

The cervicovaginal microbiome, genital inflammation and HIV acquisition in sub-Saharan African women

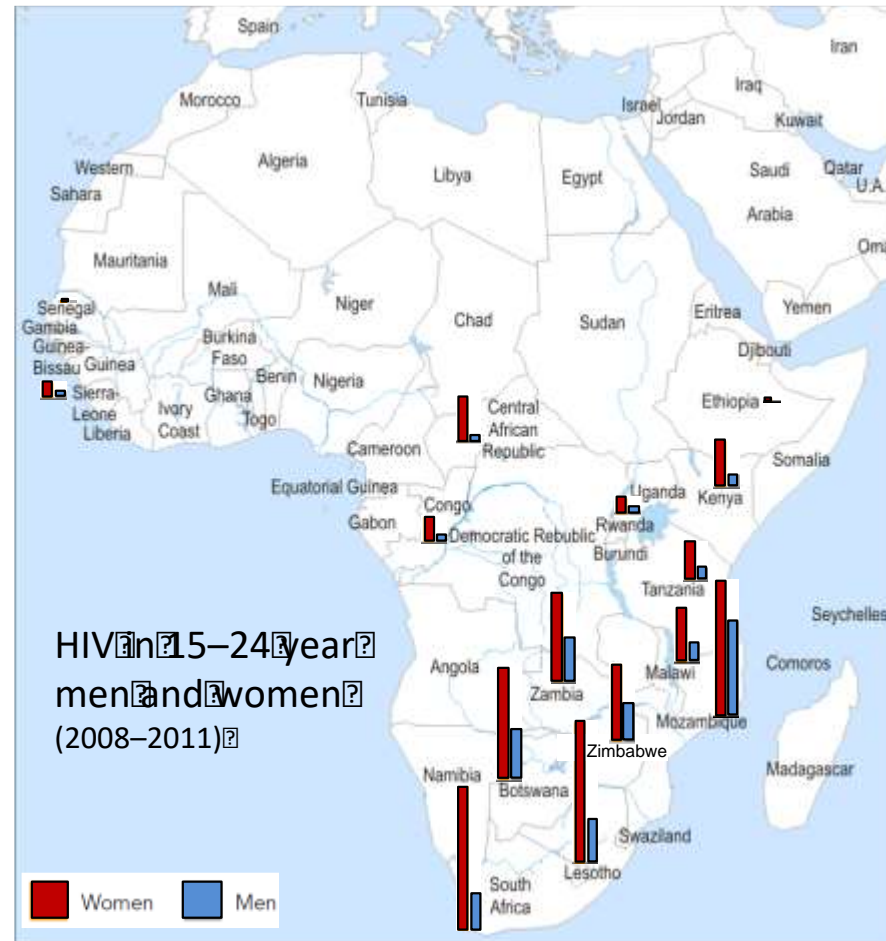
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Ragon Institute of MGH, MIT and Harvard
Harvard Medical School

MTN Annual Meeting
Washington, DC
March 20, 2017

The unequal burden of HIV in sub-Saharan Africa

HIV prevalence in young women is up to 8 times greater than young men

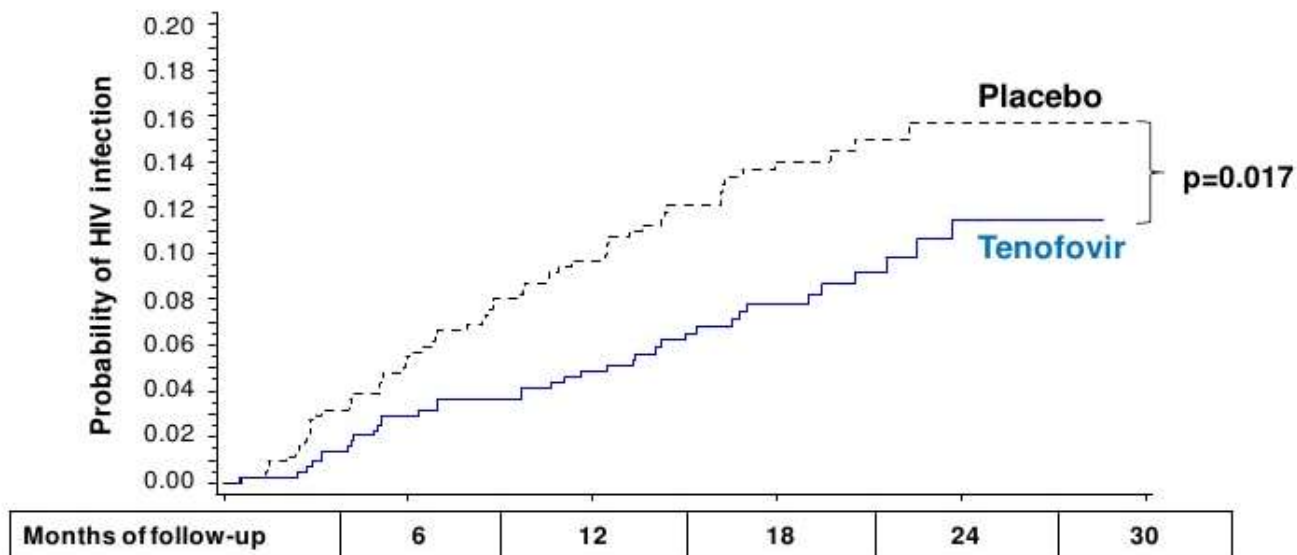


UNAIDS, courtesy of Slim Karim

Insights into the role of genital inflammation and HIV acquisition from the CAPRISA 004 trial

Effectiveness and Safety of Tenofovir Gel, an Antiretroviral Microbicide, for the Prevention of HIV Infection in Women

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Karim *et al.*, Science, 2010

- ▶ Women with high levels of genital inflammatory cytokines had a **3.2 fold** increased risk of becoming infected with HIV

Masson *et al.*, CID, 2015

FRESH Study

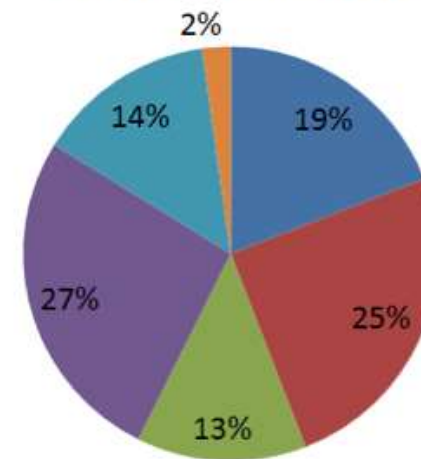


Females Rising through Education, Support and Health

- ▶ >900 HIV seronegative women between ages 18-23 in Umlazi, South Africa
- ▶ Classes twice a week – focus on poverty alleviation
- ▶ HIV viral load testing twice weekly
- ▶ Pelvic exams and blood draws every 3 months
- ▶ High frequency mucosal and blood sampling in early HIV infection



FRESH Placement Data



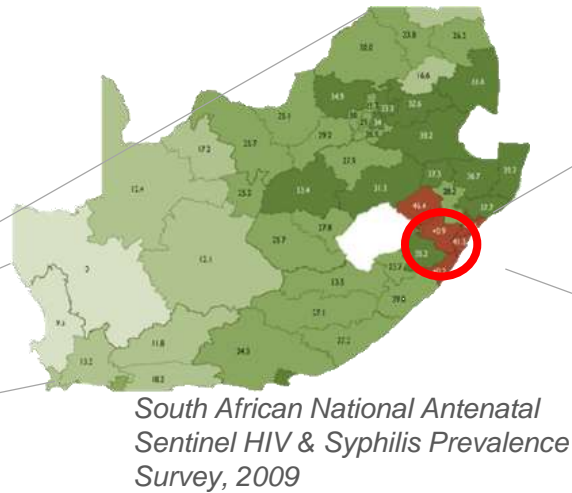
- Employment
- Internship/Learnership
- Matric Completion (exam only; return to school+exam)
- Not yet placed

Burden of HIV in sexually active young women in KwaZulu Natal, South Africa

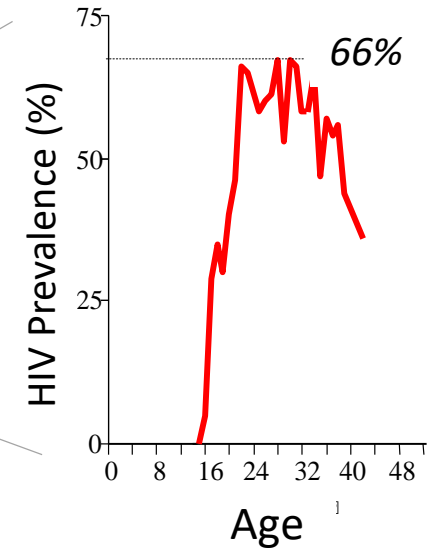
HIV Prevalence in sub-Saharan Africa



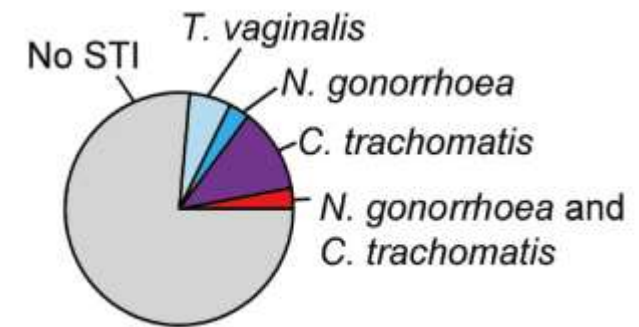
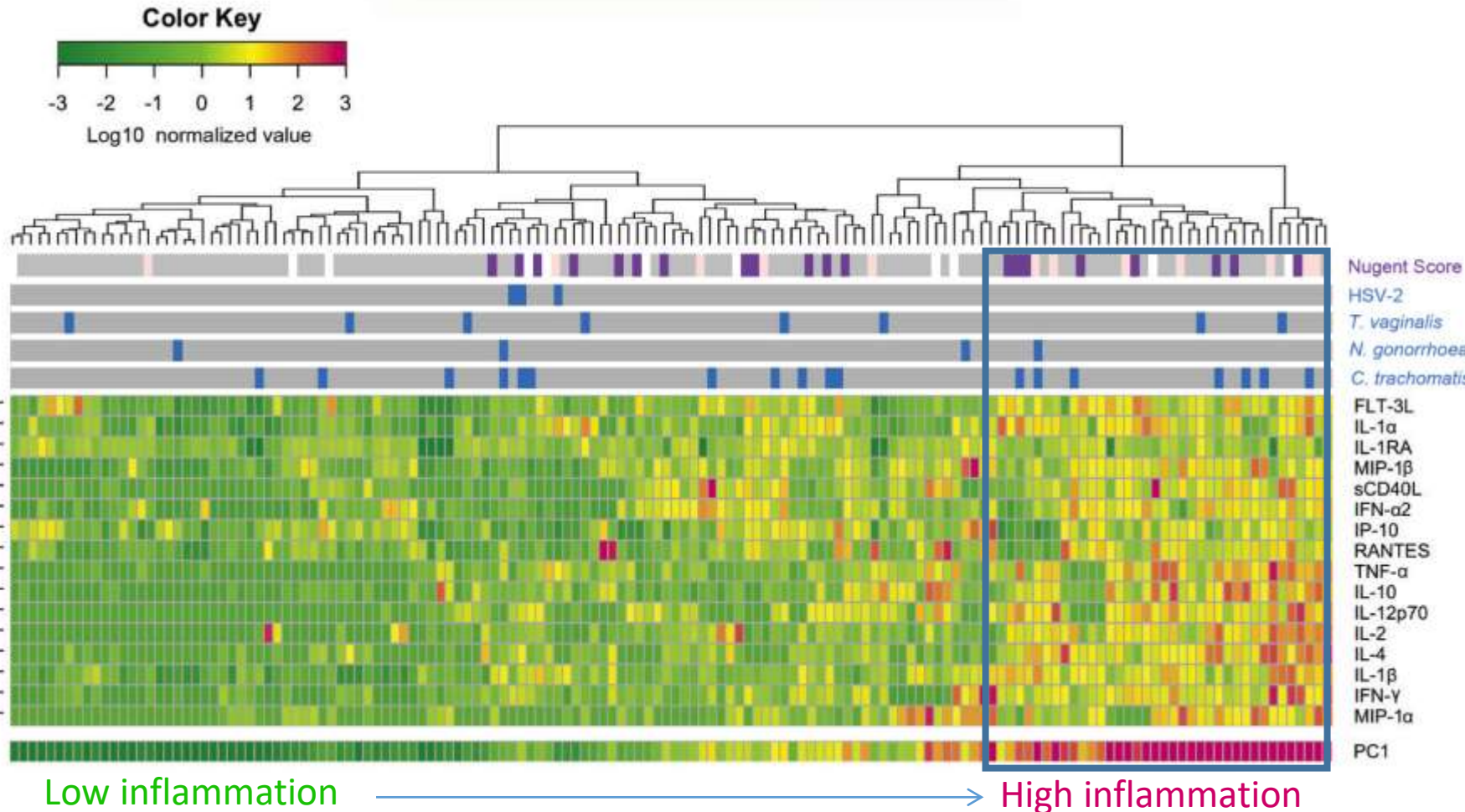
UNAIDS 2014



South African National Antenatal Sentinel HIV & Syphilis Prevalence Survey, 2009

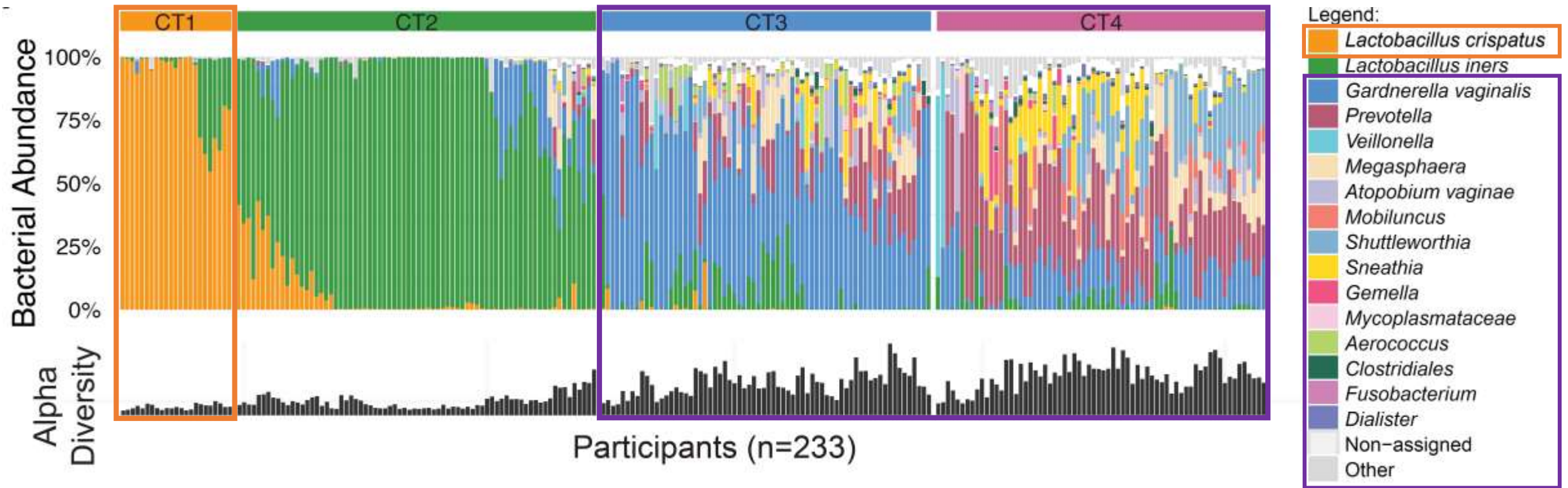


Asymptomatic women display a broad range of baseline genital inflammation

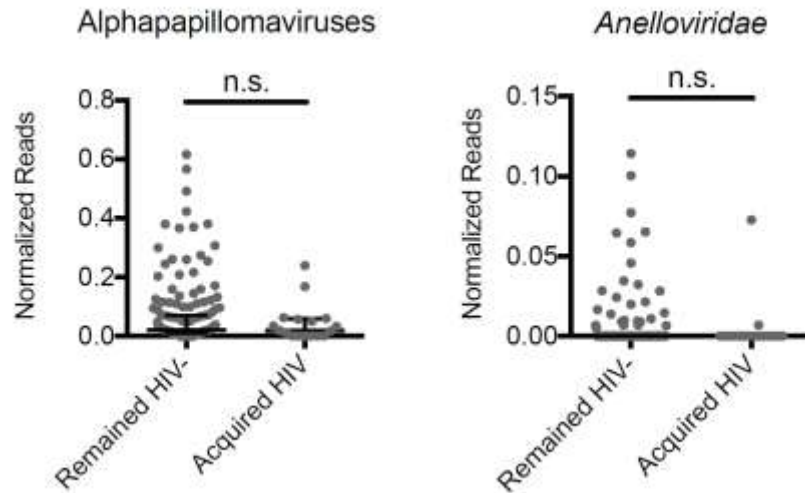
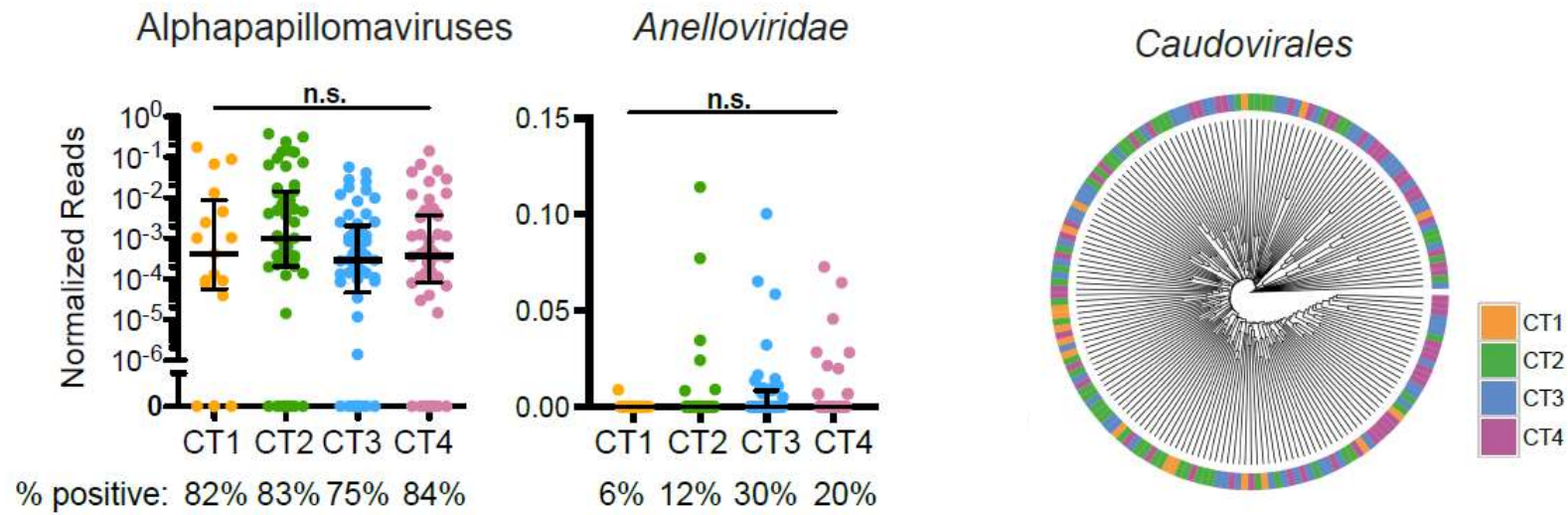


Cytokine levels were also not associated with hormonal contraceptive usage or sexual behavior

Bacterial genital microbial community structures in healthy women in FRESH have high diversity



No differences in the FGT virome across cervicotypes

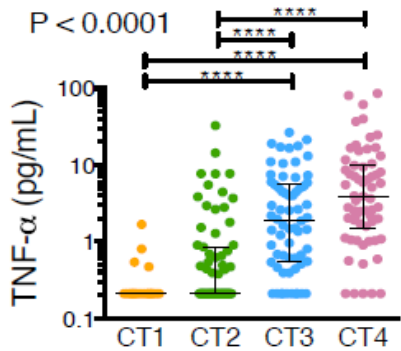
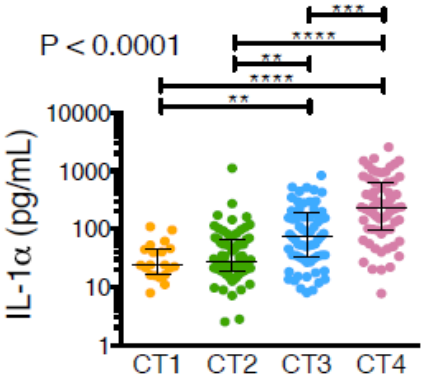
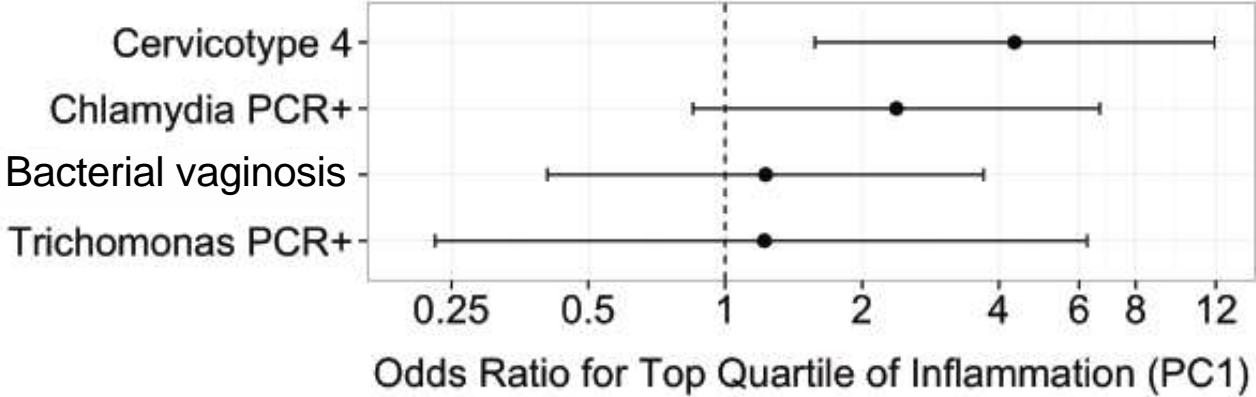
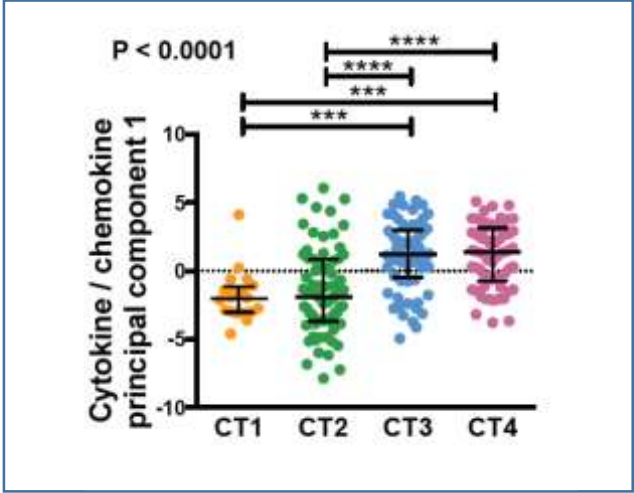


No significant differences in baseline HIV risk behavior or demographic factors between CTs

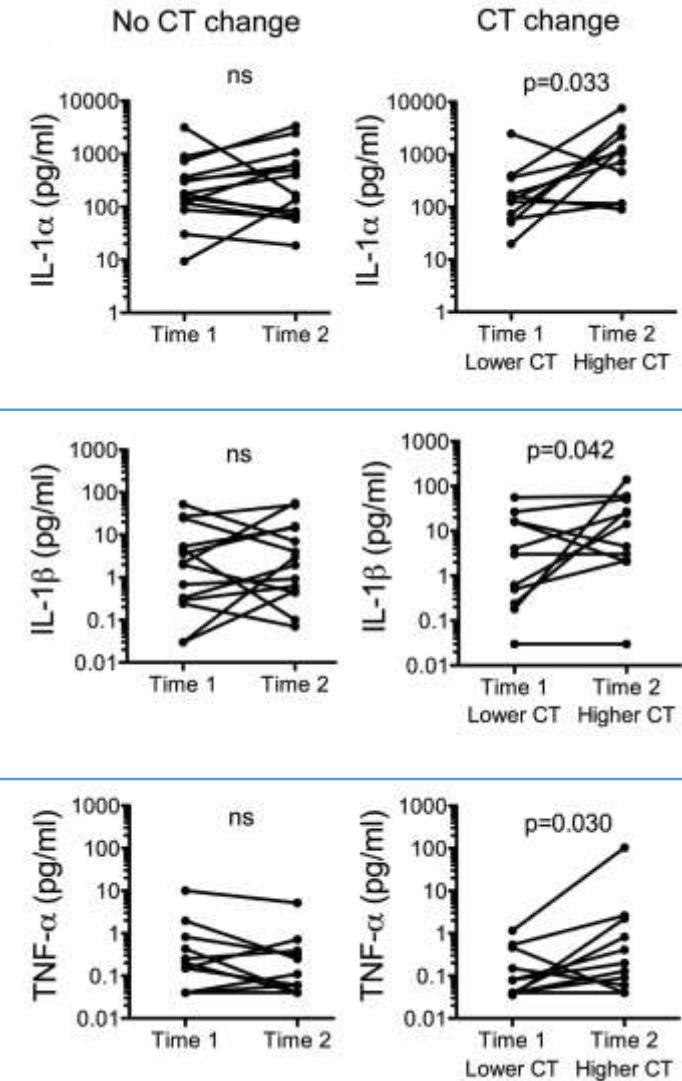
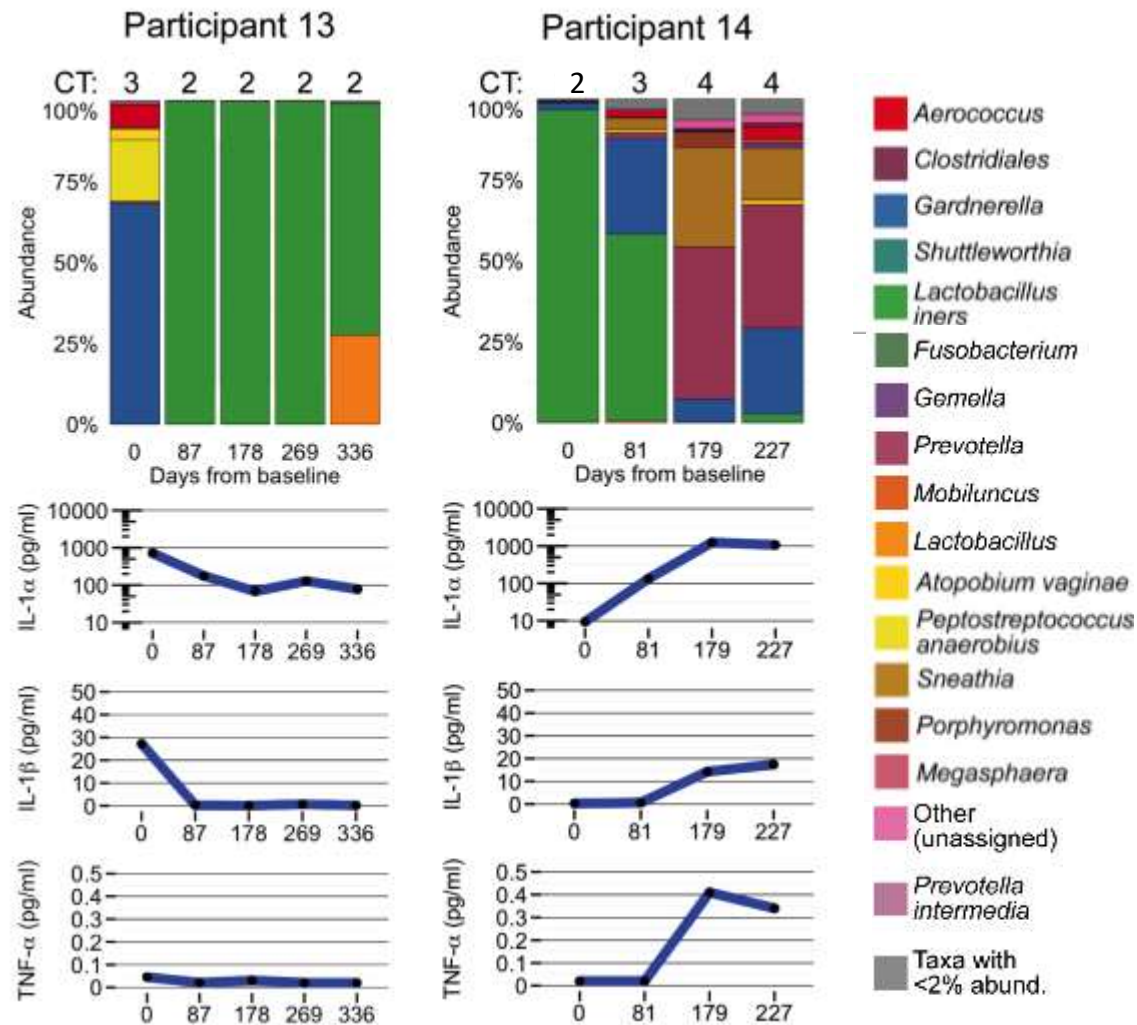
Bacterial community structures did not vary with:

- STIs
- Hormonal contraceptive use
- Condom use
- Use of intravaginal drying agents
- Frequency of sex
- Anal sex
- Demographic factors

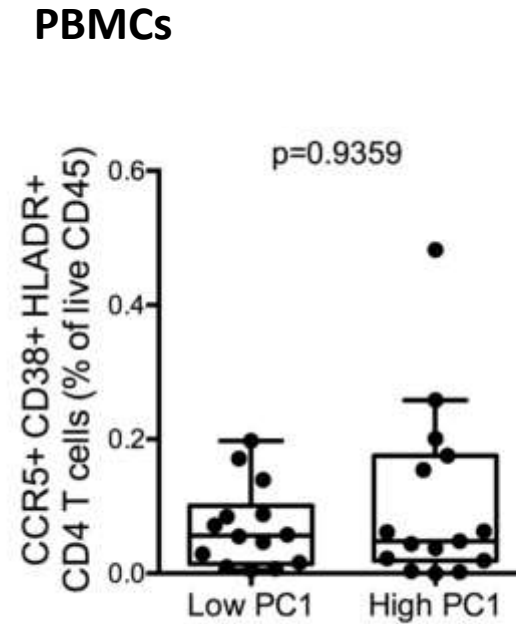
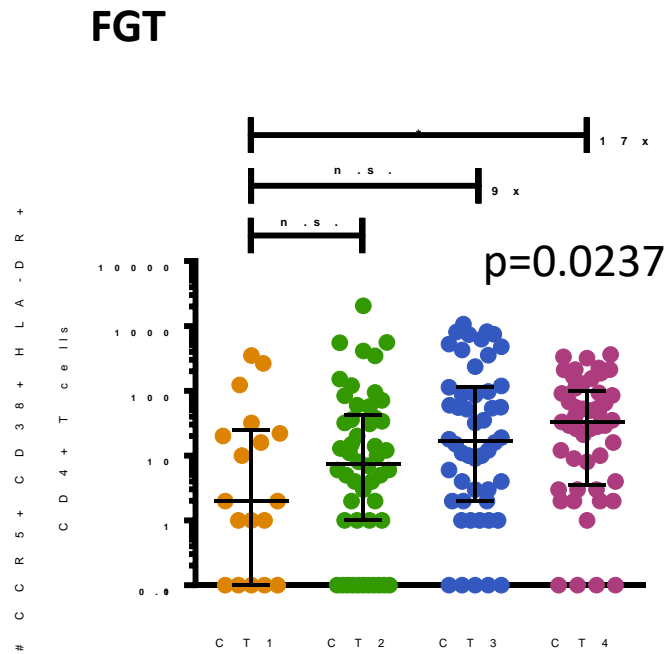
High bacterial diversity and low *Lactobacillus* abundance predicts genital inflammation



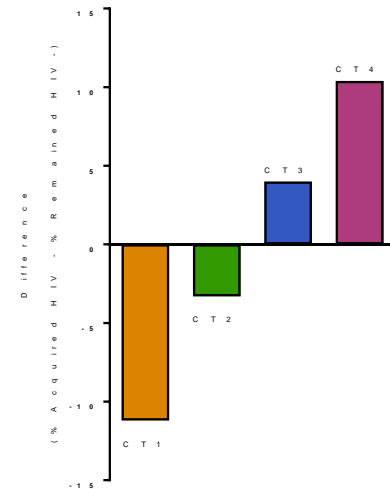
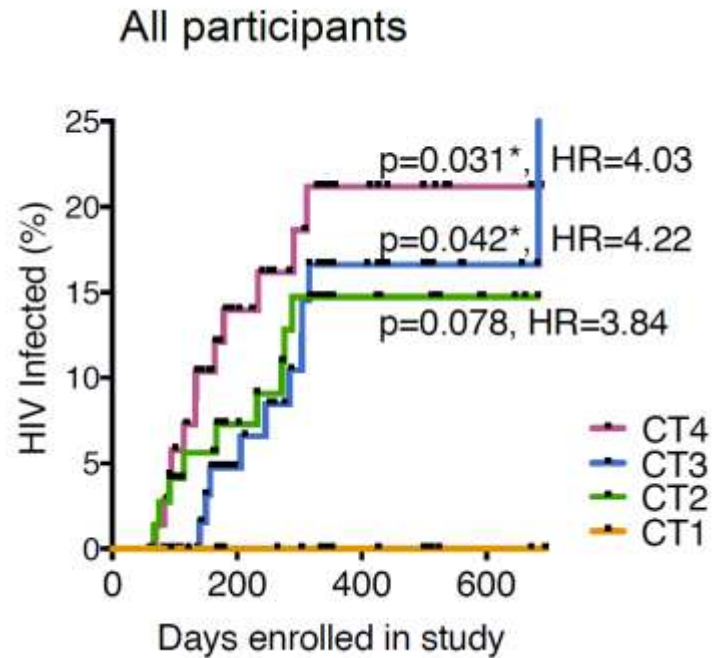
Longitudinal intra-individual correlation between vaginal bacteria and pro-inflammatory cytokines



Genital inflammation is associated with cervical HIV target cell frequency

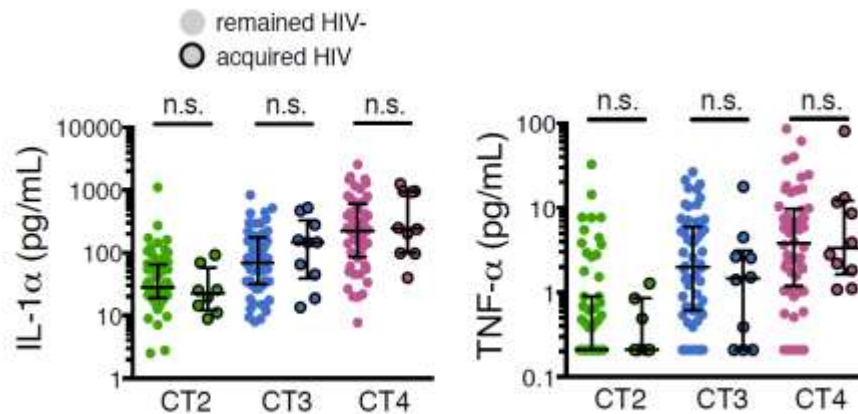
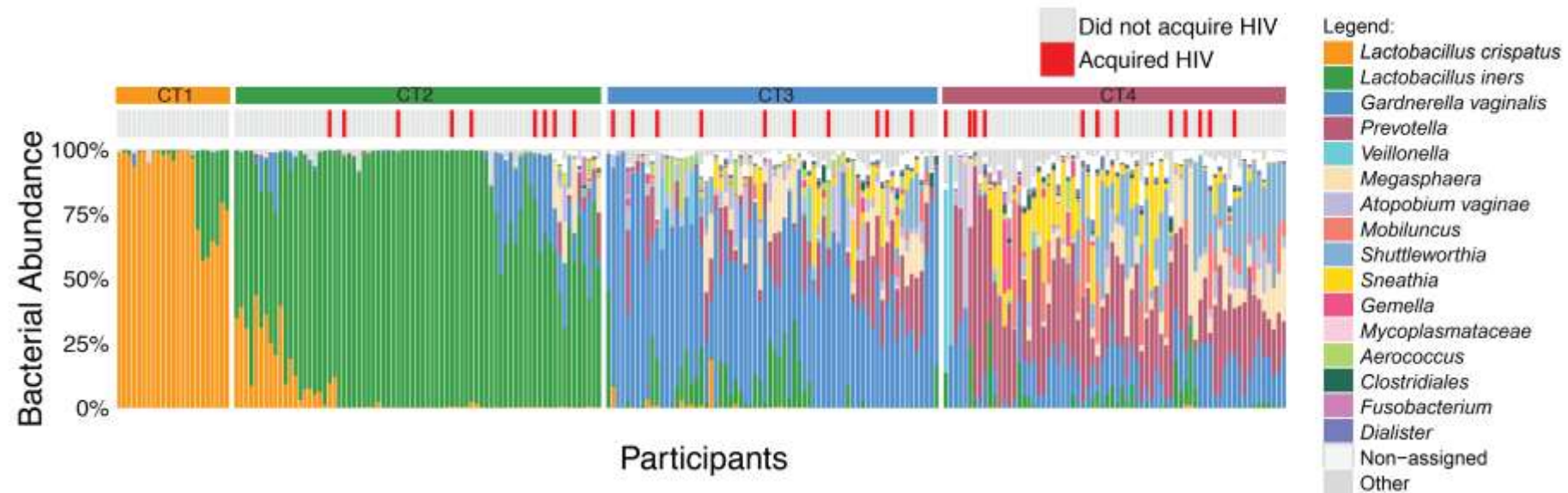


Cervicovaginal bacterial communities are associated with HIV acquisition in young women in sub-Saharan Africa



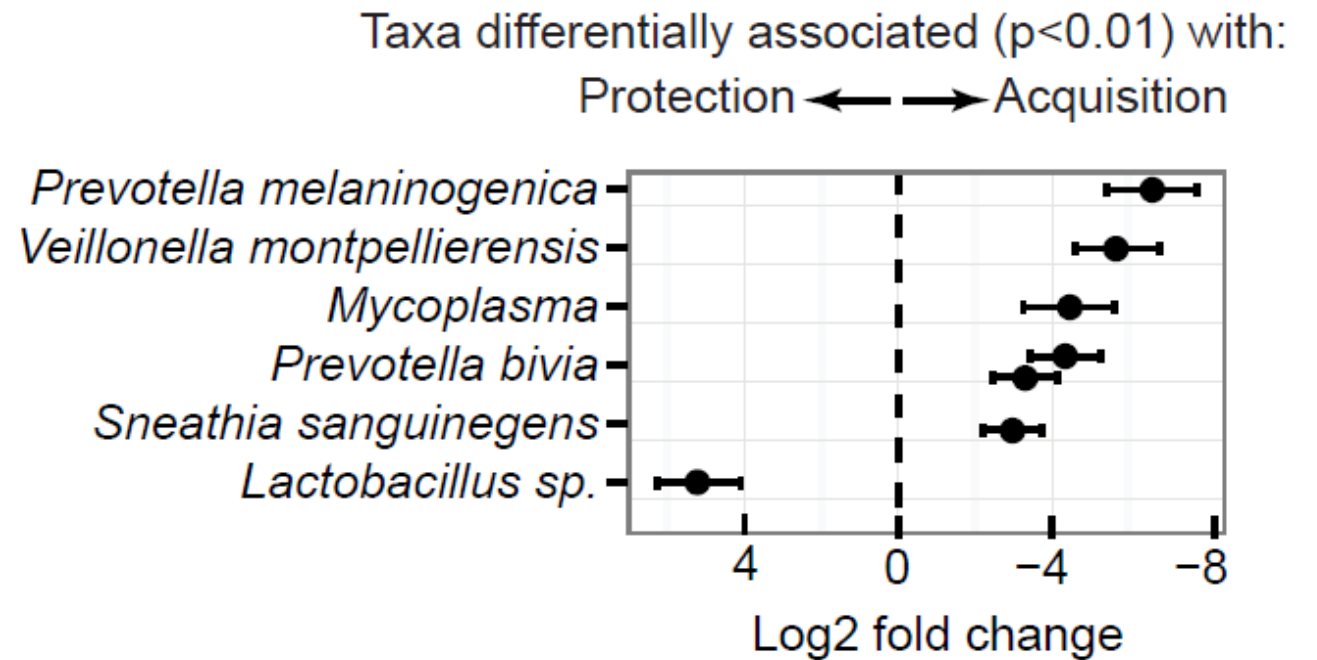
Group	Remained HIV-	Acquired HIV
%CT1 (n)	11.2 (23)	0 (0)
%CT2 (n)	32.3 (66)	29.0 (9)
%CT3 (n)	28.3 (58)	32.3 (10)
%CT4 (n)	28.3 (58)	38.7 (12)

No specific clustering of HIV acquisition within cervicovaginal community types

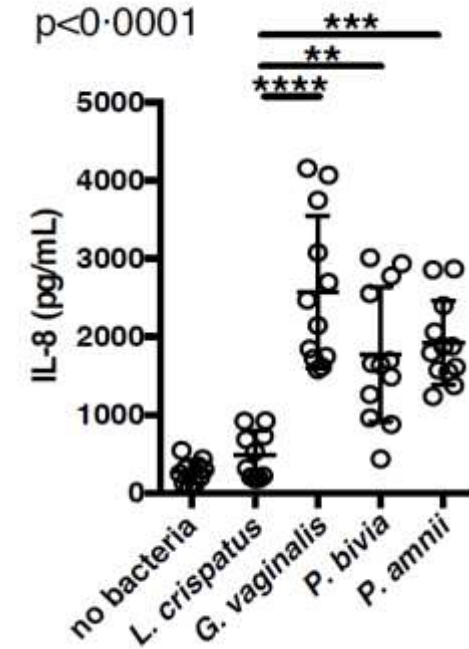
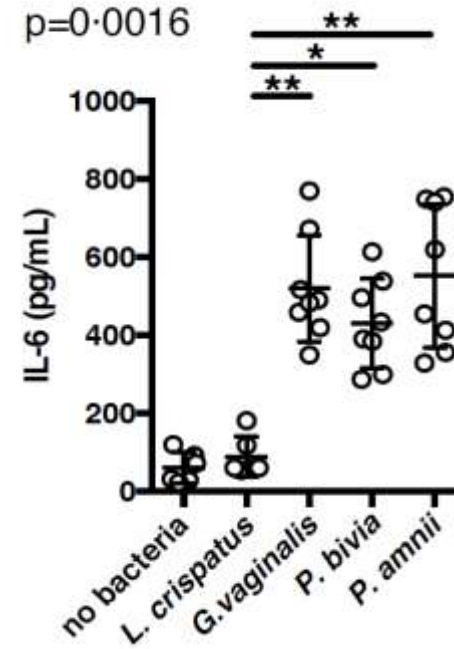
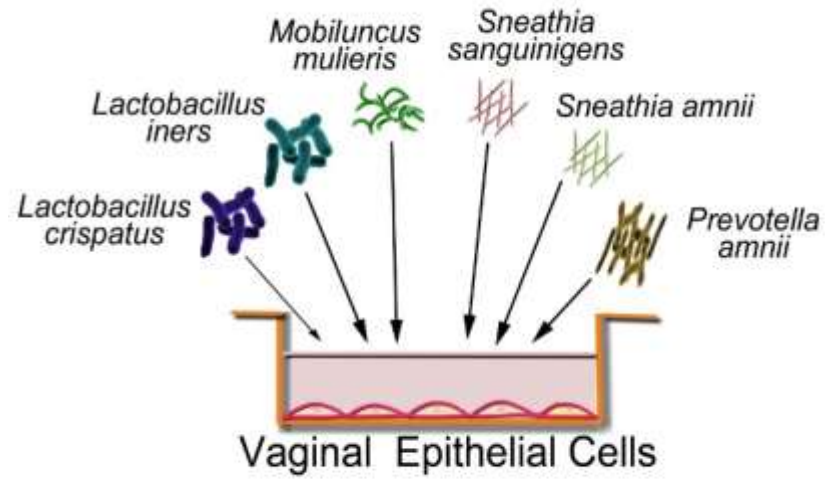


Specific bacterial taxa are significantly associated with increased genital inflammation and HIV acquisition

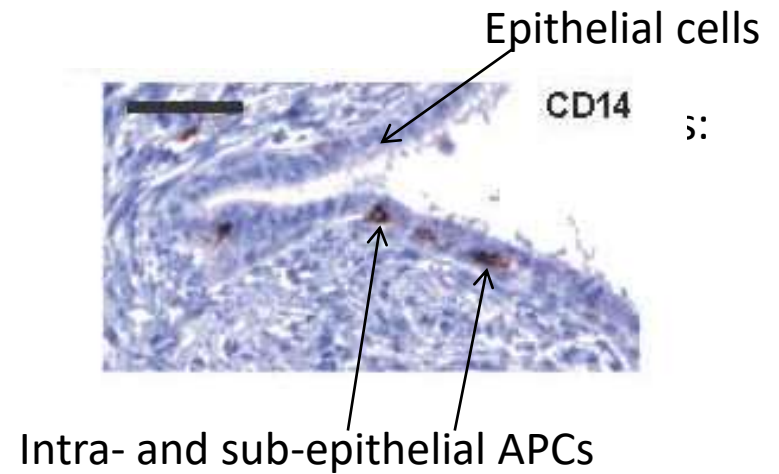
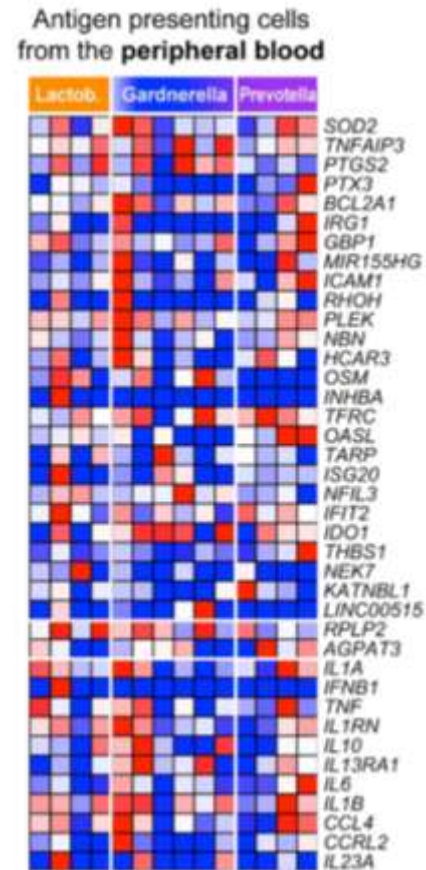
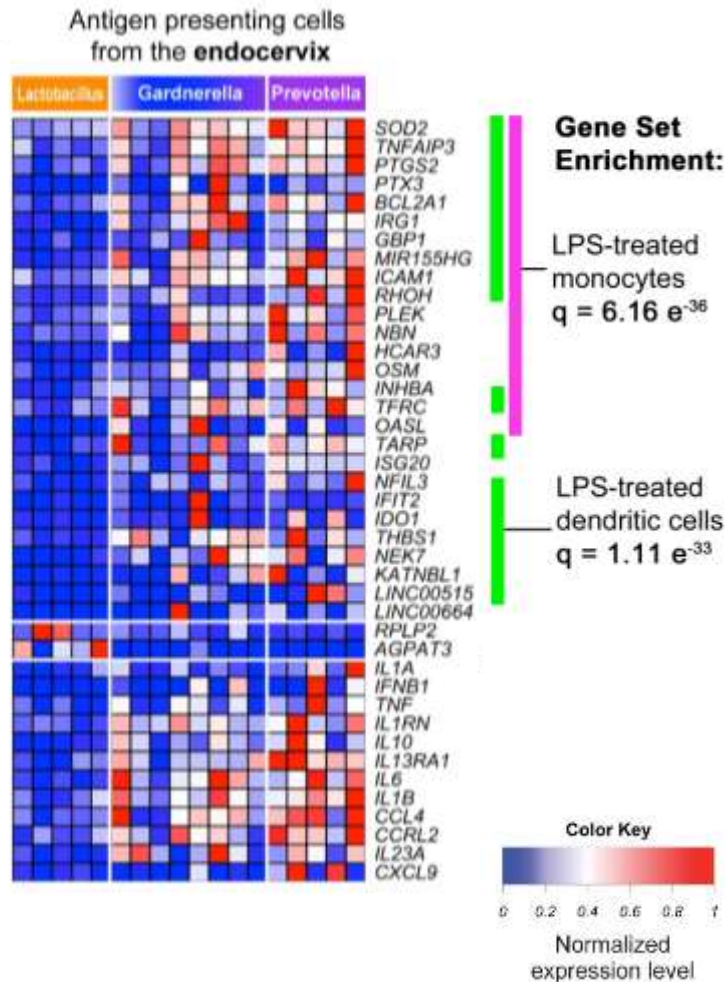
	PC1 Correlation Coefficient	Q Value
<i>Megasphaera</i>	0.60 ± 0.10	3.1e-07
<i>Clostridium</i>	0.45 ± 0.07	4.2e-07
<i>Prevotella</i>	0.43 ± 0.08	1.8e-06
<i>Atopobium vaginae</i>	0.42 ± 0.08	3e-05
<i>Sneathia</i>	0.37 ± 0.08	3.3e-04
<i>Dialister</i>	0.37 ± 0.07	2e-05
<i>Veillonellaceae</i>	0.34 ± 0.05	1.2e-07
<i>Coriobacteriaceae</i>	0.32 ± 0.07	3e-05
<i>Parvimonas</i>	0.31 ± 0.07	2.9e-04
<i>Gardnerella vaginalis</i>	0.31 ± 0.07	2.9e-04
<i>Gemella</i>	0.28 ± 0.08	6e-03
<i>Leptotrichiaceae</i>	0.26 ± 0.07	2.1e-03
<i>Mobiluncus</i>	0.25 ± 0.08	1.4e-02
<i>Lactobacillus iners</i>	-0.41 ± 0.09	3.4e-04
<i>Lactobacillus crispatus</i>	-0.46 ± 0.09	6.8e-06



In vivo proinflammatory bacterial species induce inflammatory cytokine production by human vaginal epithelial cells *in vitro*

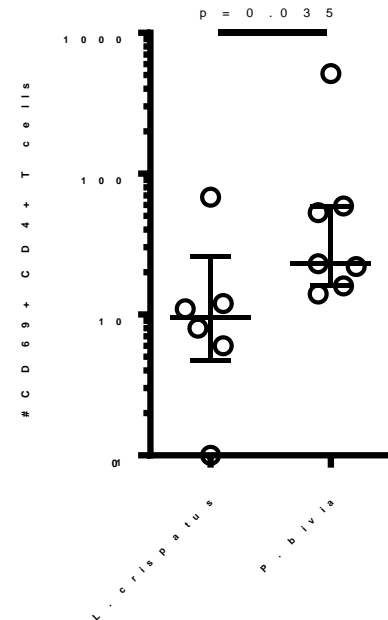
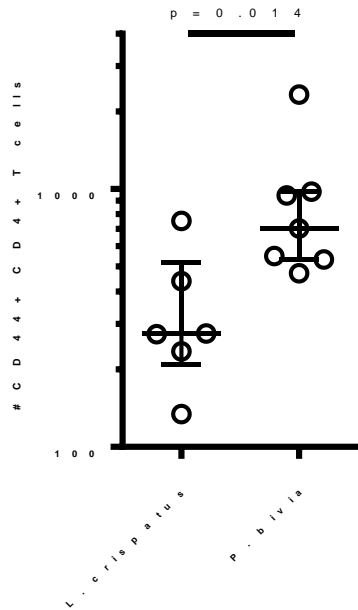
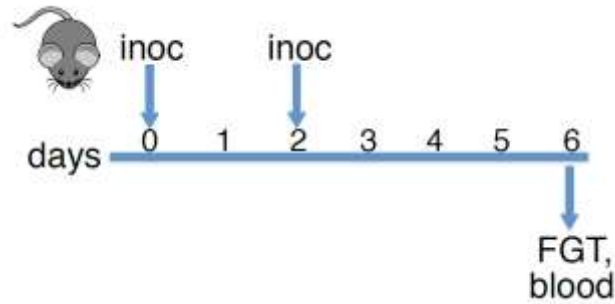


Upregulation of APC LPS-sensing pathways involved in bacterial sensing

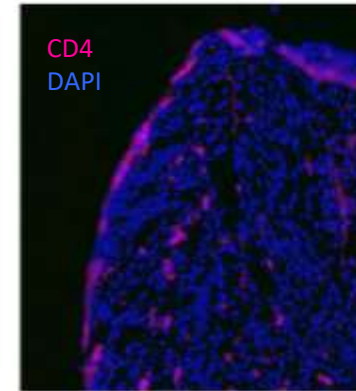


KEGG Pathway	Enriched in:	LDA Score (Log 10)
ko00780 Biotin metabolism	HighInflamm	3.290
ko00540 Lipopolysaccharide biosynthesis	HighInflamm	3.201
ko00750 Vitamin B6 metabolism	HighInflamm	3.157
ko00410 beta-Alanine metabolism	HighInflamm	3.149
ko02040 Flagellar assembly	HighInflamm	3.110

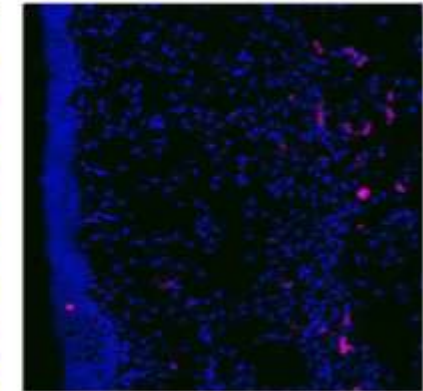
Inflammatory bacteria from women induce increased HIV target cells in the genital tract of germ free mice



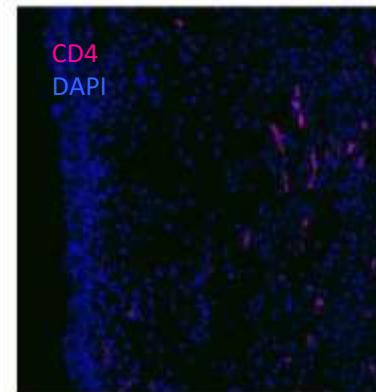
A. PBS treated



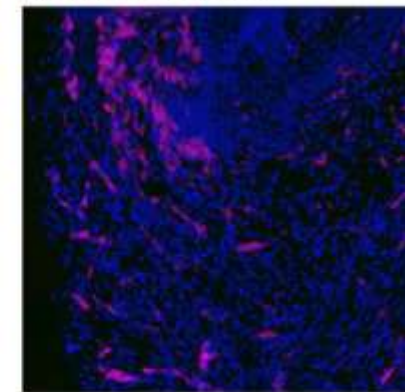
B. *Lactobacillus gasseri*



C. *Lactobacillus crispatus*



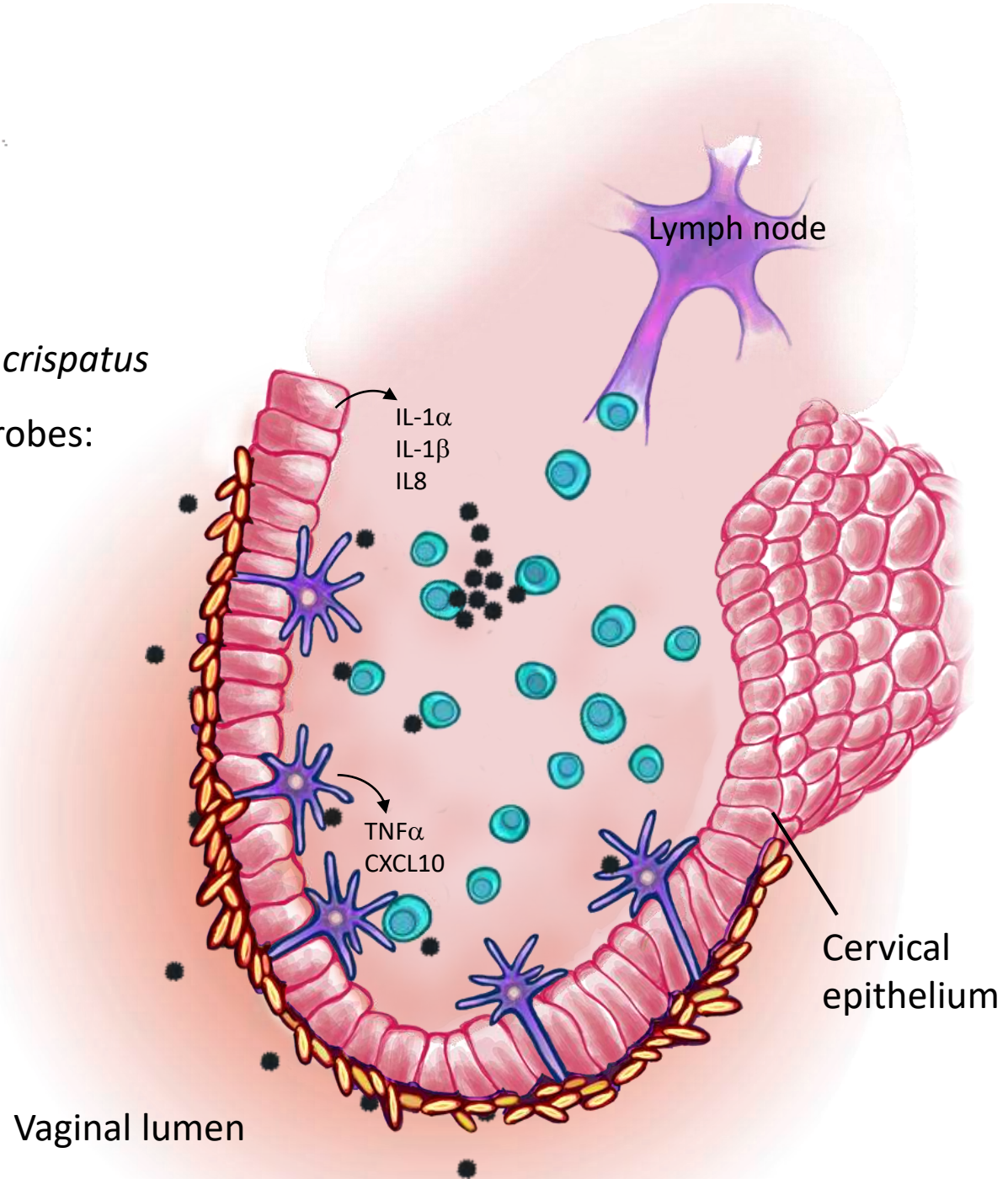
D. *Prevotella bivia*



Summary

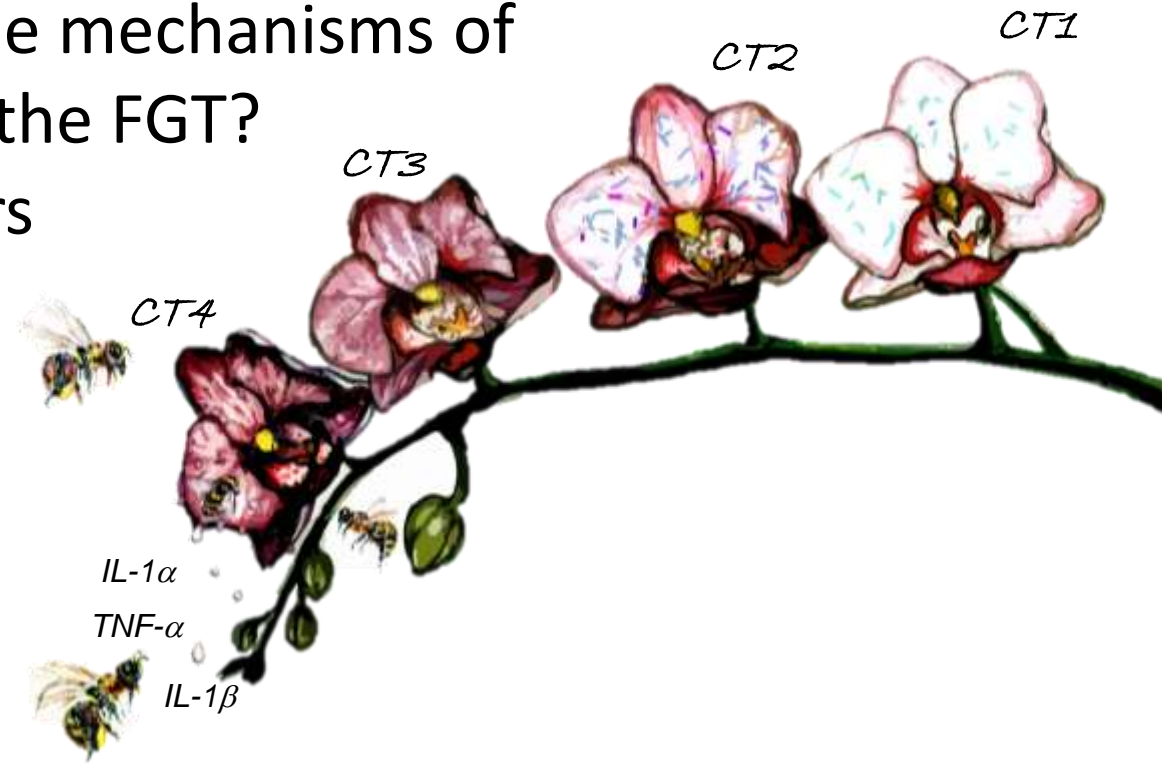
Cervicotype 1: *Lactobacillus crispatus*

Cervicotype 4: Diverse anaerobes:
Prevotella, *Gardnerella*,
Shuttleworthia, *Sneathia*,
Megasphaera



Next questions

- Can the cervicovaginal microbiome be leveraged to reduce HIV acquisition risk in women?
- What is the cause of increased baseline vaginal bacterial community diversity in South African women?
- Can we more specifically define the mechanisms of host immune sensing of bacteria in the FGT?
- What other genital mucosal factors modulate risk of HIV acquisition in women?



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Study participants!



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