UZCHS-CTRC

University of Zimbabwe College of Health Sciences - Clinical Trials Research Centre

Saving Lives Through Innovative Research Strategies

Impact of Adherence on Study Results

Experience from VOICE, ASPIRE and other Studies

Nyaradzo M Mgodi (MBChB, MMed)

Adherence to HIV Prevention and Treatment:

Key Populations in Sub-Saharan Africa

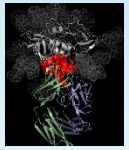
26 April 2018

Harare, Zimbabwe

Potential Conflicts and Financial Disclosure

- I have no actual or potential conflicts to declare in relation to this program and presentation.
- Grant/Research support: US National Institutes of Health, Bill and Melinda Gates Foundation, USAID.
- Consulting: US National Institutes of Health, World Health Organization, Merck.

Current HIV Prevention Strategies

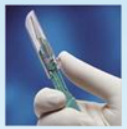


BNABs/Vaccines?
in the field

Intravaginal Rings

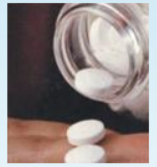
Baeten J et al 2016
Nel et al 2016

Male circumcision



Auvert B, PloS Med 2005
Gray R, Lancet 2007
Bailey R, Lancet 2007

Treatment of STIs



Grosskurth H, Lancet 2000

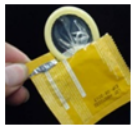
Microbicides for women

Abdool Karim Q, Science 2010

Female Condoms

HIV PREVENTION

Male Condoms



Oral pre-exposure prophylaxis

Grant R, NEJM 2010 (MSM)
Baeten J , 2011 (Couples)
Paxton L, 2011 (Heterosexuals)

HIV Counselling and Testing

Coates T, Lancet 2000

Post Exposure prophylaxis (PEP)

Scheckter M, 2002

Treatment for prevention

Donnell D, Lancet 2010
Cohen M, NEJM 2011

Behavioural Intervention

- Abstinence
- Be Faithful

Slide Credit (HPTN, Karim & Cohen)

Pre-exposure Prophylaxis (PrEP): Oral and Topical

- Several randomized clinical trials assessing ARV-based PrEP interventions for HIV-1 prevention have been completed:
  - Oral PrEP - either Tenofovir Disoporxil Fumarate (TDF) or the combination drug Tenofovir Disoporxil Fumarate /Emtricitabine (FTC)
  - Topical PrEP - 1% tenofovir gel
  - Topical PrEP – dapivirine vaginal ring
- Efficacy has been highly variable across these trials and regimens, across different populations and across different age groups.
- In trials that demonstrated efficacy high protection was evident in highly adherent populations
- Futility was associated with poor adherence

Sheth, AN. *Journal of Virus Eradication* 2016

The Best of 2010: Proof of Concept

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*

Science

Science **329**, 1168 (2010)

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

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

Outcomes of HIV Prevention Trials

Study	Population	N	Results
CAPRISA 004 *South Africa* (Tenofovir Gel)	Women	889	39% [CI = 6-60] efficacy coitally-dependent vaginal TFV gel
iPrEx *Brazil, Ecuador, Peru, South Africa, Thailand, US* (Oral Truvada)	Gay men, other MSM, transgender women	2499	44% [CI = 15-63] efficacy daily oral FTC/TDF
TDF2 Study *Botswana* (Oral Tenofovir)	Men and women	1200	62% [CI = 22-83] efficacy daily oral FTC/TDF
Partners PrEP Study *Kenya, Uganda* (Oral Truvada/ Tenofovir)	Serodiscordant couples	4758	67% [CI = 44-81] efficacy daily oral TDF 75% [CI = 55-87] efficacy daily oral FTC/TDF
FEM-PrEP *Kenya, S Africa, Tanzania* (Oral Truvada)	Women	1950	Futility of daily oral FTC/TDF 6% [CI = -52-41]

Grant, R.
NEJM 2010

Abdool Karim, Q.
Science 2010

Thigpen, MC.
NEJM 2010

Baeten, J.
NEJM 2012

Van Damme, L.
NEJM 2012

Science NOW

Human Nature Sinks HIV Prevention Trial

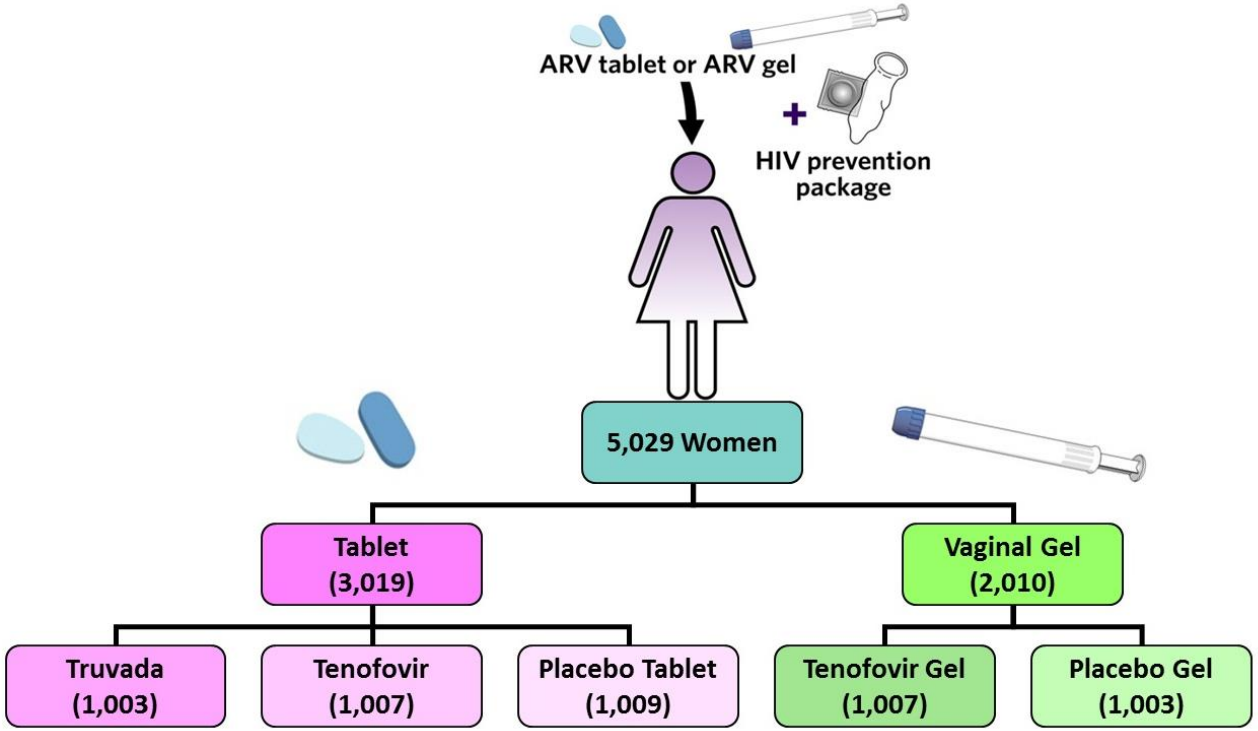
The VOICE Study

Tenofovir Gel

Truvada Tablets

Tenofovir Tablets

1. Which is effective?
2. Is each safe?
3. Which will women use?



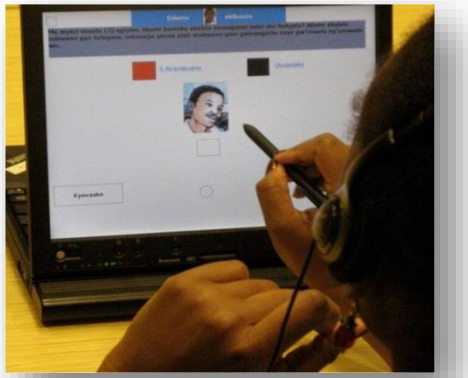
- Once daily dosing of oral tenofovir, oral Truvada and vaginal tenofovir gel was not effective
- Women were aged 18-45, more than half < 25 years
- Many were single; and those who were married or in committed relationships, did not necessarily know their partners' HIV status.

VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

Marrazzo, JM. *NEJM* 2015

MTN
microbicide trials network

Adherence Measures in VOICE



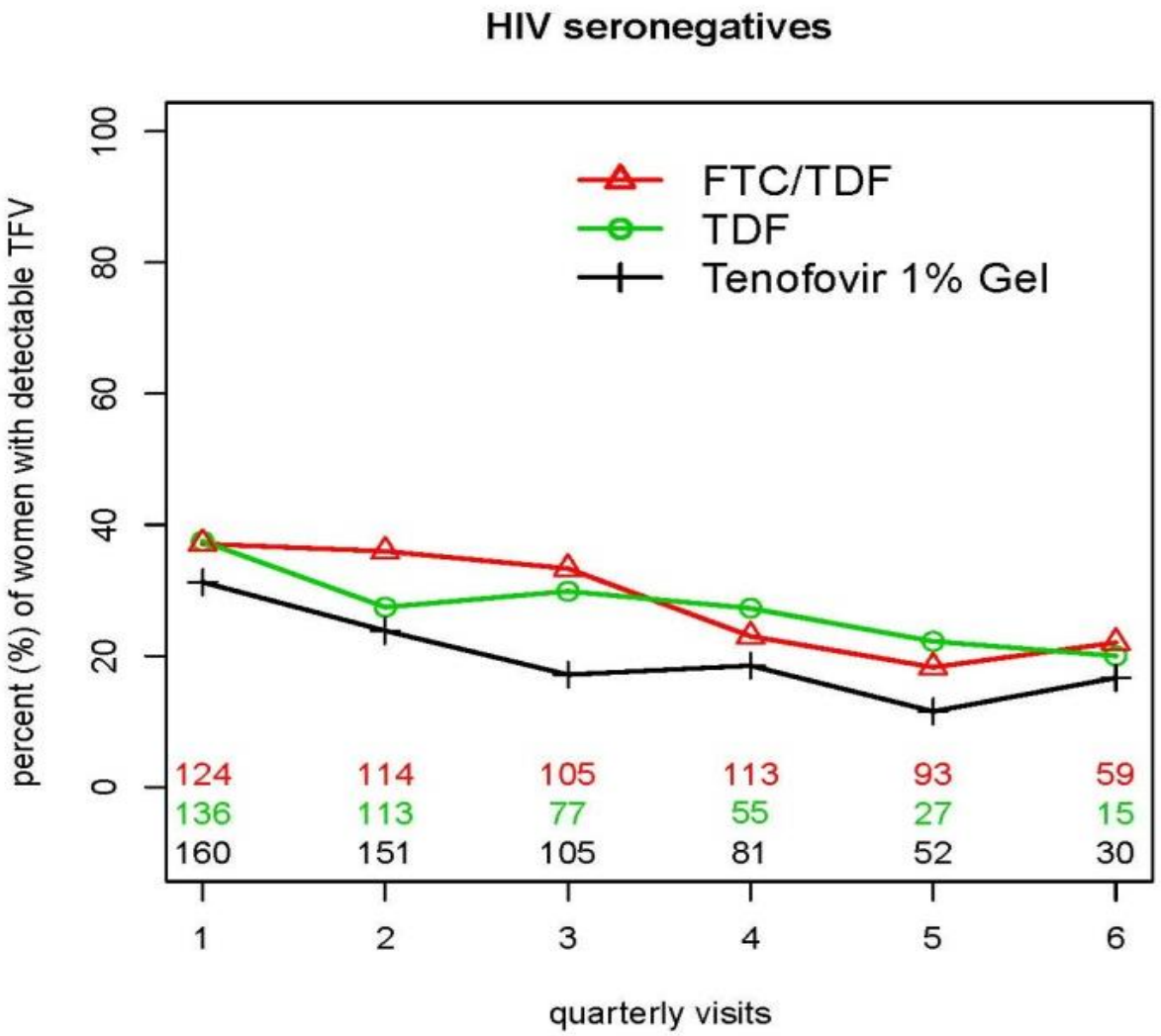
- Reported by participant:
  - ACASI – Audio Computer-Assisted Self-Interview
  - Interviewer administered questionnaires
  - Returned applicators and pill bottles
- Laboratory tests that measure drug in the body (collected during study visits **but tested at the end of the study**):
  - Blood
  - Vaginal Swabs
  - Hair

Challenges in the measurement of adherence – Monica Gandhi

Laboratory monitoring for adherence – Tinashe Mudzviti

VOICE
VAGINAL + ORAL INTERVENTIONS TO CONTROL THE EPIDEMIC

Percentage of Detectable Tenofovir in VOICE



- Most women did not use products daily as recommended
- Those least likely to use their products, single women under age 25, were also most likely to get HIV

	Truvada Tablet	Tenofovir Tablet	Tenofovir Gel
Returned Pill or Applicator Counts	92%	87%	86%
Self Report	91%	90%	90%
Drug Detected in Blood	**29%**	**28%**	**23%**

Adherence Measures in VOICE: The Game-Changer

- Highlights the need for measures of adherence that do not rely solely on self-reporting
- Measures that are not easily manipulated by participants
  - eg real-time biologic monitoring of drug levels

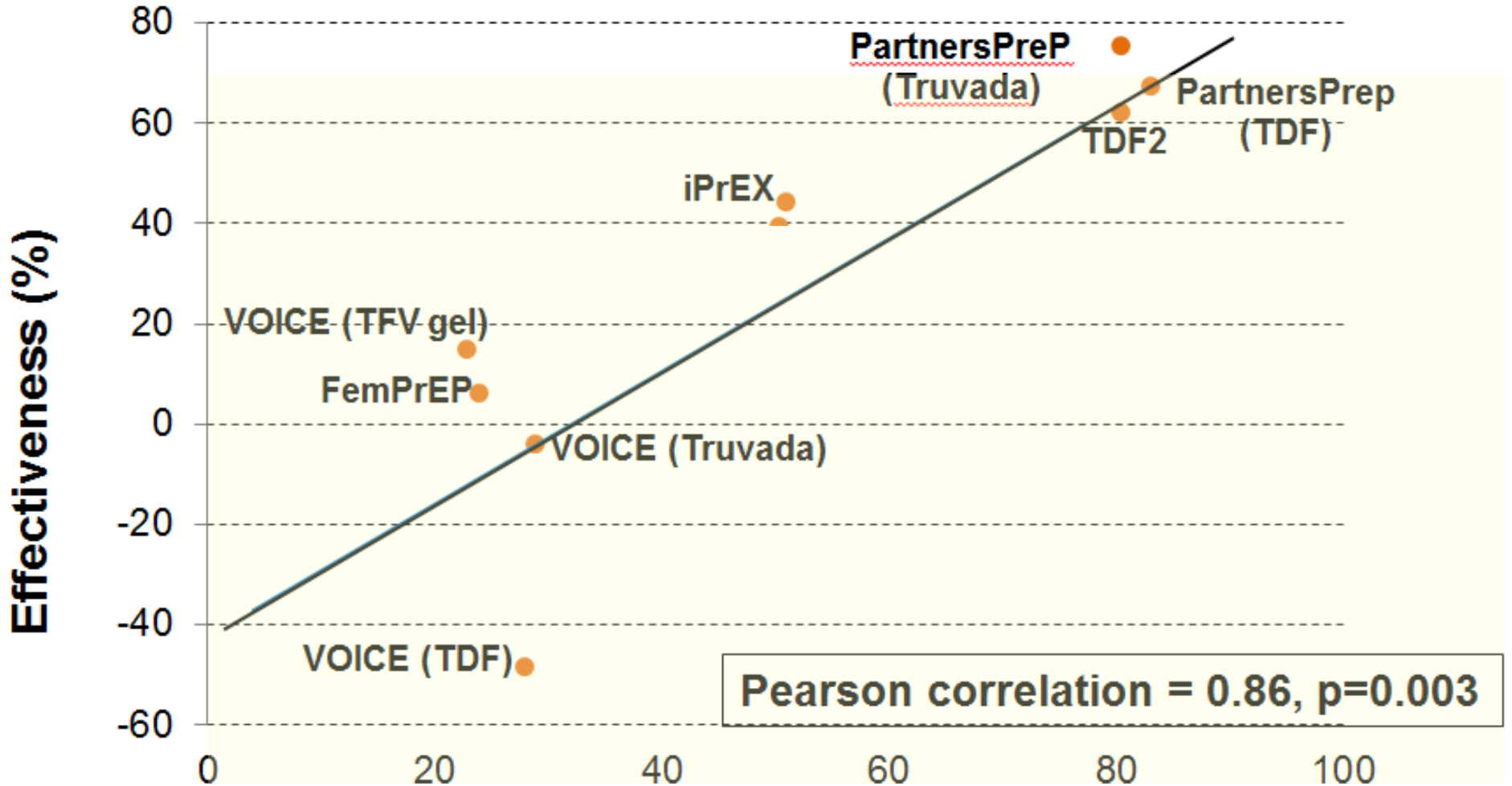
Barriers to consistent use of study products in VOICE

- The unknown efficacy of products
- Identification with HIV infection
- Lack of social support for study participation

Effective adherence interventions at societal level– Petina Musara

van der Straten A, *J Int AIDS Soc*. 2014

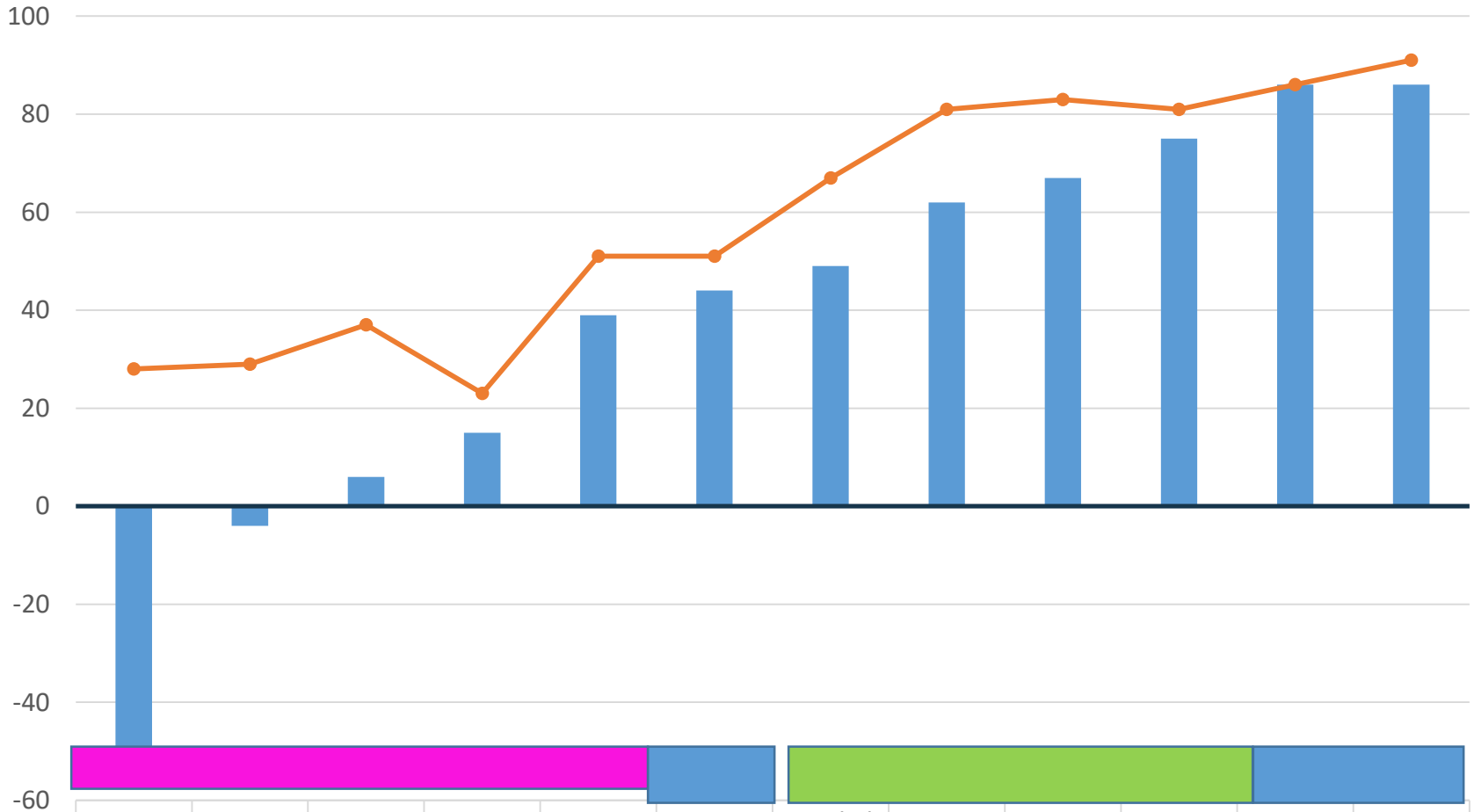
Adherence Correlates with Efficacy



Adherence (%) adjudicated by drug levels

Abdool Karim, SS IAS 2014

HIV PrEP Efficacy versus Adherence



	VOICE Tenofovir	VOICE Truvada	Fem PrEP	VOICE Tenofovir Gel	CAPRISA 004	iPrEX	Bangkok Tenofovir Study	TDF2	Partners PrEP Tenofovir	Partners PrEP Truvada	PROUD	IPERGAY
Efficacy	-49	-4	6	15	39	44	49	62	67	75	86	86
Adherence	28	29	37	23	51	51	67	81	83	81	86	91

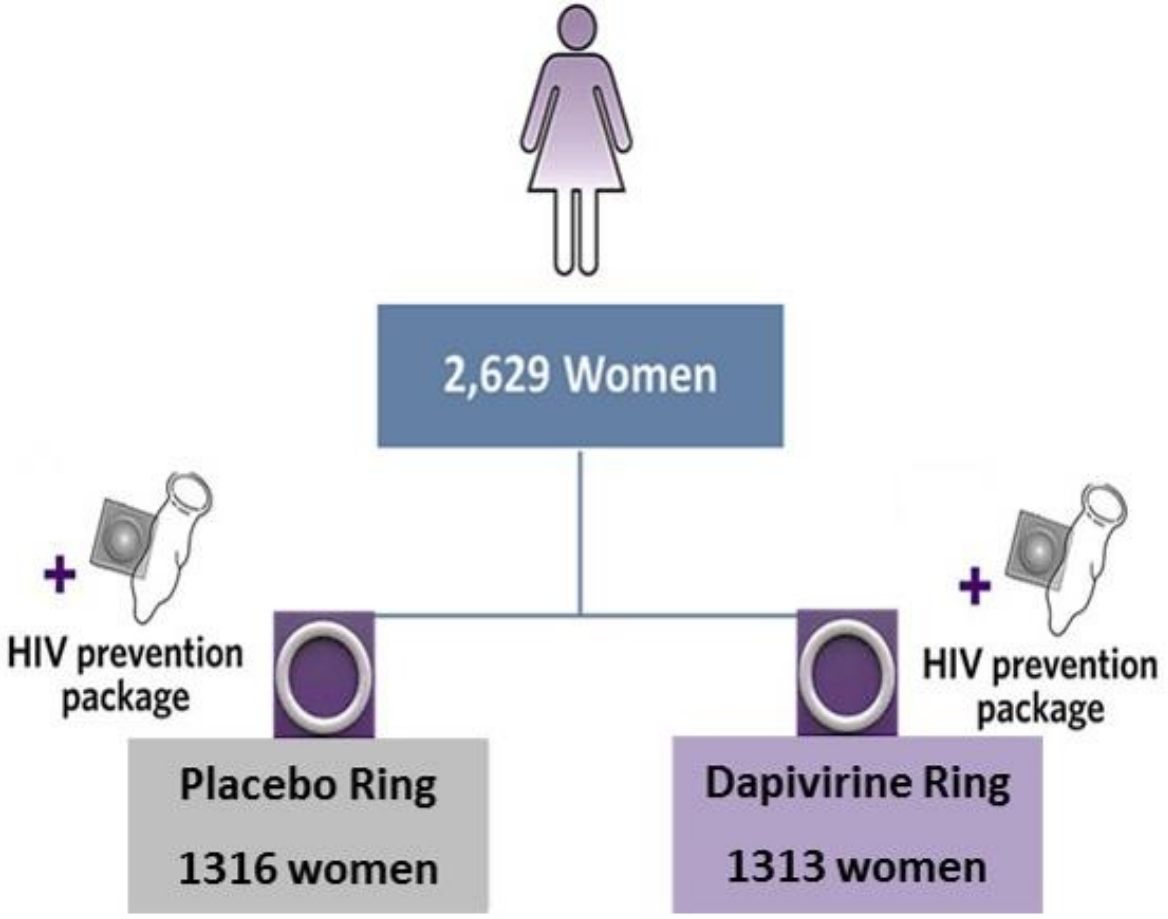
Efficacy Adherence

K. Rivet Amico and Michael J. Stirratt

MTN-020/ ASPIRE

Overall, women in the dapivirine vaginal ring arm had a 27% reduction in the rate of HIV-1 acquisition, compared to placebo.

Primary HIV-1 effectiveness intention-to-treat analysis (15 sites)		
	Dapivirine	Placebo
# HIV-1 infections	71	97
HIV-1 incidence, per 100 person-years	3.3	4.5
HIV-1 protection effectiveness 95% CI, p-value	27% (1, 46) p=0.046	

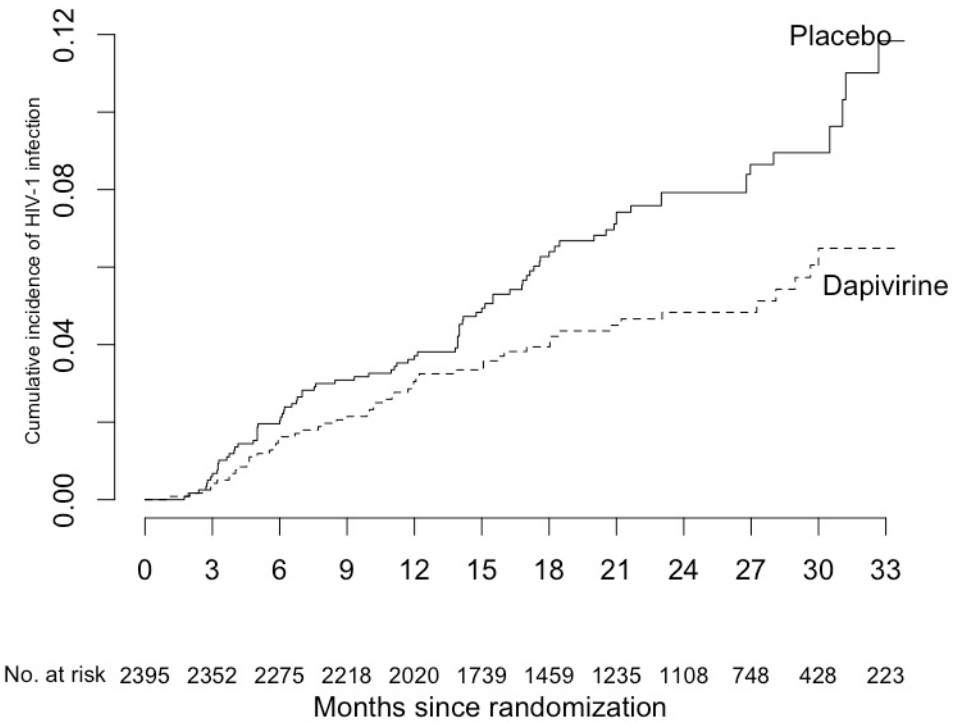


Baeten, J. *NEJM* 2015

HIV-1 Protection in ASPIRE

After excluding data from two sites with lower adherence, the dapivirine ring reduced HIV-1 acquisition by 37%.

Primary HIV-1 effectiveness intention-to-treat analysis (13 sites)		
	Dapivirine	Placebo
# HIV-1 infections	54	85
HIV-1 incidence, per 100 person-years	2.8	4.4
HIV-1 protection effectiveness 95% CI, p-value	37% (12, 56) p=0.007	



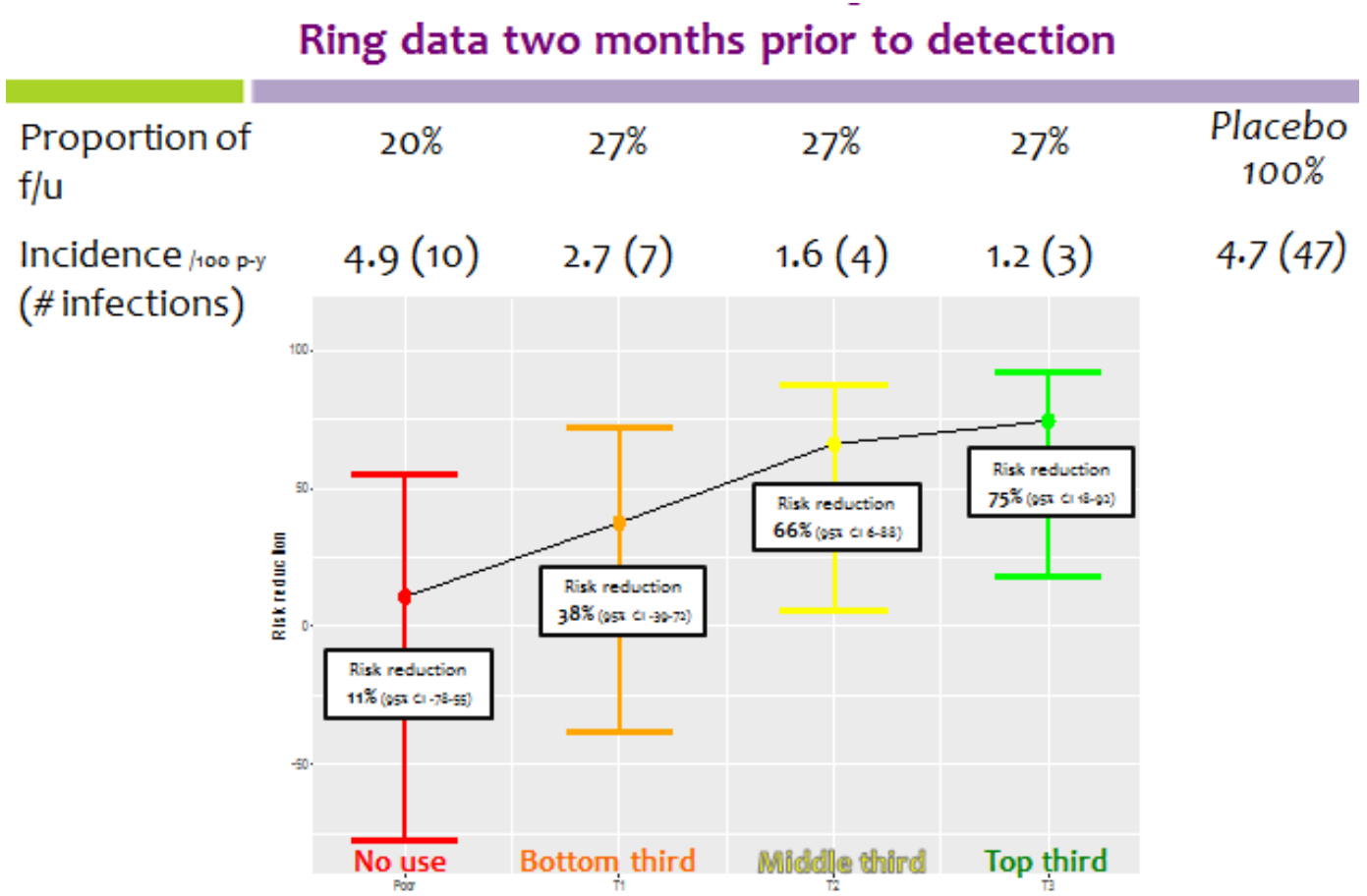
MTN microbicide trials network

ASPIRE A Study to Prevent Infection with a Ring for Extended Use

Objective Measures of Adherence

Plasma - Measured in quarterly-collected plasma samples:

Ring - Levels <23.5 mg defined adherence.



ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

Age and HIV-1 Protection

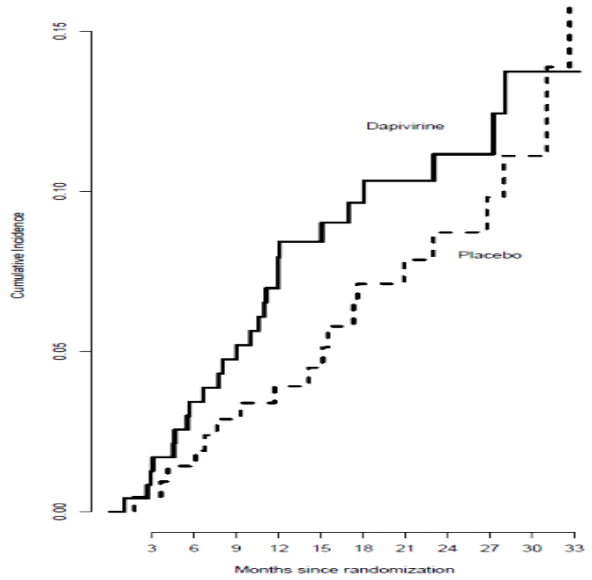
- HIV-1 protection differed significantly by age,
- With women ≥25 years demonstrating substantial HIV-1 protection
- While those <25 years of age no statistically significant reduction in HIV-1 incidence:

	Age <25	Age ≥25
HIV-1 protection effectiveness (95% CI)	10% (-41,43)	61% (32, 77)
Interaction p-value	p=0.02	

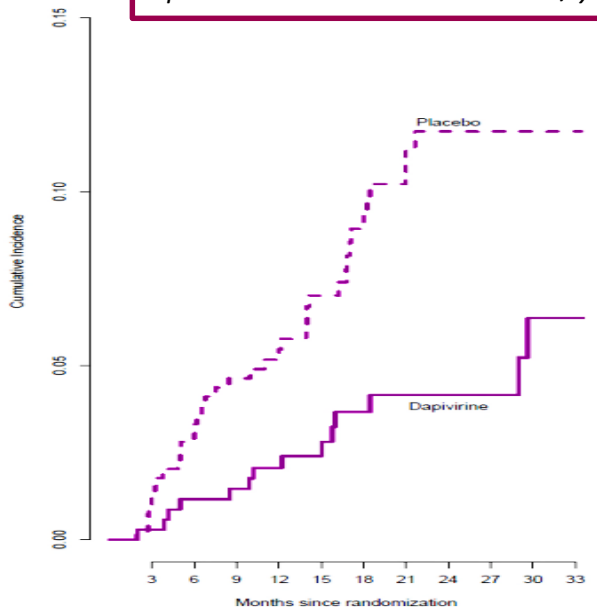
Age and HIV-1 Protection

- HIV-1 protection effectiveness was explored in additional age-stratified categories, and lack of HIV-1 protection was limited to those ≤21 years of age:

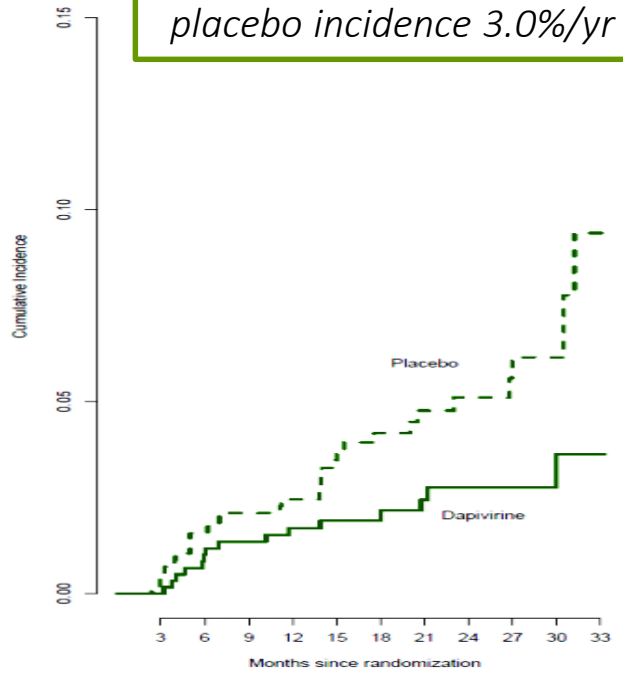
Age 18-21
-27% (-133,31)
placebo incidence 5.4%/yr



Age 22-26
56% (19,76)
placebo incidence 6.1%/yr



Age 27-45
51% (8,74)
placebo incidence 3.0%/yr



MTN microbicide trials network

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

Age and HIV-1 Protection

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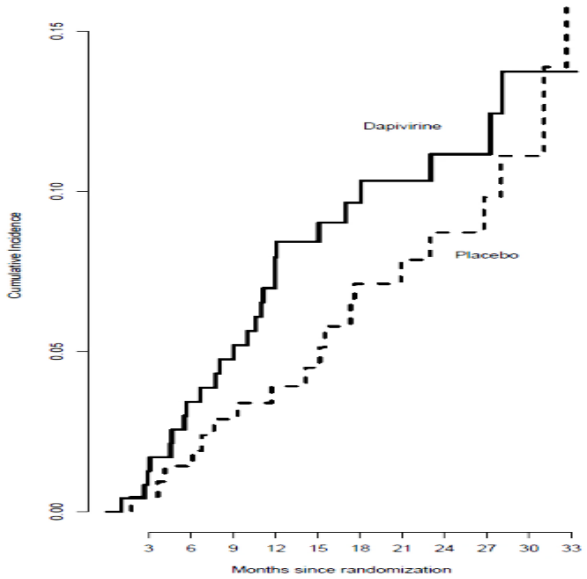

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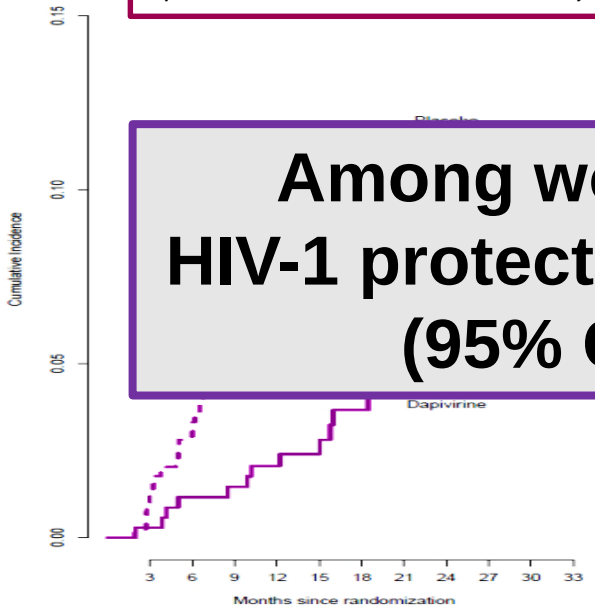

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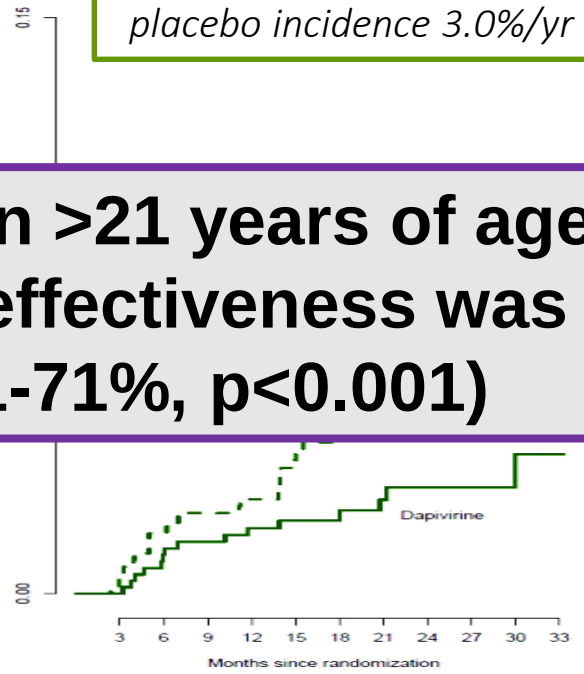


Among women >21 years of age, HIV-1 protection effectiveness was 56% (95% CI 31-71%, p<0.001)

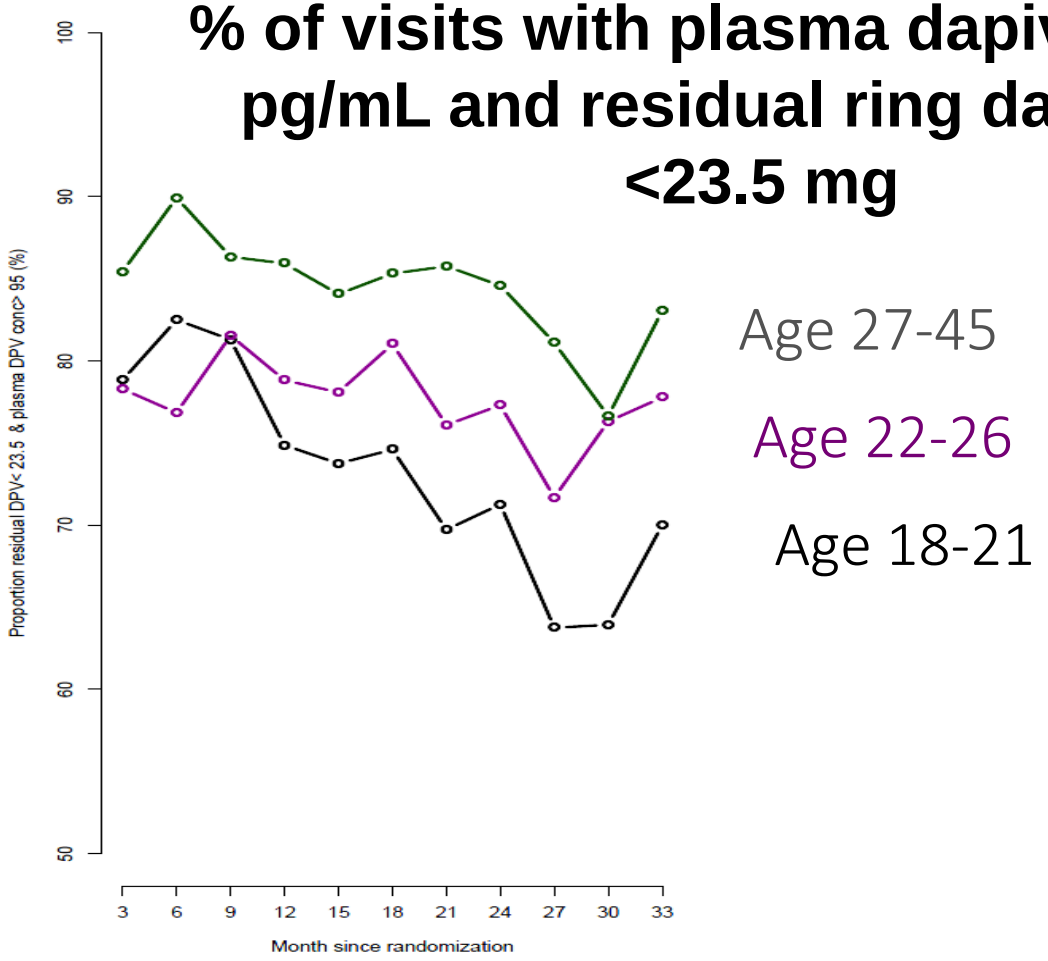
MTN microbicide trials network

ASPIRE
A Study to Prevent Infection with a Ring for Extended Use

Age and Adherence

- Adherence measures were statistically significantly lower among women 18-21 years compared to women >21 years
- **NB** - Adherence improved significantly in the open label extension

% of visits with plasma dapivirine >95 pg/mL and residual ring dapivirine <23.5 mg



Strategies to improve adherence to vaginal rings – Annalene Nel

Predictors of Poor Adherence

Strong relationships between adherence and HIV-1 protection are demonstrated in studies of HIV-1 prophylaxis.

Predictors of poor adherence

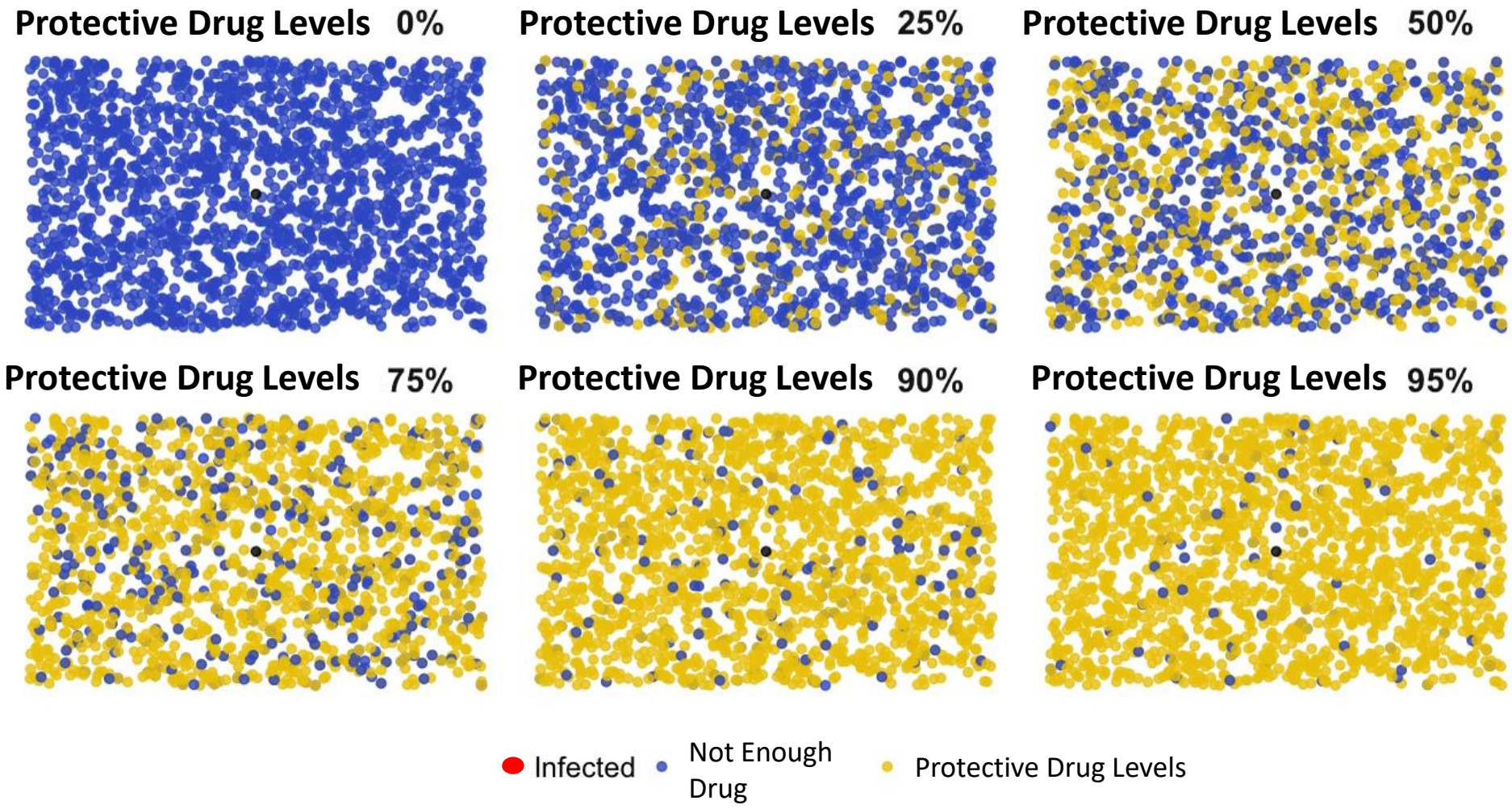
- Younger age (Partners PrEP, VOICE)
- Not partnered (VOICE, FEM-PrEP)
- Low perception of risk (VOICE, FEM-PrEP, others)
- Stigma (VOICE, FEM-PrEP, others)
- Less sex (Partners PrEP, iPrEx)
- Alcohol use (Partners PrEP)
- Not attending appointments (Partners PrEP, VOICE, others)

Increased Susceptibility to HIV

- Biological factors that may increase the susceptibility of young women to HIV infection:
  - genital mucosa immaturity or inflammation,
  - other sexually transmitted infections,
  - hormonal effects,
  - high partner HIV viral loads.
- Anaerobic bacteria linked with bacterial vaginosis have been shown to be associated with both genital inflammation and HIV risk
- Dysbiotic vaginal microbiome, comprising <50% *Lactobacillus spp*., directly influenced topical PrEP efficacy.
- *Gardnerella vaginalis*, the dominant vaginal species in dysbiotic women, was able to directly degrade tenofovir, but not dapivirine,

Sheth, AN. *Journal of Virus Eradication* 2016 Klatt, N. IAS 2017

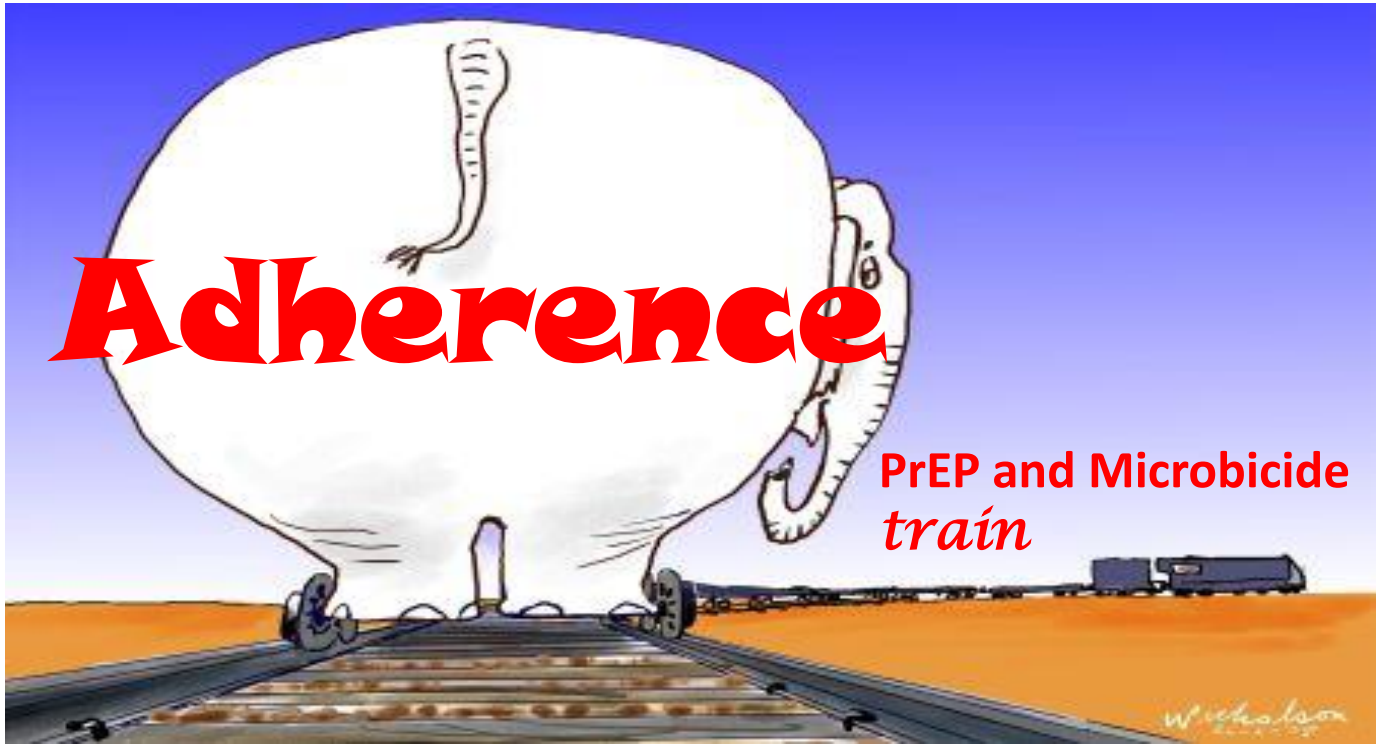
Impact of Adherence is Similar to that of Herd Immunity

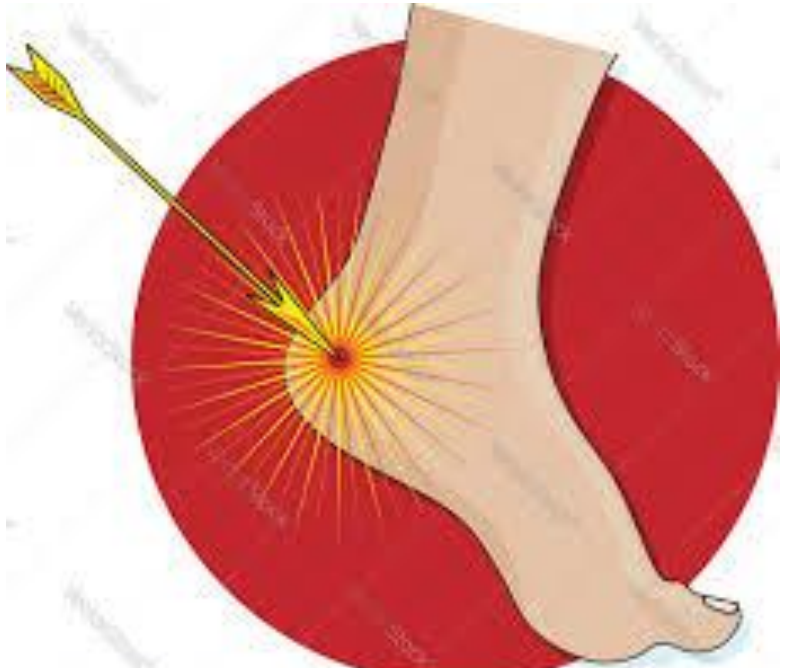


Conclusions and Recommendations

- Oral and topical PrEP studies show that PrEP generally works when used consistently, even in women.
- Trials highlight the challenge of developing prevention methods that are acceptable and easy to use, particularly for young women at risk.
- Reinforce the urgent need to:
  - Expand prevention options and optimise PrEP delivery for this population
  - Employ objective adherence markers
- There are physiologic and behavioural differences between at-risk populations → optimal PrEP interventions must be tailored to the population and/or individual.

Adherence – the Bigger Picture





Thank you, Tatenda, Siyabonga!