



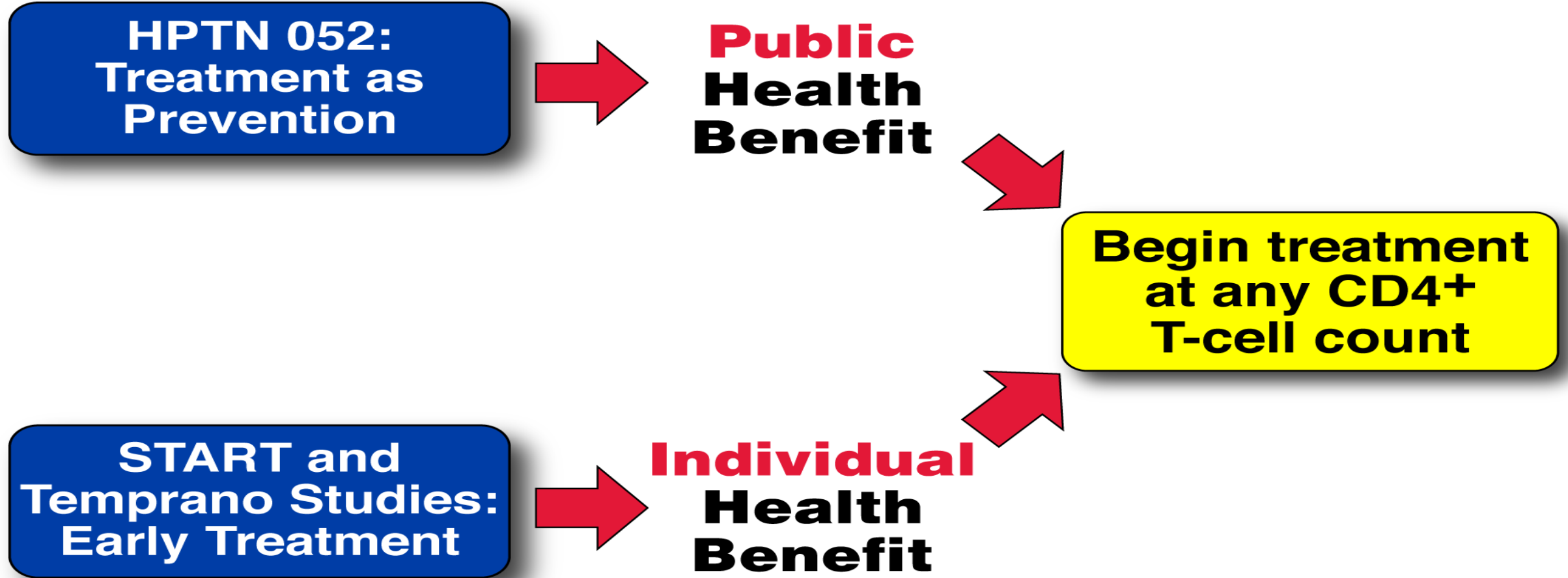
Integrating PrEP with Early Antiretroviral Initiation

Kenneth H. Mayer, MD

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2018 Controlling the HIV Epidemic Summit, Geneva

May 3rd, 2018

The Key Paradigm: Test and Treat (when ready)



Why PrEP? In the TasP Era, Reductions in New HIV Infections are Off Target

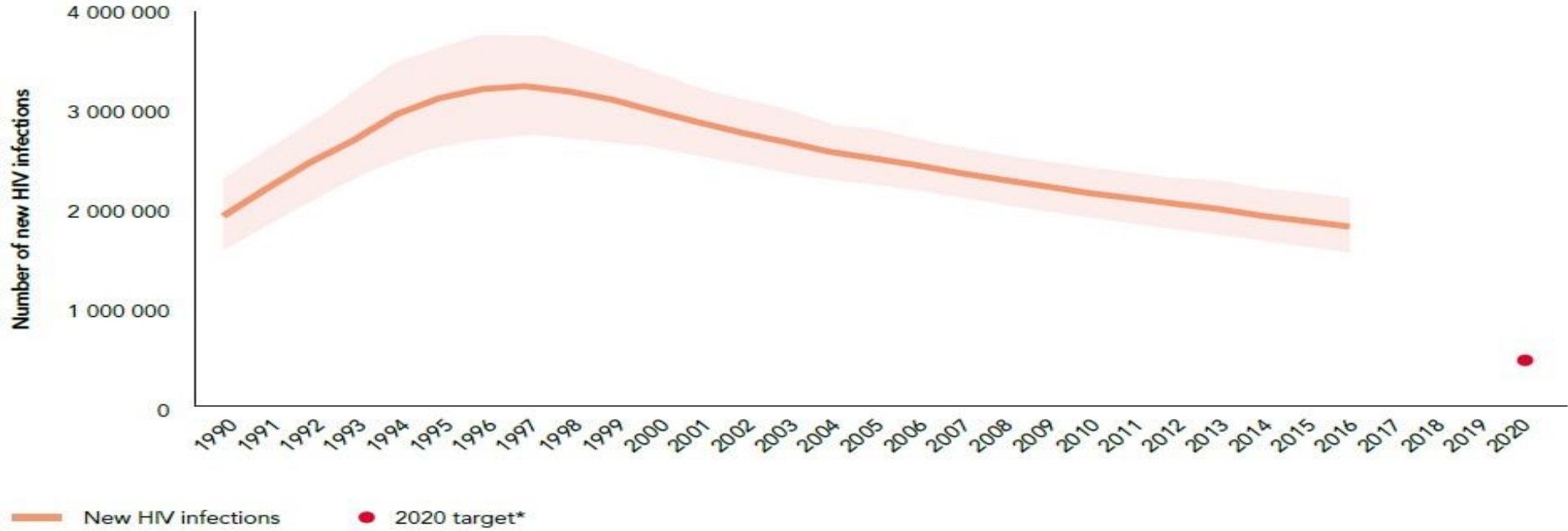
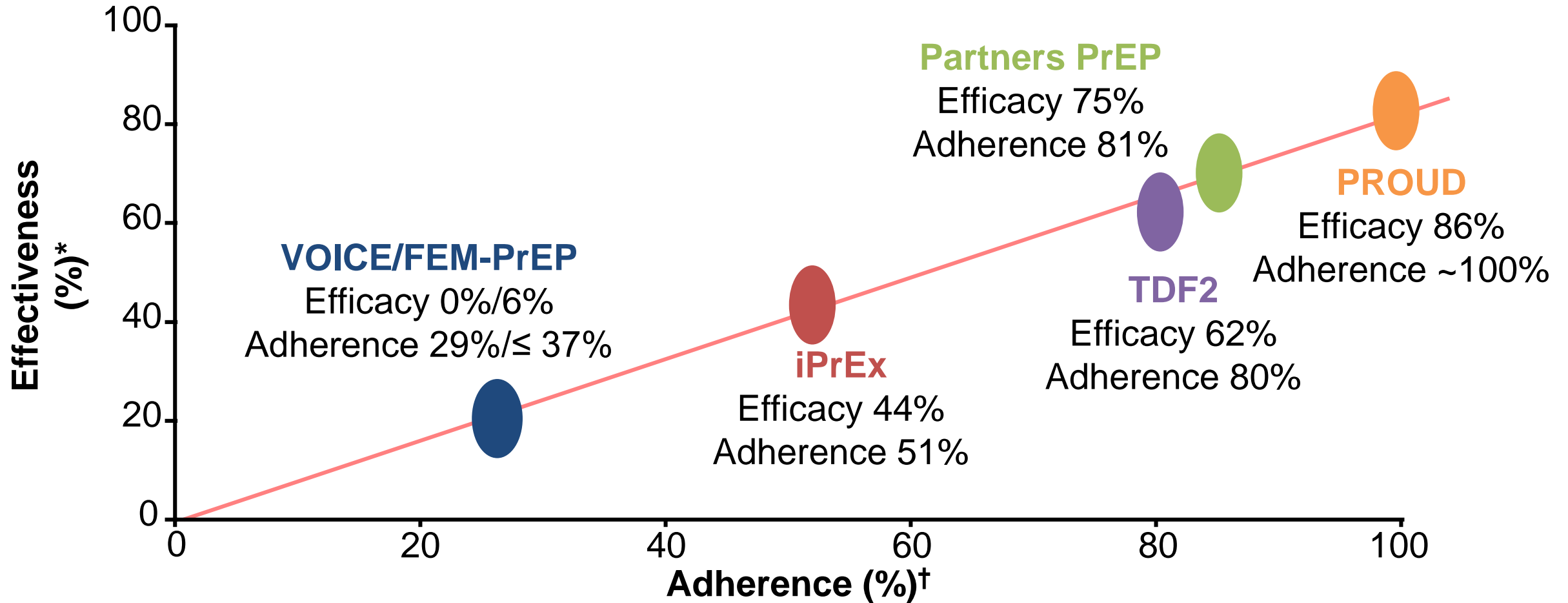


FIGURE 2.4. NEW HIV INFECTIONS, ALL AGES, GLOBAL, 1990–2016 AND 2020 TARGET

*The 2020 target is fewer than 500 000 new HIV infections, equivalent to a 75% reduction since 2010.

Source: UNAIDS 2017 estimates.

Select Daily Oral TDF/FTC PrEP Trials: Effectiveness Improves With Adherence



*Reduction in HIV incidence vs control.

†Based on pill counts or the detection of study drug in plasma.

Fonner VA, et al. AIDS. 2016

PrEP Safety: Well Tolerated and Rare Discontinuations

- At initiation of PrEP (start-up syndrome)
 - PrEP versus placebo: 1% to 18% versus 0% to 10% experienced nausea, vomiting \pm dizziness; Usually ends within the first month
- No difference between PrEP and placebo (overall and by subgroups)
 - Any adverse event (clinical and laboratory) or Grade 3/4 adverse events
- Several studies noted subclinical declines in renal function and bone mineral density among PrEP users
 - Grade 2-4 elevation in creatinine: 0.2%
 - BMD loss: 0.4% to 1.5% across total hip, spine, femoral neck, and trochanter
 - Returned to baseline with withdrawal of PrEP, no increased fracture risk

PrEP Management

Prior to PrEP initiation:

- Document negative HIV status prior to prescribing TDF/FTC
- Evaluate for signs or symptoms of acute HIV infection
- If concerned about acute HIV, obtain HIV quantitative PCR prior to rx.
- Evaluate renal function, and exclude patients with CrCl < 60 mg/ml
- Rule out active infection with HBV and document vaccination status
- Review medications to prevent administering contraindicated medications

Follow up after PrEP initiation

- Schedule follow up visits at least once every 3 months
- Refill PrEP prescription based on adherence to clinical follow-up
- Assess adherence and provide follow up adherence counseling
- Obtain HIV test, screen for bacterial STIs, monitor renal function
- For women: perform pregnancy test
- For injection drug users: link to drug treatment services and needle exchange programs

Is PrEP 100% Protective? NO

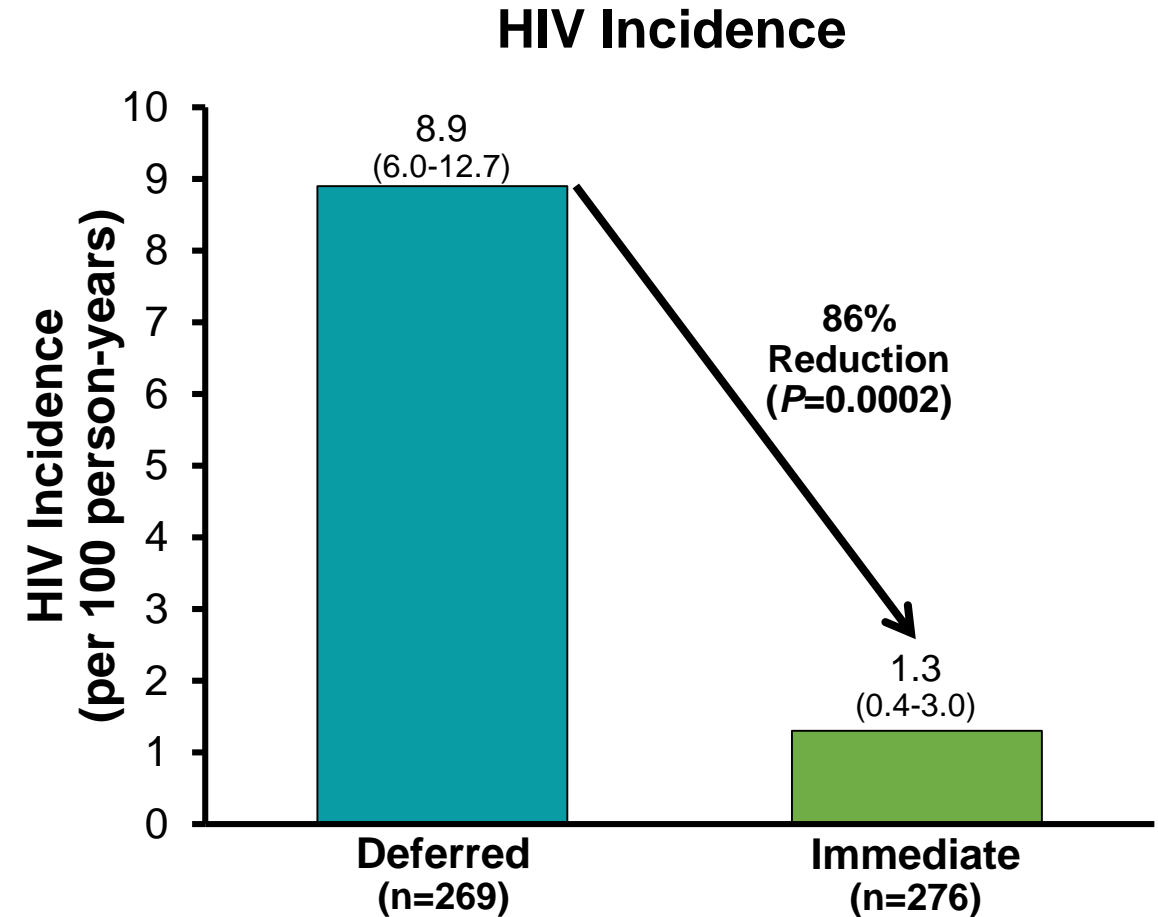
HIV Infection Rare with High Adherence to PrEP

Patient	PrEP Adherence	Seroconversion	Likely Cause of PrEP Failure
43-yr-old MSM ^[1]	24 mos, supported by pharmacy records, blood concentration analyses, and clinical history	Acquired MDR HIV infection	Exposure to PrEP-resistant, multiclass-resistant HIV strain
MSM in his 20s ^[2]	Excellent by self report, supported by blood and hair concentration analyses	Acquired MDR HIV infection after 2 instances of condomless insertive anal intercourse with 2 different partners within 11 weeks before diagnosis	Exposure to PrEP-resistant, multiclass-resistant HIV strain
50-yr-old MSM ^[3]	Excellent by self report, supported by blood analyses	Acquired wild-type HIV infection after 2-5 median condomless anal sex partners per day in each month following PrEP initiation	Chronic rectal inflammation +/- trauma

PrEP is not 100% effective, but is highly protective, so to optimize protection and decrease STDs, condoms can be helpful

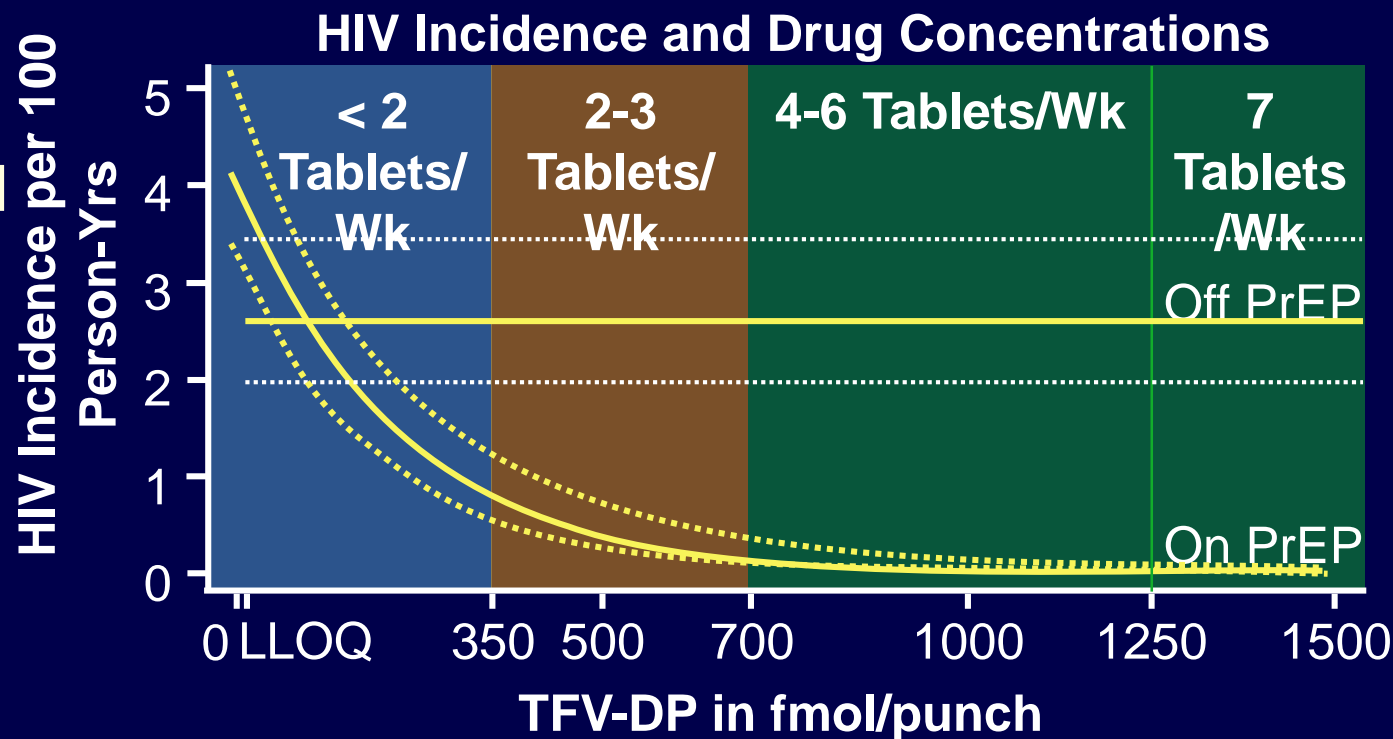
PROUD Study: High PrEP Efficacy in a Real-World Setting

- Significantly ↓ HIV infections with immediate vs deferred PrEP (3 versus 20 cases)
 - HIV infection predated PrEP start (n=1)
 - No drug/not adherent (n=2)
- Number needed to treat to prevent 1 HIV infection: 13
- PrEP was generally well tolerated



iPrEX OLE: PrEP Reduces Incidence of HIV Even With Incomplete Adherence in MSM

- Open-label extension of iPrEX trial; N = 1603 (75% receiving PrEP)
- 100% adherence was not required to attain full benefit from PrEP
 - Benefit of 4-6 tablets/wk similar to 7 tablets/wk
 - 2-3 tablets/wk also associated with significant risk reduction
- Higher levels of sexual risk taking at baseline associated with greater adherence to PrEP

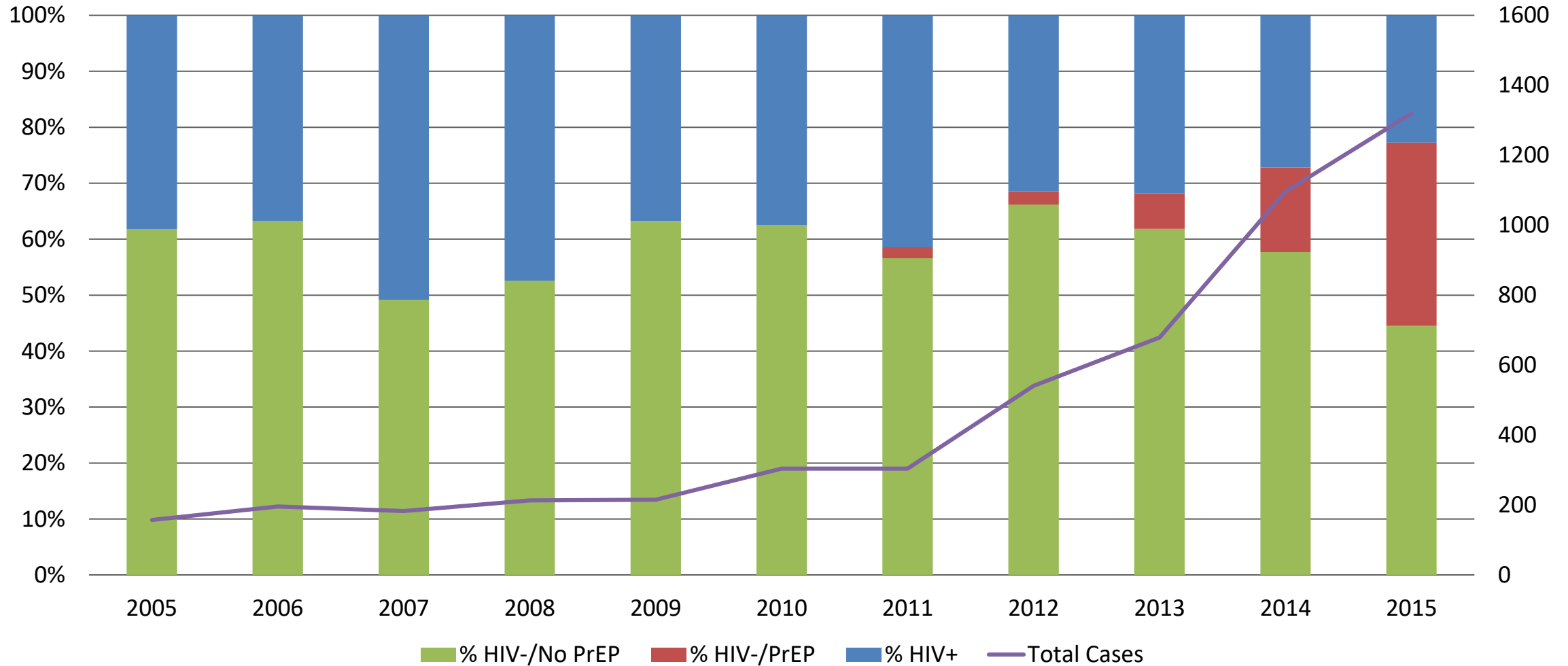


Grant RM, et al. Lancet Infect Dis. 2014;14:820-829.
Grant RM, et al. IAC 2014. Abstract TUAC0105LB.

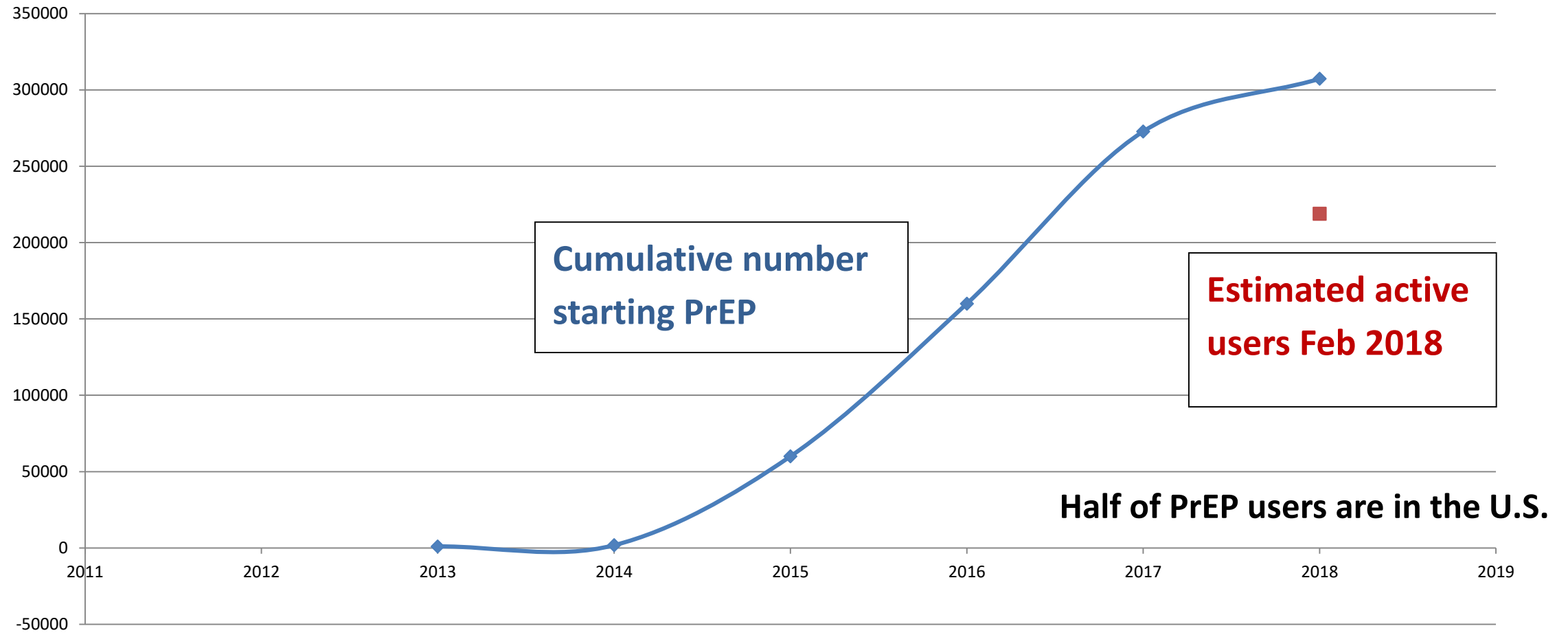
TDF/FTC PrEP and Women

- ITT estimates range from no protection to 75%
- Post-hoc analyses suggest efficacy >90% when drug consistently taken (Donnell); daily adherence is key
- Oral TDF/FTC has less avidity for cervicovaginal vs. colorectal mucosa, i.e. takes longer to achieve protective concentrations (Patterson)
- But, **daily** TDF/FTC readily achieves protective levels
- Vaginal microbiome (dysbiosis) affects topical TFV concentrations, but **not** systemic (Klatt)

Frequency of any Bacterial STI infection by HIV status and PrEP Use among Male Patients, Fenway Health

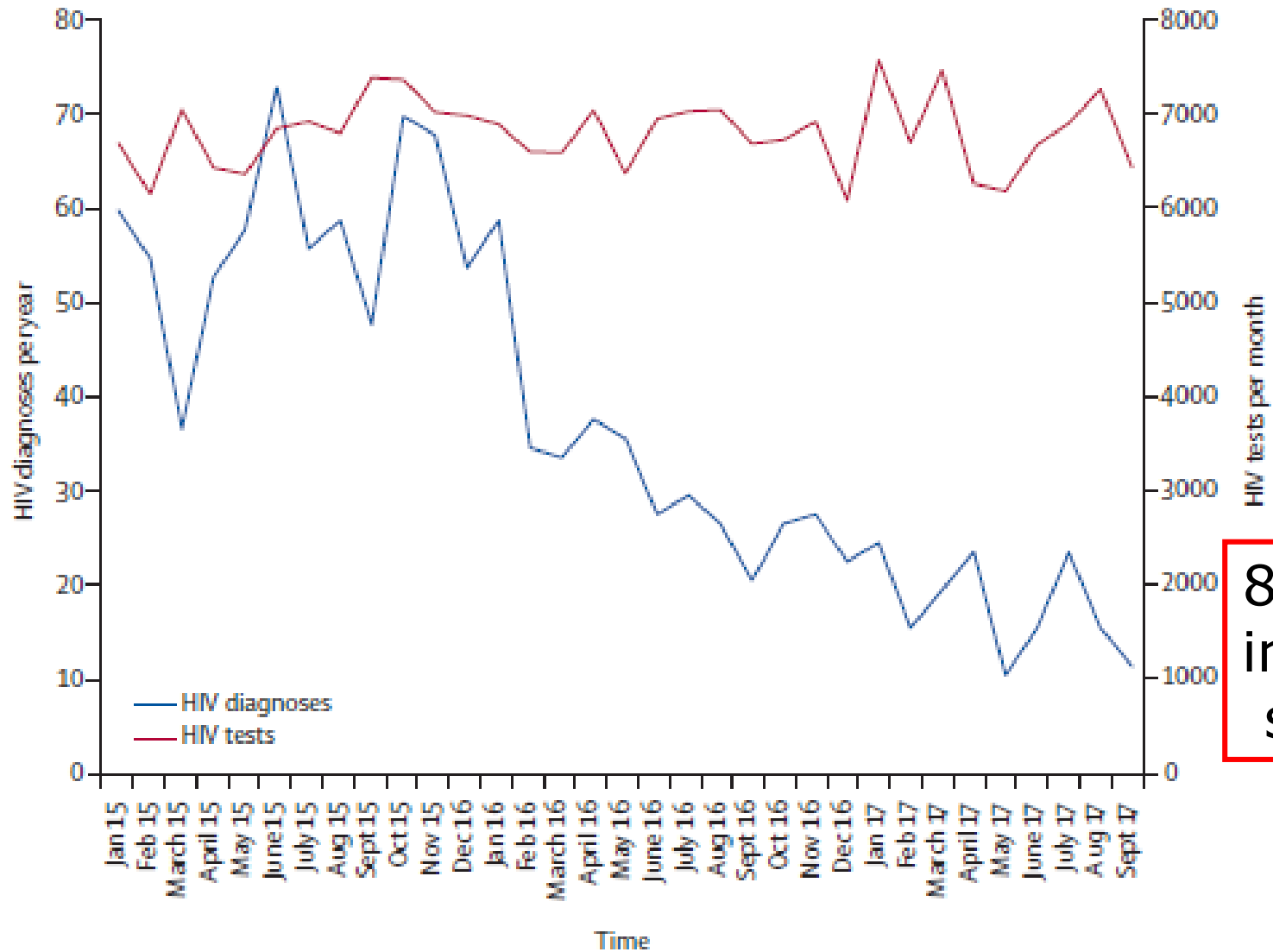


Number of people taking PrEP globally



HIV Decline at Dean Street -UK

Lancet HIV 2017
Published Online
October 20, 2017
[http://dx.doi.org/10.1016/S2352-3018\(17\)30181-9](http://dx.doi.org/10.1016/S2352-3018(17)30181-9)



80% decline in HIV cases since 2015



EPIC-NSW Cohort (N=3700): Targeted PrEP Decreasing HIV Incidence

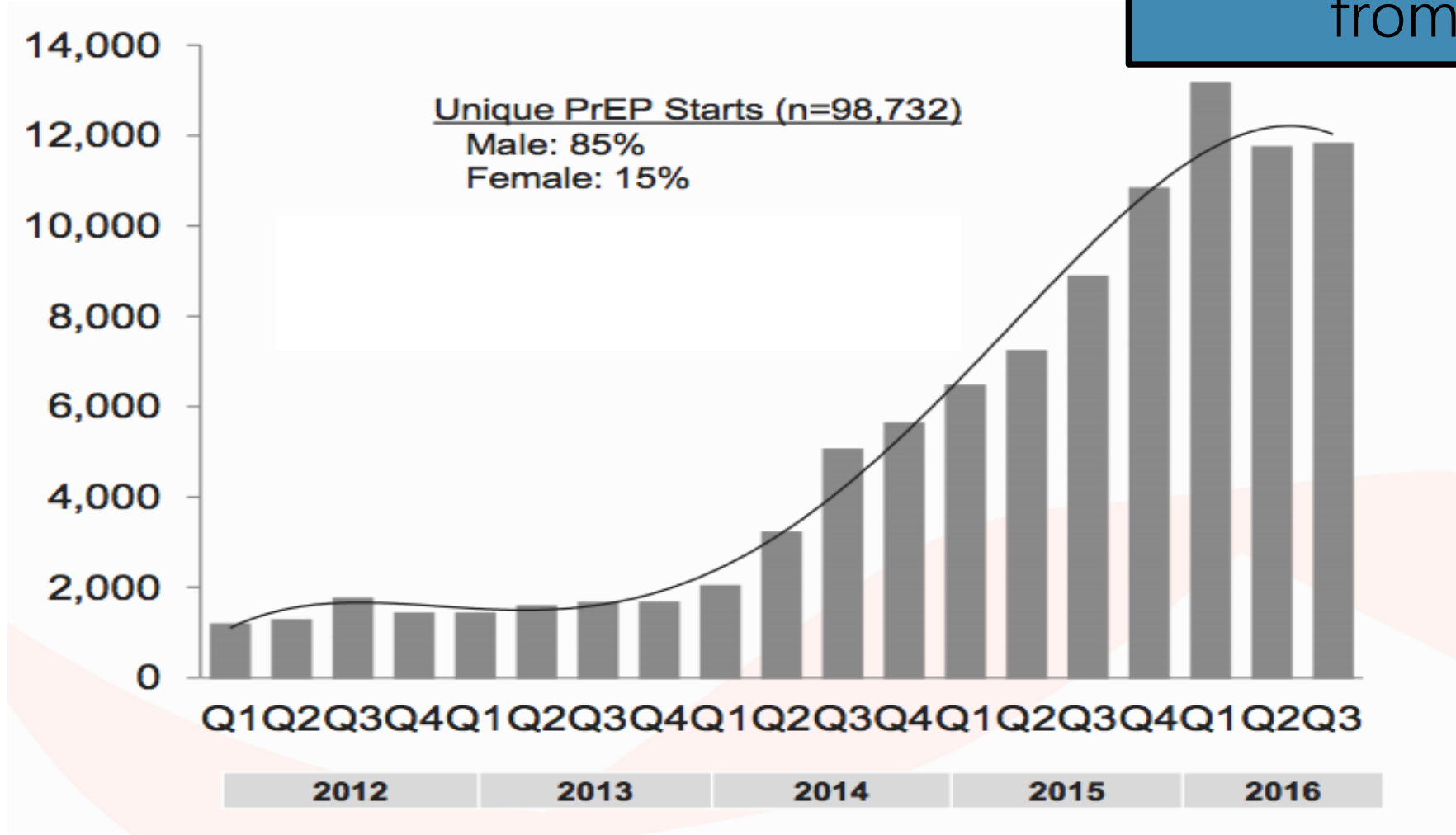
- Medication possession ratio over 12 months (having enough medication to take PrEP over 12 months)
 - Mean: 83% (95% CI 82%-84%)
- Within cohort HIV infection rate: 0.5/100 person-years
 - 2 infections over 3927 person-years
 - 1 never commenced PrEP
 - 1 took no PrEP for months prior to infection
- Population change in HIV diagnoses over the past 12 months: 32% decline (from 149 to 102 persons)
 - Least reductions
 - Young MSM
 - MSM living outside the central Sydney “gay” suburbs
 - Non-English speaking overseas-born gay men

Reduction in HIV Diagnoses (12-month before-after recruitment)

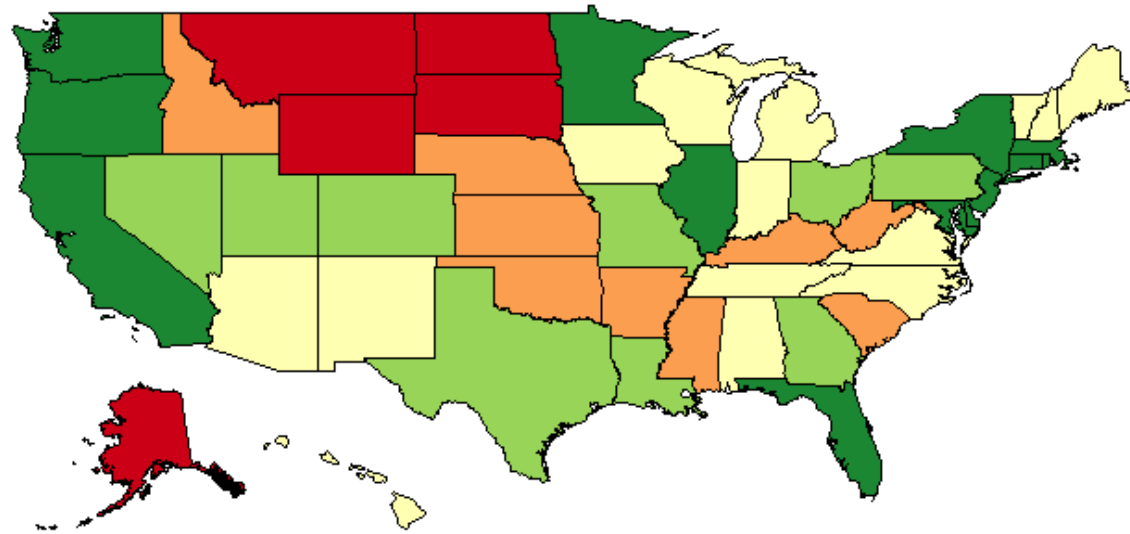
	Decline (%)
Overall	32
Years of age	
18-24	10
25-34	22
35-44	44
>44	48
Country/region of birth	
Australia	49
High-income, English speaking	33
Asia	21
Other countries	+24
Area of residence	
Gay Sydney suburbs	52
Other Sydney	7
Outside of Sydney	54

Trends in U.S. PrEP Uptake

Estimated 1.1 million people may benefit from PrEP

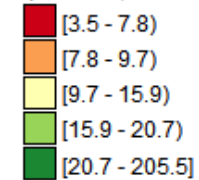


Prevalence of PrEP Users per 100,000 Population
Q2 2017

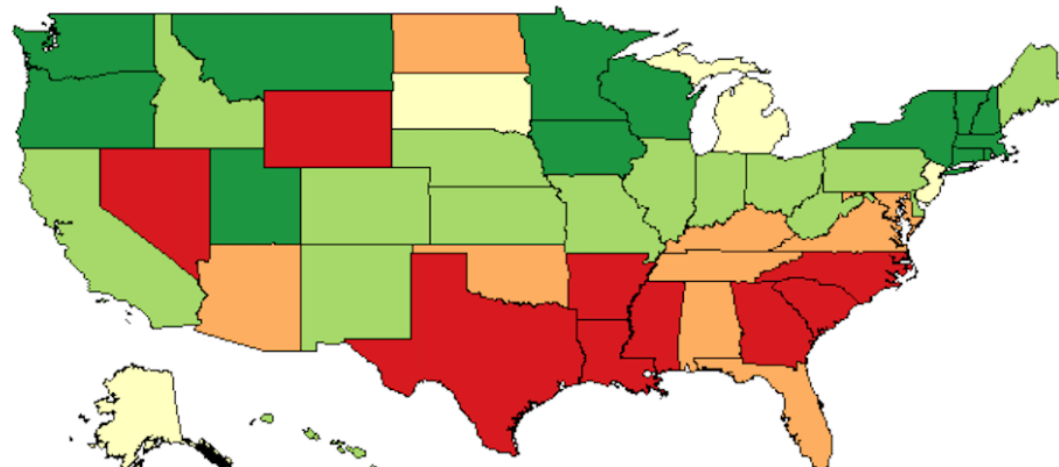


PrEPVu: Matching PrEP Uptake to PrEP Need

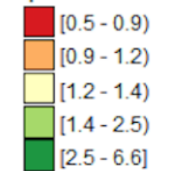
PrEP Users per 100,000 Population



PrEP-to-Need Ratio (PnR)
Q2 2017



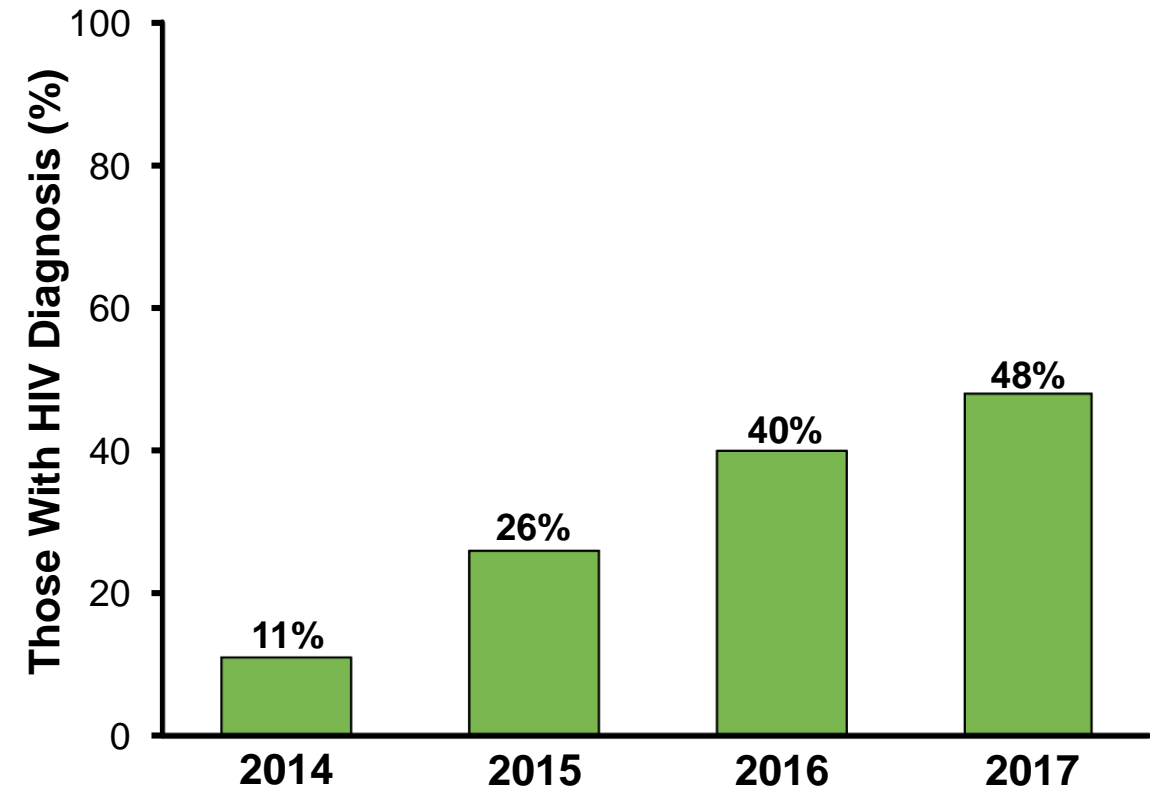
PrEP Users per New HIV Diagnoses



Impact of Targeted PrEP Implementation on HIV Diagnoses in San Francisco (2016)

- City-wide getting to zero consortium
 - Coordinated PrEP program
 - Rapid ART program
 - Linkage-engagement in care
- New HIV diagnoses in SF decreased 51% between 2012 (n=453) to 2016 (n=223)
 - Decreases seen among all race/ethnicity groups

PrEP Use Among MSM PrEP Candidates SF



PrEP candidates: HIV negative and condomless anal sex OR STI OR HIV-positive partner.

Buchbinder SP, et al. 25th CROI. Boston, 2018. Abstract 87.

PrEP in the real world: Fenway Health

- Federally qualified community health center with focus on LGBT health
- 35,000 1^o care pts, ~2200 PLHIV, ~7000 HIV- MSM
- 1st PrEP pts in New England: 2011, over past few years: >1000 PrEP starts/year; ~4000 total
- 17 pts who initiated PrEP became infected (<0.5%) compared to >2% of those who did not use PrEP
- Reasons for infection: ↓ risk perception, insurance changes, stimulant use

PrEP as a gateway to care: Fenway Health

Adjusted prevalence ratios (95% CI) comparing receipt of primary care between PrEP users and individuals not prescribed PrEP – Fenway, 2012-2016 (N=5,857)

Flu vaccination	1.57 (1.47-1.67)
Tobacco screening	1.13 (1.09-1.16)
Depression screening	1.18 (1.15-1.22)
Hemoglobin A1c or glucose testing	1.83 (1.75-1.92)
Hemoglobin A1c testing	0.89 (0.79-1.01)
Glucose testing	2.03 (1.93-2.14)

Prevalence ratios obtained from Poisson models with generalized estimating equations. Adjusted models included age, gender, race/ethnicity, insurance type, and year, with diabetes, hypertension, and overweight/obesity additionally included in models for hemoglobin A1c and glucose testing.

Adherence in clinical practice

- Refill-based PrEP adherence at Kaiser: **92%**! with >900 pts f/u
- <5% with <60% adherence (<4/week)
- 2 seroconversions b/c insurance lapses; none among those still on PrEP

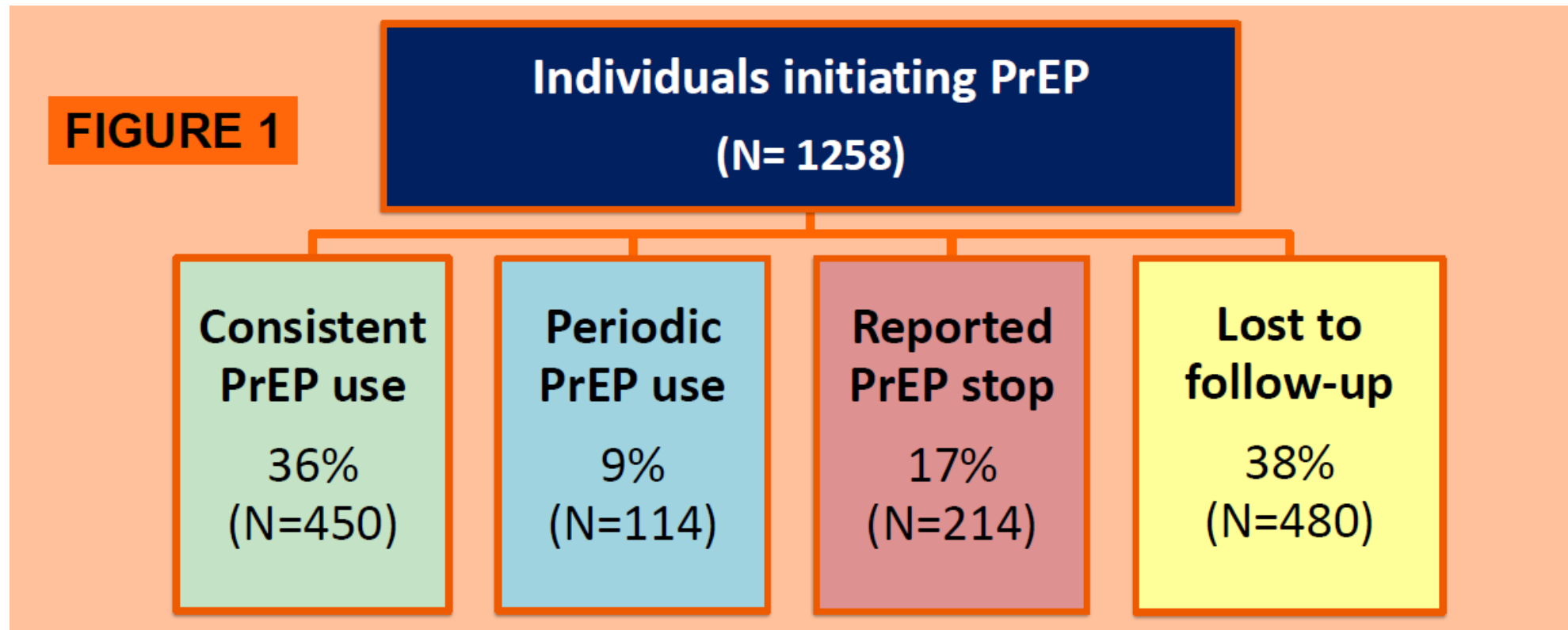
Factors associated with <80% adherence (N=915)

	Risk ratio*	(95% CI)	P
Non-Hispanic Black	3.0	(1.7-5.1)	<0.001
PrEP copay >\$50 per month	2.0	(1.2-3.3)	0.005
Smoking	1.6	(1.1-2.3)	0.025

* Risk ratios obtained from Poisson regression with robust variance and adjusted for age, sex, race/ethnicity, socioeconomic status, copay, smoking, drug/alcohol abuse, baseline STI, baseline renal function, hypertension, and diabetes

HIV Acquisition after PrEP Discontinuation (Montreal)

- Retrospective cohort study in MSM who initiated PrEP and returned for at least 1 follow-up visit



Purview paradox

HIV providers:

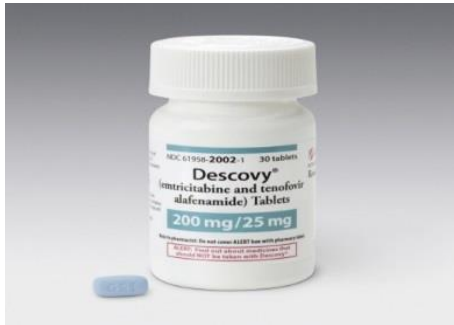
1^o care providers should
prescribe
PrEP

Primary care providers:
PrEP is for specialists



How to improve chemoprophylaxis effectiveness?

New oral PrEP drugs and dosing strategies



Novel adherence strategies



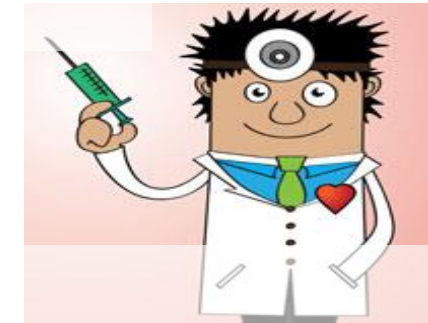
Alternative delivery systems and formulations



Vaginal & Rectal Microbicides



Intravaginal rings (Dapivirine, Tenofovir) +/- Contraception)



Injectables: ARVs and mAbs (Cabotegravir, VRC01)

HIV Incidence (mITT Analysis)

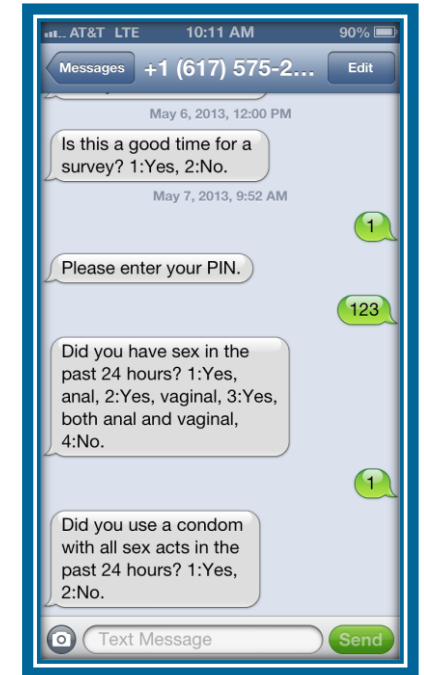
Treatment	Follow-Up Pts-years	HIV Incidence per 100 Pts-years (95% CI)
Placebo (double-blind)	212	6.60 (3.60-11.1)
TDF/FTC (double-blind)	219	0.91 (0.11-3.30)
TDF/FTC (open-label)	515	0.19 (0.01-1.08)

Median Follow-up in Open-Label Phase 18.4 months (IQR:17.5-19.1)

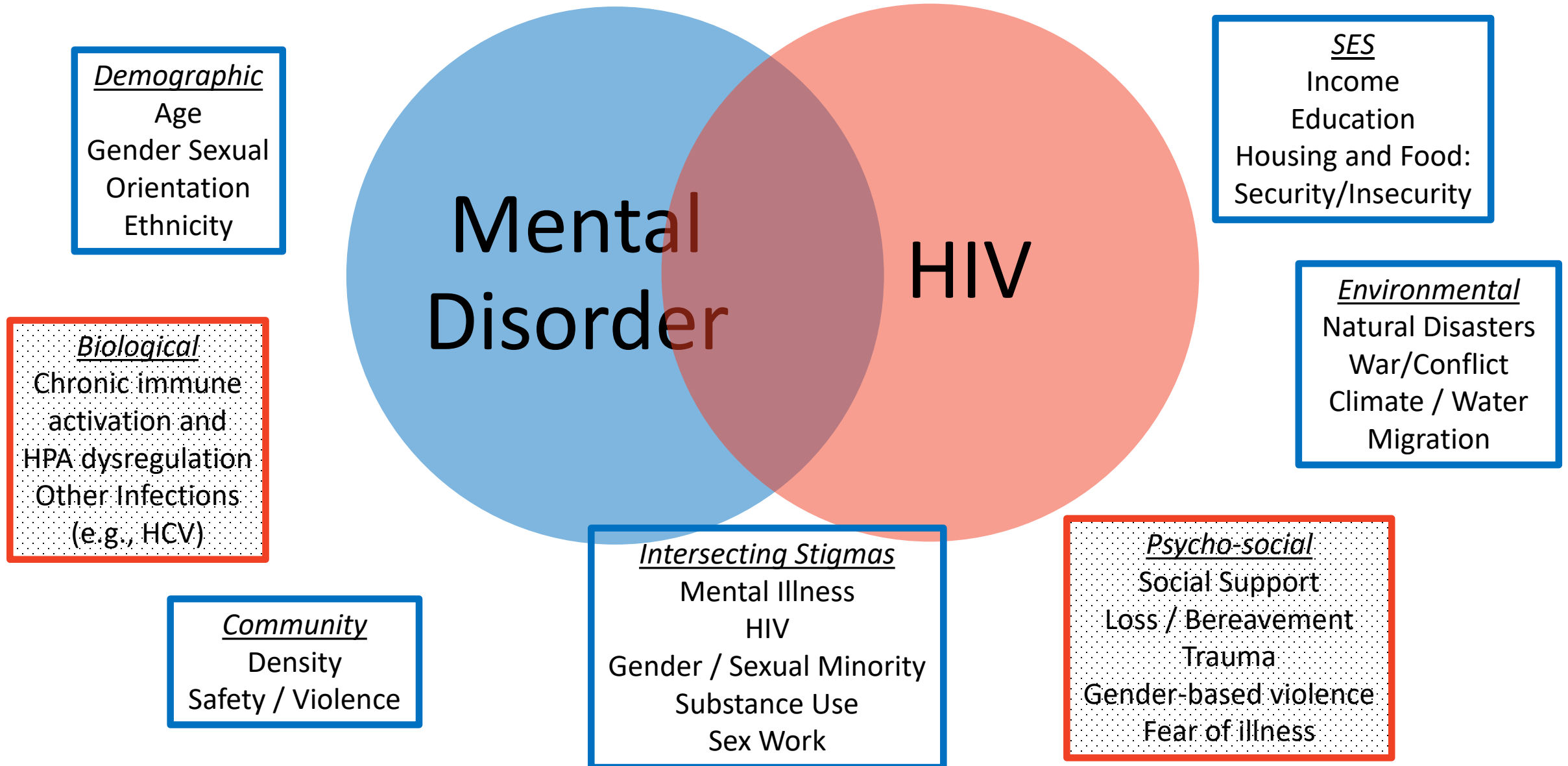
97% relative reduction vs. placebo

New technologies and PrEP engagement

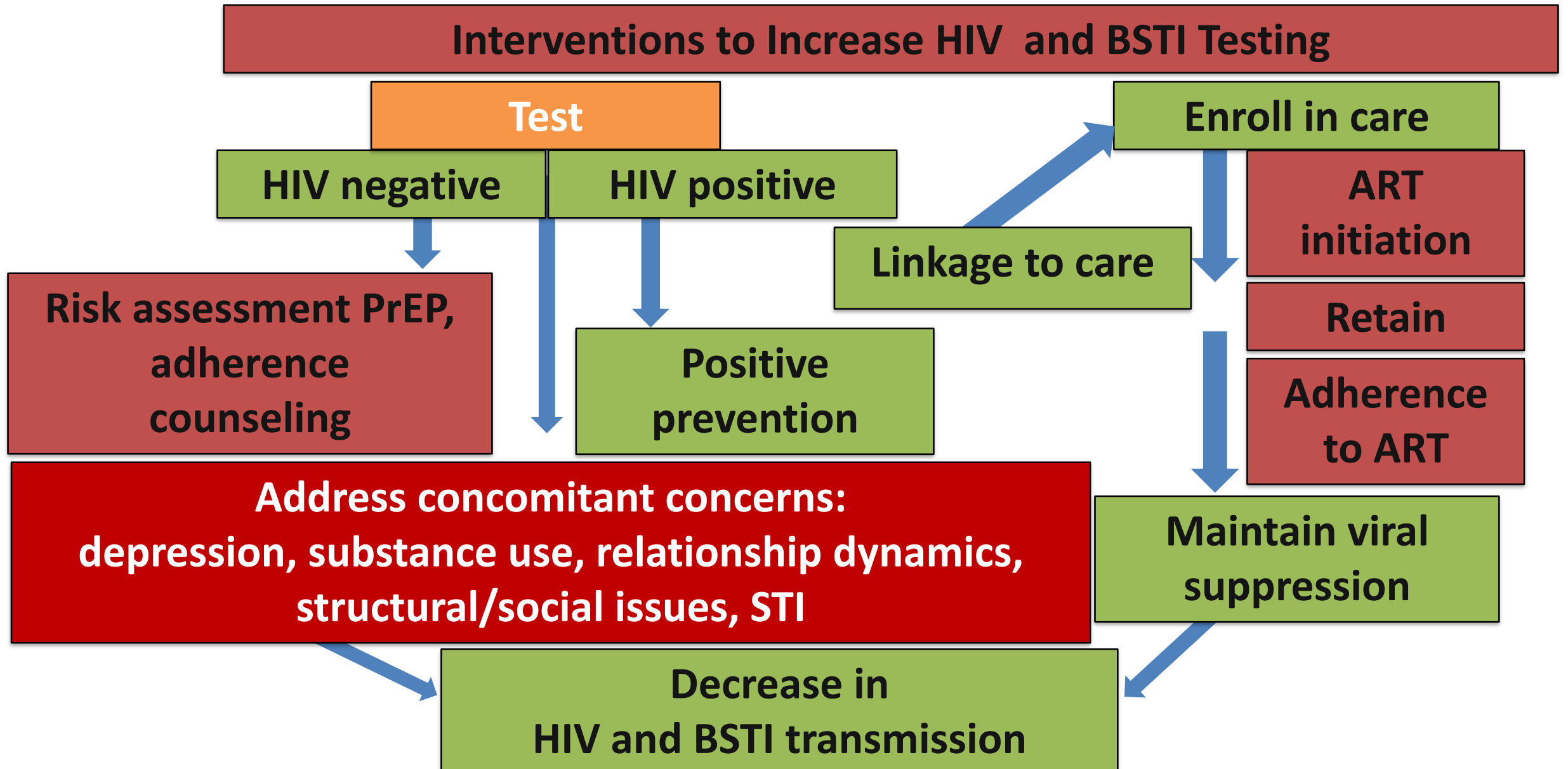
- ↑ treatment adherence with text messaging (Lester, Lancet, 2010)
- Daily SMS texting was used to supplement a nurse-delivered PrEP intervention (Safren/Mayer)
- Counseling augmented by electronic diary was associated with ↑ adherence (Amico/Hosek)
- Feedback on drug levels been studied as adjunct to counseling (Landovitz)
- SexPro and MyChoices Apps being developed for young MSM (Buchbinder/Scott/Liu; Mayer/Biello)
- But, augmented lower tech approaches, e.g. home visits, may also be effective (Haberer)



Why the high burden of mental health in HIV?



Need to Address more than PrEP (and TasP)



Thank You

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