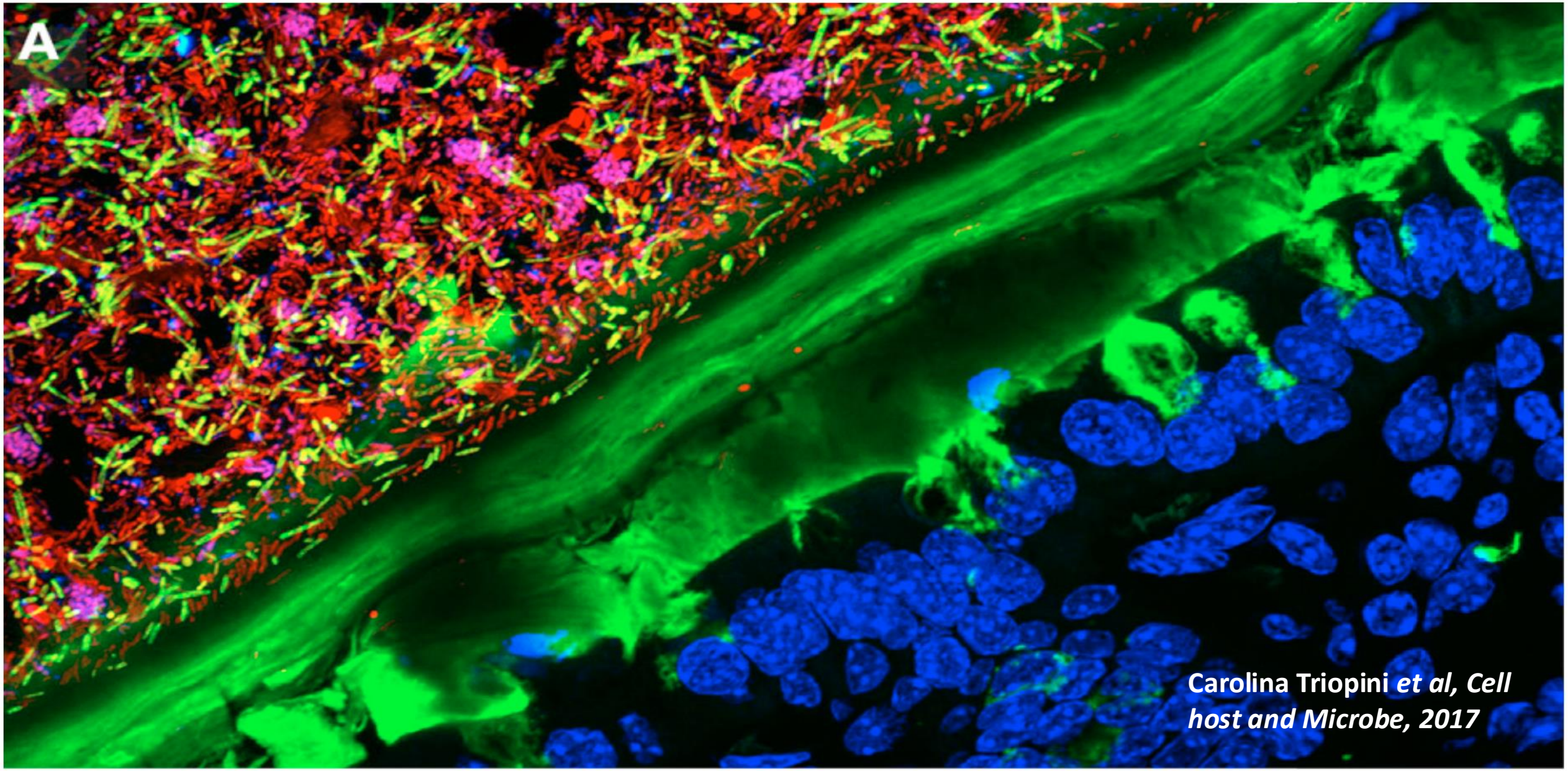
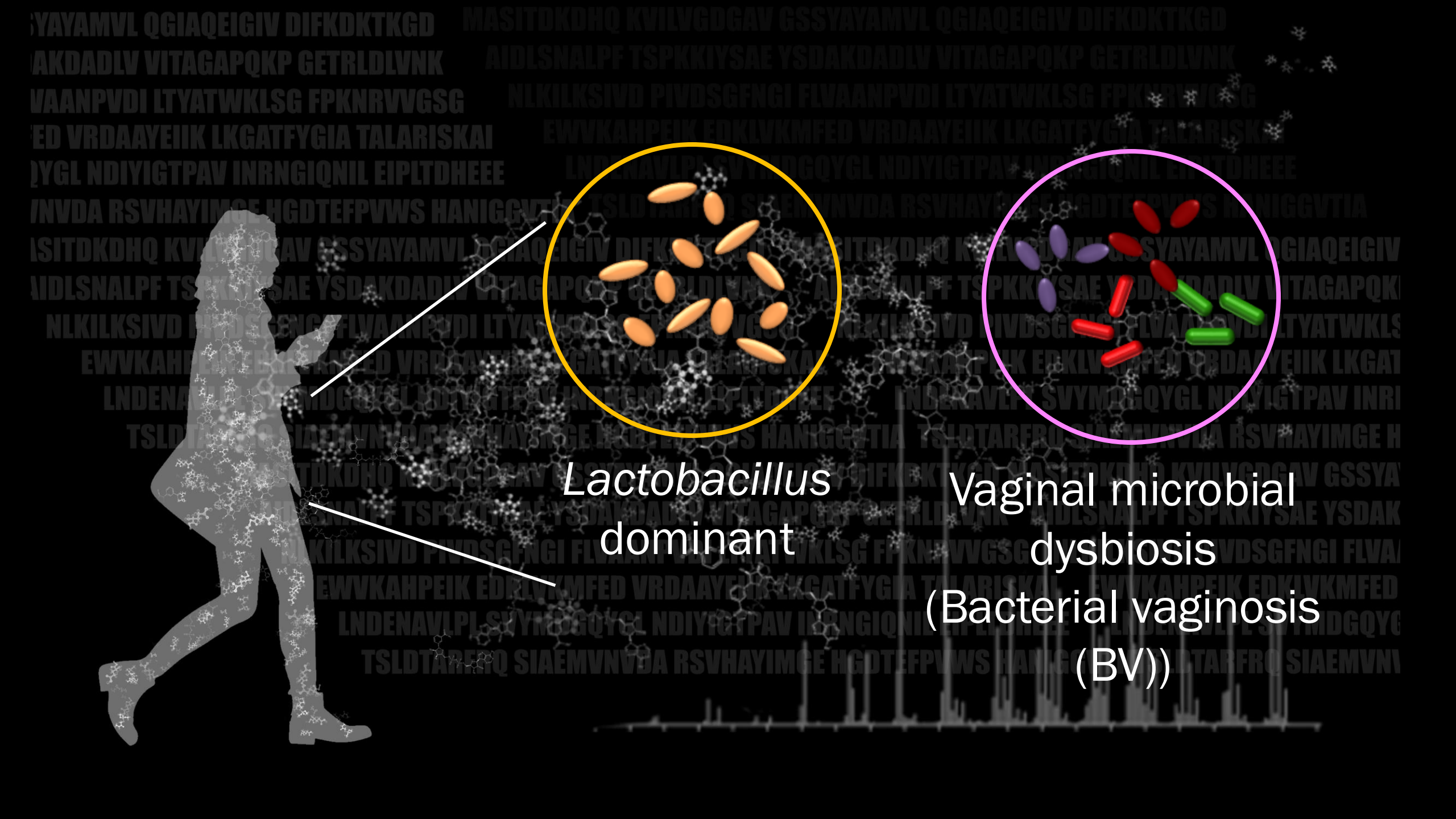
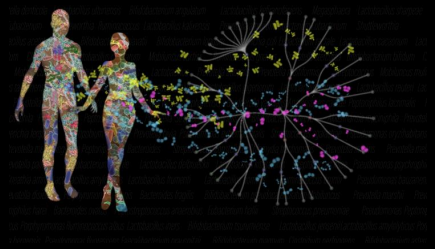
Host-microbiome correlates of immunity and HIV susceptibility in the female genital tract

Adam Burgener, Ph.D.
Director, Center for Global Health and Diseases
Case Western Reserve University


A
Carolina Triopini *et al, Cell host and Microbe, 2017*

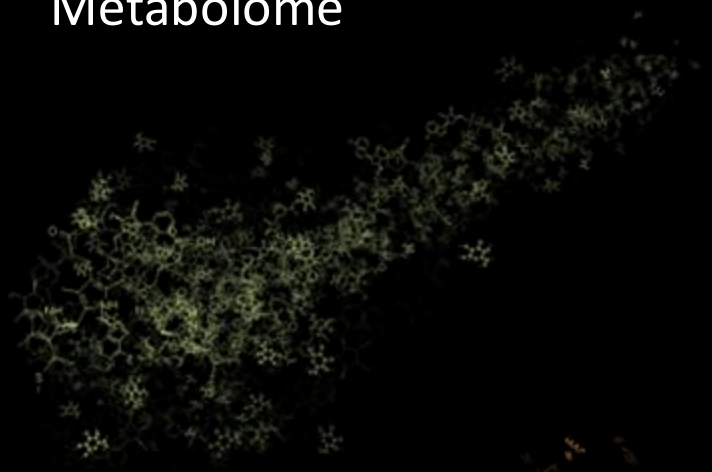

Lactobacillus dominant
Vaginal microbial dysbiosis (Bacterial vaginosis (BV))

How does the microbiome affect mucosal immunity?

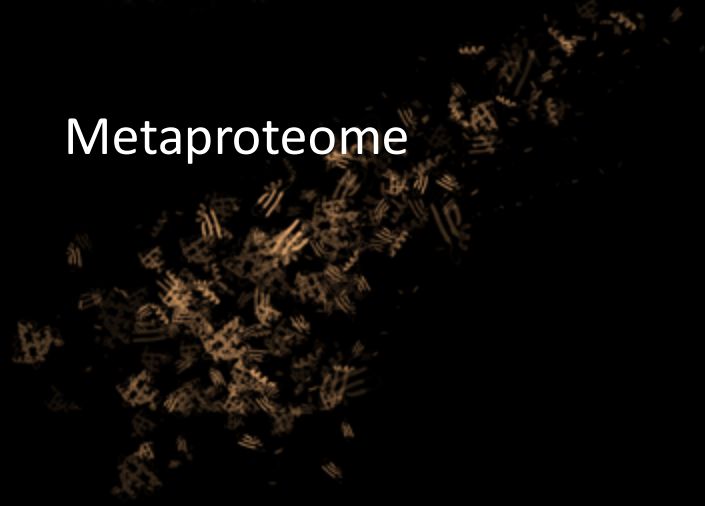


Microbiome

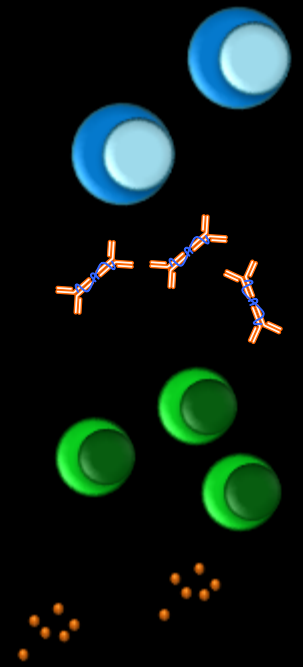
Metabolome



Metaproteome

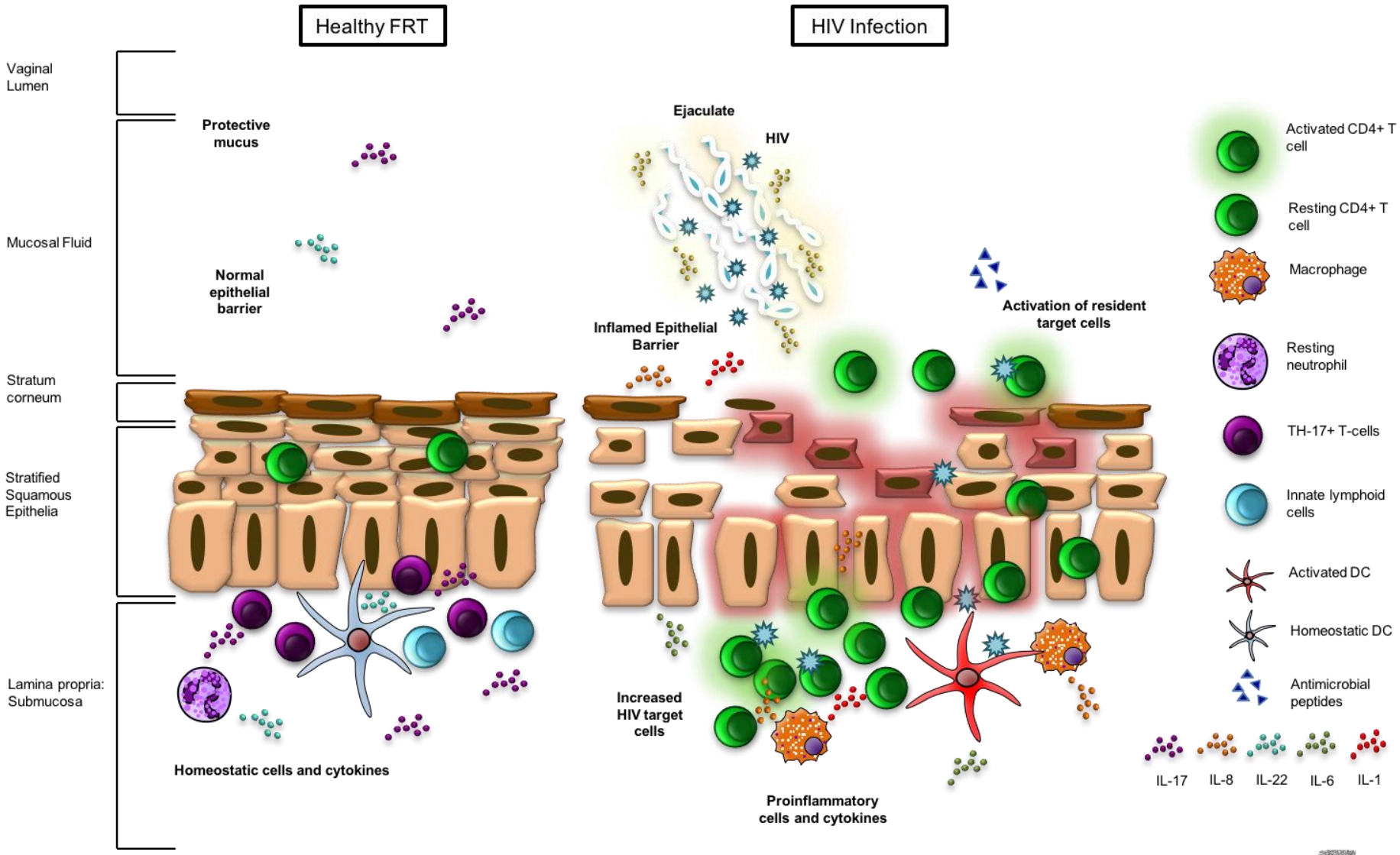


Host immunity and disease susceptibility



Mass spectrometry instrumentation

Vaginal mucosal barrier and HIV infection



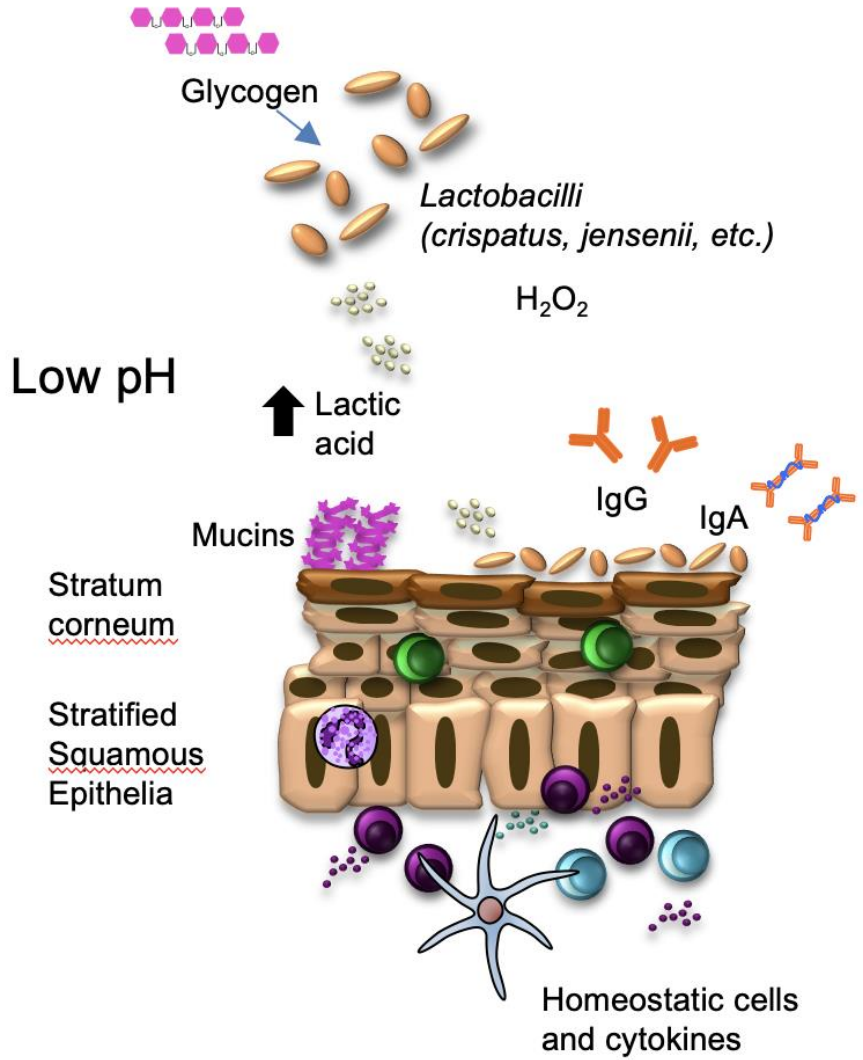
Available online at www.sciencedirect.com
ScienceDirect
Current Opinion in Immunology

HIV and mucosal barrier interactions: consequences for transmission and pathogenesis

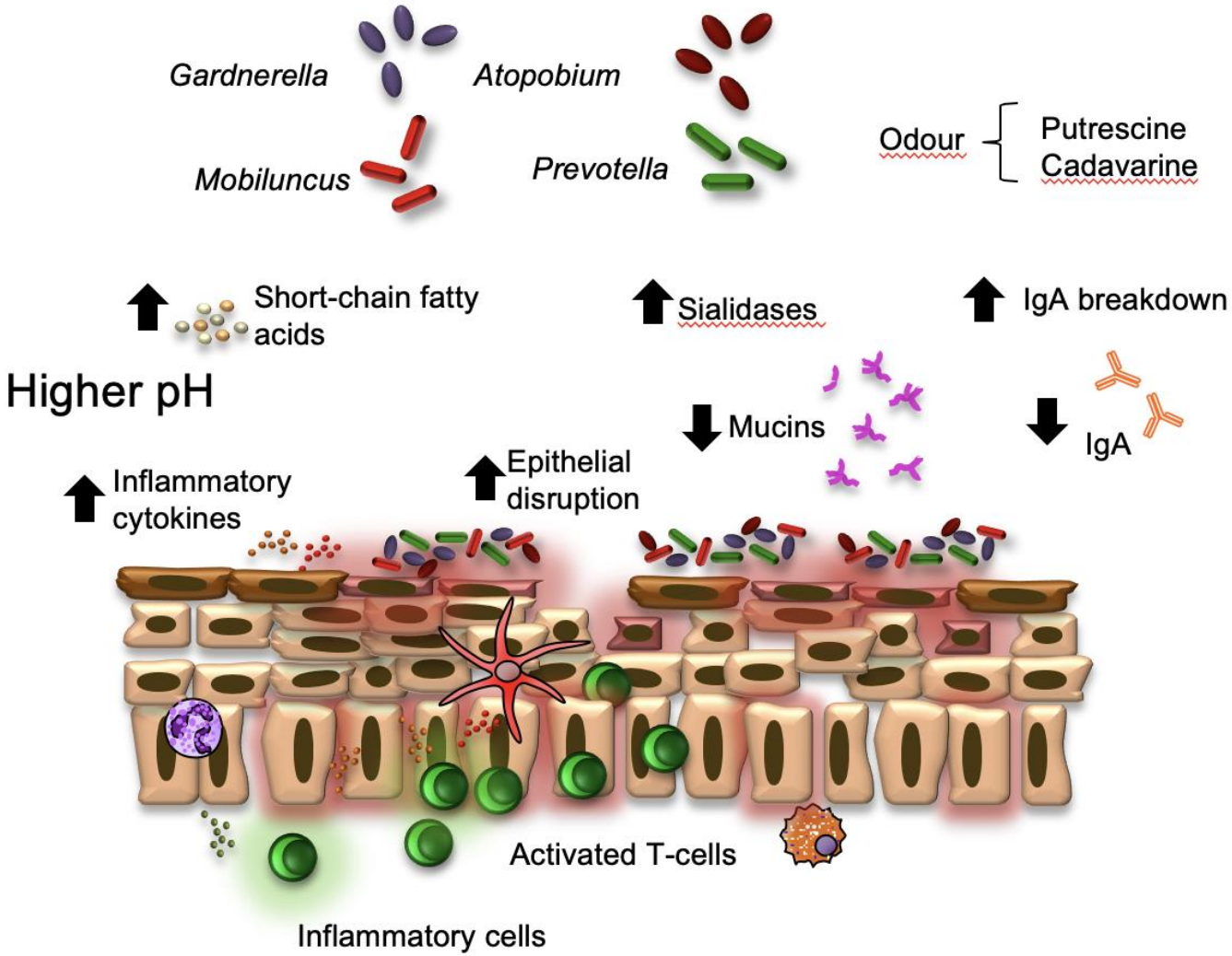
Adam Burgener[1,2,3], Ian McGowan[4,5] and Nichole R Klatt[6,7]

Vaginal microbiome affects mucosal immunity, inflammation and epithelial homeostasis

Lactobacillus dominant



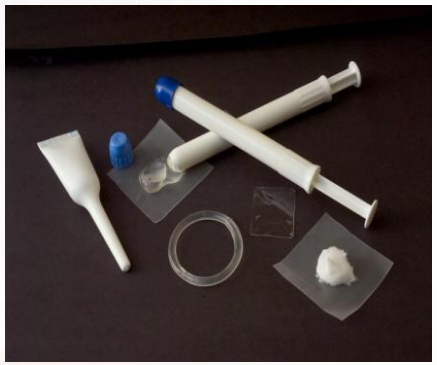
Vaginal microbial dysbiosis (Bacterial vaginosis)



Pre-exposure prophylaxis (PrEP)

- PrEP: people at high risk for HIV take HIV medicines daily or before sexual intercourse to lower their chances of getting infected.

Pill



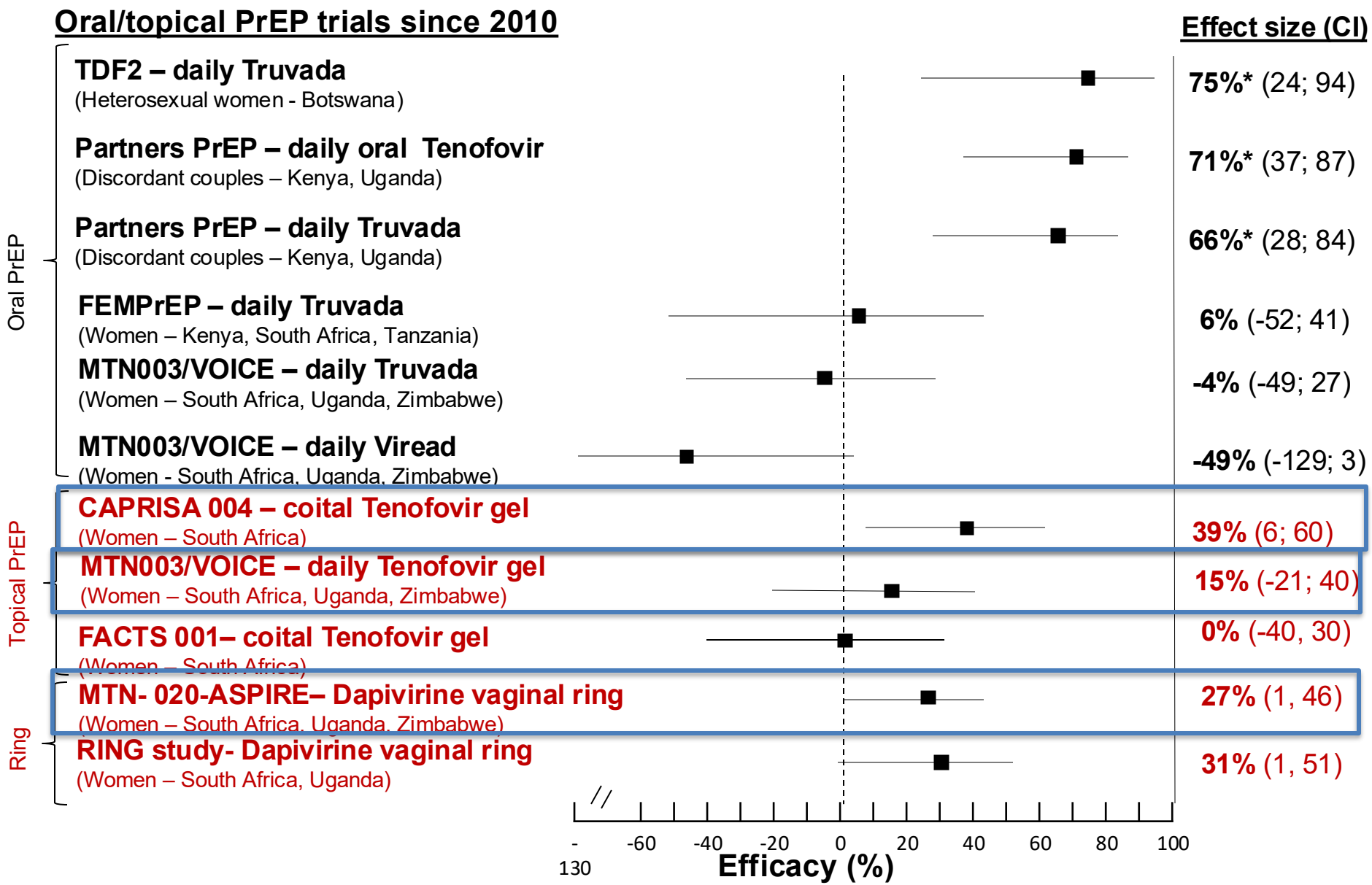
Gel

Vaginal film

Vaginal ring

Injectable

Efficacy of antiretroviral pills, gels, & rings in women for HIV prevention



S.A. Karim, Q. A. Karim, L. McKinnon

S. Hillier, J. Marrazzo, M. Chirenje

S. Hillier J. Baeten

**point estimate for women only*

Vaginal microbiome affects drugs for HIV prevention

Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women

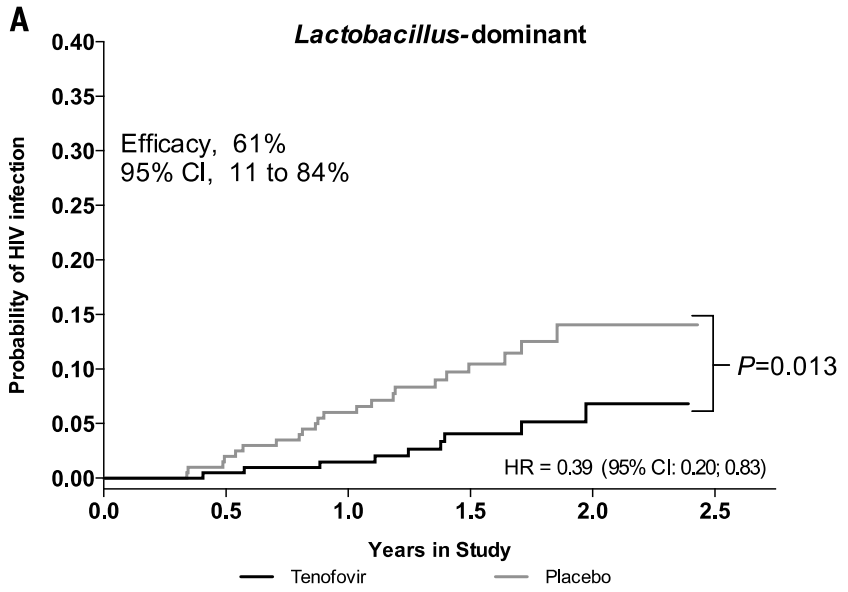
Nichole R. Klatt,[1*†] Ryan Cheu,[1‡] Kenzie Birse,[2,3‡] Alexander S. Zevin,[1‡] Michelle Perner,[2,3‡] Laura Noël-Romas,[2,3‡] Anneke Grobler,[4] Garrett Westmacott,[5] Irene Y. Xie,[2,3] Jennifer Butler,[2,3] Leila Mansoor,[4] Lyle R. McKinnon,[3,4] Jo-Ann S. Passmore,[6,4] Quarraisha Abdool Karim,[4,7] Salim S. Abdool Karim,[4,7] Adam D. Burgener[2,3,8*†]

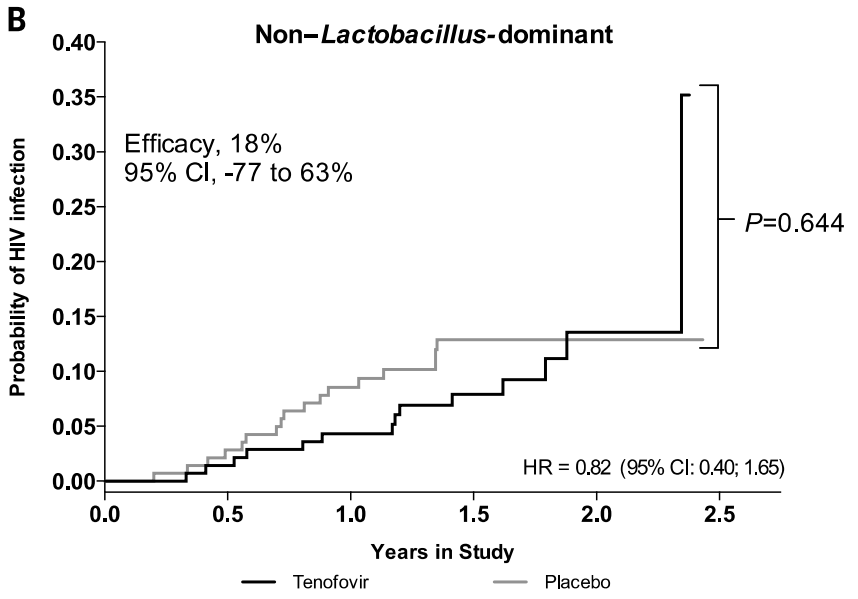
INFECTIOUS DISEASE

Vaginal microbiome affects HIV risk

Unusual bacteria in vagina help explain high infection rates in South African women

By Jon Cohen, *in Durban, South Africa* | the trial with that of 70 who remained HIV | that *P. bivia* itself releases an inflammation-





***Lactobacillus*-dominant women at risk (Cumulative number of infections)**

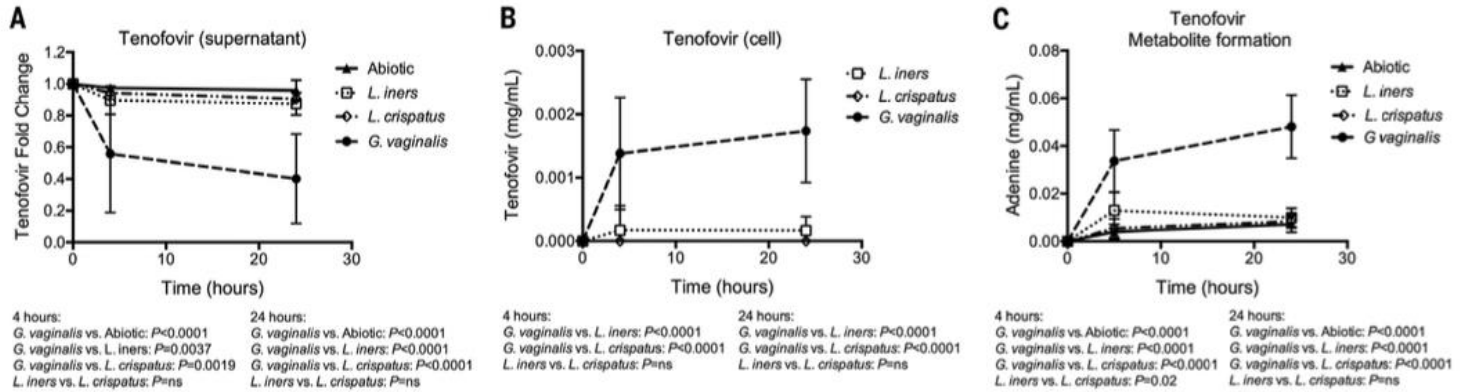
Tenofovir	205 (0)	204 (1)	183 (3)	129 (7)	46 (9)	0 (9)
Placebo	202 (0)	196 (4)	173 (12)	123 (19)	51 (22)	0 (22)

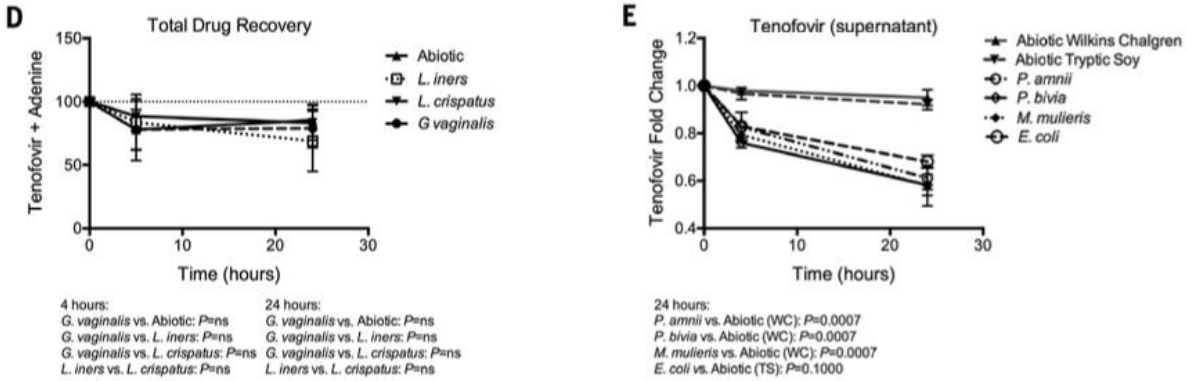
Non–*Lactobacillus*-dominant women at risk (Cumulative number of infections)

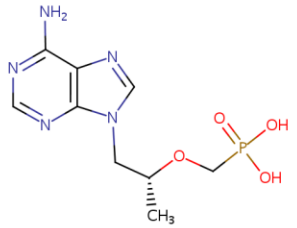
Tenofovir	140 (0)	137 (2)	123 (6)	87 (10)	32 (13)	0 (14)
Placebo	141 (0)	137 (4)	116 (12)	84 (17)	28 (17)	0 (17)

Science, **356**, 938-945 (2017)

Tenofovir is depleted in cultures with *non-Lactobacillus* vaginal bacteria

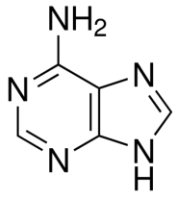






Tenofovir

G. vaginalis

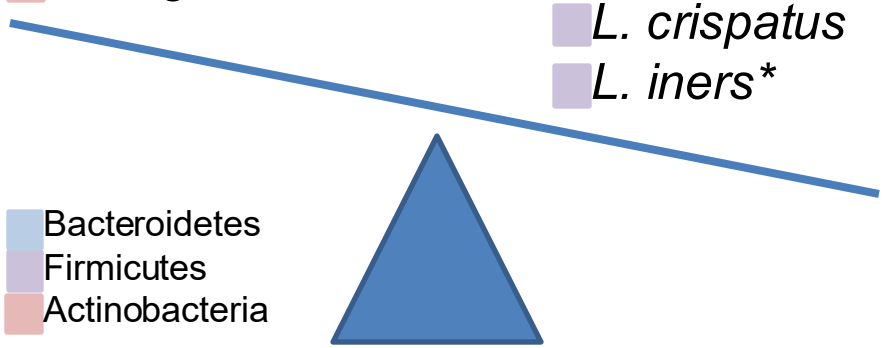


Adenine

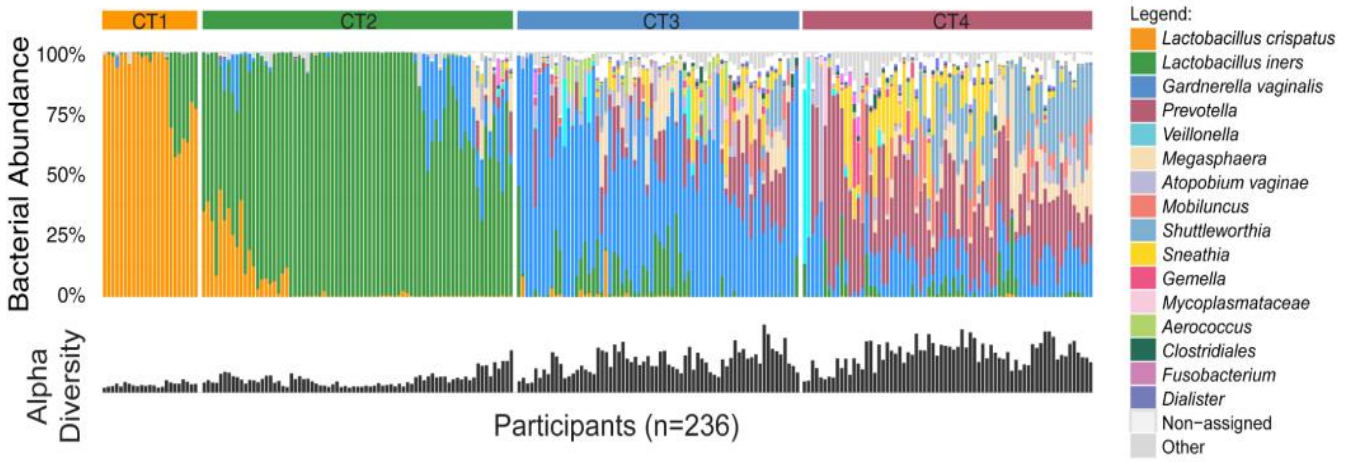
Science, **356**, 938-945 (2017)

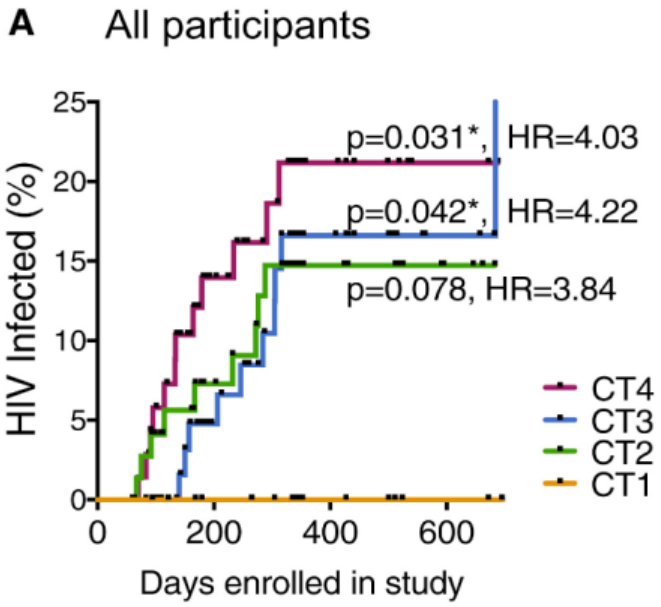
Altered vaginal microbial composition in HIV transmission and inflammation

- *Prevotella*
- *Porphyromonas*
- *Gemella*
- *Dialister*
- *Megasphaera*
- *Aerococcus*
- *Parvimonas*
- *Mycoplasma*
- *L. iners**
- *G. vaginalis*

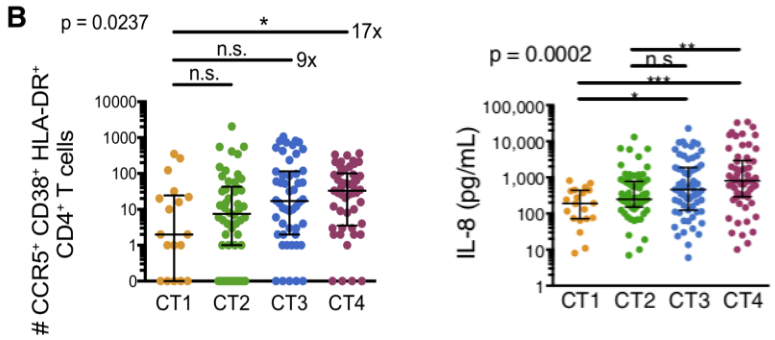


(Ahnatar, 2015; **Gosmann, 2017**; Mclelland, 2018; Srinivasan, 2018)



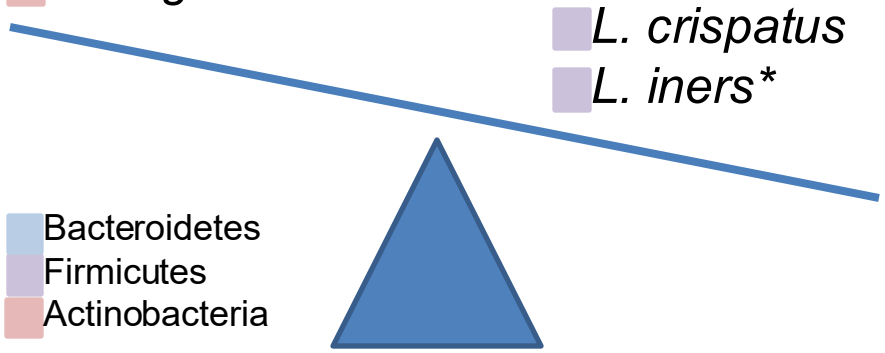


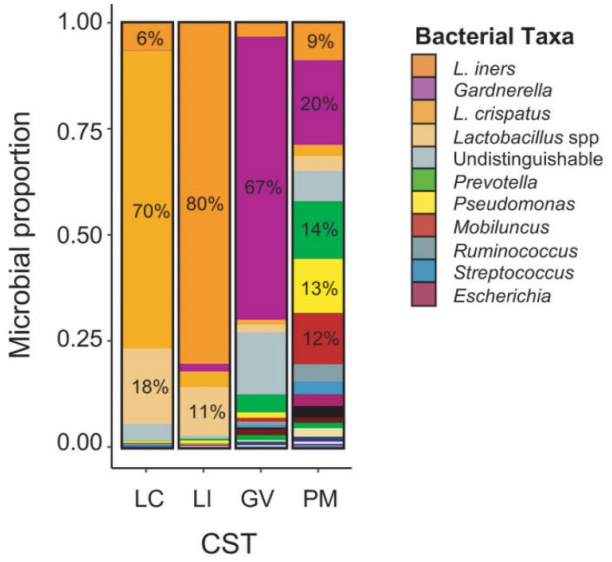
Markers of inflammation and HIV transmission risk

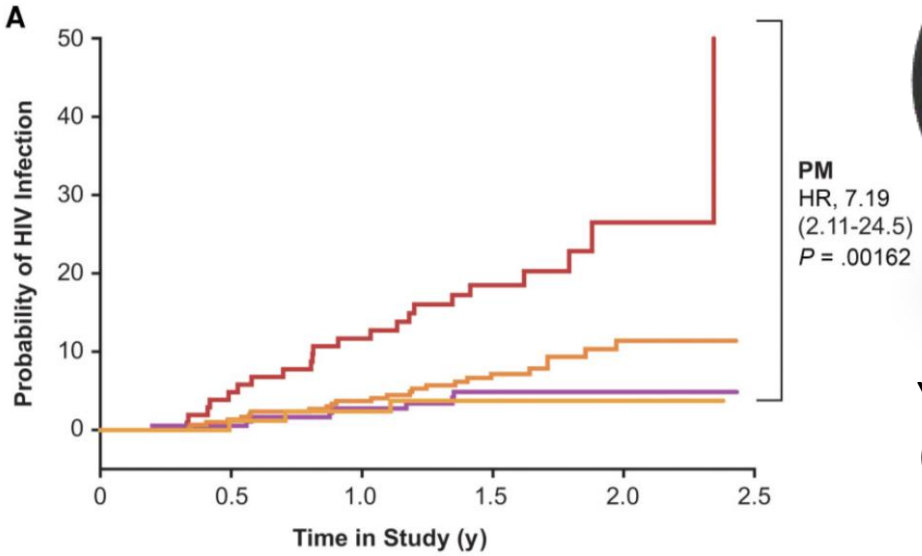


Altered vaginal microbial composition in HIV transmission

- *Prevotella*
- *Porphyromonas*
- *Gemella*
- *Dialister*
- *Megasphaera*
- *Aerococcus*
- *Parvimonas*
- *Mycoplasma*
- *L. iners**
- *G. vaginalis*

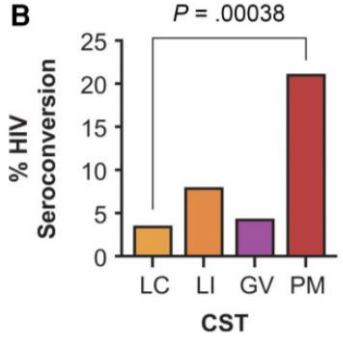






No. of participants at risk
(cumulative number of infections)

LC	84 (0)	83 (1)	74 (2)	57 (3)	20 (3)	0 (3)
LI	300 (0)	294 (4)	261 (11)	181 (19)	75 (24)	0 (24)
GV	183 (0)	182 (1)	159 (5)	115 (8)	45 (8)	0 (8)
PM	104 (0)	98 (5)	87 (12)	60 (18)	16 (21)	0 (22)



CST	No. acquired HIV (%)	No. remained HIV- (%)
LC	3 (3.6)	81 (96.4)
LI	24 (8.0)	276 (92.0)
GV	8 (4.4)	175 (95.6)
PM	22 (21.2)	82 (78.8)

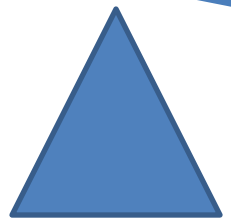
Yiran Wang
(**CID, 2022**)

(Ahnatar, 2015; Gosmann, 2017; Mclelland, 2018; Srinivasan, 2018; **Wang, 2022**, Srinivasan, 2024)

Altered vaginal microbial composition in HIV transmission

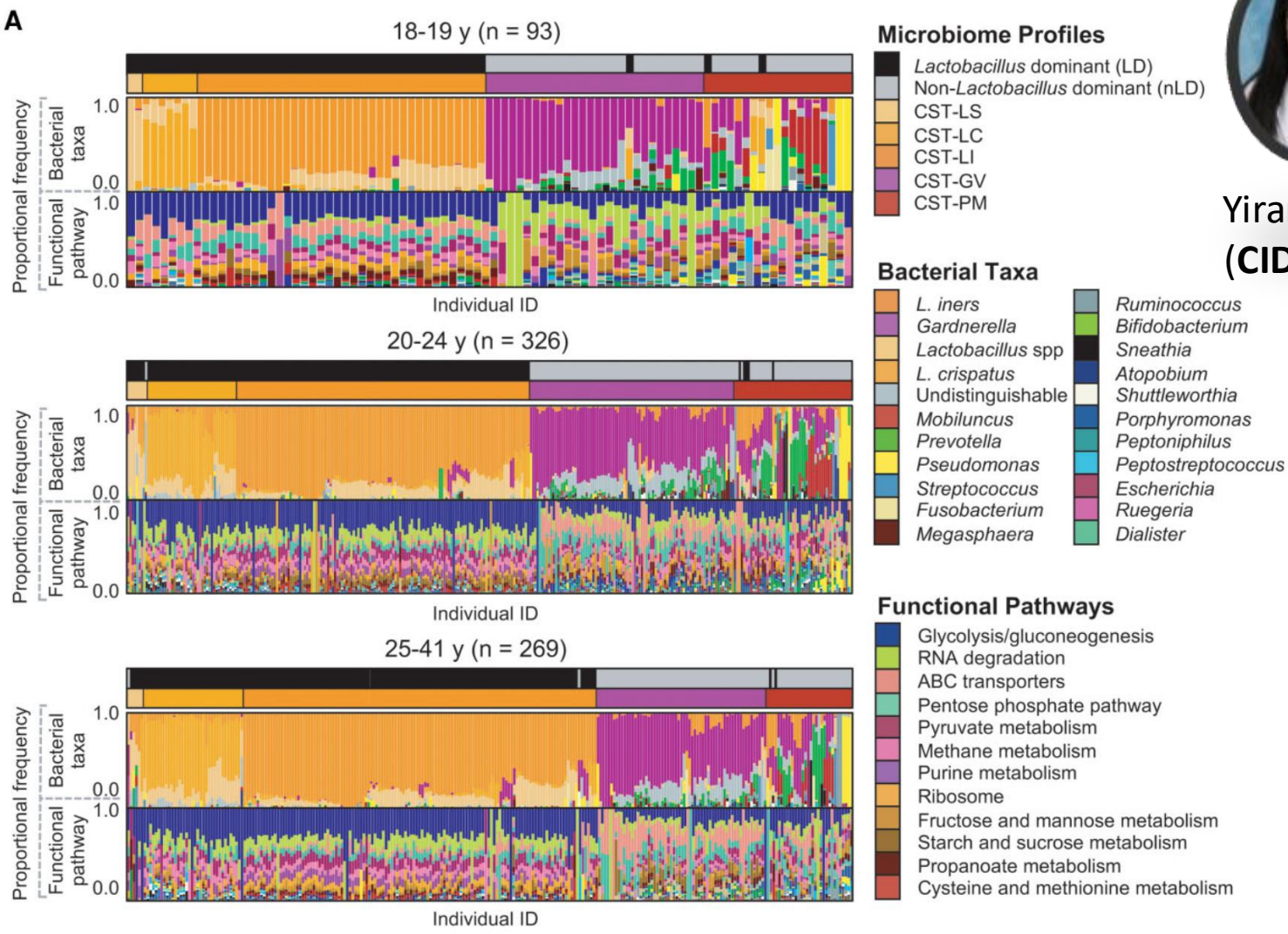
- *Prevotella*
- *Porphyromonas*
- *Gemella*
- *Dialister*
- *Megasphaera*
- *Aerococcus*
- *Parvimonas*
- *Mycoplasma*
- *L. iners**
- *G. vaginalis*

- *L. crispatus*
- *L. iners**



- Bacteroidetes
- Firmicutes
- Actinobacteria

(Ahnatar, 2015; Gosmann, 2017; Mclelland, 2018; Srinivasan, 2
Wang, 2022, Srinivasan, 2024)



Yiran Wang
(CID, 2022)

Long-acting HIV prevention tools

NIAID is funding research on 4 types of long-acting HIV prevention.

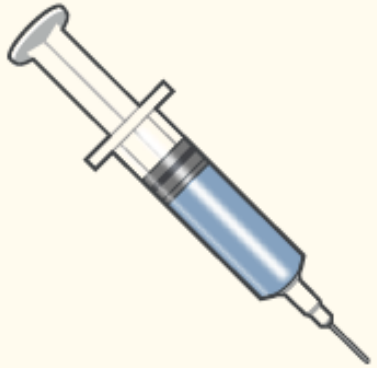
INTRAVAGINAL RING (IVR)

Polymer ring inserted into the vagina releases antiretroviral drug over time.

IMPLANT

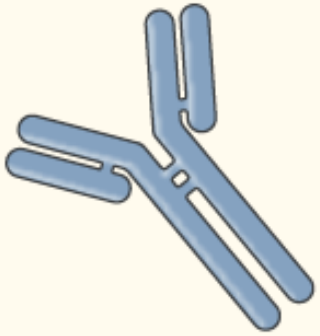
Device implanted in the body releases antiretroviral drug over time.

INJECTABLE



Long-acting antiretroviral drug is injected into the body.

ANTIBODY



Antibody is infused or injected into the body.

Prospective studies of the microbiome and mucosal immunity in HIV transmission and prevention

Clinical cohort leads and team


S. Hillier


J. Baeten


A. Scheutz


S. Vasan


V. Poliquin


A. Berard

Systems Biology

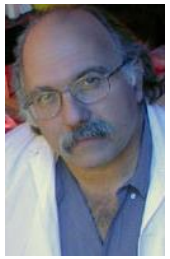

A. Burgener


C. Farr


R. Paredes


A. Borgognone

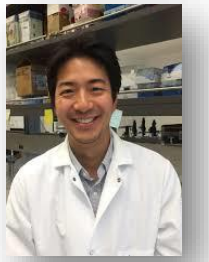

M. Noguera -Julian


R. Sekaly


D. Brubaker

Functional Immunology

T. Murooka



C. Herrera

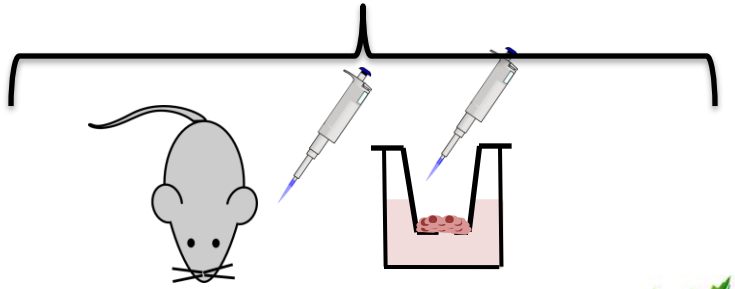
ASPIRE cohort (dapivirine)
VOICE (tenofovir)

RV306 (HIV vaccine)

THRIVE cohorts (Winnipeg, Cleveland)

Multi'-'omics of microbiome and systems immunology

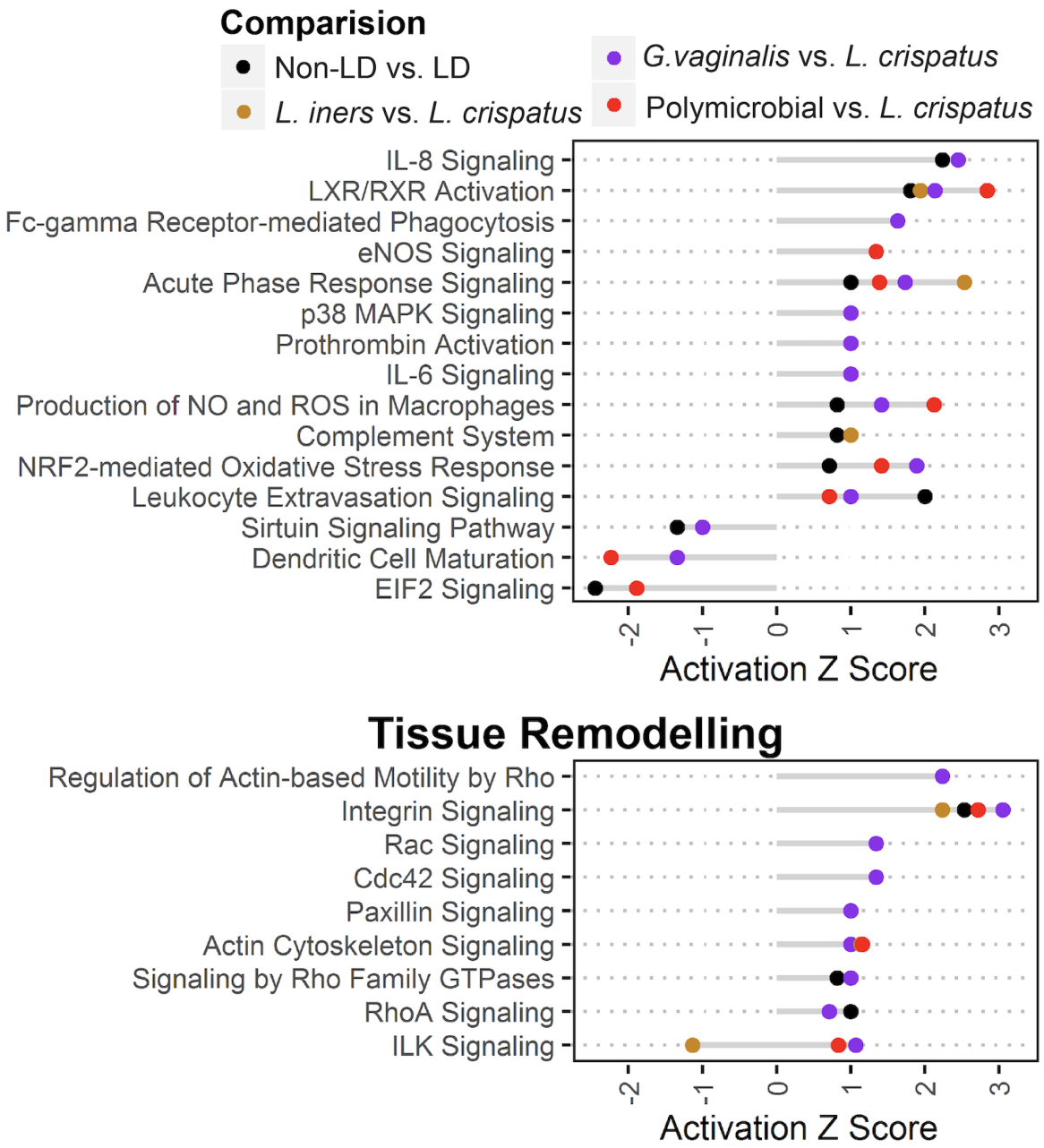
- Mucosal immunity
- HIV acquisition
- Vaccine immunity



Functional immunology

Case Western Reserve University · MHRP U.S. Military HIV Research Program · University of Pittsburgh · Imperial College London · University of Washington · University of Manitoba · IrsiCaixa Institut de Recerca de la Sida · CIHR IRSC · National Institutes of Health

Vaginal microbiomes and mucosal inflammation pathways



Noël-Romas L, Perner M, Molatlhegi R, et al, PLoS Pathogens, 2021

What are the mucosal innate immune correlates of HIV protection?

VOICE

(Vaginal and Oral Interventions to Control the Epidemic)[1]

Randomized to daily 1) oral FTC/TDF, 2) oral TDF, 3) 1% TFV gel, 4) oral PLB or 5) gel PLB

121 cases
Vaginal swabs (VS) collected 3-6 months prior to seroconversion

381 controls
VS were matched to cases by age, site and study arm

548 eligible women
Reproductive age women from South Africa, Uganda and Zimbabwe

CAPRISA 004

(Centre for the AIDS Program of Research in South Africa)[2]

Randomized to on-demand 1) 1% Tenofovir gel or 2) Placebo gel

68 cases
Cervicovaginal Lavage (CVL) collected >= 3 months prior to seroconversion

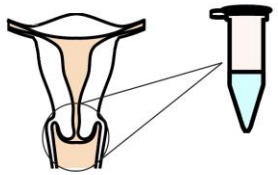
633 controls
CVL samples from all available women who remained uninfected

701 eligible women
Reproductive age women from South Africa

S.A. Karim, Q. A. Karim, L. McKinr

S. Hillier, J. Marrazzo, M. Chirenje

Mucosal immunoproteome profiling



Lower FRT samples (CVL and VS)

Protein digestion (FASP) LC cleanup

Label-free tandem mass spectrometry

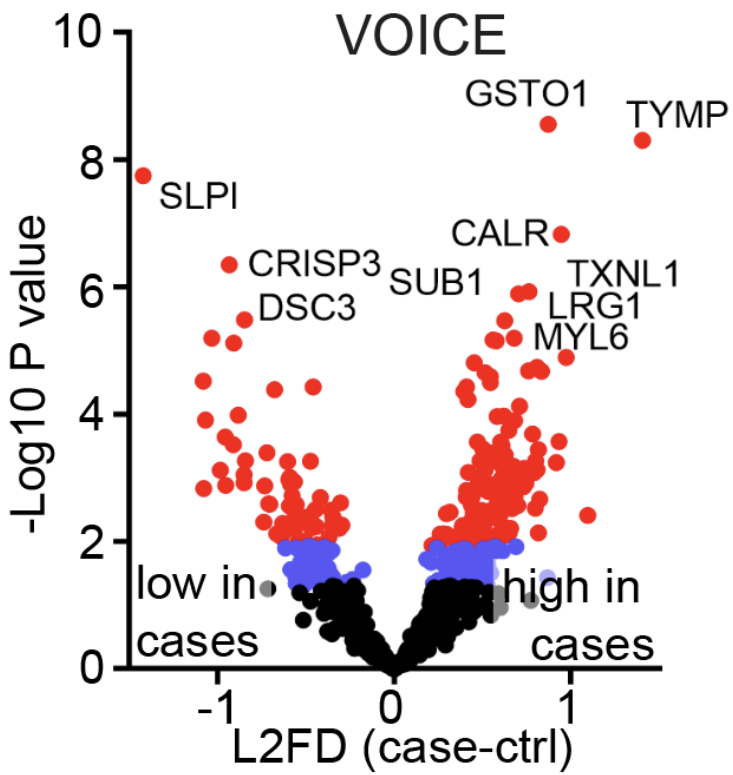
Human/bacterial protein identification, quantification and filtering

Dr. C. Farr
CWRU

Laura Noel-Romas
CWRU

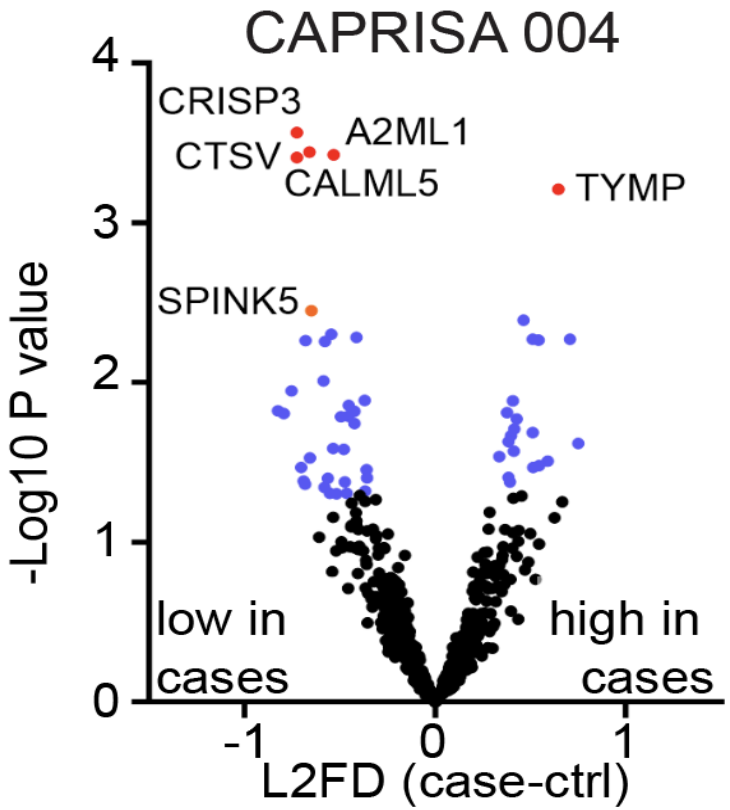
Dr. M Perner,
PHAC/UManitoba

(Noel-Romas *et al*, presented at CROI 2024)



193 (18%) FDR=5%

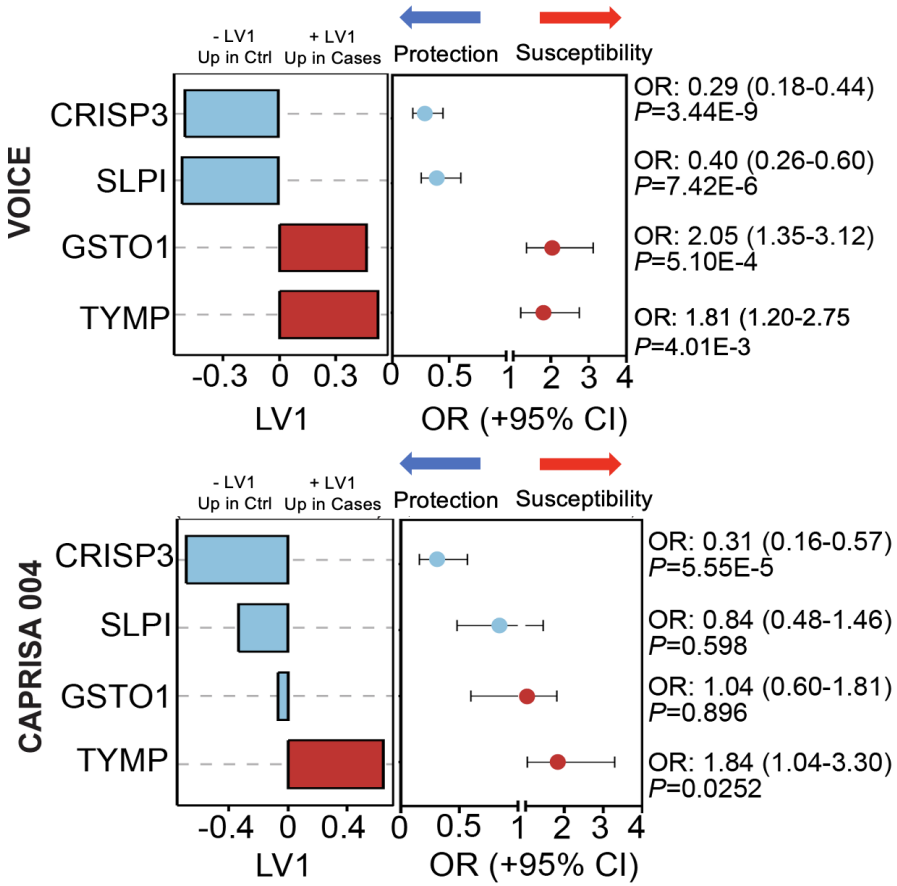
314 (38.7%) P<0.05

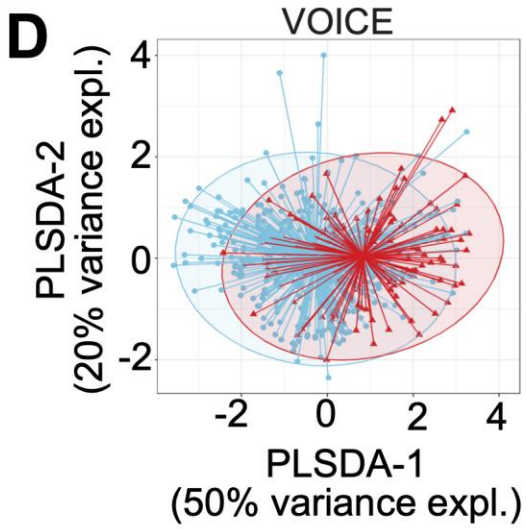


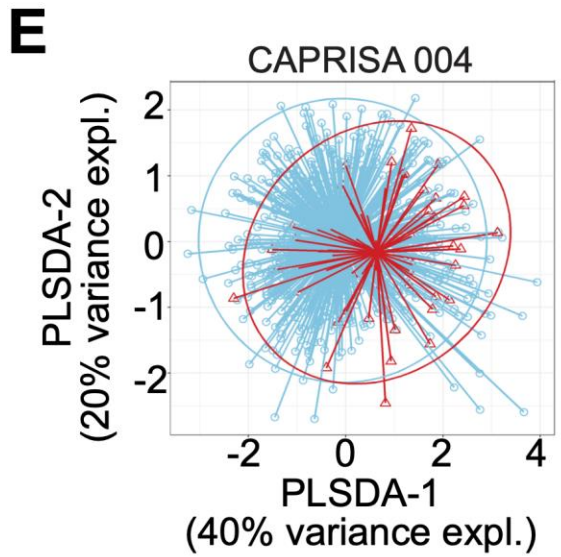
5 (0.8%) FDR=5%

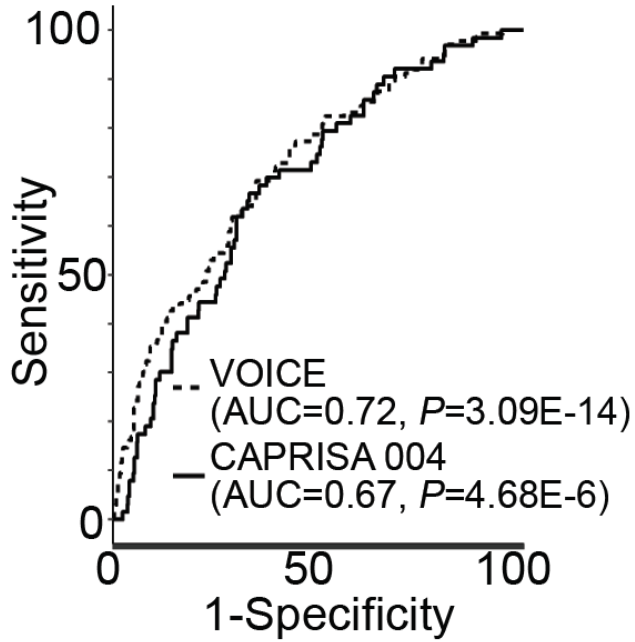
53 (9.0%) P<0.05

Cervicovaginal proteome correlates of HIV protection



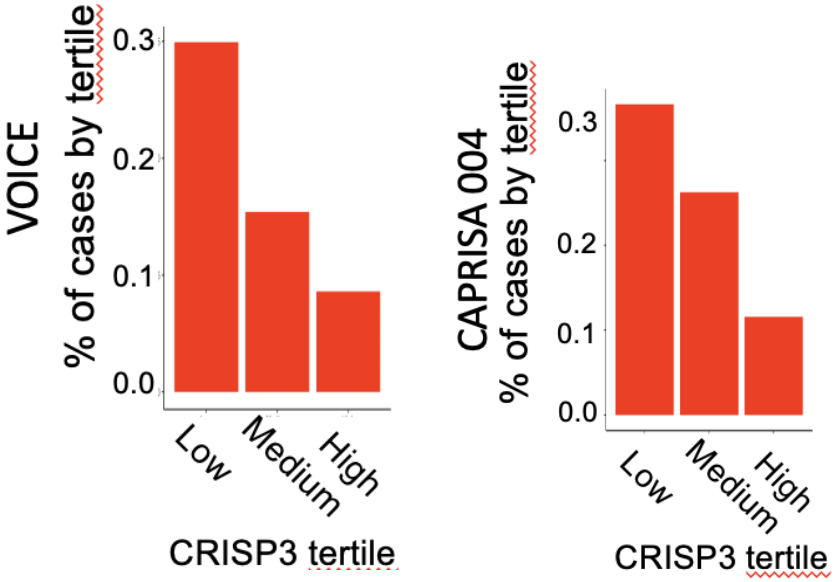


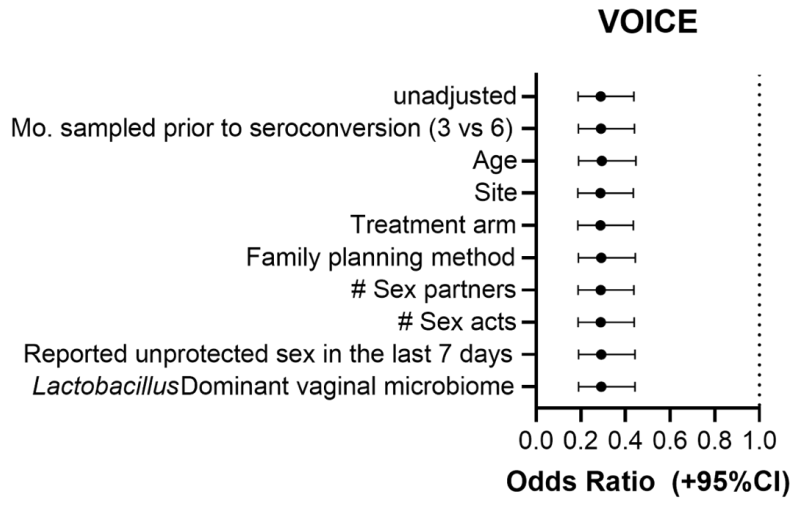




(Noel-Romas *et al*, presented at CROI 2024)

Vaginal mucosal neutrophil protein correlates with HIV protection





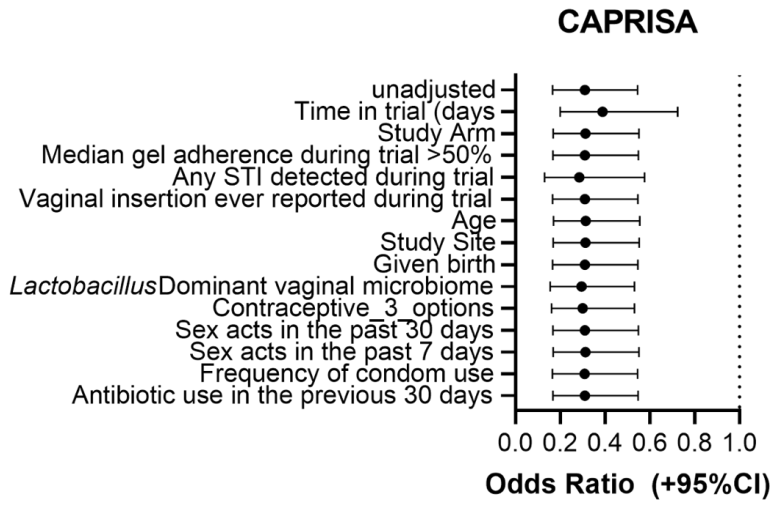
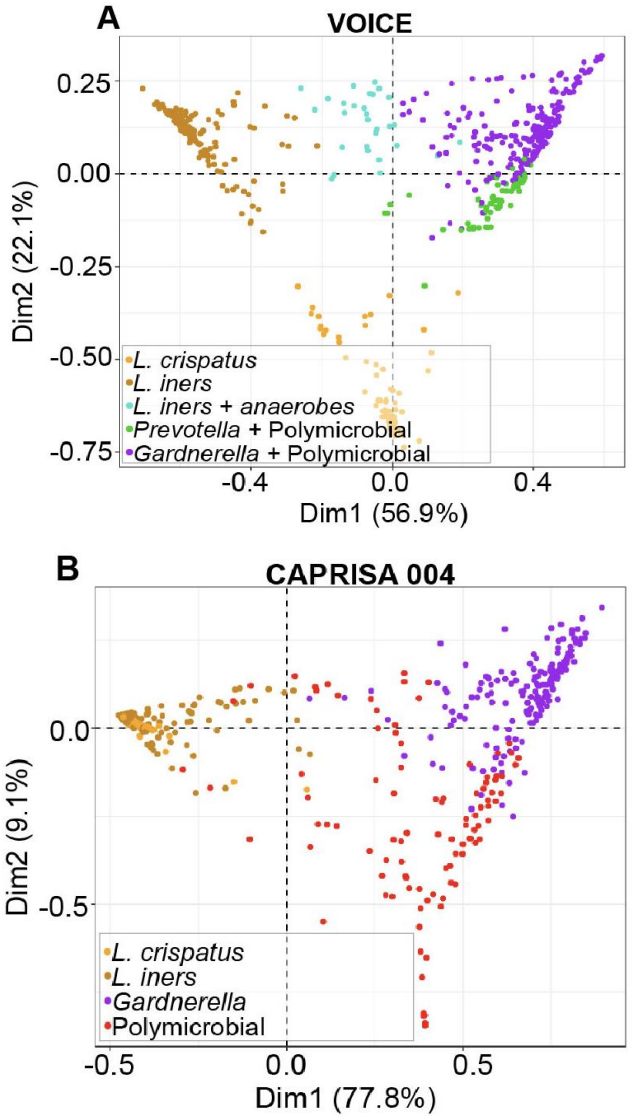


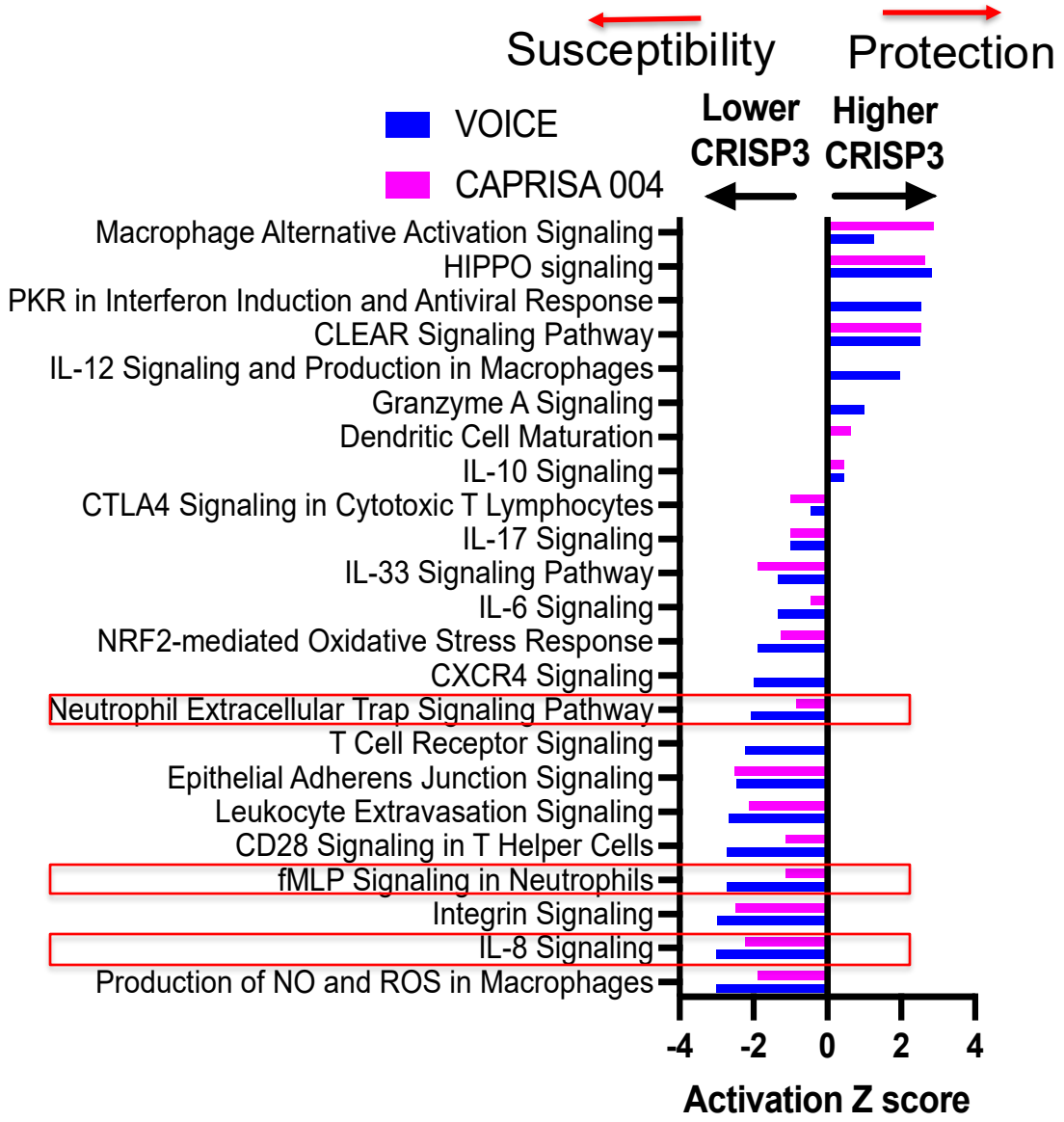
Figure 3. **Adjusted estimates for HIV protection with the abundance of cervicovaginal CRISP3 in the VOICE (left) and CAPRISA 004 (right).**

CRISP3 associates with HIV protection across different vaginal microbiomes

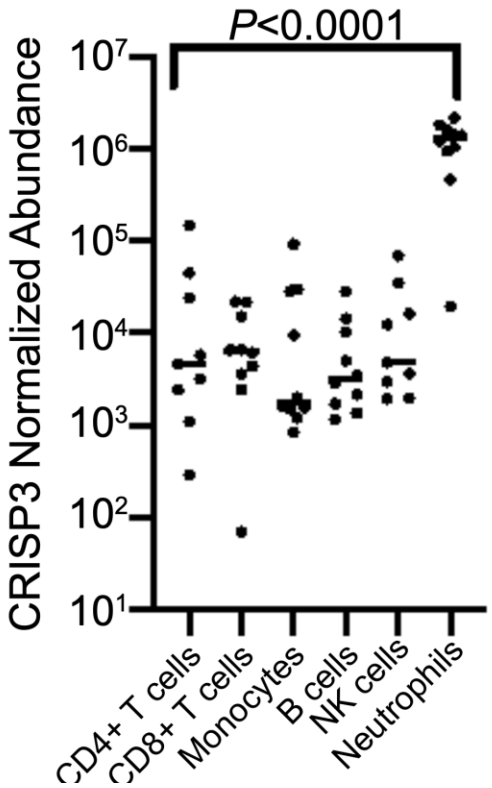


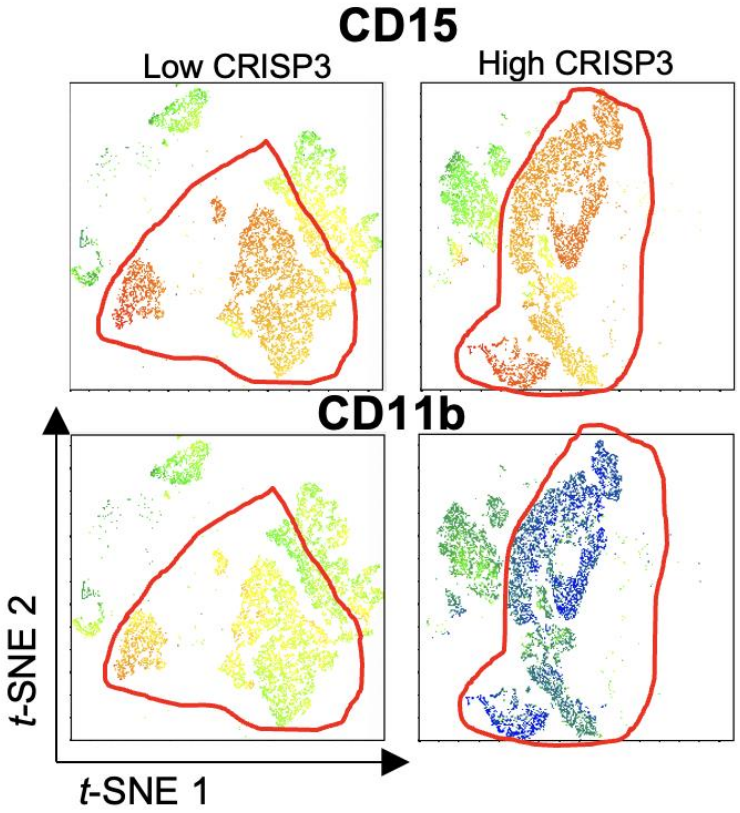
(Noel-Romas *et al*, presented at CROI 2024)

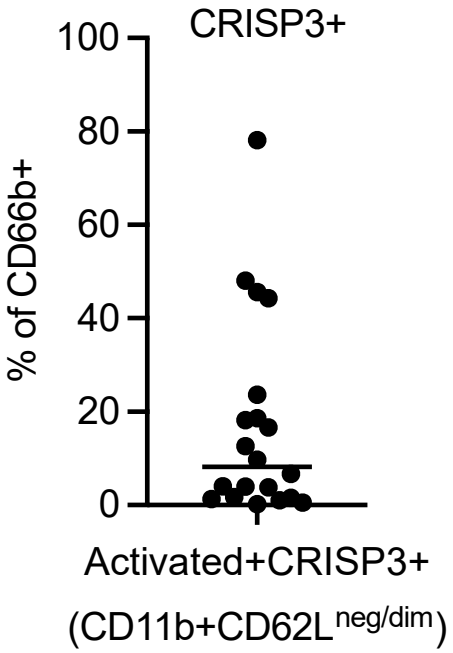
Neutrophil associated pathways associate with HIV susceptibility

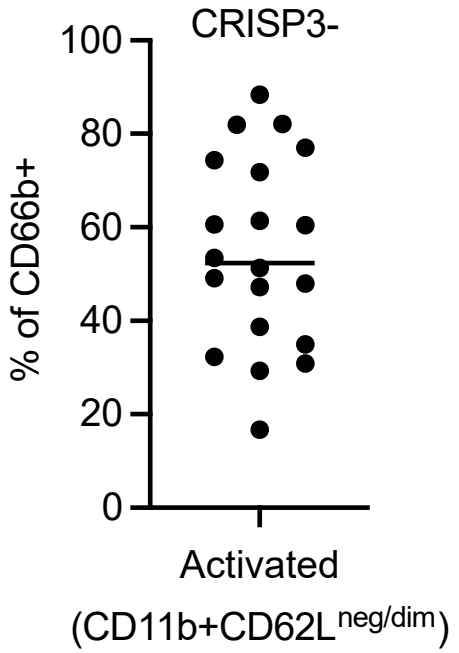


CRISP3 and cervical neutrophil phenotypes

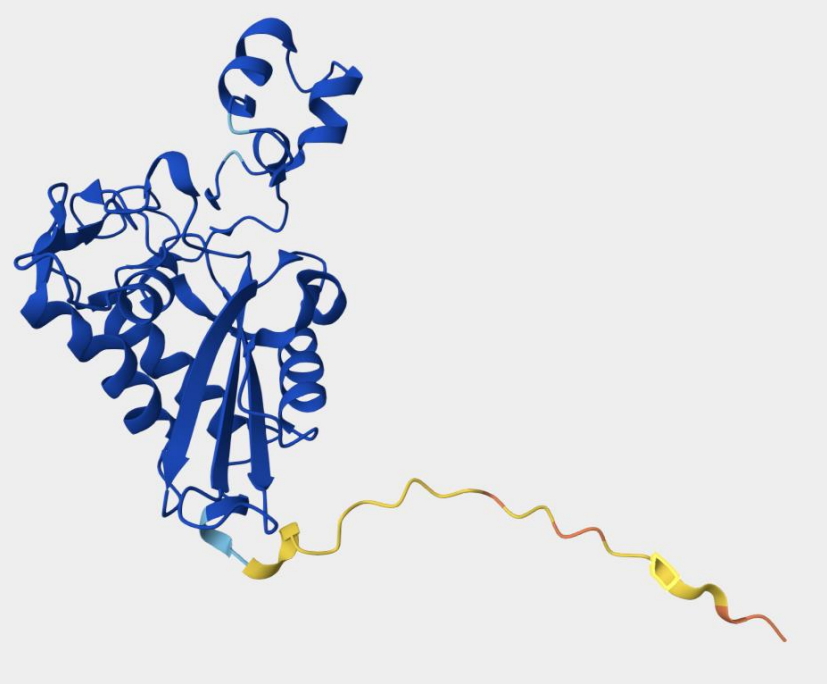








CRISP3: Cysteine-rich secretory protein 3



- CRISP3 is a 28kDa glycoprotein that belongs to a family of cysteine-rich proteins that are characterized by their content of highly conserved cysteine residues.
- CRISP3 was first described to be a component of peroxidase-negative secretory granules of neutrophils (Udby, Calafat et al. 2002)
- CRISP3 contains several domains, including the N-terminal CRISP region, a pathogenesis-related 1 protein domain, and a C-terminal ion channel regulator domain.
- CRISP3 sequence homology to pathogenesis related 1 proteins, which are plant antifungal peptides, suggest antimicrobial roles (Gibbs, Roelants and O'Bryan 2008).
- Some publications have shown it to have anti-viral activity against HCV(Lee, Nam et al. 2014), calcium mobilization activity (Gibbs, Scanlon et al. 2006), remodeling of the extracellular matrix(Gibbs, Roelants and O'Bryan 2008) and adhesion and proliferation of epithelial cells(Evans, D'Sylva et al. 2015).

KO-mouse model studies to evaluate the function of CRISP3 in mucosal immunity

Dr. C. Farr
CWRU

C57BL/6
(Crisp3-WT, Crisp3-het,
Crisp3-KO)

- Baseline immune characterization
- Neutrophil functional studies
- Virus and bacterial challenge

SOCIETY FOR MUCOSAL IMMUNOLOGY www.elsevier.com/mi

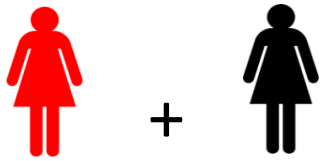
Vaginal microbiome-innate immune crosstalk in mucosal barrier function

ARTICLE

Nonoptimal bacteria species induce neutrophil-driven inflammation and barrier disruption in the female genital tract

Marina Costa-Fujishima [1], Atta Yazdanpanah [1,†], Samantha Horne [2,4,†], Alana Lamont [3,5,†], Paul Lopez [1], Christina Farr Zuend [2], Kenzie Birse [2,4], Morgan Taverner [3], Riley Greenslade [1], Max Abou [5], Laura Noel-Romas [2,4], Bernard Abrenica [5], Oluwaseun Ajibola [1], Nnamdi Ikeogu [1], Ruey-Chyi Su [3,5], Lyle R. McKinnon [3,6,7], Helen Pymar [4], Vanessa Poliquin [4], Alicia R. Berard [2,4], Adam D. Burgener [2,4,8] and Thomas T. Murooka [1,3,*]

THRIVE BV cohort



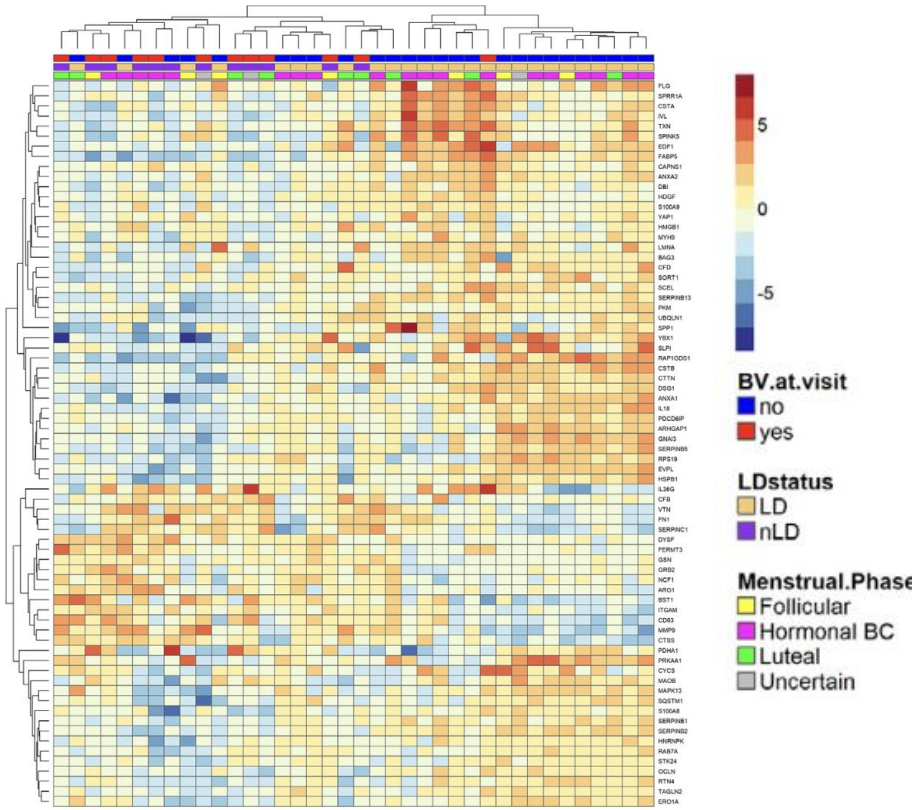
BV + (n=26)

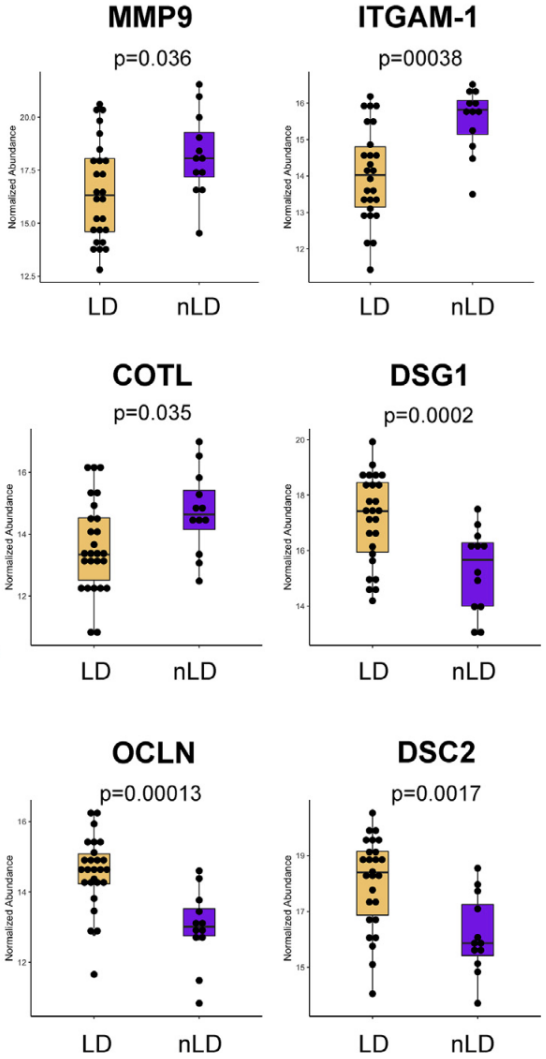
\+

BV - (n=12)

Vaginal molecular profiling

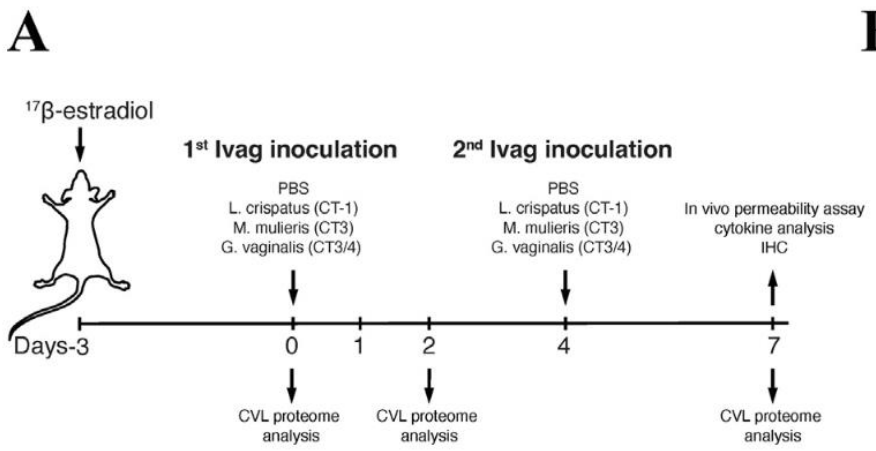
Shotgun tandem mass spectrometry

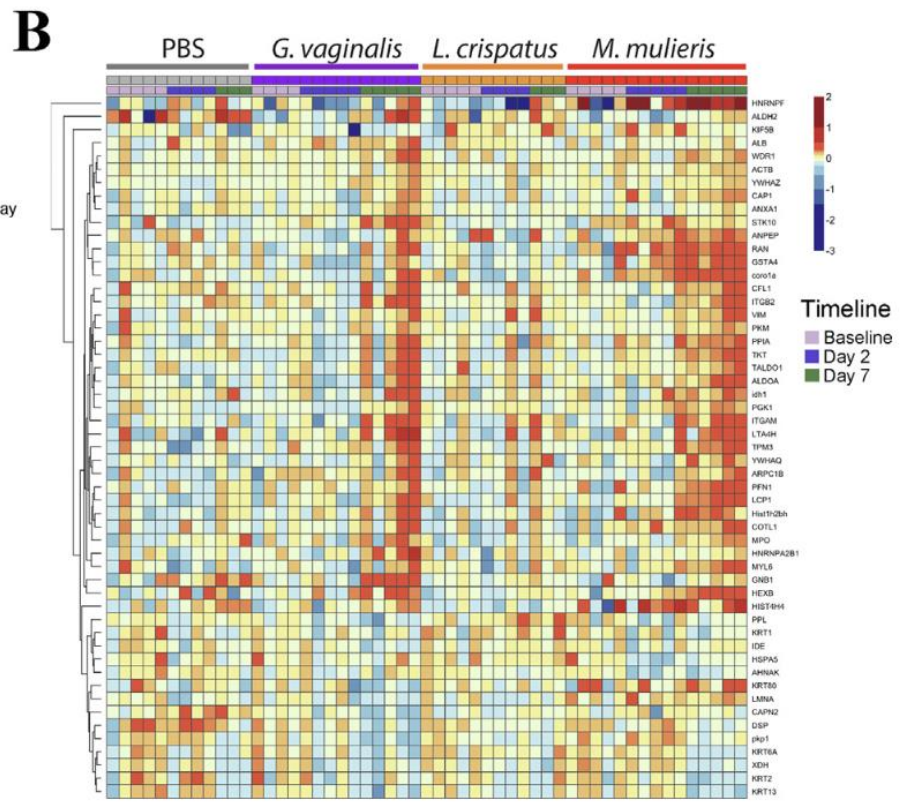




Dr. A. Berard

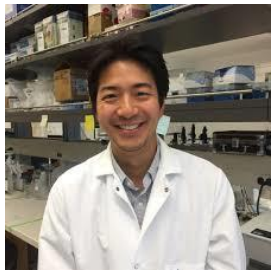
Activation of neutrophil and epithelial barrier disruptrion pathways in the mucosal proteome with intravaginal challenge with dysbtioc vaginal bacteria



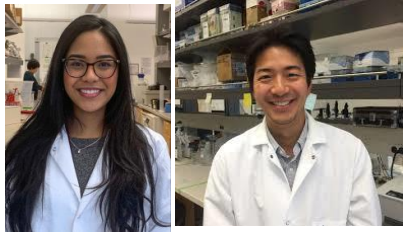



M. Costa-Fujishima


P. Lopez

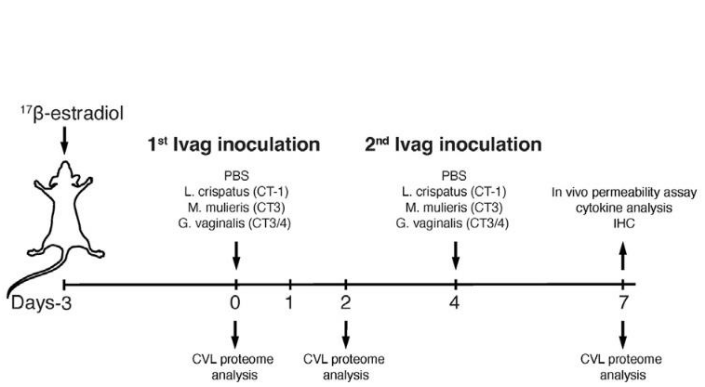

Dr. T. Murooka

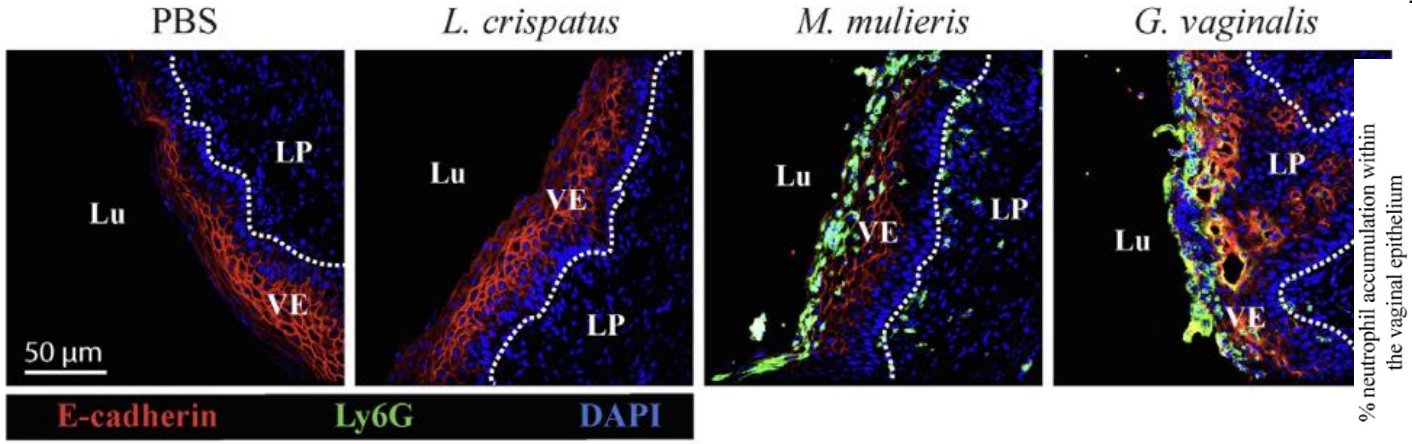
Neutrophils are key drivers of vaginal dysbiosis-related inflammation and barrier disruption in the vaginal mucosa

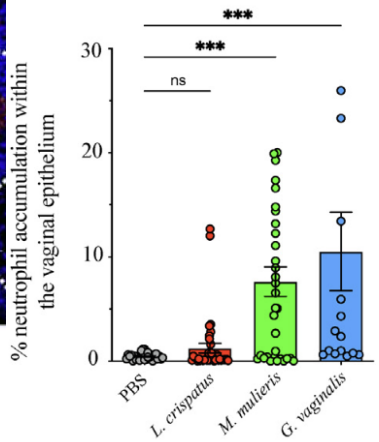


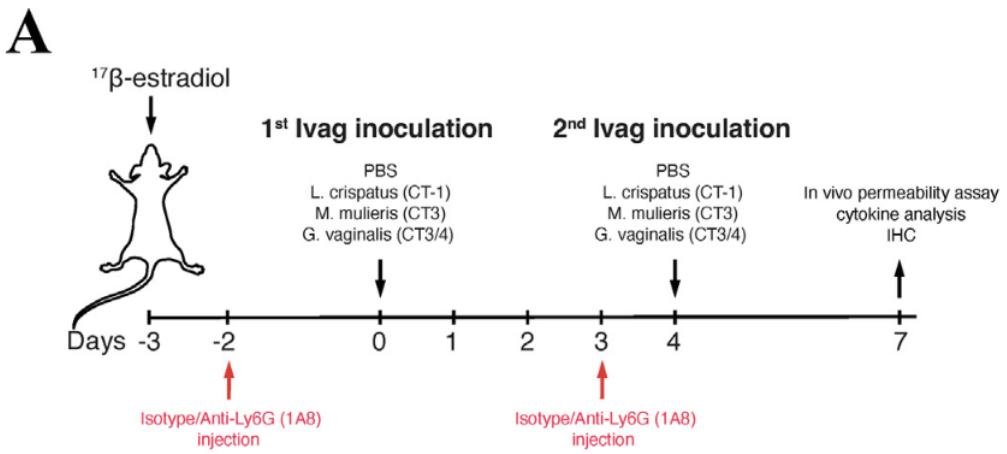
M. Costa-Fujishima

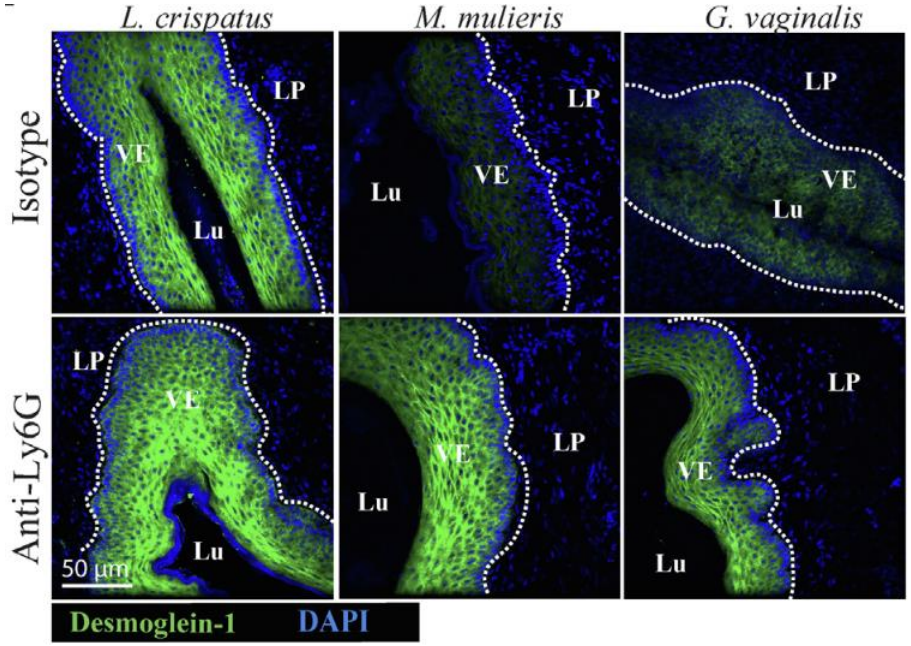
Dr. T. Murooka



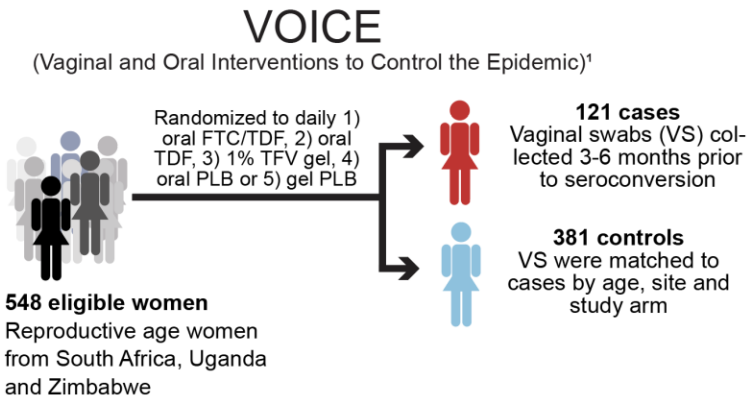




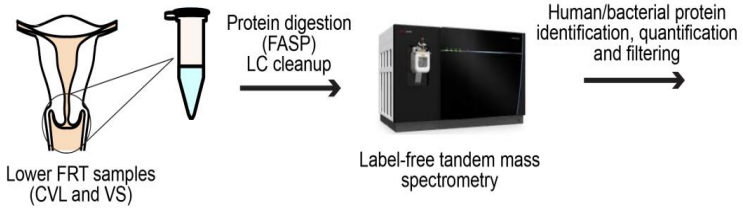




Neutrophil extracellular trap proteins in vaginal mucosa predict increased HIV acquisition

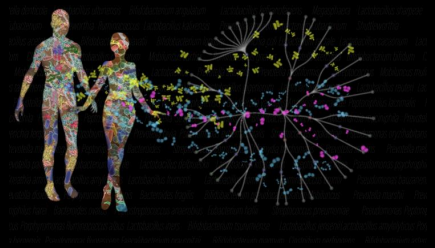


Mucosal immunoproteome profiling



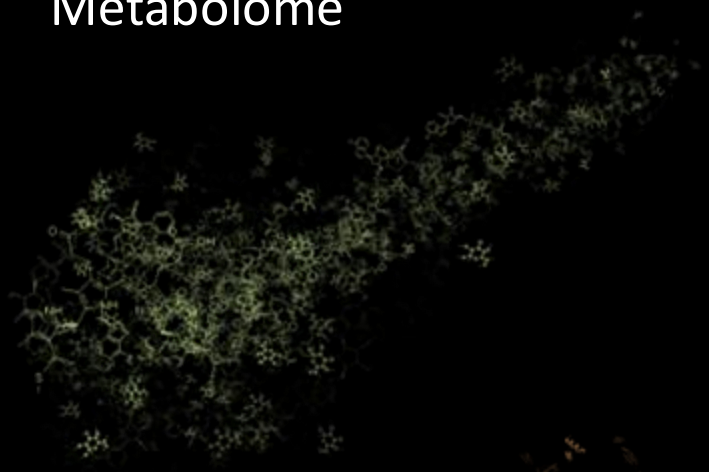
- Identified 266 proteins associated with NETS
- 95 were differentially abundant between cases and controls (FDR <0.05)

Microbial-derived small molecules and modulation of immunity

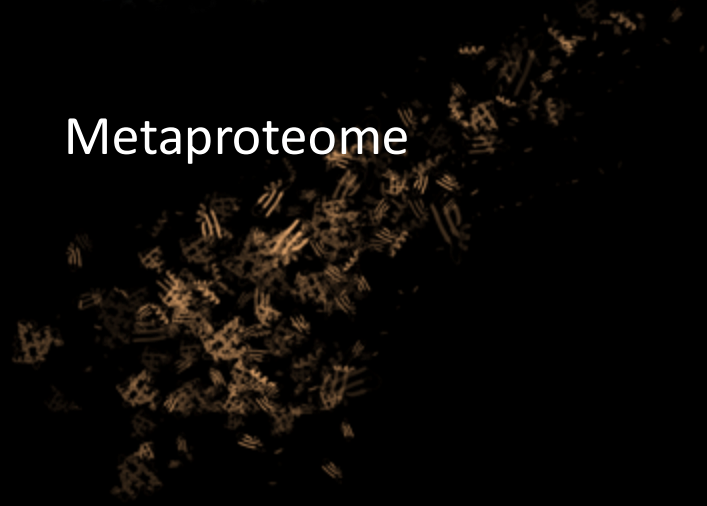


Microbiome

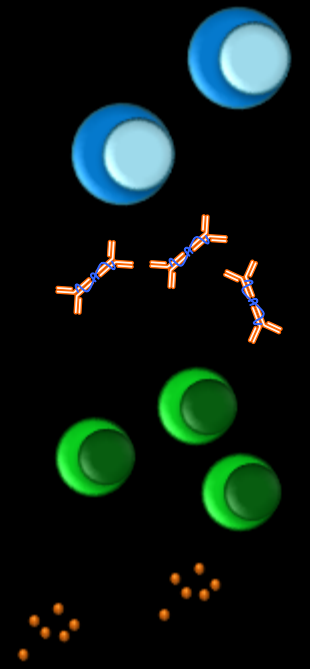
Metabolome



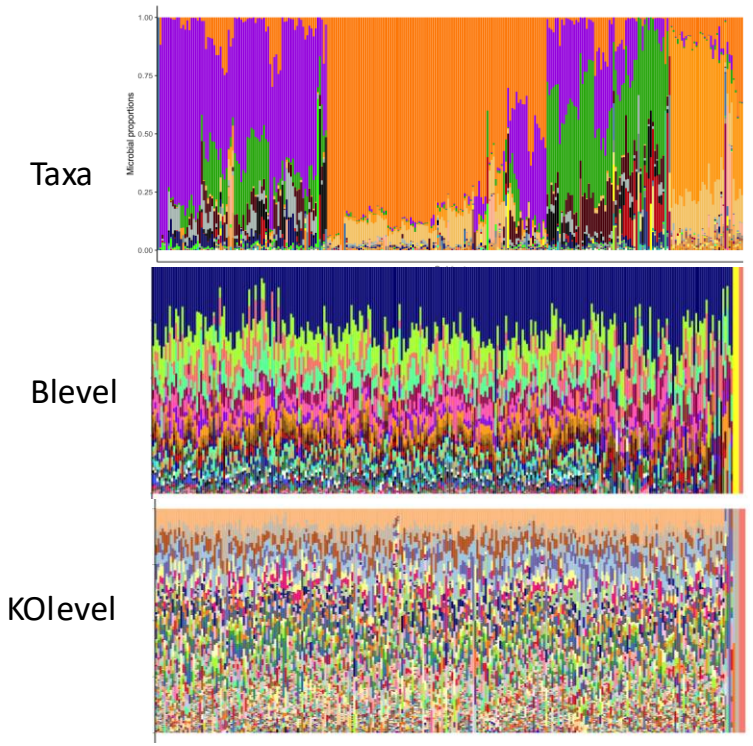
Metaproteome



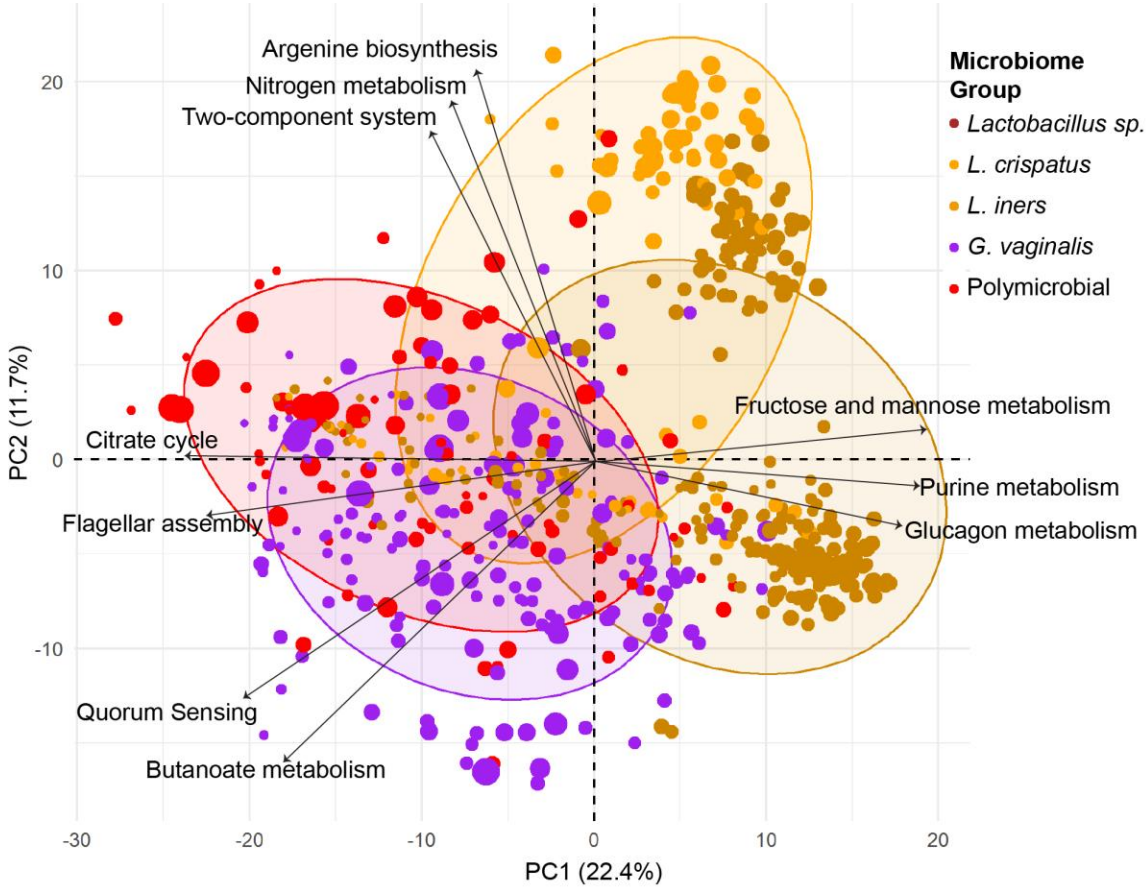
Host immunity and disease susceptibility

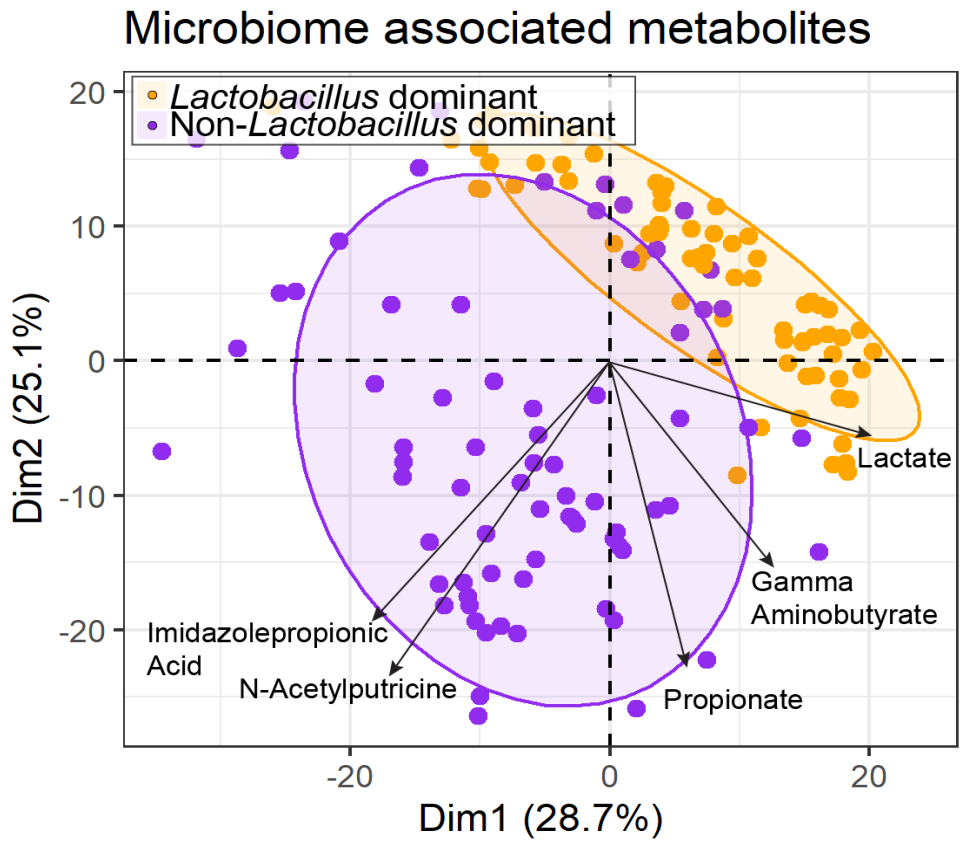


Metabolic and functional diversity of the vaginal metaproteome



Vaginal microbiome communities create unique metabolome environments





Vaginal bacterial metabolome affects mucosal barrier function

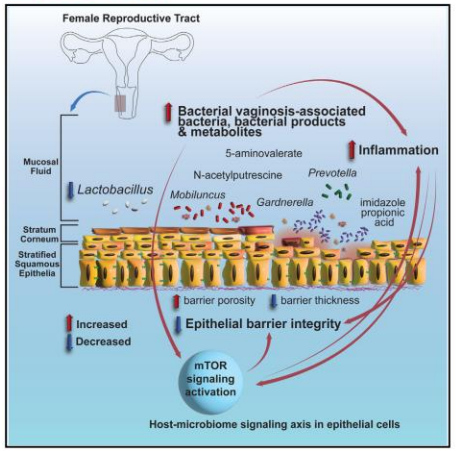
Dr. A. Berard (U Manitoba)

Dr. D. Brubaker (CWRU)

Cell Reports

Vaginal epithelial dysfunction is mediated by the microbiome, metabolome, and mTOR signaling

Graphical abstract



Authors

Alicia R. Berard, Douglas K. Brubaker, Kenzie Birse, ..., Florian Hladik, Jairam Lingappa, Adam D. Burgener

Correspondence

adam.burgener@case.edu

In brief

Berard et al. find a key cellular central signaling network, mTOR, that associates with host inflammation and epithelial barrier disruption in women with a dysbiotic vaginal microbiome and bacterial vaginosis (BV). This network, as well as barrier disruption, is directly modulated by bacterial products and BV-associated metabolites *in vitro*.

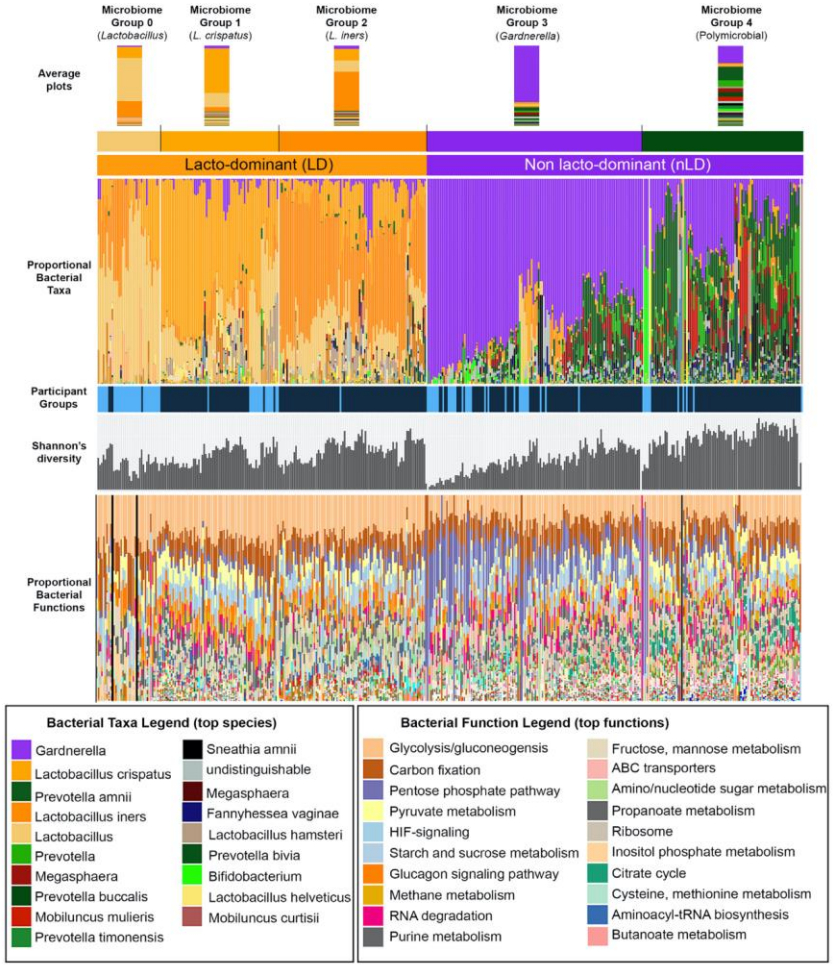
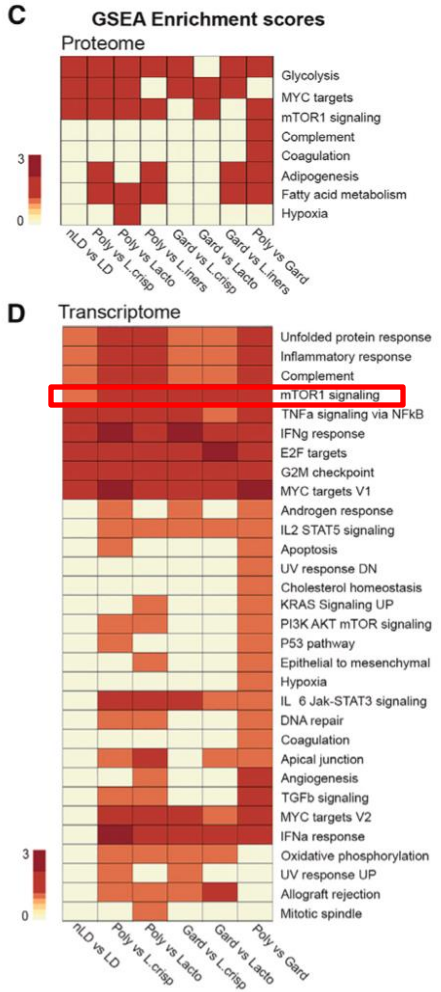


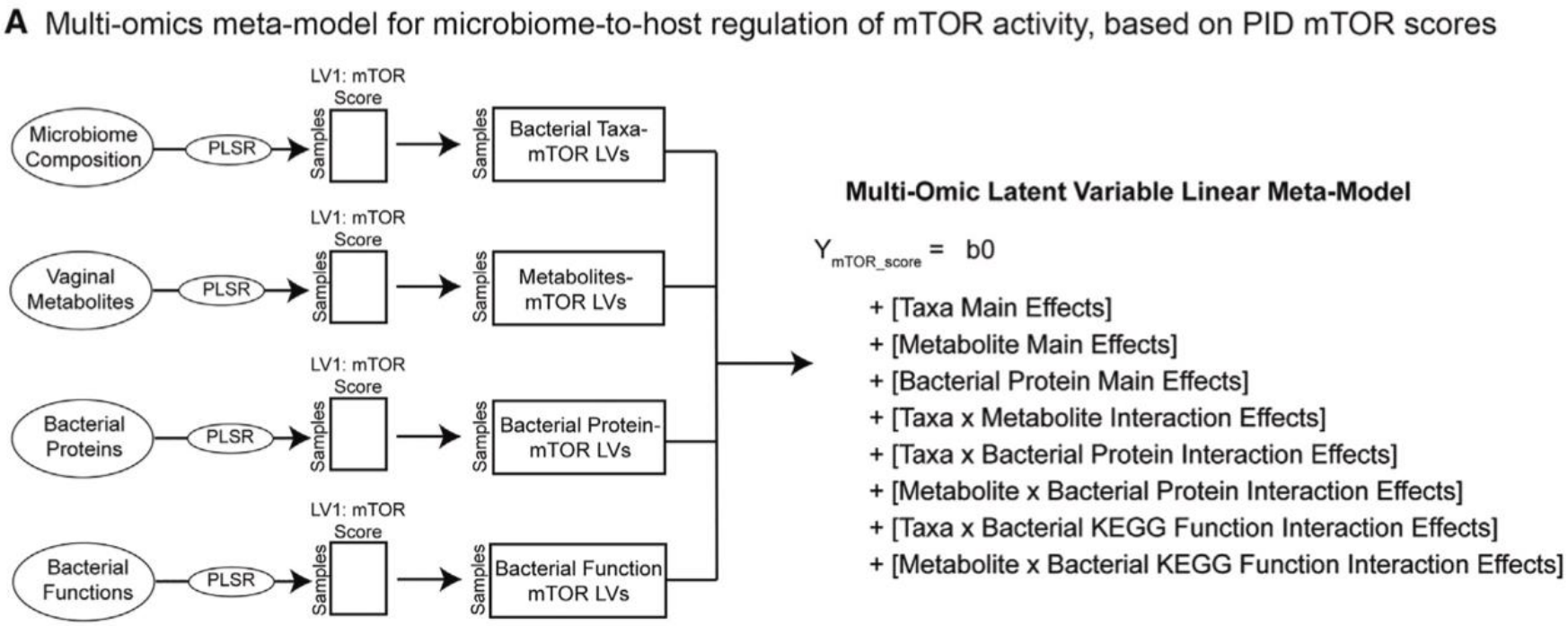
Figure 1. Vaginal microbiome composition

Vaginal swabs collected from 315 women were analyzed by mass spectrometry-based metaproteomics and passed quality control criteria (dark-blue participant group). 3,280 bacterial proteins from 20 unique genera and 142 species were identified in this group. Vaginal swab and vaginal tissues collected from another 90 HIV-negative women were analyzed by mass spectrometry and passed quality control criteria (light-blue participant group). 522 bacterial proteins from 15 unique genera were identified in this second group. All 405 samples were clustered and designated microbiome profile groups 0–4. Bacterial functions were also annotated using the KEGG database and are shown in the bottom panel in the same order as in the microbiome grouping. See also Table S2.

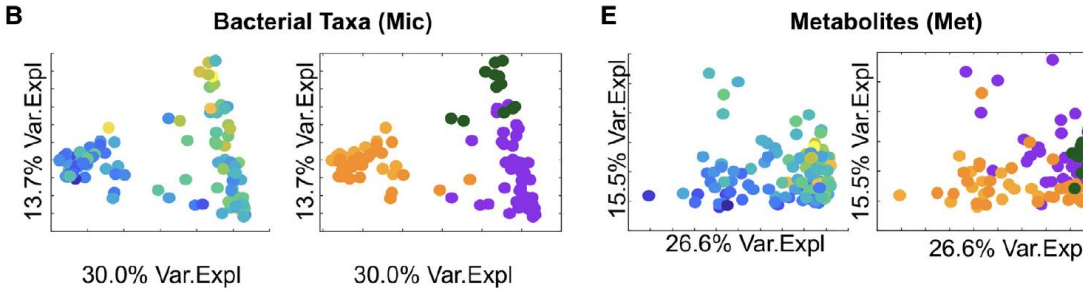
Vaginal epithelial inflammation pathways associate with imidazole propionate

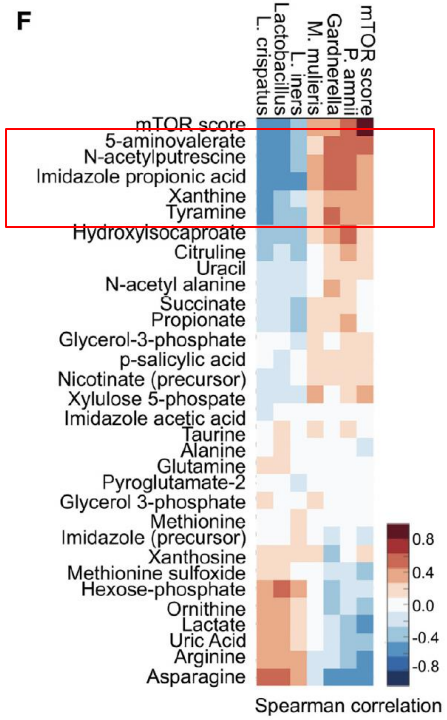
Cervical transcriptome and proteome



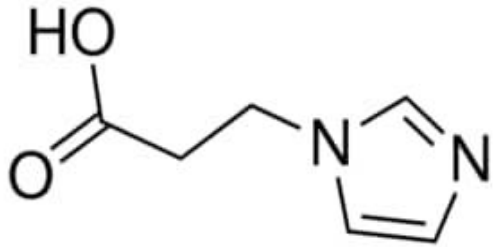


Vaginal microbiome-derived metabolites influence molecular pathways





Imidazole propionate

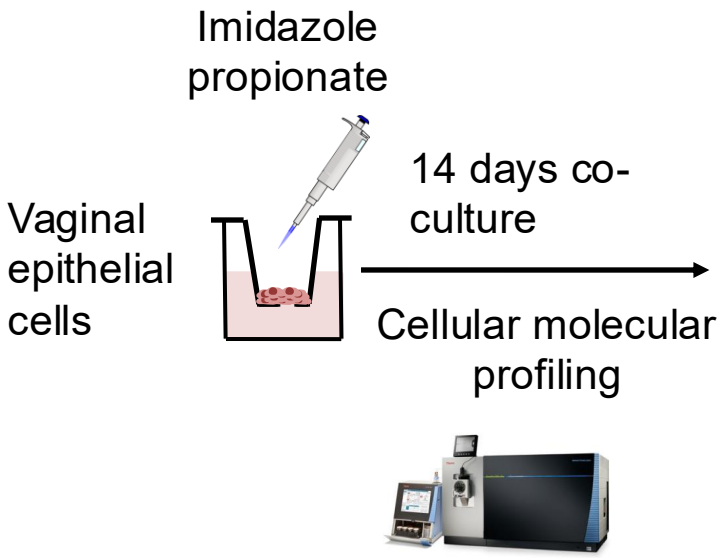


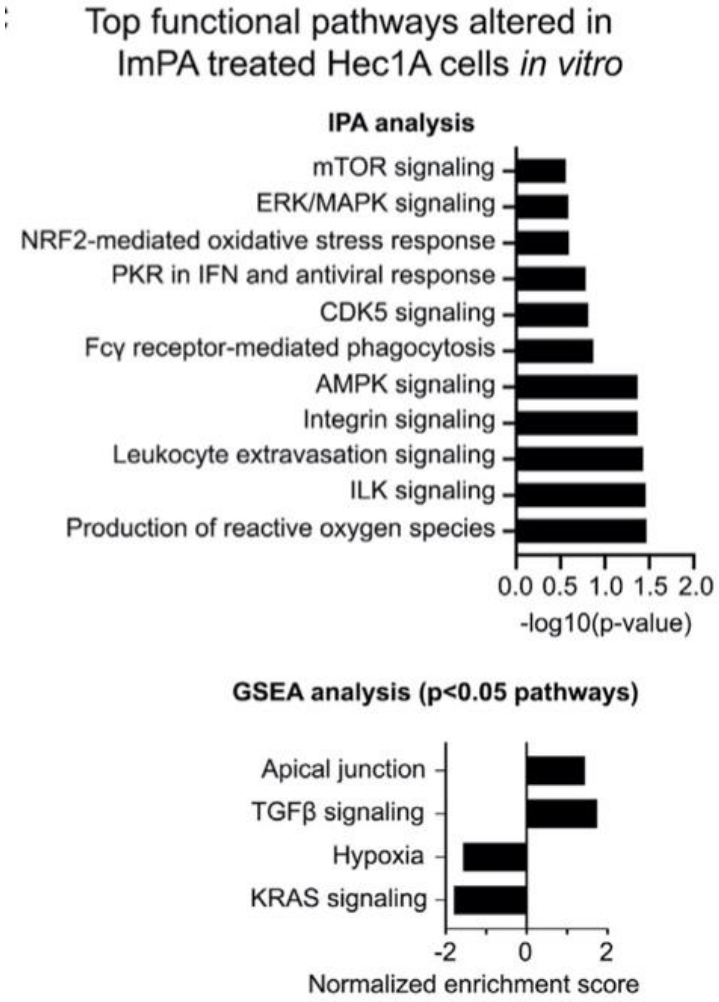
Dr. A. Berard (U Manitoba)

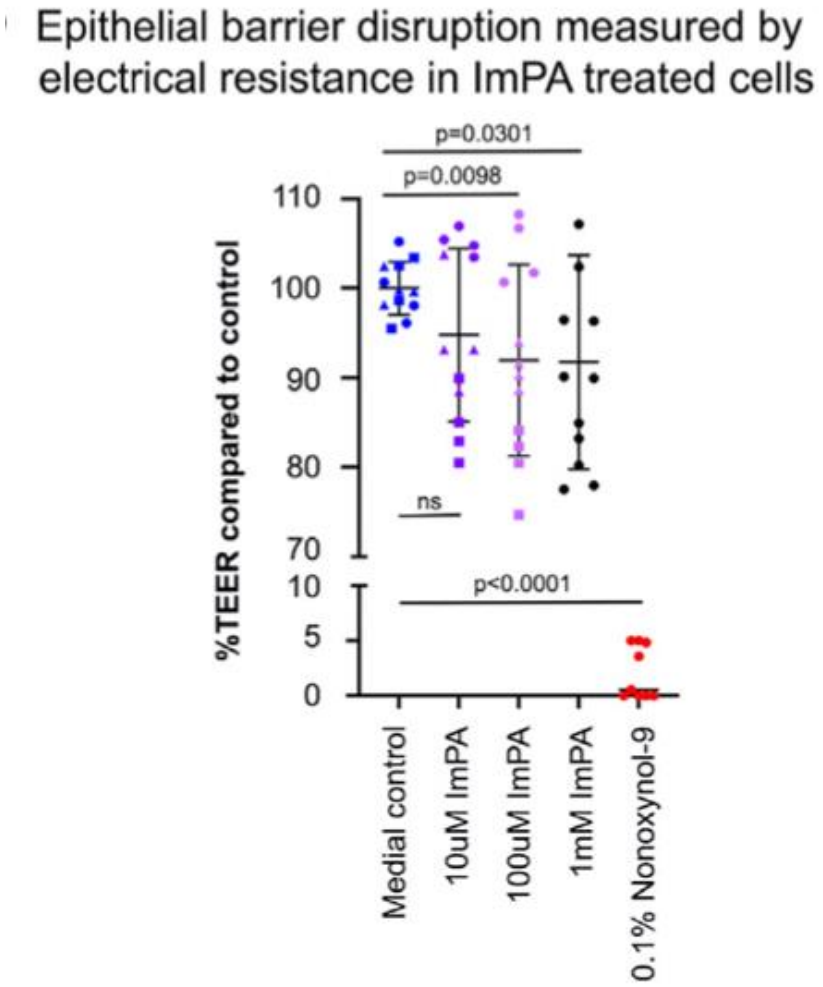
Dr. D. Brubaker (CWRU)

Berard *et al*, Cell Reports 2023

Bacterial-derived imidazole propionate impacts vaginal epithelial barrier function and mTOR signaling







Berard *et al*, Cell Reports 2023

Multi-’omic profiling of the metabolome and microbiome in HIV transmission, immunity, and PrEP

Francesc Català-Moll

R. Paredes

A. Borgognor

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 1, 2016 VOL. 375 NO. 22

Use of a Vaginal Ring Containing Dapivirine for HIV-1 Prevention in Women

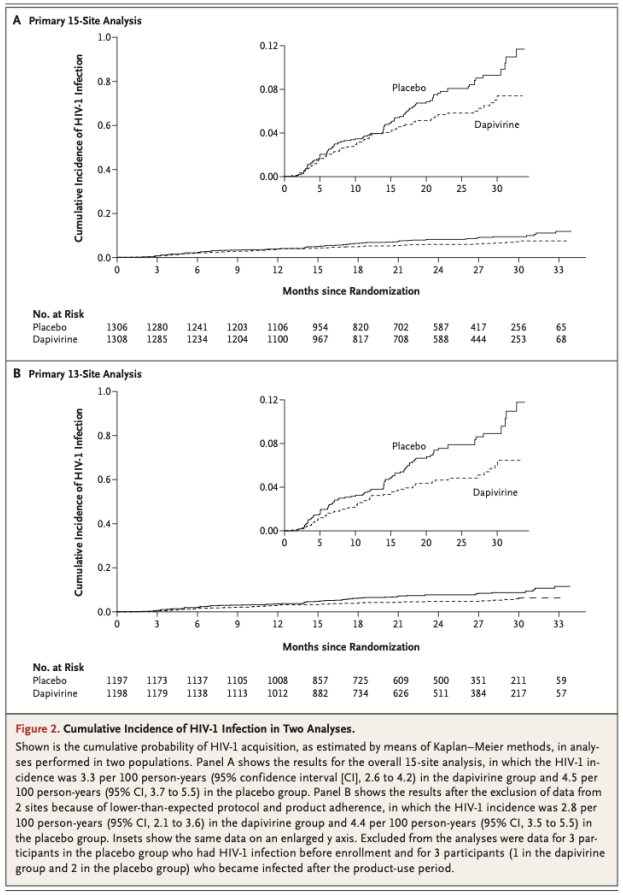


Figure 2. Cumulative Incidence of HIV-1 Infection in Two Analyses.

Shown is the cumulative probability of HIV-1 acquisition, as estimated by means of Kaplan–Meier methods, in analyses performed in two populations. Panel A shows the results for the overall 15-site analysis, in which the HIV-1 incidence was 3.3 per 100 person-years (95% confidence interval [CI], 2.6 to 4.2) in the dapivirine group and 4.5 per 100 person-years (95% CI, 3.7 to 5.5) in the placebo group. Panel B shows the results after the exclusion of data from 2 sites because of lower-than-expected protocol and product adherence, in which the HIV-1 incidence was 2.8 per 100 person-years (95% CI, 2.1 to 3.6) in the dapivirine group and 4.4 per 100 person-years (95% CI, 3.5 to 5.5) in the placebo group. Insets show the same data on an enlarged y axis. Excluded from the analyses were data for 3 participants in the placebo group who had HIV-1 infection before enrollment and for 3 participants (1 in the dapivirine group and 2 in the placebo group) who became infected after the product-use period.

Controls (n=471)

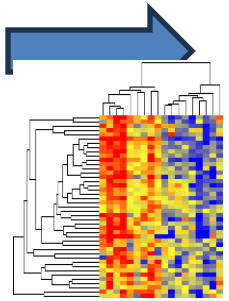
HIV cases (n=157)

Multi-’omic profiling

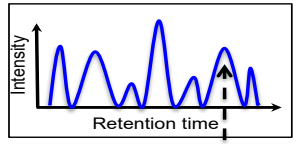
Metaproteomics

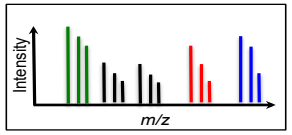
Metabolomics

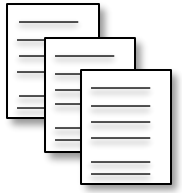
Metagenomics



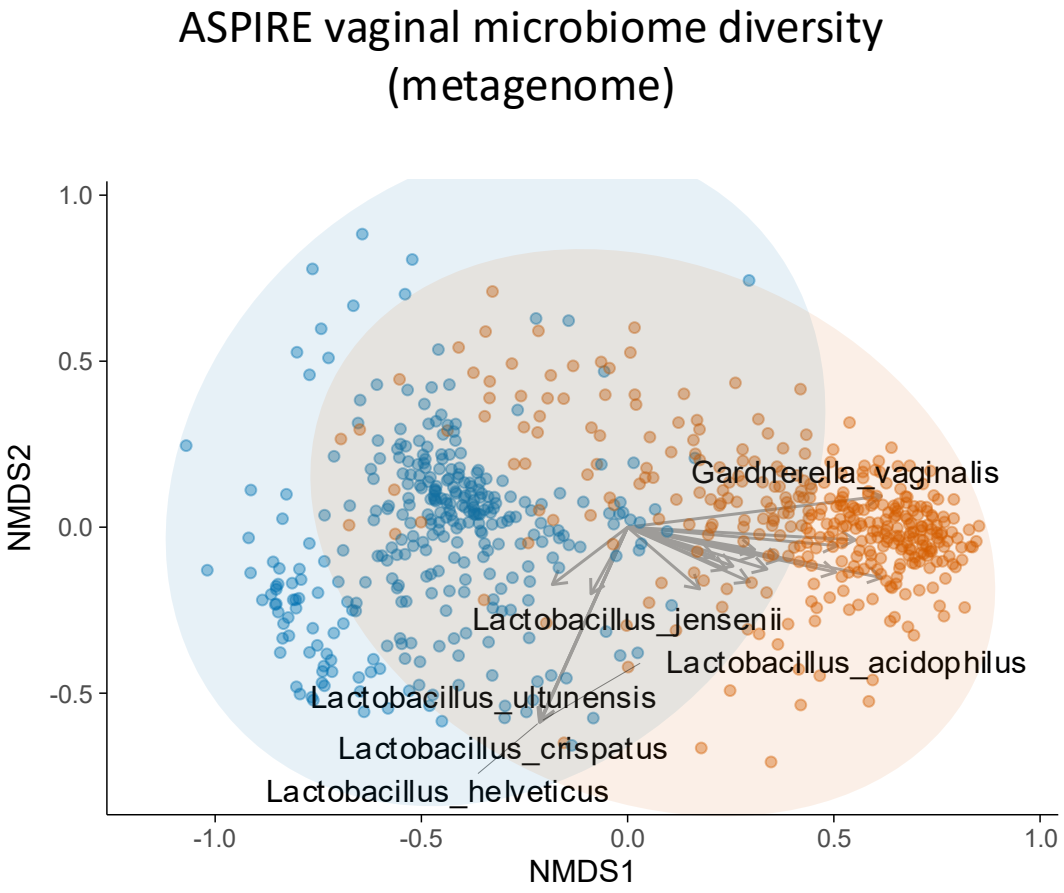
Data generation

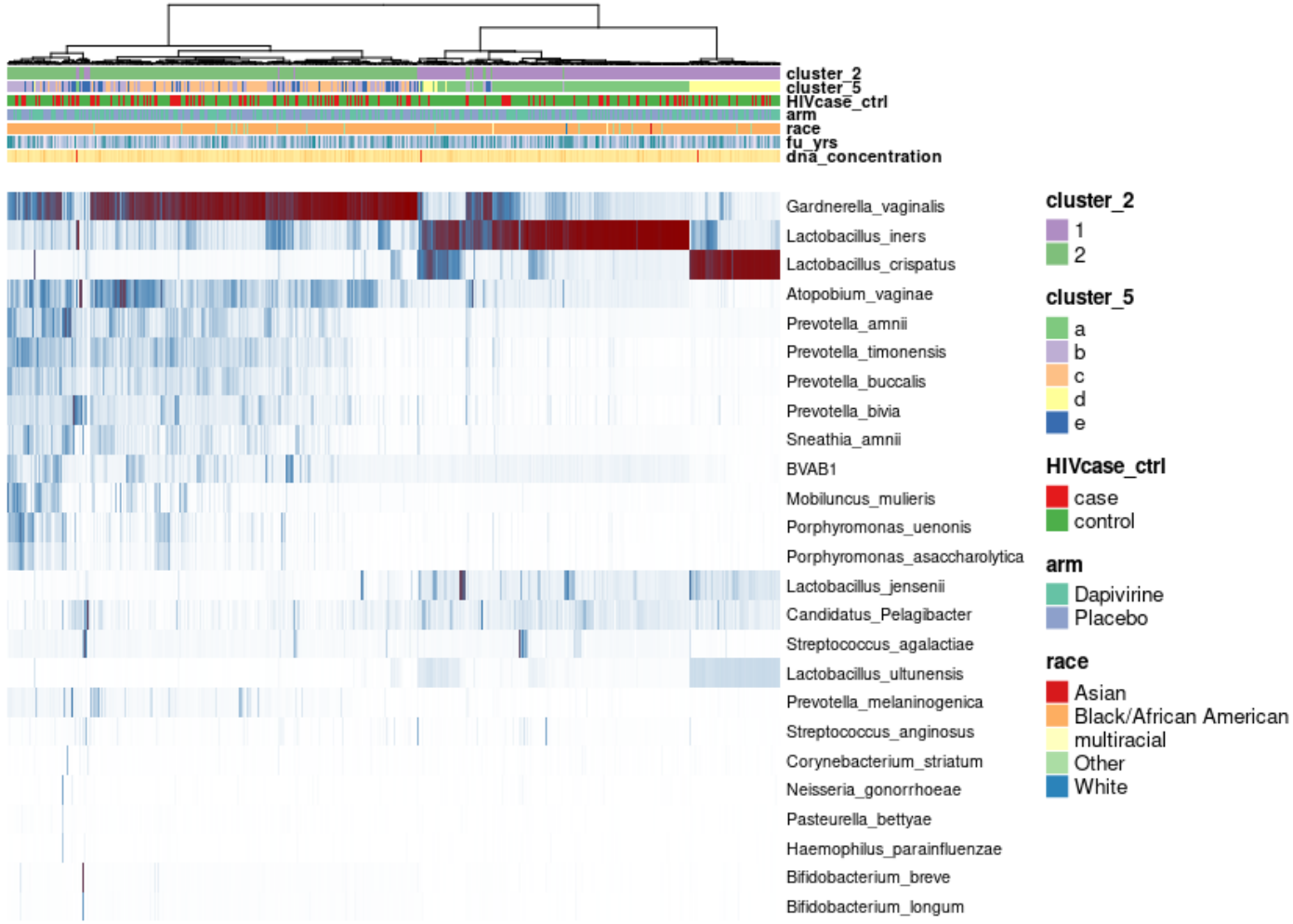




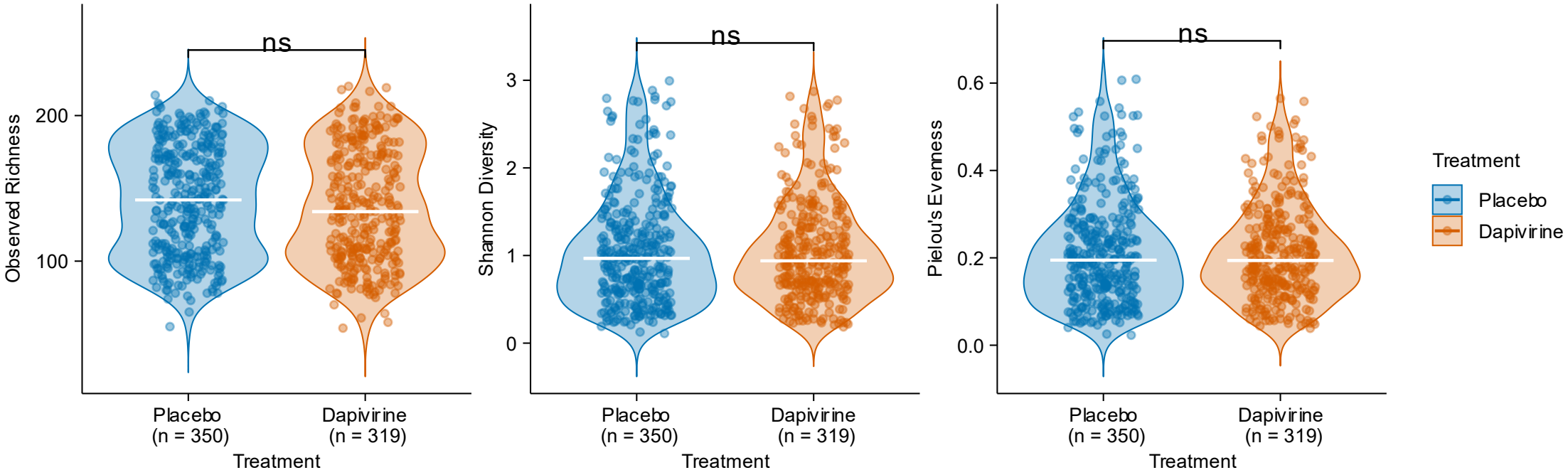


Vaginal microbiome diversity of ASPIRE participants





Vaginal microbiome vs treatment arm in ASPIRE



The vaginal mucosal metabolome HIV transmission, mucosal immunity, and dapivirine efficacy

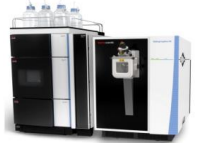
ASPIRE trial participants

Controls (n=471)

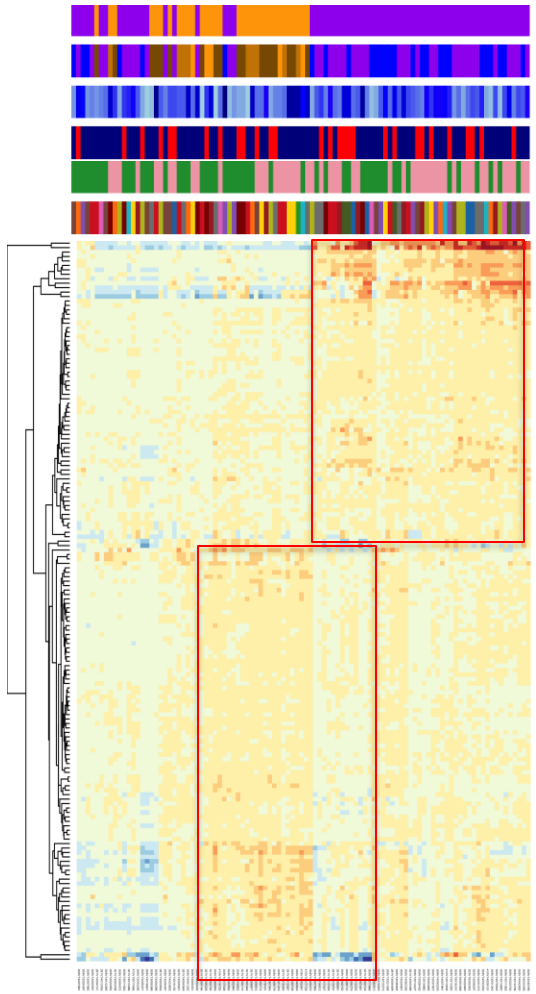
HIV cases (n=157)

Mass spectrometry

Metabolomics



Cervicovaginal metabolome (n=200)

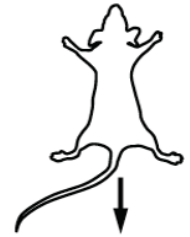


SCFA's
Polyamines
Amino acid derivatives

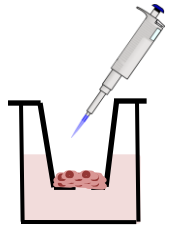
- HIV acquisition
- Mucosal immunity
- Dapivirine efficacy
- *In vitro* cell co-culture models

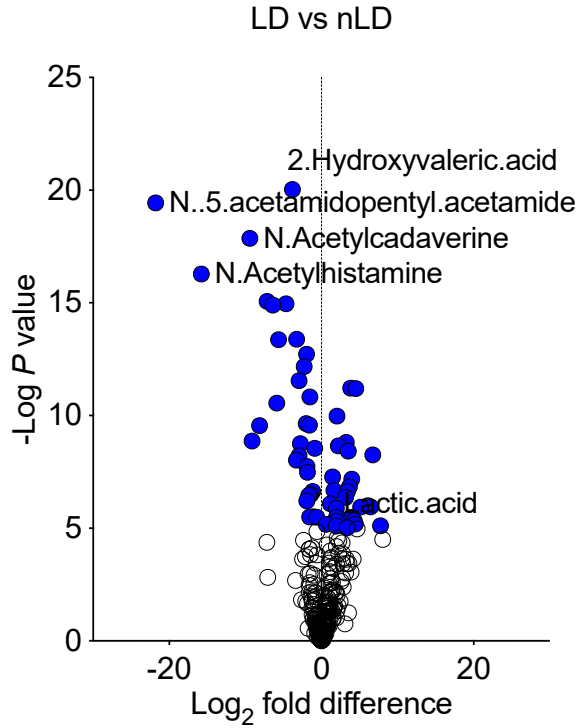
Animal models

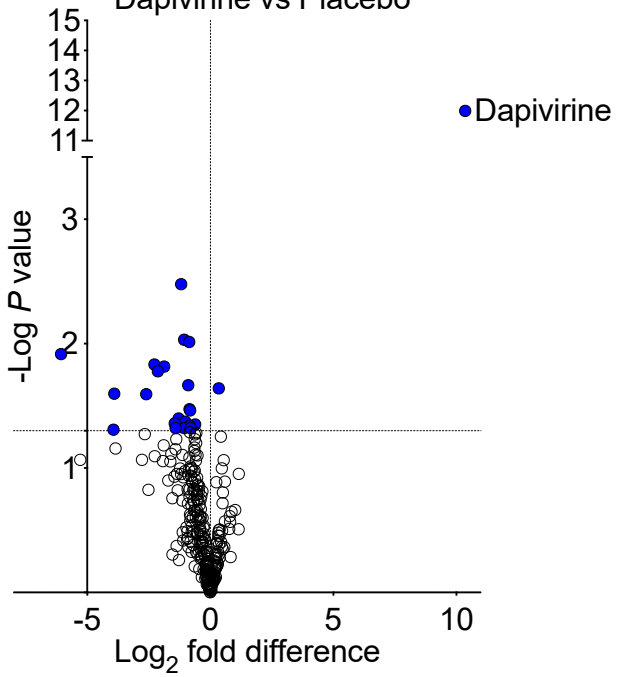
BALB/c mice



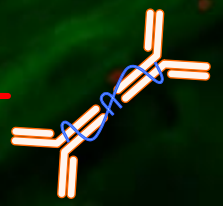
In vitro models







Microbiome and vaccine immunity



Some examples

- Yellow fever vaccine:
  - TLR5 stimulation by gut bacteria enhanced immune response)
- Rotavirus vaccine:
  - Gut microbiome differences in responders/non responders
- HIV Vaccine:
  - Ab responses diverted by cross-reactivity to gut bacteria

(**Background image:** C. Triopini, *Cell host & Microbe,* 2017) (Oh, Immunity, 2024; Harris, CHM, 2018; Harris, Gut Microbes, 2018; Williams,Science, 2015*)*

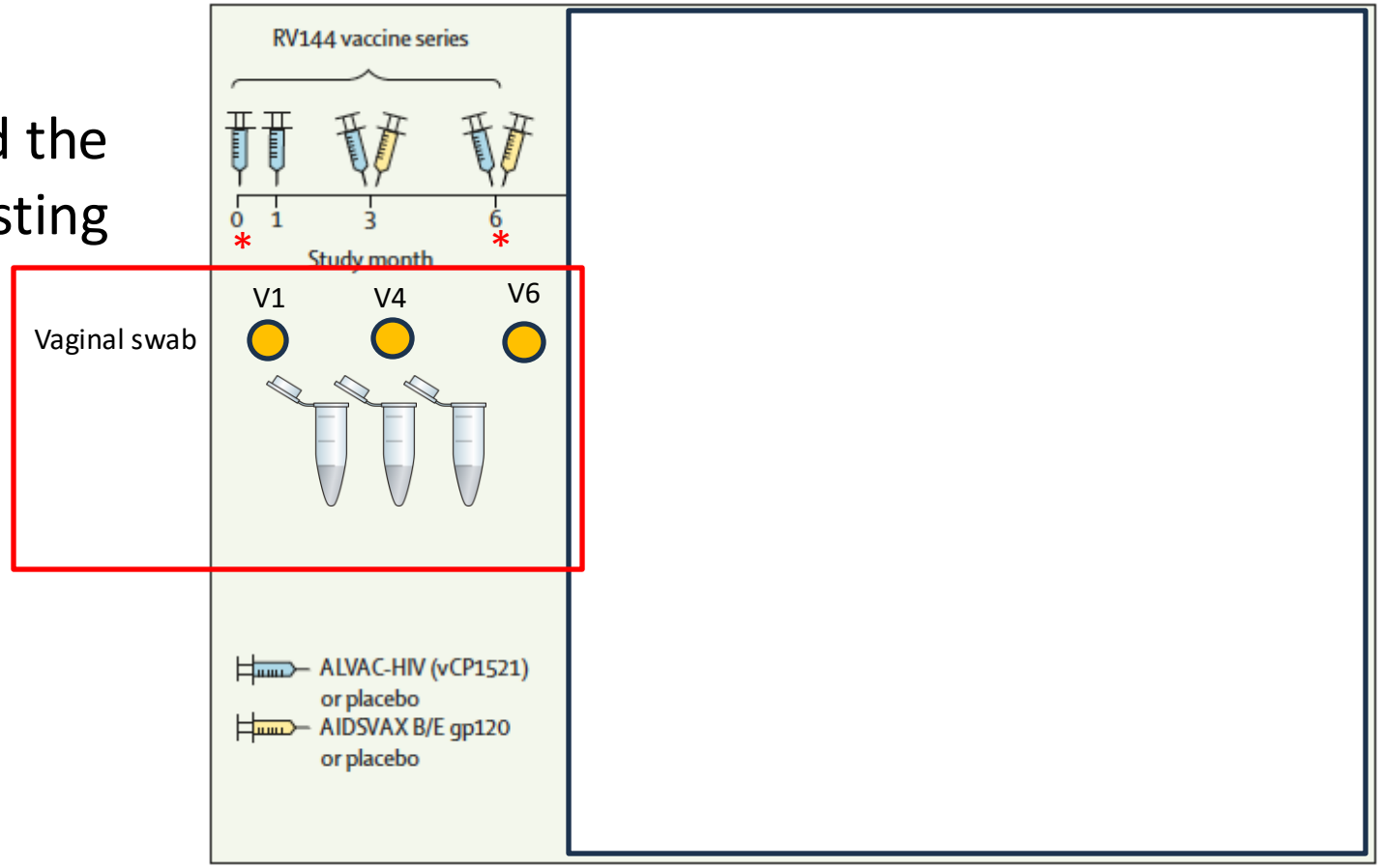
RV306 Study Design


S. Vasan A. Schuetz

Late boosting of the RV144 regimen with ALVAC-HIV and AIDSVAX B/E

RV306 enrolled and randomized 360 healthy Thai volunteers that received the RV144 regimen followed by late boosting with ALVAC-HIV/AIDSVAX B/E

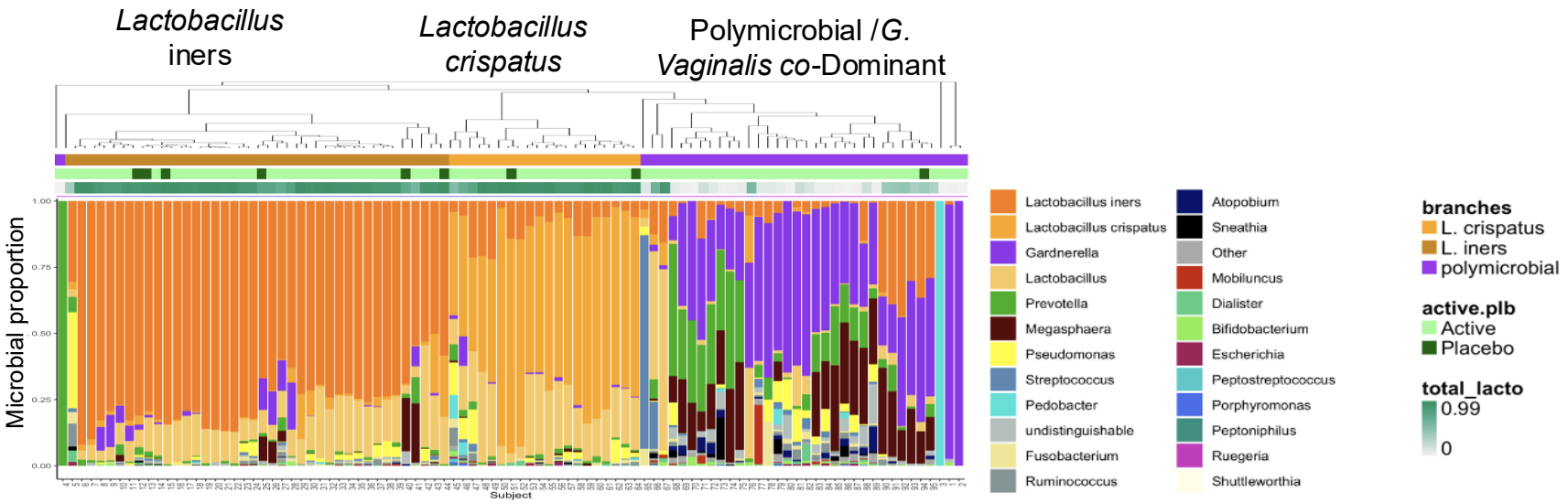
→ For this study we focused on assessment of microbiome and mucosal and systemic bAb responses at baseline (pre-vax) and 2 weeks post first and second ALVAC-HIV/AIDSVAX B-E (RV144 regimen)

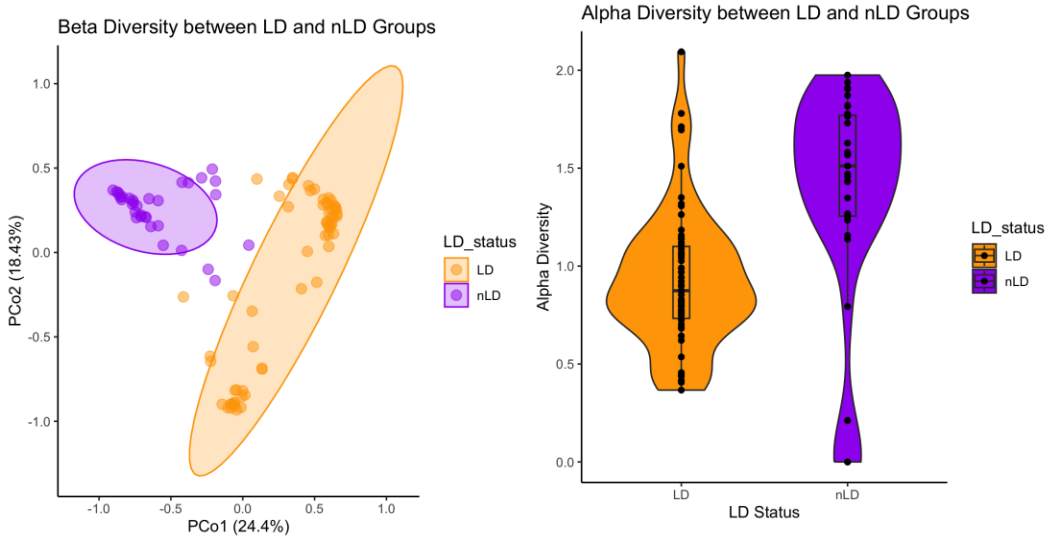


Modified from Pitisuttithum et al., Lancet HIV 2020

(L. Main, L. Noel-Romas *et al*, presented at R4P Oct 2024)

Vaginal microbiome profiles of RV306 participants





Laura Noel-Romas
CWRU

Samantha Knodel,
CWRU

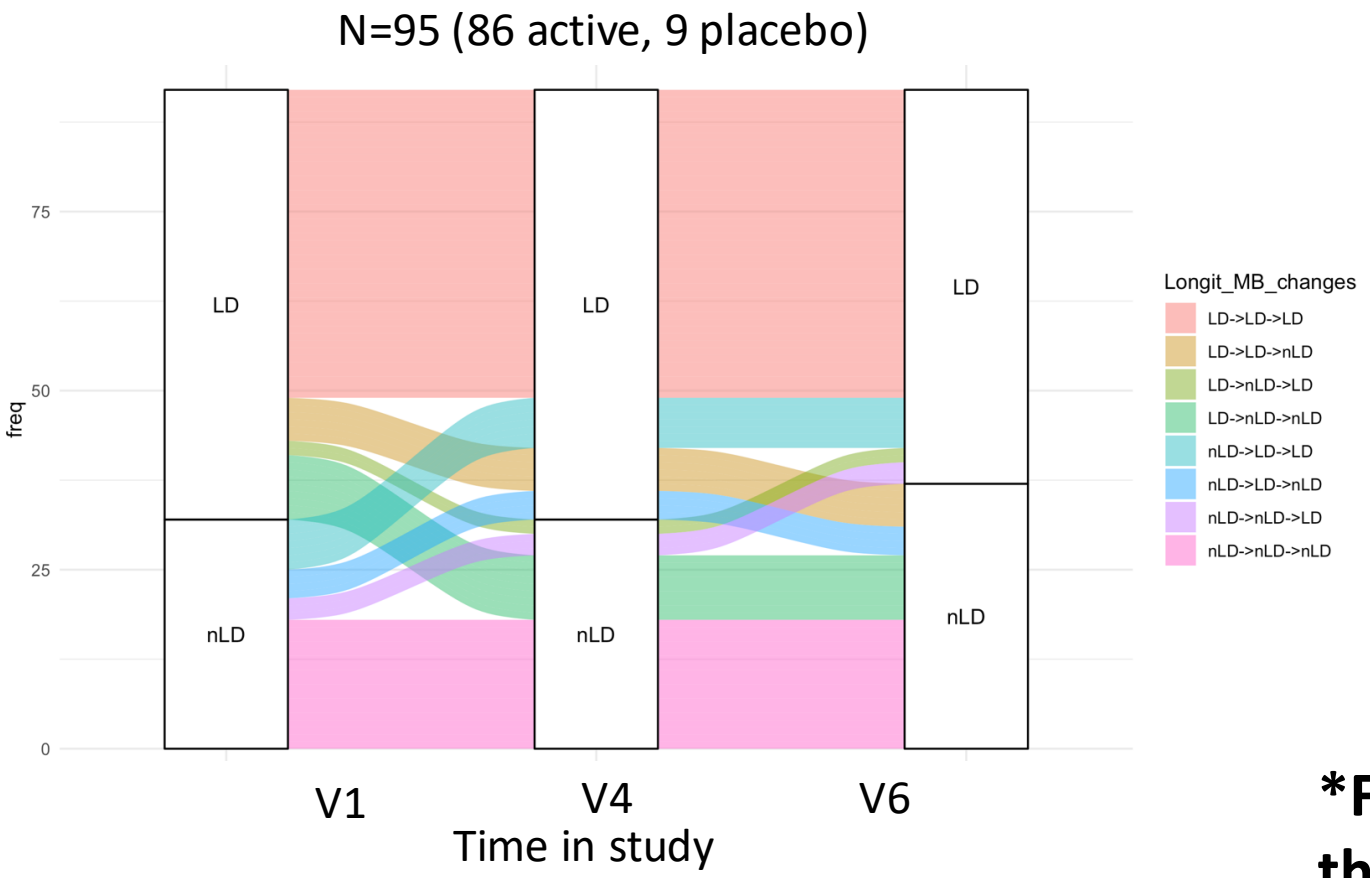
Leighanne Main,
CWRU

62 are *Lactobacillus* dominant

33 are non-*Lactobacillus* dominant

(L. Main, L. Noel-Romas *et al*, presented at R4P Oct 2024)

Longitudinal changes in vaginal microbiome of RV306 participants



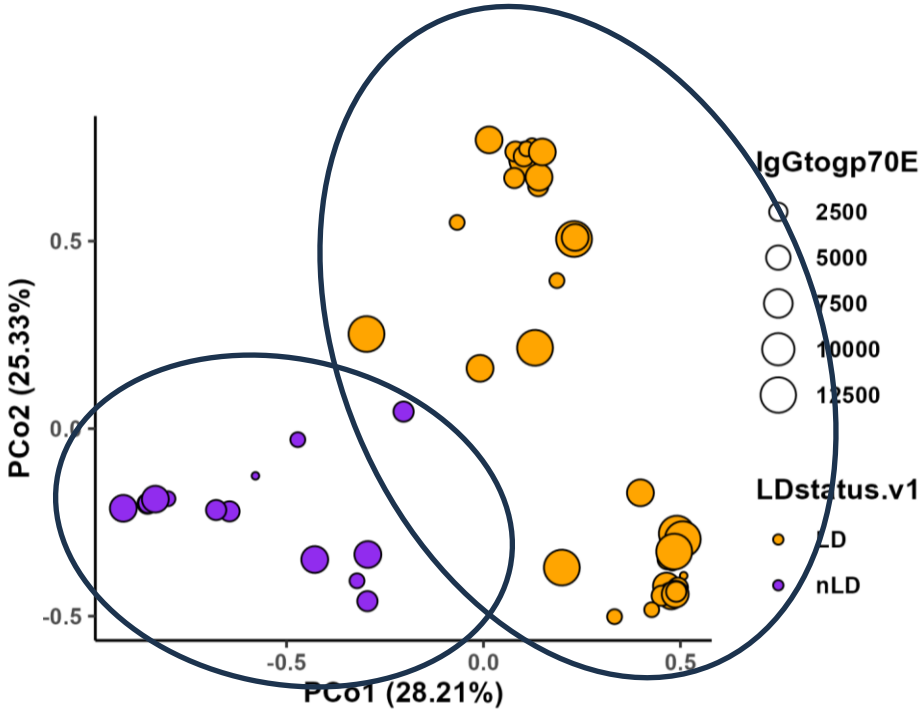
- 61 remained consistently *Lactobacillus* dominant (LD) or *non-Lactobacillus* dominant (nLD)
- 34 changed between LD and nLD

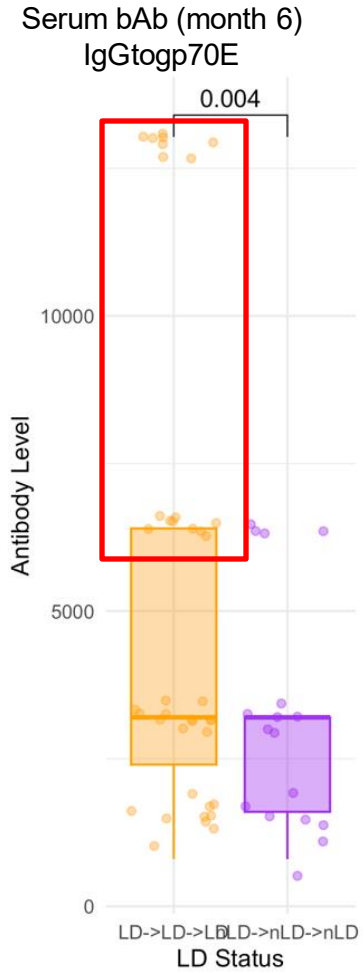
Microbiome	Active	Placebo
Stable	56	5
Unstable	27	4
FET: P = 0.4792 (OR: 1.65, 95% CI, 0.302-8.362)		

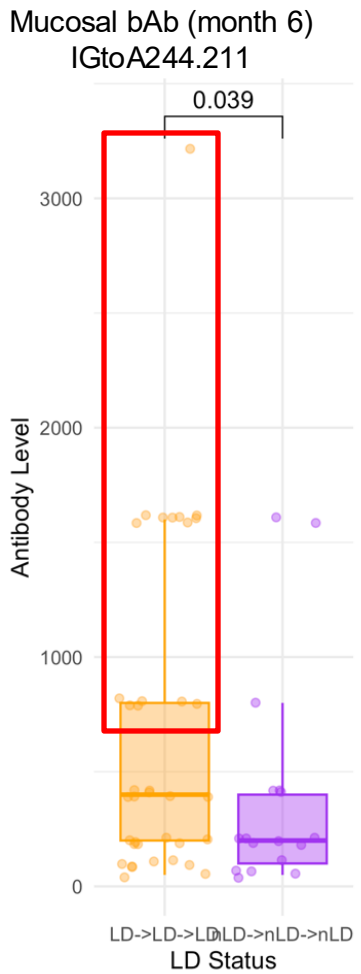
***For vaccine effects we focused on those that had stable microbiomes: 43 LD and 18 nLD**

(L. Main, L. Noel-Romas *et al*, presented at R4P Oct 2024)

Lactobacillus dominant vaginal microbiomes associate with increased mucosal and serum HIV binding antibody responses

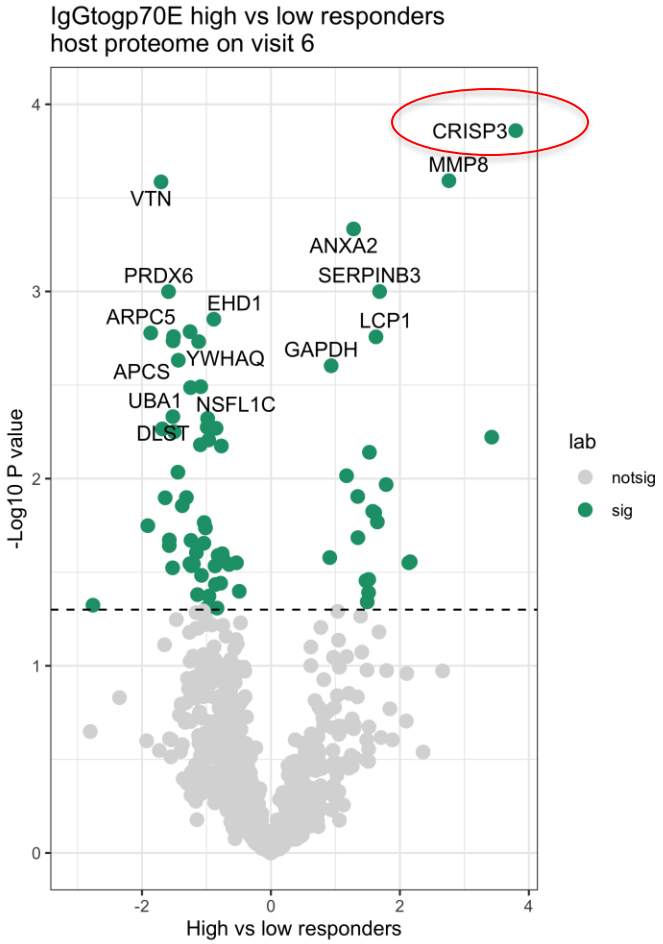




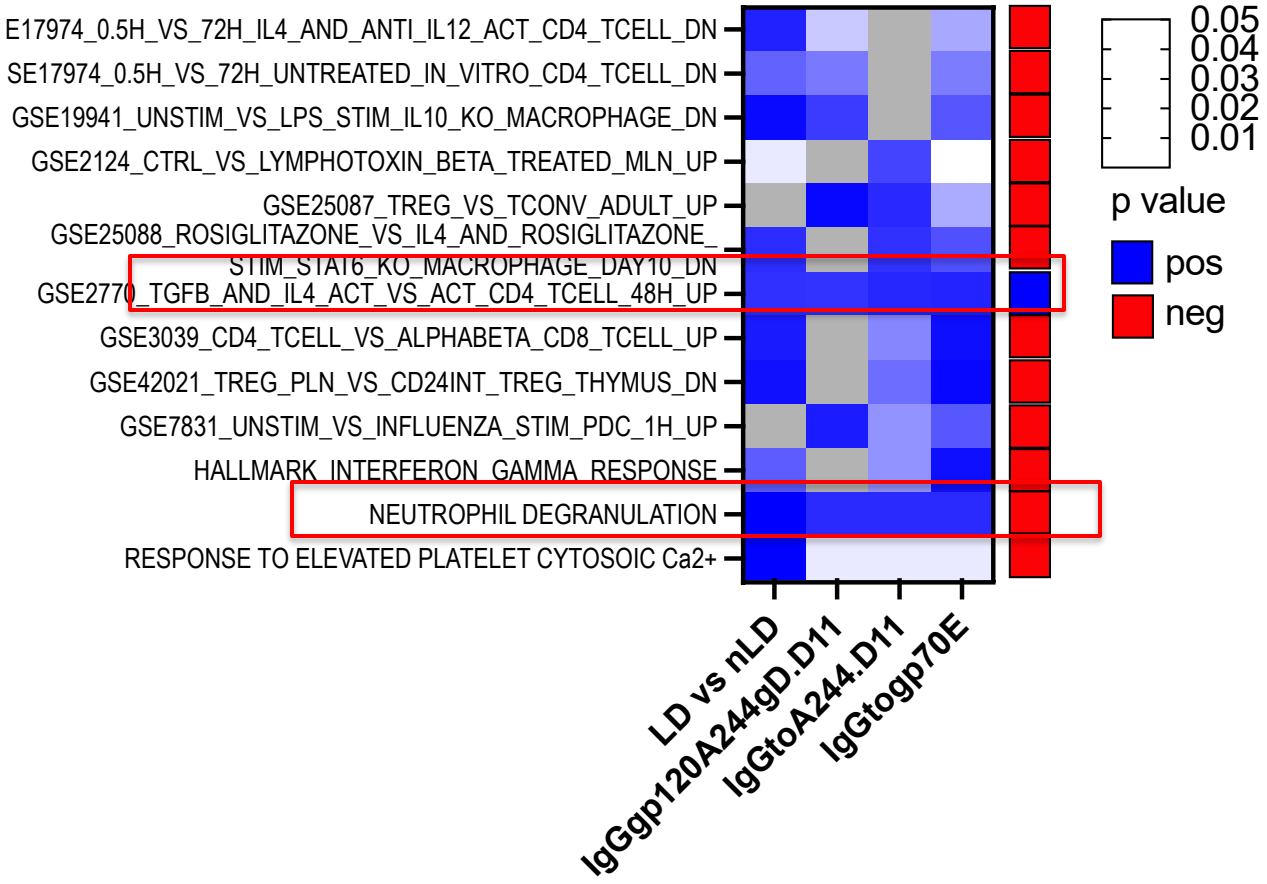


Host mucosal correlates of increased HIV-binding antibody responses

Proteome correlates of Ab responses



Gene set enrichment analysis



Leighanne Main, CWRU

(L. Main, *et al*, in preparation)

Generation of a multi-'omics host-microbial signature underlying vaccine immune responses

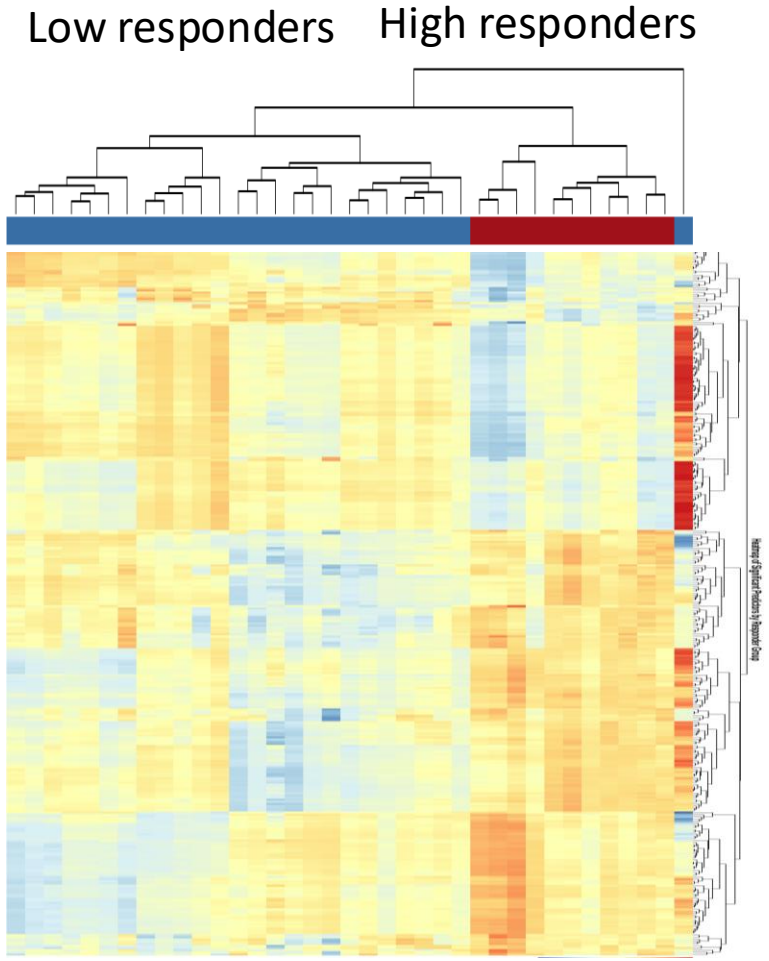
DR. Leighanne Main, CWRU

Dr. D. Brubaker (CWRU)

Multi-'omics meta model for microbiome-host regulation of vaccine induced antibody responses

$$PLSDA(y_1, Mx) \rightarrow Metabolite\ LVs$$
$$PLSDA(y_1, PHx) \rightarrow Human\ Protein\ LVs$$
$$PLSDA(y_1, PBx) \rightarrow Bacterial\ Protein\ LVs$$
$$PLSDA(y_1, Tx) \rightarrow Taxa\ LVs$$

-Perform partial least-squares discriminant analysis (PLS-DA) to extract a one-dimensional latent variable (LV), relative to the binary outcome of high/low vaccine responders.
-The glm top variables are then inserted into a linear model (lm) to find the best combination of variables to predict AB response



(L. Main, *et al*, in preparation)

Summary and potential implications

- The vaginal microbiome affects topical HIV prevention technologies
- Neutrophils are linked to the microbiome, HIV susceptibility and protection, and associate with differences in HIV vaccine immune responses
- Higher vaccine HIV-binding antibody responses associate with *Lactobacillus* dominant vaginal microbiomes
- Microbiome-derived metabolites contribute to altered host immunity, barrier disruption, and may be important for topical HIV prevention strategies
- Understanding molecular mechanisms and microbial-host interactions at mucosal barriers could improve female reproductive health and STI prevention efforts

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