While the per-contact risk of sexual HIV transmission is relatively low, it is fourfold higher in sub-Saharan Africa, and this may partly explain the major global disparities that exist in HIV prevalence. Genital immune parameters are key determinants of HIV transmission risk, including epithelial integrity and the presence of highly HIV-susceptible intraepithelial or submucosal CD4+ T cell target cells. Biological parameters that may enhance mucosal HIV susceptibility in highly HIV-affected regions of sub-Saharan Africa include increased levels of mucosal inflammation, which can affect both epithelial integrity and target cell availability, as well as the increased mucosal surface area that is afforded by an intact foreskin, contraceptive choices, and intravaginal practices. There are multifactorial causes for increased mucosal inflammation, with the prevalence and nature of common co-infections being particularly relevant.