Published in final edited form as:

AIDS. 2017 March 27; 31(6): 863–865. doi:10.1097/QAD.0000000000001410.

The Microbiota and HIV: Shedding Light on Dark Matters

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The gut, which is the major reservoir of T lymphocytes, suffers severe T-cell depletion when attacked by human immunodeficiency virus (HIV). These T cells are essential for recognizing and processing antigen, and for maintaining the integrity of the gut mucosa, the extraordinarily selective barrier between the systemic circulation and the gut's microbes and other contents. Landmark studies by Brenchley and his colleagues revealed that HIV-mediated depletion of the gut's CD4⁺ T cells results in low-grade, steady leakage of gut microbes and metabolites into the circulation, which drives immune activation and HIV's replication and pathogenesis [1, 2].

The article by Nowak et al in the current issue of AIDS adds to previous reports that are exploring the impact of HIV on the gut microbial population (the microbiota) [3-6]. As HIV-related immune deficiency affects virtually every other organ system, the expectation is that it will also affect some or all of the immunologic, metabolic, nutritional, structural, and other functions of the gut microbiota [7, 8]. Complementing but also confounding these efforts is the expectation that the gut microbiota will be affected by antiretroviral therapy (ART), just as it is by antibiotics, metformin, and other medications [9, 10].

Nowak and colleagues studied 130 young homosexual men in Abuja, Nigeria, who provided anorectal swabs, from which the team extracted DNA and then generated fecal microbiome profiles based on next-generation sequencing of 16S rRNA amplicons. They report that microbiome metrics did not differ significantly between the 55 HIV-uninfected and the 41 HIV-infected, ART naïve participants. In contrast, the 34 ART-treated men had lower diversity within the *Bacteroidetes* phylum (specifically reduced abundance of *Prevotella* and rare genera), increased abundance of three *Firmicutes* genera, and a shift within *Proteobacteria* with reduced abundance of rare genera and increased abundance of *Campylobacter*. Notably, the observed differences were not predicted a priori and would not have been significant with adjustment for multiple comparisons. The differences also do not accord with prior reports [3-5, 11], although none of those were in sub-Saharan Africans.

The covariates examined by Nowak et al, particularly classical sexually transmitted infections and their treatments, provide potential insights on their microbiome findings and lessons for the future. As one would expect, HIV-infected men had higher prevalence of anal human papillomavirus than did HIV-uninfected men. In contrast, ART-treated men had markedly lower prevalence of asymptomatic rectal gonorrhea compared to both ART-naïve men and HIV-uninfected men. Rectal gonorrhea also was significantly associated with higher abundance of *Prevotella* (and, I would speculate, rare *Bacteroidetes* and *Proteobacteria* genera). Given that ART-treated men had accessed health care, it is plausible

that they had also received recent antibiotic treatment that reduced their prevalence of gonorrhea, *Prevotella*, and other genera, allowing expansion of antibiotic-resistant genera. Nowak, et al lacked data to directly examine this hypothesis.

The observational studies published thus far have inconsistent findings, although they do suggest that HIV has little short-term impact on the gut microbiota. With chronic, long-term HIV infection, perhaps irrespective of ART, the general pattern may be for increased abundance of potential pathogens, particularly *Fusobacteria* and *Proteobacteria*, and correlations of these with mucosal or systemic immune activation and inflammation [5, 6, 12]. This would be consistent with the significantly increased translocation of *Proteobacteria*, rather than *Firmicutes* or *Bacteroidetes* taxa, to mesenteric lymph nodes and liver that has been observed in Rhesus macaques with chronic simian immunodeficiency virus (SIV) infection [13].

The primary lesson for the future is to recognize the limitations of cross-sectional observational studies. Confounding, in particular, is likely to be so severe that more such studies are unlikely to shed light on how dysbiosis (that is, alteration of the microbiota) affects HIV risk and pathogenesis. Faster and more direct progress in understanding these dark matters will require dissecting them and addressing them with hypothesis-based research [14]. Unbiased collection and banking of a fecal specimen or even an anorectal swab, as done simply by Nowak et al and our group [6], from each patient at ART initiation would provide a rich resource for such projects. In a consortium of likeminded investigators, fecal microbiome and potentially metabolome analyses of such specimens could be employed in nested case-control studies of events such as ART failure or organ- or drug-specific toxicities [15, 16].

Microbiome-related hypotheses could also be tested in clinical trials. For example, combinations of probiotics and immunomodulators may accelerate and broaden ART-mediated immunologic recovery, including in the gut. In SIV-infected Asian macaques, administration of a probiotic regimen plus interleukin-21 increased gut CD4+ cells and gut Th17 cells that are required for mucosal integrity, with increased abundance of fecal *Lactobacillus* and *Bifidobacteria* taxa and decreased systemic markers of microbial translocation [17]. Whether a similar approach will improve ART-mediated immunologic recovery and reduce systemic immune activation in people will require a blinded clinical trial with a placebo or probiotic-untreated group [18]. Fecal microbiota transplants are not recommended, given the heterogeneity of the gut microbiota in patients with HIV and confounding by pre-transplant antibiotic regimens [19].

In summary, the gut microbiota is integral to human health, and dysbiosis offers targets for disease amelioration or prevention. Moreover, the likelihood of clearer insights is increasing with continuing developments in 'omics technologies and especially in informatics pipelines that can extract information from multidimensional clinical, metagenomic, metabolomic, and potentially immunologic data [20]. However, identifying such targets will require not only unambiguous differences in microbial composition between diseased and healthy people, but also hypothesis-based research with a foundation based on comprehensive

investigations of host interactions with luminal (that is, fecal) and mucosal-adherent microbes [21].

REFERENCES

1. Brenchley JM, Price DA, Schacker TW, Asher TE, Silvestri G, Rao S, et al. Microbial translocation is a cause of systemic immune activation in chronic HIV infection. *Nat Med*. 2006; 12(12):1365–1371. [PubMed: 17115046]
2. Mudd JC, Brenchley JM. Gut Mucosal Barrier Dysfunction, Microbial Dysbiosis, and Their Role in HIV-1 Disease Progression. *J Infect Dis*. 2016; 214(Suppl 2):S58–66. [PubMed: 27625432]
3. Williams B, Landay A, Presti RM. Microbiome alterations in HIV infection a review. *Cell Microbiol*. 2016; 18(5):645–651. [PubMed: 26945815]
4. Goedert JJ. Effects of HIV, Immune Deficiency, and Confounding on the Distal Gut Microbiota. *EBioMedicine*. 2016; 5:14–15. [PubMed: 27077101]
5. McHardy IH, Li X, Tong M, Ruegger P, Jacobs J, Borneman J, et al. HIV Infection is associated with compositional and functional shifts in the rectal mucosal microbiota. *Microbiome*. 2013; 1(1): 26. [PubMed: 24451087]
6. Yu G, Fadrosch D, Ma B, Ravel J, Goedert JJ. Anal microbiota profiles in HIV-positive and HIV-negative MSM. *AIDS*. 2014; 28(5):753–760. [PubMed: 24335481]
7. Goodman AL, Gordon JI. Our unindicted coconspirators: human metabolism from a microbial perspective. *Cell Metab*. 2010; 12(2):111–116. [PubMed: 20674856]
8. Sommer F, Bäckhed F. The gut microbiota--masters of host development and physiology. *Nat Rev Microbiol*. 2013; 11(4):227–238. [PubMed: 23435359]
9. Forslund K, Hildebrand F, Nielsen T, Falony G, Le Chatelier E, Sunagawa S, et al. Disentangling type 2 diabetes and metformin treatment signatures in the human gut microbiota. *Nature*. 2015; 528(7581):262–266. [PubMed: 26633628]
10. Jackson MA, Goodrich JK, Maxan ME, Freedberg DE, Abrams JA, Poole AC, et al. Proton pump inhibitors alter the composition of the gut microbiota. *Gut*. 2016; 65(5):749–756. [PubMed: 26719299]
11. Mutlu EA, Keshavarzian A, Losurdo J, Swanson G, Siewe B, Forsyth C, et al. A compositional look at the human gastrointestinal microbiome and immune activation parameters in HIV infected subjects. *PLoS Pathog*. 2014; 10(2):e1003829. [PubMed: 24586144]
12. Vujkovic-Cvijin I, Dunham RM, Iwai S, Maher MC, Albright RG, Broadhurst MJ, et al. Dysbiosis of the gut microbiota is associated with HIV disease progression and tryptophan catabolism. *Sci Transl Med*. 2013; 5(193):193ra191.
13. Klase Z, Ortiz A, Deleage C, Mudd JC, Quiñones M, Schwartzman E, et al. Dysbiotic bacteria translocate in progressive SIV infection. *Mucosal Immunol*. 2015; 8(5):1009–1020. [PubMed: 25586559]
14. Goedert JJ. The microbiota and human health: beyond exploration. *Eur J Clin Invest*. 2013; 43(7): 657–659. [PubMed: 23611431]
15. Spanogiannopoulos P, Bess EN, Carmody RN, Turnbaugh PJ. The microbial pharmacists within us: a metagenomic view of xenobiotic metabolism. *Nat Rev Microbiol*. 2016; 14(5):273–287. [PubMed: 26972811]
16. Wilson ID, Nicholson JK. Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res*. 2017; 179:204–222. [PubMed: 27591027]
17. Ortiz AM, Klase ZA, DiNapoli SR, Vujkovic-Cvijin I, Carmack K, Perkins MR, et al. IL-21 and probiotic therapy improve Th17 frequencies, microbial translocation, and microbiome in ARV-treated, SIV-infected macaques. *Mucosal Immunol*. 2016; 9(2):458–467. [PubMed: 26286233]
18. d'Ettorre G, Ceccarelli G, Giustini N, Serafino S, Calantone N, De Girolamo G, et al. Probiotics Reduce Inflammation in Antiretroviral Treated, HIV-Infected Individuals: Results of the "Probio-HIV" Clinical Trial. *PLoS One*. 2015; 10(9):e0137200. [PubMed: 26376436]

19. Hensley-McBain T, Zevin AS, Manuzak J, Smith E, Gile J, Miller C, et al. Effects of Fecal Microbial Transplantation on Microbiome and Immunity in Simian Immunodeficiency Virus-Infected Macaques. *J Virol.* 2016; 90(10):4981–4989. [PubMed: 26937040]
20. Noecker C, McNally CP, Eng A, Borenstein E. High-resolution characterization of the human microbiome. *Transl Res.* 2017; 179:7–23. [PubMed: 27513210]
21. McHardy IH, Goudarzi M, Tong M, Ruegger PM, Schwager E, Weger JR, et al. Integrative analysis of the microbiome and metabolome of the human intestinal mucosal surface reveals exquisite inter-relationships. *Microbiome.* 2013; 1(1):17. [PubMed: 24450808]