GLADSTONE INSTITUTES

PrEP 2.0

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how2offer PrEP

putting PrEP into practice

How2OfferPrEP.org

SAN FRANCISCO AIDS FOUNDATION

UCSF

Disclosures

- Gilead Sciences donated study medication to US NIH, including iPrEx and HPTN 067.
- VIIV contracted with Gladstone to support research on long-acting injectable PrEP.
- Gilead contracted with San Francisco AIDS Foundation for a trial comparing FTC/TDF with FTC/TAF for PrEP.
- This talk is future looking and off label.

PrEP 2.0 Outline

- PrEP is Scaling up for Impact
- Making Oral FTC/TDF PrEP Easier
- Fostering Demand for PrEP among Women
- Long acting PrEP Agents and Devices
- Releasing the Phase 3 bottleneck
- An Invitation to Embrace Human Behavior

PrEP Approvals, Recommendations, and Programs

World Health Organization

FDA U.S Food and Drug Administration

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

mcc MEDICINES CONTROL COUNCIL


South Africa


France


Kenya


Australia


Brazil


United States of America

Approval and public services.

Approval, but No public Services.


Canada

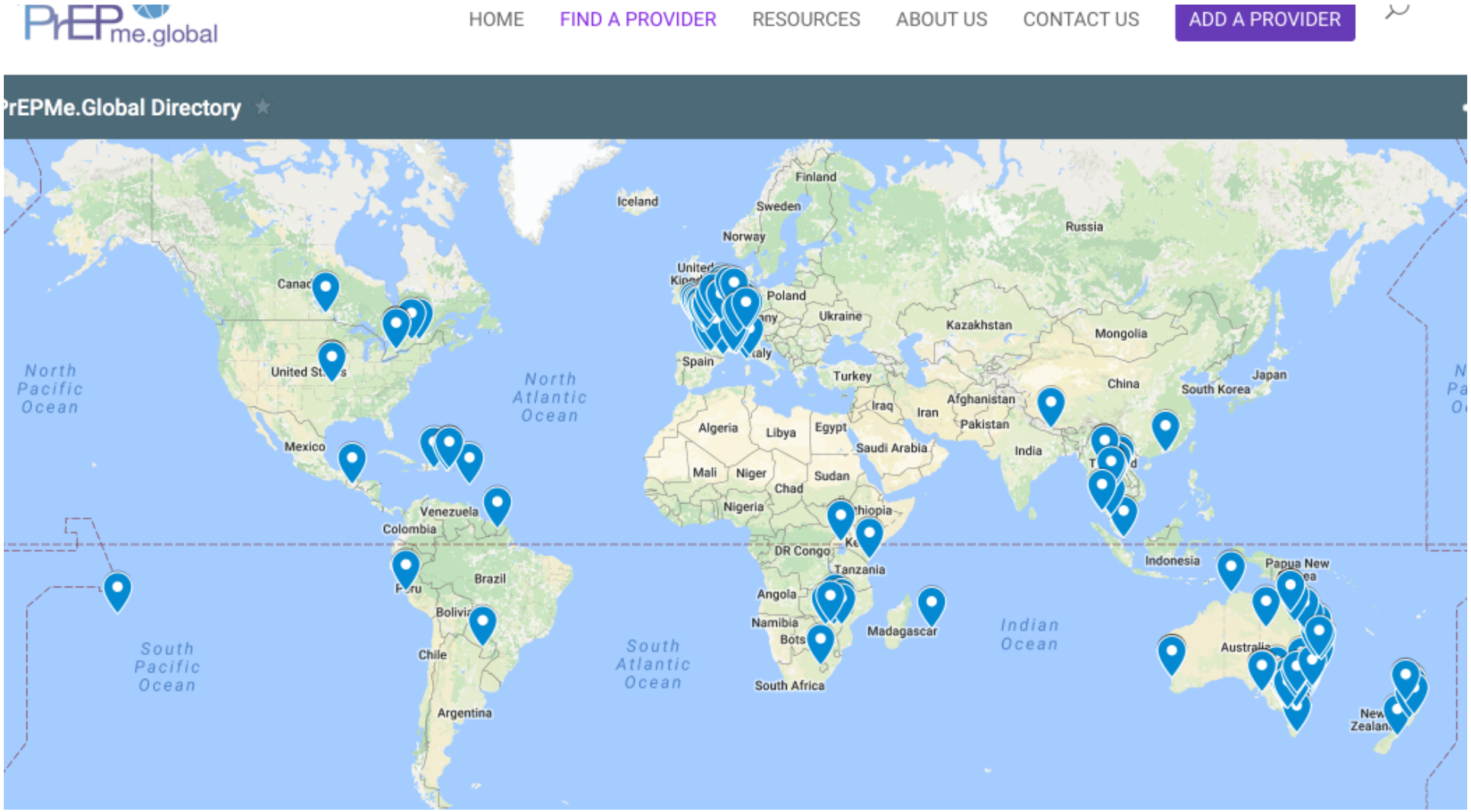

Peru


Switzerland


Israel

A Public PrEP Provider Registry:

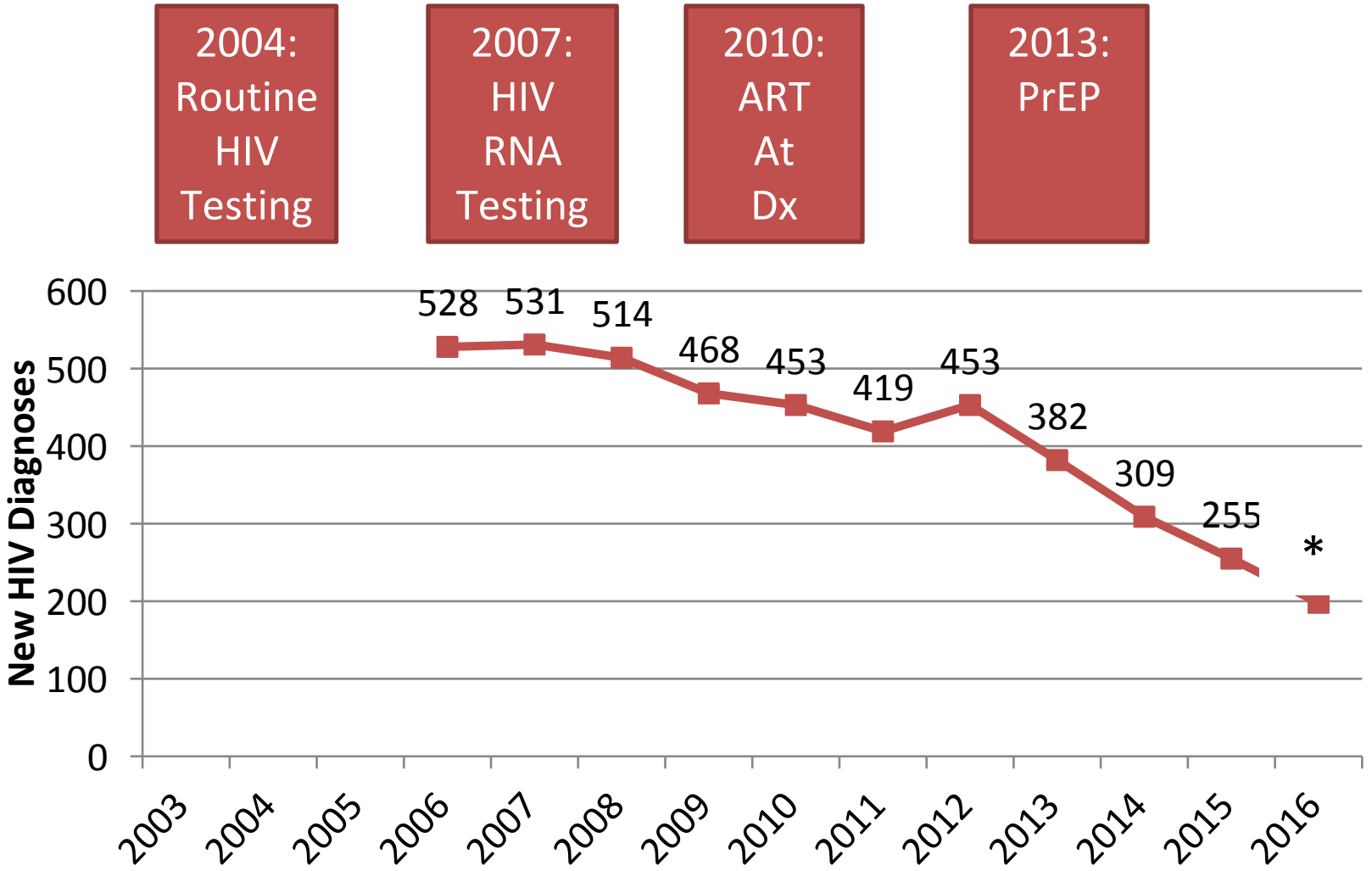
Increases visibility, normalizes, builds community.



PleasePrEPMe.global registry of private and public PrEP clinics as of June 4, 2017

New HIV Diagnoses in San Francisco

No change since 2012 in the proportion of PLWH virally suppressed



Adapted from SF DPH, HIV Epidemiology Annual Report, Published September 2016

*extrapolated from the SF DPH quarterly report, Jan through June 2016; affected by delayed reporting.

Nurses make PrEP easier at SFAF/Magnet PrEP service

- Directed and staffed by nurses (a few NPs)
- First PrEP client visited in November 16, 2014
  >2200 started PrEP through March 2017
- No charge for clinical or lab services
- Funded mainly by 340B revenues
- Point of care rapid creatinine and HIV ab testing
- PrEP and PEP are provided, started the same day
- Racially and ethnically diverse
- No HIV infections

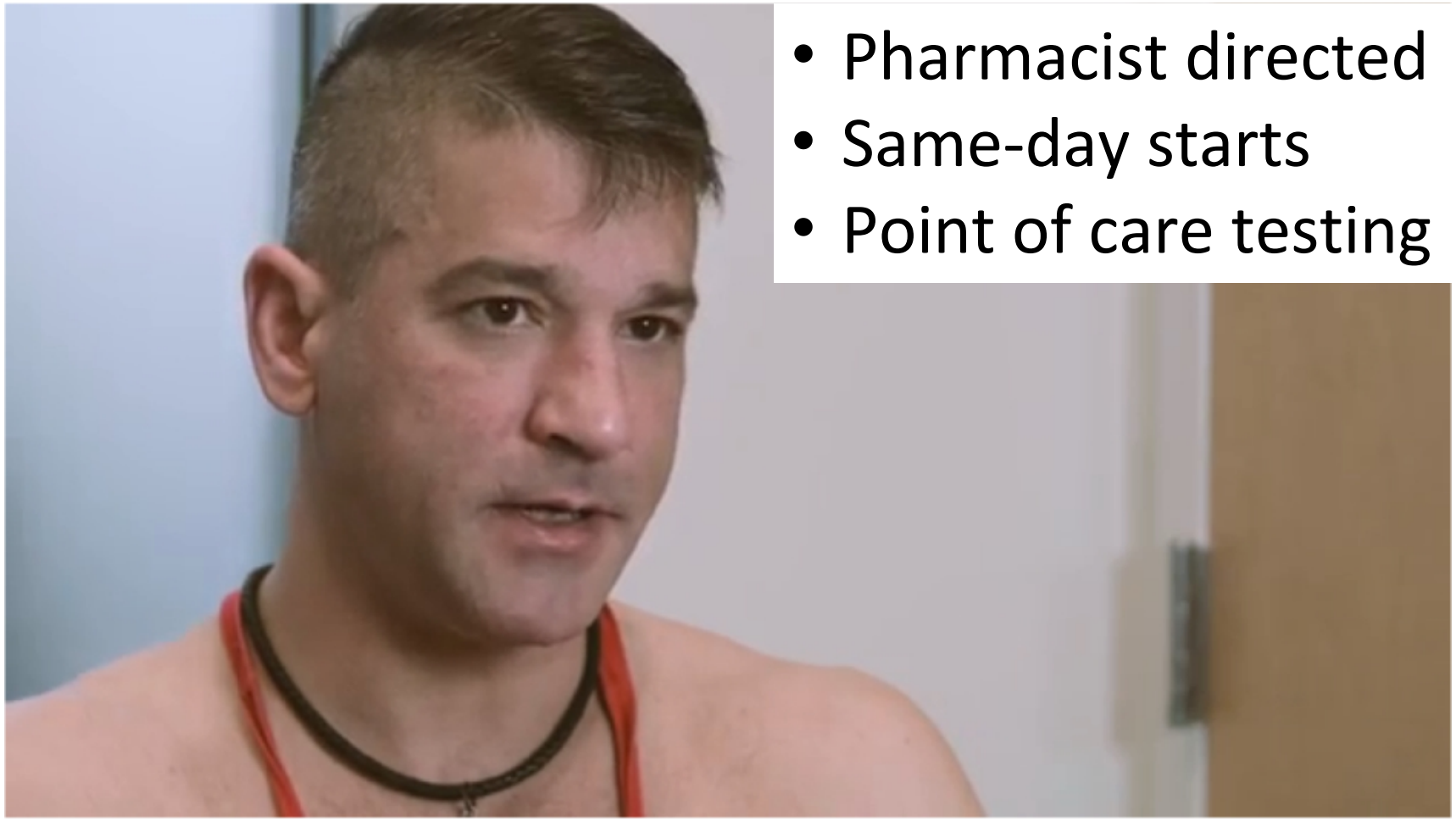
Cedric-Crouch. *Melbourne* 2016

Pharmacists make PrEP Easier at:

One Step PrEP.

KELLEY-ROSS PRESCRIPTION PHARMACY Est. 1925

Seattle, Washington



- Pharmacist directed
- Same-day starts
- Point of care testing

Most popular source of PrEP for Seattle PWID and many gay men. Eg: McMahan, CROI 2017.

An Internet Start-up Makes PrEP Easier:

1. Online history,
2. trip to a local lab,
3. PrEP delivered to home,
4. phone, email or SMS support throughout.

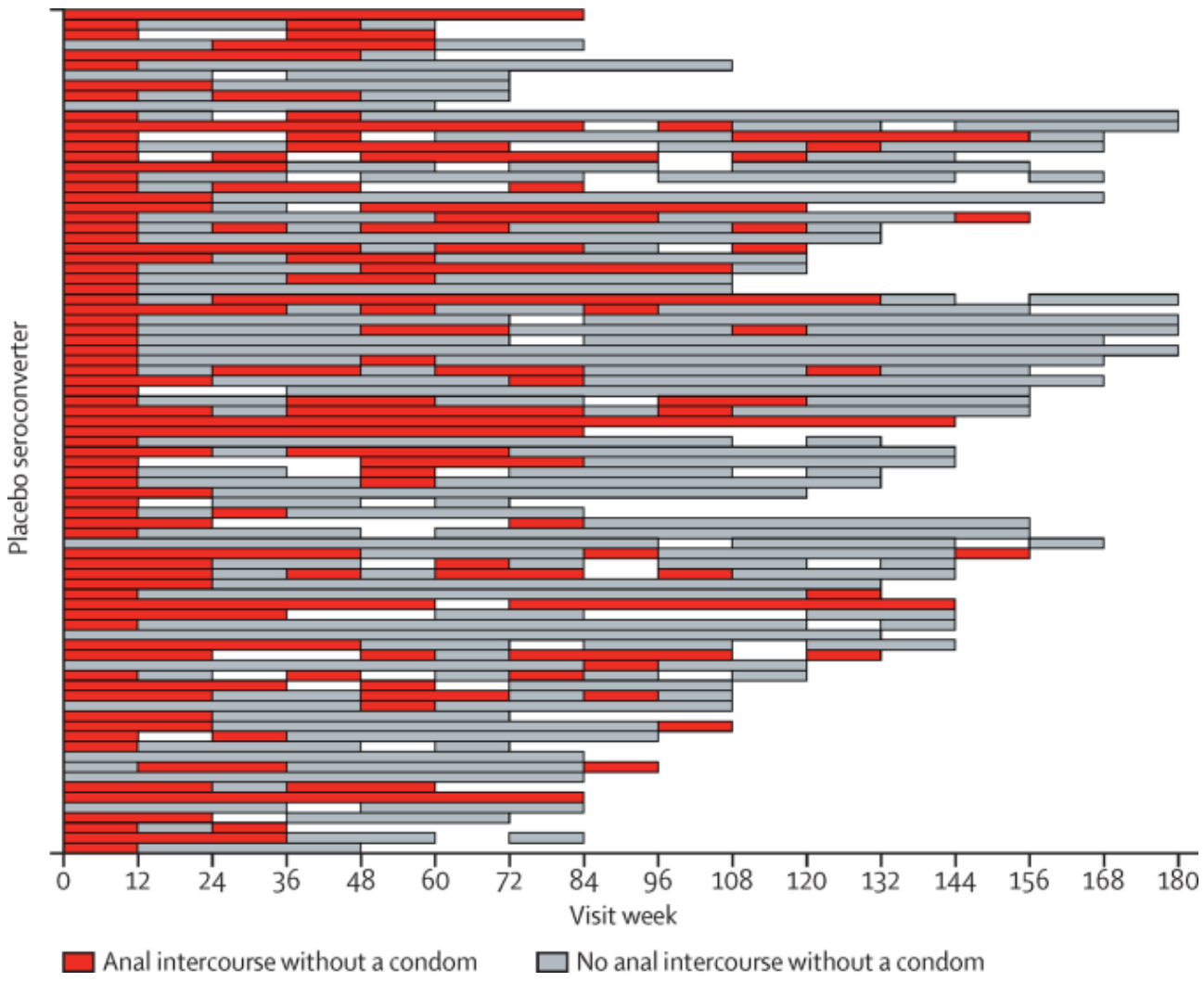
Making PrEP Easier with **Less Stigma**: No Blame, No Shame at SFAF/Magnet.

- Celebrate people reaching for goals.
- Taking risks is heroic: inherent in striving.
- Focus less on identity, more on situations.

New York Times

Seasons and Situations of Risk

"Identification of high-risk people might be less helpful than identification of high-risk moments, and the situations that cause them, such as leaving home, becoming an adult, coming out as a man who has sex with men, immigrating to a new city, ending a relationship, and others."



Grant and Glidden, Lancet 2016 387 (10027):1507–1508.

Making PrEP Easier with Less Targeting:
UCSF 360 and SFAF/Magnet Give PrEP to Anyone Who Wants It.

- No one likes being targeted.
- “Secretly” targeting people is duplicitous.
- Targeting is expensive and unattractive, especially to people who would benefit most from PrEP.
- If you offer PrEP in non-stigmatizing ways, the right people come at the right times.
- Demand for PrEP has never been overwhelming.

Grant Lancet HIV 2014; Grant CROI 2015; Cedric-Crouch Melbourne 2016

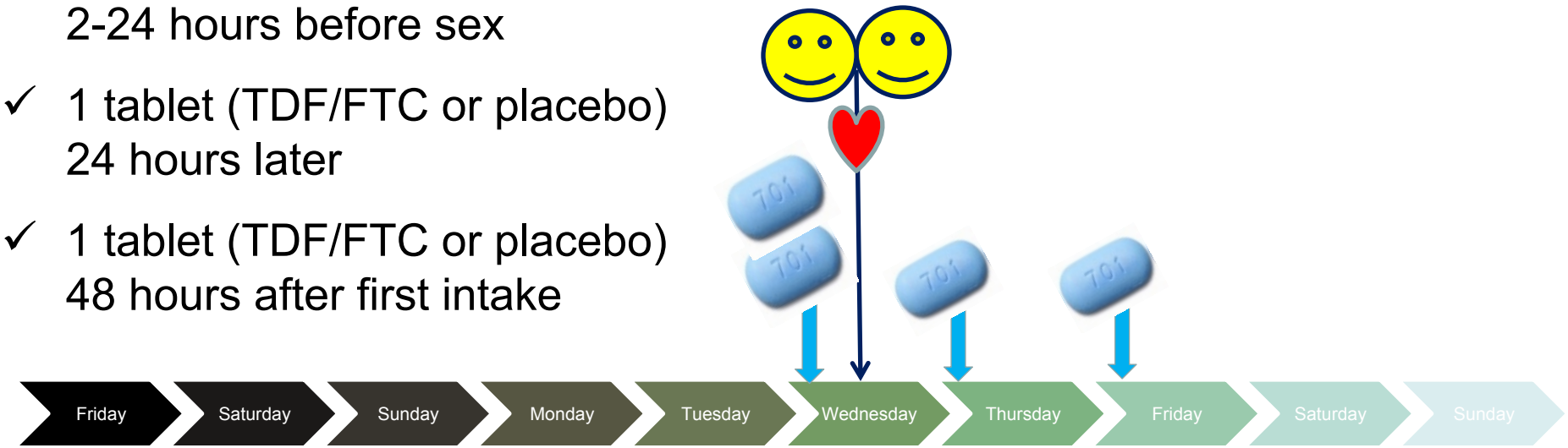
Can we make PrEP Easier with Fewer Labs?

- **Creatinine (Cr)** testing may not be required.
  - WHO only "suggests" Cr testing (not required).
  - Nearly all Cr elevations occurred among age >40 in Partners PrEP and iPrEx.
  - Evidence of no permanent renal injury from PrEP.
- Evidence of no benefit of **HBsAg testing** in PrEP.
  - Data limited to people without obvious cirrhosis.
- **HIV testing** is mainly useful when starting or restarting PrEP after a period of HIV exposure.
  - Extremely low diagnostic yield during PrEP use.
- There are ways to make **STI testing** less expensive.

WHO 2015; Hefron *Melbourne* 2016; Gandhi *JAIDS* 2016; Solomon CID 2016; Solomon *JID* 2016; Grant *Melbourne* 2016.

Making PrEP Easier with Event-Driven PrEP

- ✓ 2 tablets (TDF/FTC or placebo)
  2-24 hours before sex
- ✓ 1 tablet (TDF/FTC or placebo)
  24 hours later
- ✓ 1 tablet (TDF/FTC or placebo)
  48 hours after first intake



For MSM: 86% effective (ITT); 100% effective as treated.
Guidance for starting and stopping built into the regimen.
No evidence for on-demand PrEP for vaginal sex.

Molina, NEJM 2015

HPTN 067 BKK MSM: Tenofovir DP in PBMCs.

Proportion achieving protective concentrations.

Time period	Study Regimen Daily (D)	Study Regimen Time (T)	Study Regimen Event (E)
Week 10 (with sex in the past 7 days)	100% (n=31/31)	97% (n=28/29)	93% (n=28/30)
Week 30 (with sex in the past 7 days)	91% (N=21/23)	95% (N=18/19)	86% (N=12/14)

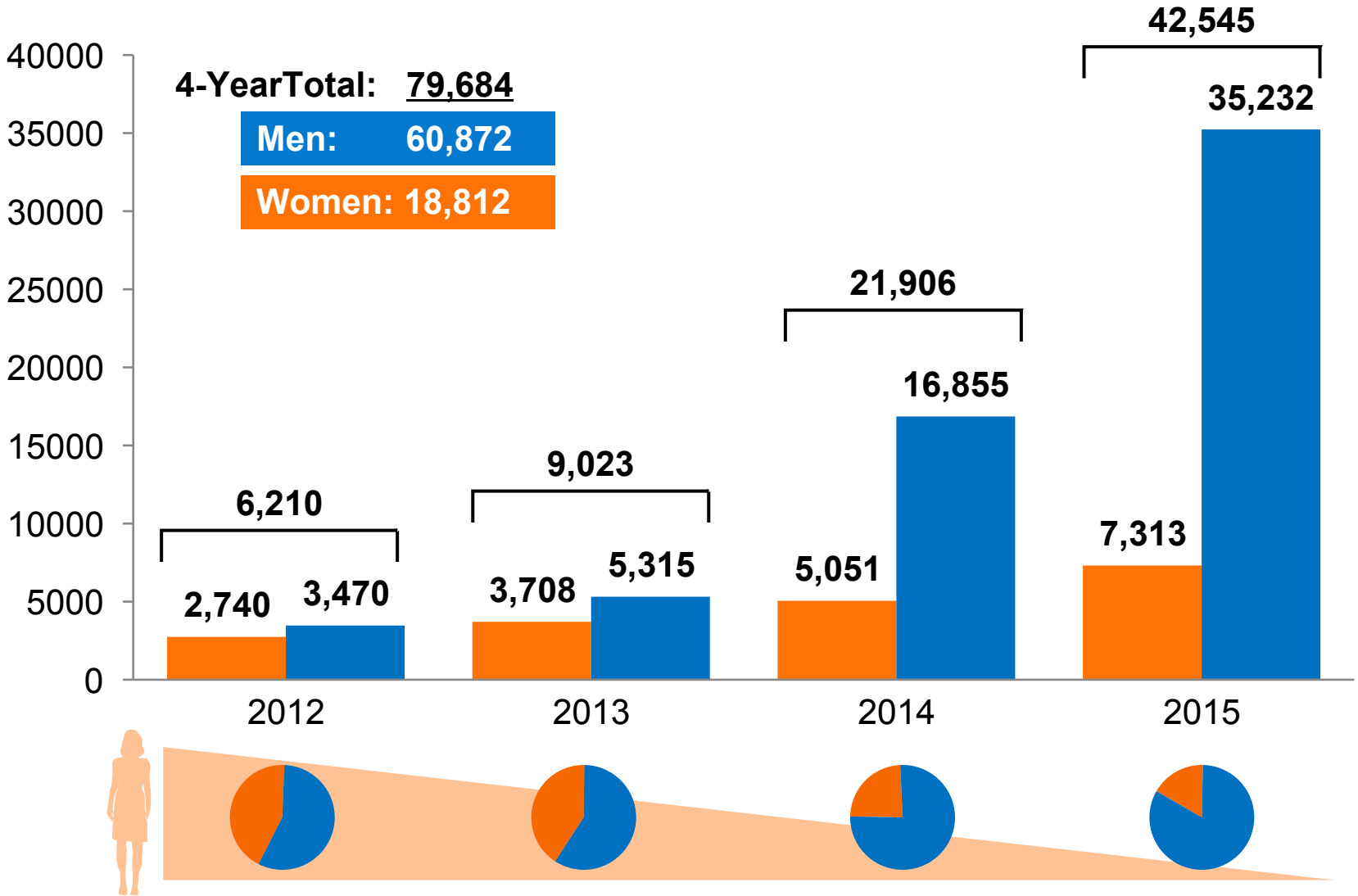
Detectable >9.1 fmol/million PBMC

D/T p = 0.90, D/T p = 0.28, T/E p = 0.35, global p = 0.48

PrEP 2.0

Foster Appropriate Demand For PrEP in Women

Men and Women Starting FTC/TDF for PrEP in US, 2012 to 2015



From K. Mayer, HPTN meeting; data adapted from Bush ASM/ICAAC 2016

Fostering Demand: Say PrEP works for women

- More women than men participated in PrEP RCTs.
- There was no difference between PrEP efficacy for men and women in the WHO GRADE analysis.
- 3 trials showed efficacy in women: Partners, TDF2, and BTS.
- No infections if drug concentrations indicated use of 6 or 7 tablets per week.
- Unlike MSM/TGW, there were some infections with 4 to 5 tablets per week.
- PK modeling suggests that about 6 to 7 tablets per week are needed for **full** protection during vaginal exposure.

Fonner *AIDS* 2016; Grant *AIDS* 2015; Cottrell *JID* 2016

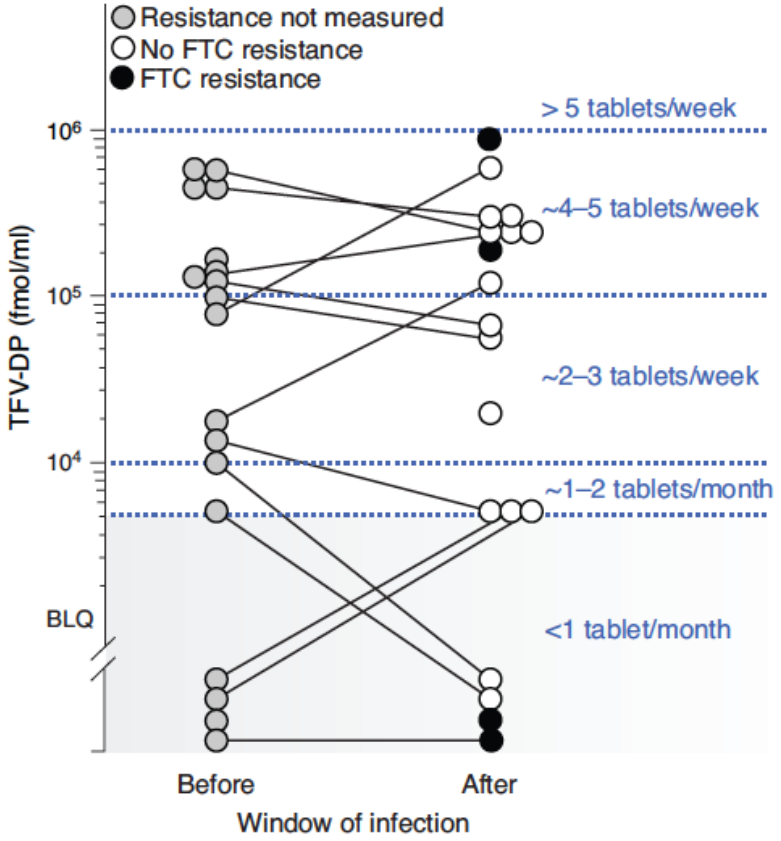
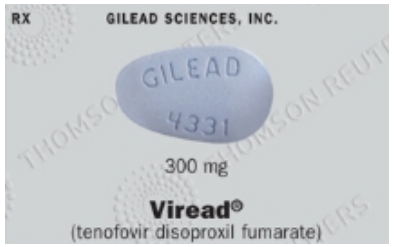


Fig. 2. Intracellular TFV-DP concentrations and clinical drug resistance. Values from active arm seroconverters with drug detected before and/or after the infection window period are plotted, and from all seroconverters with evidence of FTC resistance. Information from seroconverters with no detectable drug or drug resistance is not shown. There was no TFV resistance detected. Values below the limit of detection (5000 fmol) are plotted in the grey area. Black dots represent cases in which FTC resistance was detected using clinical assays. White dots are cases with no evidence of resistance. Resistance could not be measured before the infection window because there was no detectable virus at that visit. FTC, emtricitabine; TDF, tenofovir disoproxil fumarate; TFV-DP, tenofovir diphosphate.

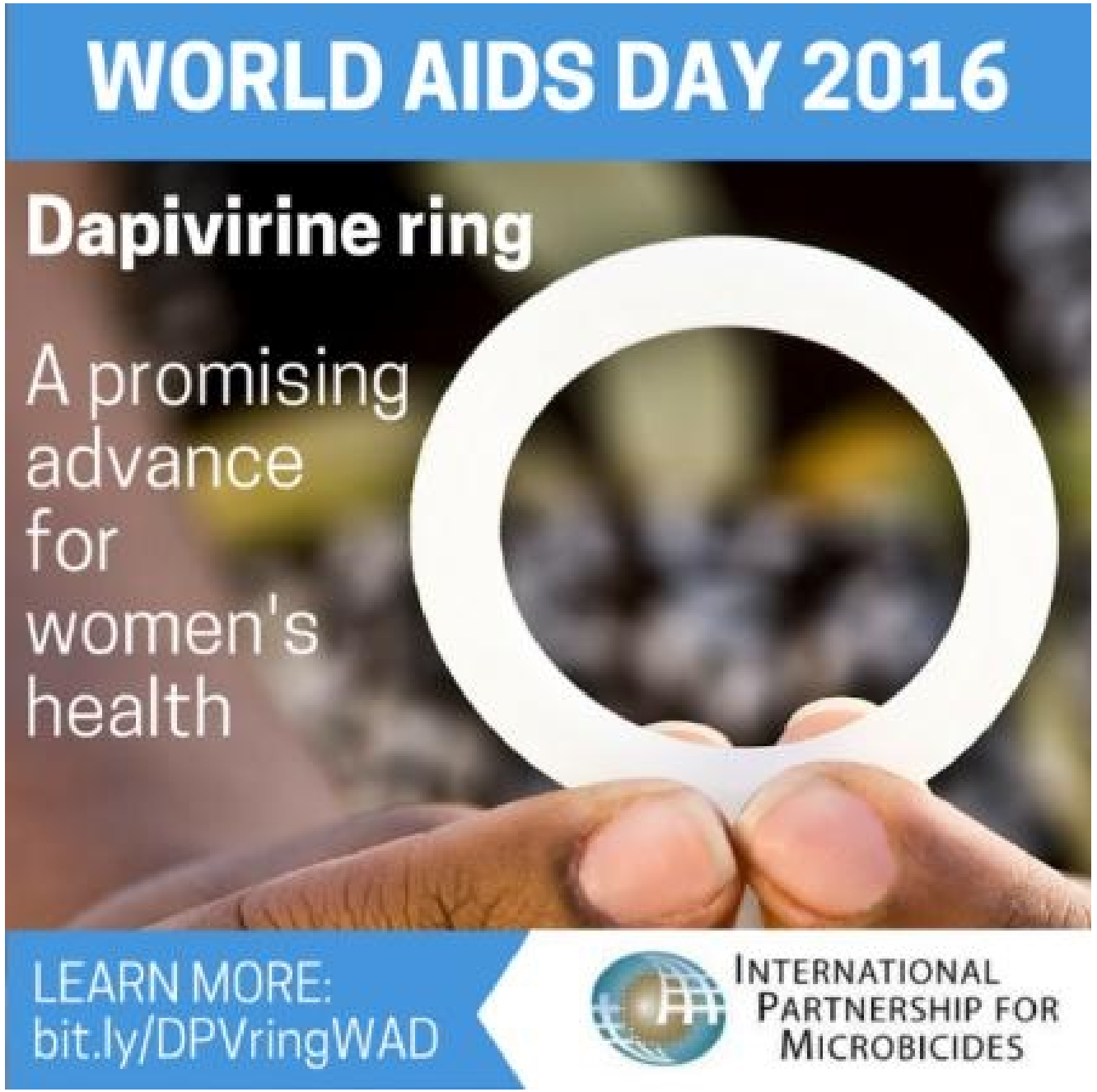


WHO review:

"Given available safety data, there does not appear to be a safety-related rationale for prohibiting PrEP during pregnancy/lactation or for discontinuing PrEP in HIV-uninfected women receiving PrEP who become pregnant and are at continuing risk of HIV acquisition."

Mofenson *et al AIDS* 2017

Mofenson Plos Med 2016; Mugwanya Plos Med 2016; Benaboud AAC 2011; Zash JAIDS 2016; Chen JID 2012; Mugo JAMA 2014; Bunge IAS Vancouver 2015.



Beaten *NEJM* 2016; Nell *NEJM* 2016.

Gain Frames for PrEP among MSM/TGW

Gain Frames for PrEP among Women

::Hangouts with HIVE::

PrEP Awareness Campaigns: Including Women

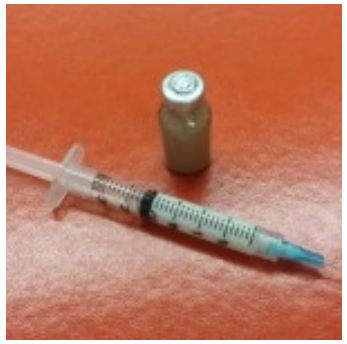
Surveys and focus groups conducted with women demonstrate:

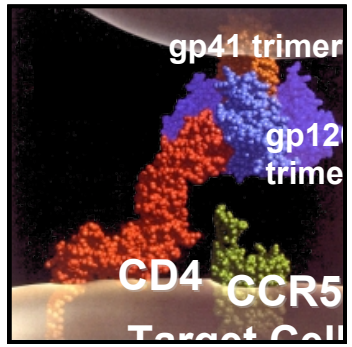
- Few women know about PrEP as an effective HIV prevention method
- Women are interested in learning more about PrEP as a potential option for themselves

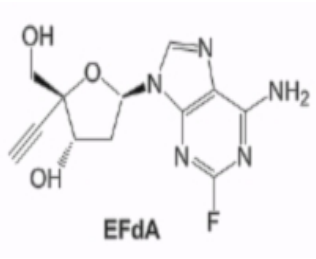
Other populations who would benefit from more PrEP…

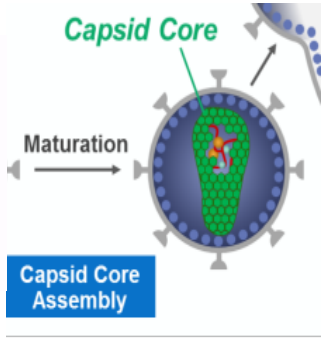
- Everyone, especially…
  - Black and brown people
  - Transgender women and men
  - Youth
  - Bisexual people
  - People who use drugs
  - Gay men
  - Others

PrEP 2.0: New PrEP Agents









F/TDF *v.* F/TAF
Smaller tablet.
Less cost of goods.
Safe for HIV Rx:
Less renal and bone toxicity.
Worked in monkeys.
In Phase 3.

Long Acting Cabotegravir
Every 2 month IM.
Worked in monkeys.
Safe in Phase 2 for MSM.
In Phase 2 for women.
In phase 3 for MSM.

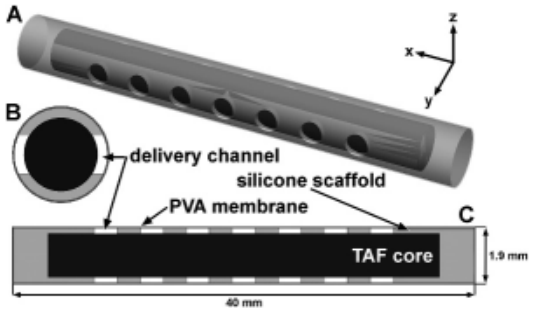
VRC01
Antibody neutralizes 90% of HIV strains.
Injectable SQ or IV.
Implications for vaccines.
In Phase 2.

EFdA (MK-5891)
Once a week oral 10mg or twice a year injectable.
Subnanomolar potency.
Active against resistant HIV.
In phase 1.

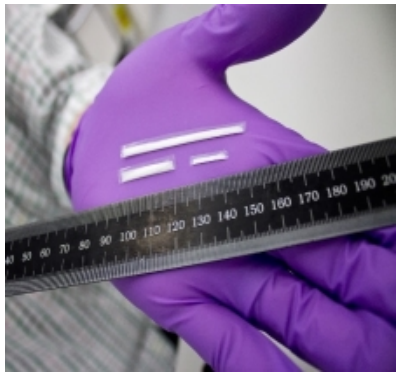
GS-CA1
Long half-life: stays 9 times higher than paEC95 after 10 weeks.
Nanomolar potency.
No x-resistance with existing therapy.
Preclinical.

Markowitz *CROI* 2017; Mills *Lancet Infect Dis* 2016; 16: 43–52; Gallant et al;
Tse W, et al. CROI 2017. Seattle, WA. #38; Globler CROI 2017; HPTN/HVTN websites.

PrEP 2.0: Sustained Release Implantables

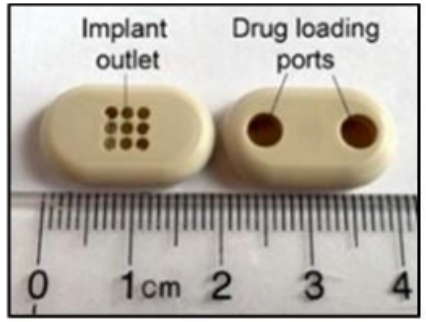


Silicon Implant
SQ implant.
1.9mm x 40mm.
Protective concentrations of TAF in beagles.



TFPD Injectable for Prevention.
SQ implant.
Biodegradable.
Removable.
Absorbable.

Osmotic Pump.
SQ implant.
Consistent dosing over time.



Nanochannels
SQ implant.
Consistent dosing over time.
Refillable.
Achieved protective concentrations in primates for 70d.

All require highly potent medications (more potent than TDF or FTC)

Manjula *Antimicrob. Agents Chemother.* 2015;59:3913-3919; Leah Johnson et al, # 879 CROI 2016; Grattoni et al, #422LB, CROI 2017.

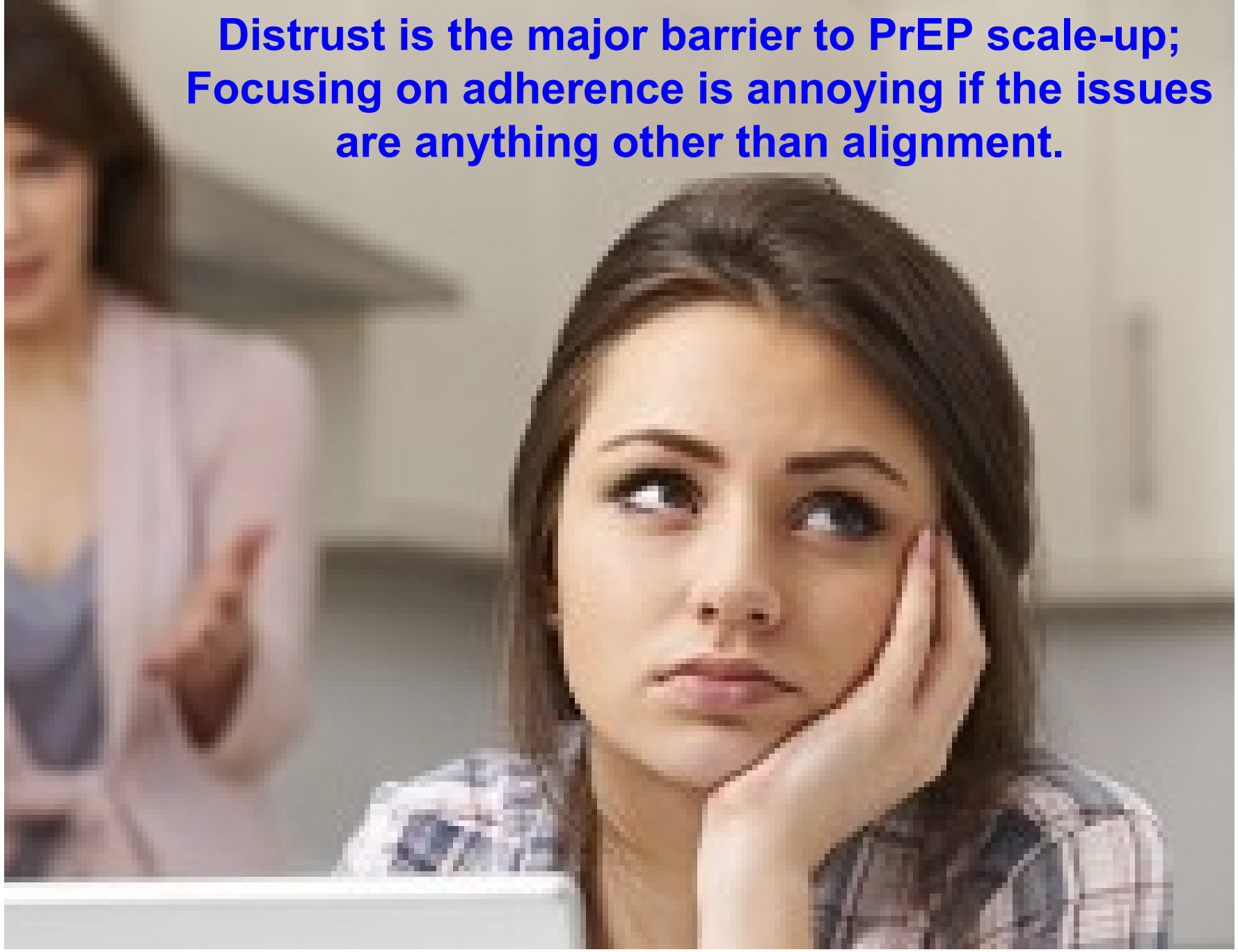
Possible Pitfalls of New PrEP Candidate Medications and Devices

- We do not know if they are effective.
- They address only one barrier to scale up.
  - Not the most substantial barrier.
- Providers may be afraid to use them.
  - And provider fear is a major barrier.
- No clear regulatory pathway.

Distrust	Uncertainty	Alignment	Mutuality
Different Questions About PrEP			
Why are you still talking?	*What is PrEP?*	*How can I use PrEP?*	*How do we get more?*
Different Goals for the Care Team			
Build Trust For Disclosure	*Support Exploration With Information*	*Problem solving; SMS; Build Skills; long acting agents.*	*Let Her Lead*

Adapted from Amico, **Mutuality Model**, *AIDS and Behavior.* 2017

Distrust is the major barrier to PrEP scale-up; Focusing on adherence is annoying if the issues are anything other than alignment.



Adapted from Amico, **Mutuality Model**, *AIDS and Behavior.* 2017

Provider Non-adherence is the Bigger Problem.

- HBV vaccination is a safe, cheap, and convenient prophylactic for a potentially fatal viral infection.
  - Vaccination rates among recommended groups are typically less than 30% world-wide.
  - Non-adherence appears to be on the part of the provider: Vaccine uptake was >90% among MSM/TGW when offered the HBV vaccine in iPrEx.
- Providers express concerns that PrEP will cause risk compensation, STI transmission, long term toxicity, drug resistance, and cost.
  - These concerns may be greater with long acting PrEP.

Solomon *JAIDS* 2016

Injection Site Pain

Long Acting Cabotegravir ÉCLAIR trial

	PBO (N=21) n (%)	CAB (N=94) n (%)
Grade 1-4 adverse events	19 (90)	92 (98)
Grade 2-4 adverse events (>5% in CAB arm)	10 (48)	75 (80)
Injection site pain	**1 (5)**	**55 (59)**
Pyrexia	0	7 (7)
Injection site pruritus	0	6 (6)
Injection site swelling	0	6 (6)
Serious adverse events[a]	1 (5)	1 (<1)

- Most participants said they preferred injections over oral;
- There were no dose limiting laboratory adverse events.

[a]PBO: deep vein thrombosis (drug-related); CAB: appendicitis.

Markowitz et al. CROI 2016; Boston, MA. Abstract 106.

NNRTI Resistance Selected During the Tail of Rilpivirine Concentrations

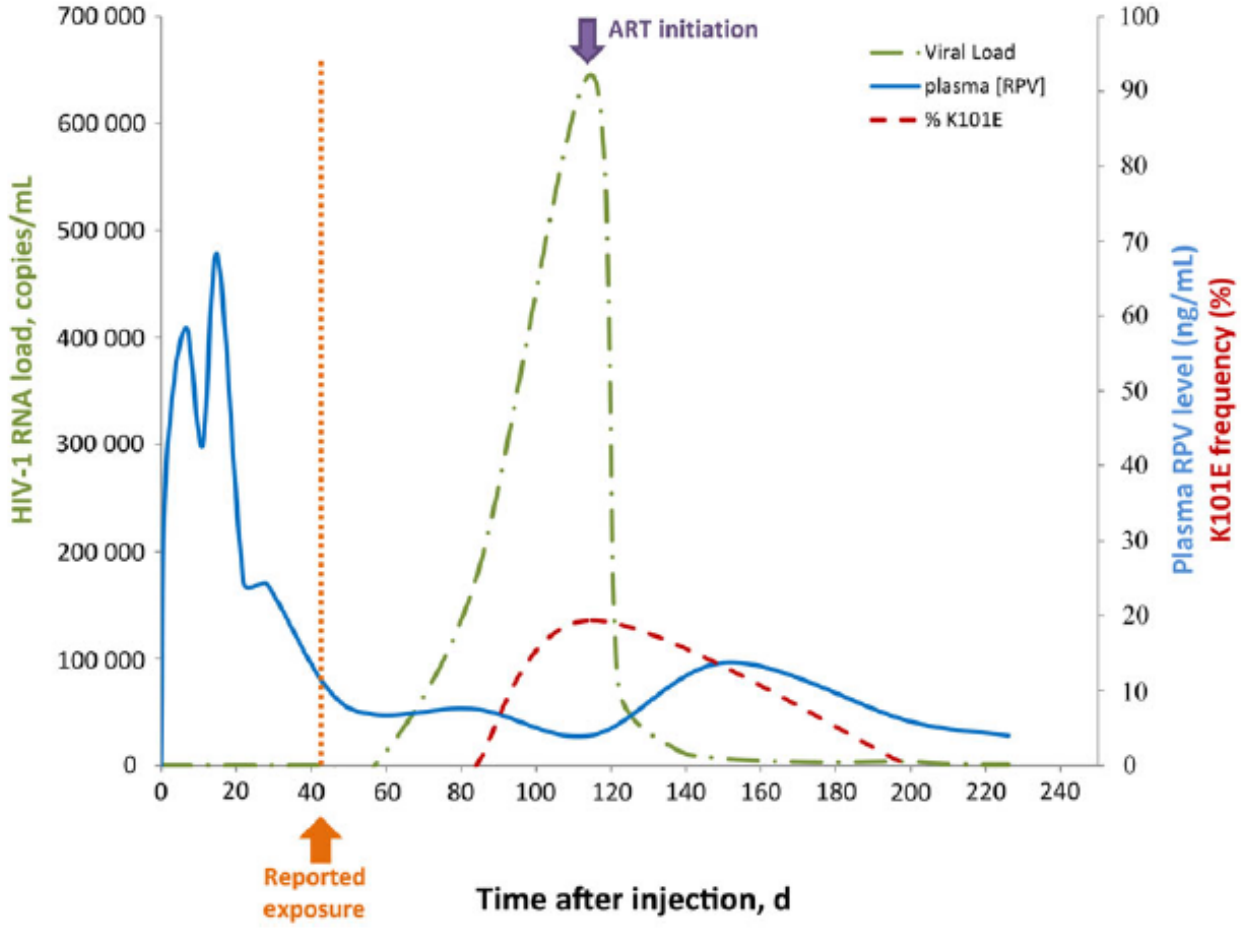


Figure 1. Timeline of human immunodeficiency virus type 1 (HIV-1) RNA load (dash-dotted line), plasma rilpivirine (RPV) concentration (solid line), and selection of the K101E mutation (dashed line) in 1 participant from the SSAT040 study. HIV-1 exposure was reported to have occurred on day 41 (dotted vertical line), and antiretroviral therapy (ART; tenofovir/emtricitabine and ritonavir-boosted darunavir [800/100 mg]) began on day 115.

The PrEP Trial Bottleneck:

Phase 3 trials of PrEP Agents as of May 2017

	Effectiveness
Daily oral FTC/TAF	Results expected 2019
Injectable LA Cabotegravir	Results expected 2020

Non-inferiority Trials for PrEP: A regulatory bottleneck.

- Per trial costs are >$150M, need >4 years.
- Non-inferiority trials are prone to bias:
  - Tendency to oversample populations who are known to struggle with the SOC (standard of care).
  - Even if non-inferior, the new agent may be less efficacious than SOC, which did not work perfectly.
  - Increased trial size and duration leads to decreased precision in measurement (esp. less retention), creating a bias in favor of non-inferiority.

Alternatives to Non-Inferiority Trails

- **Single arm with external controls (eg: benchmarks)**
  - Used to approve most contraception,
  - Use to evaluate and approve some HCV medications,
  - Was used to evaluate PEP efficacy,
  - Eg: Partners PrEP demonstration project.
- **Surrogates of Incidence.**
  - Lead-in cohorts,
  - Recency Assays (HIV RNA, Lag Avidity, S/CO ratios),
  - STI incidence.
- **Drug concentrations by incident HIV infection:**
  - An effective PrEP agent will be detected less frequently among seroconverters compared with people who remain seronegative.
  - Compelling if drug detection is higher with higher HIV exposure; otherwise confounding will be a concern.

Miller *Clin. Pharm. Therap.* 2014; Dunn *Curr. Op. HIV/AIDS* 2016

Liberal Theory

John Locke

1632-1704

(also Hume, Rousseau, Kant)

Potrait by Godfrey Kneller, 1697

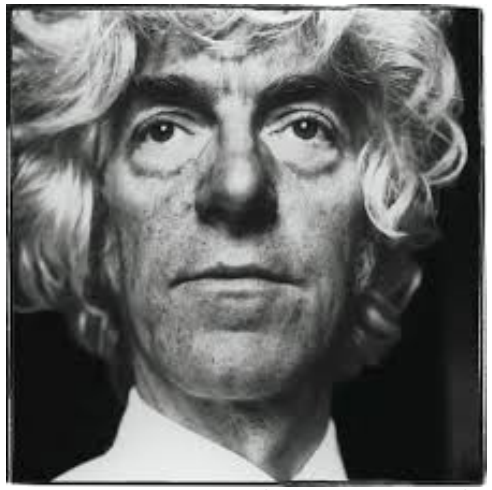
- Personhood is individual; continuous over time.
- Behavior is individual (selfish).
- Fear regulates pleasure for good.

Social Theory

Derek Parfit

1942-2017

(also Foucault, Halperin, Butler, Hill-Collins)



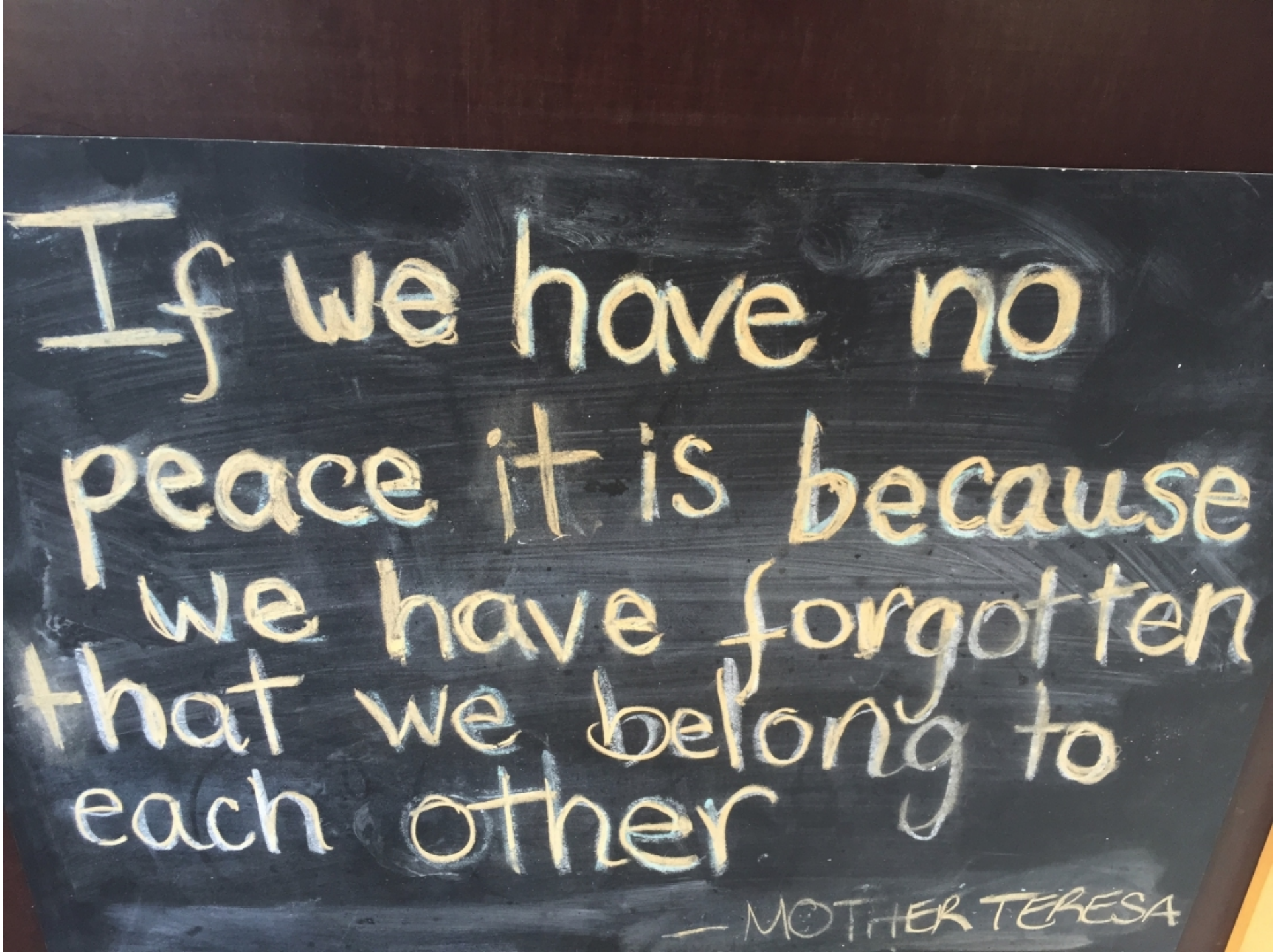
Larissa MacFarquhar, *New Yorker*

- Personhood is social; shifts over time.
- Behavior is social.
- Social connection fosters good.

Possible implications for PrEP

- I think therefore I am.
- Risk perception (fear) is key.
- Risk compensation is human.

- I am because we are (Ubuntu).
- Social mobilization is key.
- Social connection is human.


If we have no
peace it is because
we have forgotten
that we belong to
each other
— MOTHER TERESA

Summary

- Oral FTC/TDF PrEP can be easier
- Oral FTC/TDF PrEP is safe and effective for women (and others); Simple and evidence-based messages would foster demand.
- New PrEP candidates and devices have longer action and greater potency and unknown effectiveness.
- PrEP findings challenge medicine to modernize its conventional formulations of individual personhood and morals.


PrEP was made possible
by mostly young
study participants
who believed that research
could improve their lives