



HPTN

HIV Prevention
Trials Network

Adherence to Daily Truvada

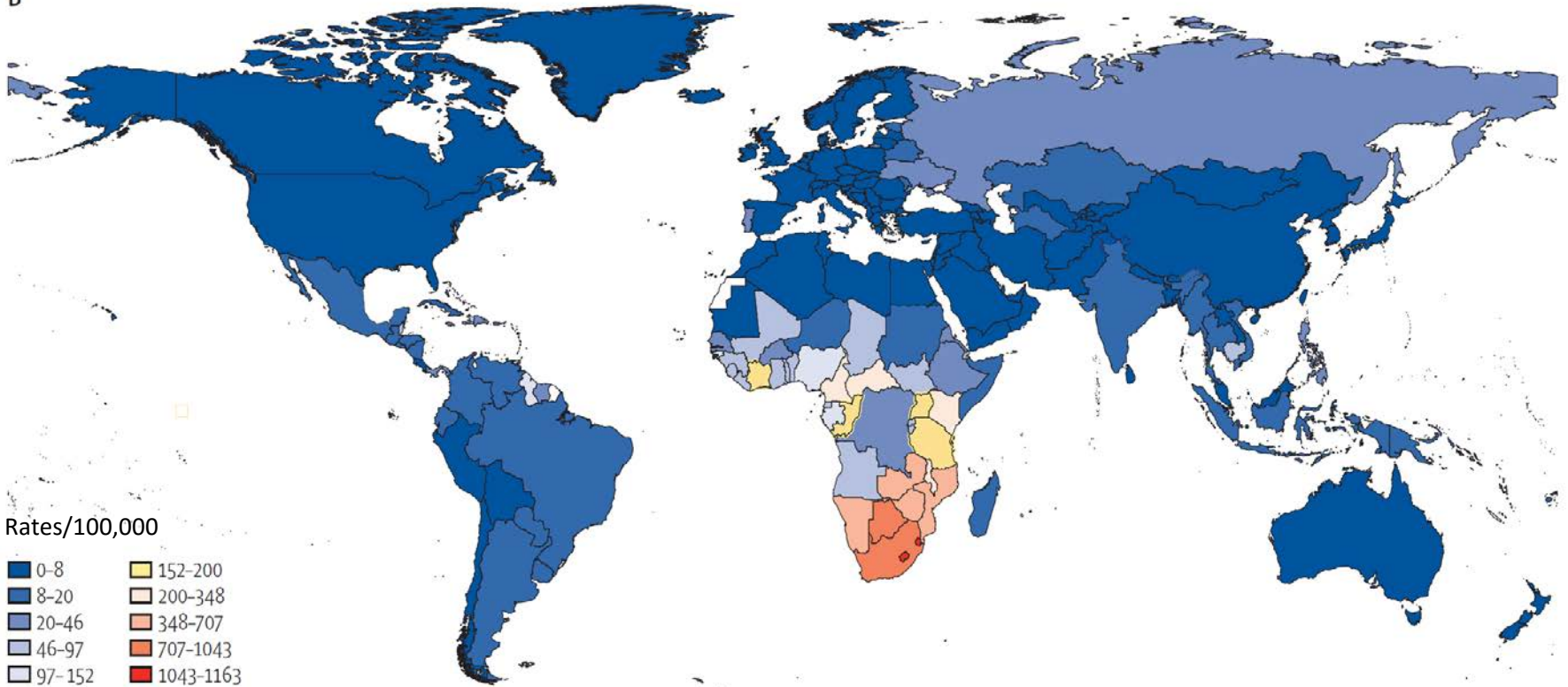
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Controlling HIV Epidemic

- UNAIDS published HIV prevention Roadmap in Oct 2017 targeting reduction of new infections by 75% (current 1.7 million in 2016 to 500 000 in 2020)
- New infections are concentrated among key populations AGYW, MSM and IDU
- Focus is on Few Pillars:
 - Combination prevention programs
 - behavioral change
 - VMMC and
 - PrEP by provision of daily Truvada

Global HIV Incidence, 2015

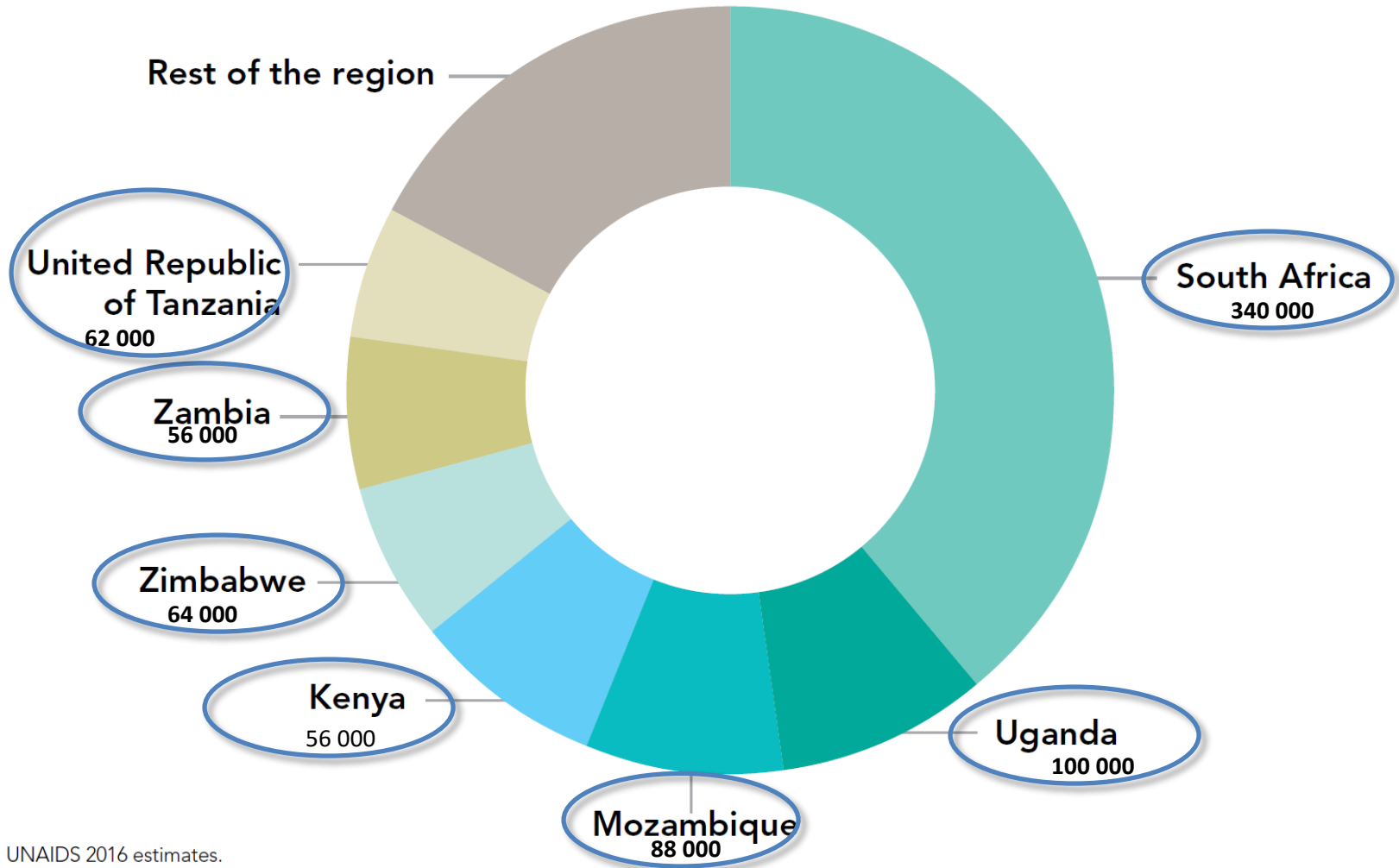
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Highest disease burden in ECSA

Global Burden of Disease, Lancet HIV 2016

New HIV Infections in Southern and East Africa 2015



Source: UNAIDS 2016 estimates.

Evidence of HIV Incidence in the Placebo Arm of Efficacy Trials

Trial	Years	Age	HIV Incidence/100 py
Phambili + 503S	2007-2014	18-35 yrs	5.0
FACTS 001	2011-2014	18-30 yrs	4.0
VOICE	2009-2013	18-45 yrs	5.7
ASPIRE	2012-2015	18-45 yrs	4.5
The Ring Study	2012-2015	18-45 yrs	6.1
Fem-PrEP	2009-2012	18-35 yrs	5.0

Average placebo incidence: 5.1/100 py

Oral PrEP as another tool to control HIV epidemic

- Oral PrEP is effective when taken as prescribed
- Challenges of adherence among women < 25yr
- Fewer tables(2-3/week) are adequate for rectal protection in MSM compared to 6-7 tablets/week vaginal protection in women
- We need approaches that support PrEP adherence to optimize public health impact of this valuable HIV prevention method – HPTN 082 will provide valuable data

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**PrEP for HIV Prevention in Men Who Have Sex
with Men. Grant et al, 2010**

- Truvada had a **44%** protection against HIV infection among MSM and transgender women who have sex with men
- Protection increased to **73%** with adherence **> 90%** days covered by daily oral dose of Truvada

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**Antiretroviral Prophylaxis for HIV Prevention in
Heterosexual Men and Women.**

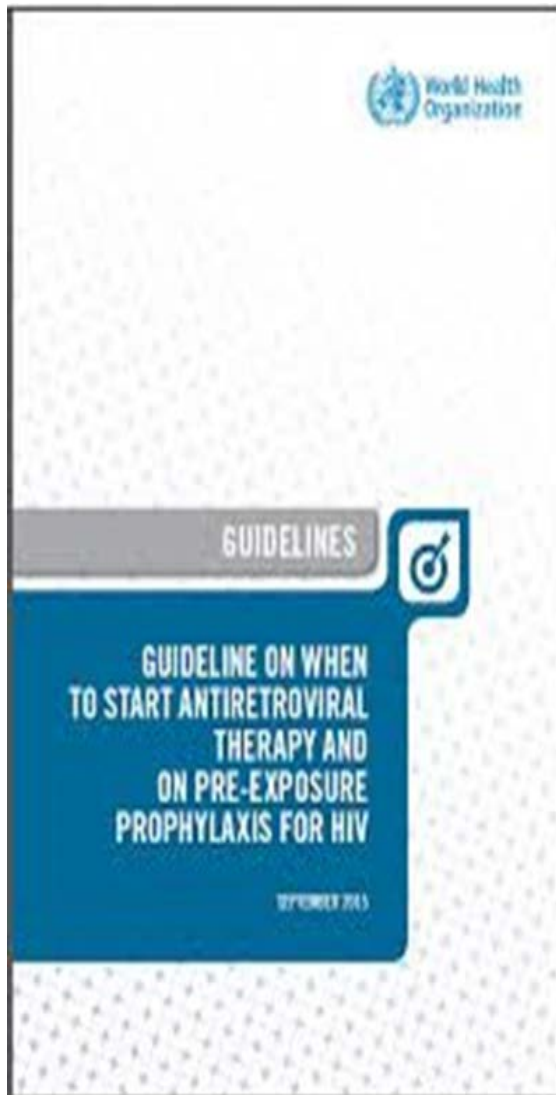
Baeten et al, Aug 2012

- Truvada had a **75%** protection against HIV infection
- TDF was detected in **82%** of randomly selected participants
- July 16, 2012 FDA Approved TDF/FTC use as PrEP based on iPrEX and Partners PrEP results

WHO GUIDELINES

September 2015

Guideline on when to start antiretroviral therapy and on pre-exposure prophylaxis for HIV



2.2 Oral pre-exposure prophylaxis for preventing the acquisition of HIV infection

Recommendation

NEW

Oral PrEP containing TDF should be offered as an additional prevention choice for people at substantial risk of HIV infection as part of combination HIV prevention approaches (*strong recommendation, high-quality evidence*).

WHO Meta-Analysis: PrEP Effectiveness

Analysis	No. of studies	Risk Ratio (95% CI)	p-value	P-value (meta-regression)
Overall	10	0.49 (0.33-0.73)	0.001	--
Adherence				
High (>70%)	3	0.30 (0.21-0.45)	<0.0001	<0.0001
Moderate (41-70%)	2	0.55 (0.39-0.76)	<0.0001	0.009
Low (≤40%)	2	0.95 (0.74-1.23)	0.70	<i>ref</i>
Mode of Acquisition				
Rectal	4	0.34 (0.15-0.80)	0.01	0.36
Vaginal/penile	6	0.54 (0.32-0.90)	0.02	
Age²				
18 to 24 years	3	0.71 (0.47-1.06)	0.09	0.29
≥25 years	3	0.45 (0.22-0.91)	0.03	

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**Pre-exposure Prophylaxis for HIV Infection
among African Women. L. Van Damme et al,
Aug 2012**

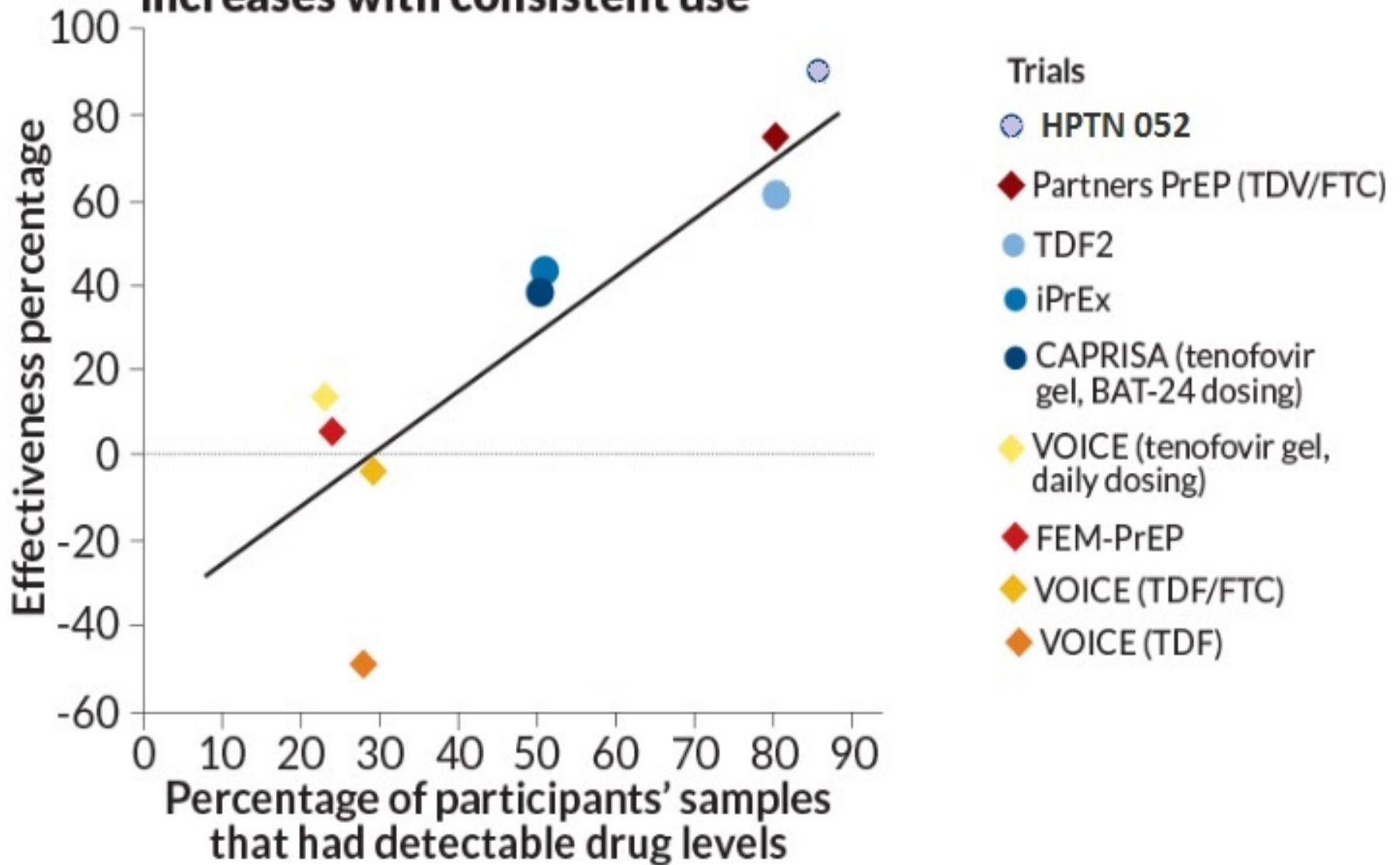
- Prophylaxis of Truvada did not significantly reduce HIV transmission among the 2 120 women in the FEM-PrEP study.
- TDF was detected in only **6%** of participants

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Tenofovir-Based Preexposure Prophylaxis for HIV Infection among African Women, J Marazzo et al, Feb 2015

- Once Daily dosing of oral Truvada was not effective in preventing HIV among women
- Poor adherence to study drug was observed (TDF was detected in <30% of plasma samples from participants)

Effectiveness of tenofovir-based preventions increases with consistent use



Adapted from Abdool Karim SS, 2011

Oral PrEP in women: heterogeneity of results

- Inadequate adherence at time of HIV risk exposure
- Others:
 - low HIV risk perception
 - lack of motivation to taking daily pill - concerns about side effects
 - HIV stigma associated with pill taking lack of partner/family support
- ? vaginal dysbiosis(vaginal microbiota not dominated by protective lactobacilli species)

Evidence that Efficacy daily Truvada is Not affected by Vaginal Micribiota status

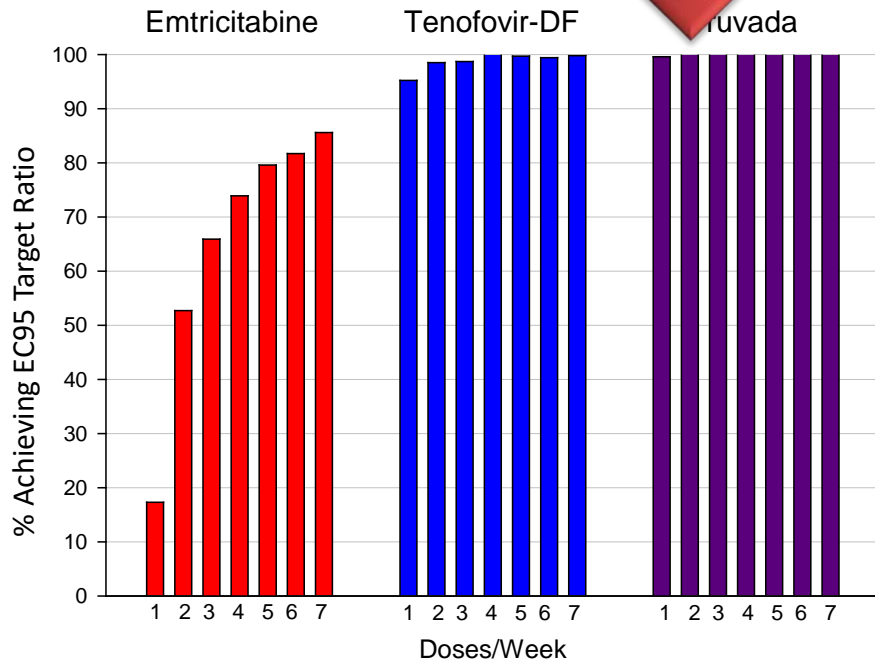
	Incidence per 100 person-years (control group)	Incidence per 100 person-years (Tenofovir group)	Tenofovir efficacy (95% CI)	Efficacy in lactobacilli-dominated microbiota (95% CI)		Efficacy in vaginal dysbiosis (95% CI)
Partners PreP						
Overall (HIV)	2.8	0.9	71% (37-87)	
Sub analysis(HIV)	2.8	0.9	70% (45-84)	77%(43to 90)		73% (6-92)
CAPRISA 004						
Overall (HIV)	9.1	5.6	39% (6-60)
Subanalysis(HIV)	7.3	4.2	57%(36-96)	61% (11to 84)		18% (-77 to 63)

How much drug is required to achieve adequate protection from HIV?

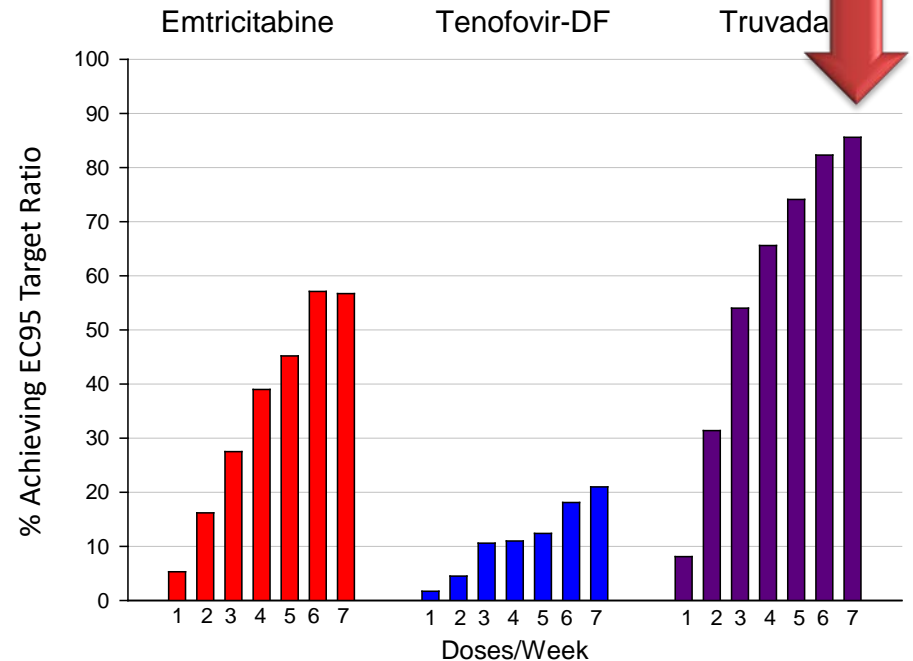
- Must achieve adequate concentrations and activity at all vulnerable sites of infection **Vagina, cervix, rectum**
- Women require 6 or 7 daily oral Truvada/week to be adequately protected from HIV infection (Donnell D, JAIDS 2014)
- MSM/TGF are protected with 4 or 5 tablets/week Grant, JID 2017)

The Right Concentration

Colorectal Tissue



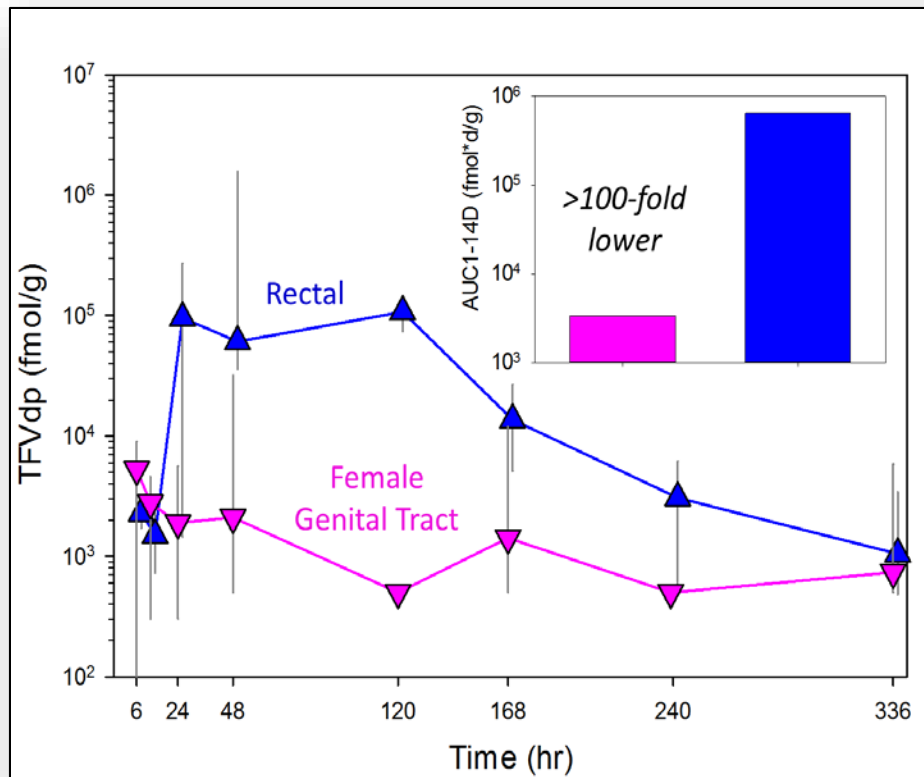
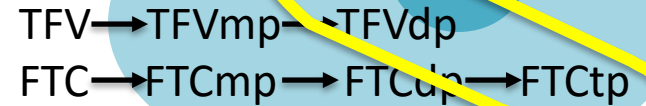
Female Genital Tract



iPrEx OLE= ↓ HIV incidence by 90%
with 2 Truvada doses per week

Partners PrEP= ↓ HIV incidence by 90%
with 7 Truvada doses per week

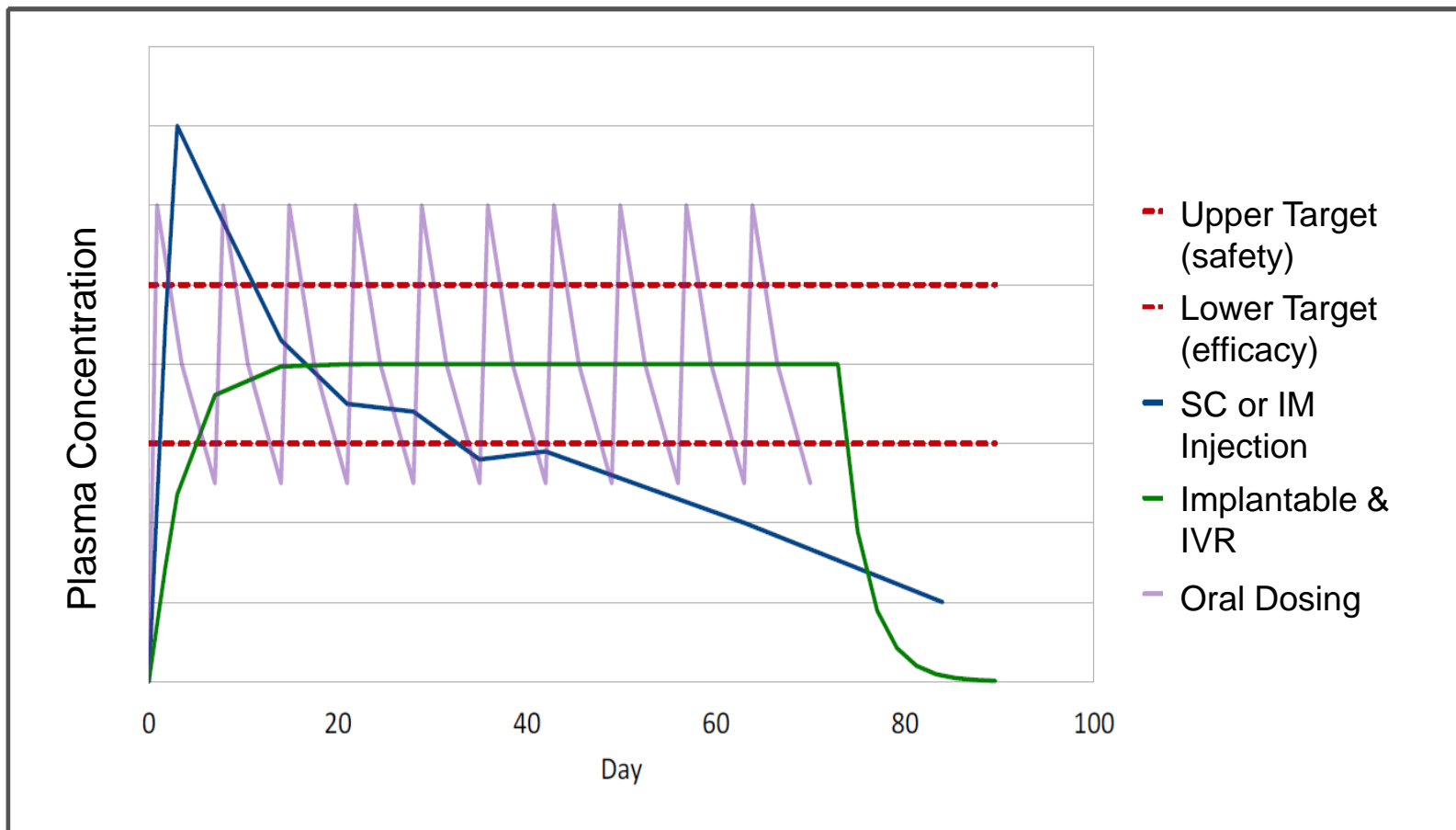
The Right Concentration: *TFVdp In Mucosal Tissues*



Female
Genital Tract

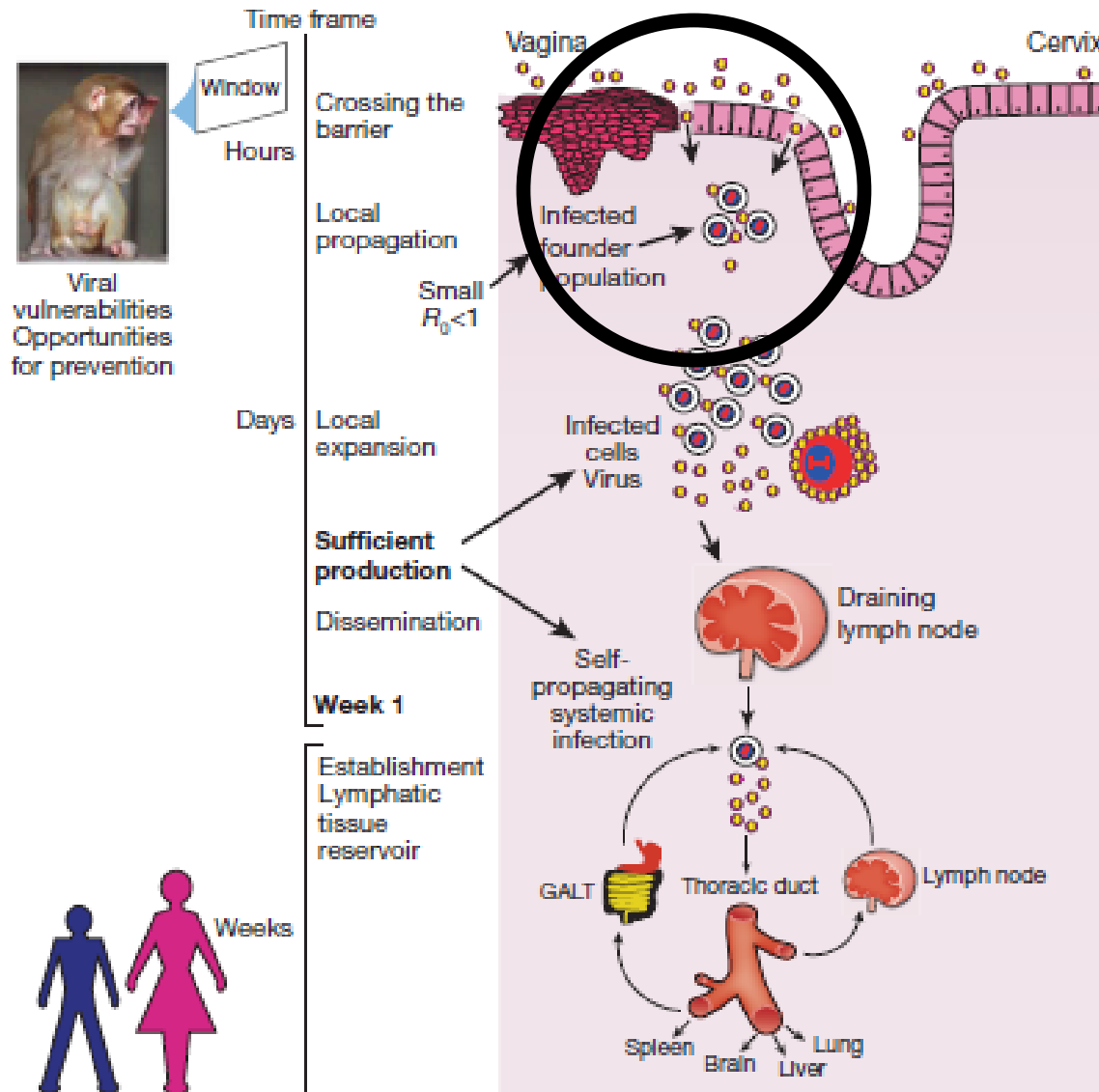
Rectal

Formulation PK Profiles Compared



Courtesy Ariane van der Straten

A Model of HIV Entry Into Female Genital Tract



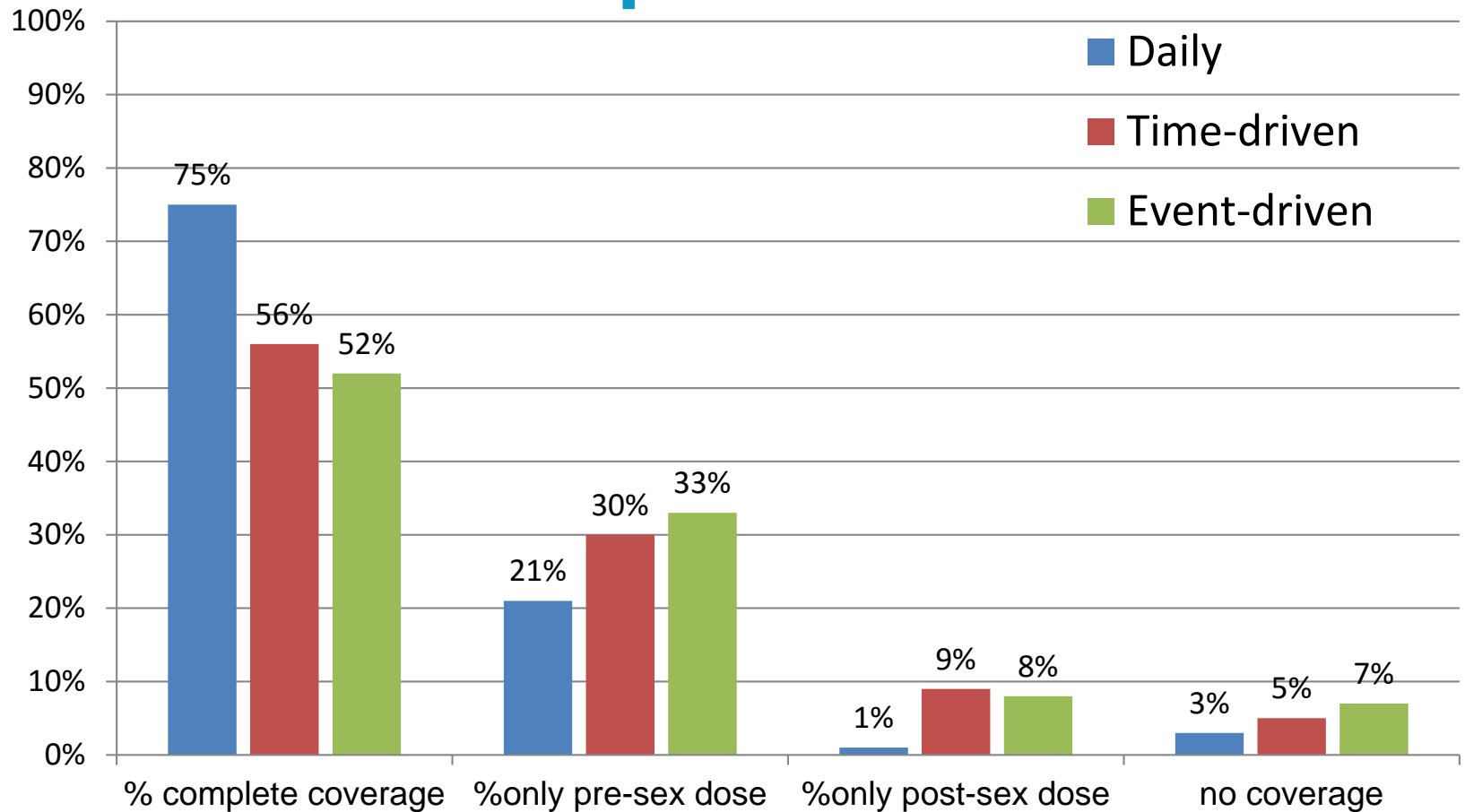
Epithelial Disruption that allows viral entry

Right time, right place, correct dose to block infection

On Demand PrEP

- Standard oral PrEP is one tablet Truvada/day
- Time Driven: 1 tablet/2x week with a post sex boost
- Event Driven: 1 tablet pre-sex and 1 tablet post sex
- N:B no more than 2 tablets daily or 7 tablets/week

Coverage of Sex Events – Women in Cape Town



Reasons of missed post-sex doses: Not at home, concern about disclosing PrEP use to partner, pills not with me, change in routine, not in the mood to worry.

Sex event defined as vaginal or anal intercourse

Time/Daily p = 0.0007, Event/Daily p < 0.0001, Time/Event p = 0.43

Adherence and efficacy in clinical trials, open-label extensions and demonstration projects

Study Design	Adherence	Efficacy /Effectiveness
Men who have sex with men (multiple geographic regions)		
iPrEx	51% by drug detection	44%
iPrEx OLE	71% by drug detection	49%
PROUD	86% of days participants would be taking PrEP if everyone's adherence were 100%	86%
IPIRGAY	Median 16 pills/month by pill count; 43% optimal use, 25% suboptimal use by ACASI	86%
Serodiscordant couples in Africa		
Partners PrEP Study	82% by drug detection	TDF: 67% FTC/TDF: 75%
Partners Demonstration Project	86% by drug detection	96%

Incidence Rates for Curable STIs In VOICE study

Baseline Risk Factor		Chlamydia Incidence (95% CI)	Gonorrhoea Incidence (95% CI)	Syphilis Incidence (95% CI)	Trichomoniasis Incidence (95% CI)
Participants with Follow-up STI results		4790	4790	4781	4577
Person Years at Risk		5543.7	5543.7	5533.0	5230.5
Country	South Africa	15.9	3.8	0.7	6.6
	Uganda	9.7	5.9	4.0	7.4
	Zimbabwe	4.5	1.1	0.2	6.0
Age	<21 years	26.8	6.8	1.0	7.9
	>30 years	3.7	1.5	1.2	7.2
Marital Status	Unmarried	16.4	4.1	0.9	6.8
Alcohol Consumption	None	12.7	2.9	0.7	6.5

Current Landscape of oral PrEP

- Several Ongoing demonstration projects targeting FSW, AGYW, MSM(SA, Kenya, Zim etc)
- Some Gaps still remain:
 - Strong advocacy to provide PrEP to high risk populations urgently: Sinead Delany-Moretlwe
 - Need more behavioral research to understand barriers and facilitators of adherence in women
 - Determine efficacy of Intermittent PrEP in women

Summary

- PrEP has tremendous public health benefit through potential significant reduction HIV incidence at risk population
- Some women may choose daily oral Truvada, others vaginal ring, in future IM as their choice of HIV prevention method
- Its all about CHOICES as we have seen successfully in contraceptive method mix

ACKNOWLEDGEMENTS

Study Participants

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UZCHS-CTU

THANK YOU