The Rectal Microbiome and HIV Risk in MSM
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Project Scope
Men who have sex with men (MSM) are at high risk of HIV acquisition due in part to the relative ease of transmission across the rectal mucosa during condomless receptive anal intercourse (CRAI). In order to design highly effective biomedical HIV prevention interventions for MSM, there is a need to better understand the immunologic context of HIV transmission in the rectal mucosa. An increased understanding of the cross talk between the gut mucosal microbiota and mucosal immune environment has highlighted the potential importance of the mucosal microbiota on HIV susceptibility. For example, certain microbial species have been shown to induce anti-inflammatory or pro-inflammatory T cell phenotypes. During CRAI, the rectal mucosa may be exposed to enemas, lubricants, mechanical trauma, and/or semen, which could exert pro-inflammatory effects on the rectal mucosa and facilitate HIV transmission. In addition to these factors, the gut microbiota are likely altered as a result of CRAI, and there may be additional exposure of the mucosa to the microbiota due to products used and microtrauma induced during CRAI. Therefore, we propose to examine associations between the gut mucosal microbiome and markers of increased HIV susceptibility such as inflammation and T cell activation in the rectal mucosa in a cohort of MSM who are engaging in CRAI and male controls who have not engaged in anal intercourse. Dr. Kelley (co-project director) is currently conducting a study examining rectal mucosal changes associated with CRAI (AIK23108335-01). She is recruiting HIV negative MSM who engage in CRAI and controls (men who have never engaged in anal intercourse) into a longitudinal study with blood and rectal biopsy collections at intervals timed with CRAI episodes. Mucosal swabs are currently being collected and stored from these study visits to facilitate future microbiome analyses. The requested CFAR supplement and ongoing study will allow the unique opportunity to examine the rectal mucosal microbiome in MSM engaging in CRAI and controls and relate changes to markers of epithelial damage, inflammation, and/or immune activation in the rectal mucosa. Results from this study will contribute to the understanding of the association of the gut mucosal microbiome with rectal mucosal HIV susceptibility. In addition, if certain microbiota profiles are associated with markers of increased susceptibility, this could suggest new pathways to augment efficacy of existing and future biomedical HIV prevention interventions, including an HIV vaccine, specifically for MSM.

Specific Aims
1. To examine changes in the diversity and composition of the rectal mucosal microbiome associated with CRAI in MSM as compared to men who do not engage in anal intercourse.

Hypothesis: Due to possible enema, lubricant, mechanical trauma, and/or semen microbiota exposure, MSM engaging in CRAI will have altered microbiota profiles in the rectal mucosa as measured by a reduction in microbial diversity or enrichment of ‘pro-inflammatory’ species. These alterations could increase susceptibility to HIV in MSM engaging in CRAI if they result in increased HIV target cell availability, inflammation, and/or immune activation as described in Aim 2.

2. To examine the associations between the diversity and composition of the rectal microbiome and 1) HIV target cell availability, 2) markers of epithelial cell inflammation, 3) epithelial cell junction complex disruption, and 4) lamina propria T cell activation in the rectal mucosa in a cohort of MSM engaging in CRAI and men who have never engaged in CRAI.

Hypothesis: Rectal mucosal samples from study participants with decreased rectal microbiome diversity or with lower prevalence of ‘anti-inflammatory’ microbiota species (e.g. Bacteroides sp. and/or Bifidobacterium sp.) will demonstrate greater levels of HIV target cell availability, epithelial cell inflammation, epithelial cell junction complex disruption, and/or T cell activation, which could influence HIV susceptibility.

In addition to adding crucial information to the current knowledge base of mucosal HIV transmission, completion of the above aims will foster a new collaboration between Drs. Kraft and Kelley and their mentors. Dr. Kraft’s specific interest and expertise in altering the mucosal microbiome for therapeutic purposes and Dr. Kelley’s interest in applying translational immunology to improve efficacy of biomedical prevention interventions for populations at high risk of HIV will be combined for this novel project. Their mentors, Drs. Rama Amara, a renowned HIV/SIV immunologist and vaccinologist, and Andrew Neish, an accomplished epithelial cell biologist, will foster and guide this collaboration. This supplement will lead to future studies of the microbiome and host HIV susceptibility, which could include mechanistic studies to examine the causal effect of alterations in the gut microbiome with HIV susceptibility or therapeutic interventions to alter the mucosal microbiome and reduce susceptibility to HIV.