translocation and inflammation. *J Acquir Immune Defic Syndr* 62: 129-134.
48. Marchetti G, Bellistri GM, Borghi E, Tincati C, Ferramosca S, et al. (2008) Microbial translocation is associated with sustained failure in CD4+ T-cell reconstitution in HIV-infected patients on long-term highly active antiretroviral therapy. *AIDS* 22: 2035-2038
49. Novati S, Sacchi P, Cima S, Zuccaro V, Columpsi P, et al. (2015) General issues on microbial translocation in HIV-infected patients. *Eur Rev Med Pharmacol Sci* 19: 866-878.
50. Meng J, Sindberg GM, Roy S (2015) Disruption of gut homeostasis by opioids accelerates HIV disease progression. *Front Microbiol* 6: 643.
51. Paiardini M, Pandrea I, Apetrei C, Silvestri G (2009) Lessons learned from the natural hosts of HIV-related viruses. *Annu Rev Med* 60:485-495
52. Klatt NR, Harris LD, Vinton CL, Sung H, Briant JA, et al. (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 Immunol* 3: 387-398
53. Guadalupe M, Reay E, Sankaran S, Prindiville T, Flamm J, et al. (2003) Severe CD4+ T-cell depletion in gut lymphoid tissue during primary human immunodeficiency virus type 1 infection and substantial delay in restoration following highly active antiretroviral therapy. *J Virol* 77: 11708-11717
54. Palella FJ Jr, Baker RK, Moorman AC, Chmiel JS, Wood KC, et al. (2006) Mortality in the highly active antiretroviral therapy era: changing causes of death and disease in the HIV outpatient study. *J Acquir Immune Defic Syndr* 43: 27-34.
55. Hayes TL, Asmuth DM, Critchfield JW, Knight TH, McLaughlin BE, et al. (2013) Impact of highly active antiretroviral therapy initiation on CD4(+) T-cell repopulation in duodenal and rectal mucosa. *AIDS* 27: 867-877.
56. Karris MY1, Kao YT, Patel D, Dawson M, Woods SP, et al. (2014) Predictors of virologic response in persons who start antiretroviral therapy during recent HIV infection. *AIDS* 28: 841-849.
57. Epple HJ, Zeitz M (2012) HIV infection and the intestinal mucosal barrier. *Ann N Y Acad Sci* 1258:19-24
58. Redd AD1, Dabitao D, Bream JH, Charvat B, Laeyendecker O, et al. (2009) Microbial translocation, the innate cytokine response, and HIV-1 disease progression in Africa. *Proc Natl Acad Sci U S A* 106: 6718-6723.
59. Guadalupe M, Sankaran S, George MD, Reay E, Verhoeven D, et al. (2006) Viral suppression and immune restoration in the gastrointestinal mucosa of human immunodeficiency virus type 1-infected patients initiating therapy during primary or chronic infection. *J Virol* 80: 8236-8247.
60. Sankaran S, Guadalupe M, Reay E, George MD, Flamm J, et al. (2005) Gut mucosal T cell responses and gene expression correlate with protection against disease in long-term HIV-1-infected nonprogressors. *Proc Natl Acad Sci U S A* 102: 9860-9865.
61. Lederman MM, Funderburg NT, Sekaly RP, Klatt NR, Hunt PW (2013) Residual immune dysregulation syndrome in treated HIV infection. *Adv Immunol* 119: 51-83.
62. Toossi Z, Funderburg NT, Sirdeshmuk S, Whalen CC, Nanteza MW, et al. (2013) Systemic immune activation and microbial translocation in dual HIV/tuberculosis-infected subjects. *J Infect Dis* 207: 1841-1849.
63. Cassol E, Malfeld S, Mahasha P, van der Merwe S, Cassol S, et al. (2010) Persistent microbial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. *J Infect Dis* 202: 723-733
64. Pappasavvas E, Azzoni L, Foulkes A, Violari A, Cotton MF, et al. (2011) Increased microbial translocation in \leq 180 days old perinatally human immunodeficiency virus-positive infants as compared with human immunodeficiency virus-exposed uninfected infants of similar age. *Pediatr Infect Dis J* 30: 877-882.
65. Balagopal A, Ray SC, De Oca RM, Sutcliffe CG, Vivekanandan P, et al. (2009) Kupffer cells are depleted with HIV immunodeficiency and partially recovered with antiretroviral immune reconstitution. *AIDS* 23: 2397-2404.
66. Sinha B, Rubens M (2014) Systemic immune activation in HIV and potential therapeutic options. *Immunopharmacol Immunotoxicol* 36: 89-95
67. Lozupone CA, Li M, Campbell TB, Flores SC, Linderman D, et al. (2013) Alterations in the gut microbiota associated with HIV-1 infection. *Cell Host Microbe* 14: 329-339.
68. Vujkovic-Cvijin I, Dunham RM, Iwai S, Maher MC, Albright RG, et al. (2013) Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. *Sci Transl Med* 5: 193ra91.