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Commentary

# Effects of HIV, Immune Deficiency, and Confounding on the Distal Gut Microbiota

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Human immunodeficiency virus (HIV) infection progressively destroys CD4+ mononuclear cells leading to profound cellular immune deficiency that manifests as life threatening opportunistic infections and malignancies, i.e., the acquired immune deficiency syndrome (AIDS). The gut mucosa-associated lymphoid tissue (MALT, e.g., Peyer's patches) is a major locus of CD4+ cells. HIV's asymptomatic and insidious destruction of these cells compromises the integrity of the gut mucosa, allowing translocation (leakage) of microbes and other luminal contents into the circulation (Brenchley et al., 2004). Microbial translocation induces subtle but sustained and widespread immune activation, which is a major contributor to HIV's pathogenesis (Brenchley et al., 2006).

Given these effects of HIV on the gut mucosa, it is not surprising that several groups have reported alterations of the gut microbial population (the microbiota) in people with HIV, including those in whom HIV is well controlled with antiretroviral therapy (ART) (Lozupone et al., 2014; Nowak et al., 2015). These studies comprised heterogeneous or poorly defined populations, used various methods, and have been very small — collectively fewer than 100 HIV-infected subjects including those with early HIV, HIV on ART, chronic HIV viremia without ART, and "elite controllers" (non-viremic without ART). In one recent report (Nowak et al., 2015), species-level diversity (termed richness or "alpha diversity") in feces in 28 HIV viremic patients was significantly lower than in 9 controls; alpha diversity correlated positively with CD4+ cell counts and inversely with plasma markers of microbial translocation and monocyte activation. After ART initiation in these subjects, fecal alpha diversity continued to decrease (Nowak et al., 2015), which corroborates findings from others (Lozupone et al., 2014). In contrast, a more recent and comprehensive study (Mutlu et al., 2014) reported that fecal alpha diversity did not differ between 21 HIV-infected subjects and 22 demographically similar, HIV-uninfected controls, although their HIV subjects did have significantly lower alpha diversity in multiple distal-gut biopsy specimens. These latter findings conflict with the conclusion by Lozupone et al. (2014) that mucosal alpha diversity does not differ consistently with untreated HIV.

Considering the composition of the microbial community (termed "beta diversity" or, colloquially, "who's there"), the review by Lozupone et al. (2014) noted a shift in a major phylum of the gut microbiota, Bacteroidetes. Compared to various uninfected controls, colon mucosal biopsies and also feces from HIV-infected subjects, irrespective of ART, had lower abundance of Bacteroides and higher abundance of Prevotella. Independently, three studies reported that the HIV-infected subjects had increased abundance of Proteobacteria, including several potential pathogens, in biopsies but not in feces [reviewed in (Lozupone et al., 2014)]. Higher abundance of mucosal-adherent Proteobacteria supports the hypothesis that an altered microbiota ("dysbiosis") contributes to a vicious cycle of inflammation, gut permeability, microbial translocation, and progressive immune deficiency through depletion of CD4+ mononuclear cells (Vyboh et al., 2015).

In this issue of EBioMedicine, Noguera-Julian et al. (2016) push this topic in a new direction in their study of men who have sex with men (MSM) and others in Barcelona and Stockholm. Their participants, 129 HIV-positives (60% MSM) and 27 HIV-negatives (85% MSM) in Barcelona, and 77 HIV-positives (25% MSM) and 7 HIV-negatives (none MSM) in Stockholm, provided one sample of feces. Microbiota profiles in the fecal DNA were generated by amplifying and next-generation sequencing 16S rRNA genes. The sequences were assigned to prokaryotic taxa and processed to generate diversity metrics. Like some previous studies (Nowak et al., 2015), fecal microbiota richness was lower in most HIV subjects. Unlike some previous studies, HIV was not associated with higher Prevotella-related and lower Bacteroides-related taxa (Lozupone et al., 2014).

The novelty of the current report is the focus on HIV risk group, specifically MSM (Noguera-Julian et al., 2016), whereas sexual orientation and other HIV risk categories were largely ignored in the previous reports. Noguera-Julian and colleagues reported that Prevotella taxa predominated in MSM, whereas Bacteroides taxa predominated in non-MSM. Compared to non-MSM, MSM also had higher richness partially attributable to their lower HIV prevalence (60% vs 85% in Barcelona, 62% vs 100% in Stockholm). Given that HIV-negative MSM are largely healthy, the differences noted by sexual orientation stretch the concept of "dysbiosis."

The possibility that these new associations reflect confounding should be considered, particularly with the heterogeneity of the study populations. The authors looked for but could not ascribe the gut microbiota alterations to MSM-related differences in diet or particular co-

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infections (hepatitis B and C, syphilis, anal human papillomavirus, *Chlamydia trachomatis*). However, current or prior enteric parasites with relatively high prevalence in MSM (e.g., amoebiasis (Hung et al., 2012)) were not considered. Antibiotic use could be a major confounder. Most subjects were excluded if they had received antibiotics during the previous 3 months, but cumulative or prior antibiotic exposure (within 6 months noted for 24% of HIV-positive, 15% of HIV-negative, 20% of MSM, and 27% of non-MSM in Barcelona) could have contributed.

In our study of 76 MSM from a well defined population, we found that the anal microbiota (which closely resembled the fecal microbiota) had altered composition and reduced richness with uncontrolled, advanced HIV infection (Yu et al., 2014). Importantly, these alterations in the microbial population were partially attributable to antibiotic use but not to T-cell subset levels, smoking, or sexual practices (e.g., anal intercourse, anilingus) (Yu et al., 2014).

Validation, and indeed formal testing of the hypothesis posed by Noguera-Julian and colleagues, that the gut microbiota differs by sexual orientation, will be needed. Such a study would be challenging, given the need to avoid or minimize confounding by demographics, diet, physical activity, HIV and other infections, and medications particularly antibiotics. In the meantime, all studies of HIV-microbiota relationships should carefully investigate possible confounding or effect modification by sexual orientation, injection drug use, and demographics.

## Disclosure

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