



# **HIV, PrEP & adolescent girls and young women: Understanding the evidence**

Center for Health & Gender Equity Webinar, November 2016

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CAPRISA is the UNAIDS Collaborating Centre for HIV Research and Policy



CAPRISA hosts a DST-NRF Centre of Excellence in HIV Prevention



CAPRISA hosts a MRC HIV-TB Pathogenesis and Treatment Research Unit





# Overview

- **HIV in adolescent girls and young women**
- **Evidence on the effectiveness of PrEP in women**
- **The challenge of PrEP adherence in women**
- **The vaginal microbiome and PrEP effectiveness**
- **Biological factors influencing HIV risk in women**
- **Conclusion**



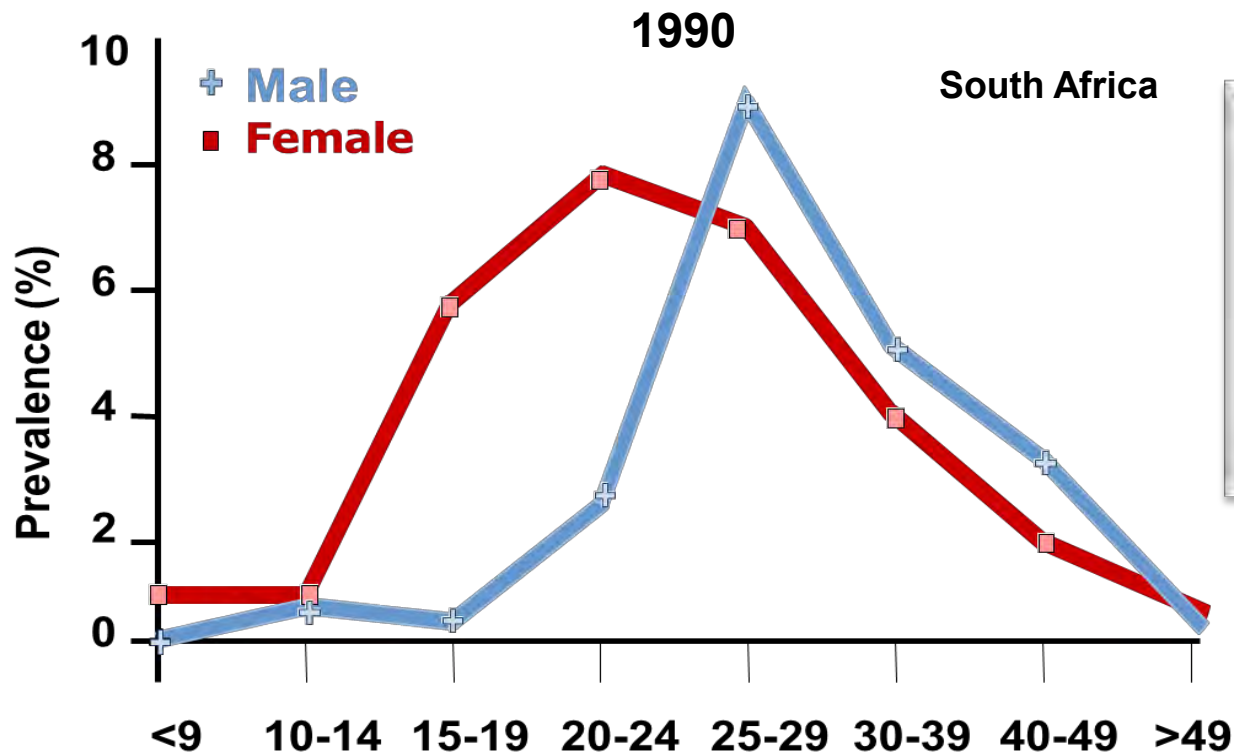
# Since 1990 - known that young women have a higher burden of HIV in Africa



## Seroprevalence of HIV infection in rural South Africa

AIDS 1992, 6:1535-1539

Quarraisha Abdool Karim, Salim S. Abdool Karim,  
Bipraj Singh\*, Richard Short† and Sipho Ngxongo‡



**1990: One of the earliest community-based HIV prevalence surveys in Africa**



# High rates of HIV in adolescent girls and young women in South Africa



ORIGINAL ARTICLE

## Prevalence of HIV, HSV-2 and pregnancy among high school students in rural KwaZulu-Natal, South Africa: a bio-behavioural cross-sectional survey

Quarraisha Abdool Karim,<sup>1,2</sup> Ayesha B M Kharsany,<sup>1</sup> Kerry Leask,<sup>1</sup> Fanelisibonge Ntombela,<sup>1</sup> Hilton Humphries,<sup>1</sup> Janet A Frohlich,<sup>1</sup> Natasha Samsunder,<sup>1</sup> Anneke Grobler,<sup>1</sup> Rachael Dellar,<sup>1</sup> Salim S Abdool Karim<sup>1,2</sup>

Age Group (years)	HIV Prevalence (2010) % (95% Confidence Interval)
	Male (n=1252)
≤15	<b>1.0</b> (0.0 - 2.2)
16-17	<b>1.1</b> (0.2 - 2.0)
18-19	<b>1.5</b> (0 - 3.7)
≥20	<b>1.8</b> (0 - 3.9)



# High rates of HIV in adolescent girls and young women in South Africa



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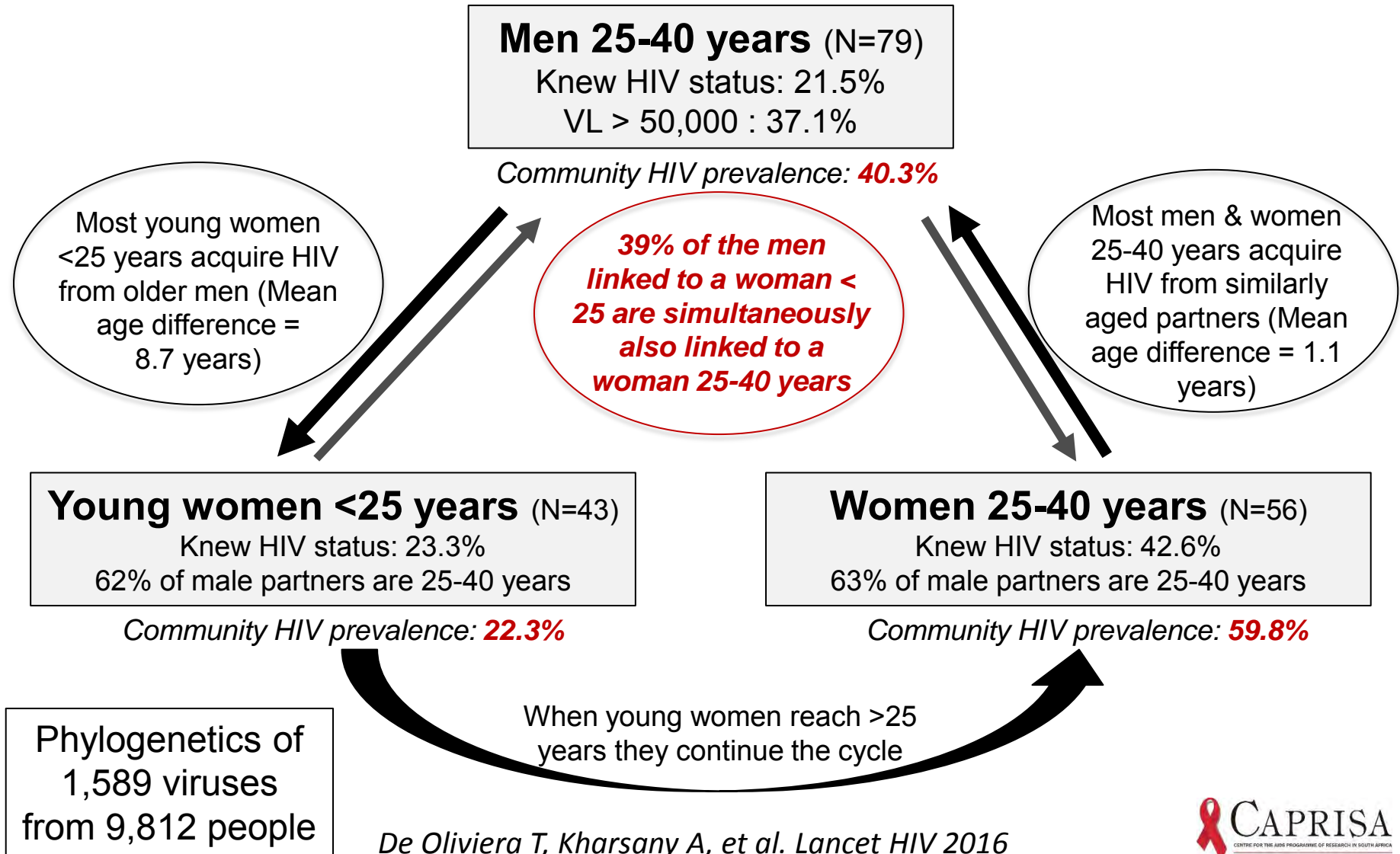
Quarraisha Abdool Karim,<sup>1,2</sup> Ayesha B M Kharsany,<sup>1</sup> Kerry Leask,<sup>1</sup> Fanelisibonge Ntombela,<sup>1</sup> Hilton Humphries,<sup>1</sup> Janet A Frohlich,<sup>1</sup> Natasha Samsunder,<sup>1</sup> Anneke Grobler,<sup>1</sup> Rachael Dellar,<sup>1</sup> Salim S Abdool Karim<sup>1,2</sup>

Age Group (years)	HIV Prevalence (2010) % (95% Confidence Interval)	
	Male (n=1252)	Female (n= 1423)
≤15	<b>1.0</b> (0.0 - 2.2)	<b>2.6</b> (1.2 - 4.0)
16-17	<b>1.1</b> (0.2 - 2.0)	<b>6.1</b> (2.6 - 9.6)
18-19	<b>1.5</b> (0 - 3.7)	<b>13.6</b> (9.0 - 18.1)
≥20	<b>1.8</b> (0 - 3.9)	<b>24.7</b> (6.3 - 43.1)



# Cycle of HIV transmission in rural KZN

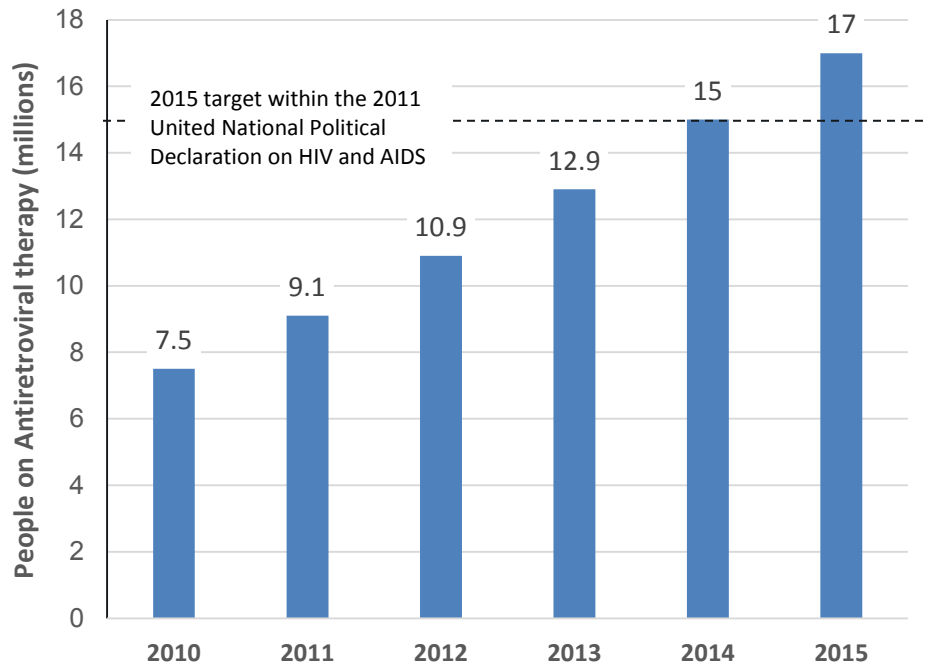
Schematic of sexual networks from clusters with heterosexual transmission



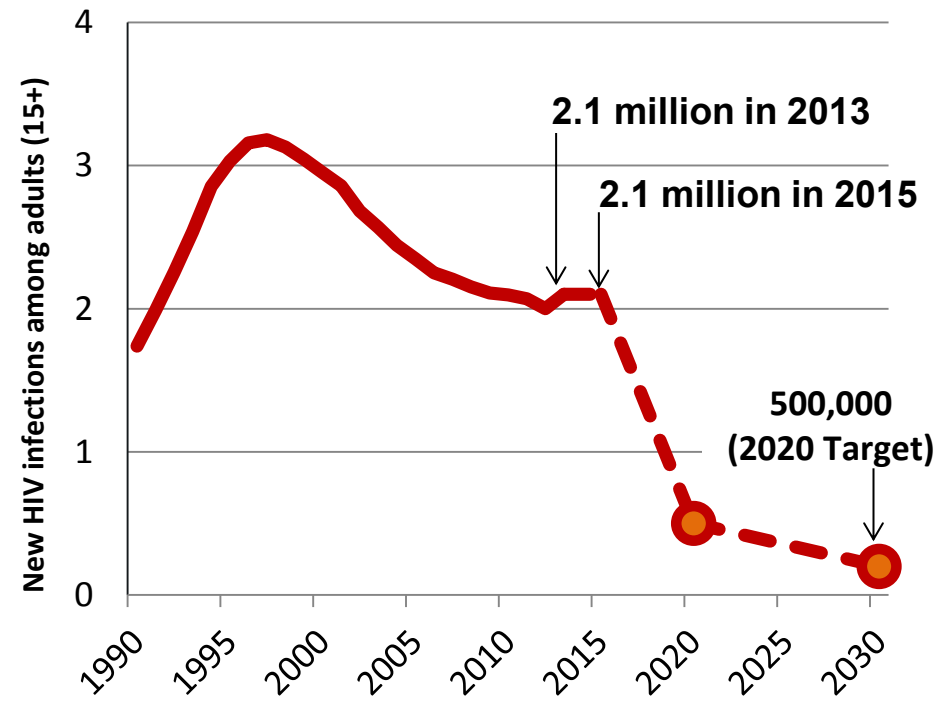


# Great progress on increasing HIV treatment but we are lagging in prevention

Number of people receiving antiretroviral therapy, by WHO region, 2003–2015



0% reduction in new infections 2013 - 2015



Source: Global AIDS Response Progress Report.



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# July 2010: ARVs prevent HIV in women

**First evidence of tenofovir PrEP (in gel) presented at the 2010 International AIDS Conference in Vienna**



## RESEARCH ARTICLES

**Science**

AAAS

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

Quarraisha Abdool Karim,<sup>1,2\*</sup>† Salim S. Abdool Karim,<sup>1,2,3\*</sup> Janet A. Frohlich,<sup>1</sup> Anneke C. Grobler,<sup>1</sup> Cheryl Baxter,<sup>1</sup> Leila E. Mansoor,<sup>1</sup> Ayesha B. M. Kharsany,<sup>1</sup> Sengeziwe Sibeko,<sup>1</sup> Koleka P. Mlisana,<sup>1</sup> Zaheen Omar,<sup>1</sup> Tanuja N. Gengiah,<sup>1</sup> Silvia Maarschalk,<sup>1</sup> Natasha Arulappan,<sup>1</sup> Mukelisiwe Mlotshwa,<sup>1</sup> Lynn Morris,<sup>4</sup> Douglas Taylor,<sup>5</sup> on behalf of the CAPRISA 004 Trial Group†

The Centre for the AIDS Program of Research in South Africa (CAPRISA) 004 trial assessed the effectiveness and safety of a 1% vaginal gel formulation of tenofovir, a nucleotide reverse transcriptase

### **Tenofovir gel prevents HIV in women**

- 39% protection against HIV overall
- 54% effective in women with high adherence
- 74% protection with high tenofovir levels

### **Tenofovir gel prevents HSV-2 infection in women (NEJM 2015)**

- 51% reduction in HSV-2 incidence





# November 2010: Oral PrEP prevents HIV in MSM – iPrEx trial

**131 infections after randomization**

↙ ↘

**48 in FTC/TDF**      **83 in placebo**

## *The* NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

DECEMBER 30, 2010

VOL. 363 NO. 27

### Preexposure Chemoprophylaxis for HIV Prevention in Men Who Have Sex with Men

Robert M. Grant, M.D., M.P.H., Javier R. Lama, M.D., M.P.H., Peter L. Anderson, Pharm.D., Vanessa McMahan, B.S., Albert Y. Liu, M.D., M.P.H., Lorena Vargas, Pedro Goicochea, M.Sc., Martín Casapía, M.D., M.P.H., Juan Vicente Guanira-Carranza, M.D., M.P.H., Maria E. Ramirez-Cardich, M.D., Orlando Montoya-Herrera, M.Sc., Telmo Fernández, M.D., Valdilea G. Veloso, M.D., Ph.D., Susan P. Buchbinder, M.D., Suwat Chariyalertsak, M.D., Dr.P.H., Mauro Schechter, M.D., Ph.D., Linda-Gail Bekker, M.B., Ch.B., Ph.D., Kenneth H. Mayer, M.D., Esper Georges Kallás, M.D., Ph.D., K. Rivet Amico, Ph.D., Kathleen Mulligan, Ph.D., Lane R. Bushman, B.Chem., Robert J. Hance, A.A., Carmela Ganoza, M.D., Patricia Defechereux, Ph.D., Brian Postle, B.S., Furong Wang, M.D., J. Jeff McConnell, M.A., Jia-Hua Zheng, Ph.D., Jeanny Lee, B.S., James F. Rooney, M.D., Howard S. Jaffe, M.D., Ana I. Martinez, R.Ph., David N. Burns, M.D., M.P.H., and David V. Glidden, Ph.D., for the iPrEx Study Team\*

**2499 Men who have sex with Men**  
**Effect of daily TDF-FTC on HIV: 42% (CI: 15% - 63%)**





# July 2011: Oral PrEP prevents HIV transmission in discordant couples (PartnersPrEP)



The NEW ENGLAND  
JOURNAL of MEDICINE

## Antiretroviral Prophylaxis for HIV Prevention in Heterosexual Men and Women

J.M. Baeten, D. Donnell, P. Ndase, N.R. Mugo, J.D. Campbell, J. Wangisi, J.W. Tappero, E.A. Bukusi, C.R. Cohen, E. Katabira, A. Ronald, E. Tumwesigye, E. Were, K.H. Fife, J. Kiarie, C. Farquhar, G. John-Stewart, A. Kakia, J. Odoyo, A. Mucunguzi, E. Nakku-Joloba, R. Twesigye, K. Ngure, C. Apaka, H. Tamoooh, F. Gabona, A. Mujugira, D. Panteleeff, K.K. Thomas, L. Kidoguchi, M. Krows, J. Revall, S. Morrison, H. Haugen, M. Emmanuel-Ogier, L. Ondrejcek, R.W. Coombs, L. Frenkel, C. Hendrix, N.N. Bumpus, D. Bangsberg, J.E. Haberer, W.S. Stevens, J.R. Lingappa, and C. Celum, for the Partners PrEP Study Team\*

**4,758 HIV discordant couples in Kenya & Uganda**

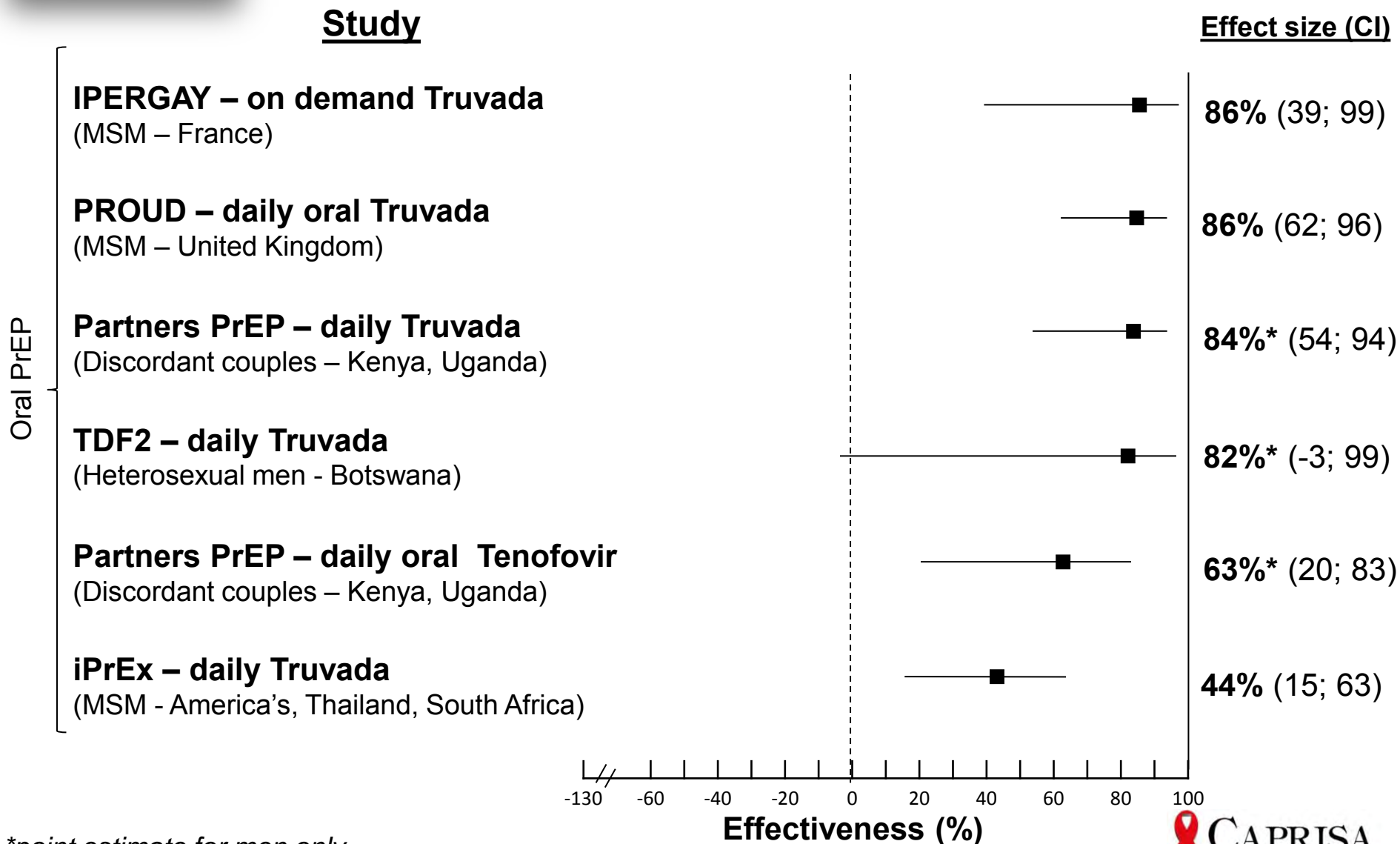
**Effect of TDF on HIV: 67% (CI: 44% - 81%)**

**Effect of FTC/TDF on HIV: 75% (CI: 55% - 87%)**





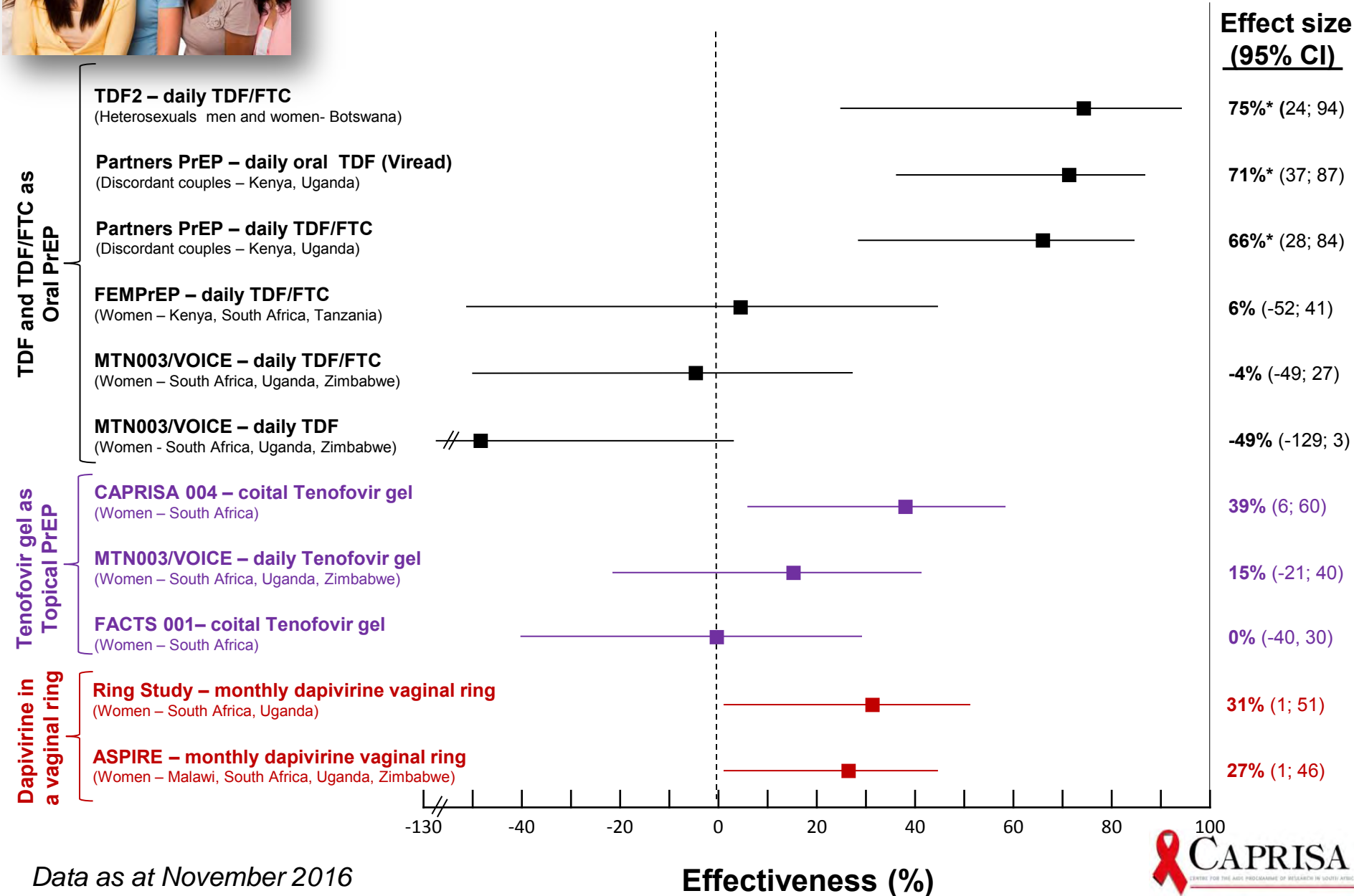
# Effectiveness of PrEP in men







# Clinical trials of PrEP in women





# New WHO policy on PrEP to prevent the spread of HIV by sex

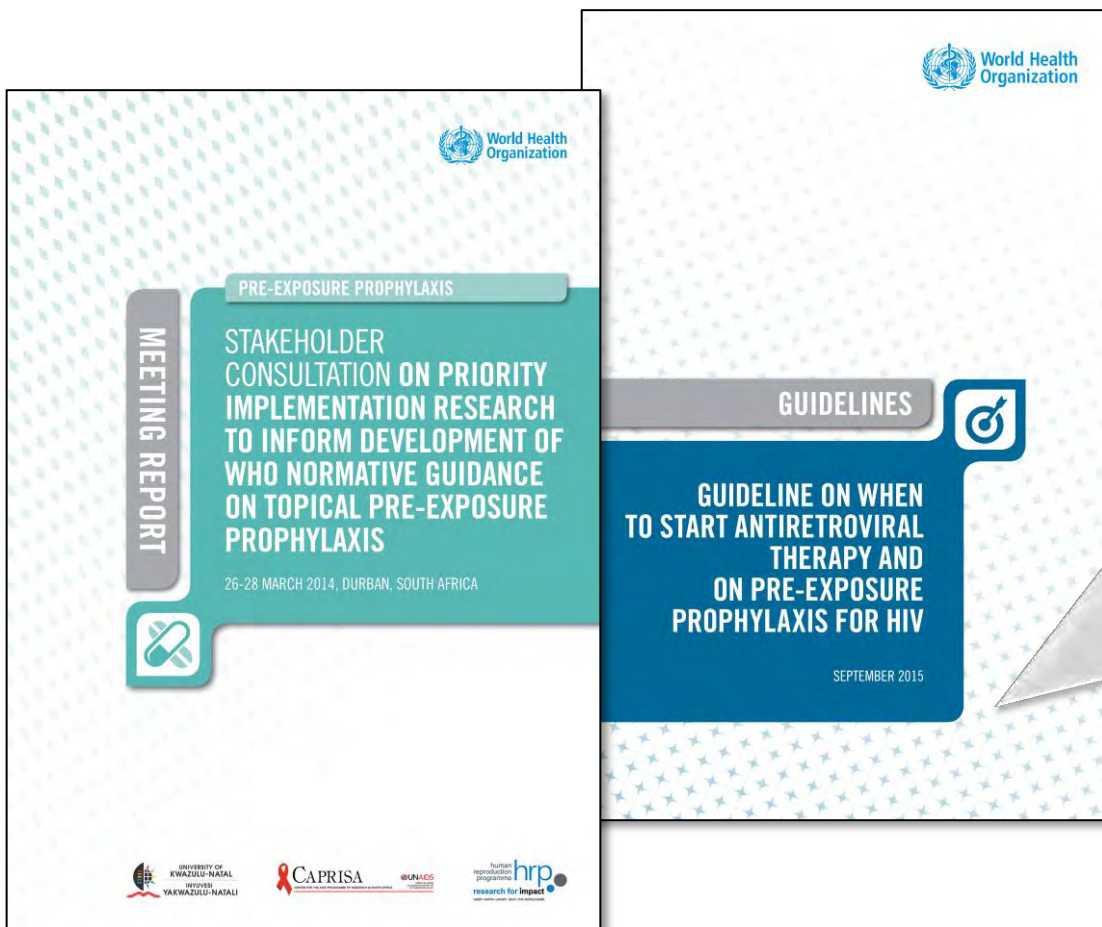
**PrEP recommended as global standard for all at high risk, including young women**



Daily Truvada

## New WHO PrEP guidelines

“..the use of daily oral pre-exposure prophylaxis is recommended as an additional prevention choice for people at substantial risk of HIV infection as part of combination prevention approaches..”





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# High adherence is essential for PrEP

	# HIV	N	HIV incidence		Effect	p-value
			TFV	Placebo		
<b>High adherers</b> (>80% gel adherence)	36	336	4.2	9.3	<b>54%</b>	0.03
<b>Intermediate adherers</b> (50-80% adherence)	20	181	6.3	10.0	<b>38%</b>	0.29
<b>Low adherers</b> (<50% gel adherence)	41	367	6.2	8.6	<b>28%</b>	0.30



CAPRISA 004 was developed... .."after extensive consultation with international scientific experts and review of monkey challenge data."

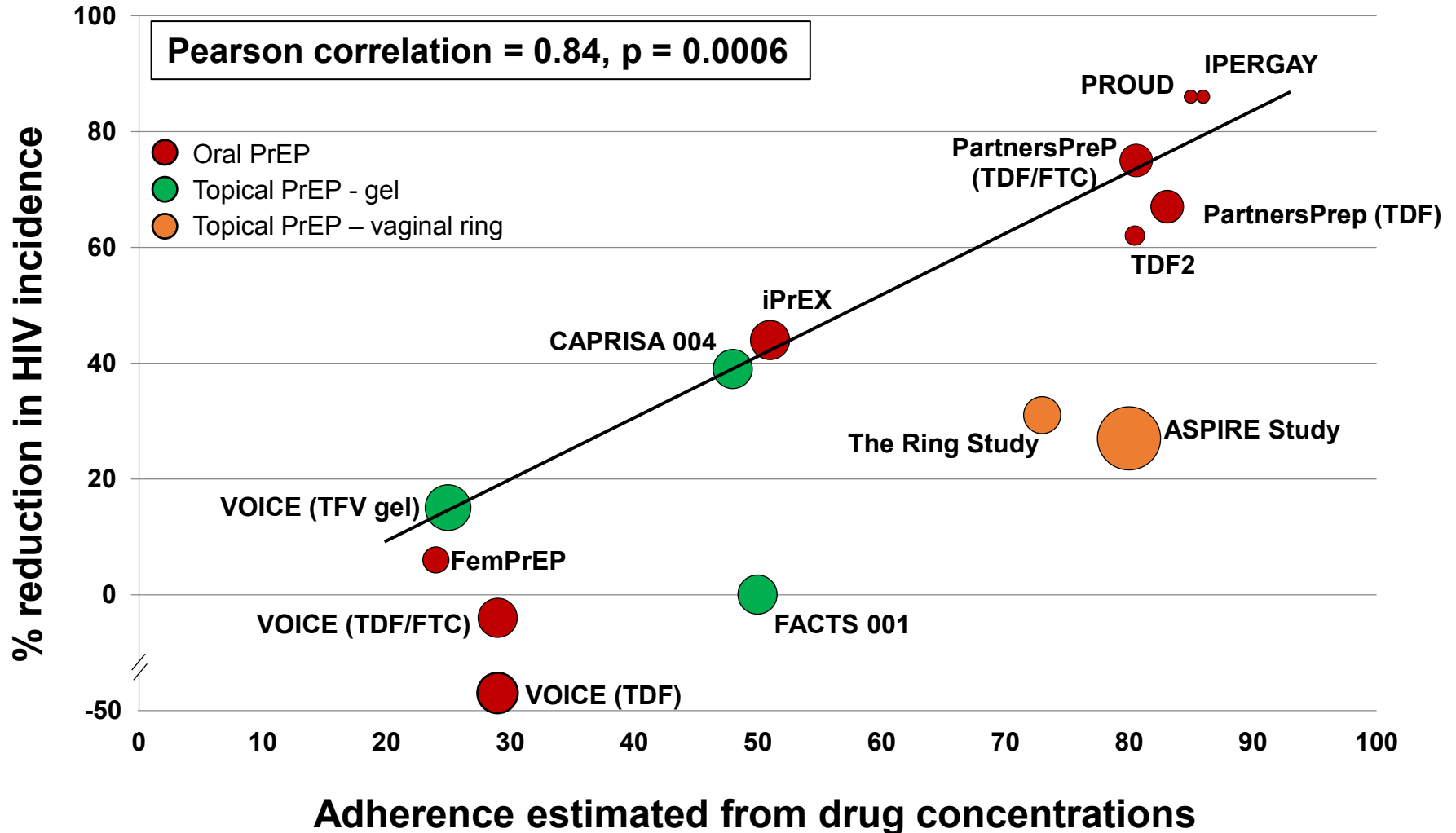
**"Just as importantly, it followed detailed consultation with the communities involved."**

Source: Abdool Karim S, Abdool Karim Q, Nature, 446; 2007

Source of data in table: Abdool Karim Q, Abdool Karim SS, Frohlich J, et al. Science 2010



# Adherence and effectiveness: HIV incidence reductions in relation to drug detection levels



*Note: The diameter of circles is proportional to number of HIV infections in the control group.  
For daily dosing, adherence is based on % of the participants with detected drug.  
For coital dosing, adherence is estimated on detected drug adjusted for reported recent coitus.*



# High adherence is essential

## Association between drug detection and HIV incidence in tenofovir gel studies

### Clinical trials

**CAPRISA 004 – coital Tenofovir gel**  
(Women – South Africa)

**MTN003/VOICE – daily Tenofovir gel**  
(Women – South Africa, Uganda, Zimbabwe)

**FACTS 001– coital Tenofovir gel**  
(Women – South Africa)

### Effect size (CI)

39% (6; 60)

15% (-21; 40)

0% (-40, 30)

### Case-cohort analyses of gel trials:

**MTN003/VOICE – daily Tenofovir gel**  
(South Africa, Uganda, Zimbabwe)

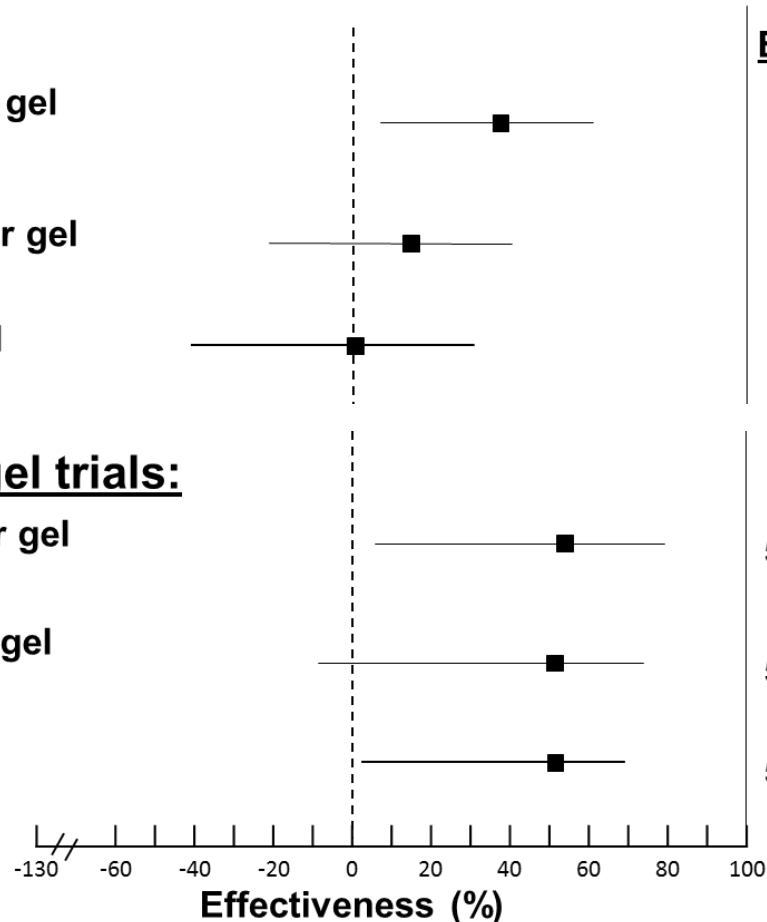
**CAPRISA 004 – coital Tenofovir gel**  
(South Africa)

**FACTS 001– coital Tenofovir gel**  
(South Africa)

57% (8; 80)<sup>a</sup>

53% (-8; 79)<sup>b</sup>

52% (3, 72)<sup>c</sup>



*a - Marrazzo et al. NEJM 2015; b - Kashuba et al. JAIDS 2015; c - Rees et al. CROI 2015*

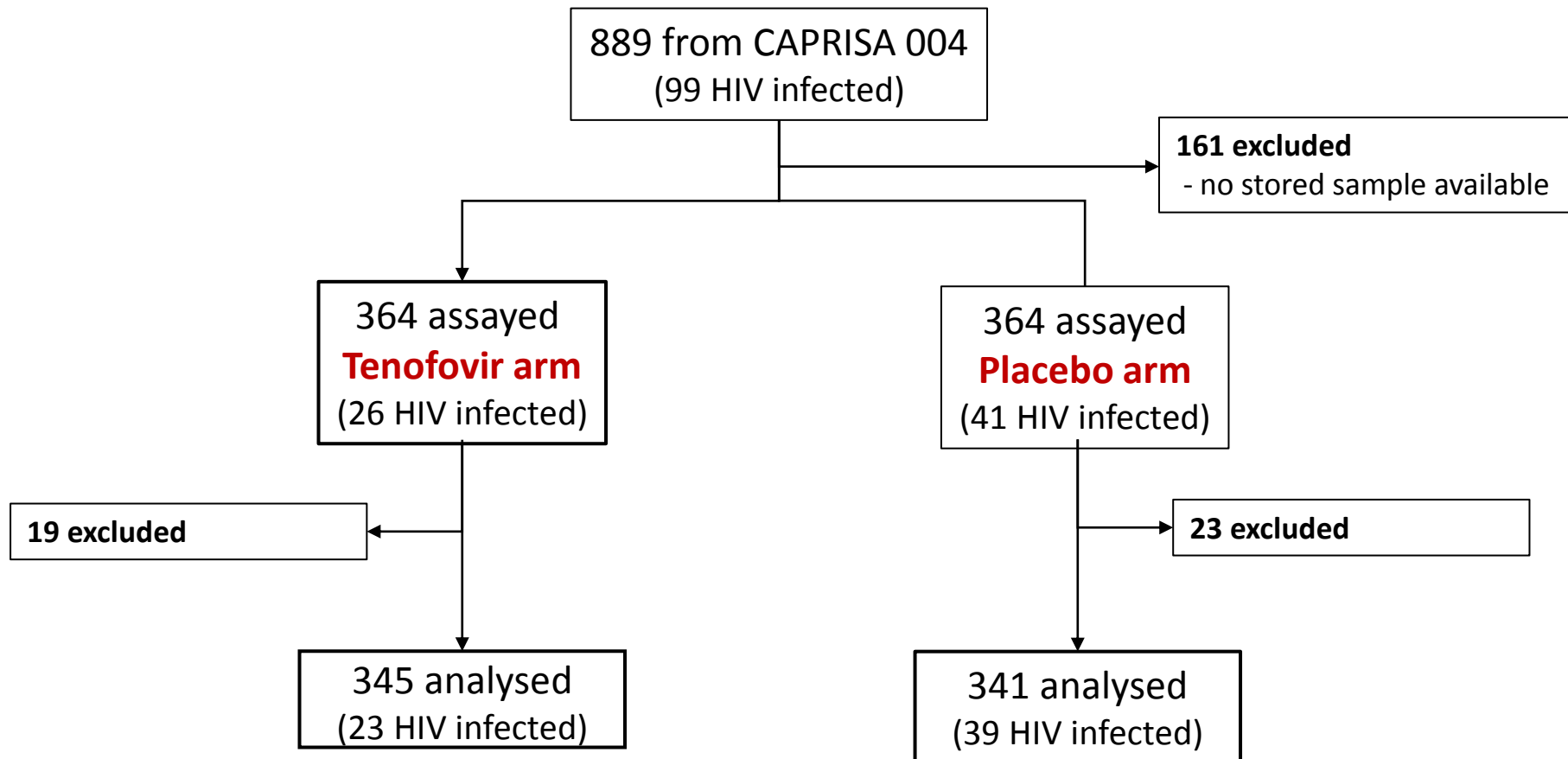


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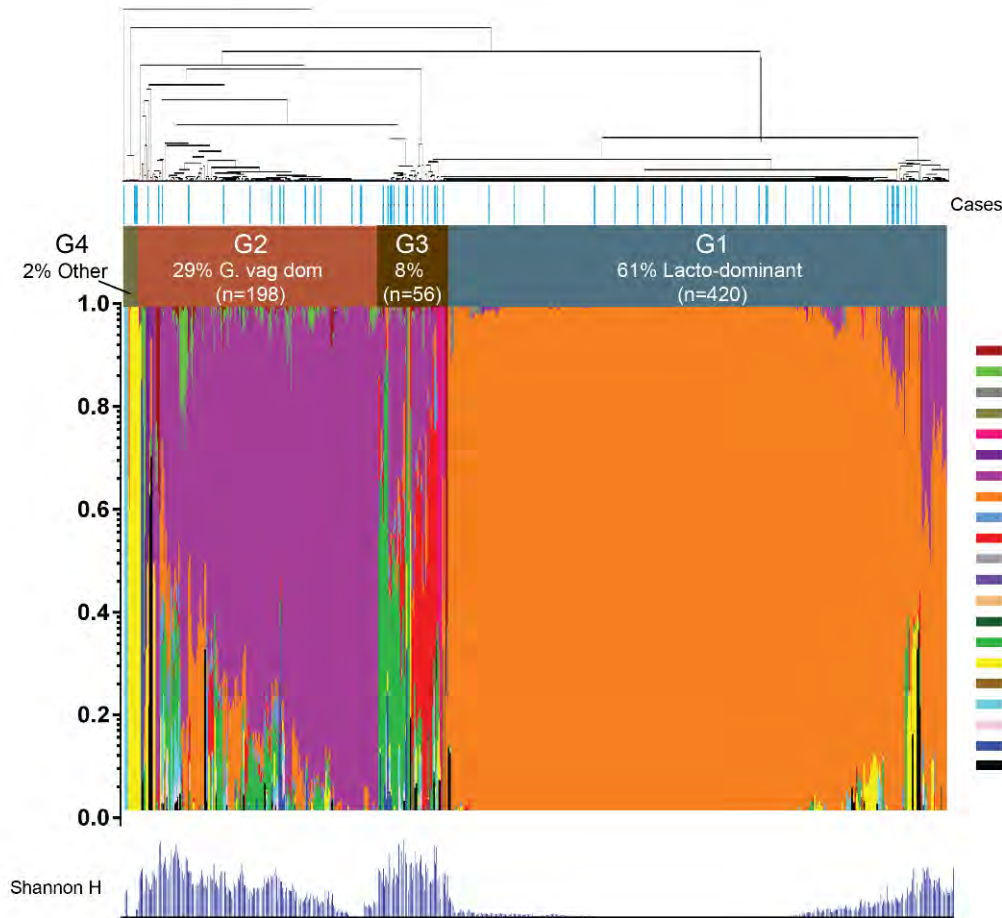
# Factors undermining PrEP efficacy in women: Proteomics reveal diminished tenofovir efficacy in women who do not have vaginal Lactobacilli dominance



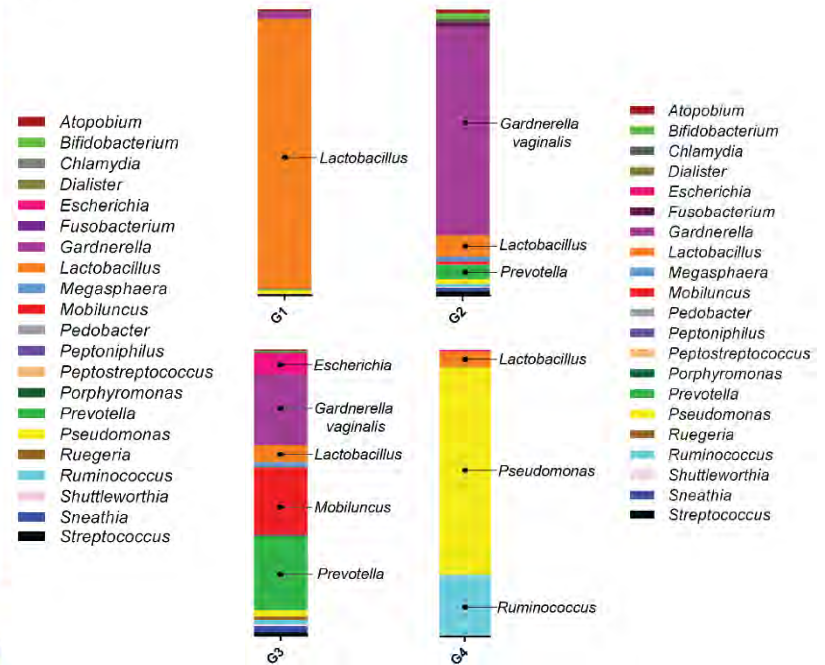


# Factors undermining PrEP efficacy in women:

Vaginal bacterial profiling by mass spectrometry identifies four major community groups



Average bacterial community group structure for each profile G1, G2, G3, and G4.



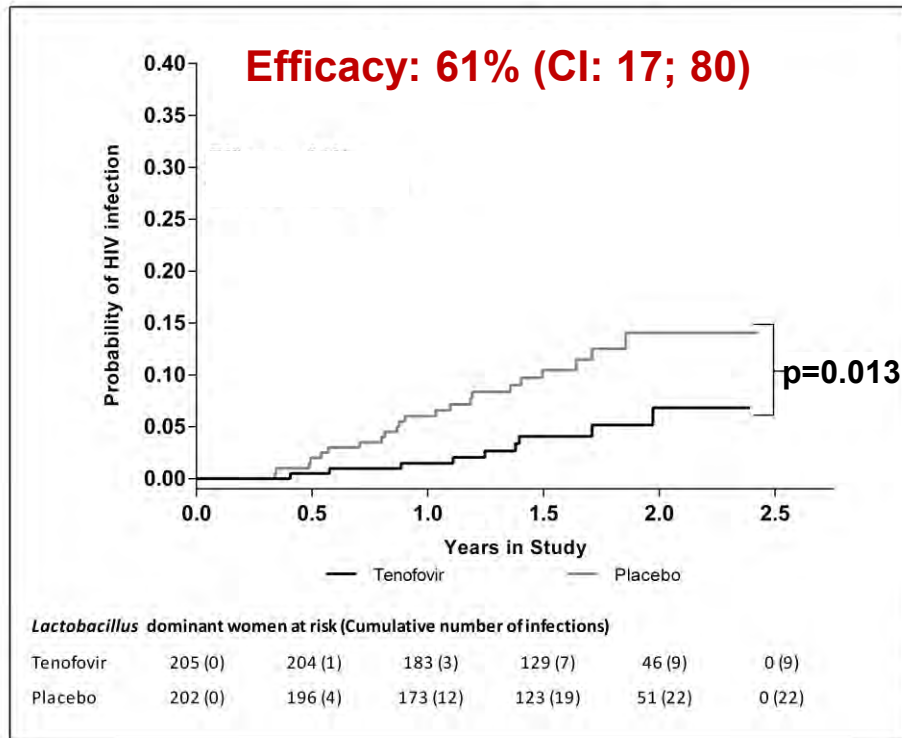
Overall diversity plot of all women



# Factors undermining PrEP efficacy in women:

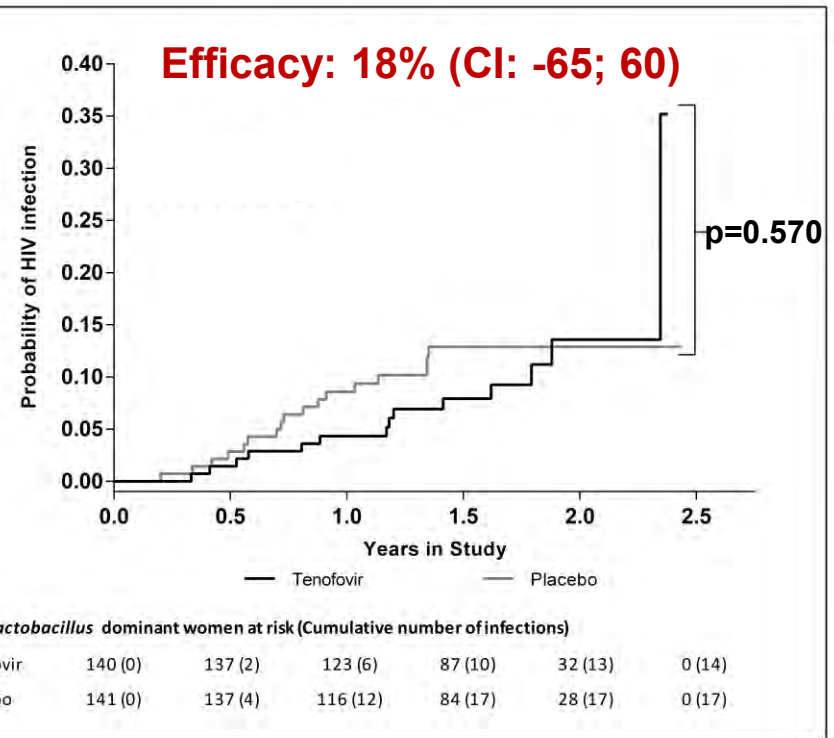
Proteomics reveal diminished tenofovir efficacy in women who do not have vaginal Lactobacilli dominance

## Women with Lactobacillus dominance



**HR = 0.39 (CI: 0.20; 0.83)**  
**Logrank p-value = 0.013**

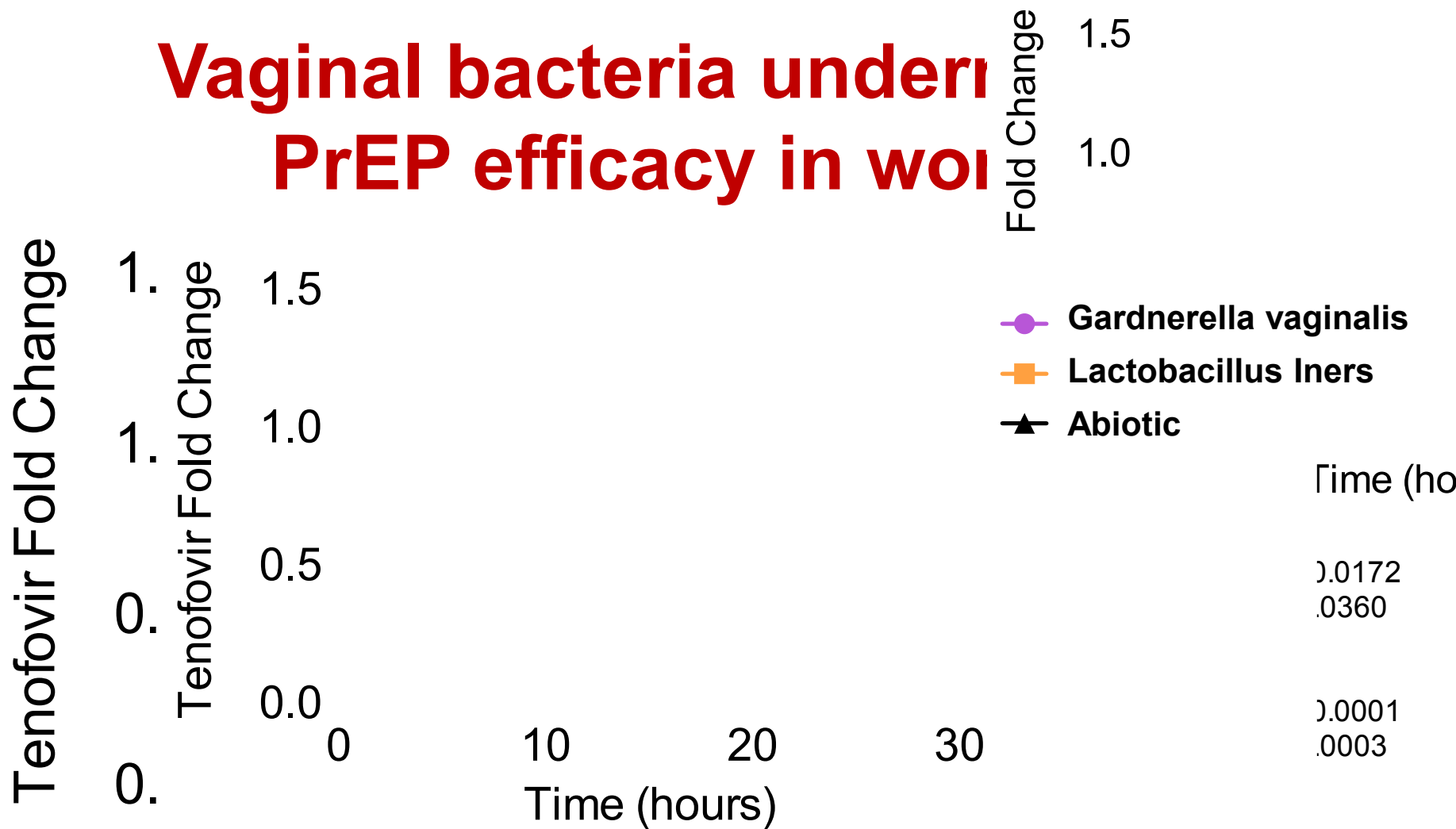
## Women with <50% Lactobacilli



**HR = 0.82 (95% CI: 0.40; 1.65)**  
**Logrank p-value = 0.760**



# Vaginal bacteria under PrEP efficacy in women



## 4 hours:

G. vag vs. L. iners:  $p=0.0172$

G. vag vs Abiotic:  $p=0.0360$

## 4 hours:

G. vag

G. vag

## 24 hours:

G. vag vs. L. iners:  $p<0.0001$

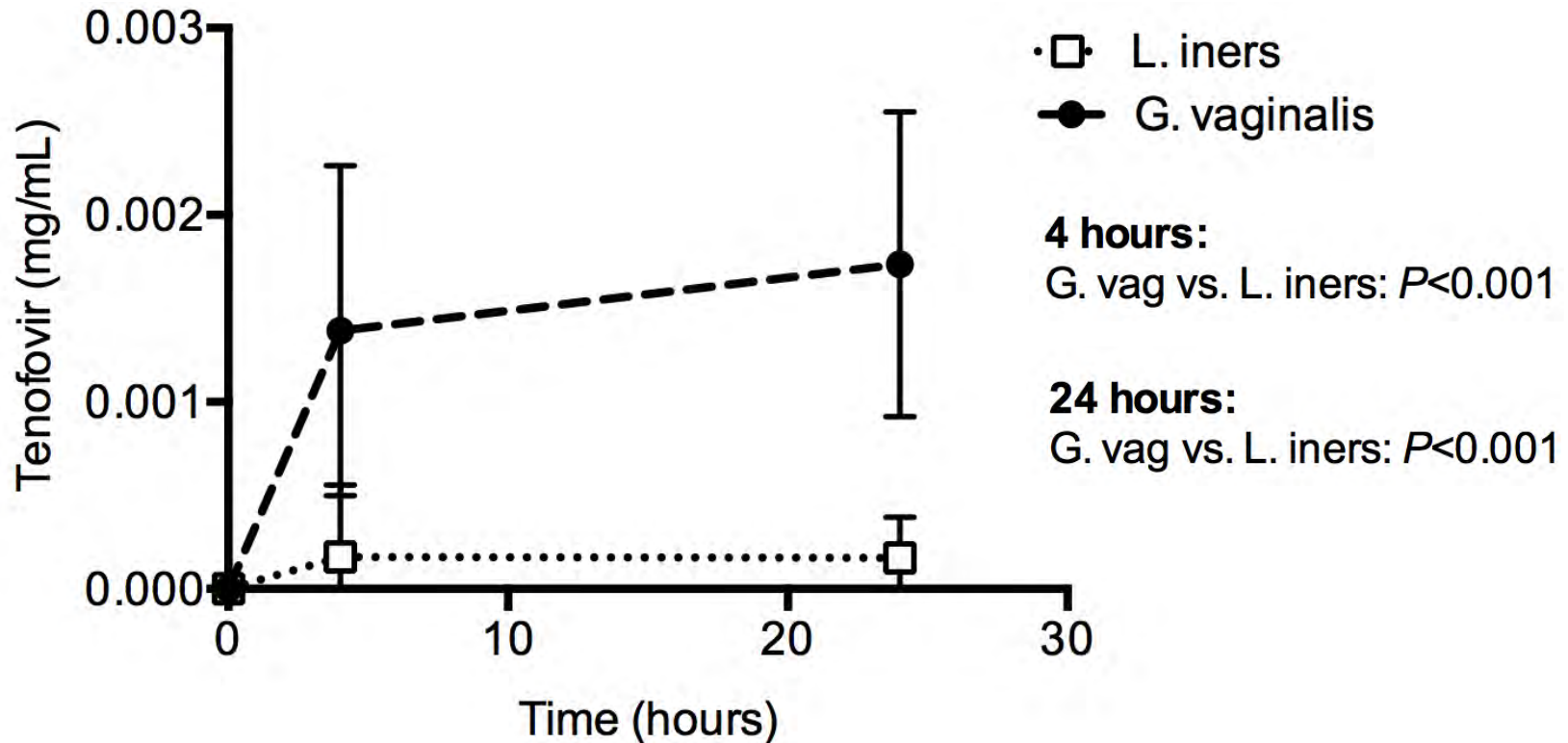
G. vag vs Abiotic:  $p=0.0003$



# Vaginal bacteria undermining PrEP efficacy in women:

## Intracellular tenofovir absorption by *G. vaginalis*

Intracellular tenofovir concentration



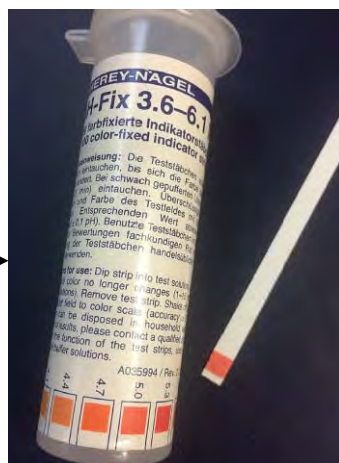


# Potential implications for PrEP implementation in women

One approach: Integration of PrEP scale-up with sexual & reproductive health services ie. STI & FP services



Link to  
SRH services



Vaginal pH testing

Metronidazole treatment to  
promote a “healthy”  
(Lactobacillus dominant) vagina



If pH > 4.5

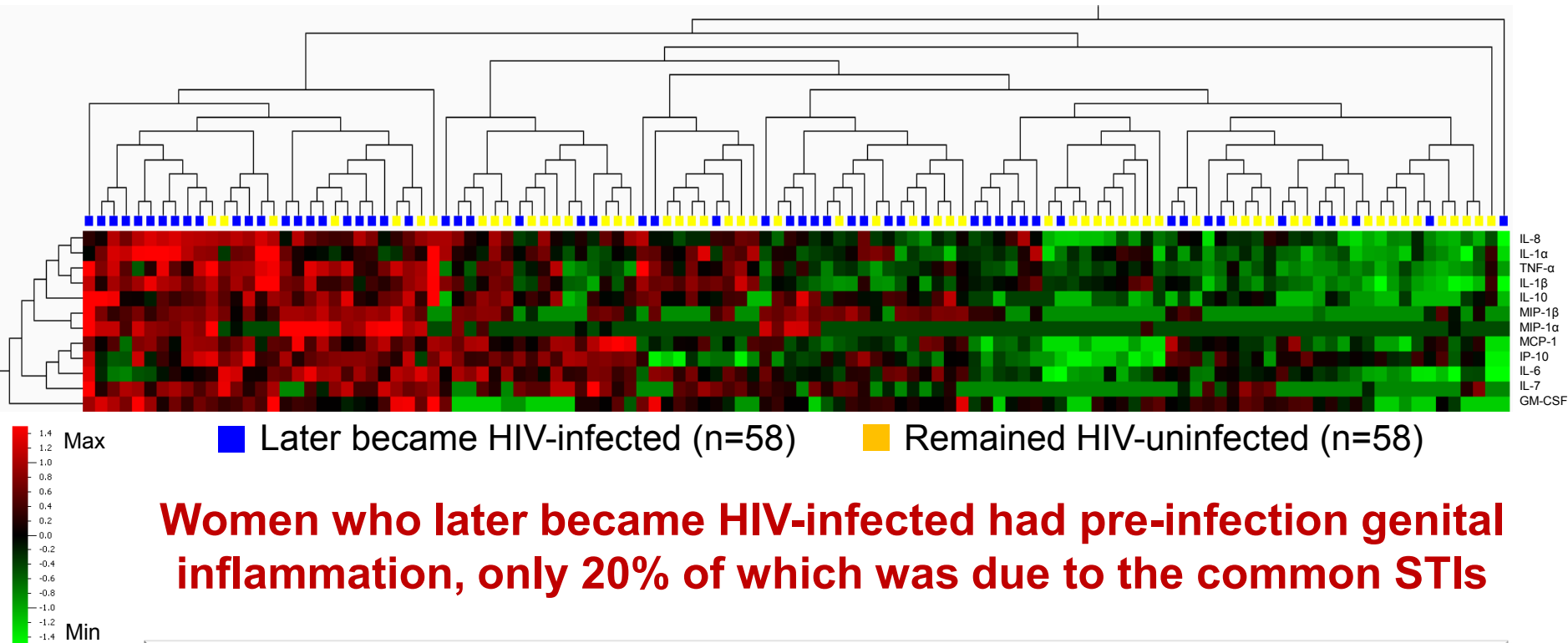


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# High risk of acquisition in young women: Role of genital inflammation



**Women who later became HIV-infected had pre-infection genital inflammation, only 20% of which was due to the common STIs**

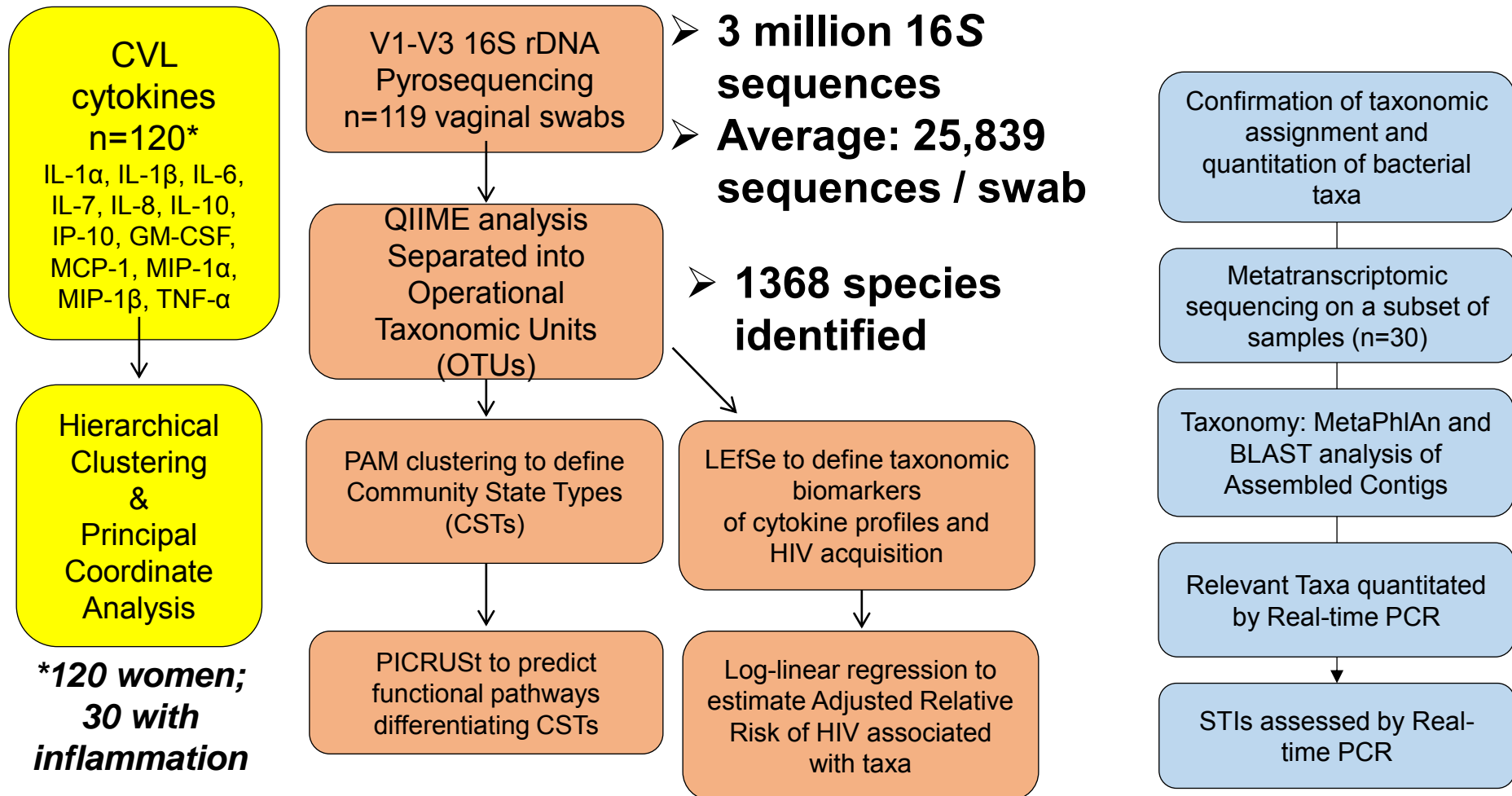
**So, what is the cause of the genital inflammation that is enhancing HIV acquisition?**

Source: Masson et al. *Clinical Infect Dis*, 2015; 61(2):260-9



# High risk of acquisition in young women:

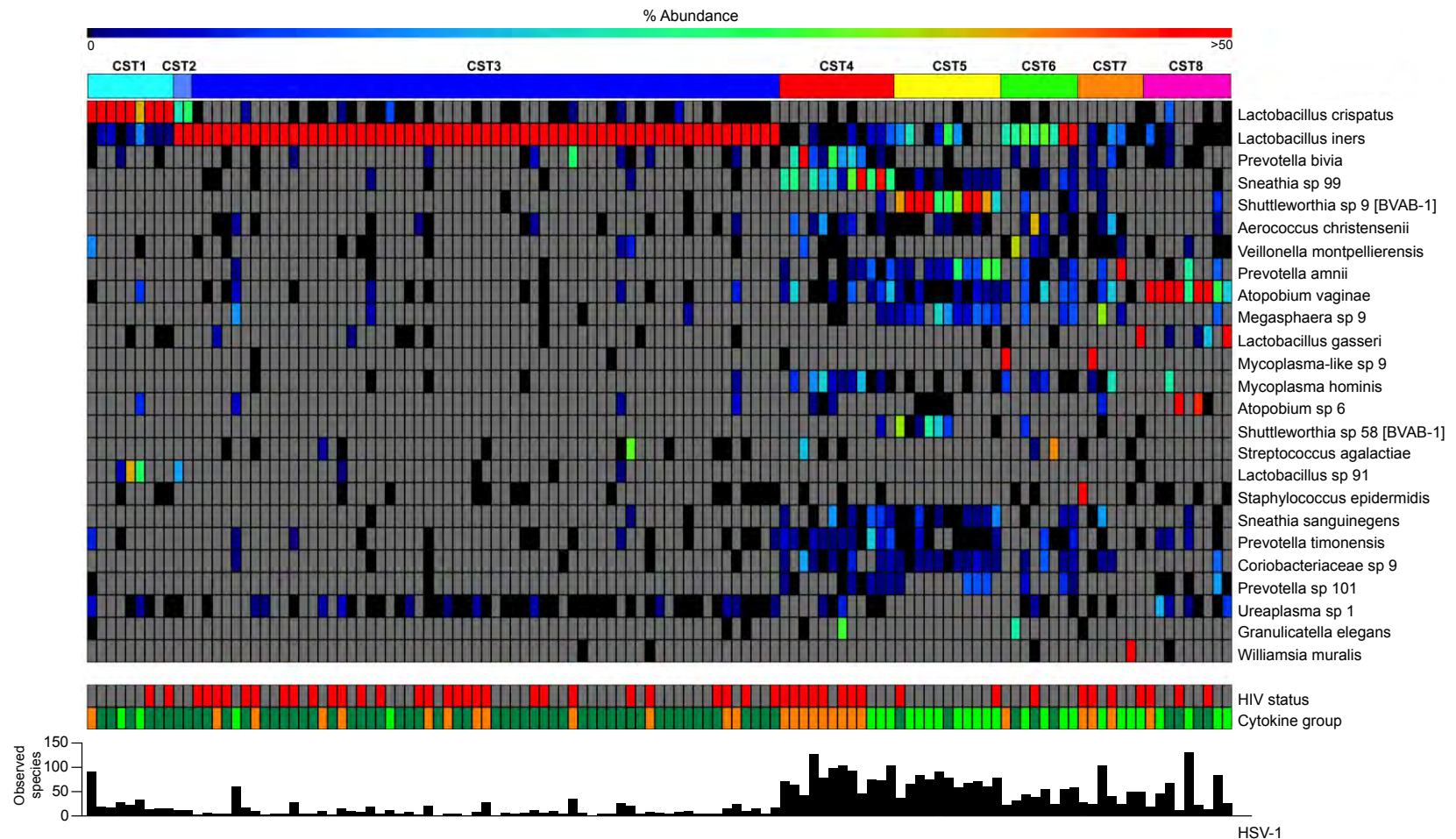
## Searching for the cause of genital inflammation in the vaginal microbiome





# High risk of acquisition in young women:

In the vaginal microbiome, *Prevotella bivia* enhances HIV acquisition in women exposed to the virus





# High risk of acquisition in young women:

In the vaginal microbiome, *Prevotella bivia* enhances HIV acquisition in women exposed to the virus

	P. Bivia +	P. Bivia -
Cases (Genital Inflamm +)	10 (37.0%)	17 (63.0%)
Controls (Genital Inflamm -)	3 (3.3%)	89 (96.7%)

**OR\*: 19.2 (95%CI: 4.0-92.4),  $p < 0.001$**

**Women with genital inflammation were  
19 times more likely to have *P. bivia***

**22 women were HIV positive & had inflammation – 9/22 (41%) had *P. bivia***

\* Odds ratio adjusted . Unadjusted OR = 17.5



# Contributions by other organisms that may cause genital infections

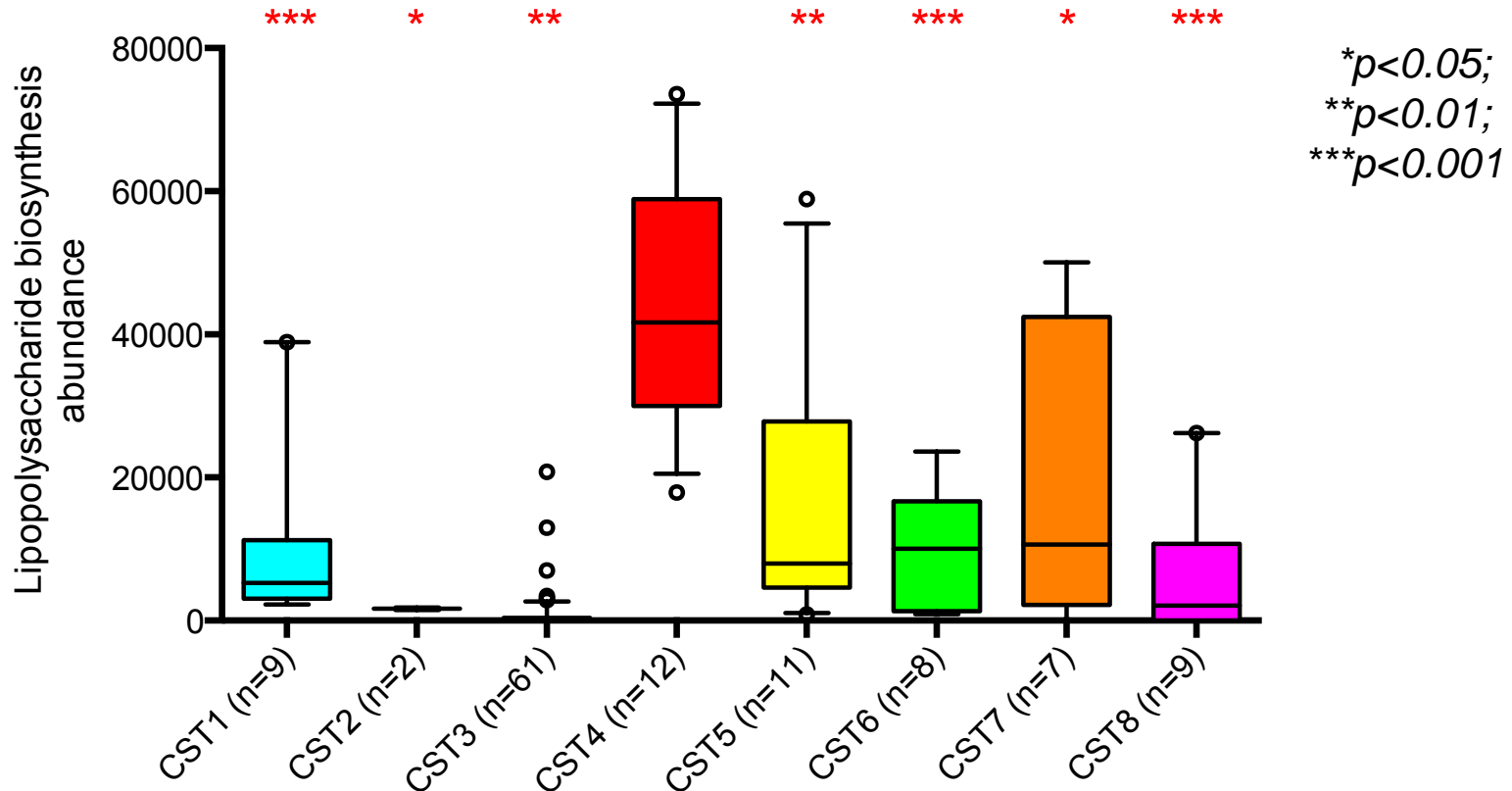
Organism	HC women N (%)	LC women N (%)	Odds Ratio (95% CI), P-value
<i>Trichomonas vaginalis</i>	11 (41%)	14 (15%)	3.8 (1.5-9.8), p=0.007
<i>Chlamydia trachomatis</i>	6 (22%)	11 (12%)	2.1 (0.7-6.2), p=0.213
<i>Neisseria gonorrhoeae</i>	1 (4%)	3 (3%)	1.1 (0.2-8.1), p=1.000
HSV-2 / HSV-1	1 (4%) / 0 (0%)	2 (2%) / 0 (0%)	1.7 (0.2-13.7), p=0.541
<i>Treponema pallidum</i>	0 (0%)	0 (0%)	-
<i>Haemophilus ducreyi</i>	0 (0%)	0 (0%)	-
<i>Schistosoma</i>	0 (0%)	0 (0%)	-



# High risk of acquisition in young women:

Potential mechanism:  $\uparrow$  *P. bivia* =  $\uparrow$  LPS

In the *P. bivia* microbiome cluster (CST4) there is a higher abundance of genes involved in Lipopolysaccharide (LPS) biosynthesis compared to all other microbiome clusters





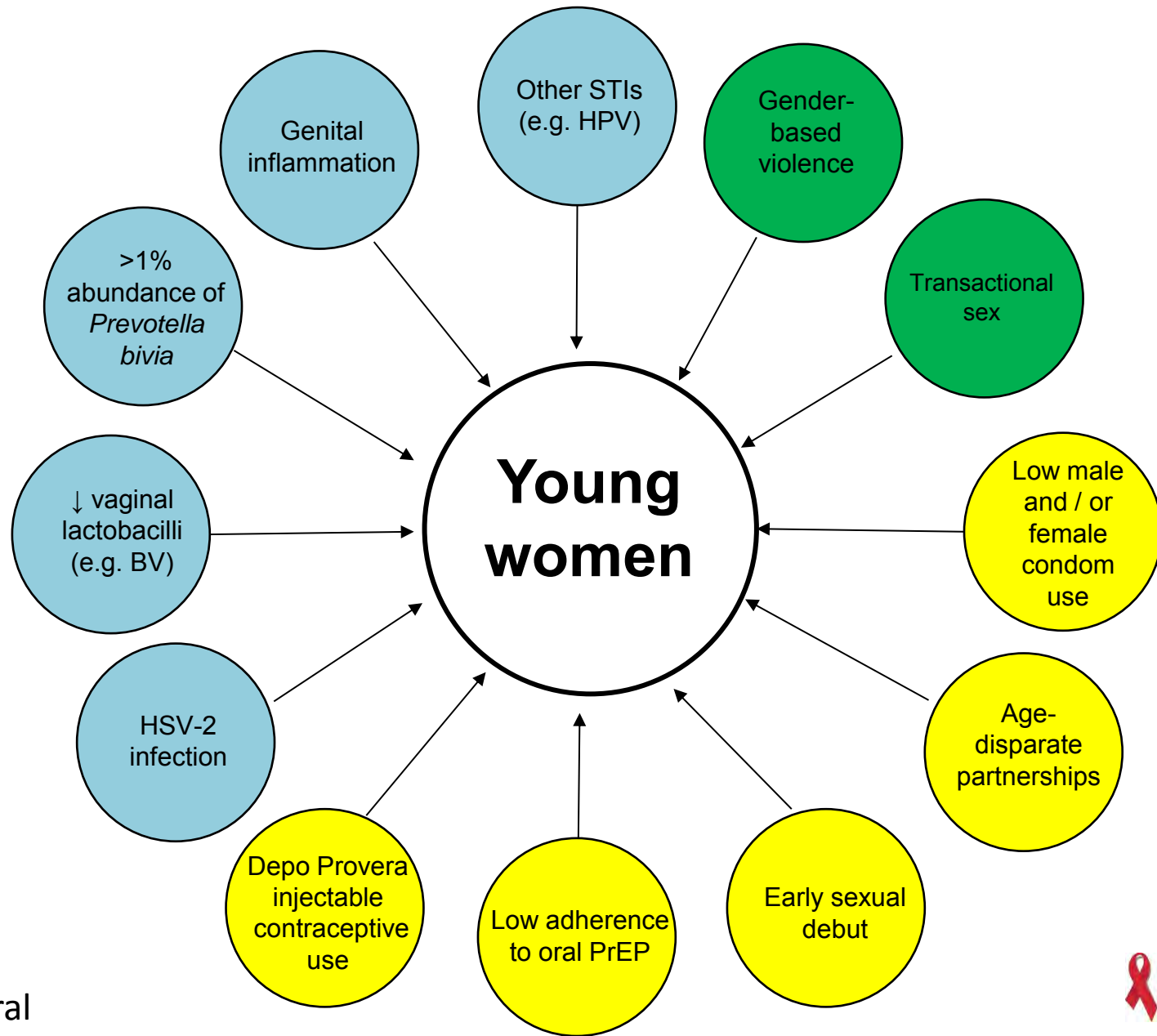
# Microbial translocation is a cause of systemic immune activation in chronic HIV infection

Jason M Brenchley<sup>1</sup>, David A Price<sup>1</sup>, Timothy W Schacker<sup>2</sup>, Tedi E Asher<sup>1</sup>, Guido Silvestri<sup>3</sup>, Srinivas Rao<sup>4</sup>, Zachary Kazzaz<sup>1</sup>, Ethan Bornstein<sup>1</sup>, Olivier Lambotte<sup>5</sup>, Daniel Altmann<sup>6</sup>, Bruce R Blazar<sup>7</sup>, Benigno Rodriguez<sup>8</sup>, Leia Teixeira-Johnson<sup>8</sup>, Alan Landay<sup>9</sup>, Jeffrey N Martin<sup>10</sup>, Frederick M Hecht<sup>10</sup>, Louis J Picker<sup>11</sup>, Michael M Lederman<sup>8</sup>, Steven G Deeks<sup>10</sup> & Daniel C Douek<sup>1</sup>

Chronic activation of the immune system is a hallmark of progressive HIV infection and better predicts disease outcome than plasma viral load, yet its etiology remains obscure. Here we show that circulating microbial products, probably derived from the gastrointestinal tract, are a cause of HIV-related systemic immune activation. Circulating lipopolysaccharide, which we used as an indicator of microbial translocation, was significantly increased in chronically HIV-infected individuals and in simian immunodeficiency virus (SIV)-infected rhesus macaques ( $P \leq 0.002$ ). We show that increased lipopolysaccharide is bioactive *in vivo* and correlates with measures of innate and adaptive immune activation. Effective antiretroviral therapy seemed to reduce microbial translocation partially. Furthermore, in nonpathogenic SIV infection of sooty mangabeys, microbial translocation did not seem to occur. These data establish a mechanism for chronic immune activation in the context of a compromised gastrointestinal mucosal surface and provide new directions for therapeutic interventions that modify the consequences of acute HIV infection.



# Conclusion: HIV risk factors in women



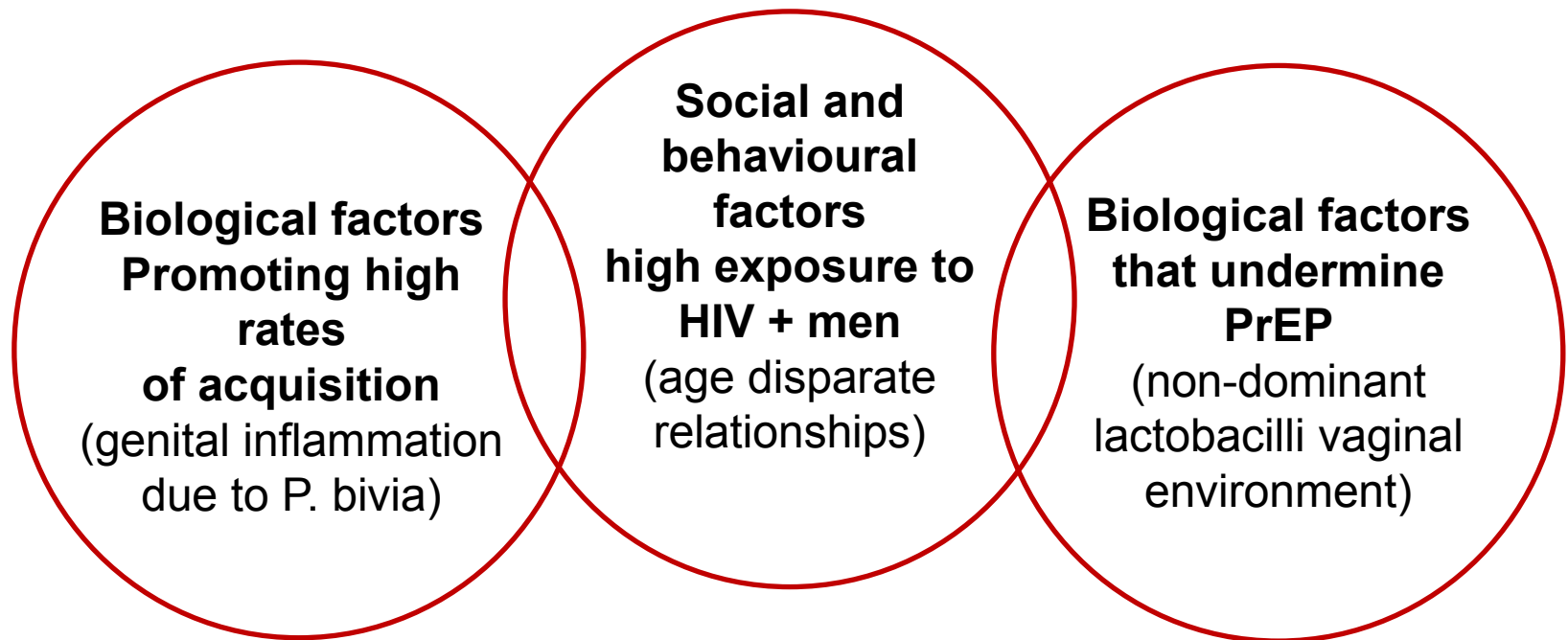
● Biological  
● Structural  
● Behavioural



# **Conclusion:**

## **Understanding high rates of HIV in young women in Africa:**

Implications of new epidemiological, phylogenetic, genomic and proteomic evidence



*Most important group that needs to be addressed to reach UNAIDS goal of ending HIV as a public health threat*



# Key implications of the new results

- **New findings from the CAPRISA consortium of researchers from South Africa and North America shed light on why young women in Africa are at such high risk of HIV & how to better protect them from HIV**
- **Combination prevention in women must now include:**
  - Interventions to reduce age-disparate sex in young women & aggressively promote circumcision in young men & PrEP in young women (while Test & Treat is being scaled-up)
  - Interventions to diagnose & treat BV (incl. *Prevotella bivia*)
  - Interventions to link PrEP scale-up with sexual & reproductive health services for vaginal pH testing and treatment for  $\text{pH} > 4.5$  to promote a “healthy” (*Lactobacillus* dominant) vagina



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  - Michelle Perner
  - Kenzie Birse
  - Laura Romas
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  - Matthew Cook
  - Lauren Girard
  - Alicia Berard
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  - Trisha Vera
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  - Simone Formisano
  - Allison Hicks
  - Mansi Vasishtha
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  - Quarraisha Abdool Karim
  - Anneke Grobler
  - Leila Mansoor
  - Natasha Samsunder
  - Sinaye Ngcapu
  - Kerry Leask
  - Kim Cousins
- **University of Cape Town**
  - Jo-Ann Passmore
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- **Klatt lab, University of Washington**
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  - Ryan Cheu
  - Tiffany Hensley-McBain
  - Jennifer Manuzak
  - Charlene Miller
  - Kevin Fogassey
  - Ernesto Coronado
  - Lydia Sweet
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CAPRISA 004 study participants, without whom these studies wouldn't be possible



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- National Research Foundation (NRF)
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- National Institutes of Health (NIH)



National Institute  
of Allergy and  
Infectious Diseases