Burnet Institute
Medical Research. Practical Action.

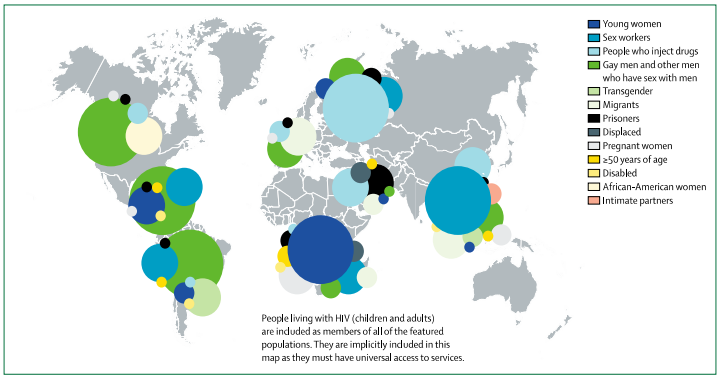
Role of the Vaginal Microbiota in HIV Susceptibility

Prof Gilda Tachedjian
Head, Life Sciences Discipline
Co-Head, Eliminate HIV
Head, Retroviral Biology and Antivirals Laboratory

ASHM 2017

1. PrEP efficacy has been inconsistent in women due to suboptimal adherence; but do biological factors contribute to inconsistent topical PrEP efficacy?

High HIV Burden in Women in Africa



Estimated 37 million individuals living with HIV globally in 2016
1.8 million new infections and 1 million deaths in 2016

Globally 50% of HIV+ people are women

Eastern and Southern Africa, women and girls account for 59% of the total number of people living with HIV

Burnet Institute *UNAIDS 2016* *Mathur et al 2016 Lancet HIV* *Piot et al 2015 The Lancet*

Urgent need for Pre-Exposure Prophylaxis (PrEP) Approaches that Can be Used by Women to Prevent HIV Acquisition

Antiretroviral based topical PrEP (e.g. tenofovir) formulated in a gel, cream, film, tablet or ring to prevent or reduce the sexual transmission of HIV when applied to the vagina or rectum.

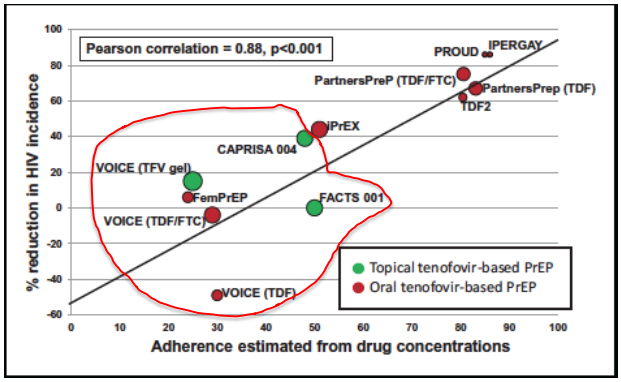
- Oral pre-exposure prophylaxis (PrEP)
  Tenofovir (TFV)-based, FDA approved
- Long acting PrEP injectable versions of antiretrovirals

Most of the HIV prevention clinical studies have been performed with TFV based topical gels and oral PrEP

Burnet Institute

Inconsistent Topical and Oral PrEP Efficacy in Women Largely Attributable to Poor Adherence

Correlation between % of Participants Samples with detectable Drug and PrEP Effectiveness



Oral PrEP:

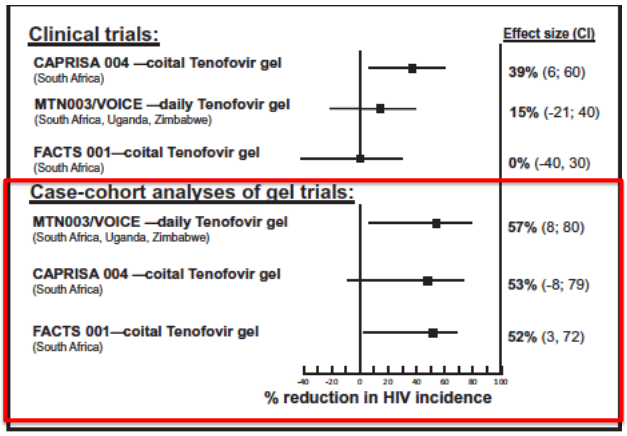
Partners PrEP
-discordant couples

TDF2
-heterosexuals

Efficacy in women

Burnet Institute *Abdool Karim et al 2017 Curr Opin HIV AIDS 12*

Case Control Analysis of Three TFV Gel Trials in Women with Detectable Drug Levels show Modest Efficacy



Only modest 52 – 57% efficacy in adherent women?

Suggesting Biological Factors Could be Modulating Topical PrEP Efficacy

Burnet Institute *Abdool Karim et al 2017 Curr Opin HIV AIDS 12*

2. Does genital inflammation associated with high diversity vaginal microbiota increase risk of HIV acquisition in women?

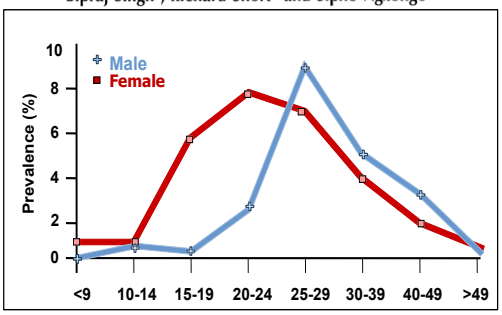
Disproportionate Burden of the HIV Epidemic in Young Women in sub-Saharan Africa

AIDS 1992

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‡



Older male sexual partners

Biological factors
Genital inflammation (subclinical)

STIs (including asymptomatic)

Up to 8-fold increased HIV prevalence in young African women compared to young men

UNAIDS 2010; 2014, 2015, Passmore et al 2016 Curr Opin HIV AIDS 11:156

Vaginal Microbiome Affects HIV Risk in Young Women in Sub-Saharan Africa

INFECTIOUS DISEASE

Vaginal microbiome affects HIV risk

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

"high diversity microbiota = suboptimal microbiota = dysbiosis"

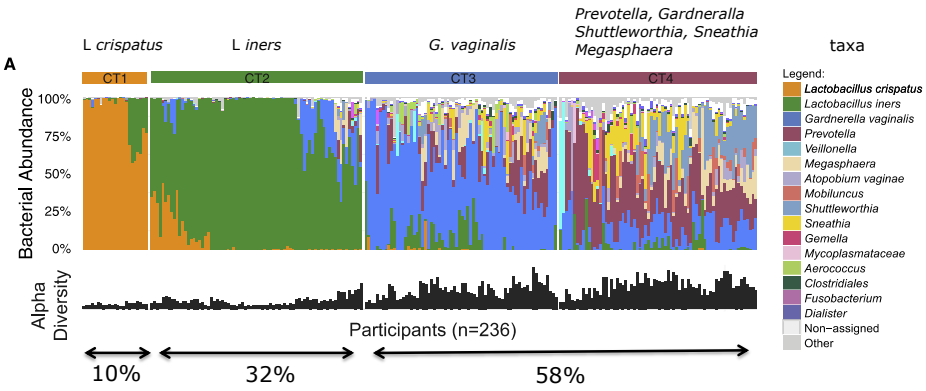
90% of Asymptomatic Reproductive-Age Women Have Vaginal Microbiota Dominated by *Lactobacillus* spp.(USA)

Group	Bacterial communities (CST)	
I	*Lactobacillus crispatus*	< pH 4.0*
II	*Lactobacillus gasseri*	pH 5.0
III	*Lactobacillus iners*	pH 4.4
IVA	Modest *Lactobacillus sp.*, *Anaerococcus, Corynebacterium, Finegoldia* and *Streptococcus* (high diversity)	pH 5.3
IVB	No *Lactobacillus sp.* detected, *Atopobium, Prevotella, Sneathia, Mobiluncus, Peptoniphilus* and several other taxa (high diversity)	pH 5.3
V	*Lactobacillus jensenii*	pH 4.7

L crispatus most protective against STIs including HIV
acidifies vagina to lower pH by lactic acid

L. iners least protective and less stable - transitions to CST IV
similar to asymptomatic **bacterial vaginosis (BV)** –
suboptimal microbiota associated with increased HIV risk in women and men

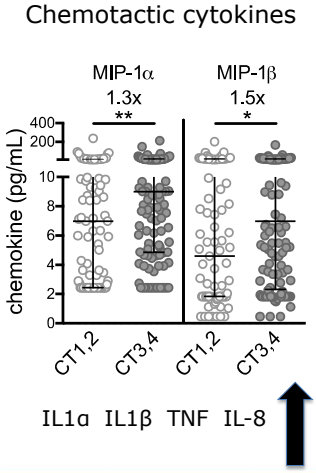
Vaginal Microbiome of Young Healthy South African Women Dominated by High Bacterial Community Diversity

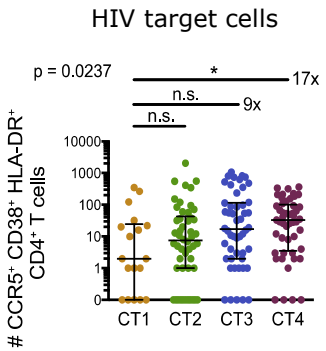


Prospective observational study (19 – 23 years of age HIV neg)
FRESH – Females rising through Education, Support and Health Cohort

75% no identifiable STI
Excluded sex acts, dry sex

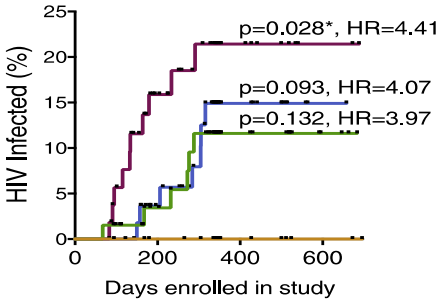
High Diversity Bacterial Communities Associated with Increased Genital Inflammation and HIV Target Cells





High Cervicovaginal Bacterial Diversity (CT4) Increases Risk of HIV Acquisition by 4.4-fold

L. crispatus CT1
L. iners CT2
G. vaginalis CT3
Highly diverse CT4

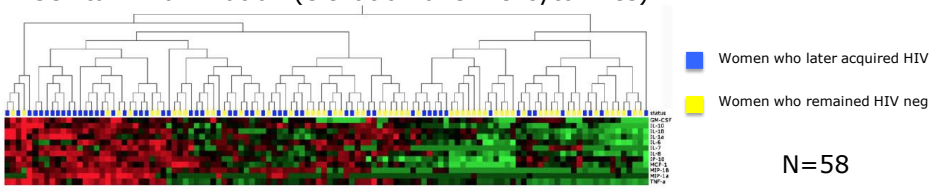


High diversity VMB is associated with increased genital inflammation and HIV acquisition while *Lactobacillus* spp. (not iners) helps protect against HIV

Burnet Institute *Gosman et al 2017 Immunity 46:1*

CAPRISA 004 1% TFV Gel Study: Women with genital inflammation were 3X more likely to acquire HIV than those who remained HIV negative

Genital Inflammation (elevation of 5 – 9 cytokines)



N=58

	HIV +	HIV -	Total
Genital inflammation present	19	6	25
Genital inflammation absent	39	52	91
Total	58	58	116

Increased risk observed in women assigned to tenofovir or placebo gel

Odds Ratio 3.2 (95% CI: 1.3 – 7.9), p=0.014

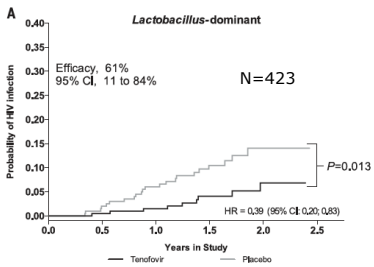
Burnet Institute *Masson et al 2015 Clin Infect Dis 61:260*

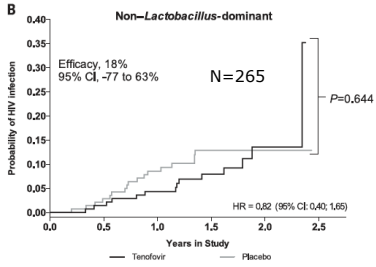
3. Do highly diverse vaginal microbiota metabolise antiretrovirals to potentially decrease topical PrEP efficacy?

Burnet Institute

CAPRISA 004: Diminished Tenofovir Efficacy in Women with Vaginal Microbiota NOT Dominated with Lactobacilli

Mass Spec metaproteomics analysis of bacteria proteins in vaginal swabs





TFV gel reduced HIV incidence c/w placebo gel

61% (p=0.013)

18% (p=0.644)

N=688

Similar clinical, behavioural, demographic characteristics at baseline as well as similar sexual behaviour and gel adherence during trial
Similar proportion of women with L crispatus in gel vs placebo group in LD category

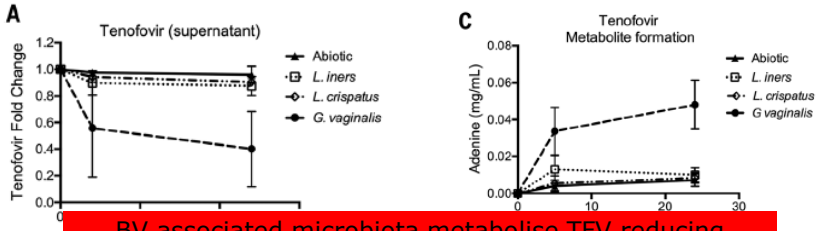
TFV gel is less effective against HIV in women with non-Lactobacillus dominant vs women with Lactobacillus-dominant microbiota

Burnet Institute *Klatt et al 2017 Science 356:938*

CAPRISA 004: Tenofovir metabolised to adenine by G. vaginalis but not *L crispatus* or *L iners*

CVL samples	**Detectable TFV**	**Genital TFV Concentration** (upper quartile)	
LD Women	46.2% (72/156)	8020 ng/ml	
Non-LD Women	29.8% (34/114) p=0.008	24.3 ng/ml p = 0.0077	*n=270*

Sub-analysis: Genital [TFV] negatively correlated with *G. vaginalis* and Prevotella



BV associated microbiota metabolise TFV reducing extracellular drug availability

LD = h

Burnet Institute *Klatt et al 2017 Science 356:938*

Tenofovir metabolised by vaginal microbiota for topical but not oral TFV PrEP

Topical TFV PrEP metabolism confirmed by *in vivo* study

Women with BV associated *G. vaginalis* had decreased levels of TFV diphosphate in cervical tissues and plasma following 2 hours of directly observed product application vs women with lactobacillus-dominant microbiota

Oral PrEP

Women in the Partners PrEP Study (oral daily TFV-based PrEP)

No difference in PrEP efficacy for women with bacterial vaginosis vs women with lactobacillus-dominant microbiota (Based on Nugent Score)

HIV-infected women on suppressive TFV therapy

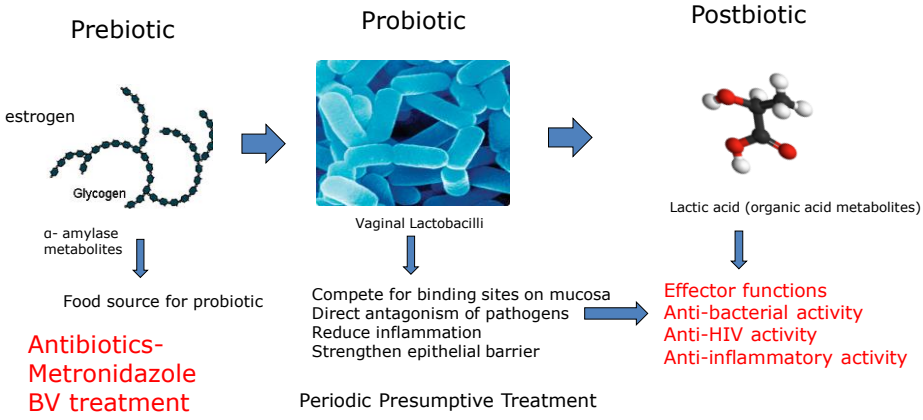
Ratio of FGT:plasma TFV concentrations decreased with low (lactobacillus dominant) and high diversity microbiota but not intermediate diversity

Impact of microbiota on oral PrEP appears to be more complex

Burnet Institute *Hillier et al 2017 CROI* *Heffron et al 2017 Lancet HIV 4:e449* *Carlson et al 2017 JID* *Taneva et al HIV R4P 2016 Chicago*

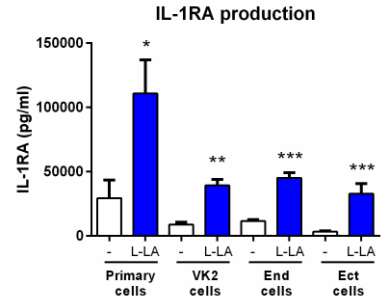
4. Are there strategies to promote beneficial lactobacillus dominated vaginal microbiota and decrease genital inflammation to help protect against HIV and promote PrEP efficacy

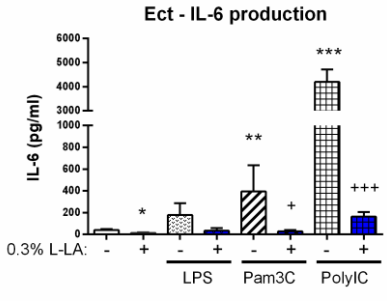
Alter the Vaginal Microbiota and Reduce Genital Inflammation by Delivering a Lactobacillus Probiotic or Postbiotic as Adjunct to PrEP



[1]O'Hanlon et al 2011 BMC Infect Dis 11; [2]O'Hanlon et al 2013 PLoS One 8:e80074; [3]Aldunate et al 2013 J Antimicrob Chemother; [4]Tachedjian et al 2017 Res Microbiol 2017 Apr 20

Lactic Acid (LA) is Anti-inflammatory on Cervicovaginal Epithelial Cells – patent granted





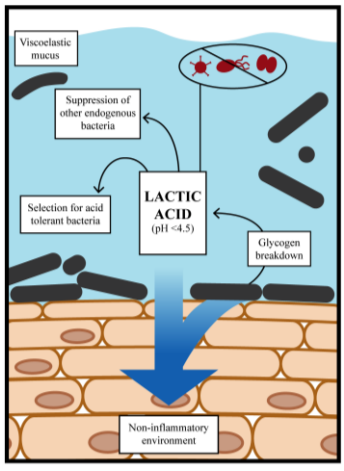
Similar increase in IL-1RA with TLR agonists: polyIC, LPS, Pam3C
Mops up IL1a and IL1b – increase HIV

Similar effects IL-8, TNF, RANTES, MIP3α

Not just a low pH effect (same effect not seen with HCl)
Pretreat cells 1 h wash, then add TLR agonists, same effect
Inhibits inflammation in presence of genital secretions and due to TNF

Lactobacillus Dominant Vaginal Microbiota to Decrease HIV Susceptibility and Promote PrEP Efficacy – Adjunct to ARV PrEP

Lactobacillus spp.



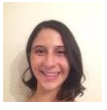
Topical PrEP

HIV STIs

Acknowledgments

Tachedjian Lab

Muriel Aldunate



Daniela Srbinovski

David Tyssen

Burnet Institute

Raffi Gugasyan

David Delgado Diaz

Anna Hearps

Joshua Hayward

Monash Bioinformatics Platform

David Powell and team

Johns Hopkins Univ

Thomas Moench

Richard Cone

Lois Bayigga

Deborah Anderson

Boston University

Jacques Ravel

Univ of Maryland School of Medicine

Vipul Bansal

RMIT University