Microbial Translocation: A Marker of Advanced HIV-1 Infection and a Predictor of Treatment Failure?

To the Editor—We agree that the issue of whether microbial translocation (MT) is a cause or consequence of human immunodeficiency virus type 1 (HIV-1) disease progression is an important question that can only be addressed through longitudinal analyses of natural history cohorts such as the study by Redd et al [1]. A timely and definitive answer to this question will depend on the availability of archived specimens that have been well characterized and properly stored. Specimen banks of this nature are relatively rare in Africa.

However, there are issues of equal importance, namely, whether microbiota-associated immune activation persists during highly active antiretroviral therapy (HAART) and whether this has an adverse effect on therapeutic outcome. There is already a growing body of evidence indicating that HAART-treated patients have elevated levels of bacterial DNA and plasma lipopolysaccharide (LPS) for at least 2 years after starting therapy [2], with one North American study showing decreased levels of LPS and CD4 T cell cycling after >5 years of maximally suppressive HAART [3]. There is also increasing evidence that elevated levels of LPS are associated with monocyte-macrophage activation and disease pathology, not only in HIV-1-infected patients with dementia [4] and hepatitis C–related liver disease [5], but also in HIV–1–negative patients with tuberculosis [6] and inflammatory bowel disease [7]. LPS has also been linked to T cell activation and proliferation [3], presumably via secretion of proinflammatory mediators by monocyte-macrophages.

However, as emphasized by Redd et al, MT does not account for all aspects of immune activation in patients with late-stage disease. We examined the relationship between plasma LPS, HIV-1 viral load, and immune activation, before and after 1 year of nucleoside reverse transcriptase inhibitor/non-nucleoside reverse transcriptase inhibitor-based antiretroviral therapy (ART), in Africans with advanced HIV-1 disease and CD4 counts <200 cells/μL [8]. We found that some aspects of monocyte activation (CCL2, CXCL10, the frequency of CD14+CD16+ monocytes) were associated with high levels of HIV-1 RNA, whereas others (tumor necrosis factor [TNF], soluble CD14 [sCD14]) were more closely linked to plasma concentrations of LPS or the presence of opportunistic co-infections (interleukin 6). In addition to being independent of HIV-1 replication, LPS-associated activation, as measured by sCD14 and TNF, was independent of T cell activation and was only partially curtailed after 1 year of successful ART.

These findings may help explain the results of Rempel et al [9]. Similar to our study, these investigators found that LPS and sCD14 remained elevated in HAART-treated patients. They also found that monocytes isolated from patients with high levels of residual viremia exhibited different patterns of gene expression after in vitro stimulation with LPS and interferon (IFN)–α. IFN–α activation resembled that observed in patients, while the LPS pattern differed from that normally induced following activation with whole bacteria (interleukin 10) or Fc/ complement receptor–mediated phagocytosis (interleukin 6, interleukin 1β), leading to the conclusion that these monocytes were not responsive to LPS. However, LPS induced the up-regulation of a large number of genes (n = 992), a finding that is consistent with the ability of LPS to induce 5 different signaling cascades [10]. Whether these altered LPS patterns are due to a superimposed (or counterbalancing) effect of HIV-1 on monocyte activation or a defect in endotoxin tolerance remains to be determined. Additional studies should include HAART-treated patients with undetectable viremia and be performed using whole bacteria and LPS/LPS-binding protein (LBP) in addition to monomeric LPS. To rule out activation during positive selection with anti-CD14 antibodies, monocytes should be isolated using negative as well as positive selection methods.

Additional studies are also needed to unravel the relationships between LPS, sCD14, and immune activation. CD14 binds and presents LBP-bound LPS to its signaling complex, lymphocyte antigen 96 (MD-2)/toll-like receptor 4 (TLR4), triggering monocyte-macrophage activation and the release of sCD14 [11]. sCD14 contributes to cell activation by transferring monomeric LPS to membrane CD14 (mCD14), or directly to the MD-2/TLR4 complex in cells that lack mCD14. However, sCD14 can also induce endotoxin tolerance by removing LPS from mCD14 and diverting it to plasma lipoproteins [11], a process that may decrease CD14 shedding. This is further complicated by studies showing that HIV-1 RNA can enhance TLR4-mediated response to LPS, causing dysregulation of endotoxin tolerance [12].

The complex relationships between HIV-1, MT, and immune activation are likely to depend on the integrity of gastrointestinal epithelium, the level of HIV-1 replication, plasma concentrations of...
LPS-binding protein and endotoxin core antibody, and the presence/absence and type of opportunistic co-infections, as well as the combined effects of these infections on TLR signaling cascades. Understanding these interactions may be critical to the design of strategies aimed at enhancing therapeutic efficacy in Africa where treatment is often delayed until CD4 counts drop to <200 cells/µL.

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