Correspondence

Is Microbial Translocation a Cause or Consequence of HIV Disease Progression?

To the Editor—Two recent articles in the *Journal of Infectious Diseases* described associations between increased levels of microbial translocation as measured by plasma levels of lipopolysaccharide (LPS) and late-stage human immunodeficiency virus (HIV) disease in South Africa [1] and Guinea-Bissau [2]. These cross-sectional studies are seemingly in disagreement with a longitudinal analysis using data from Rakai, Uganda, which found no association between microbial translocation and subsequent HIV-1 disease progression [3, 4]. This apparent discrepancy in the role of microbial translocation in HIV disease has also been observed in other cross-sectional [5–8] and longitudinal human studies [9, 10]. Even in animal models, it was recently shown that LPS levels are not predictive of simian immunodeficiency virus (SIV) disease progression in rhesus macaques [11], although elevated LPS levels prior to SIV infection appear to contribute to the faster disease progression in pigtailed macaques [12]. These discrepancies are primarily due to the fact that, as the 2 groups state, one cannot infer causality from cross-sectional studies; therefore, it is impossible to determine whether the elevation of LPS levels in AIDS is a cause or a consequence of disease progression.

In the Nowroozalizadeh et al [2] report, investigators found differences in microbial translocation only when comparing HIV-negative individuals with patients with AIDS, but not in chronically infected individuals, whether infected with HIV-1 or HIV-2. Additionally, the investigators did not observe a difference in LPS levels between HIV-1 and HIV-2 at either stage of disease. This is somewhat surprising since HIV-1 and HIV-2 differ dramatically in their rates of disease progression.

It was proposed that microbial translocation affects HIV disease progression in part by LPS activation of monocytes, leading to increased production of soluble CD14 (sCD14) [6, 7]. Cassol et al [1] found a significant positive correlation between LPS and sCD14 levels in patients with AIDS who did not have opportunistic infections, but they found a negative correlation between LPS and sCD14 levels in individuals with an opportunistic infection, even though the levels of sCD14 were similar between the 2 groups. It was speculated by the investigators that "[t]his observation suggests that, in untreated patients, the increase in sCD14 was driven predominantly by microbial translocation" [1]. However, a recent study by Rempel et al [13] demonstrated that monocytes from HIV-1-infected individuals with high viral loads are not activated by LPS. Moreover, in our longitudinal study we found no association between disease progression rates and sCD14 levels [3]. This suggests that the increased levels of sCD14 seen in late-stage HIV disease are not directly caused by microbial translocation.

The cross-sectional data from Africa [1, 2, 8], as well as North America and Europe [5–7], demonstrate that there is most likely an association between low levels of microbial translocation and advanced HIV disease, and this has led to the inference that "microbial translocation contributes to immune activation and disease progression during chronic HIV-1 infection" [1]. However, this proposed causal relationship between microbial translocation and HIV-1 disease progression has never been directly demonstrated. In addition, in longitudinal studies, which can address causality, LPS levels did not significantly contribute to HIV-1 disease progression even in the presence of immune activation [3, 4, 10]. Therefore, a direct causal relationship between microbial translocation and HIV disease progression is unlikely.

Alternatively, we propose that increased microbial translocation and LPS levels are a consequence of advanced HIV-1 disease and AIDS. This model is supported by both the cross-sectional and longitudinal data, and may explain why there were no differences in LPS levels between HIV-1 and HIV-2, despite well-established differences in rates of disease progression [2]. Moreover, a consequential relationship is also supported by the finding that LPS levels in HIV-infected individuals successfully treated with antiretrovirals for >5 years are similar to those found in HIV-uninfected individuals [14].

Determining the role of microbial translocation in HIV disease progression is important as it may have a significant impact on future clinical care in a variety of settings. To resolve this issue, we propose these additional studies that should help clarify this matter: (1) examine more longitudinal cohorts for the relationship between disease progression, microbial translocation, antibacterial immune responses, and immune activation; (2) design and test better assays to quantify bacterial products in the bloodstream, as highlighted by Ferri et al [15]; (3) determine the biological relevance of low-level microbial translocation in the absence of HIV;

(4) explore the possible clinical benefit of treating low-level microbial translocation directly [7]; and (5) examine if earlier initiation of antiretroviral treatment can minimize this effect and by doing so improve clinical outcomes.

Funding

This work was supported by the Division of Intramural Research, National Institute of Allergies and Infectious Diseases, National Institute of Health (A.D.R. and T.C.Q.).

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References

1. Cassol E, Malfeld S, Mahasha P, et al. Persistent microbial translocation and immune activation in HIV-1-infected South Africans receiving combination antiretroviral therapy. J Infect Dis **2010**; 202:723–33.
2. Nowroozalizadeh S, Mansson F, da Silva Z, et al. Microbial translocation correlates with the severity of both HIV-1 and HIV-2 infections. J Infect Dis **2010**; 201:1150–4.
3. Redd AD, Dabitao D, Bream JH, et al. Microbial translocation, the innate cytokine response, and HIV-1 disease progression in Africa. Proc Natl Acad Sci U S A **2009**; 106:6718–23.
4. Redd AD, Eaton KP, Kong X, et al. C-reactive protein levels increase during HIV-1 disease progression in Rakai, Uganda, despite the absence of microbial translocation. J Acquir Immune Defic Syndr **2010**; 54: 556–9.
5. Gori A, Tincati C, Rizzardini G, et al. Early impairment of gut function and gut flora supporting a role for alteration of gastrointestinal mucosa in human immunodeficiency virus pathogenesis. J Clin Microbiol **2008**; 46:757–8.
6. Brenchley JM, Price DA, Schacker TW, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. Nat Med **2006**; 12:1365–71.
7. Ancuta P, Kamat A, Kunstman KJ, et al. Microbial translocation is associated with increased monocyte activation and dementia in AIDS patients. PLoS ONE **2008**; 3:e2516.
8. Lester RT, Yao XD, Ball TB, et al. HIV-1 RNA dysregulates the natural TLR response to subclinical endotoxemia in Kenyan female sex-workers. PLoS One **2009**; 4:e5644.
9. Wallet MA, Rodriguez CA, Yin L, et al. Microbial translocation induces persistent macrophage activation unrelated to HIV-1 levels or T-cell activation following therapy. AIDS **2010**; 24:1281–90.
10. Papasavvas E, Pistilli M, Reynolds G, et al. Delayed loss of control of plasma lipopolysaccharide levels after therapy interruption in chronically HIV-1-infected patients. AIDS **2009**; 23:369–75.
11. Leinert C, Stahl-Hennig C, Ecker A, et al. Microbial translocation in simian immunodeficiency virus (SIV)-infected rhesus monkeys (Macaca mulatta). J Med Primatol **2010**; 39:243–51.
12. Klatt NR, Harris LD, Vinton CL, et al. 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 **2010**; 3:387–98.
13. Rempel H, Sun B, Calosing C, Pillai SK, Pulliam L, et al. Interferon-alpha drives monocyte gene expression in chronic unsuppressed HIV-1 infection. AIDS **2010**; 24: 1415–23.
14. Ciccone EJ, Read SW, Mannon PJ, et al. Cycling of gut mucosal CD4+ T cells decreases after prolonged anti-retroviral therapy and is associated with plasma LPS levels. Mucosal Immunol **2010**; 3:172–81.
15. Ferri E, Novati S, Casiraghi M, et al. Plasma levels of bacterial DNA in HIV infection: The limits of quantitative polymerase chain reaction. J Infect Dis **2010**; 202:176–7; author reply 178.

Received 24 August 2010; accepted 23 November 2010.
Potential conflicts of interest: none reported.
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The Journal of Infectious Diseases 2011;203:744–745
Published by Oxford University Press on behalf of the Infectious Diseases Society of America 2011.
1537-6613/2011/2035-0001$15.00
DOI: 10.1093/infdis/jiq107