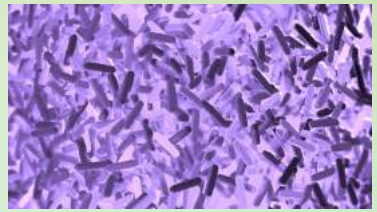
HIV Prevention and the Vaginal Microbiome



Betsy C. Herold, M.D.
Albert Einstein College of Medicine
Children's Hospital at Montefiore
Bronx, NY

HPTN ANNUAL MEETING 2021

HPTN
HIV Prevention Trials Network

HPTN
HIV Prevention Trials Network

Efficacy of Oral and Vaginal TFV-Based PrEP is Variable; Especially in Women

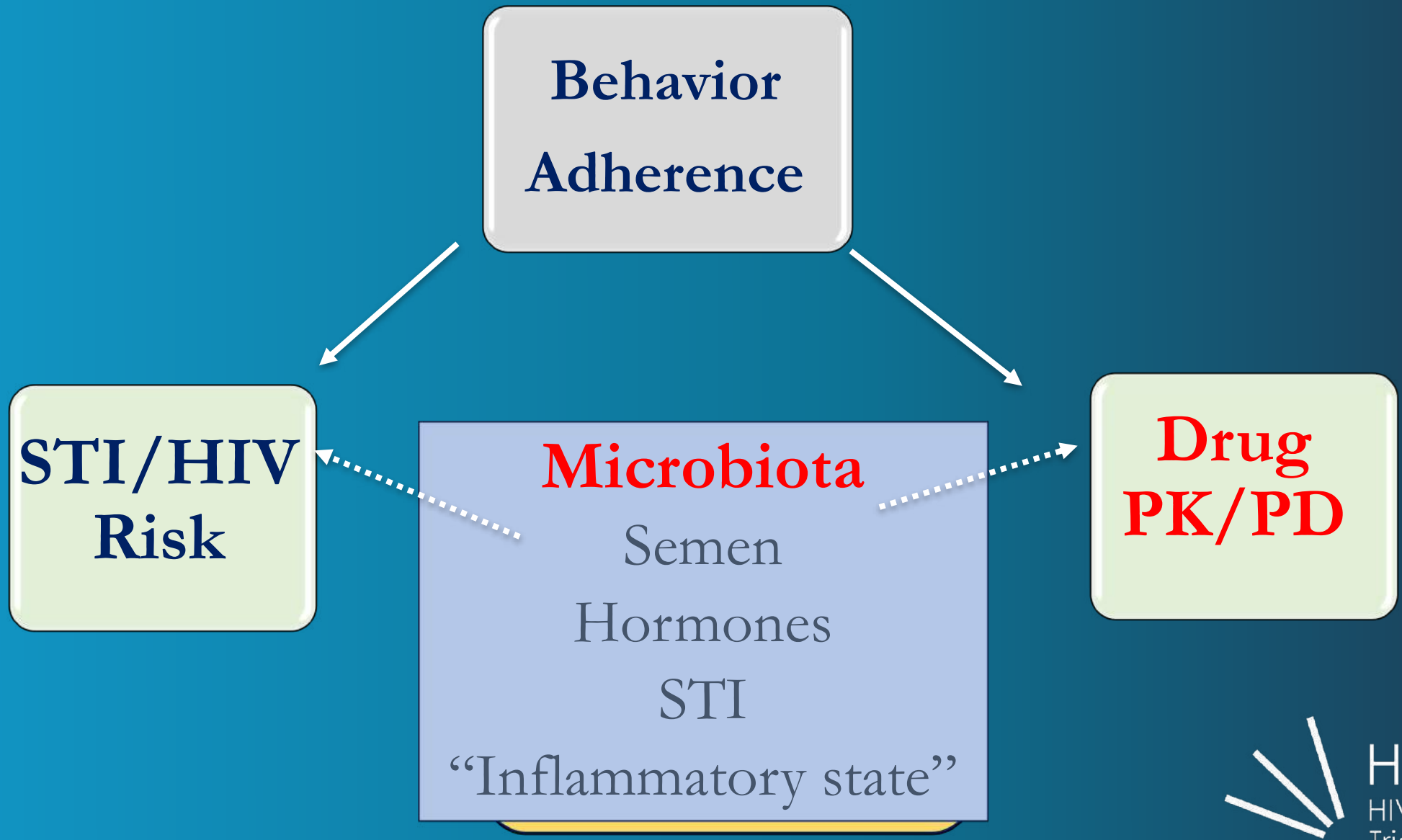
Study (location)	Population	Design	Relative reduction in HIV incidence in intention-to-treat analysis	PrEP detection in blood samples from non-seroconverters
Completed trials (ordered by decreasing HIV risk reduction in primary intention-to-treat analysis)				
Partners PrEP Study (Kenya, Uganda)	4747 heterosexual men and women with HIV infected partners (serodiscordant couples)	1:1:1 randomization to daily oral TDF, FTC/TDF, or placebo	TDF: 67% (95% CI 44-81%, p<0.0001) FTC/TDF: 75% (95% CI 55-87%, p<0.0001)	82% Detection of tenofovir in blood associated with 86-90% HIV protection.
TDF2 Study (Botswana)	1219 heterosexual men and women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 63% (95% CI 22-83%, p=0.01)	79%
iPrEx (Brazil, Ecuador, Peru, South Africa, Thailand, US)	2499 MSM and transgender women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: 44% (95% CI 15-63%, p=0.005)	51% Detection of tenofovir associated with 92% HIV protection, high adherence with >95% protection.
CAPRISA 004 (South Africa)	889 women	1:1 randomization to intercourse-associated use of tenfovir vaginal gel or placebo	Tenofovir gel: 39% (95% CI 6-60%, p=0.02)	Detection of high concentrations of tenofovir (>1000 ng/mL) in cervicovaginal fluid associated with 74% reduced HIV risk.
FEM-PrEP (Kenya, South Africa, Tanzania)	2120 women	1:1 randomization to daily oral FTC/TDF or placebo	FTC/TDF: No HIV protection	35-38% at a single visit, 26% at two consecutive visits
VOICE (South Africa, Uganda, Zimbabwe)	5029 women	1:1:1:1:1 randomization to daily oral TDF, FTC/TDF, oral placebo, tenofovir vaginal gel, or gel placebo	TDF: No HIV protection FTC/TDF: No HIV protection Tenofovir gel: No HIV protection	≤30% of samples had tenofovir detected. ≥50% of women in each of the active arms never had tenofovir detected, at any time during their follow-up

HPTN
HIV Prevention Trials Network

Variable and Modest Efficacy of Dapivirine Ring

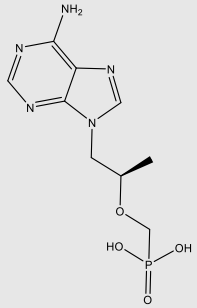
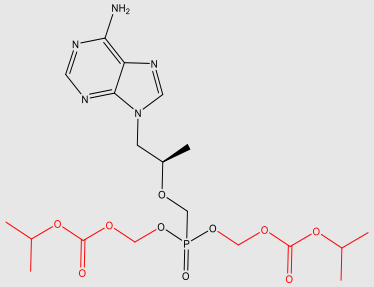
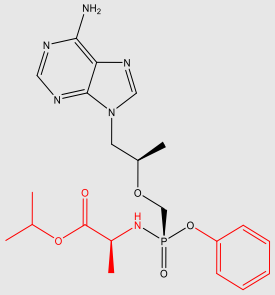
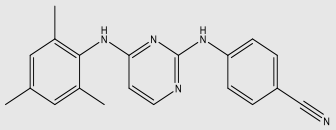
	IPM 027	**MTN 020**	**HOPE**
Enrollment	1959 women 18-45 years 1300 active arm	2629 women 18-45 years 1325 active arm	1456 women from MTN020 Open-label
Results	31% [1-51] effective	27% [1-46]	39% estimated protection (35 infections)
HIV incidence	4.1% active; 6.1% placebo	3.3% active; 4.5% placebo	2.7% [1.9-3.8] vs 4.4 [3.2-5.8]

Factors that may impact PrEP efficacy



HPTN
HIV Prevention Trials Network

Mechanisms of drug transport into and out of target cells

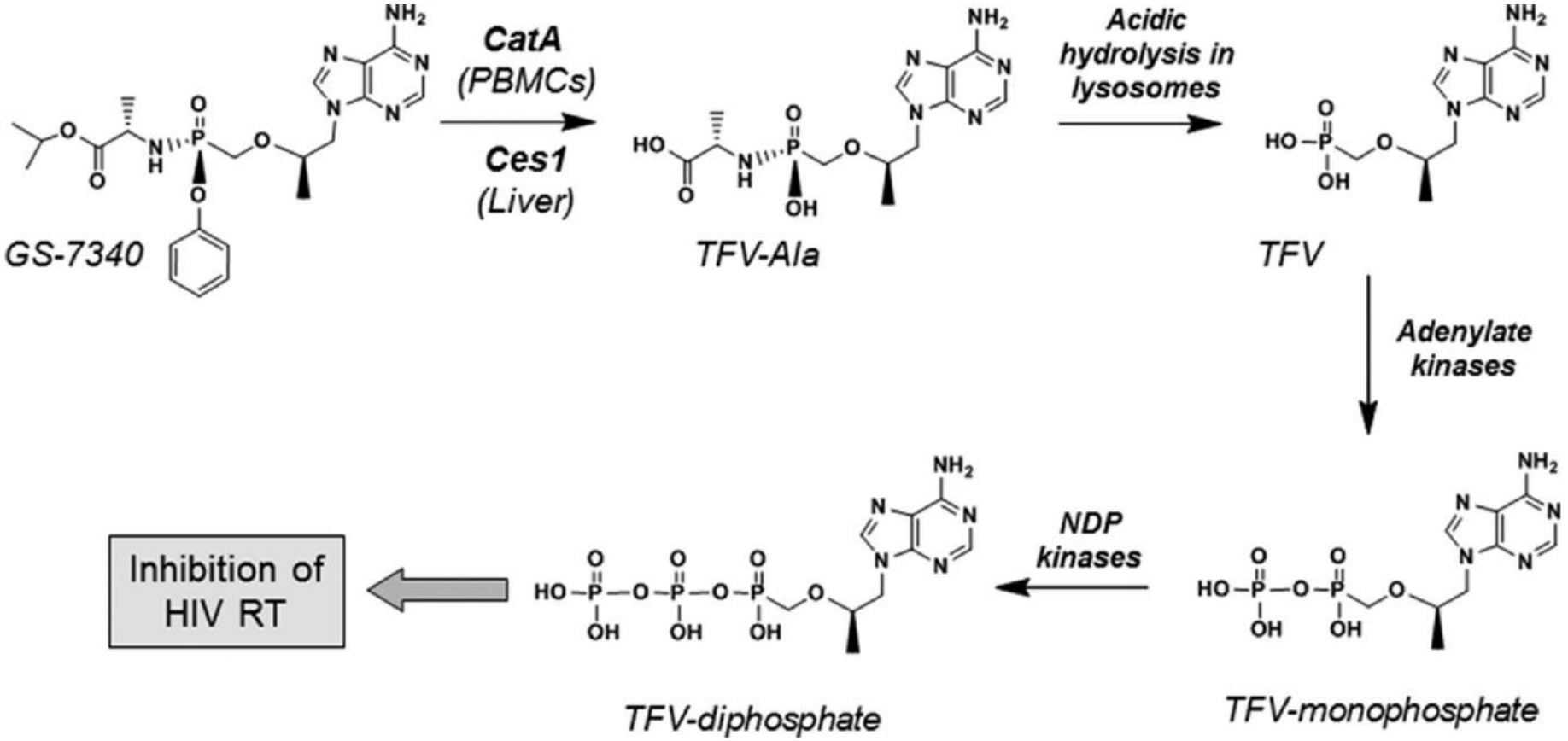
Drug	Tenofovir (TFV)	TFV disoproxil fumarate (TDF)	TFV alafenamide (TAF)	Dapivirine (DPV)
Structure				
IC_{50} (µM)	2.5	0.1	0.05	0.002
Transport mechanism	**Endocytosis**	**Passive diffusion**	**Passive diffusion**	**Passive diffusion ?**
Energy dependency Saturability Enzymes	ATP-dependent non-saturable	ATP-independent saturable Carboxylesterase-1 rate-limiting	ATP-independent saturable Cathepsin A rate-limiting	Unknown uptake/efflux mechanisms Metabolized by CYP4503A4/5
Source	Taneva et al., *AAC*, 2015	Taneva et al., *AAC*, 2015	Taneva et al., (in prep)	To et al., *Biochem Pharmacol*, 2015

TFV entry into FGT epithelial and immune cells by endocytosis reflects limited expression of organic anion transports (Taneva, AAC 2015)

HPTN
HIV Prevention Trials Network

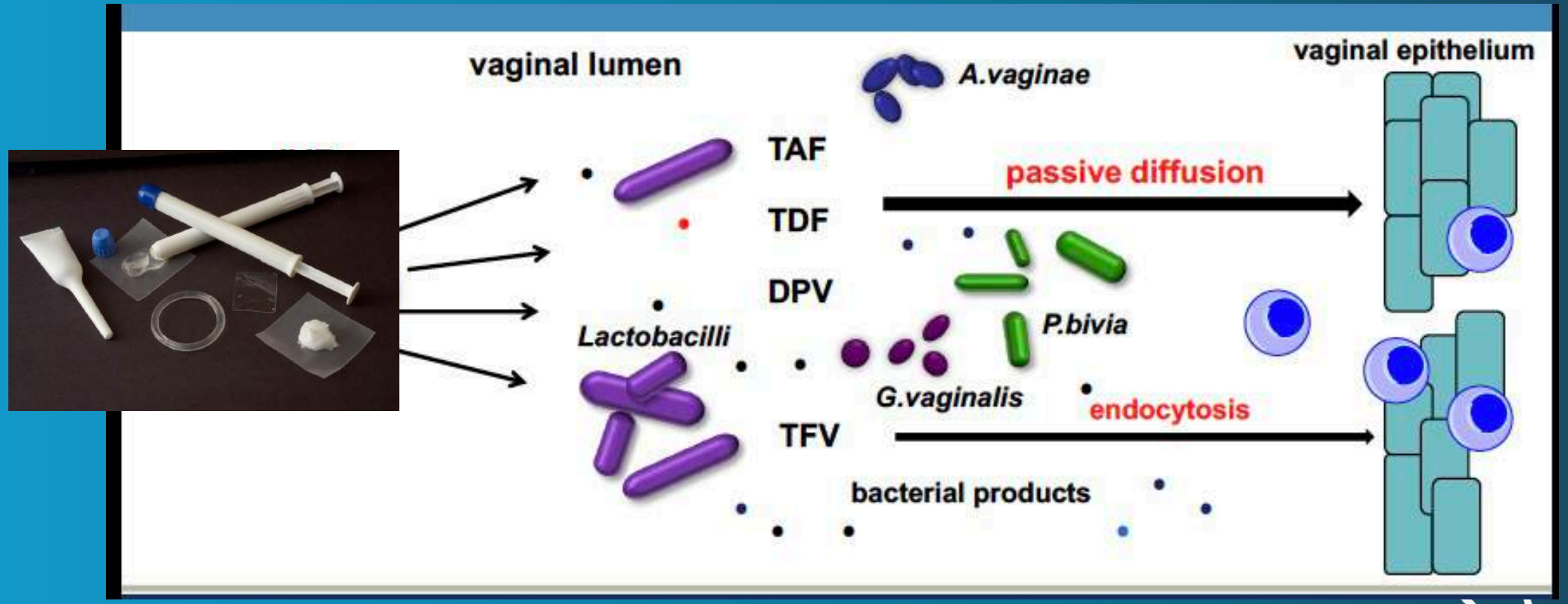
HPTN
HIV Prevention Trials Network

Complexities of Drug PK Mechanism of intracellular activation of TAF



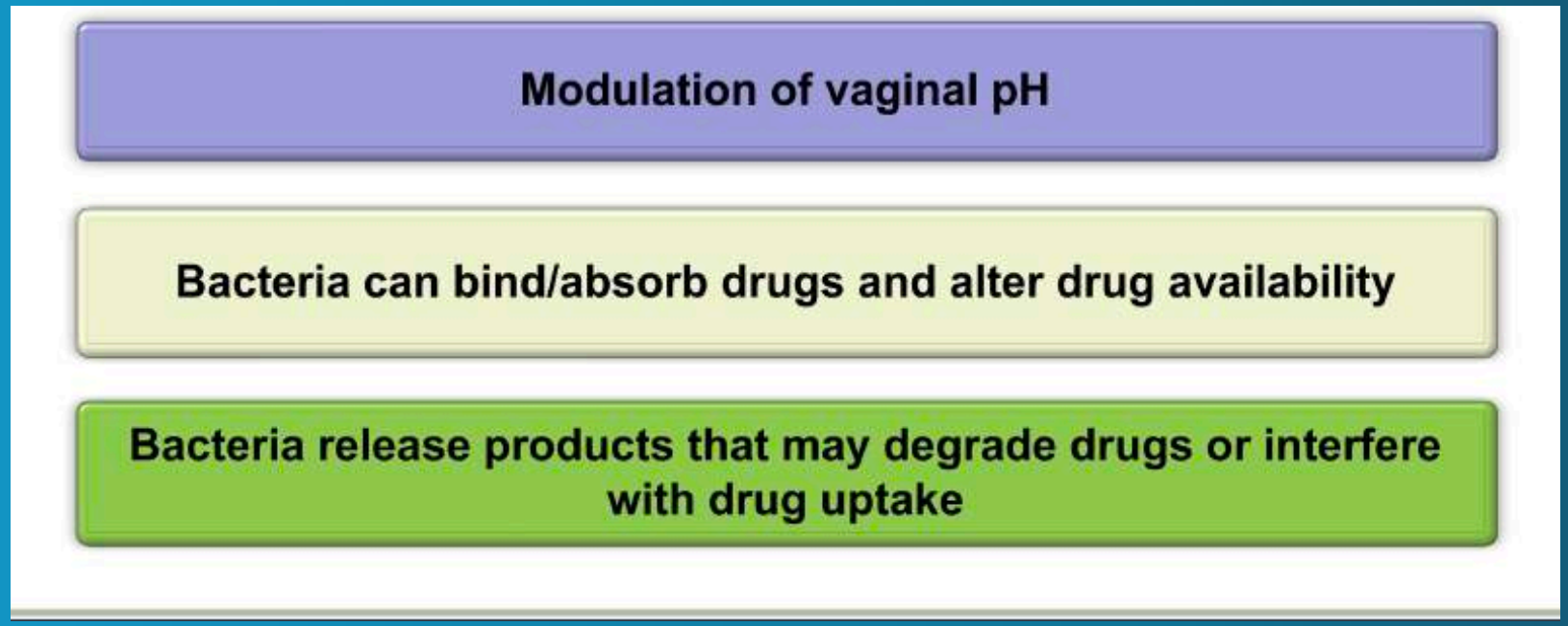
Gabriel Birkus et al. Antimicrob. Agents Chemother. 2016; doi:10.1128/AAC.01834-15

Drugs released into complex environment that may modulate drug PK and Efficacy



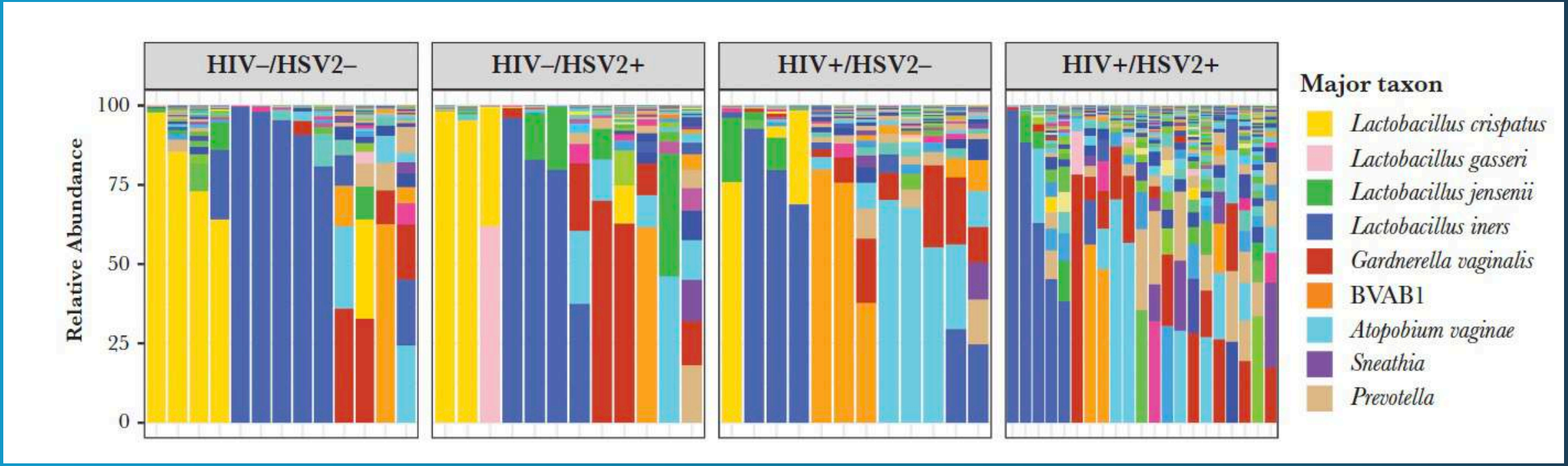
HPTN
HIV Prevention
Trials Network

Hypothesis: Vaginal Microbiota Differ Across Populations and Impact PK/PD by the following mechanisms:



HPTN
HIV Prevention Trials Network

Hypothesis: Vaginal Microbiota Differ Across Populations and Modulate PK



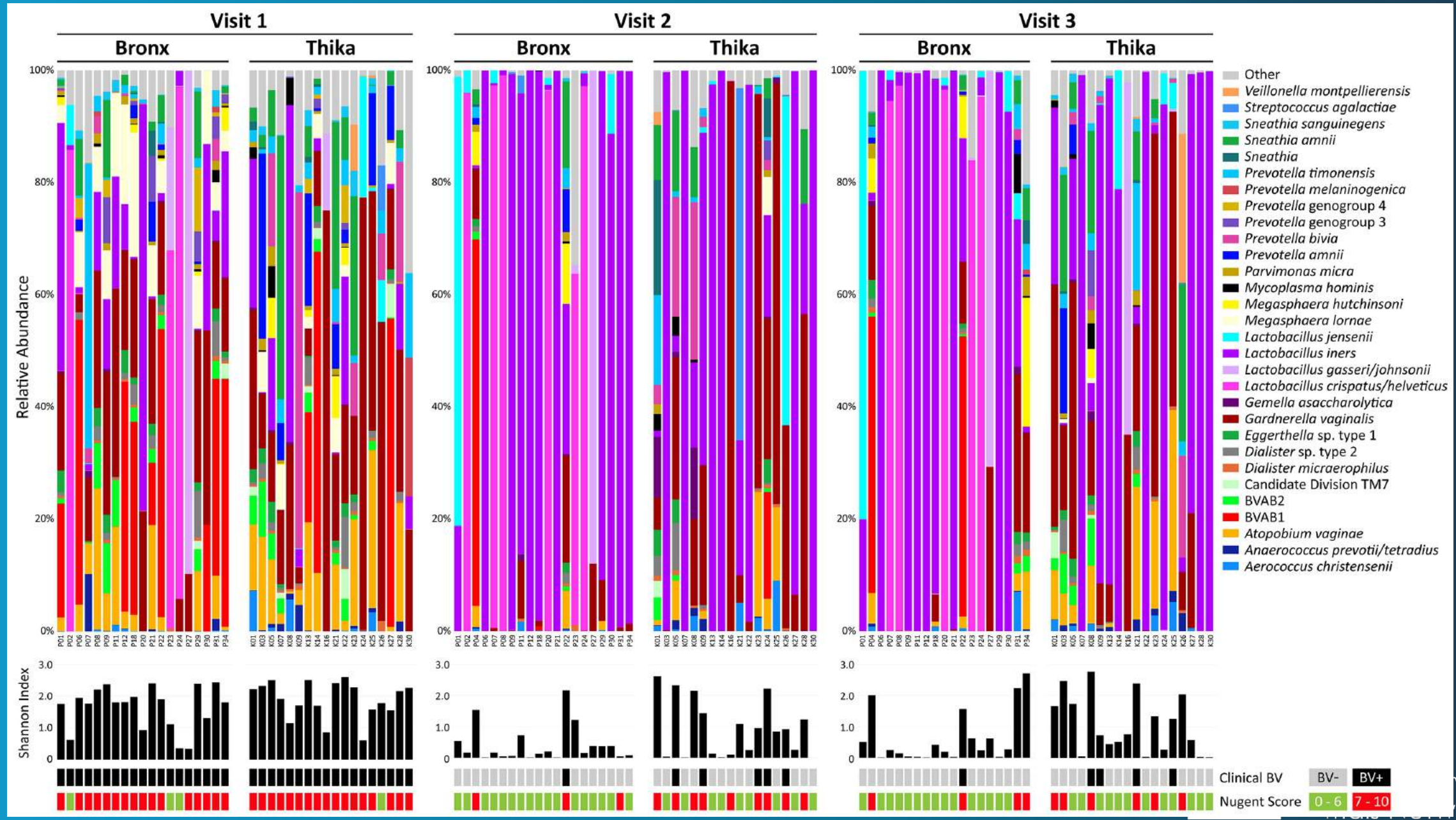
The Journal of Infectious Diseases
MAJOR ARTICLE

Impact of Herpes Simplex Virus Type 2 and Human Immunodeficiency Virus Dual Infection on Female Genital Tract Mucosal Immunity and the Vaginal Microbiome

Marla J. Keller,[1] Ashley Huber,[2,a] Lilia Espinoza,[1] Myrna G. Serrano,[3,4] Hardik I. Parikh,[4] Gregory A. Buck,[3,4,5] Jeremy A. Gold,[3,b] Yiqun Wu,[1,c] Tao Wang,[1] and Betsy C. Herold[6,8]

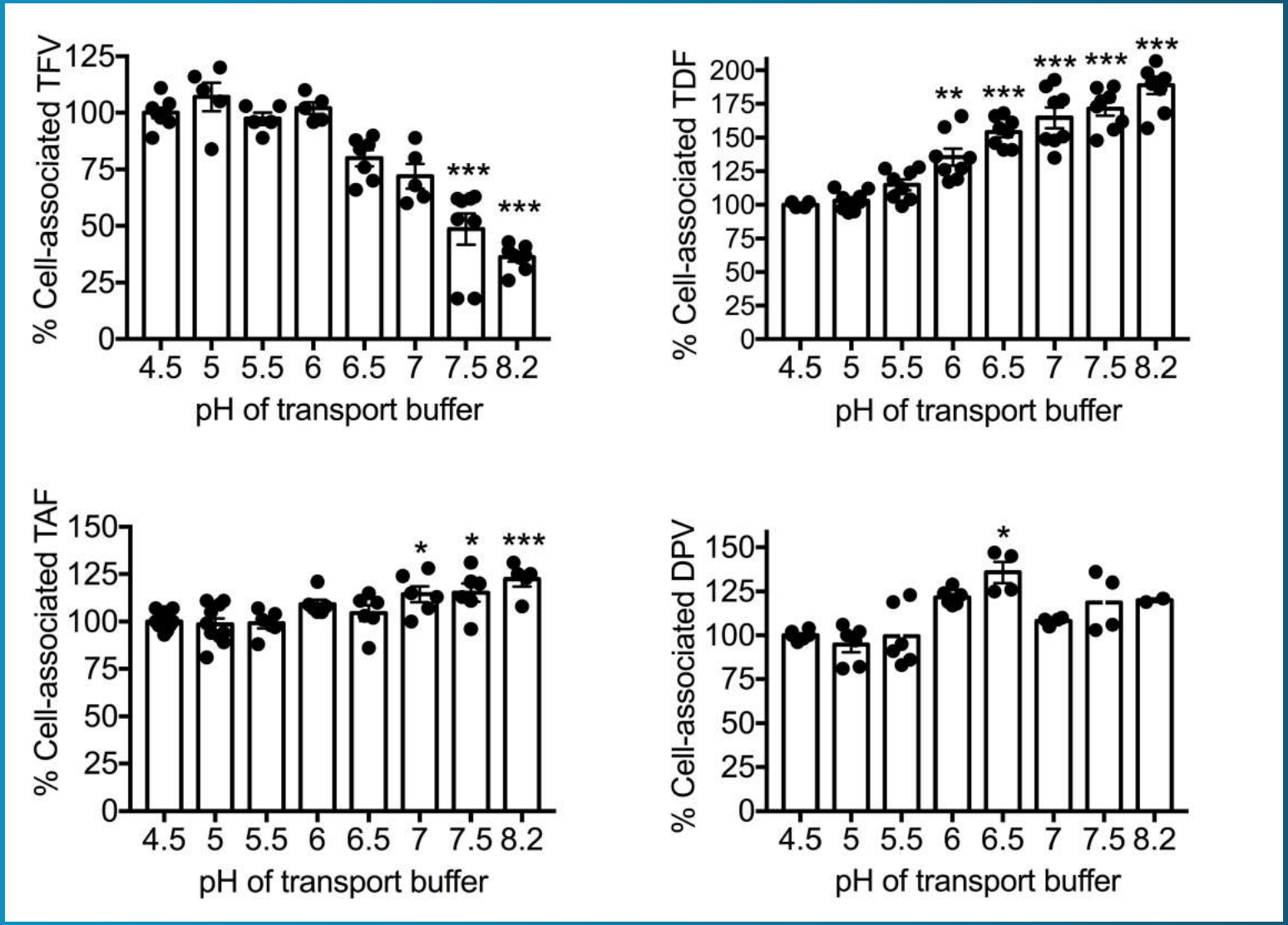
HPTN
HIV Prevention Trials Network

Bronx and Thika Women Treated for BV



Serebrenik Sultan[1], Wang[2], Hunte[1], Srinivasan[3], …Keller, Herold, in review

pH Modulates Intracellular (T cell) drug levels

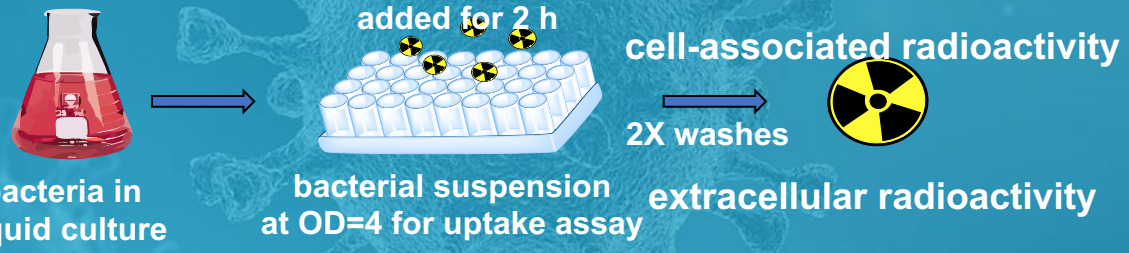


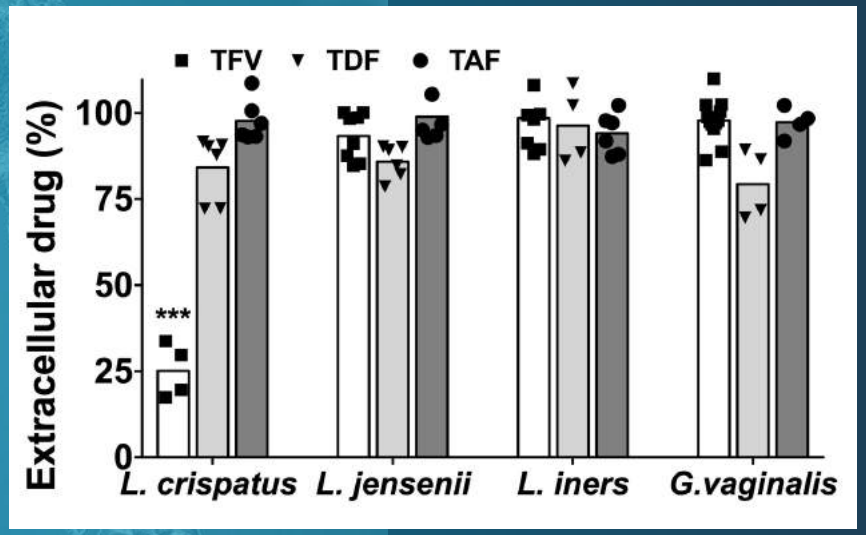
HPTN
HIV Prevention
Trials Network

Taneva et al, JCI Insight, 2018, Jul 12;3(13).

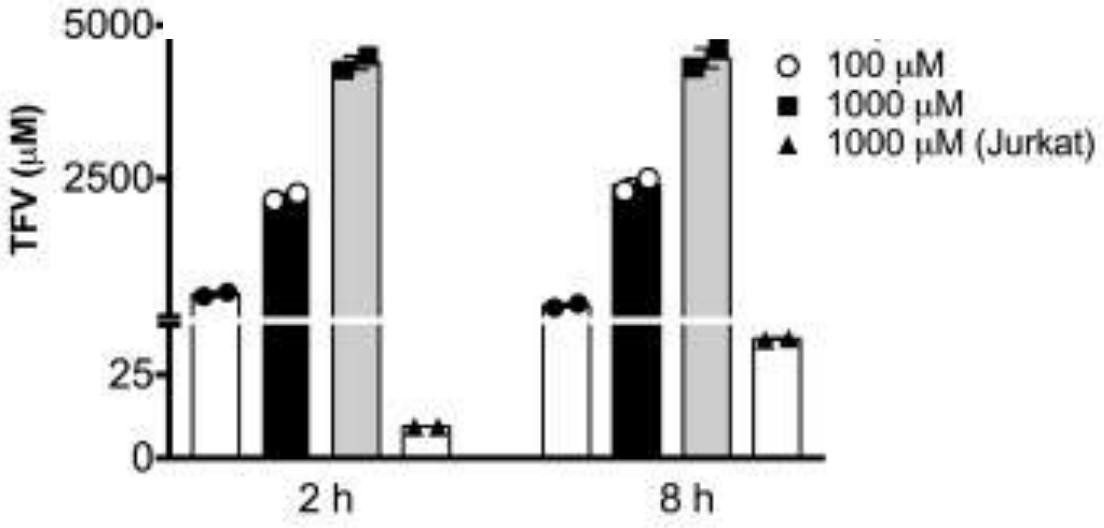
HPTN
HIV Prevention Trials Network

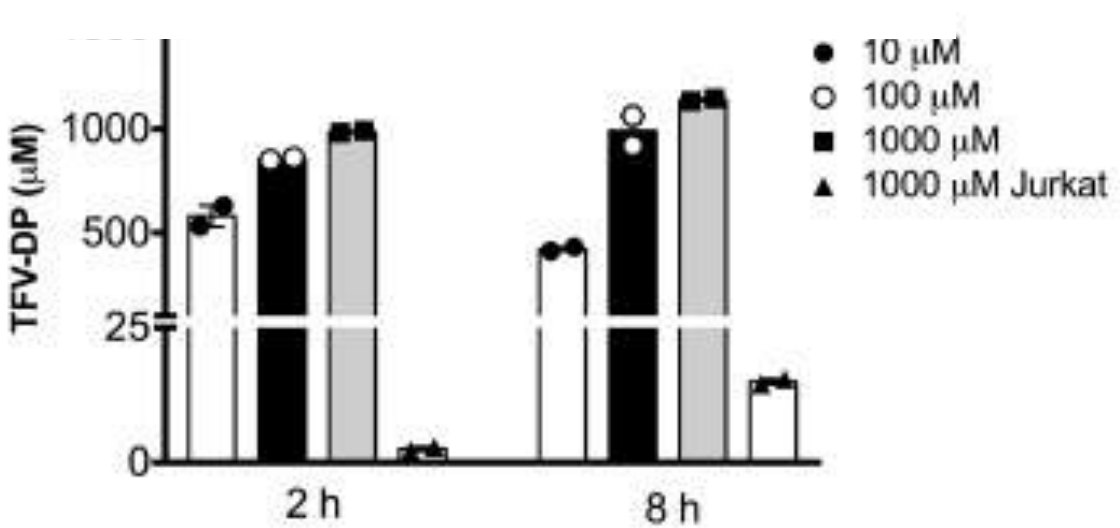
Bacteria can bind/absorb drugs and alter drug availability





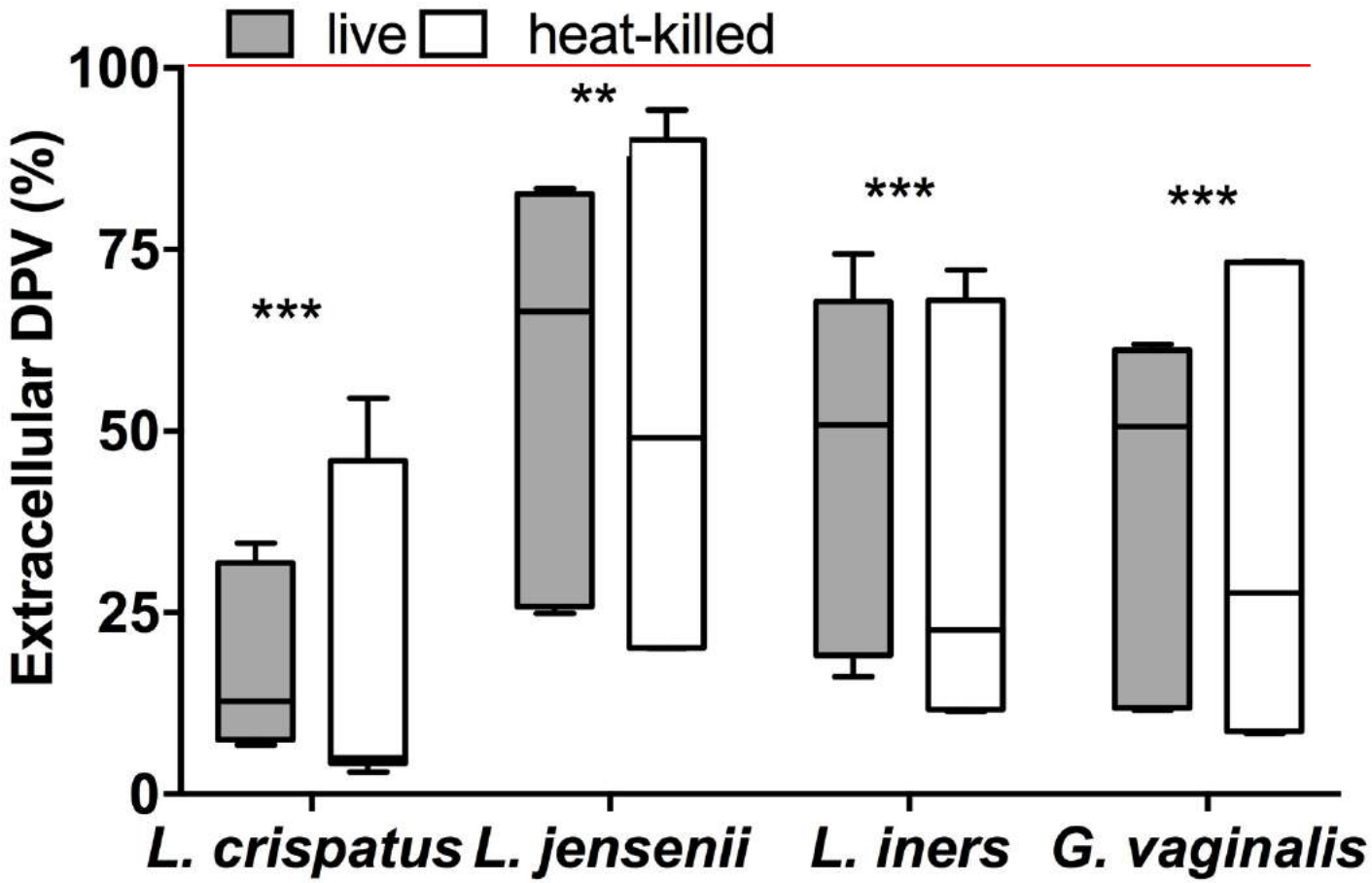
L. crispatus actively transports and phosphorylates TFV





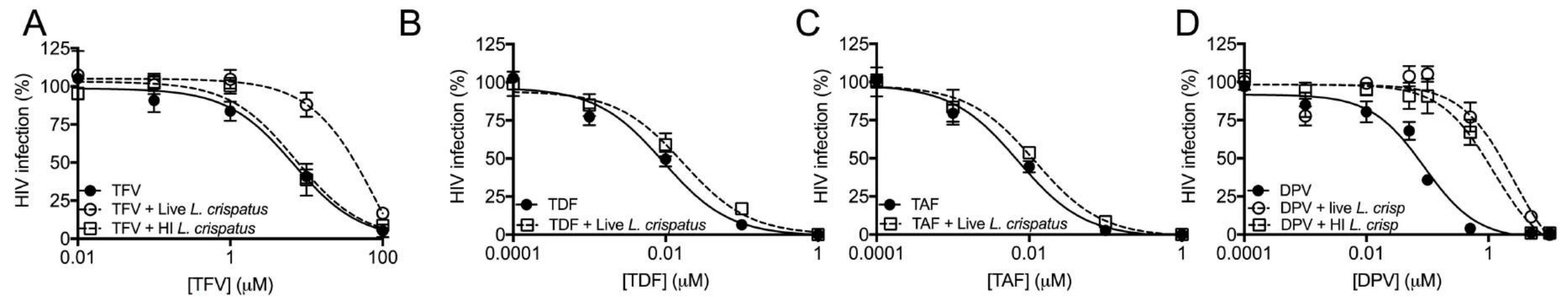
Bacteria can bind/absorb drugs and alter drug availability

Dapivirine is "Sticky"
Adheres to Live or Heat-Killed Bacteria

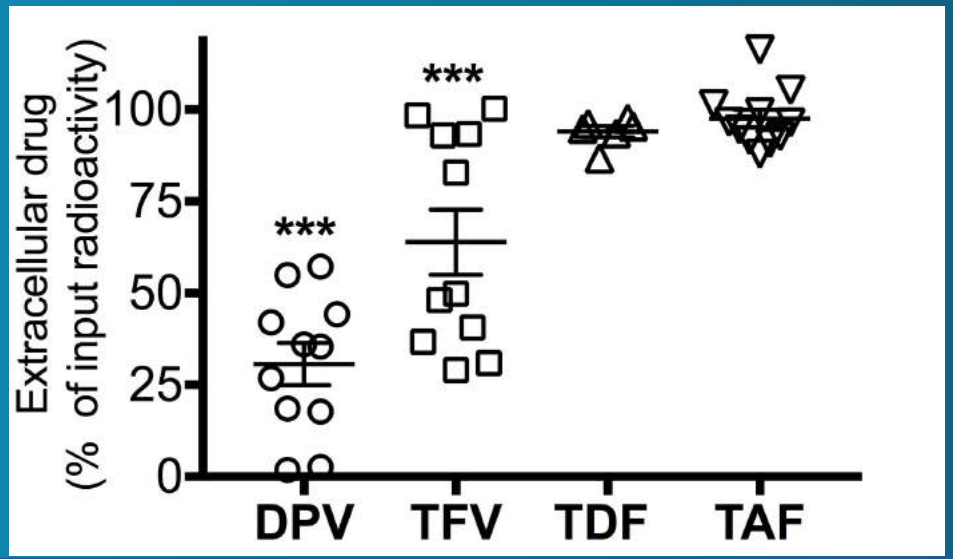


HPTN
HIV Prevention
Trials Network

Translates into decreased antiviral activity



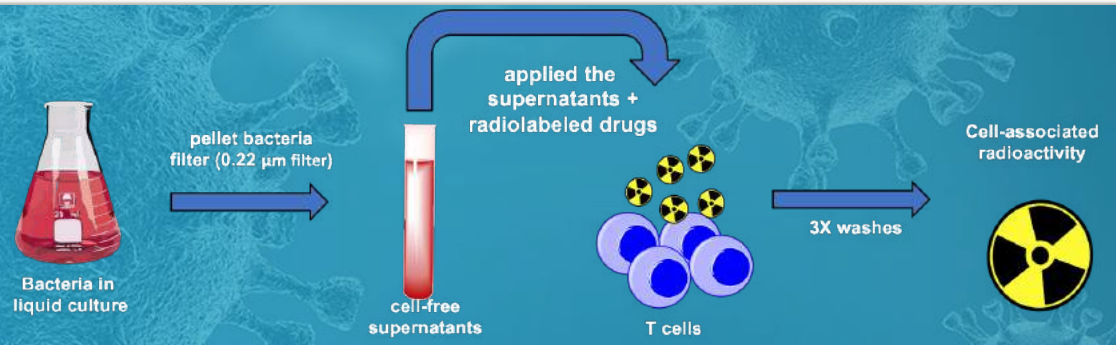
Similar effects on drug bioavailability with fresh vaginal swabs

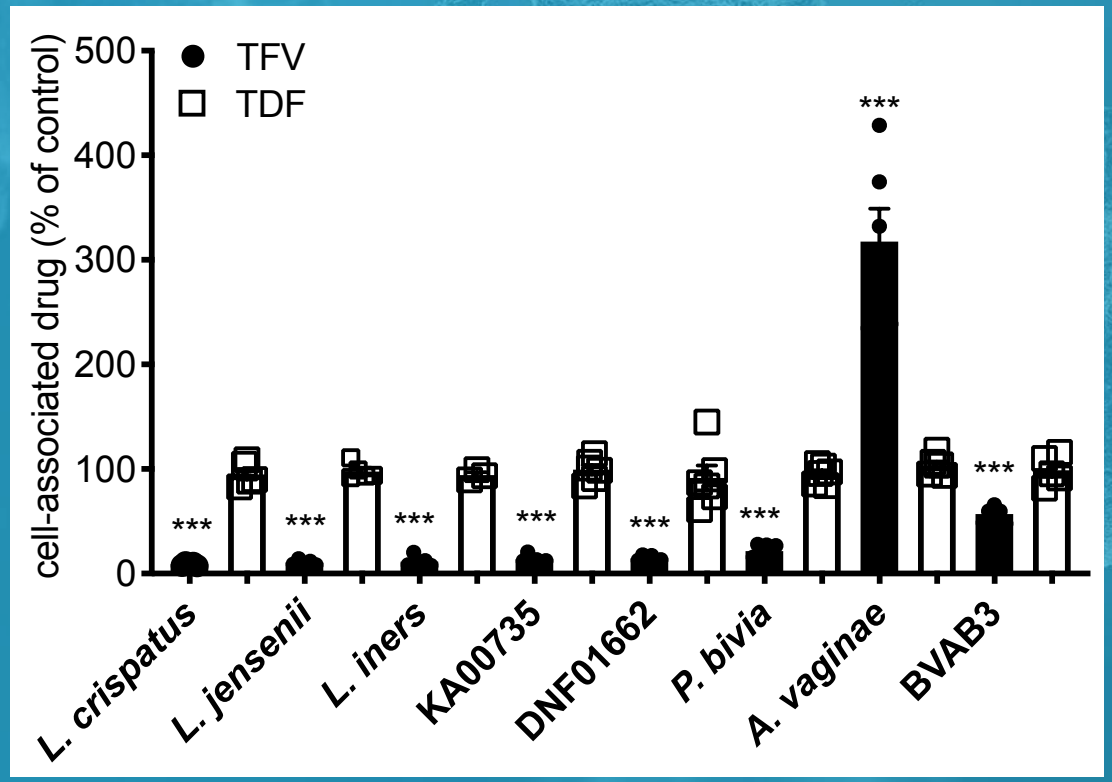


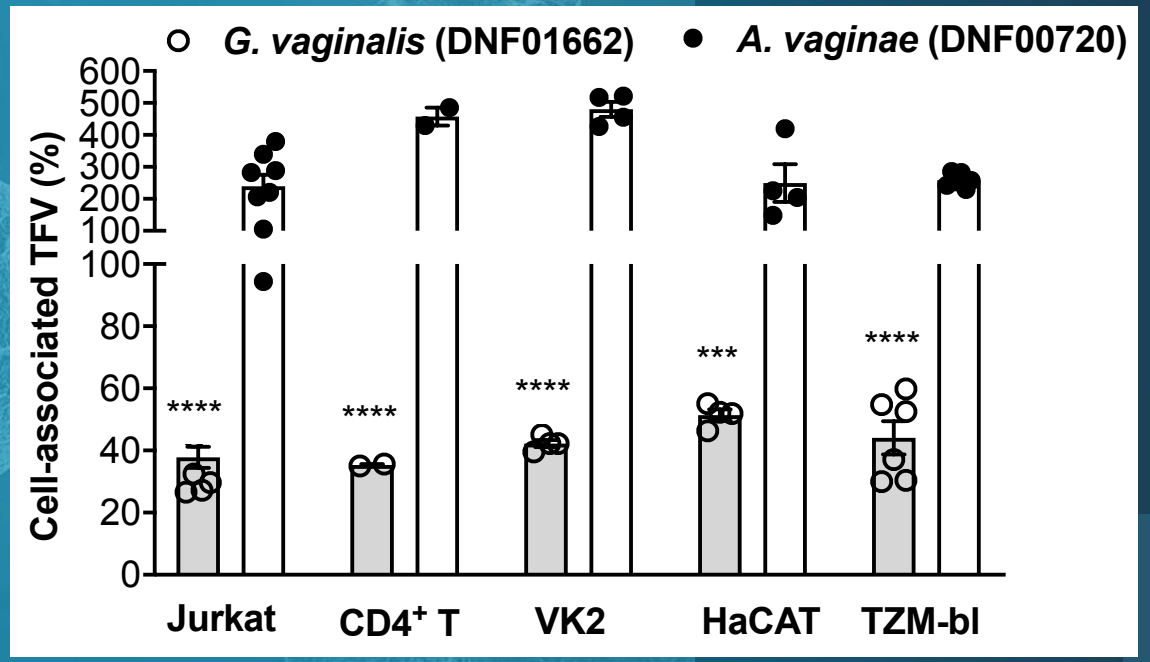
HPTN
HIV Prevention
Trials Network

HPTN
HIV Prevention Trials Network

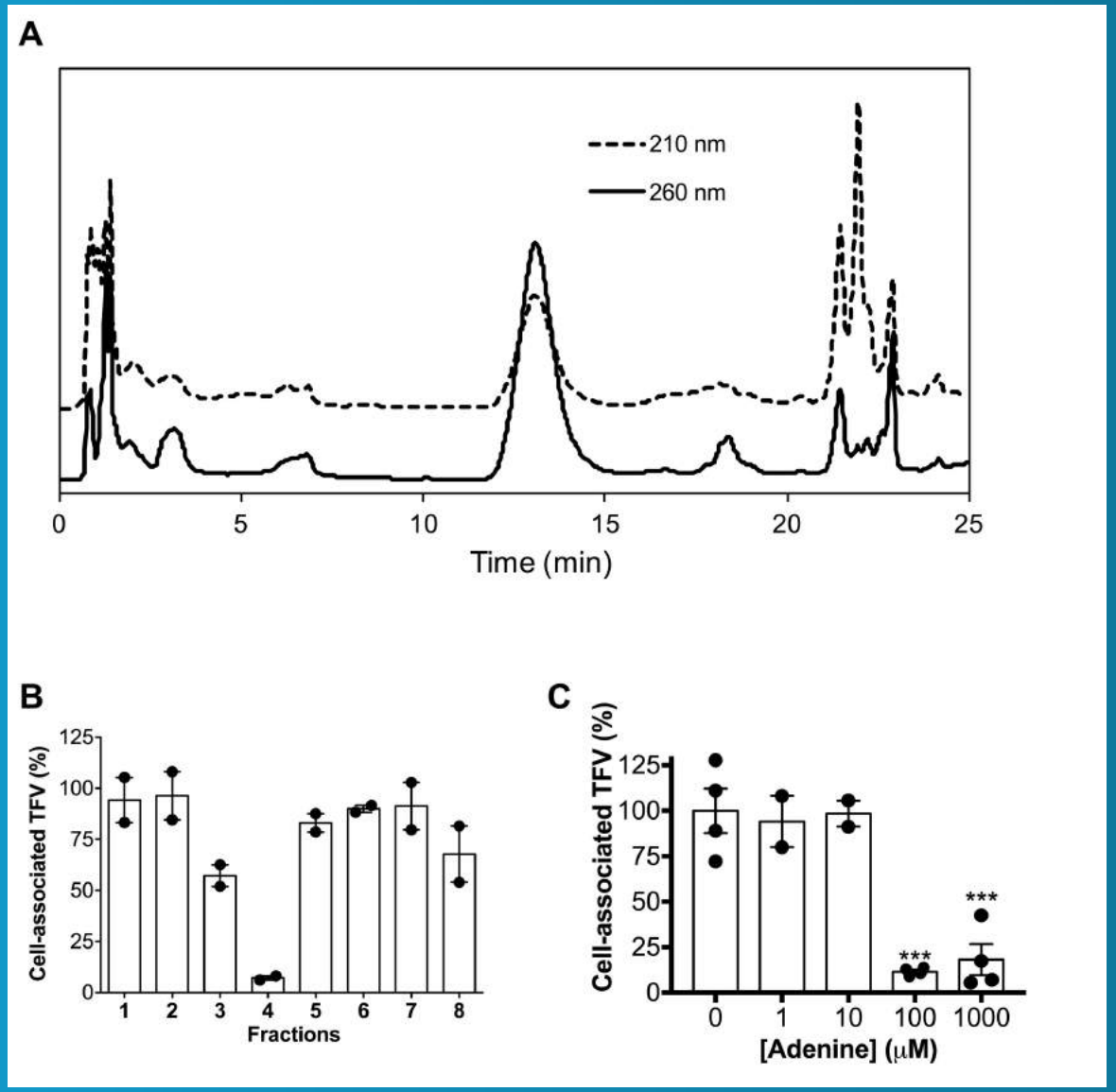
Bacteria release products that may degrade drugs or interfere with drug uptake

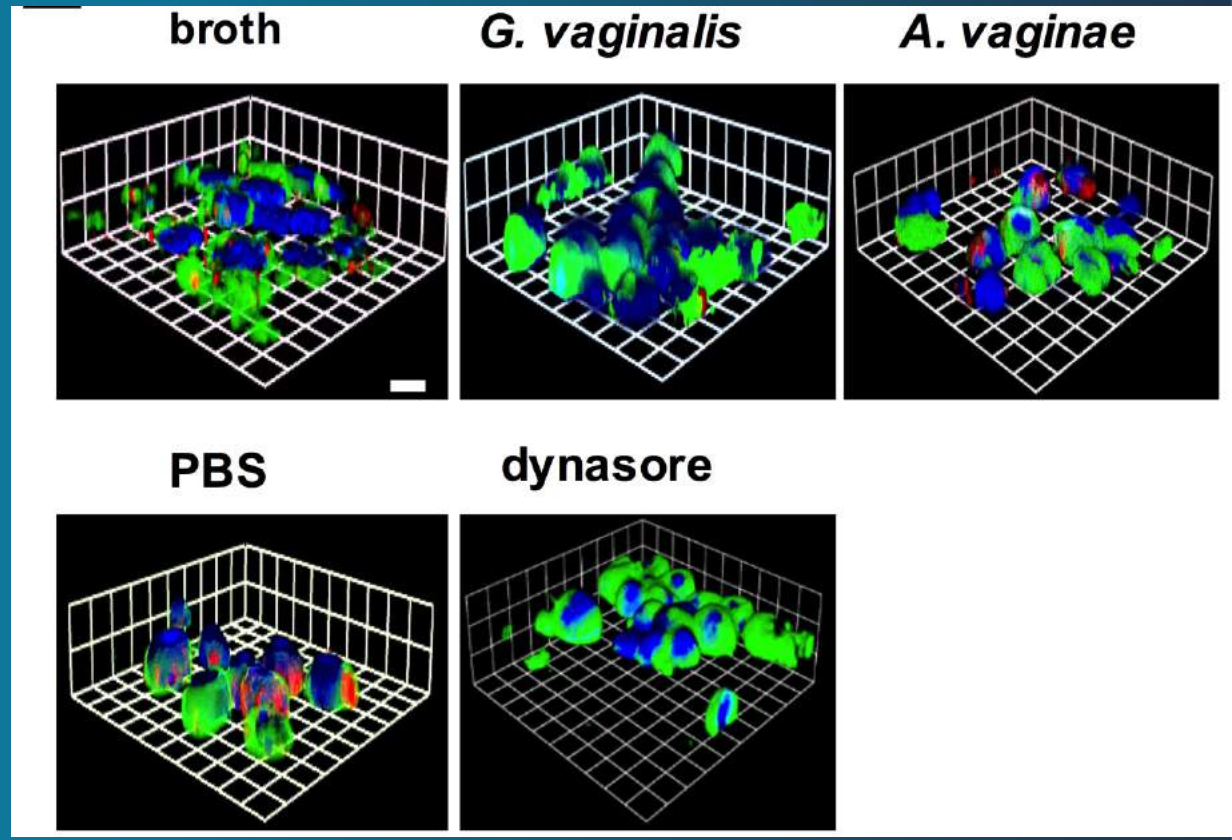






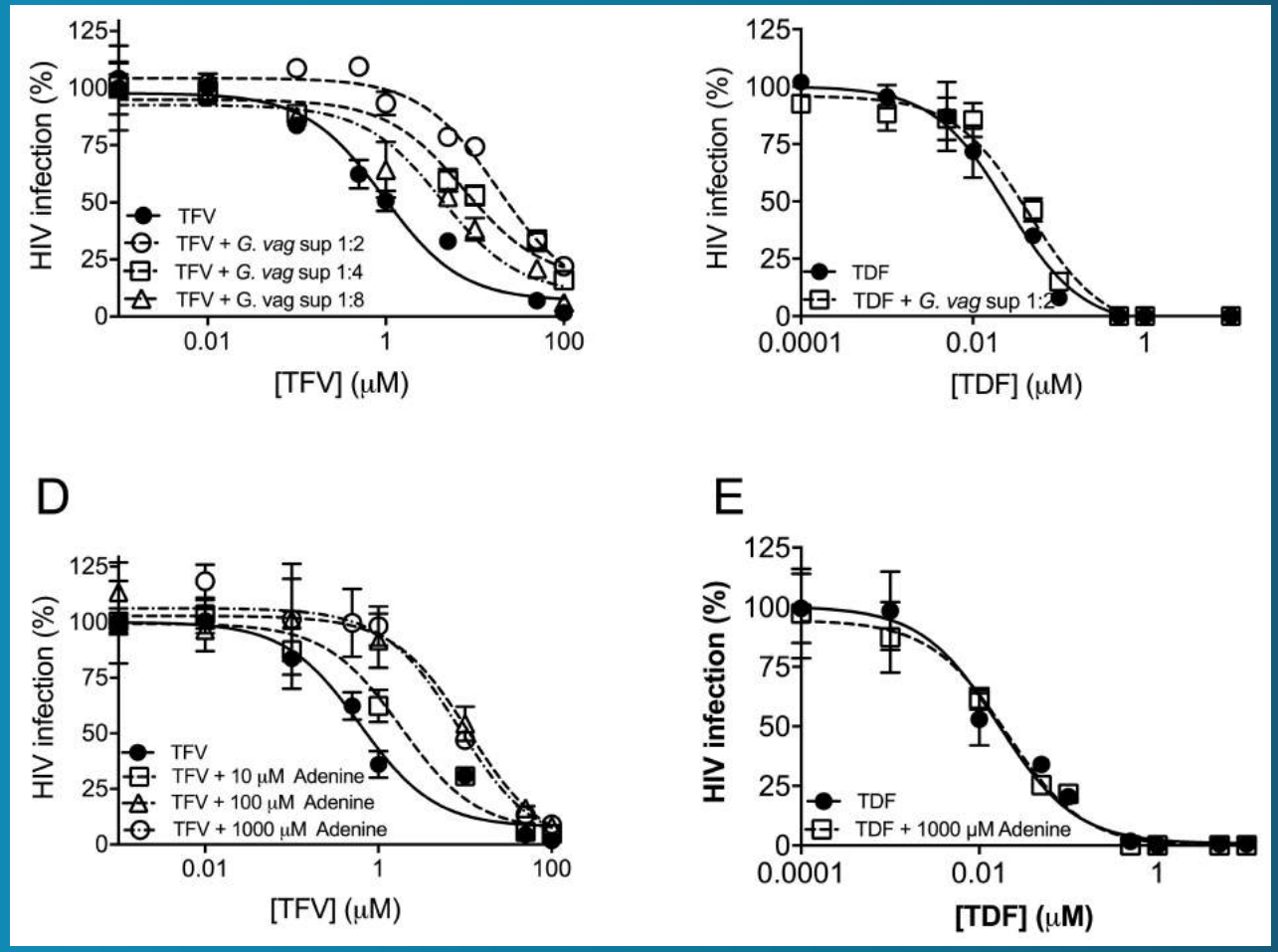
G. vaginalis and other bacteria secrete adenine which blocks TFV Endocytosis; *A. vaginae* consumes adenine





HPTN
HIV Prevention Trials Network

Adenine (and bacterial culture supernatants) shift the TFV Antiviral Dose Response Curve



Adenine levels	Broth:	66 μM
	G. vag sups	246 μM
	A vag sups	9.5 μM
	L. crispatus	281 μM

HPTN
HIV Prevention Trials Network

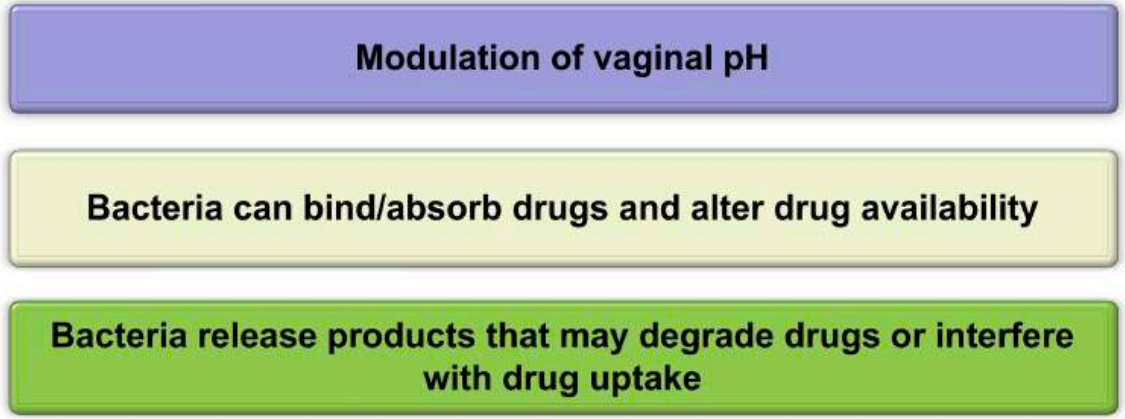
HPTN
HIV Prevention Trials Network

Putting it all together

Microbiome modulates drug PK/PD through multiple mechanisms

- Tenofovir transport (endocytosis) is reduced at higher pH
- Bacteria bind indiscriminantly to dapvirine
- TFV is actively transported and phosphorylated by bacteria (*L. crispatus*) which may then serve as a drug reservoir
- *G. vaginalis* (and others) release adenine which inhibits endocytosis thus reducing TFV bioavailability

- Strong **adherence** and **optimized drug release** overcome the effects of microbiome (and semen) on drug PK/D



HPTN
HIV Prevention Trials Network

Implications and future directions

- Preclinical and early clinical studies should assess impact of microbiota, pH and mucosal molecules on drug PK/PD within the genital tract
  - Ongoing studies suggest little effect of vaginal microbiota on rilpivirine (NNRTI) and dolutegravir (integrase inhibitor) PK
- The impact of vaginal microbiota on systemically delivered HIV PrEP not well studied
  - May be more limited as the site of protection is likely peripheral blood/lymph nodes and not within the female genital tract
- Microbiome and mucosal immune environment also modulate risk of HIV acquisition/transmission
  - Higher rates of HIV acquisition/transmission with BV
- Protection is a balance between viral inoculum and drug PK/PD

Acknowledgments

Herold Lab

Natalia Cheshenko
Christina D'Arco
Matthew Gromisch
Sandra Guerguis
Richard Hunte
Joyce Serebrenik
Carl Pierce
Sarah Singer
Sharlene Sy
Maria Visciano
Kelsey Vinzant

Former Members

Ekaterina Taneva
Shada SInclair
Pedro Mesquita

Clinical Reserch Team

Marla Keller
Kerry Murphy
Jessica McWalters
Lilly Talal
Jesica Atrio

Statistical team: Tao Wang

Collaborators

Sujatha Srinivasan
David Fredricks
Fred Hutchinson Cancer Center
Myrna Serrano
Gregory Buck
Virginia Commonwealth University
Gregory Tharp
Steven Bosinger
Yerkes National Primate Research Center
Jeanne Marrazzo
University of Alabama
Nelly Mugo
Kenneth Ngure
Elizabeth Irungu
Kenya Medical Research Institute

Funding

R01 HD098977
R01 AI134367
U19 AI03461
P30 AI124414
UL1 TR002556
MTN

HPTN
HIV Prevention
Trials Network

Acknowledgments

- Overall support for the HIV Prevention Trials Network (HPTN) is provided by the National Institute of Allergy and Infectious Diseases (NIAID), Office of the Director (OD), National Institutes of Health (NIH), National Institute on Drug Abuse (NIDA), and the National Institute of Mental Health (NIMH) under Award Numbers UM1AI068619-15 (HPTN Leadership and Operations Center), UM1AI068617-15 (HPTN Statistical and Data Management Center), and UM1AI068613-15 (HPTN Laboratory Center).

- The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.