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A microbiome variable in the HIV-prevention equation:

Vaginal microbes thwart an antiretroviral microbicide

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The healthy vaginal microbiota is typically characterized by the predominance of *Lactobacillus* species (including *L. crispatus*, *L. jensenii*, *L. gasseri*, and *L. iners*). These bacteria are thought to protect against pathogens through a variety of mechanisms, including competitive inhibition, secretion of bacteriocins (substances that inhibit the growth of bacteria), and the production of lactic acid, which lowers the vaginal pH and has immunomodulatory effects (1). Consequently, vaginal dysbiosis is currently defined by the presence of polymicrobial bacterial populations with reduced or absent lactobacilli. This low-lactobacillus state characterizes bacterial vaginosis, a clinical condition that is a common cause of vaginal symptoms in reproductive-aged women (2). Decreased bacterial diversity in the gut has been linked to a number of pathologic conditions (3), whereas increased vaginal bacterial diversity has been associated with a variety of poor patient outcomes including preterm birth and the acquisition and spread of sexually transmitted infections (4, 5). On page 938 of this issue, Klatt *et al.* (6) add to this list a decrease in the efficacy of the vaginal antiretroviral gel tenofovir to prevent HIV acquisition.

Klatt *et al.* used samples collected from a subset of participants in a randomized controlled trial that evaluated the efficacy of tenofovir intravaginal gel for the prevention of HIV acquisition in South African women (7). Using mass spectrometry to estimate microbial relative abundance in cervicovaginal lavage samples, the authors broadly grouped the samples into *Lactobacillus*-dominant, or diverse, non-*Lactobacillus*-dominant categories. The authors found that even in women with high drug adherence, vaginal tenofovir concentrations were lower and the drug was substantially less efficacious in preventing HIV acquisition in the non-*Lactobacillus*-dominant group. In vitro studies showed that *Gardnerella vaginalis* and other anaerobes metabolized tenofovir, but two *Lactobacillus* species did not. There are important limitations in the data that the authors acknowledge, such as a cross-sectional design that fails to take into account the temporal dynamics of the vaginal microbiota, the absence of clinical information on bacterial vaginosis, and the lack of a mechanism for tenofovir metabolism. Nevertheless, the findings of Klatt *et al.* are strengthened by other in vitro (8) and human studies (9).

As understanding of the vaginal microbiota and its potential impact on women's health continues to develop, the study by Klatt *et al.* highlights the importance of "pharmacomicrobiomics"—a term that reflects the study of drug-microbiota interactions (10). The finding that components of the human microbiota may affect the concentration of a drug in vivo is not without precedent. The ability of specific gut bacteria to metabolize medications is well established. One of the best-known examples is digoxin, a drug used to

treat various heart conditions. Metabolism of digoxin was recently attributed to *Eggerthella lenta* (3). Although the mechanistic details of how *G. vaginalis* and other anaerobes metabolize tenofovir are not defined, Klatt *et al.* show that individual variability in tenofovir concentrations among study participants goes beyond drug adherence, thereby adding yet another variable to the HIV-prevention equation.

The introduction of “multiomic” technologies to examine nucleic acid, protein, and other profiles, elicited high hopes that the mysteries of vaginal eubiosis and dysbiosis— that is, optimal and suboptimal vaginal bacterial communities—would be quickly elucidated. Although the study by Klatt *et al.* simply grouped participants into *Lactobacillus*-dominant (i.e., eubiotic) and non-*Lactobacillus*-dominant (i.e., dysbiotic) groups, emerging data now hint that the complexities of these conditions are considerably more nuanced, perhaps an important lesson for the broader field of microbiota research. Molecular techniques that enable species-level classification of Lactobacilli suggest that not all Lactobacilli are created equal with respect to their ability to protect the female reproductive tract. For example, vaginal microbiota dominated by *L. iners* have been associated with increased acquisition of sexually transmitted infections (11) and preterm birth (12). There is emerging evidence that within the same species, different strains of *L. iners* may be more or less beneficial (13). Similarly, strain-specific differences in the anaerobe *Gardnerella* have been documented (14).

Precision medicine, defined by the U.S. National Institutes of Health as “an emerging approach for disease treatment and prevention that takes into account individual variability in genes, environment, and lifestyle for each person,” must also account for the variability of the individual’s microbiota. This raises a critical question: Can a woman’s vaginal microbiota be altered? Unfortunately, dysbiosis is difficult to treat: Although in the short-term, antibiotic therapy substantially alters the structure and composition of the vaginal microbiota in women with bacterial vaginosis, nearly 60% will have a recurrence within a year following therapy (15). Thus, effective antibiotic-sparing pre- and probiotics are actively being sought.

To date, variability in study designs, outcomes (prevention versus treatment of dysbiosis as well as methods of measurement of the vaginal microbiota), and strains limit the ability to draw definitive conclusions on probiotic efficacy. The study by Klatt *et al.* is a reminder that without a deeper understanding of the structure, function, and dynamics of the vaginal microbiome, successful interventions to optimize it and improve women’s health will remain elusive.

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Figure 1.
The microbicide tenofovir prevents retroviral replication. As a vaginal gel, it offers a feasible method for preventing HIV infection.