

# PrEP Update

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***AIDS Clinical Conference, January 2020***



# Disclosure

*Dr. Baeten's disclosure.*

The information or content or conclusions are those of the author and should not be construed as the official position or policy of nor should any endorsements be inferred by HRSA, HHS or the U.S. Government.



# 11 years ago

## Pre-exposure prophylaxis (PrEP) for HIV prevention: current studies and potential implementation

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Jared Baeten, MD, PhD  
University of Washington

AIDS Clinical Conference  
January 2009

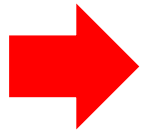


PARTNERS PrEP STUDY

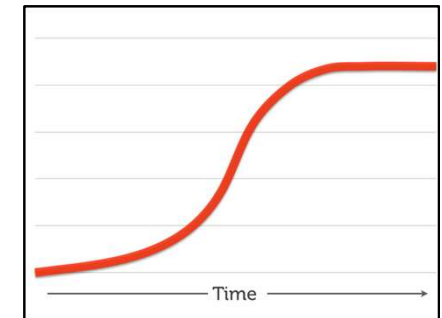
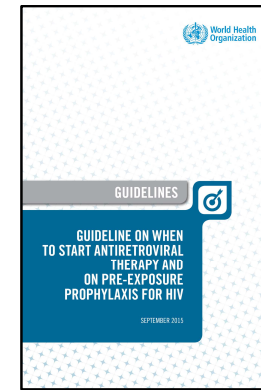
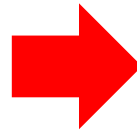
# A lot has happened...

- Clinical trials demonstrate oral TDF/FTC PrEP is effective and safe
- FDA/CDC/WHO/etc. recommendations
- Prescribing worldwide, including good amount of use in Seattle

# The reality of discovery to impact...



The NEW ENGLAND  
JOURNAL of MEDICINE

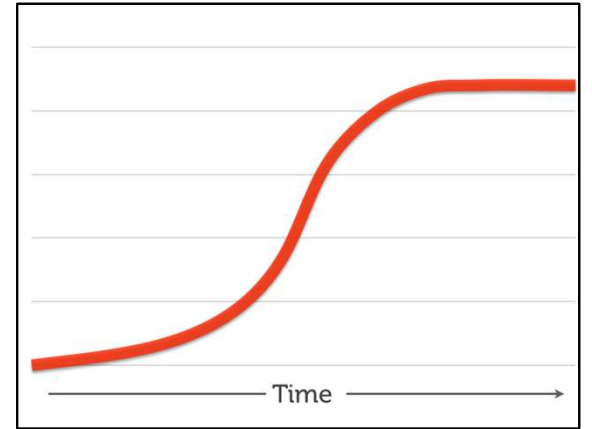




PrEP status



Recent research updates



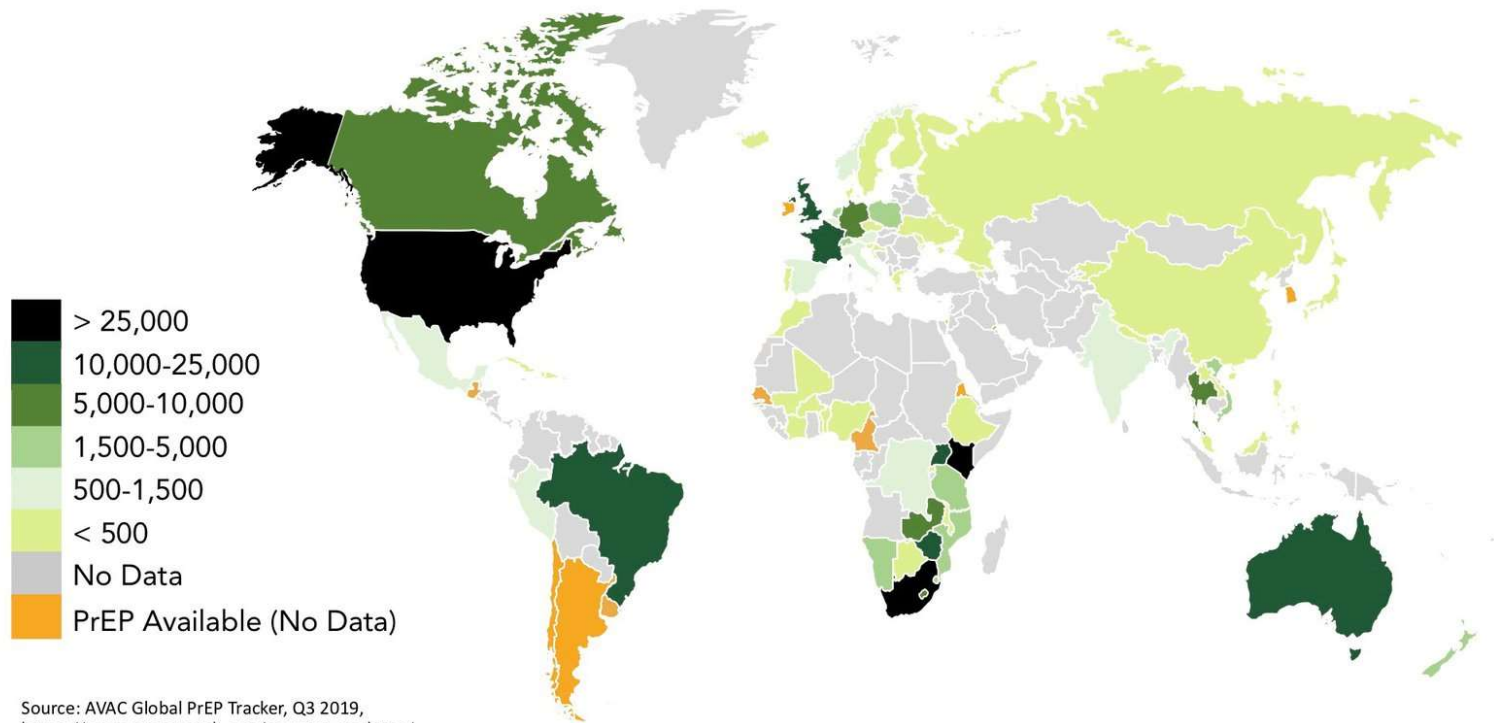
Defining success



PrEP status

# Global numbers

## PrEP Initiations by Country, October 2019



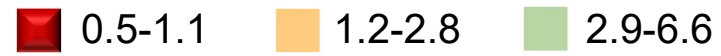
Source: AVAC Global PrEP Tracker, Q3 2019,  
<https://www.prepwatch.org/country-updates/>

**~400,000 on PrEP currently globally**

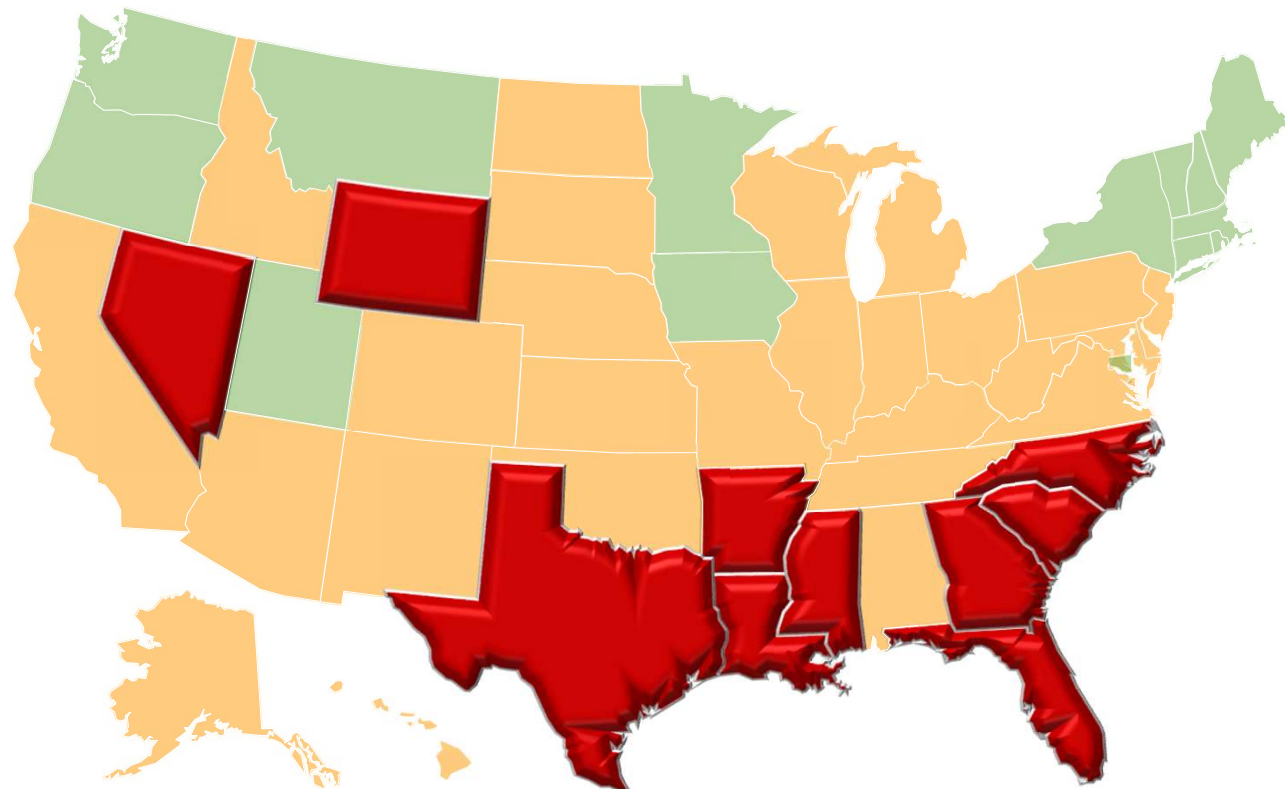


# US numbers

## Ratio New PrEP Rx:HIV Dx



Active PrEP prescriptions  
for Q4 2017 (n=70,395)



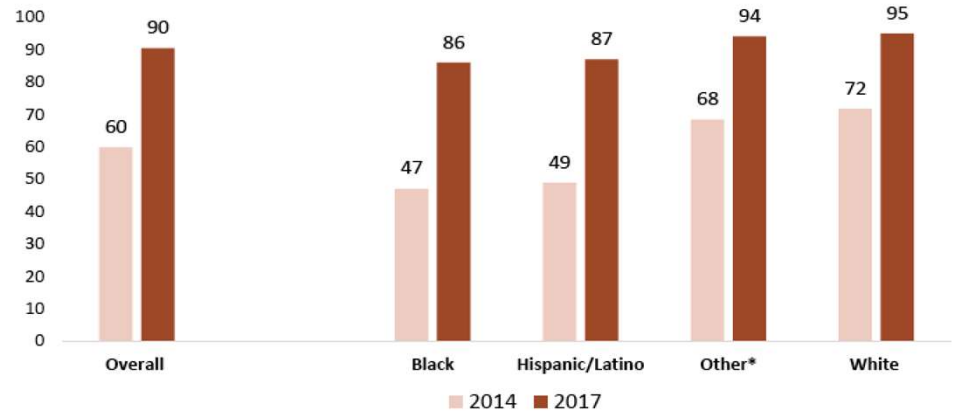
# US PrEP awareness & use

- 50% increase in awareness in US MSM
- 500% increase in use

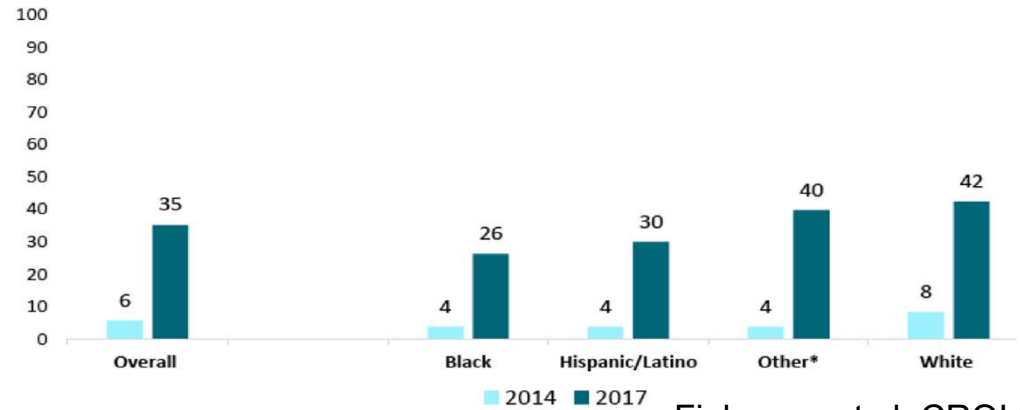


Data from NHBS

Percentage of MSM at risk for HIV infection<sup>5</sup> who reported PrEP awareness, 2014 and 2017



Percentage of MSM at risk for HIV infection<sup>5</sup> who reported PrEP use, 2014 and 2017

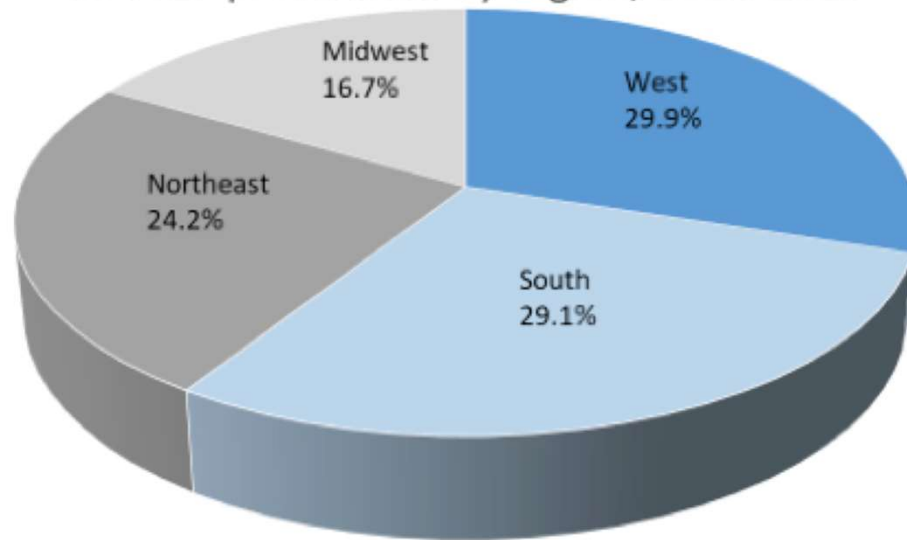


Finlayson et al. CROI 2019.

# US prescribers

**5-fold increase in prescriber #s 2014-2017: 6K to 35K**

US PrEP prescribers by region, 2014-2017



# USPSTF

JAMA | US Preventive Services Task Force | **RECOMMENDATION STATEMENT**

## Preexposure Prophylaxis for the Prevention of HIV Infection US Preventive Services Task Force Recommendation Statement

**CONCLUSIONS AND RECOMMENDATION** The USPSTF recommends offering PrEP with effective antiretroviral therapy to persons at high risk of HIV acquisition.  
(A recommendation)



Owens et al. JAMA 2019.

# Ending the HIV Epidemic

EDITORIAL

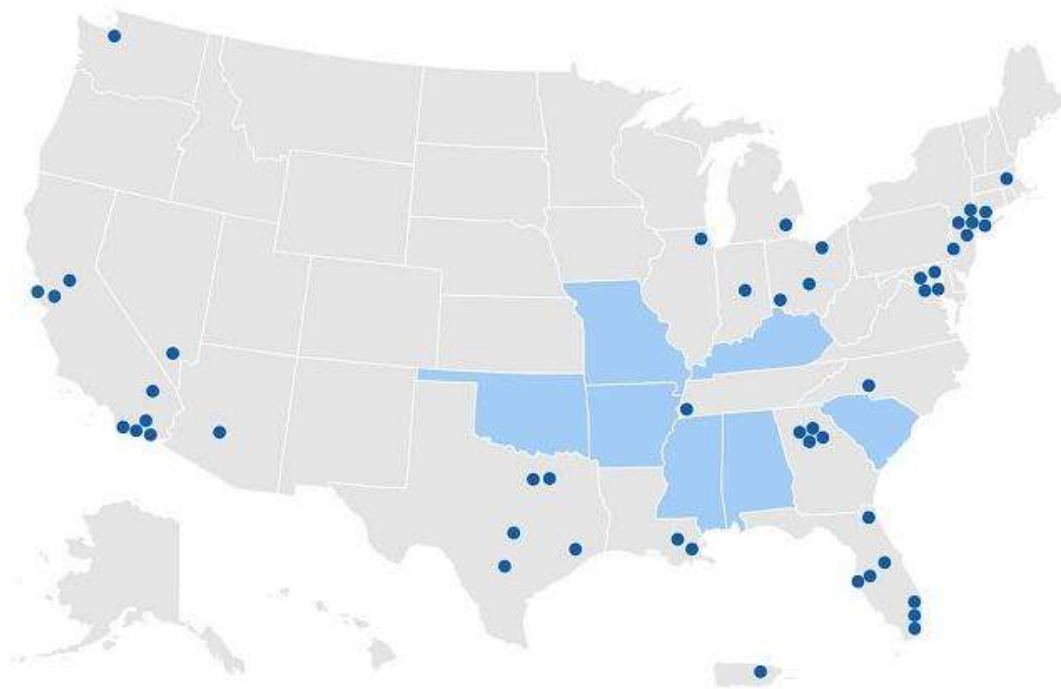
## Ending the HIV Epidemic A Plan for the United States

Anthony S. Fauci, MD; Robert R. Redfield, MD; George Stgounas, MS, PhD;  
Michael D. Weahkee, MHA, MBA; Brett P. Giroir, MD

The strategic initiative includes 4 pillars:

1. diagnose all individuals with HIV as early as possible after infection;
2. treat HIV infection rapidly and effectively to achieve sustained viral suppression;
3. prevent at-risk individuals from acquiring HIV infection, including the use of pre-exposure prophylaxis (PrEP); and
4. rapidly detect and respond to emerging clusters of HIV infection to further reduce new transmissions.

# Ending the HIV Epidemic






## GOAL:

**75%**  
reduction in new  
HIV infections  
in 5 years  
and at least  
**90%**  
reduction  
in 10 years.

Source = HRSA

# PrEP as part of EHE

Center for Disease Control and Prevention  
**MMWR** | **PrEP: An Essential Tool to End HIV**

Pre-exposure Prophylaxis (PrEP)	More PrEP Use is Needed	Healthcare Providers Can Help End HIV!
<ul style="list-style-type: none"><li>• A powerful way to prevent HIV</li><li>• Used daily, PrEP dramatically reduces risk of acquiring HIV through sex</li></ul> 	 <p>PrEP use up from 6% to 35% among MSM**</p> <p>PrEP use <b>still too low</b>, especially among Black and Hispanic MSM</p>	<ul style="list-style-type: none"><li>✓ Test for HIV</li><li>✓ Assess patient risk</li><li>✓ Prescribe PrEP as needed</li><li>✓ Use CDC resources*</li></ul> 

Footnote: Data from CDC's National HIV Behavioral Surveillance (NHBS) (20 cities) as reported in Fodayson et al. MMWR 2018. <http://bit.ly/CDCNA29>  
\*PrEP clinical practice guidelines. <https://www.cdc.gov/hiv/pdf/tra/prp/cdc-hiv-prp-guidelines-2017.pdf>  
\*\*Men who have sex with men

WWW.CDC.GOV

# UNAIDS – 3M on PrEP by 2020...



**FAST-TRACK  
COMMITMENTS  
TO END AIDS  
BY 2030**

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- Ensure that 90% of people at risk of HIV infection have access to comprehensive HIV prevention services, including sex workers and their clients, men who have sex with men, transgender people, people who inject drugs and prisoners.
- Ensure that 90% of young people have the skills, knowledge and capacity to protect themselves from HIV.
- Ensure universal access to quality and affordable sexual and reproductive health-care services, including HIV services, for women.
- Ensure access to harm reduction programmes.
- Reach 3 million people with pre-exposure prophylaxis by 2020.
- Reach 25 million men with voluntary medical male circumcision in high-incidence countries by 2020.
- Make 20 billion condoms available annually by 2020 in low- and middle-income countries.
- Invest at least a quarter of AIDS spending on HIV prevention by 2020.





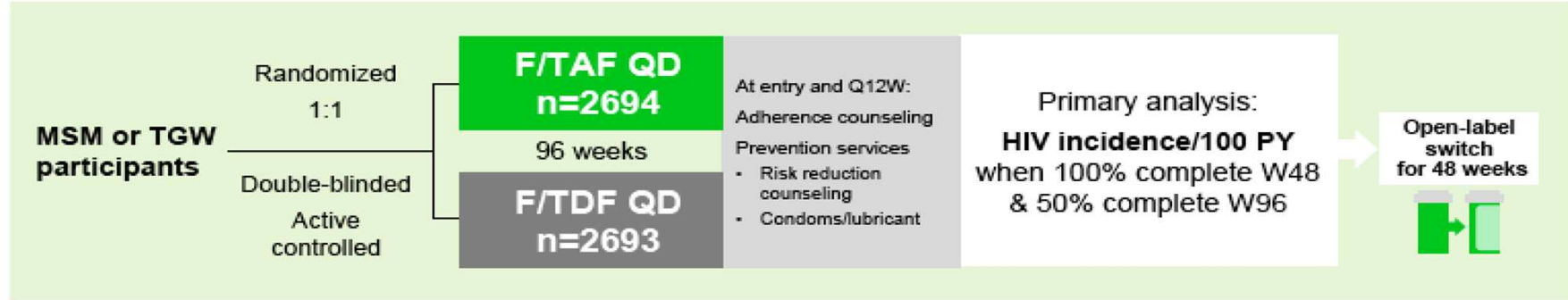
Recent research updates

# TAF



# TAF

## DISCOVER: A Randomized, Noninferiority Trial of F/TAF for PrEP



### Eligibility required high sexual risk of HIV

- 2+ episodes condomless anal sex in past 12W or rectal gonorrhea/chlamydia, syphilis in past 24W
- HIV & HBV negative, eGFR  $\geq 60$  mL/min
- Prior use of PrEP allowed



### Study conducted in NA, EU in cities/sites with high HIV incidence

- 94 sites in 11 countries
- Participants: US, 60%; EU, 34%; Canada, 7%



### Primary efficacy endpoint: HIV incidence

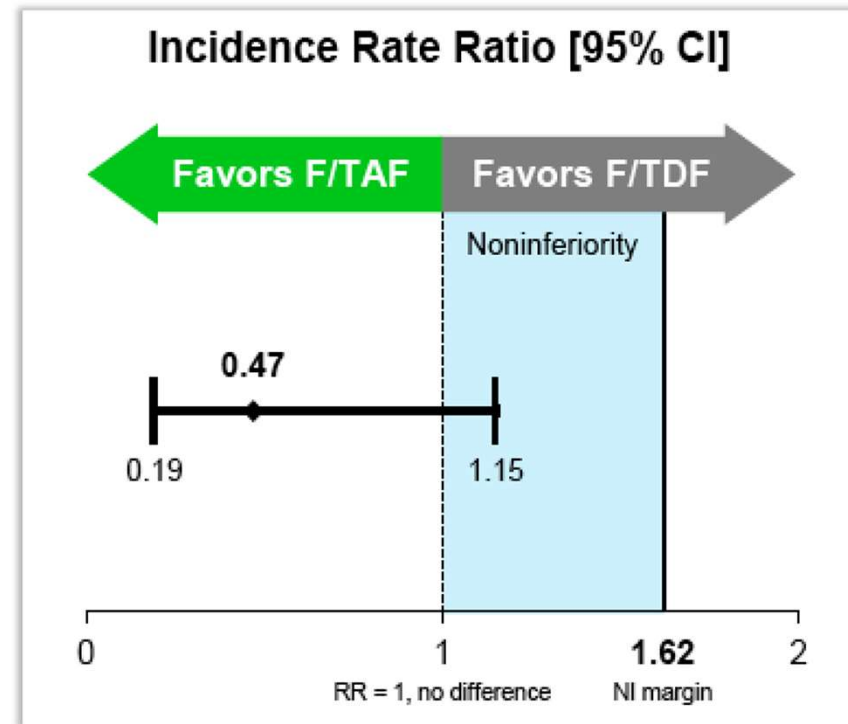
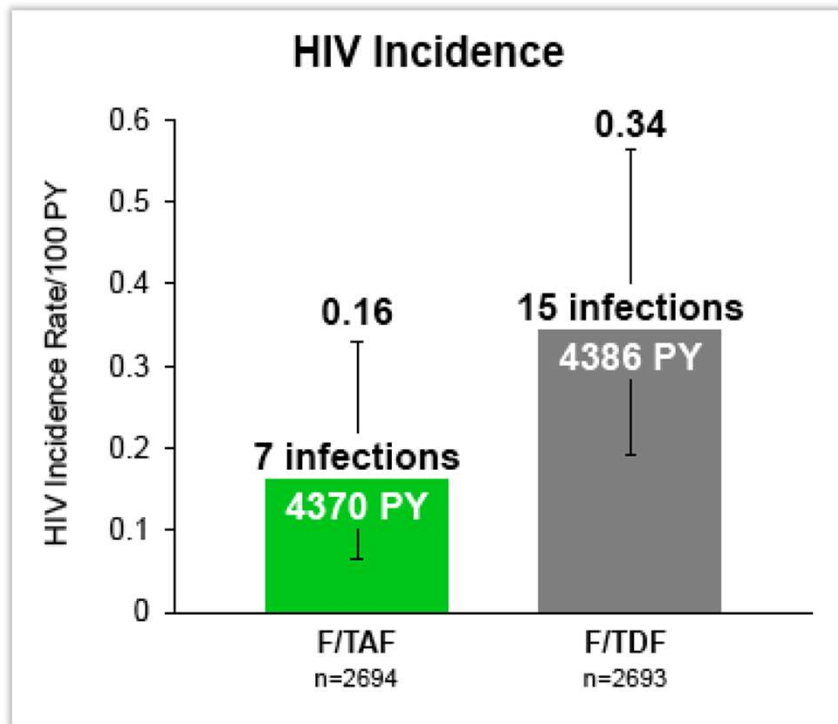
- Evaluated by rate ratio with noninferiority (NI) margin  $< 1.62$
- Expected incidence of 1.44/100 PY based on pooled studies: iPrEx, PROUD, IPERGAY

F/TAF dose: 200/25 mg; F/TDF dose: 200/300 mg. eGFR, estimated glomerular filtration rate.

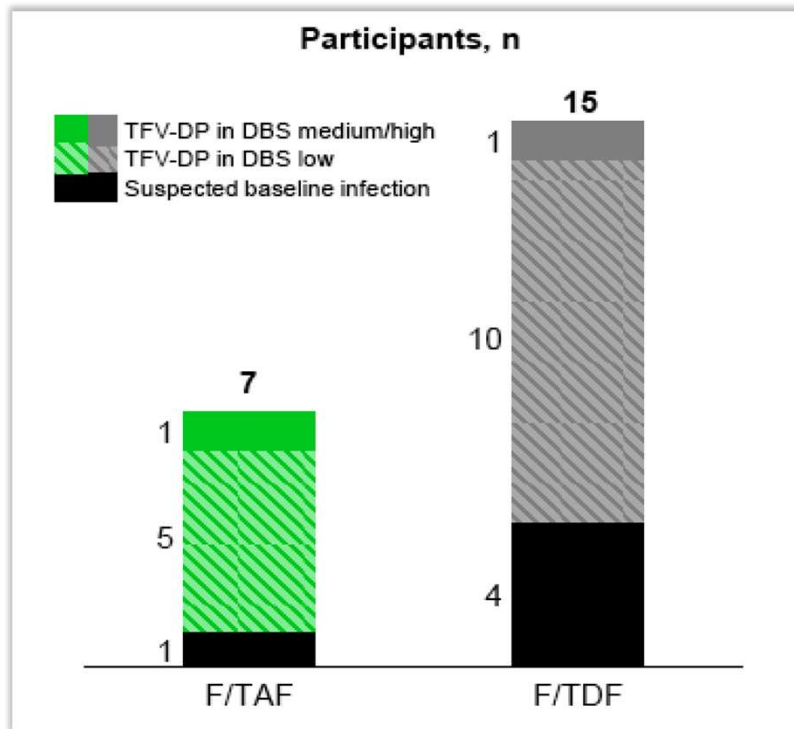
Hare et al. CROI 2019

# TAF

22 HIV infections in 8756 PY of follow-up



# TAF



- 7 F/TAF infections: 1 suspected baseline infection, 5 low levels of TFV-DP in DBS, 1 medium level
- 15 F/TDF infections: 4 suspected baseline infections, 10 low levels of TFV-DP in DBS, 1 high level
- In a sensitivity analysis that excluded suspected baseline infections, noninferiority was maintained (0.55 [0.20, 1.48])

n	F/TAF n=7	F/TDF n=15
Resistance genotyped*	6	13
Resistance to study drugs		
FTC	0	4 <sup>†</sup>
TFV	0	0

\*3 samples could not be amplified; <sup>†</sup>All 4 participants with resistance were suspected baseline infections.

# TAF

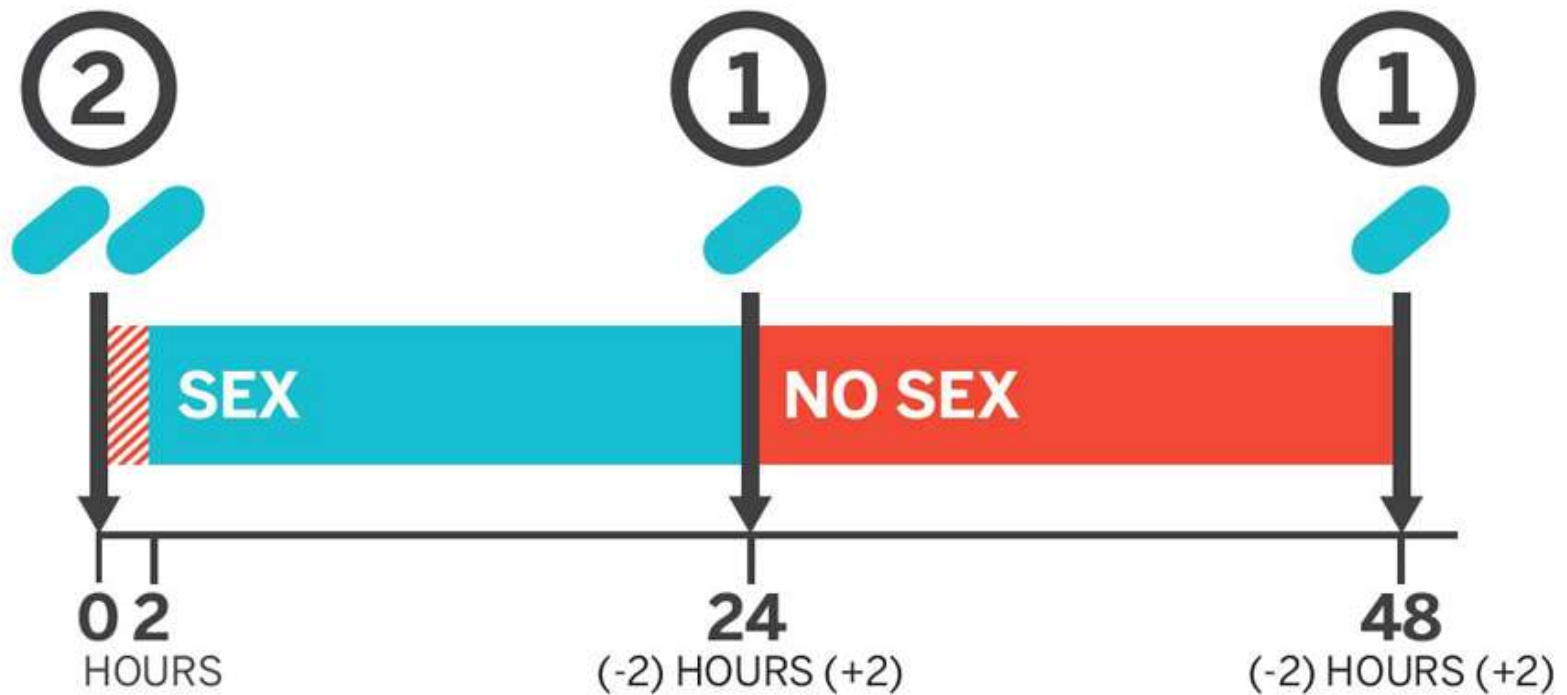


Advisory Panel August 2019 →  
FDA approval October 2019

*Approval excludes individuals  
practicing receptive vaginal sex*

# On demand PrEP

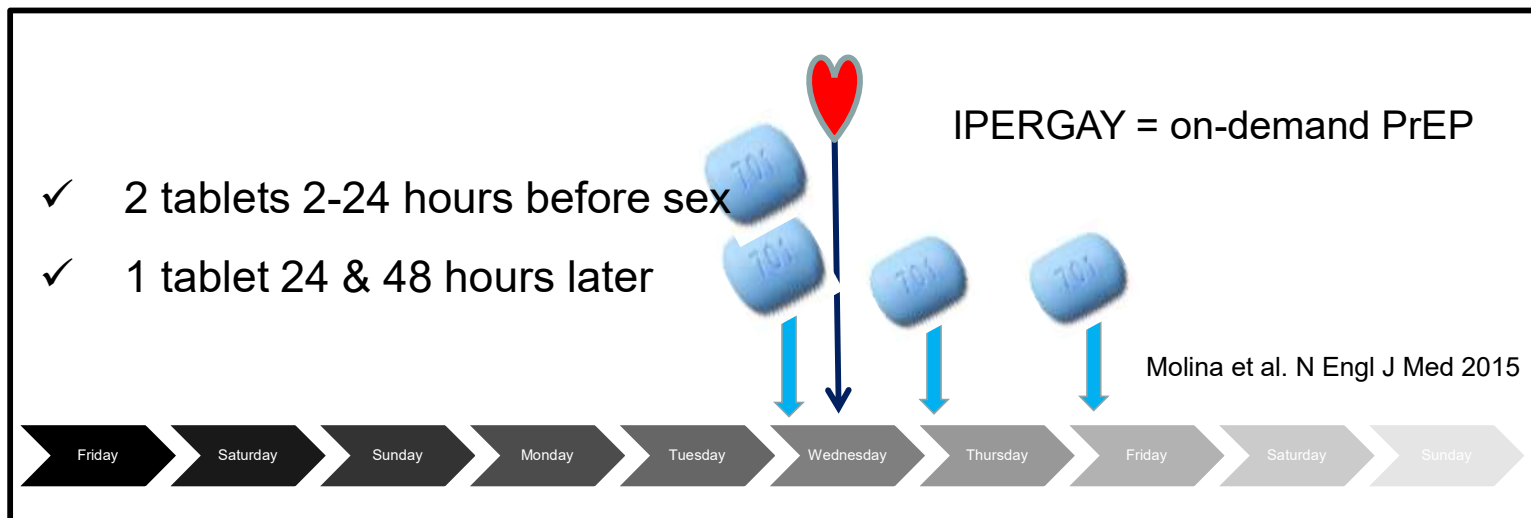
**SEX WITHIN 24 HOURS OF THE FIRST DOSE**



Source: SFAF

# On demand PrEP

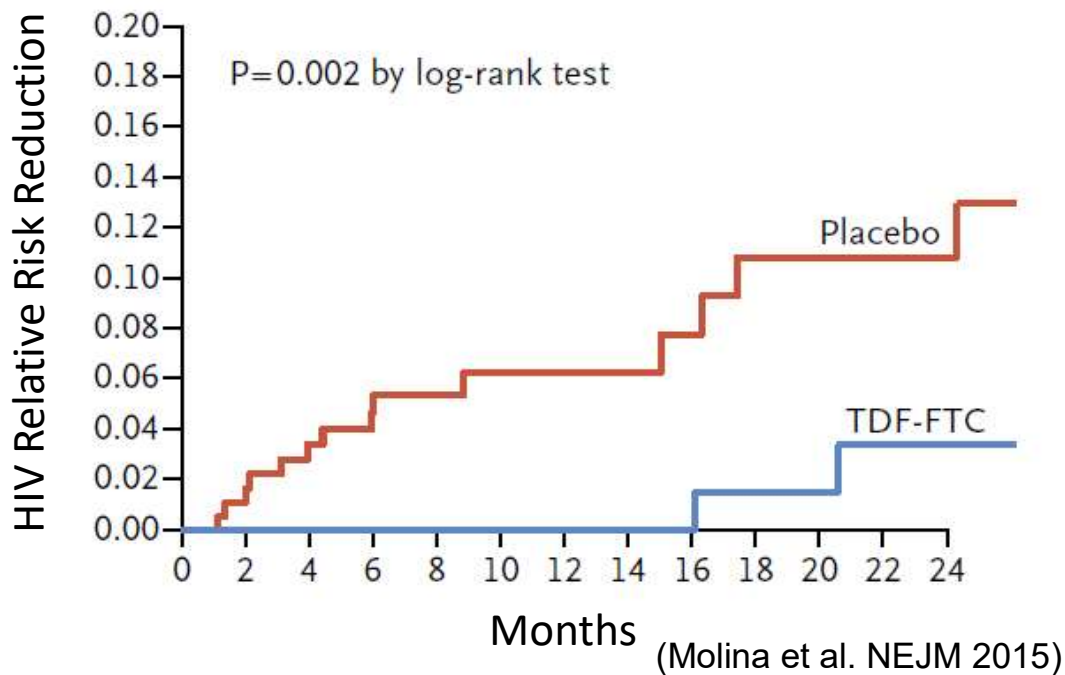
- Intermittent PrEP use has been assessed in one trial (IPERGAY) & subsequent open-label research (e.g., PREVENIR):
  - Average of 16 pills used/month (IQR 10-23) [~4/week à la iPrEx OLE?]
  - High background HIV rate; high STI rates





# On demand PrEP

## Proof of concept for on-demand PrEP



- IPERGAY: Near complete HIV protection (86%, only 2 infections and neither was using PrEP)
- Subsequent analyses show high protection, including among subset with less frequent sex (Antoni et al Lancet HIV 2019)
- In demonstration project work in France and Netherlands, daily and 2-1-1 use is about 50:50 and men frequently switch back and forth

# On demand PrEP



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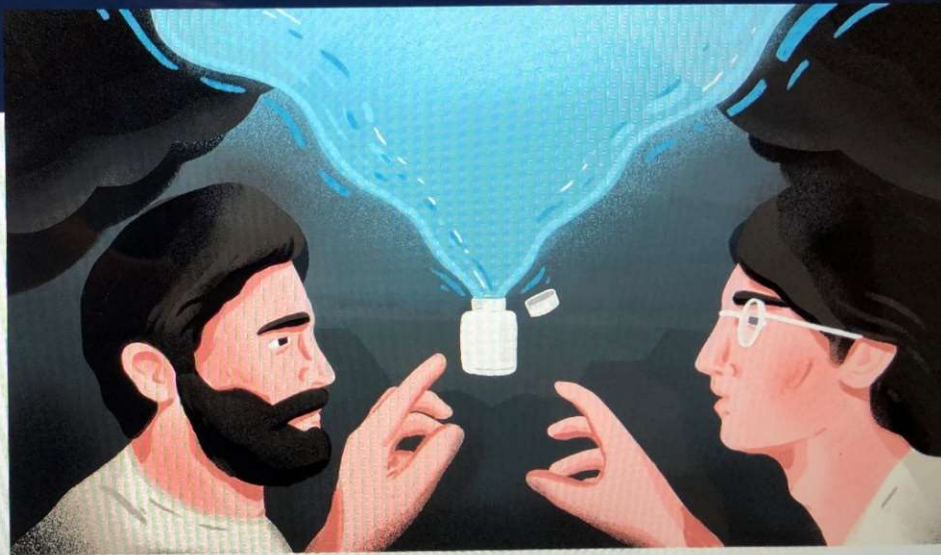
NBC NEWS NOW NIGHTLY NEWS MEET THE PRESS DATELINE MSNBC TODAY

**NBC NEWS** IRAN CRISIS IMPEACHMENT POLITICS U.S. NEWS BUSINESS WORLD TECH & MEDIA OPINION HEALTH SPORTS

OUT HEALTH AND WELLNESS

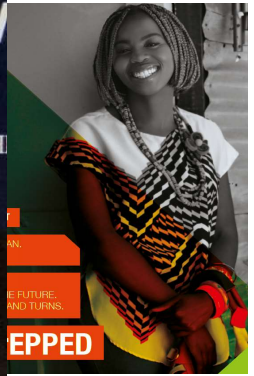
# PrEP's unexpected side effect: reduced 'HIV anxiety'

Use of the HIV prevention drug is associated with lower levels of anxiety about contracting HIV. But for gay men who remember AIDS, the specter of HIV is a hard ghost to shake.



A new study has found that use of pre-exposure prophylaxis, or PrEP, reduces HIV anxiety in gay and bisexual men.  
Col. McElva Linn / for NBC News

jama\_owens\_2019....pdf ^



# More options

PRE-CLINICAL	PHASE I	PHASE III/IIIb	DELIVERY SYSTEM	ACTIVE DRUG
IPCP NIAID IPM ViiV CDC ViiV/Pfizer PBS Rockefeller University IPM Pop Council Gilead Pop Council Merck CAPRISA RTI Intarcia CONRAD Oak Crest Northwestern University CONRAD IPM IPM Northwestern University Houston Methodist University of Pittsburgh ImQuest Merck	IPM* Johns Hopkins IPM ImQuest	GSK/ViiV Gilead IPM	Oral pills Vaginal gel Vaginal ring Vaginal film PBS Enema fast-dissolve insert Intrauterine device Vaginal tablet Rectal gel Long-acting injectable Micro-array patch Nano-fiber Subcutaneous injection Diaphragm Implant	TFV Tenofvir bNABs Broadly neutralizing antibody TDF Tenofovir disoproxil fumarate TAF Tenofovir Alafenamide TFV/FTC Tenofovir/ emtricitabine TDF/FTC Tenofovir disoproxil fumarate/ emtricitabine EVG Elvitegravir 1005 PC-1005 MVA Maraviroc PR Progestin MK-8591 AZ Acyclovir-Zovirax 7013 SPL7013-VivaGel Aa Ascorbic acid Ba Betulonic acid DAR Darunavir DAP Dapivirine GRF Griffithsin DS 003 DS003 (BMS793) IQP IQP-0528 5P12 SP12-RANTES 744 Cabotegravir/ GSK 744 MAb Monoclonal antibody MK-2048 TAF/FTC Tenofovir alafenamide/ emtricitabine FG Ferrous gluconate PPa Polyamino-Polycarboxylic acid Levo Levonorgestrel Ee Ethinyl estradiol DBBI Different drugs being investigated
<b>Multipurpose Prevention Technologies (MPTs)</b>				
Auritec CONRAD CONRAD Pop Council PATH/Pop Council Star Pharma SRI Int'l University of Louisville CONRAD/PATH/Pop Council/Kessel RTI Pop Council CONRAD PATH	Pop Council IPM* Pop Council CONRAD* Pop Council CONRAD* CONRAD			

\* This formulation is for a 3-month vaginal ring

# More options

## There is need

38 million infected  
23 million on treatment  
1.7 million newly infected

- New infections **outpace** treatment initiations.
- Prevention tools are not being provided on an **adequate scale**.
  - Women and girls continue to be **disproportionately affected**.
- **Stigma and discrimination** impede prevention for men who have sex with men, sex workers and transgender persons.

# More options

High uptake

Good adherence (better than in phase III)

Well-tolerated safety profile (consistent with phase III data)

Lower HIV-1 incidence than expected in the absence of ring access

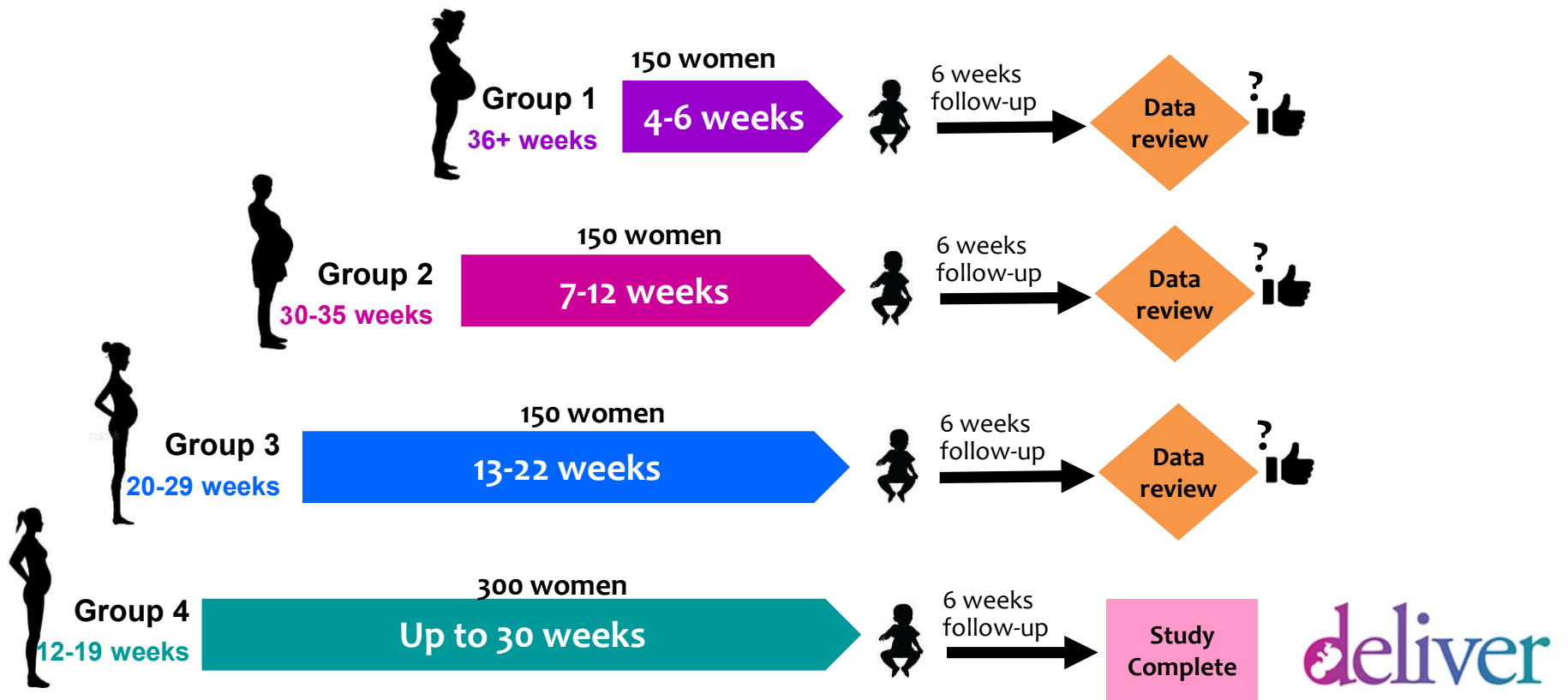
*DREAM = SA AIDS 2019*

*HOPE = IAS 2019*

**(And, 90 day ring in development!)**



# More options



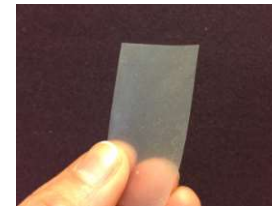
# More options

## Films, inserts, lubricants, douches

Small, easy to store & hide,  
inexpensive, stable

Private to use, quick to reach  
preventive concentrations, also quick  
to reverse  
(right drug, right place, right time)

End-user studies = high interest



Credit: CONRAD

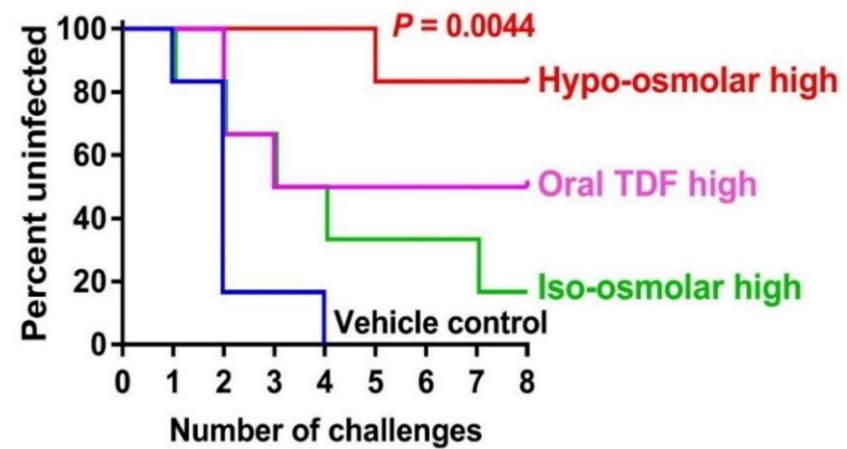
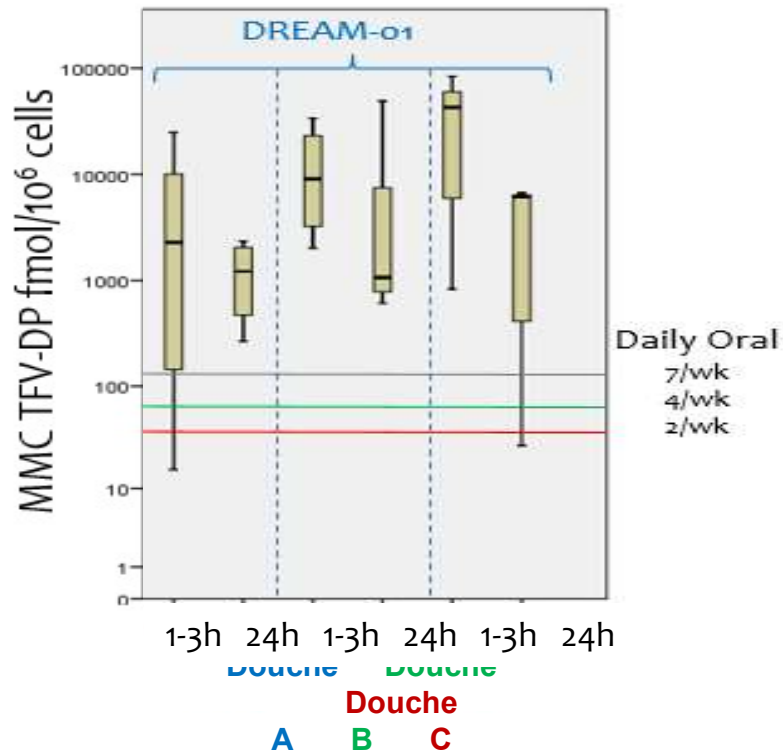




# More options

Human colon PK = levels exceeding that achieved by oral PrEP

NHP challenge = high SIV protection

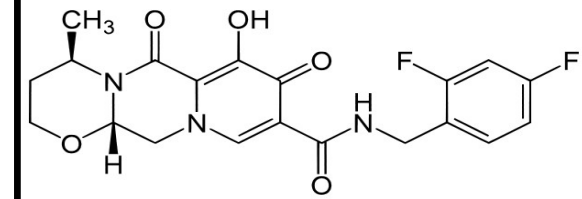


(Hendrix et al CROI 2018 & Villinger et al. CROI LB 2018)

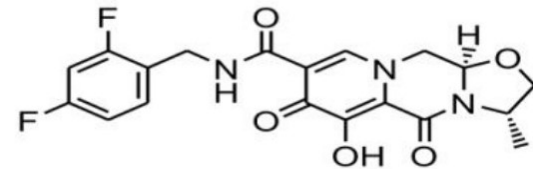
# More options

- **Cabotegravir LA = integrase strand-transfer inhibitor, long-acting suspension for delivery via IM injection**
- **Half-life:**
  - Oral: 40 hours
  - Injectable: 40-65 days

**DOLUTEGRAVIR**



**CABOTEGRAVIR**



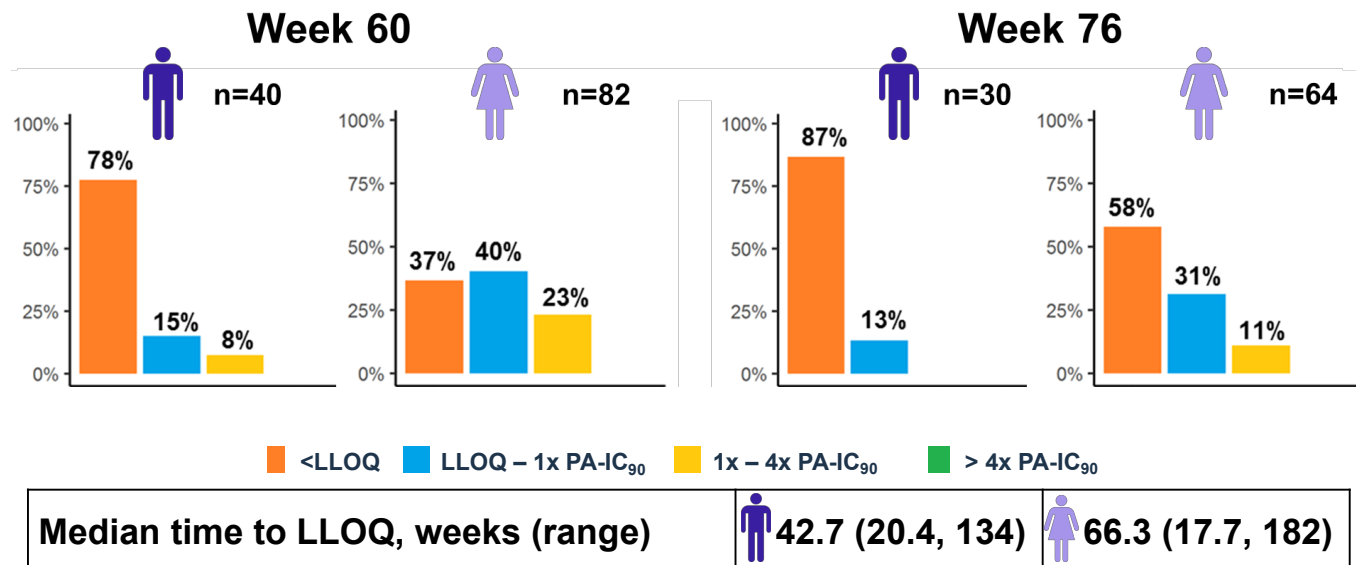
# More options

**HPTN 083 & 084. Objective:** To evaluate the safety and efficacy of CAB LA compared to TDF/FTC for PrEP in HIV uninfected MSM/TGW (083) and cisgender women (084)



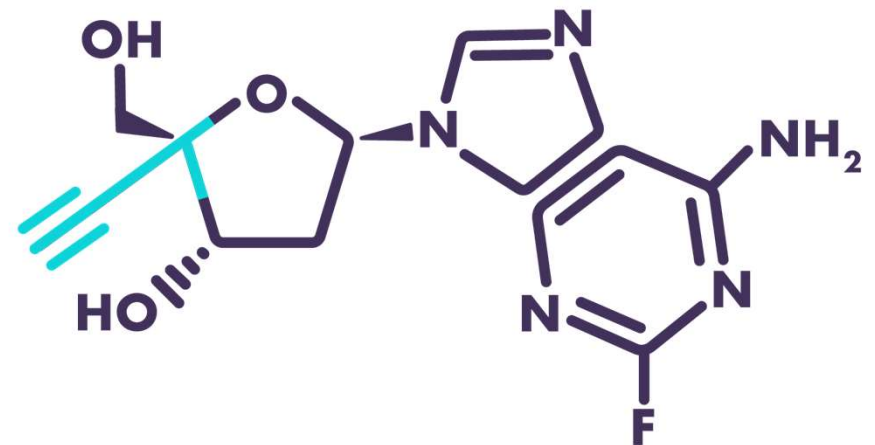
# More options

## CAB LA Pharmacokinetic Tail



# More options

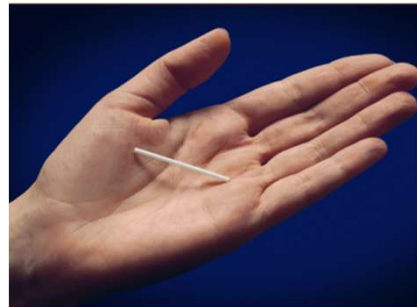
Islatravir (MK-8591):  
A First-in-Class Nucleoside Reverse  
Transcriptase Translocation Inhibitor  
(NRTTI)



ISL implant based on  
Implanon<sup>®</sup>/Nexplanon<sup>®</sup>

Uses same polymer

Removable (not bioerodible)



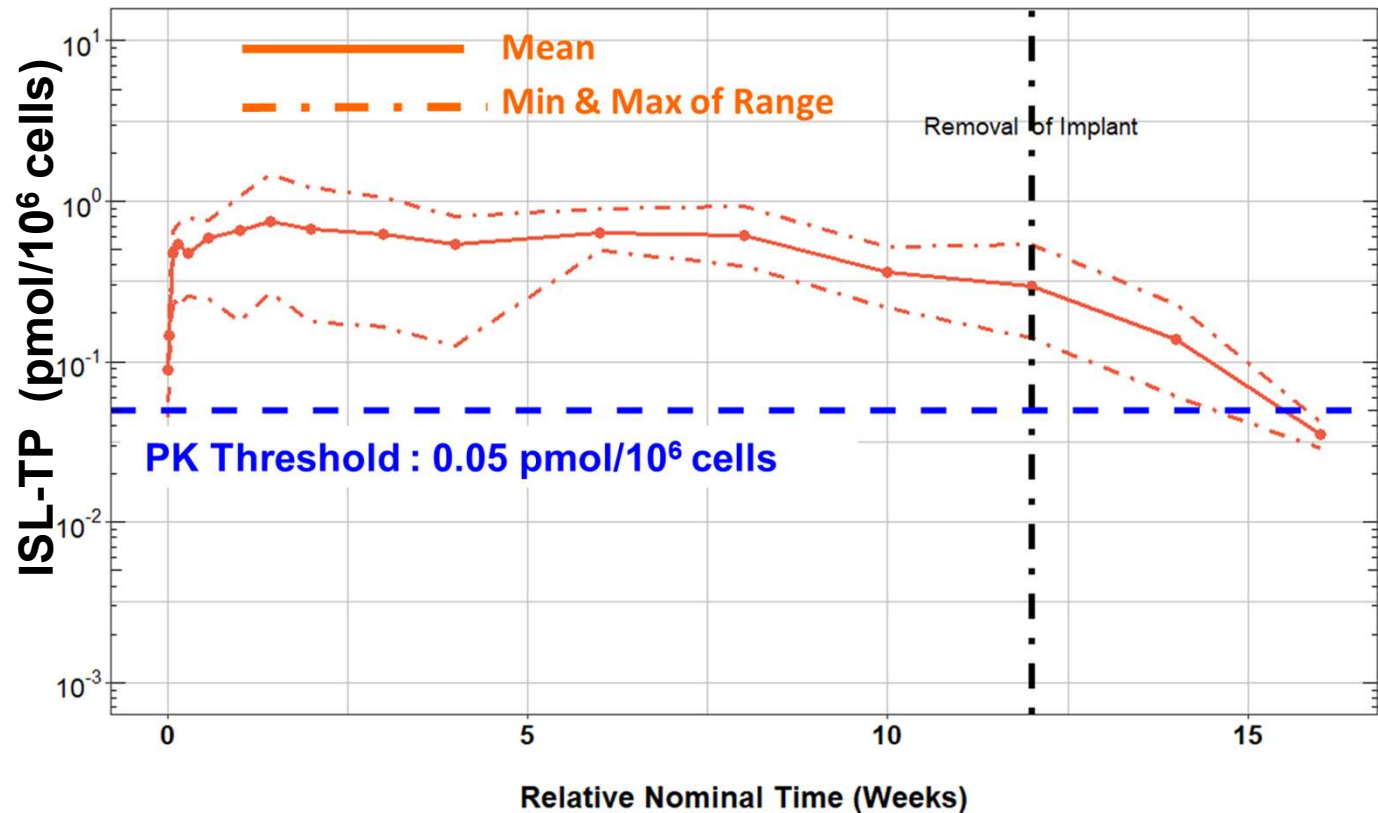
4 cm 2 mm

Matthews et al IAS 2019

# More options

62 mg Implant

Implant  
Projected to  
Lead to  
Concentrations  
Above Threshold  
for >12 Months



# More options

Testing PrEP options & engaging people on their PrEP choices

MTN-034/REACH  
n=300 AGYW aged 16-21  
Kenya, South Africa,  
Uganda, Zimbabwe



6 months



6 months



6 months



6 months



# More options

- Behavior science testing different placebo female topical PrEP products

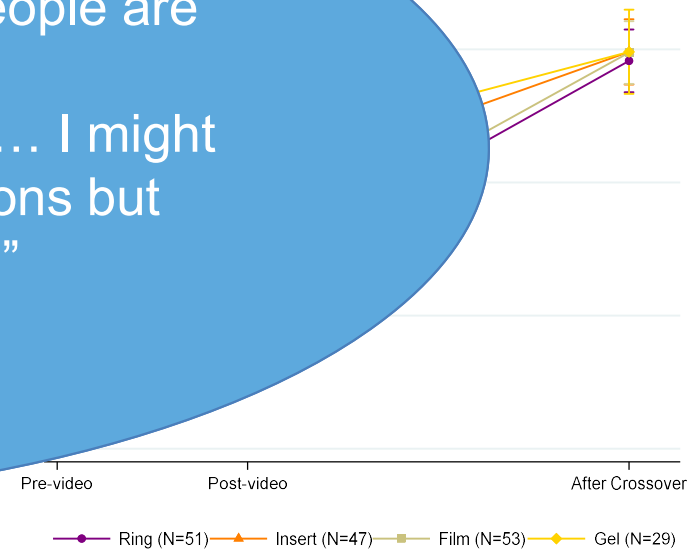
*PrEP with Experience*

“We are not the same. Some they will like the ring. Some they will like the tablet ... People are not the same.”

“...As people we have different choices ... I might not like the, the pills ... and the injections but there's other people who would.”

(Shapley-Quin et al. Intl J Women's Health 2019. TRIO study)

■ South Africa	25%	10%	10%
■ Zimbabwe	29%	10%	10%



\* Significantly different,  $p < 0.05$

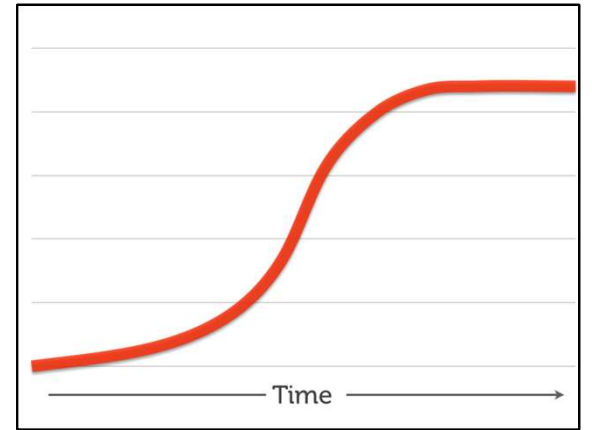
(Montgomery et al. QUATRO study, R4P 2018 & JIAS 2019)



# More options

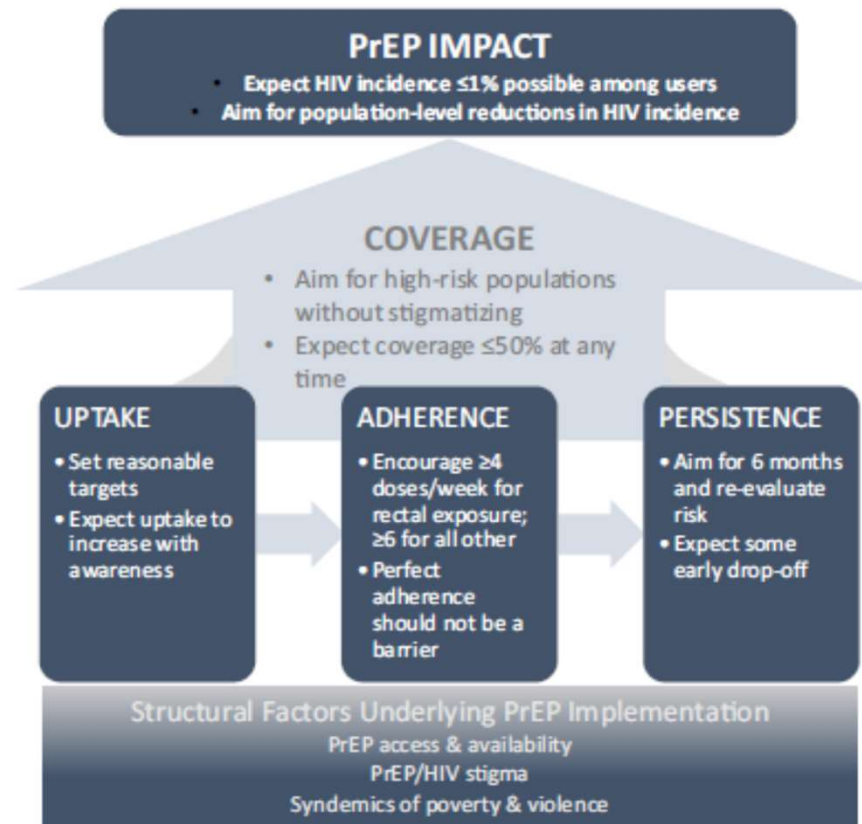


Options → choices → coverage → impact

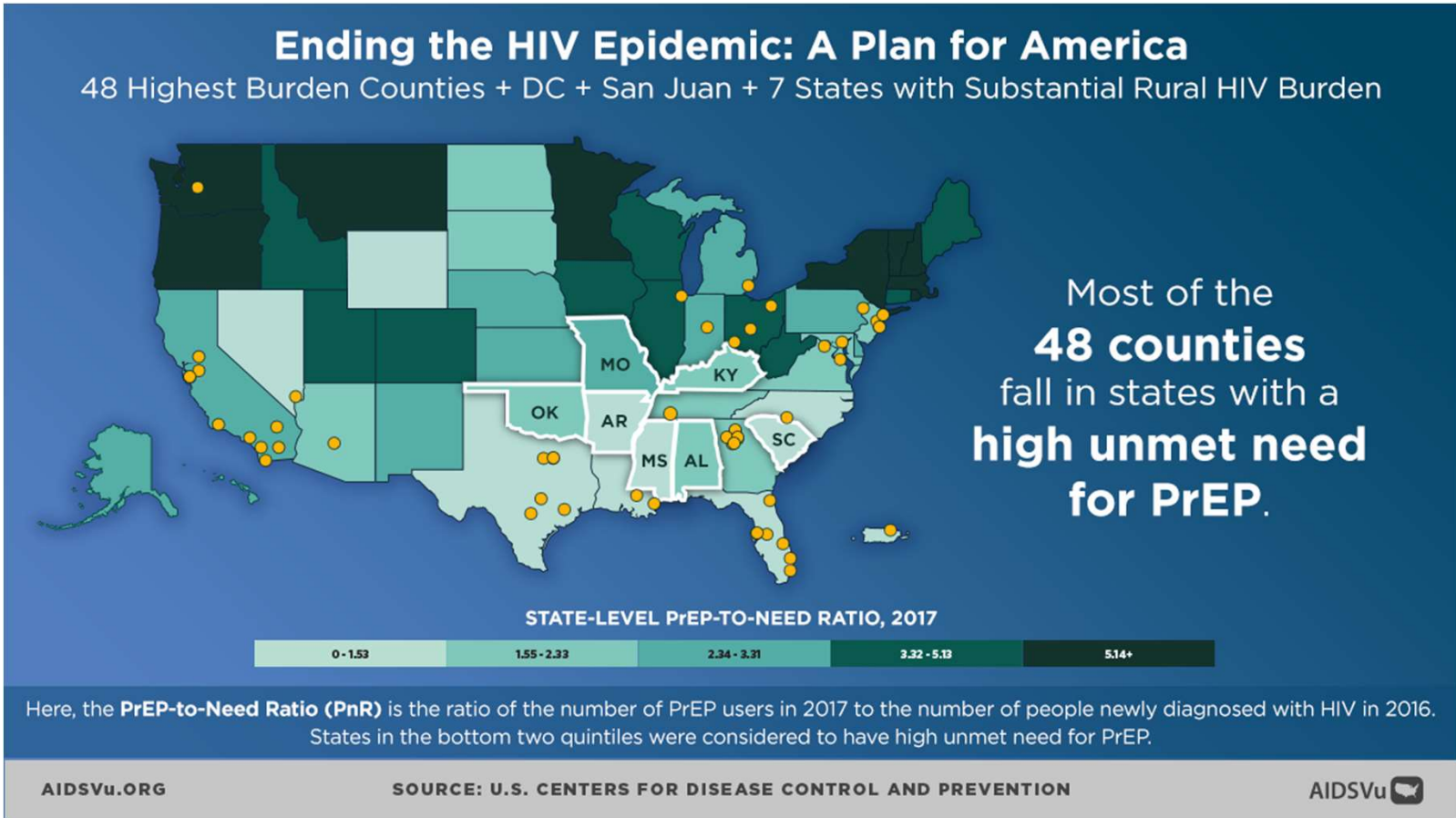


Defining success

# Benchmarks: what is good enough?



# EHE PrEP



# US targets

## ESTIMATED NUMBER OF ADULTS WHO COULD POTENTIALLY BENEFIT FROM PREP, UNITED STATES, 2015

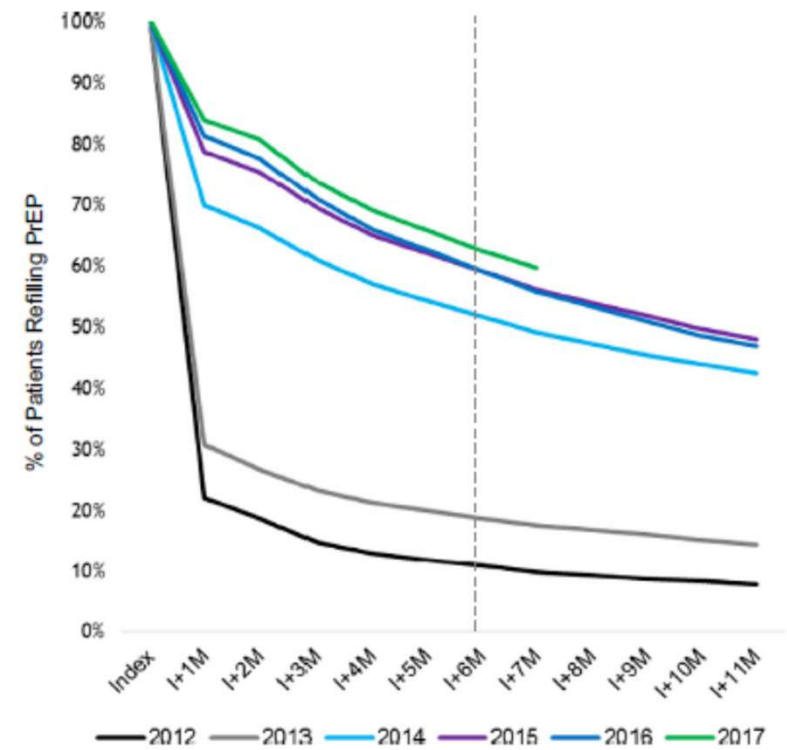
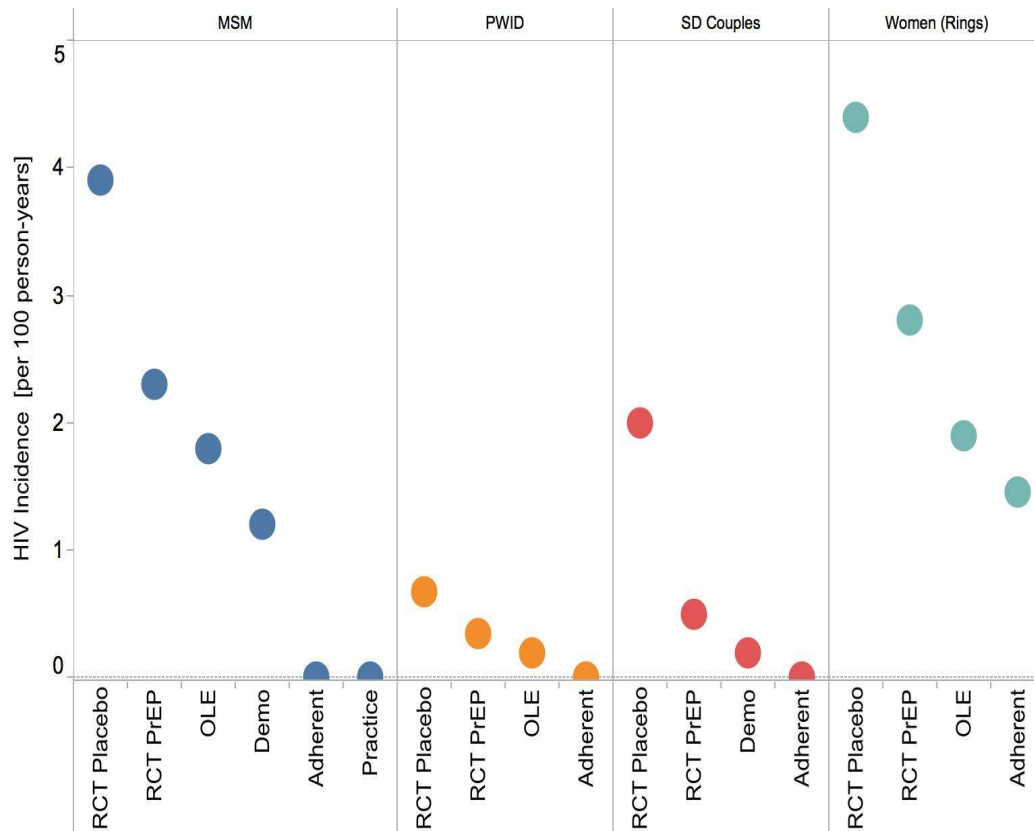
	Gay, bisexual, or other men who have sex with men	Heterosexually active adults	Persons who inject drugs	Total by race/ethnicity
Black/African American, non-Hispanic	309,190	164,660	26,490	500,340
Hispanic/Latino	220,760	46,580	14,920	282,260
White, non-Hispanic	238,670	36,540	28,020	303,230
Total who could potentially benefit from PrEP	<b>813,970</b>	<b>258,080</b>	<b>72,510</b>	<b>1,144,550</b>

Notes: PrEP=pre-exposure prophylaxis; data for "other race/ethnicity" are not shown



U.S. Department of  
Health and Human Services  
Centers for Disease  
Control and Prevention

# Effectiveness & persistence



Pyra et al JIAS 2019

# US persistence

	<b>Commercial insurance (n = 4172)</b>	<b>Medicaid (n = 177)</b>
<b>Adherence (proportion of days covered)</b>	89.0%	71.0%
<b>Proportion of days covered <math>\geq 90\%</math></b>	49.0%	24.3%
<b>Gap between PrEP refills (days)</b>	7.7	9.5
<b>Persistence (months)</b>	13.7	7.2

Huang et al. 2019 National HIV Prevention Conference 2019.

# US persistence

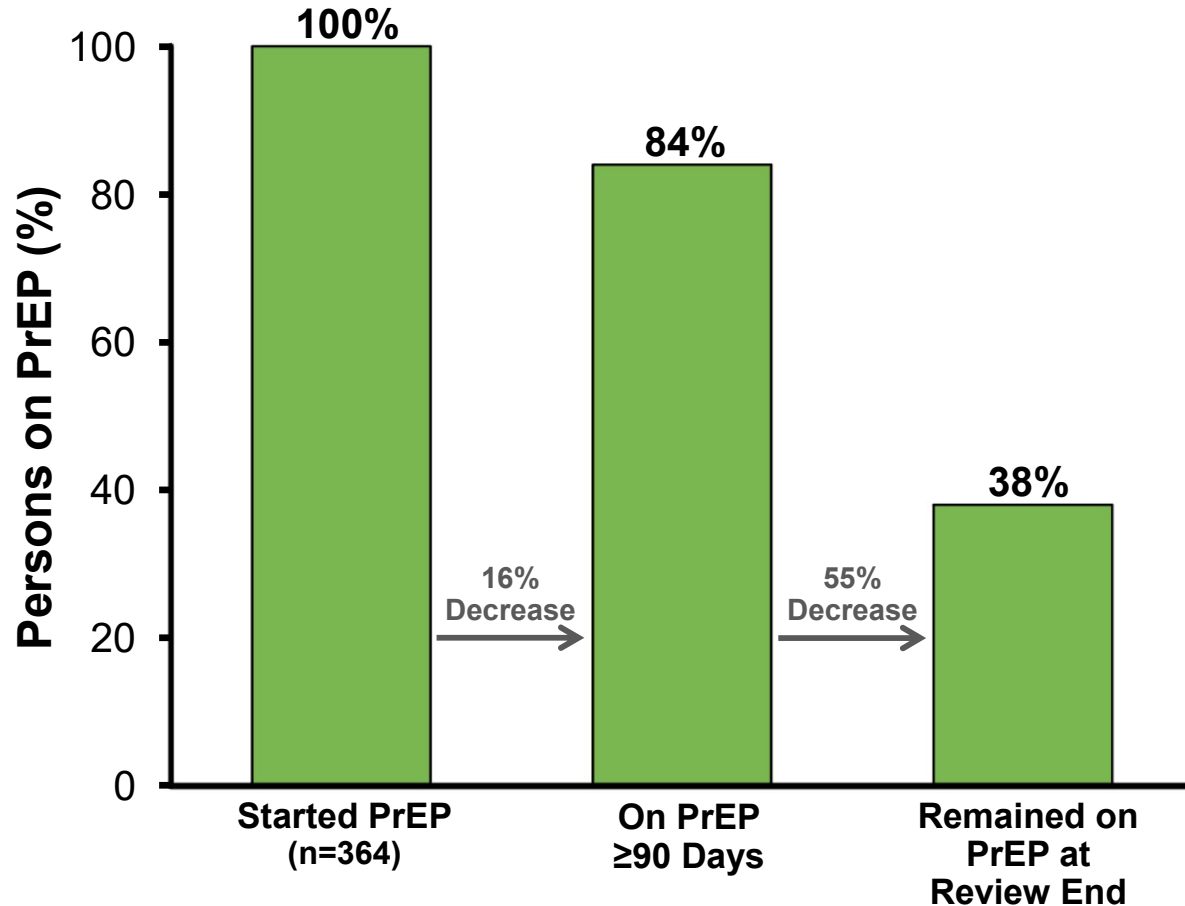
Chart review of safety net primary care network of 15 clinics in SF (through 1/2017)

Among those on PrEP for  $\geq 1$  year, 63% attended  $\geq 3$  quarterly visits

Predictors of PrEP discontinuation

<90 days: transwomen versus MSM ( $P < 0.001$ )

$\geq 90$  days: younger individuals, PWUD, missed visit in prior PrEP use quarter (all  $P < 0.001$ )

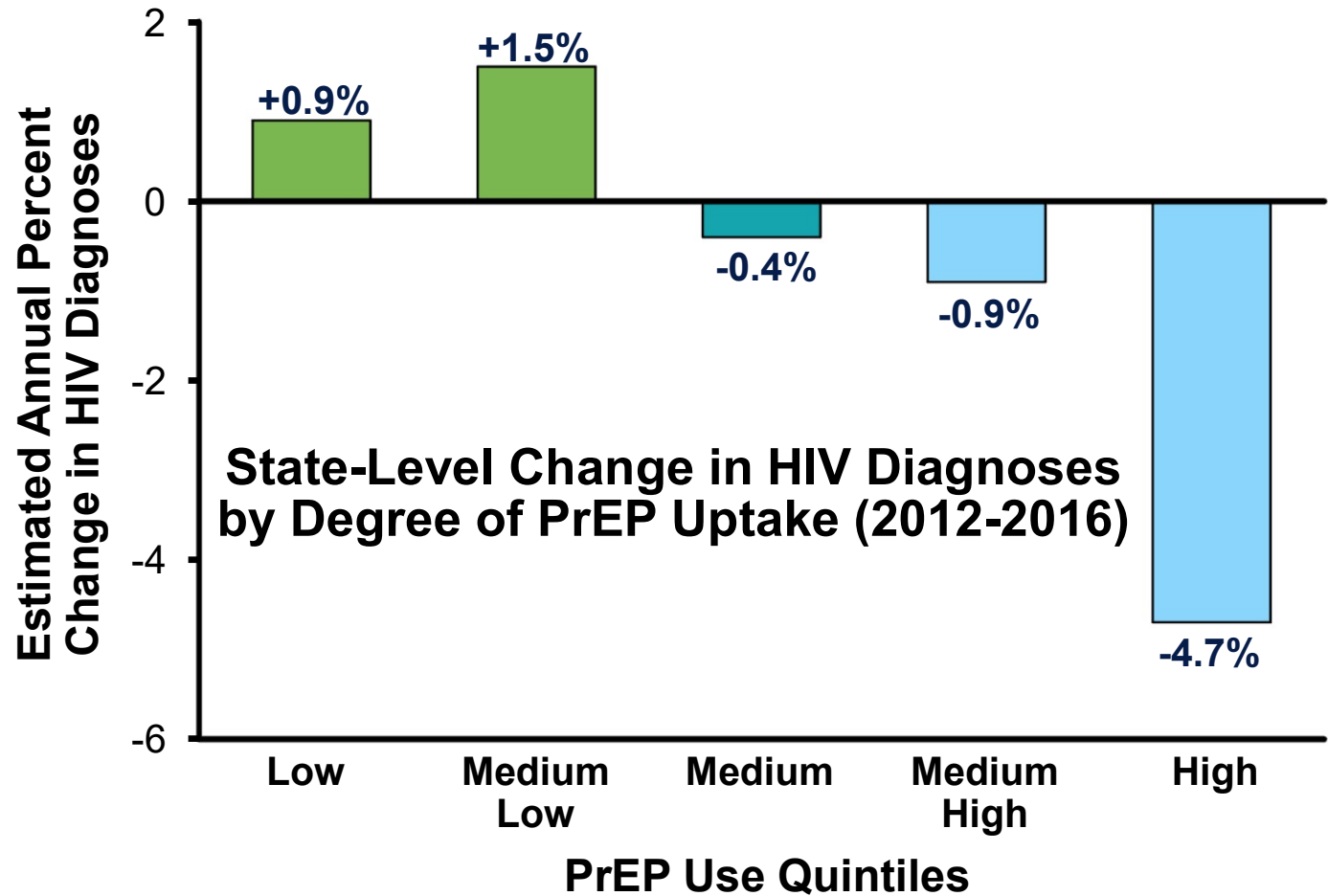


Spinelli et al. Open Forum Infect Dis 2019.

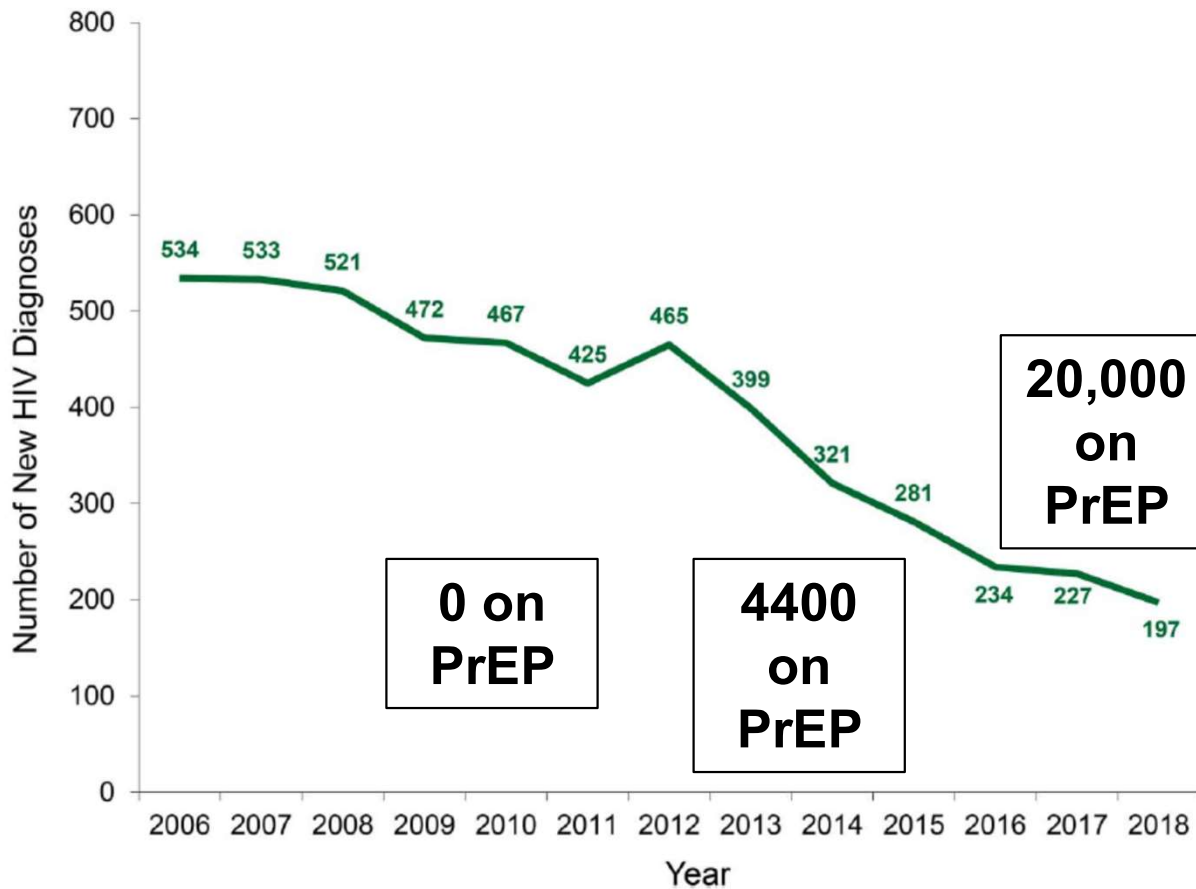


# PrEP impact

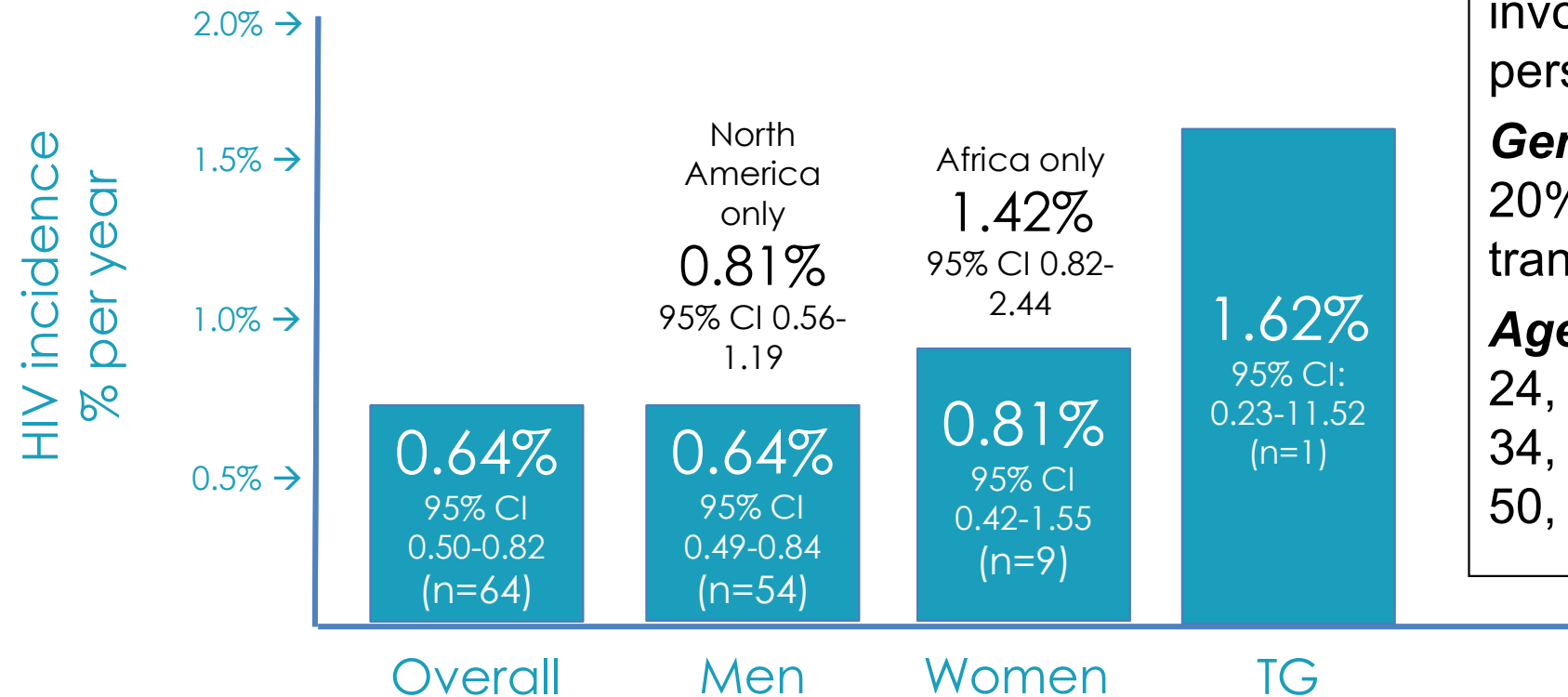
- US model 2012 to 2016
- Rate of PrEP uptake was significantly associated with decline in HIV diagnoses (controlled for state-level viral suppression)\*
  - Largest decreases in HIV diagnoses were among states with the highest PrEP uptake



# San Francisco



# Global summary data



46 projects,  
involving 10,609  
persons:

**Gender:** 76% male,  
20% female, 0.7%  
transgender (n=74)

**Age:** 25% aged 13-  
24, 36% aged 25-  
34, 25% aged 35-  
50, 6% aged >50

# New PrEP options

“The era of placebo-controlled trials is over; it is impossible to do trials.”

- *many people*

“There have to be more PrEP options.”

- *those same people*

# The brief history of HIV prevention



Risk  
reduction  
counseling

Condoms  
(both M  
and F)

STI testing  
and  
treatment

Injection  
harm  
reduction

VMMC

PEP

Partner  
testing /  
couples  
counseling

# Standard of prevention, pre-PrEP/ART

*The feeling was that the background package was both ethical and individually beneficial, but did little to alter the design, interpretability, or potential for success for a trial.*

*Thus, the prevention benefits of the new prevention tool were over and above those of standard-of-care prevention services.*



# Evolving prevention trials:

## PrEP as part of standard prevention package

### *Assumptions:*

- Not everyone will use FTC/TDF PrEP & thus HIV incidence will be sufficient for trial to be able to answer its question
- FTC/TDF use will be balanced between randomized groups

### *Advantages:*

- The placebo comparison is the gold standard for a clear evaluation of safety & efficacy
- All participants have access to PrEP if they want it

### *Disadvantages:*

- Currently, it is difficult to predict the fraction who will use FTC/TDF PrEP and thus what impact that will have on HIV incidence (& on trial size and duration)
- There is theoretically a potential for drug-drug/product interactions with FTC/TDF, but that's good to figure out in a trial rather than later....



*FTC/TDF PrEP is part of the background, like previous comp*

# Evolving prevention trials:

## PrEP as active comparator

### *Assumptions:*

- Credible assumption that new prevention agent will work (e.g., another antiretroviral, otherwise half the study gets something for sure that works and the other half gets something much more unknown)
- Desirable to want a direct comparison to FTC/TDF & the new option will be same or better (in terms of convenience, side effects, adherence, etc.)

### *Advantages:*

- Provides safety & efficacy relative to FTC/TDF
- Provides a PrEP agent to all in the trial (albeit investigational for half)

### *Disadvantages:*

- Tests safety & efficacy relative to FTC/TDF but not placebo (directly)
- Double-placebo may be cumbersome to deliver and complex to explain
- The results might be challenging to understand



*FTC/TDF PrEP is the comparison, maybe with double-dummy placebo*



# Evolving prevention trials:

trials among those for whom PrEP is not for them

## Assumptions:

- Individuals have **access** to PrEP, can **voluntarily decline** it, and can **freely enroll** into a placebo-controlled trial of a new agent, and can change one's mind later and then freely **access PrEP** once enrolled

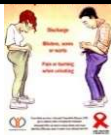
## Advantages:

- Becomes a standard placebo-controlled comparison, with all the gold standard evidence that arises

VS.

## Disadvantages:

- Very few disadvantages
- However, making **access, voluntary decline & enrollment**, and **then PrEP access** successful is not necessarily simple



*FTC/TDF PrEP as part of package, if minds change*

# Choice

**BEDSIDER**

[birth control methods](#)

[where to get it](#)

[reminders](#)

[features](#)

[questions](#)

METHOD EXPLORER /

★  
most effective

Y  
party ready

♥  
STI prevention

⊖  
hormone free

🔍  
easy to hide

♥  
do me now

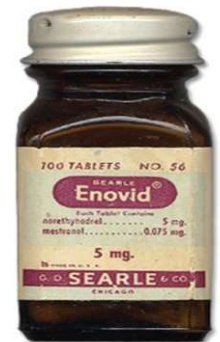


share this /



# Choice

	<b>PrEP &amp; contraception share many features Oral contraceptive pills</b>
<b>Medication history</b>	Initially developed for treatment → repurposed for prevention
<b>Deep benefits</b>	Offer individual control over prevention
<b>Balancing risks and benefits</b>	Mixed effects on sexual behavior, requires adherence, potential side effects
<b>No demand of perfection</b>	Perfect use is the ideal, but real-world use has real individual and population-level benefits



Myers and Sepkowitz A pill for HIV prevention: déjà vu all over again? CID 2013

# Choice

## Commentary

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### HIV Prevention: The Need for Methods Women Can Use

ZENA A. STEIN, MA, MB, BCh

“...a less efficacious barrier (one that fails more often than another on each sexual encounter), if frequently used, might serve the public health as well or better than a more efficacious but less frequently used barrier, and **could in the end play an important role in preventing transmission at the population level.**”

*(Am J Pub Health, 1990)*

# Choice

Effectiveness does not drive all decision-making

Perception of safety is similarly important

Many other factors are important too

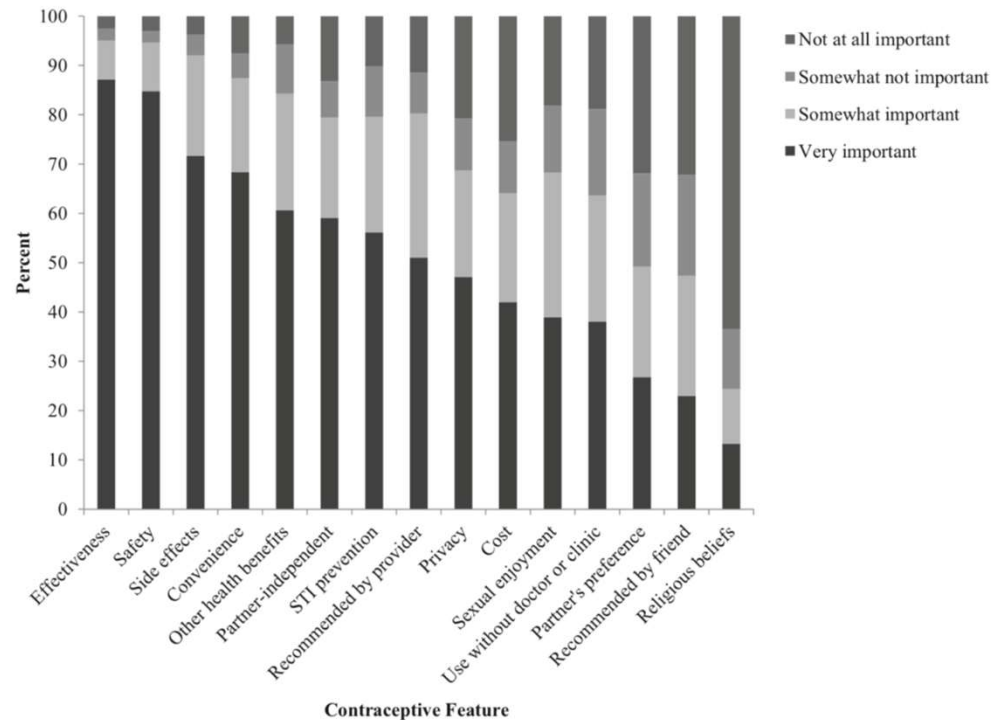


Figure 1. Contraceptive features by importance to adolescent and young women.

(Walker et al. J Adolesc Health 2019)

# Choice

WHO Systematic Review (231 articles)

**CHOICE** associated with better:

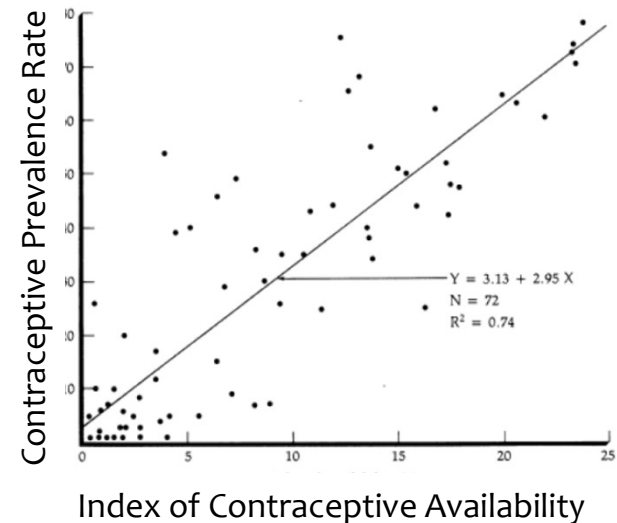
contraceptive uptake

contraceptive persistence

health outcomes (↓ pregnancies, ↓ STIs)

**CHOICE** varies over the lifetime

**Why would PrEP be different?**



**EACH add'l product option yields 12% increase in contraceptive use**

(Gray AL, et al. WHO RHRU 2006 & Jain AK, et al. *Stud Fam Plan* 1989)

# Gaps

- The science



## The reality



Slide adapted from Thes Palanee-Phillips

# Closing gaps



Easier places, more places

- Youth clinics, mobile clinics
- Family planning clinics
- Pharmacies
- Antenatal settings



Easier delivery

- Same day start, optional labs
- Text message reminders
- HIV self-testing for efficiency



# Gaps

*“What’s the most important progress we’ve made this decade in the HIV epidemic? “*

**“Treatment as prevention and preexposure prophylaxis, because if we really implement them properly, theoretically **you could shut the epidemic off.**”**  
- Anthony Fauci, JAMA, July 2018

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