S13.3 PENILE MICROBIOTA, INFLAMMATION, AND HIV RISK

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Introduction The interplay between the genital microbiome and the host immune system may modify one's susceptibility to sexually transmitted infections. We examined the impact of circumcision on the penile microbiome and how it affects local immune response and potentially modifies the host's risk for HIV.
Methods Using real-time PCR, DNA sequencing, and Luminex multiplex assays, we studied the penile microbiome and levels of pro-inflammatory cytokines in the coronal sulcus of adult men who were randomized to immediate or delayed male circumcision in Rakai, Uganda.
Results Uncircumcised men frequently had high abundances of anaerobic bacteria, including *Prevotella*, *Porphyromonas*, and species of Clostridiales Family XI. Penile anaerobes decreased after male circumcision, replaced by low abundances of skin-associated bacteria such as *Staphylococcus* and *Corynebacterium*. Among the pro-inflammatory cytokines measured, the level of IL-8 correlated significantly with penile anaerobe abundance, which remained persistently elevated in uncircumcised men but decreased after circumcised men.
Discussion Our findings suggest that the penile microbiome may play a role in host susceptibility to HIV. Circumcision significantly decreased penile anaerobes and local production of pro-inflammatory cytokines, which may reduce HIV target cells recruitment and activation in the penile epithelium.

S13.4 THE VAGINAL MICROBIOME AND STI

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Our systematic review of 63 molecular vaginal microbiome (VMB) studies conducted between 2008 and 2013 confirmed that lactobacilli-dominated VMB are associated with a healthy vaginal micro-environment and that bacterial vaginosis (BV) is best described as a polybacterial dysbiosis. However, not all lactobacilli seem to be equally healthy (e.g. a *Lactobacillus* iners-dominated VMB is more likely to shift to dysbiosis than an *L. crispatus*-dominated VMB and *L. iners* often remains present during dysbiosis) and multiple dysbiosis entities with clinical relevance seem to exist. Some women with BV have a highly diverse VMB consisting of high loads of planktonic anaerobic bacteria, while others have a vaginal biofilm (typically including *Gardnerella vaginalis*). Furthermore, a small but clinically relevant proportion of women have a VMB dominated by *Streptococci* and/or *Escherichia coli*. Vaginal colonisation with *Candida* spp. is more common in women with a lactobacilli-dominated VMB than in women with dysbiosis, and women who receive antibiotic treatment for BV often subsequently develop vaginal candidiasis. Research has shown that all of these conditions cause disruption of the cervicovaginal mucosal barrier as well as cervicovaginal inflammation, which in turn might cause serious complications such as increased HIV acquisition, pre-term birth, and maternal/neonatal sepsis. At the moment, asymptomatic BV (by microscopic and clinical criteria) is usually not treated and symptomatic BV is treated with oral or vaginal metronidazole or clindamycine. However, recurrence rates are very high (up to 50% within six months) and novel treatments – such as vaginal biofilm disruption and vaginal probiotics – are therefore needed. Furthermore, the different dysbiosis entities, or combinations of entities, likely require different clinical management approaches. Systems biology has now become more affordable and should be incorporated into epidemiological studies to address associations of different dysbiotic entities with clinical outcomes, and to evaluate interventions aimed at restoring and maintaining a lactobacilli-dominated VMB.

S14 - Causal interactions among structural, behavioural and biological drivers of STD/HIV epidemics

S14.1 TRANSITIONS AROUND SEX WORK AND THEIR SIGNIFICANCE IN STI/HIV EPIDEMICS

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In many regions of the world, the importance of formal sex work in driving HIV epidemics is well-established and it is recognised that female sex workers (FSWs) experience a disproportionately high risk of HIV globally. Sex work and sex work networks are complex and continuously evolving and therefore FSW research needs to address this changing nature of HIV risk as well as the contribution of other important factors to the overall HIV epidemic, such as macro-structural determinants, sub-population-level social and sexual networks, individual behaviours and host and viral biological factors. Further, early HIV and STI risk has been particularly identified as being an important area of programmatic and research focus. In an effort to understand the complexity and risk trajectory associated with sex work, the "Transitions" study examines the HIV risk and vulnerability among young women and FSWs over the life course from the structural, network, behavioural and biological perspectives. Transitions also aims to dissect the contribution and interaction of factors within these different areas (structural, network, behavioural and biological) that drive HIV risk and transmission at an individual- and population-level. Disentangling the role of these contributing factors in HIV risk could shed light on the optimal mix of HIV interventions that is proportionate to the relative influence of these drivers.

This presentation will introduce a framework that demonstrates how Transitions brings together the various perspectives in its work in the different epidemiological contexts of Ukraine and Kenya. For the latter, mapping results from Ukraine and Kenya will be reviewed. This presentation will also show how such a framework is used to guide research and inquiry in order to generate meaningful and concrete findings that could have implications on HIV prevention and control programming.

S14.2 AGE, SEXUAL EXPERIENCE AND MUCOSAL INFLAMMATION: WHAT DO WE KNOW?

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HIV transmission rates are low on a per-coital level, but increased by various transmission co-factors. One implication of

this is that the mucosal environment of female reproductive tract – in the case of male-to-female transmission – is generally capable of repelling the virus. Several lines of evidence have linked HIV transmission co-factors with altered mucosal immune parameters. Mucosal inflammation, defined by elevated cytokine concentrations in cervicovaginal secretions, was associated with increased rates of HIV acquisition in the CAPRISA 004 study. While the causes of these remain unclear, we have also shown that mucosal cytokines are associated with an altered mucosal proteome including impaired barrier function, and increased frequencies of HIV target cells in the mucosa. A further proteomic analysis of HIV cases and controls demonstrated that HIV outcome could be predicted with 97% accuracy on the basis of 10 key proteins. Proteins overrepresented in cases included those associated with inflammation, while barrier-associated proteins were overrepresented in controls. Application of this model to younger women, who in the sub-Saharan African epidemic represent the group with the highest incidence rates, will be important to understanding HIV risk. In particular, the role of sex work-related exposures including rates of condom use, partner change, vaginal practices, microbiome, and other infections in driving immune changes remains poorly described. A better understanding of HIV transmission at a mucosal level may reveal novel HIV prevention options.

S14.3 IMMUNE ACTIVATION, GENE EXPRESSION AND HIV ACQUISITION RISK

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Background Sexual transmission of HIV is actually fairly inefficient and when it does occur usually a single virus is responsible for establishing the infection. Since activated HIV target cells (CD4+CCR5+) are known to be 1000x more susceptible to HIV infection than quiescent cells, one of the known risk factors for HIV acquisition is elevated baseline levels of immune activation. This study was designed to determine if oral administration of low doses of anti-inflammatory agents, acetylsalicylic acid (ASA) and hydroxychloroquine (HCQ), would reduce the number of HIV target cells in the female genital tract.

Methods 80 low-risk women from Nairobi, Kenya established baseline immune activation levels and then were randomized to 6 weeks oral administration of low doses of either ASA (81 mg/day) or HCQ (200 mg/day). Cellular activation (CD69, HLA-DR, CD95, CCR5) was assessed by flow cytometry of peripheral blood mononuclear cells (PBMC) and cervical mononuclear cells (CMC).

Results In PBMCs, a reduction in the percentage of CD4+CD69+ ($p = 0.01$) and CD4+CCR5+ ($p = 0.03$) T cells was observed in the ASA arm and a significant decrease of CD95 ($p < 0.0001$) and CCR5 ($p = 0.01$) expression on CD4+ T cells was observed following HCQ treatment. At the mucosal level, CMCs showed reduced levels of CD4+CCR5+ T cells following ASA treatment (p -0.02) and lower expression of the activation marker CD69 on CD4+ cells in the HCQ arm ($p = 0.05$).

Conclusions Reducing the number of HIV target cells in the female genital tract, represents a new approach to reducing HIV risk. This study showed that daily administration of low-dose anti-inflammatory drugs reduces the number of HIV target cells in the female genital tract. Further studies are required to determine if a similar reduction in mucosal HIV target cells can be observed in women at high-risk of acquiring HIV and if those reduction provide any protective benefit.

S15 - Multipurpose Technologies (MPTs): developing interventions to simultaneously prevent STIs, HIV and pregnancy

S15.2 GLOBAL MAPPING OF STI, HIV AND UNPLANNED PREGNANCY: WHERE DO THESE EPIDEMICS INTERSECT?

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Worldwide, women face sexual and reproductive health (SRH) risks including unintended pregnancy and sexually transmitted infections (STIs) including HIV. Multipurpose prevention technologies (MPTs) combine protection against two or more SRH risks into one product. Male and female condoms are the only currently available MPT products, but several other forms of MPTs are in development. We conducted a comprehensive analysis to examine the global distribution of selected SRH issues to determine where various risks have the greatest geographical overlap.

We examined four indicators relevant to MPTs in development: HIV prevalence, herpes simplex virus type 2 (HSV-2) prevalence, human papillomavirus (HPV) prevalence, and the proportion of women with unmet need for modern contraception. Using ArcGIS Desktop, we mapped these indicators individually and in combination on chloropleth and graduated symbol maps. We conducted a principal components analysis to reduce data and enable visual mapping of all four indicators on one graphic to identify overlap. Our findings document the greatest overlapping risks in sub-Saharan Africa, and we specify countries in greatest need by specific MPT indication. These results can inform strategic planning for MPT introduction, market segmentation, and demand generation, but data limitations also highlight the need for improved (non-HIV) STI surveillance globally.

S15.3 MAKING THE CASE FOR MPTS: PREVENTIONS OF INFERTILITY AND OTHER STI SEQUELAE

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In regions of sub-Saharan Africa where HIV is highly prevalent, HIV-affected couples require multipurpose prevention technologies (MPTs) to enhance their reproductive healthcare options beyond contraception and prevention of HIV and sexually transmitted infections (STIs). HIV-affected couples are living longer, healthier lives and are requesting options that will include assistance in becoming pregnant and establishing a family. These couples face unique challenges that require access to specialized information and reproductive services to prevent STIs or HIV transmission while attempting pregnancy. The male condom is the oldest and least expensive available MPT that effectively