



# Do Vaginas Demand Perfection?

Implications for Event-Driven PrEP

Date: September 24, 2024

Time: 9 AM to 10:30 AM Eastern Time

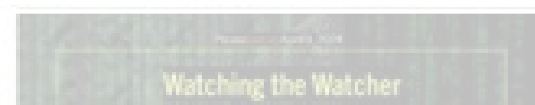
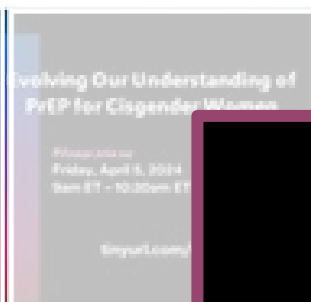
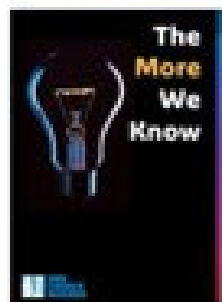
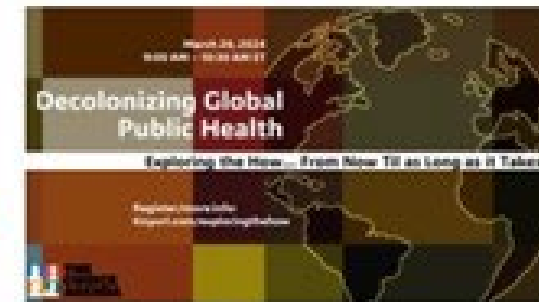
Welcome All!



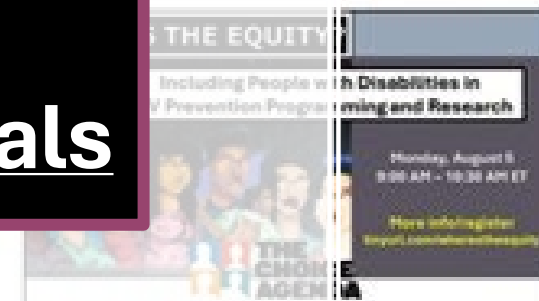


HIV prevention research - a new forum  
for advocacy on the latest

[avac.org/project/choice-agenda](http://avac.org/project/choice-agenda)



Check out all TCA webinar recordings, slides and info resources here: [tinyurl.com/tcawebinarmaterials](https://tinyurl.com/tcawebinarmaterials)



# Sept 24 TCA Playlist

Sweet Lovin'  
Sigala & Bryn Christopher

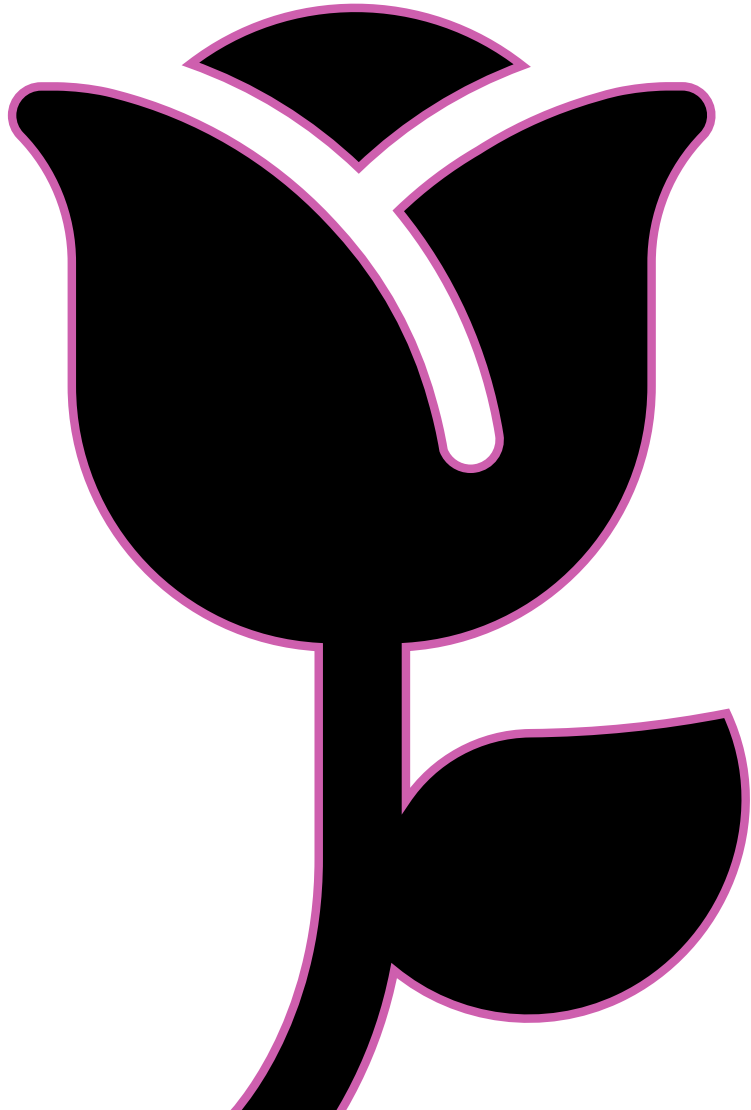
Deeper Love  
Valntna & ManyFew

Woof  
Sofi Tukker & Kah-Lo

Free  
Ultra Nate

DJ Jimberly

## Today's Run of Show



9 – 10 AM  
Presentation and QA  
**Dr. Jenell Stewart**  
Do Vaginas Demand Perfection?



10 – 10:30 AM  
Meet 'n Greet  
**Anna Miti**  
TCA's new co-moderator





# Do Vaginas Demand Perfection? Event-Driven PrEP Beyond Cisgender Men

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Physician-Scientist, Division of Infectious Diseases,  
Hennepin Healthcare

Disclosures: None

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# Overview

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Importance of choice

Data on Event-Driven PrEP

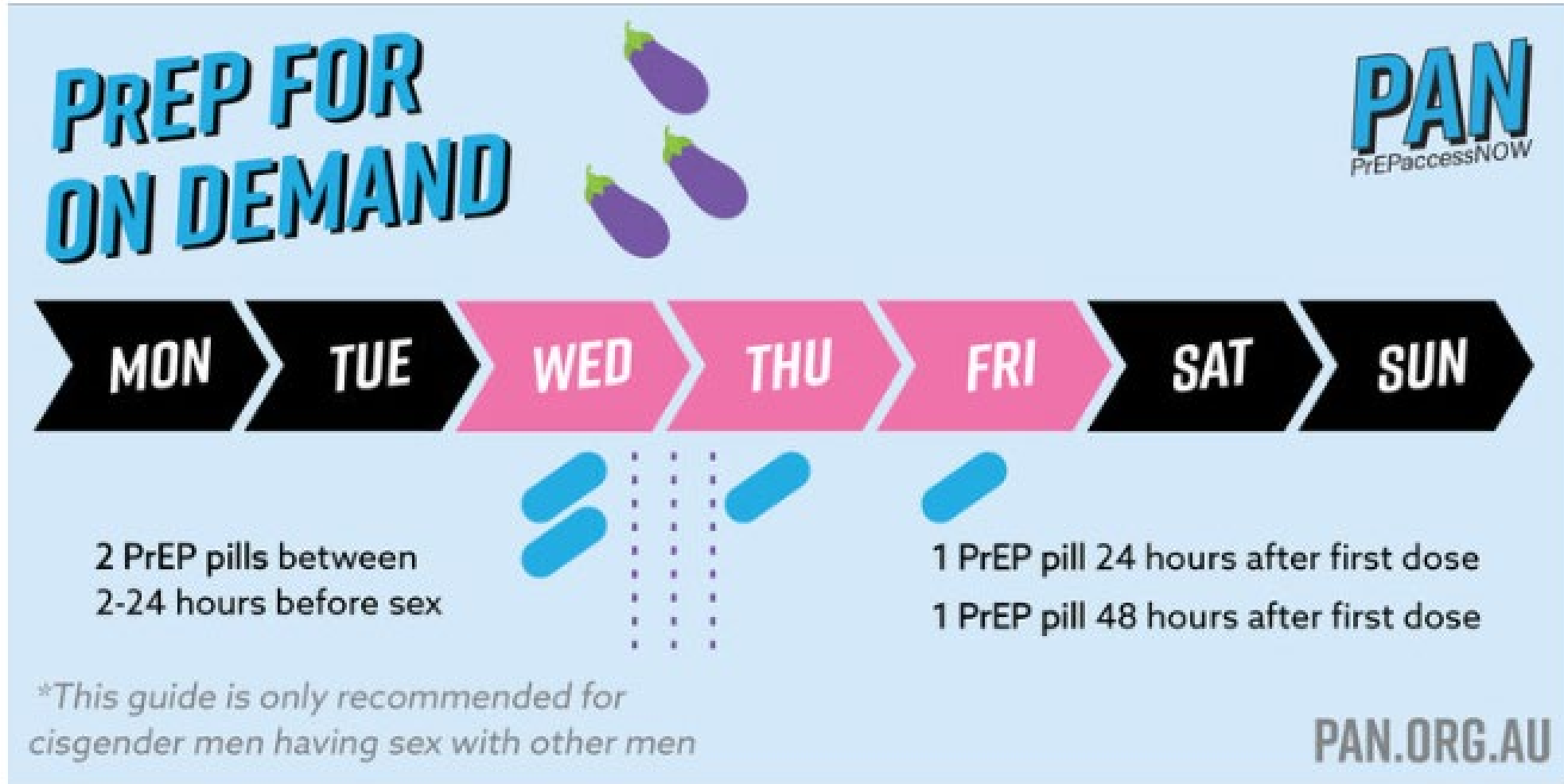
Impact of hormones on PrEP

Drug levels at sexual exposure sites

Alternative Event-Driven PrEP options

# Event-Driven PrEP

(aka 2-1-1 PrEP, aka On Demand PrEP)

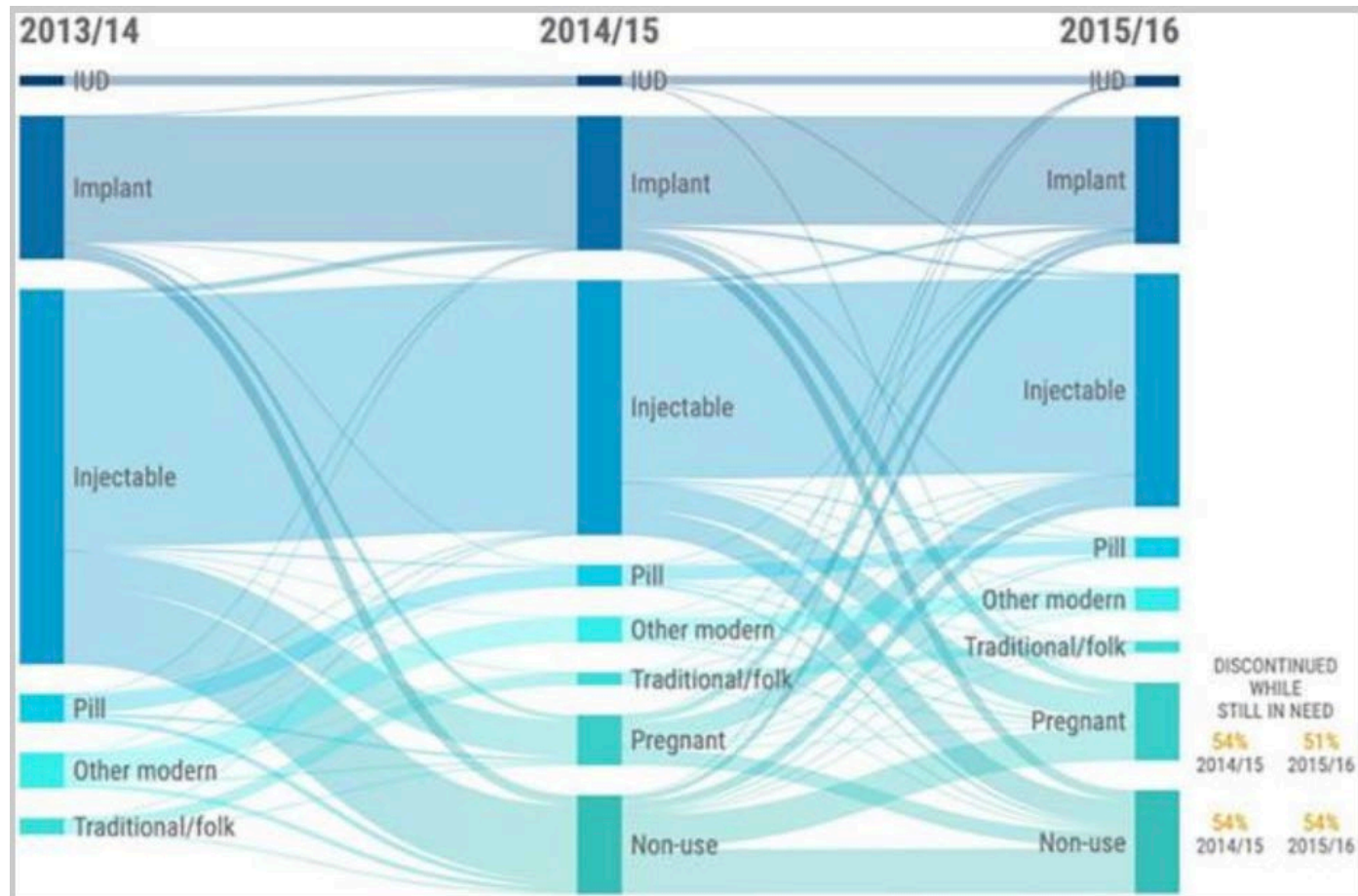


\*\*PrEP pill =  
tenofovir  
disoproxil  
fumarate (TDF)  
300mg -  
emtricitabine  
(FTC) 200mg



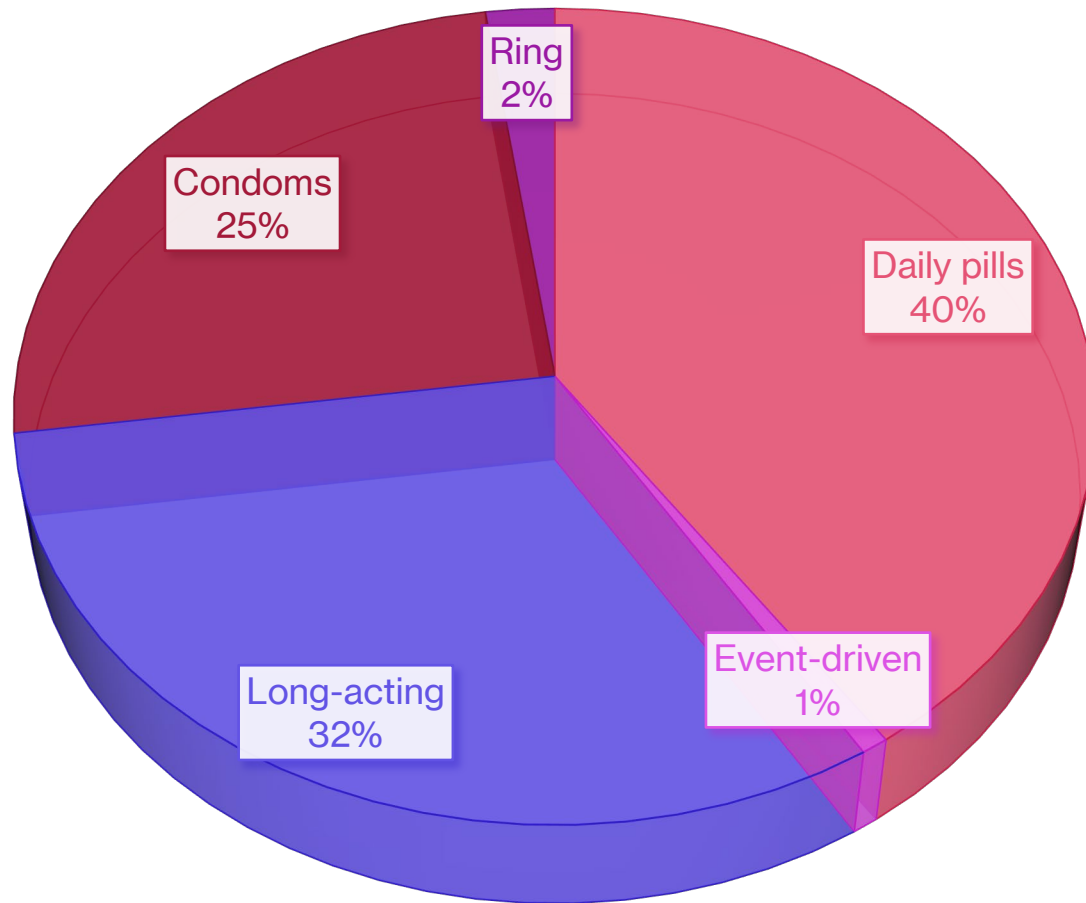
# Importance of choice and flexibility – as observed with contraceptive

Malawi: 2013-2016



# Importance of choice and flexibility – as observed with contraceptive

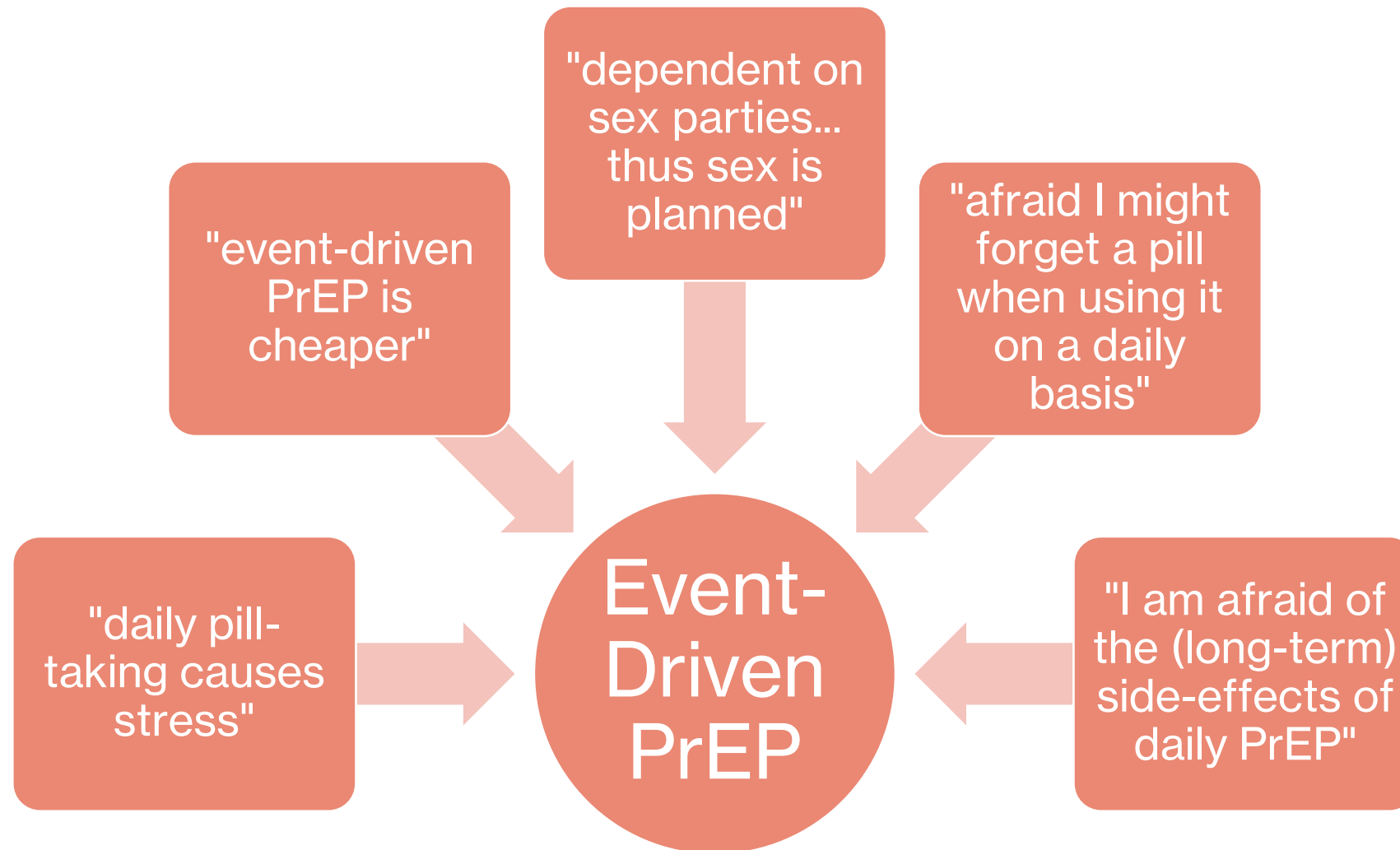
USA: 2018



23%

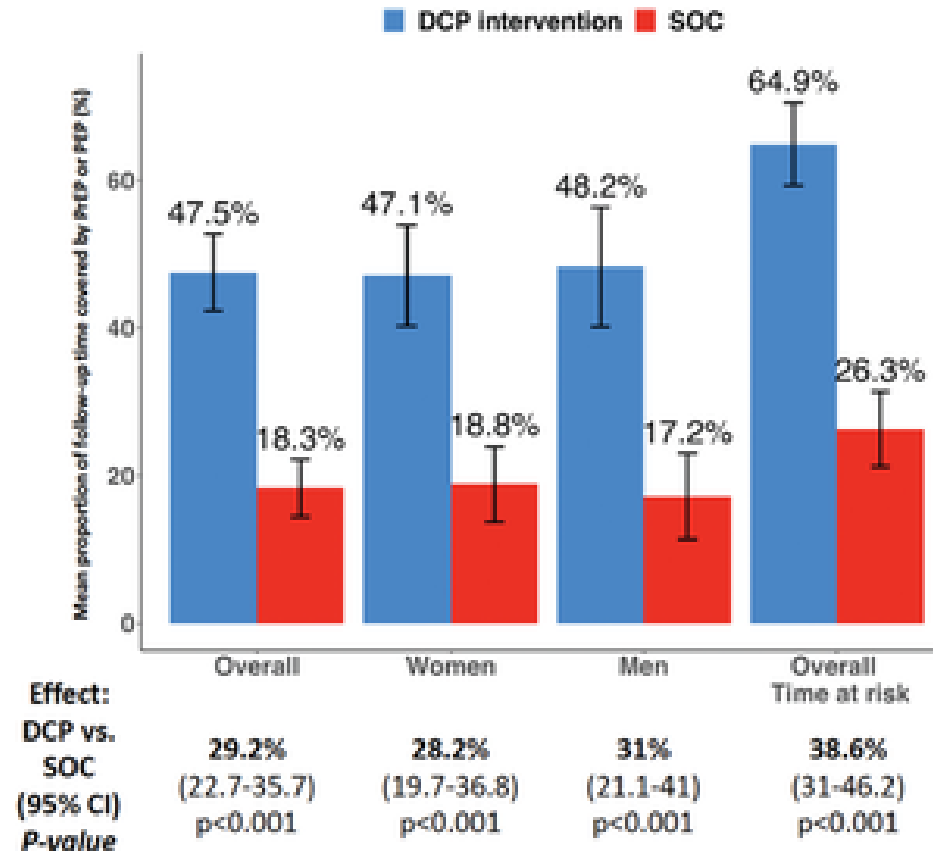
of sexually experienced U.S. women aged 15–44 in 2015 had ever used emergency contraceptive pills, up from 11% in 2008 <sup>4</sup>

# Diversity in motivation for event-driven PrEP



# PrEP Method Choice Is Key

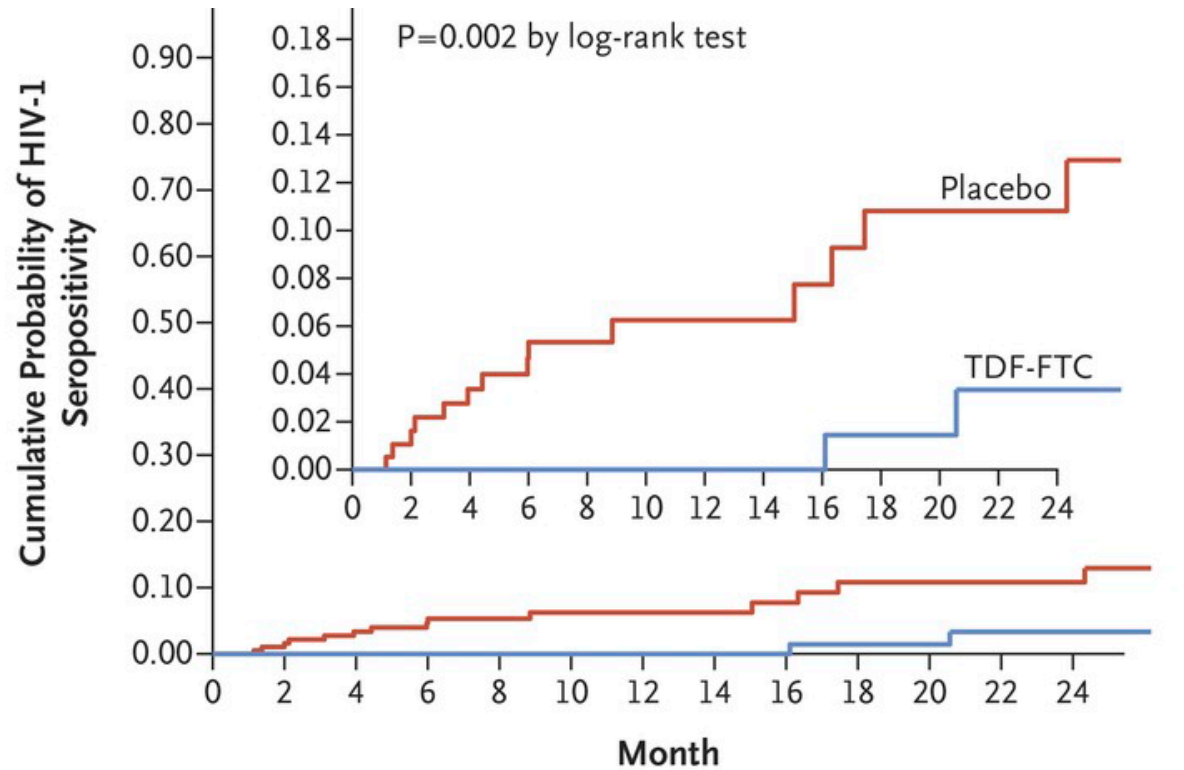
The SEARCH Trial of 403 people in Uganda and Kenya evaluated proportion of time covered by preexposure prophylaxis or postexposure prophylaxis, by arm.



# Proven efficacy in placebo-controlled RCT

ORIGINAL ARTICLE

## On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection



### No. at Risk

Placebo	201	141	74	55	42
TDF-FTC	199	141	82	58	43

400 MSM mostly in France (43 in Canada)

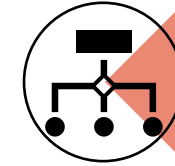
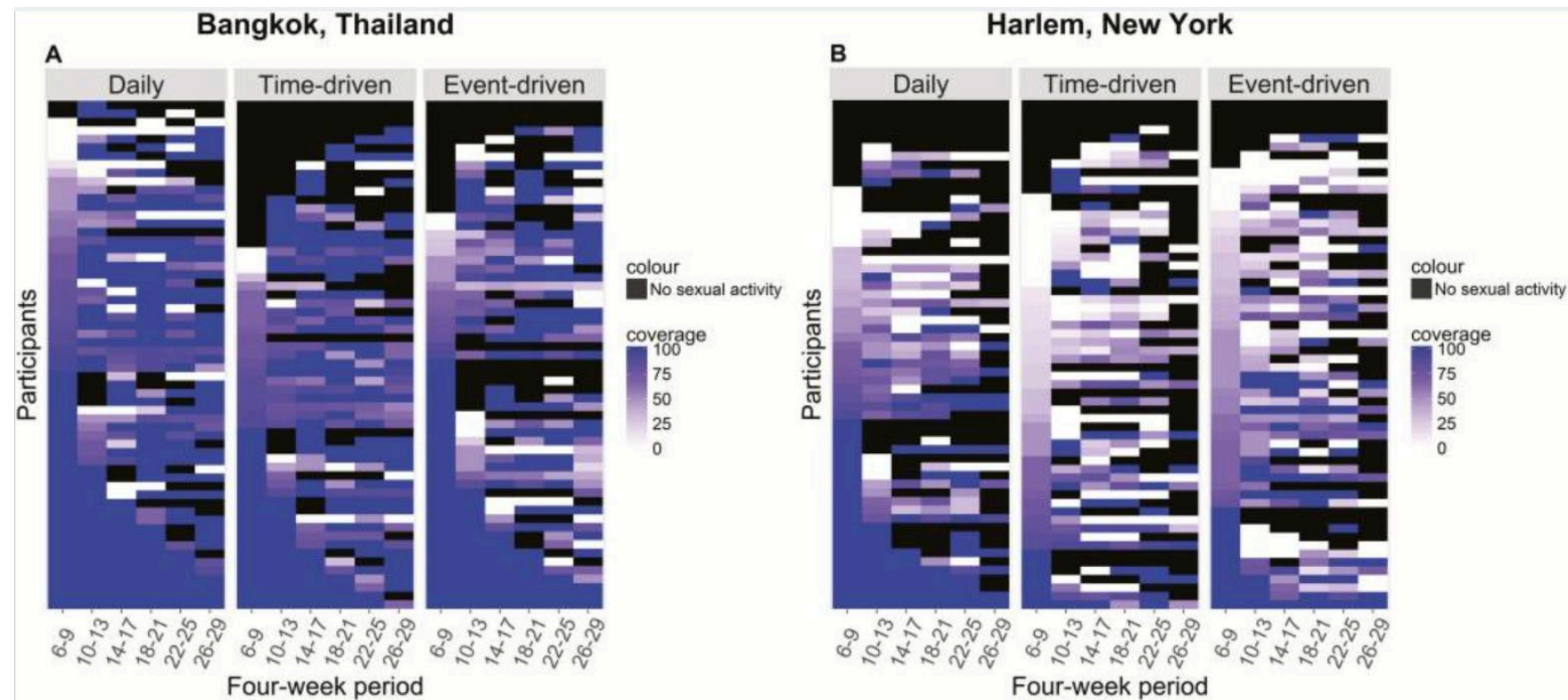
16 HIV infections with 2 assigned to event-driven PrEP for 86% reduction in HIV (P=0.002).

Breakthrough infections were due to nonuse

Median of 4 pills per week

ANRS IPERGAY  
Molina et al, NEJM, 2015

# Higher coverage when assigned to daily use



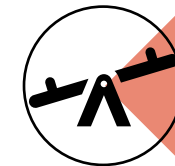
Randomized, open-label 1:1:1 assigned to daily, weekly, or pre-/post-sex PrEP (2012-2014)



357 MSM were enrolled in Thailand and the USA.

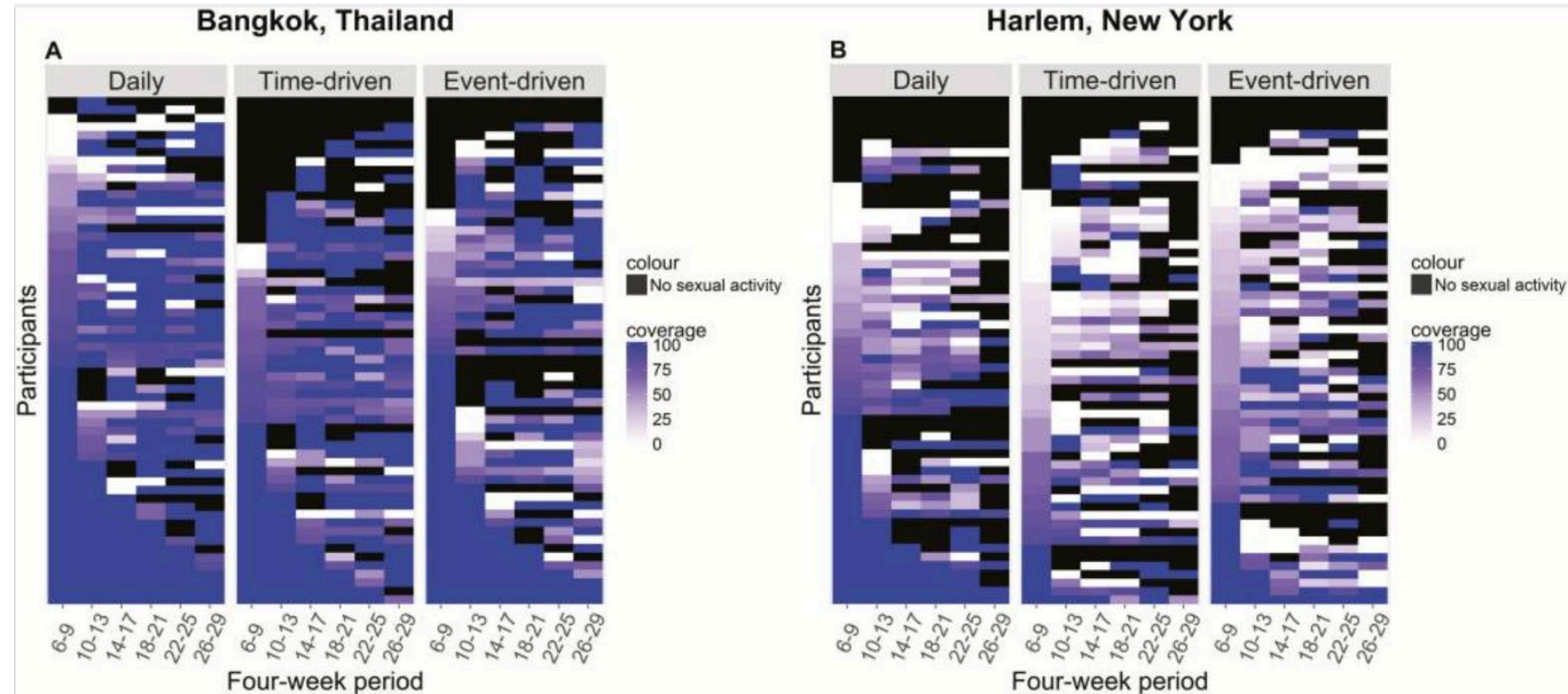


In Bangkok, coverage didn't differ by arm (85% v 79%);



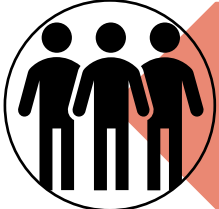
In Harlem, decreased coverage with pre-/post- (41%) compared with daily (65%)

# Higher coverage when assigned to daily use but effective with intermittent use

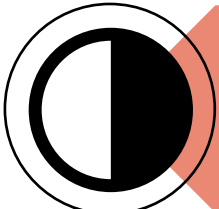


One seroconversion:  
among a participant  
in Harlem assigned  
daily PrEP.

# Event-driven PrEP is utilized in cohort study



3065 mostly MSM  
(TGW <1%) in France



50% chose event-driven with  
41% using method flexibility



Median of 3 pills/week with  
event driven and 5 pills/week  
with daily

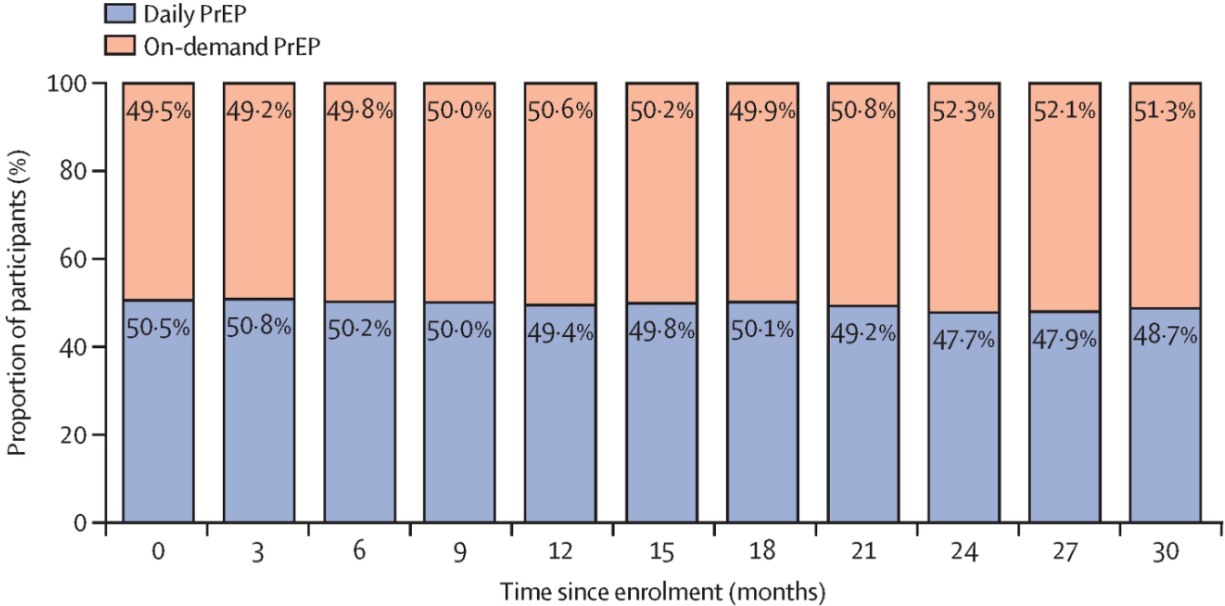


Figure 2  
Proportions of participants using each PrEP dosing regimen over time  
PrEP=pre-exposure prophylaxis.



# Event-driven PrEP is effective in cohort study

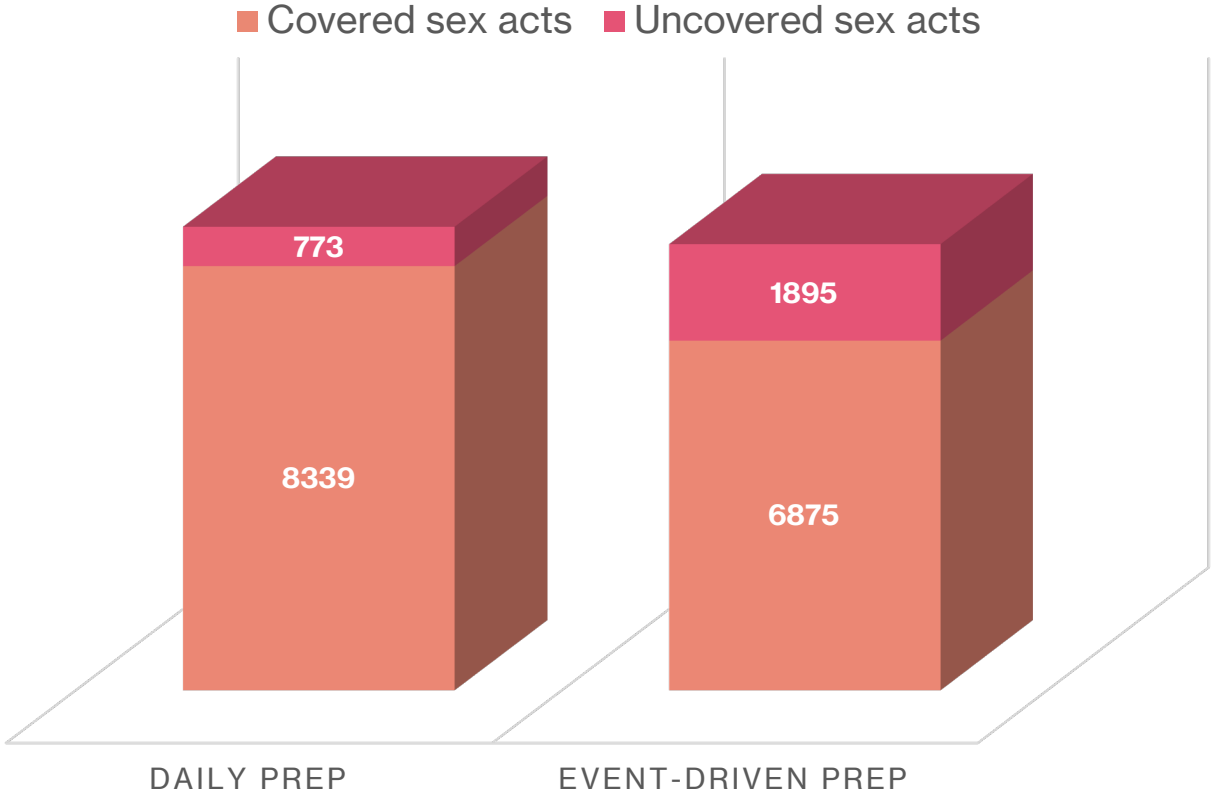


92% coverage with daily PrEP vs. 78% coverage with event-driven PrEP

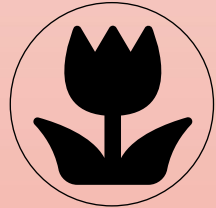


6 incident HIV: 3 on daily and 3 on event-driven

## COVERAGE OF SEX ACTS WITH PREP



# Real-world evidence in multiple countries



Amsterdam,  
**Netherlands**<sup>1</sup>  
2015-2016

374 MSM  
+ 2 TGW



Antwerp,  
**Belgium**<sup>2</sup>  
2017-2018

200 MSM



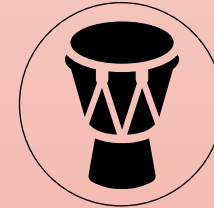
Kaohsiung City,  
Taipei City, and  
Tainan City,  
**Taiwan**<sup>3</sup>  
2018-2019

374 MSM



San Francisco,  
**USA**<sup>4</sup>  
2019

2338 MSM

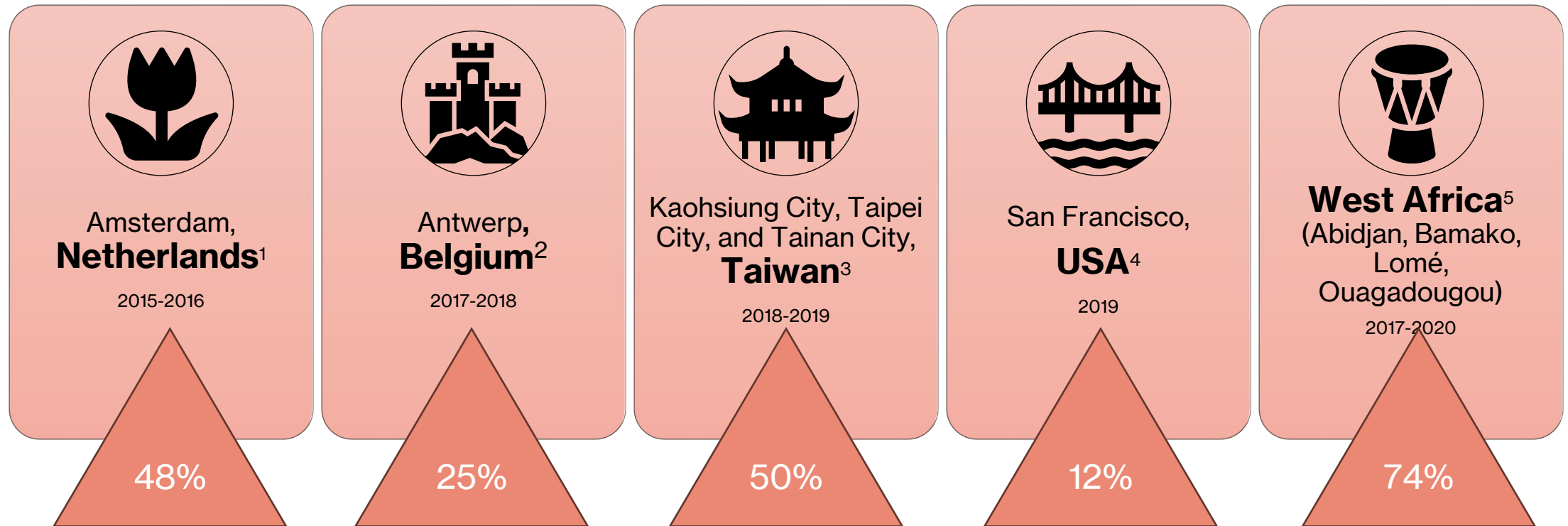


**West Africa**<sup>5</sup>  
(Abidjan, Bamako,  
Lomé,  
Ouagadougou)  
2017-2020

598 MSM

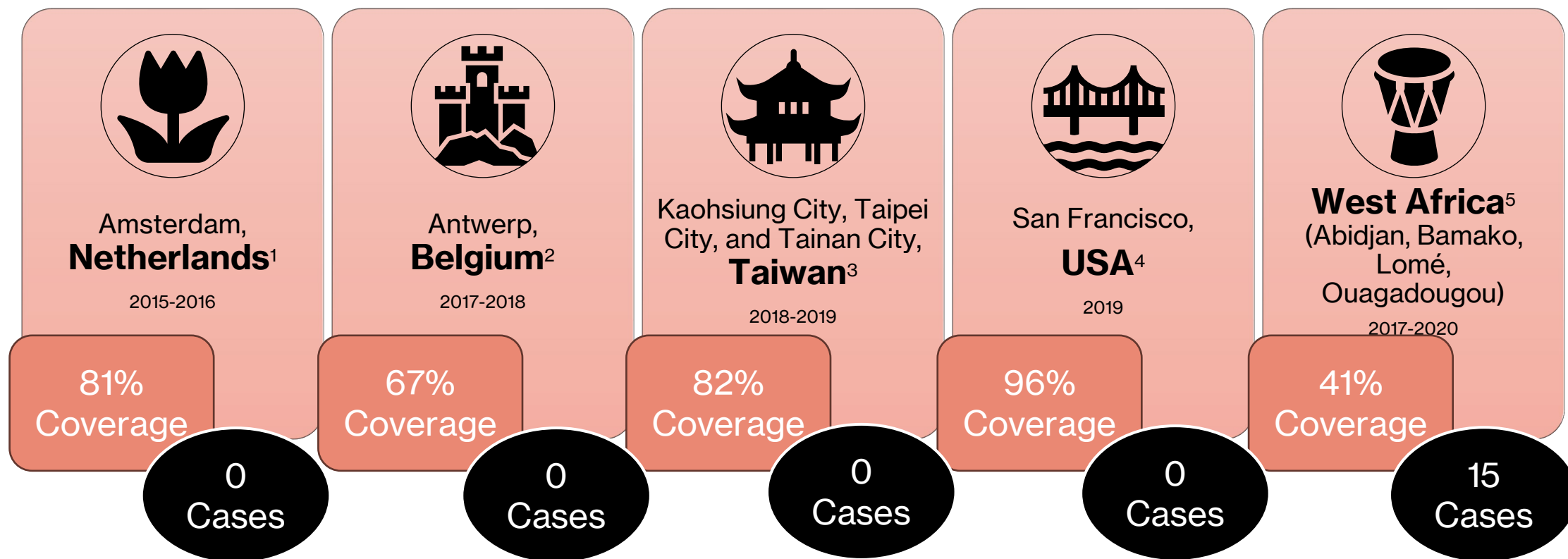
<sup>1</sup>Hoornenborg et al, Lancet HIV, 2019; <sup>2</sup>Vuylsteke et al, JIAS, 2019; <sup>3</sup> Wu et al, JIAS, 2021;  
<sup>4</sup>Hojilla et al, CID, 2020; <sup>5</sup>Laurent et al, Lancet HIV, 2021;

# Uptake of event-driven PrEP across settings



<sup>1</sup>Hoornenborg et al, Lancet HIV, 2019; <sup>2</sup>Vuylsteke et al, JIAS, 2019; <sup>3</sup> Wu et al, JIAS, 2021; <sup>4</sup>Hojilla et al, CID, 2020; <sup>5</sup>Laurent et al, Lancet HIV, 2021;

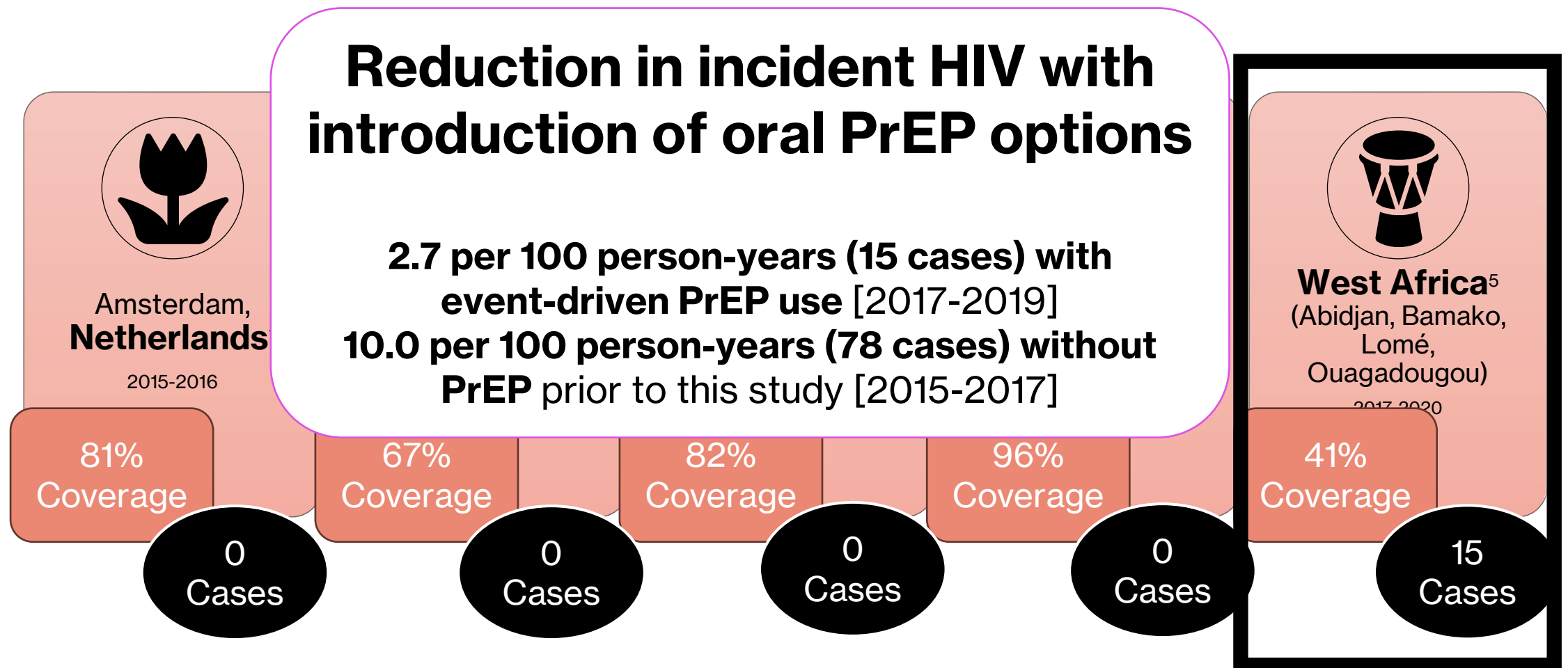
# Imperfect coverage yet effective



<sup>1</sup>Hoornenborg et al, Lancet HIV, 2019; <sup>2</sup>Vuylsteke et al, JIAS, 2019; <sup>3</sup> Wu et al, JIAS, 2021;

<sup>4</sup>Hojilla et al, CID, 2020; <sup>5</sup>Laurent et al, Lancet HIV, 2021;

# Imperfect coverage yet effective

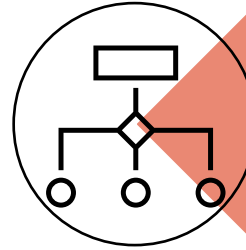


<sup>1</sup>Hoornenborg et al, Lancet HIV, 2019; <sup>2</sup>Vuylsteke et al, JIAS, 2019; <sup>3</sup> Wu et al, JIAS, 2021;

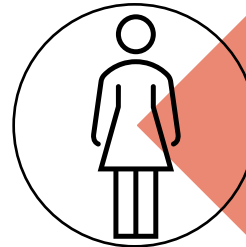
<sup>4</sup>Hojilla et al, CID, 2020; <sup>5</sup>Laurent et al, Lancet HIV, 2021;

# Decreased coverage when assigned to take intermittent PrEP

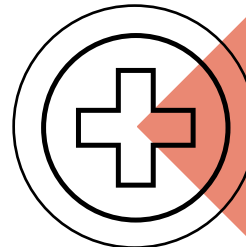
**Decreased coverage with event-driven pre/post PrEP compared with daily PrEP (52% vs 75%)**



Randomized, open-label 1:1:1 assigned to daily, weekly, or pre/post PrEP (2012-2014)

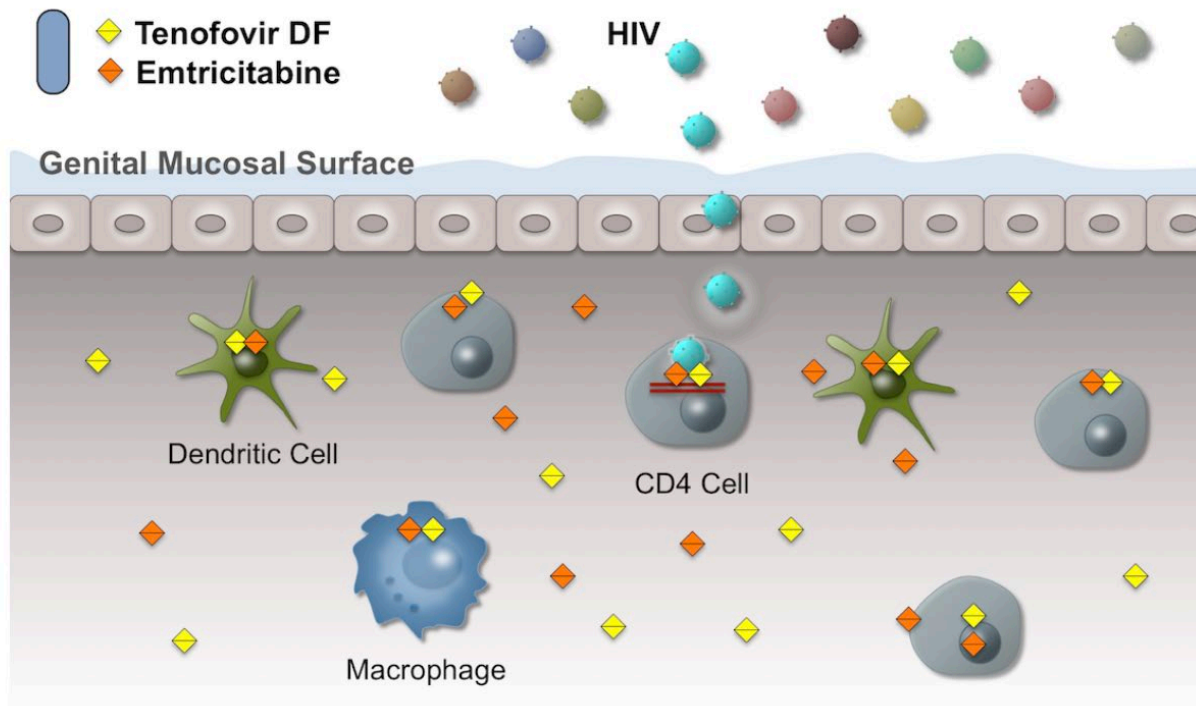


191 cisgender women in Cape Town, South Africa



Women in Cape Town had 4 seroconversions

- 2 among weekly group and 2 among with pre/post use



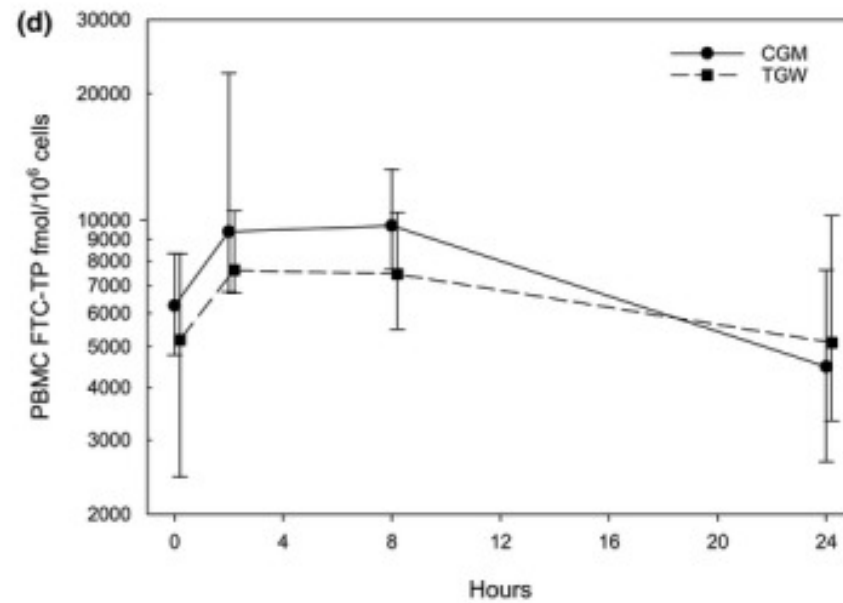
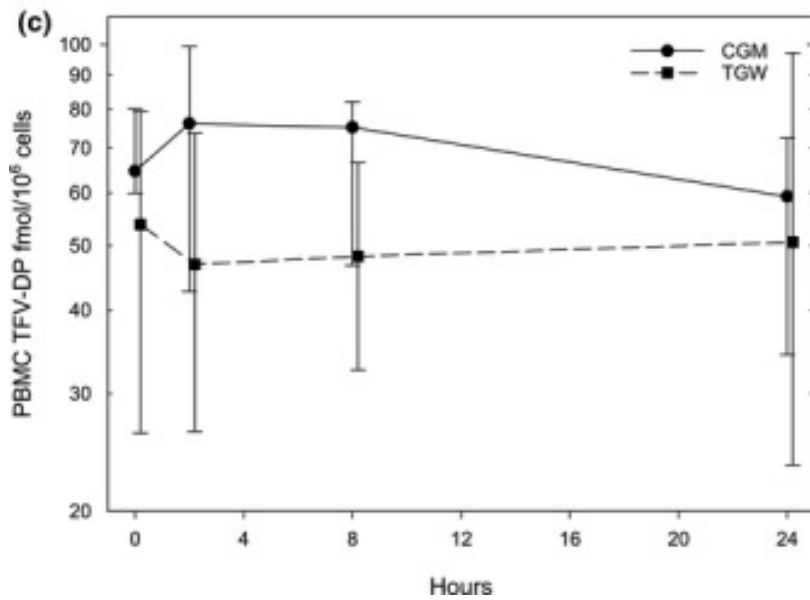
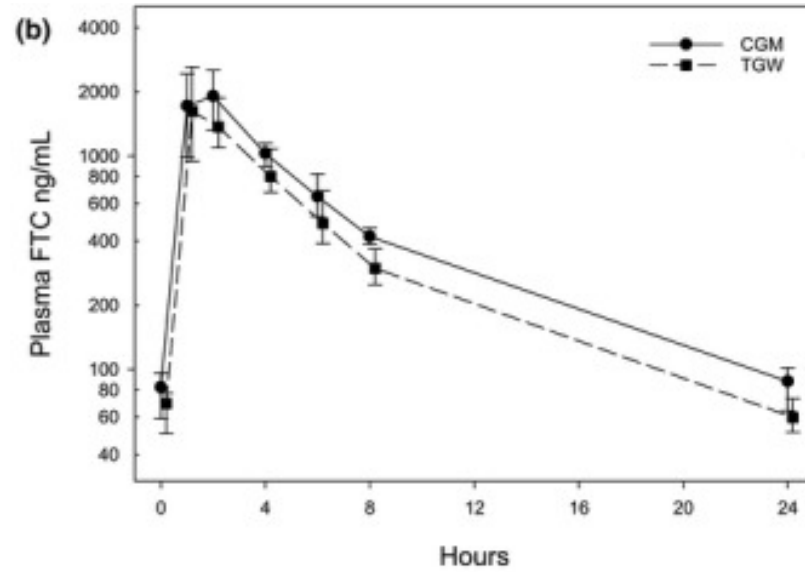
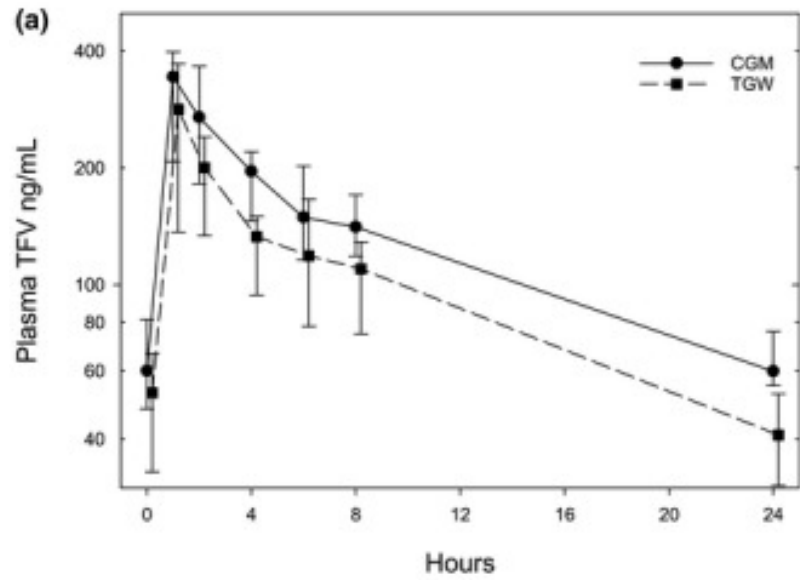
**Figure 2 (Image Series) - HIV PrEP for Sexual Transmission of HIV**  
**C. Tenofovir and Emtricitabine Blocking HIV Replication**

In an individual taking PrEP who has high intracellular levels of tenofovir diphosphate and emtricitabine triphosphate, HIV infection of submucosal cells results in a dead end, since the medications block HIV reverse transcription. Thus, in this situation, HIV transmission is blocked since HIV cannot replicate and spread to other cells.

Illustration by David H. Spach, MD

# HIV Prevention with TDF/FTC is in CD4 cells

PBMC = peripheral blood mononuclear cells



**Estrogen has minimal impact on TFV drug levels**



# Testosterone has minimal impact on TFV drug levels

Covariate	Assigned male at birth (n=27)			Assigned female at birth (n=12)		
	No GAHT (n=9)	GAHT (n=18)	p- value	No GAHT (n=2)	GAHT (n=10)	p- value
TFV-DP while on TDF/FTC in fmol/punch, median (IQR)	1839 (1131 – 2014)	1657 (1486 – 2280)	0.50	1643 (1188 – N/A) <sup>b</sup>	1607 (796 – 2174)	0.21
TFV-DP while on TAF/FTC in fmol/punches	2842 (2375 – 3474)	3252 (2384 – 4365)	0.40	1246 (266 – N/A) <sup>b</sup>	2528 (1202 – 2836)	0.37

# Data from Cabotegravir suggests efficacy with low rectal drug levels

Tissue Type	400 mg IM Unsplit (Cohort 8) (n = 4/Visit)			400 mg IM Split (2 × 200 mg IM, Cohort 9) (n = 4/Visit)		
	Week 2 (µg/g)	Week 8 (µg/g)	Overall Tissue:Plasma	Week 4	Week 12	Overall Tissue:Plasma
Cervical	0.081 (NQ-0.17)	0.096 (0.06–0.19)	0.20 (0.0–0.40)	0.177 (0.07–0.50)	0.133 (NQ-0.21) <sup>†</sup>	0.16 (0.0–0.4)
Vaginal	0.121 (NQ-0.18)	0.184 (0.09–0.44)	0.28 (0.0–0.7)	0.155 (NQ-0.90)	0.181 (NQ-0.35)	0.19 (0.0–0.7)
Rectal	NQ (NQ-0.10)	NQ (NQ-0.05)	0.00 (0.0–0.1)	0.079 (NQ-0.20)	0.063 (NQ-0.08)	0.08 (0.0–0.2)

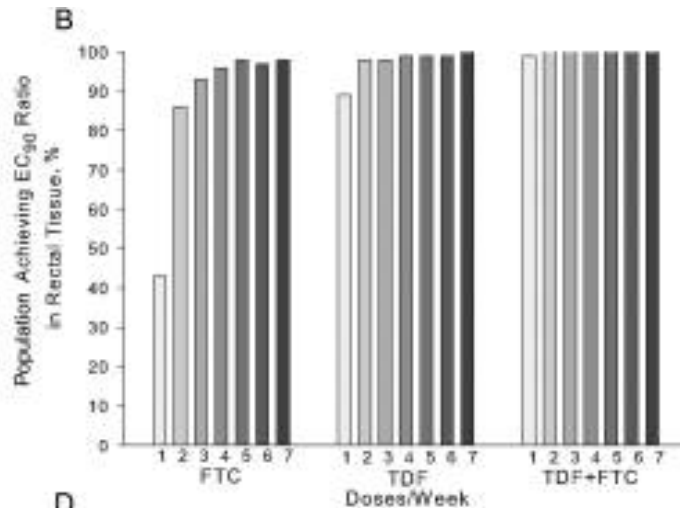
\*Median (range).  
<sup>†</sup>n = 3.  
 NQ, nonquantifiable concentration measured as below the lower limit of quantitation (50 µg/g).

Phase I – open label of 8 participants receiving CAB-LA IM:  
 4 cisgender men and 4 cisgender women  
 Sample collection at weeks 2, 4, 8, and 12

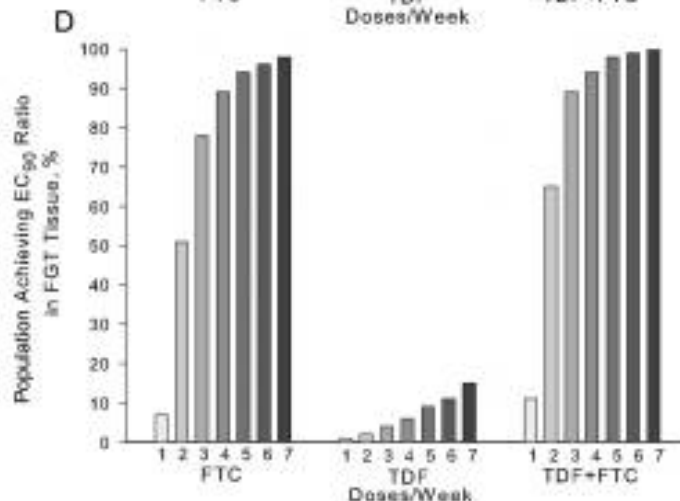
# TDF drug levels are higher in rectum than vagina

47 cisgender women given TDF/FTC to predict time to protective EC90

Rectal Tissue



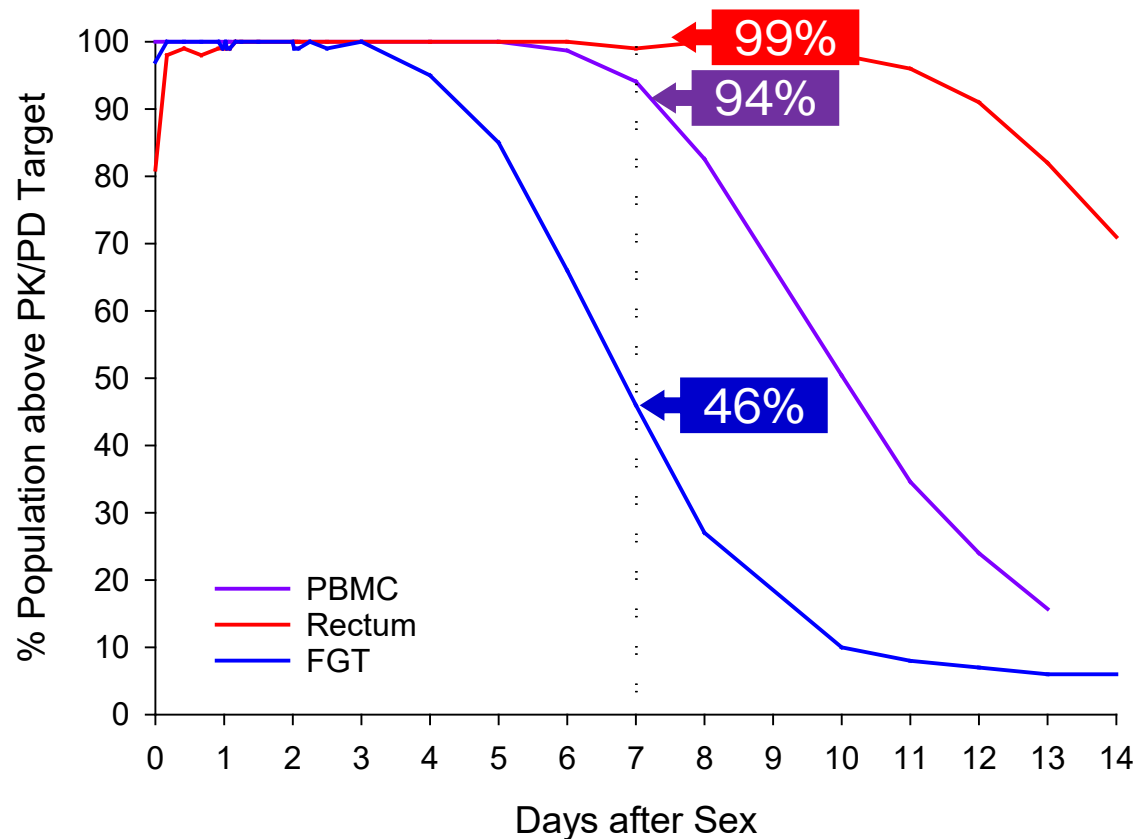
Vaginal Tissue



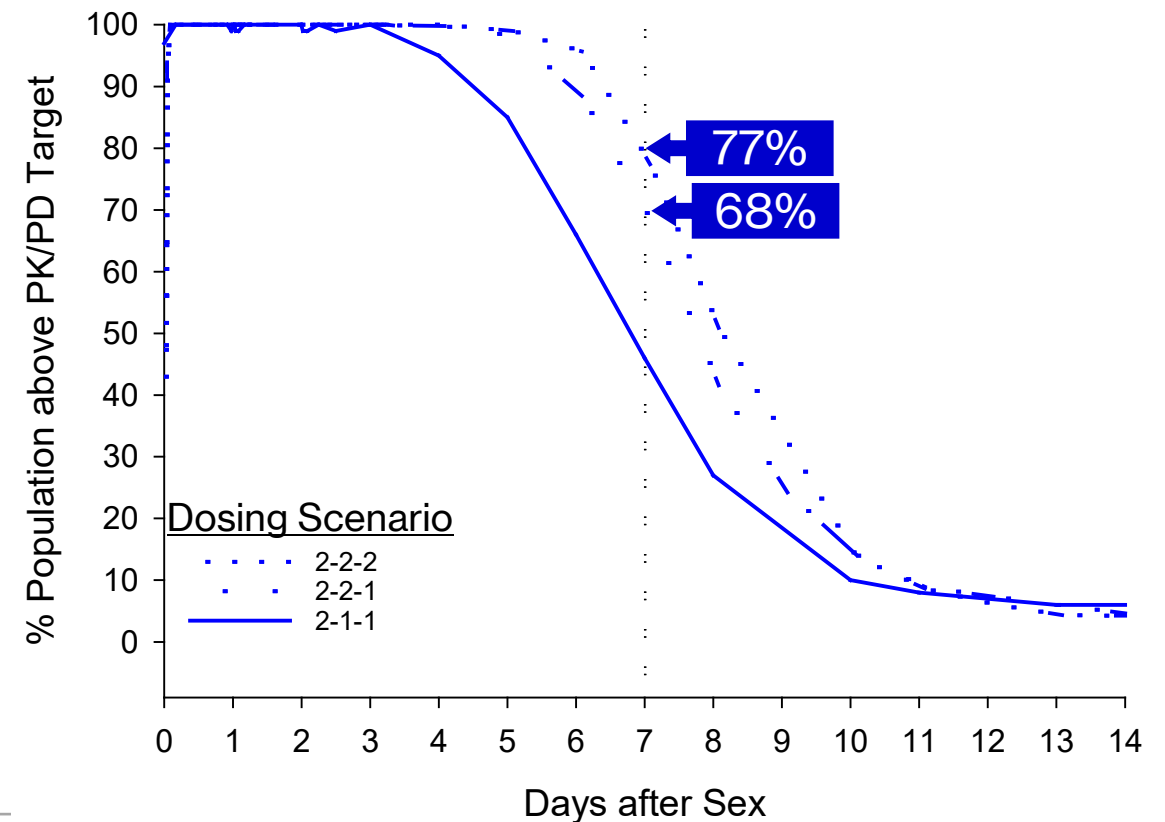
Daily TDF/FTC is proven to be protective for vaginal/front sex

# Modeling & Simulation to Optimize Event-Driven PrEP dosing for AFAB

Lowest 2-1-1 efficacy predicted in FGT vs blood and rectum



2-2-2 dosing increases predicted efficacy in FGT by >30%

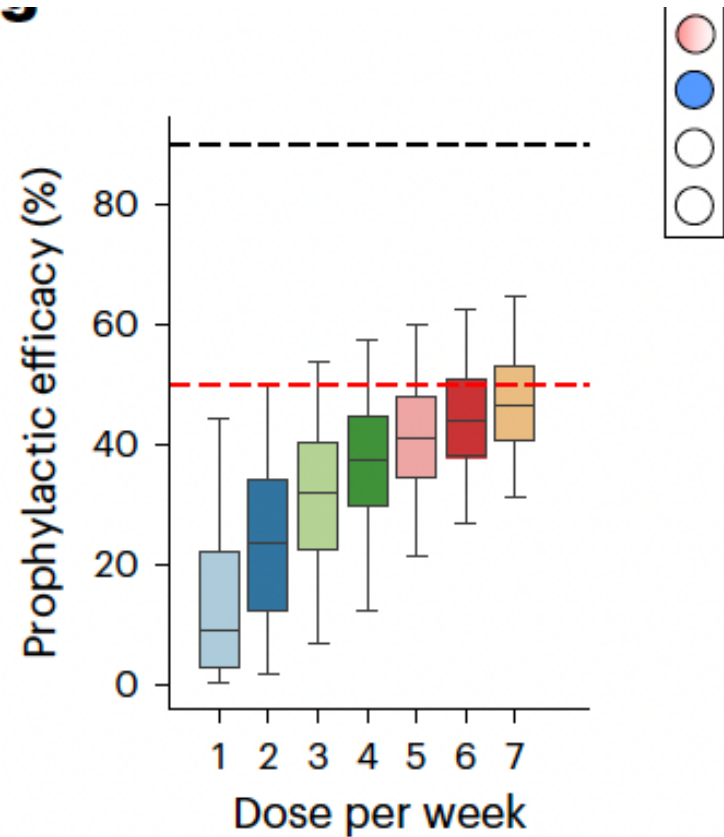


Adapted from Cottrell ML et al. *J Infect Dis.* 2016 Jul 1;214(1):55-64 and Garrett KL et al. *J Pharmacol Exp Ther.* 2018 Nov; 367 (2):245-251.

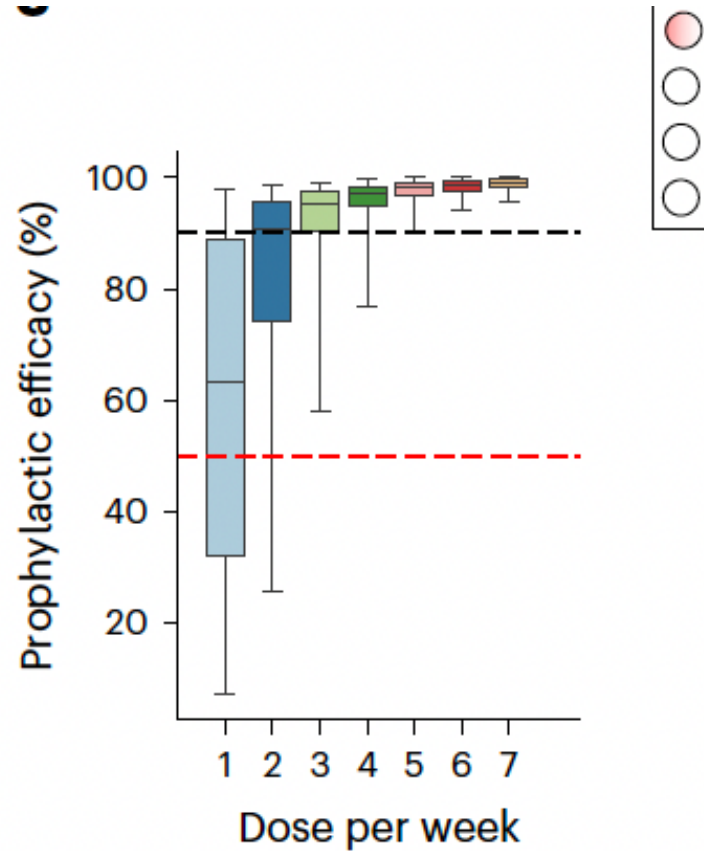
Simulations by Dumond JB using Leung et al *CPT PSP* 2023 (12):1922-1930.

# Clinical data incongruent with vaginal drug levels

Estimates of dose-dependent effectiveness based on vaginal PK data



Estimates of dose-dependent effectiveness based on PBMC PK data



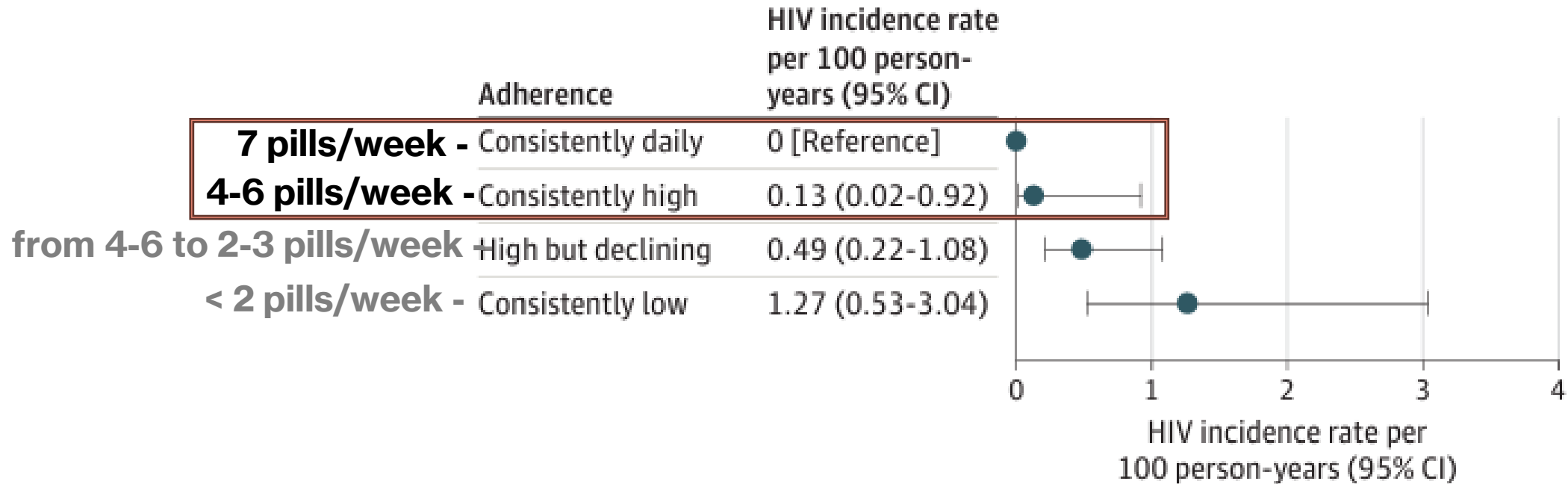
# PrEP Efficacy Data Comparing Adherence Patterns among Cisgender Women

	Efficacy data source	Adherence or PK data source	Adherence patterns			
			<2 doses/ week	2-3 doses/ week	4-6 doses/ week	daily
Anderson et al, Sci Transl Med, 2021	iPrEX	PBMC adherence bands determined from directly observed dosing (STRAND)		76 (95% CI 56-96)	96 (95% CI 90->99)	99 (95% CI 96->99)
Anderson et al, CID, 2023	HPTN 083/084	DBS adherence bands determined from directly observed therapy	16 (95%CI 0-60)	80 (95%CI 32-97)	88 (95%CI 43-99)	99 (95%CI 0-99)
Cottrell et al, JID, 2016	In vitro EC <sub>90</sub> in CD4+ T cells	Population PK study built from directly observed dosing study	10% population >EC <sub>90</sub>	65% population >EC <sub>90</sub>	99% population >EC <sub>90</sub>	100% population >EC <sub>90</sub>
Moore et al, Nat Med, 2023	FEM-PrEP VOICE Partners PrEP	TFV plasma used to impute TFVdp and estimate adherence bands from HPTN 082		59 (95% CrI <sup>^</sup> 30-96)	84 (95% CrI <sup>^</sup> 52-100)	96 (95% CrI <sup>^</sup> 73-100)
Zhang et al, Nat Med, 2023	Molecular mechanism modeling	Simulated PBMC concentrations from population PK models	74 (95% CI 10-99)	96 (95% CI 58-99)	>99 (95% CI 96->99)	>99 (95% CI 99 ->99)
		Simulated tissue concentrations from population PK models	37 (95% CI 3-75)	64 (95% CI 25-84)	74 (95% CI 44-88 IQR)	78 (95% CI 52-89)

Table created by Melanie Nicol for manuscript under review. (Irie W et al.)

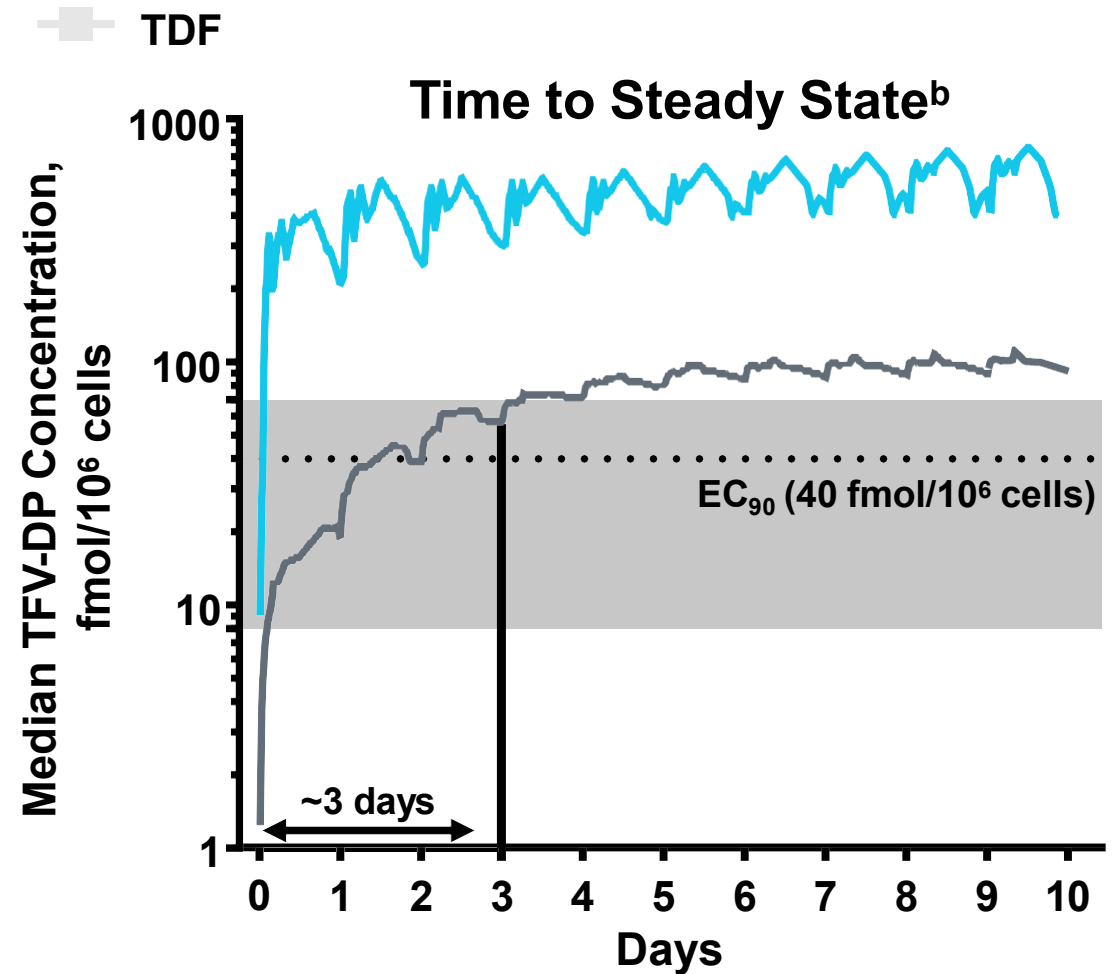
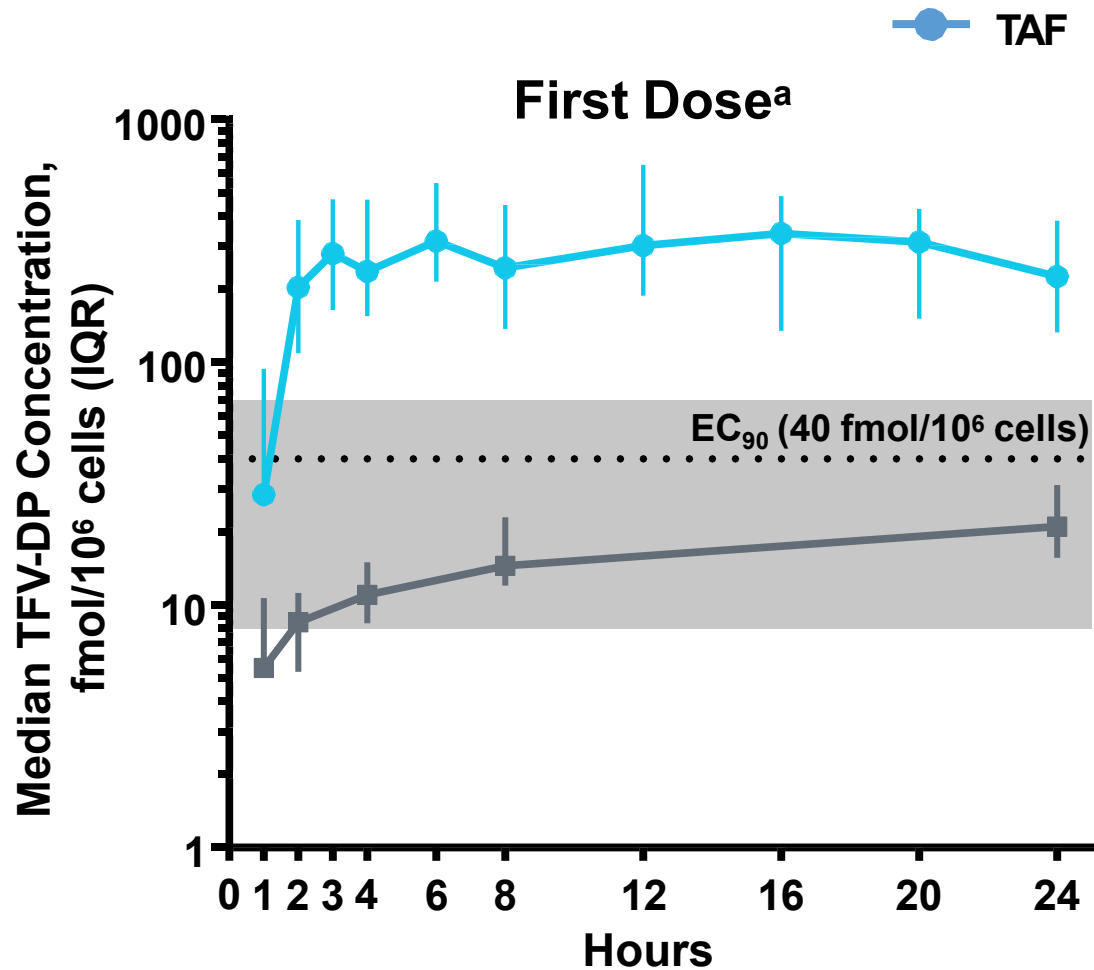
# Do vaginas demand perfection?

Figure 4. HIV Incidence Rates Among Cisgender Women by Adherence Trajectory (n = 2954)



Pooled data from 11 F/TDF PrEP studies among cisgender women in 6 countries [2012 to 2020]

# TAF has higher drug levels in PBMCs



EC<sub>90</sub>=90% effective concentration (40 fmoI/10<sup>6</sup> cells, Anderson PL, et al. CROI 2012); IQR=interquartile range.  
a. DVY data from bicitgravir/F/TAF 50/200/25 mg in volunteers (N=26) and TVD data from Schwartz JL, et al. HIV Research for Prevention 2018 (n=25), Cottrell 2017; b. Mean simulated time to steady state.

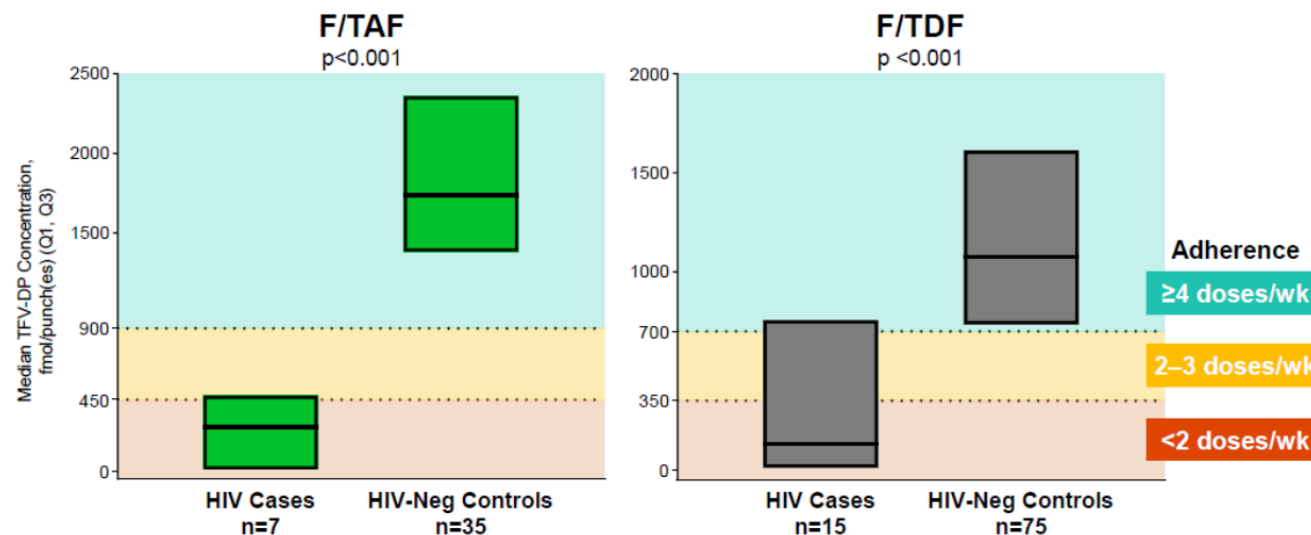


# TAF has potential for use in event-driven PrEP

## Adherence Levels Associated with TFV-DP Concentrations for F/TAF and F/TDF

Adherence Level	Doses/week	F/TAF TFV-DP fmol/punches	F/TDF TFV-DP fmol/punch
Low	<2 doses/week	<450	<350
Medium	≤2 to <4 doses/week	≥450 to <900	≥350 to <700
High	≥ 4 doses/week	≥900	≥700

Figure S3. Adherence by DBS at HIV Diagnosis Visit: Case-Control Study (Cases=22; Controls=109)



Yager et al, CROI, 2019  
 Meyer et al, Lancet, 2020

# Next steps

## Gender inclusive trials

- Need to assess PrEP effectiveness across a broader spectrum of individuals

## Identify Optimal Dosing Strategy

- Event-driven dosing may differ by sex and gender.

## Harm reduction approach to PrEP

- Choice is trauma-informed care, and some PrEP is better than no PrEP.
-

# Thank you



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