THE INFLUENCE OF MUCOSAL INLAMMATION AND MICROBIOTA METABOLITES ON HIV TRANSMISSION IN WOMEN

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HIV transmission and the effectiveness of topical HIV prevention strategies are influenced by the presence of mucosal inflammation in the lower female reproductive tract (FRT), which promotes activation and recruitment of HIV target cells. A pro-inflammatory mucosal milieu is mediated by sexually transmitted infections (STIs) as well as "suboptimal microbiota" or vaginal dysbiosis as exemplified by bacterial vaginosis (BV). BV is an imbalance in the vaginal microbiota characterised by a dramatic depletion of beneficial *Lactobacillus* spp. and an increase in load and diversity of obligate and facultative anaerobic bacteria. Highly diverse vaginal microbiota are prevalent in adolescent girls and young women in sub-Saharan Africa, where around 3 out of 4 new HIV infections occur in 15-19 year old girls. In contrast, women with "optimal" vaginal microbiota dominated by beneficial *Lactobacillus* spp. have a lower risk of acquiring HIV. As well as genital inflammation, other distinguishing features between women with BV compared to those colonised with beneficial *Lactobacillus* spp. include a breakdown of the protective mucosal barrier, an increase in vaginal pH, a dramatic depletion of the vaginal microbiota metabolite (VMB), lactic acid, and increased levels of the VMBs, succinic acid and short chain fatty acids (SCFAs) such as acetic acid. Lactic acid, produced by lactobacilli, elicits the production of an anti-inflammatory cytokine and inhibits the production of pro-inflammatory mediators from cervicovaginal epithelial cells that could potentially reduce inflammation and subsequent HIV risk. In contrast, SCFAs and succinic acid lack immune modulatory effects on FRT epithelium under conditions found during BV. In contrast to *Lactobacillus* spp., BV-associated bacteria also metabolise topical PrEP providing an additional mechanism by which the microbiota attenuate PrEP efficacy. These findings highlight the important role of optimal vaginal microbiota in HIV prevention and suggest potential strategies to manipulate the vaginal microbiota to maximize PrEP effectiveness.

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