



# CROI Report Back

April 1, 2015

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# Disclosures

I have no financial disclosures.

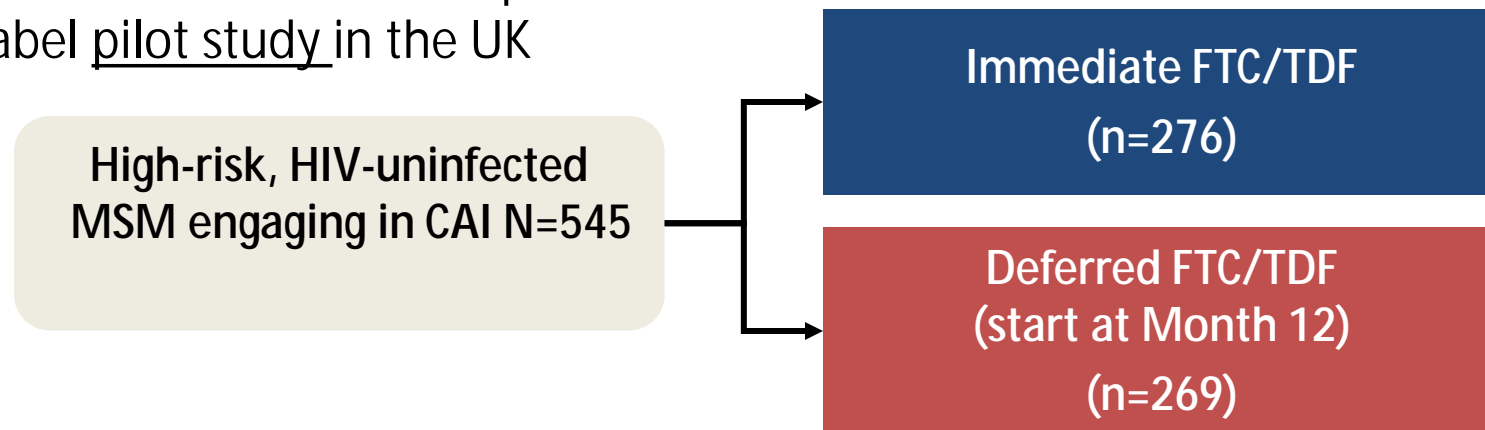
The views expressed herein do not necessarily reflect the official policies of the City and County of San Francisco; nor does mention of the San Francisco Department of Public Health imply its endorsement.

# Outline

- § Pre-Exposure Prophylaxis
  - PROUD
  - Ipergay
  - Partners PrEP + TasP
  - FACTS 001
  - Safety
- § HIV Epidemiology
- § Hormonal Contraception
- § A few other interesting abstracts

# Pragmatic Open-Label Randomized Trial of Pre-Exposure Prophylaxis: PROUD Study

Randomized, multicenter, open-label pilot study in the UK



**Primary endpoint:** HIV seroconversion between randomization and Month 12  
**Secondary endpoints:** Safety, adherence, sexual behavior, resistance development

**Oct 16, 2014: the PROUD Trial Steering Committee announced that participants on the deferred arm of the study, who had not yet started PrEP, would be offered the opportunity to begin PrEP ahead of schedule**

# Demographics and PrEP Use

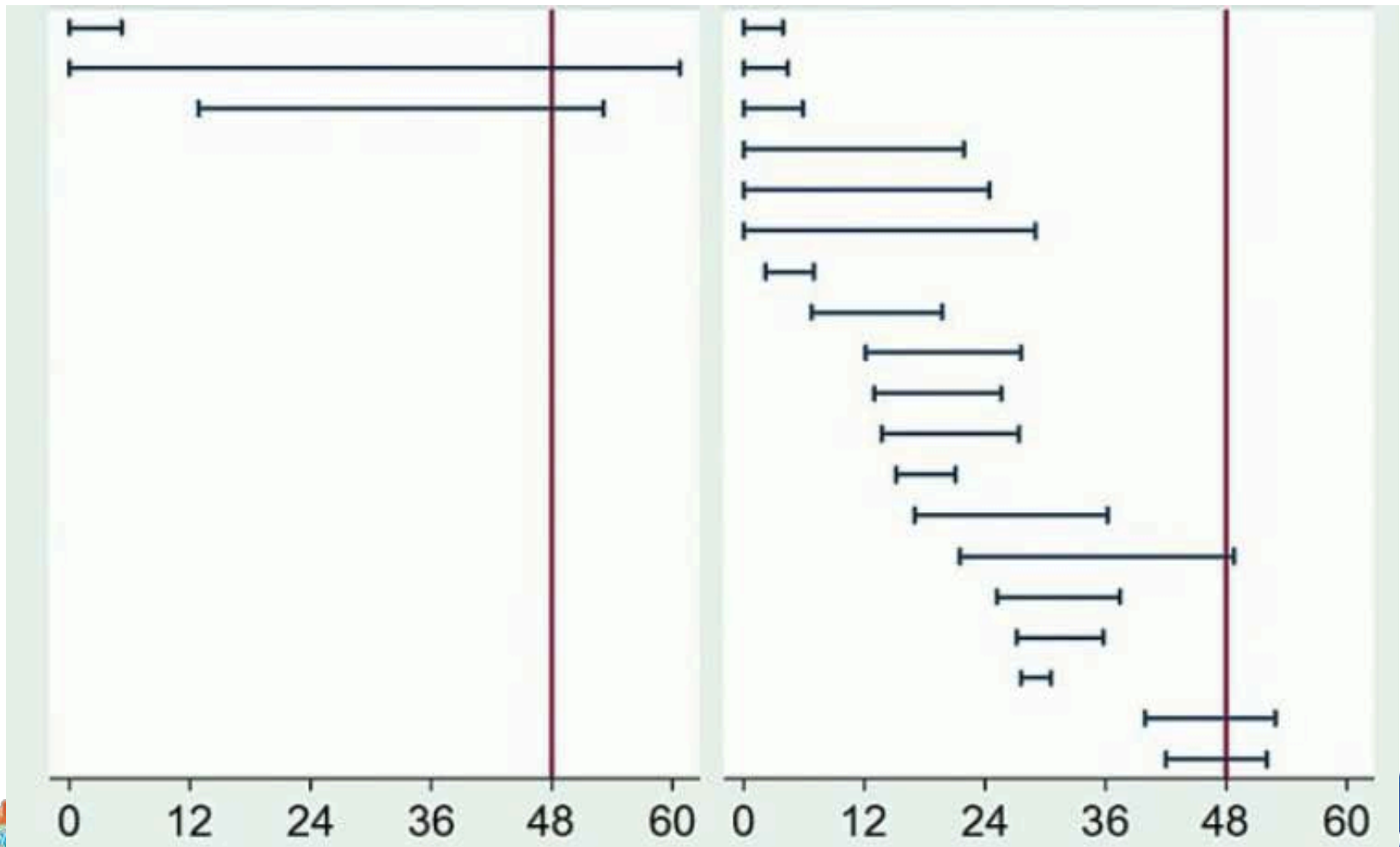
|                        | Immediate  | Deferred   |
|------------------------|------------|------------|
| Age, median (IQR)      | 35 (30-43) | 35 (29-42) |
| White Race             | 80%        | 82%        |
| Born UK (No)           | 40%        | 40%        |
| Education (University) | 59%        | 60%        |
| Full Time Employment   | 70%        | 73%        |
| Currently Single       | 53%        | 55%        |
| Recreational drug use  | 76%        | 64%        |

- 14 (5%) of those in the immediate arm never started PrEP.
- Overall, drug prescribed covered 86% of days of follow-up.
- Rare use of PrEP in the deferred arm
- PEP use common 83 (31%) of participants

# Individual Incident HIV Infections

Immediate N=3

Delayed N=19



# PROUD Results

## HIV Incidence

| Group     | Infections, n | Follow-up (PY) | Incidence/100 person-years<br>(90% CI) |
|-----------|---------------|----------------|--|
| Overall   | 22            | 453            | 4.9 (3.4-6.8)                          |
| Immediate | 3             | 239            | 1.3 (0.4-3.0)                          |
| Deferred  | 19            | 214            | 8.9 (6.0-12.7)                         |

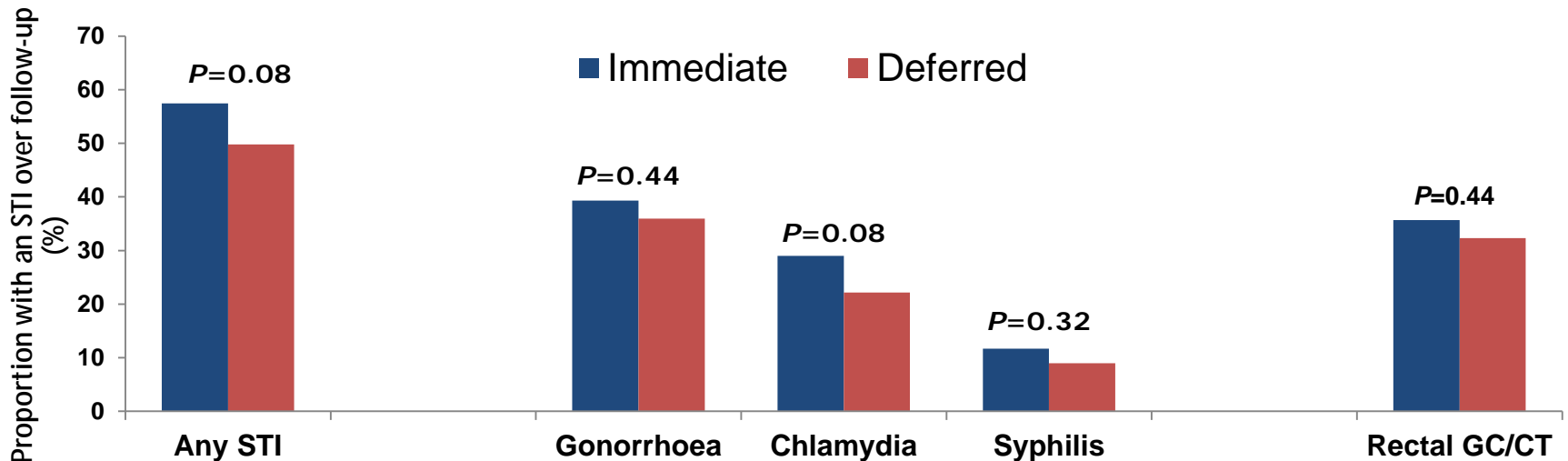
86% (90% CI 58-96%) Risk Reduction  $P=0.0002$

**Number needed to treat=13 (90% CI: 9-25)**

Resistance: 3 individuals developed M184V/I, no K65R

# Reported Sexual Risk Behavior and STIs

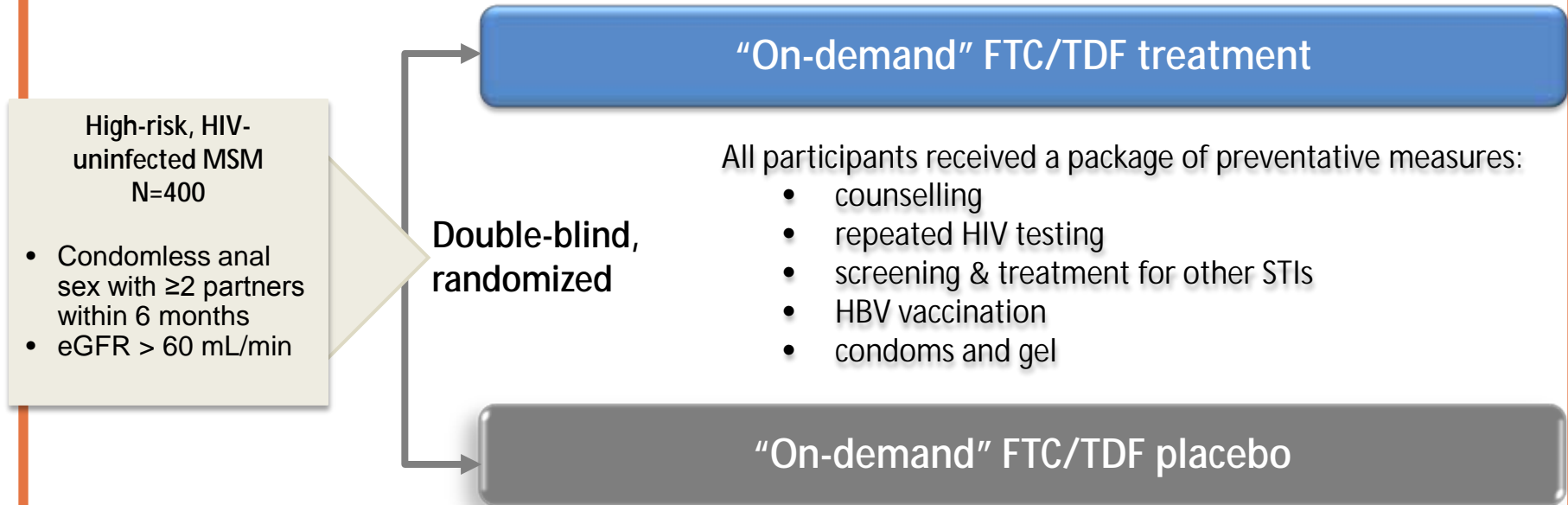
| Anal sex partners in past 90 days, median (IQR) | Baseline, n=539 |           |
|---|-----------------|-----------|
|   | Immediate       | Deferred  |
| Total   | 10.5 (5-20)     | 10 (4-20) |
| Condomless receptive                            | 3 (1-5)         | 2 (1-5)   |
| Condomless insertive                            | 2.5 (1-6)       | 3 (1-7)   |



974 Screens in Immediate Group  
749 Screens in the Delayed Group



# Ipergay Trial



“On-demand” regimen constitutes:

- 2 FTC/TDF or 2 placebo 2 - 24 hrs prior to sexual intercourse exposure
- 1 FTC/TDF or placebo 24 hrs and then 48 hrs after first intake

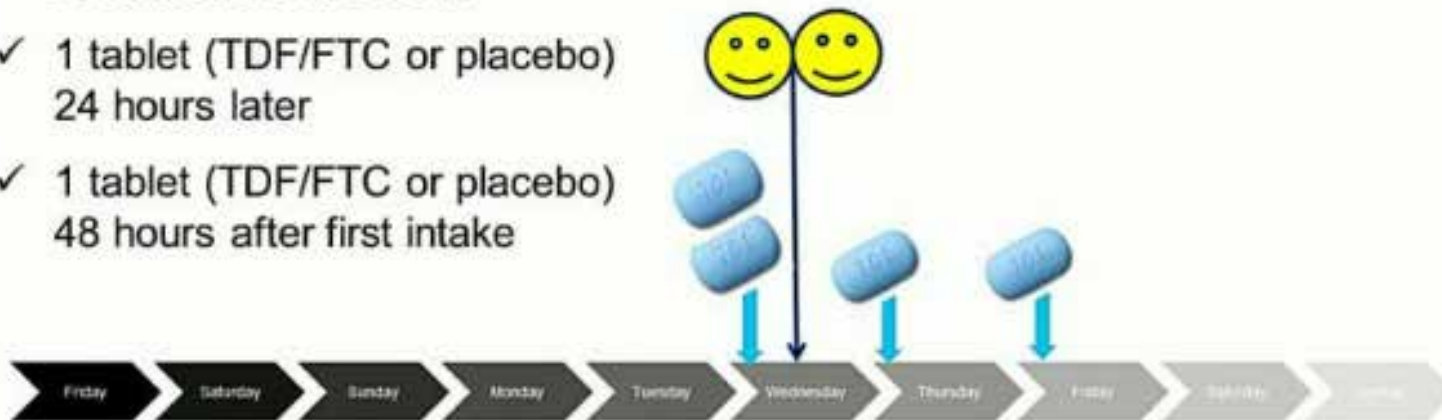
**Primary endpoint:** HIV seroconversion

**Secondary endpoints:** Sexual behavior, safety events, adherence

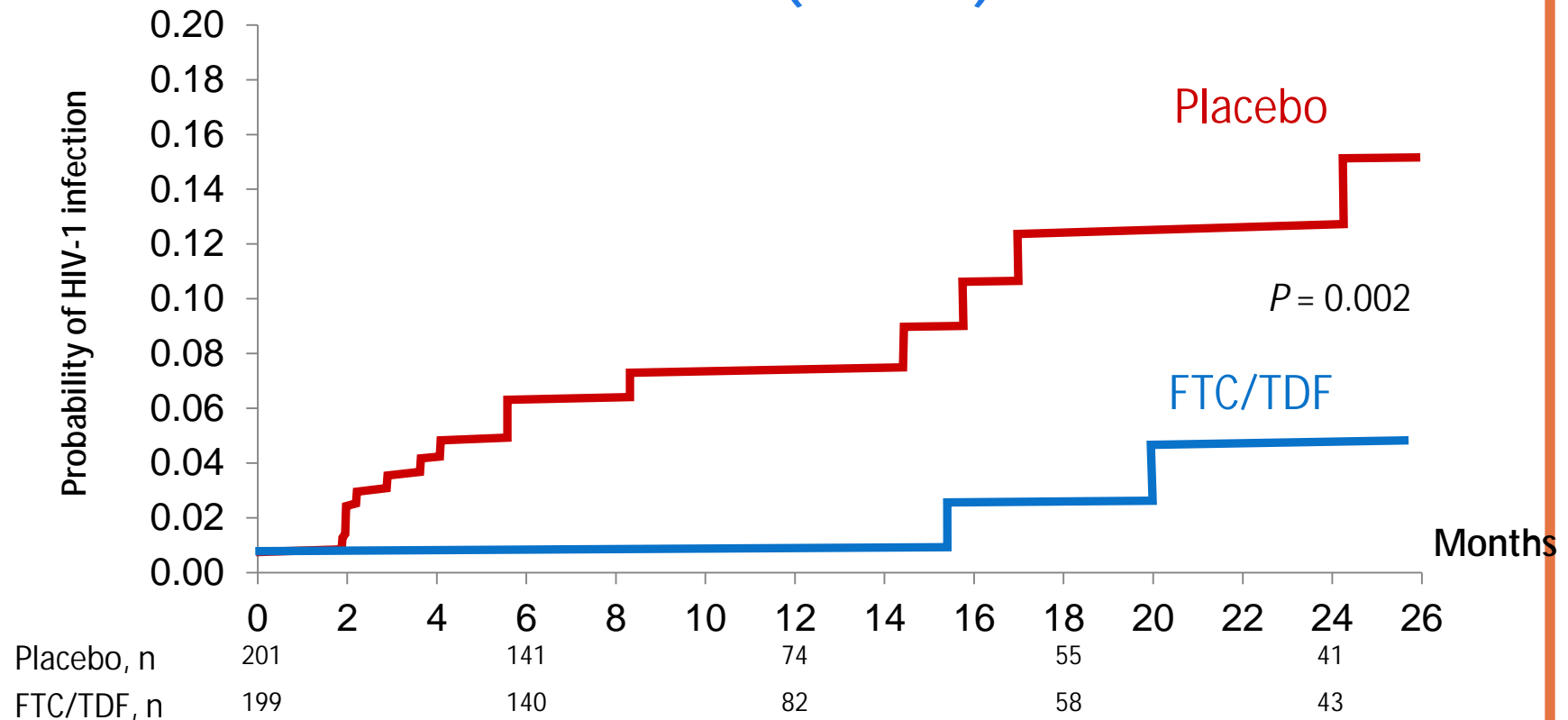
**Oct. 23, 2014, the DSMB recommended that the placebo arm be discontinued and patients be offered switching into the treatment arm.**

# Ipergay Event Level 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



# Kaplan-Meier Estimates of Time to HIV-1 Infection (mITT)



86% relative reduction (95% CI: 40-99,  $P=0.002$ )

16 subjects infected

Placebo=14 Incidence 6.6; FTC/TDF=2 Incidence 0.94

Number needed to treat: 18

# Safety

- § PrEP interrupted by 28 participants (from both groups)
- § Only **13 thought to be related to Truvada:**
  - Nausea, diarrhea, abd pain, or fatigue (n=5)
  - Decline in CrCl (n=2)
  - Headache (n=2)
  - Joint pain (w fatigue in one case) (n=2)
  - Sleep disturbance (n=1)
  - Flu-like illness (n=1)
- § PrEP was **restarted in 11/13 participants.**

# Adherence to PrEP Surrounding Recent Sexual Intercourse – CASI Assessment

| PrEP use, %<br>(min-max) | FTC/TDF<br>n=649 sex events | Placebo<br>n=563 sex events | Total<br>% (min-max) |
|--------------------------|-----------------------------|-----------------------------|----------------------|
| Correct use*             | 45 (36-57)                  | 40 (22-49)                  | 43 (35-51)           |
| Suboptimal use           | 27 (14-35)                  | 31 (18-44)                  | 29 (20-38)           |
| No PrEP                  | 27 (15-37)                  | 29 (24-44)                  | 28 (20-38)           |

\*According to the protocol or at least one pill before and one pill after sex

Median Number of pills used per month

16 (10-23) in placebo arm

16 (12-24) in FTC/TDF arm



# Sexually Transmitted Infections

|           | FTC/TDF<br>n=199<br>N (%) | Placebo<br>n=201<br>N (%) | P-value |
|-----------|---------------------------|---------------------------|---------|
| Chlamydia | 43 (22)                   | 34 (17)                   | 0.23    |
| Gonorrhea | 38(19)                    | 45 (22)                   | 0.42    |
| Syphilis  | 19 (10)                   | 19 (10)                   | 0.98    |
| HCV       | 3 (<2)                    | 3 (<2)                    | 1.0     |
| Any STI   | 76 (38)                   | 65 (32)                   | 0.22    |

70% reported condomless anal sex throughout the study

# Adverse Events

|                       | FTC/TDF, n=199<br>N (%) | Placebo, n=201<br>N (%) | P-value |
|-----------------------|-------------------------|-------------------------|---------|
| Any AE                | 184 (92)                | 178 (89)                | 0.18    |
| Any Serious AE        | 18 (9)                  | 16 (8)                  | 0.70    |
| Any Grade 3 or 4 AE   | 17 (9)                  | 14 (7)                  | 0.56    |
| Tx D/C 2° to AE       | 1                       | 0                       |         |
| Drug Related GI AEs   | 25 (13)                 | 11 (6)                  | 0.013   |
| Nausea/vomiting       | 15                      | 2                       |         |
| Abd pain              | 11                      | 4                       |         |
| Diarrhea              | 7                       | 5                       |         |
| Grade 1 Creatinine    | 28 (14)                 | 15 (7)                  | 0.042   |
| Proteinuria $\geq$ 2+ | 10 (5)                  | 9 (5)                   | 0.83    |
| Glycosuria $\geq$ 2+  | 1 (1)                   | 0 (0)                   | 1.00    |
| All Grade ALT         | 33 (17%)                | 26 (13%)                | 0.37    |
| Grade 3 or 4 ALT      | 1 (1)*                  | 4 (4)**                 | 0.36    |

\* Acute HCV infection

\*\* Acute HCV in 3 and syphilis in one

# CDC Press Statement

For Immediate Release: Tuesday, February 24, 2015

Contact: [National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention](#)

(404) 639-8895

[NCHHSTPMediaTeam@cdc.gov](mailto:NCHHSTPMediaTeam@cdc.gov)

## CDC Statement on IPERGAY Trial of Pre-Exposure Prophylaxis (PrEP) for HIV Prevention among Men Who Have Sex with Men

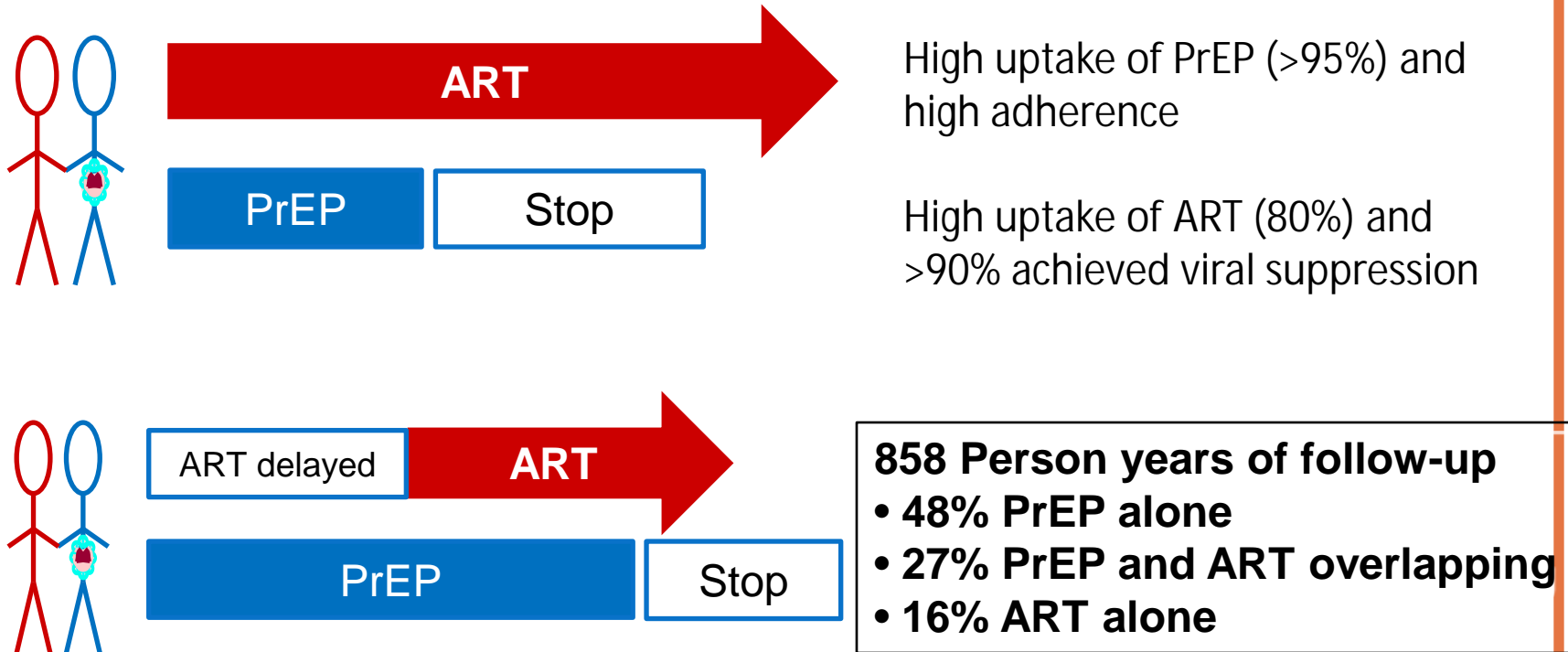
“...CDC continues to recommend daily dosing of PrEP and urges people at substantial risk for HIV infection and their health care providers to continue to follow current CDC guidelines.”



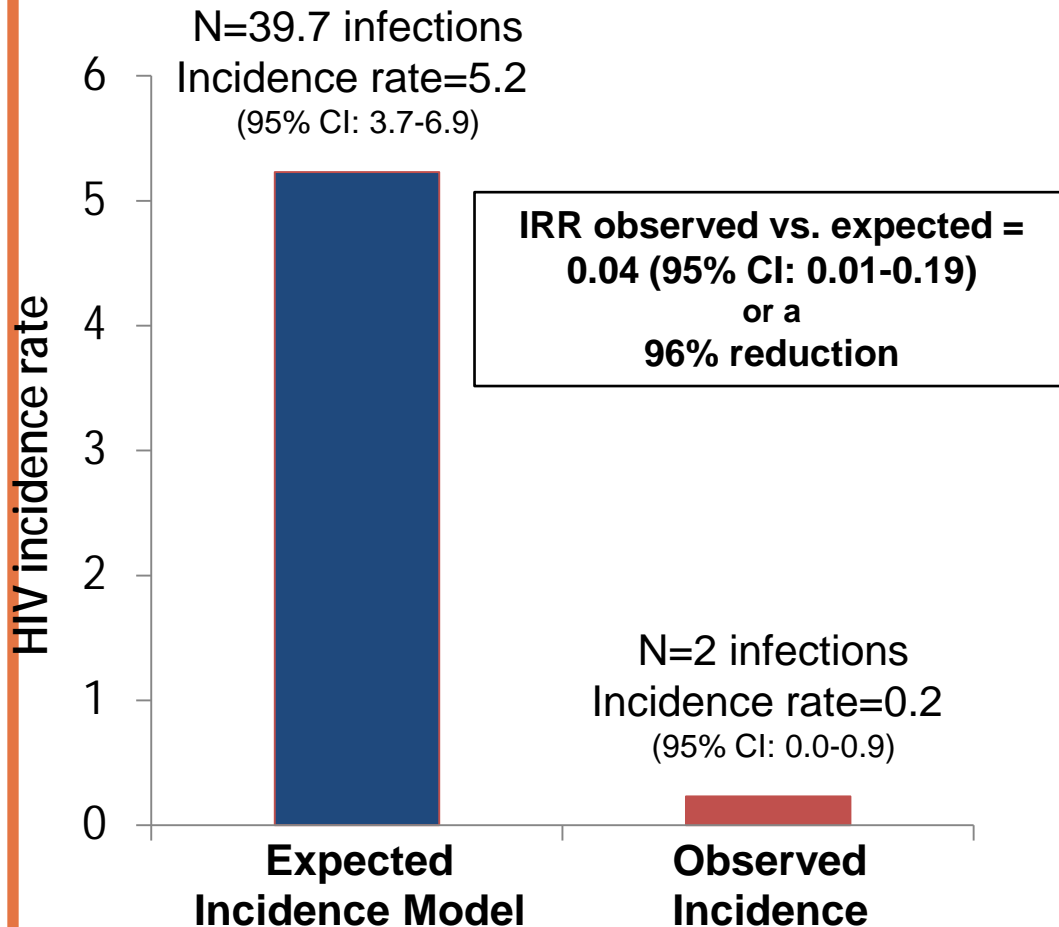


# Partners PrEP + TasP for HIV Serodiscordant Couples

PrEP is offered as a 'bridge' for the first 6 months after ART initiation by the HIV-infected partner



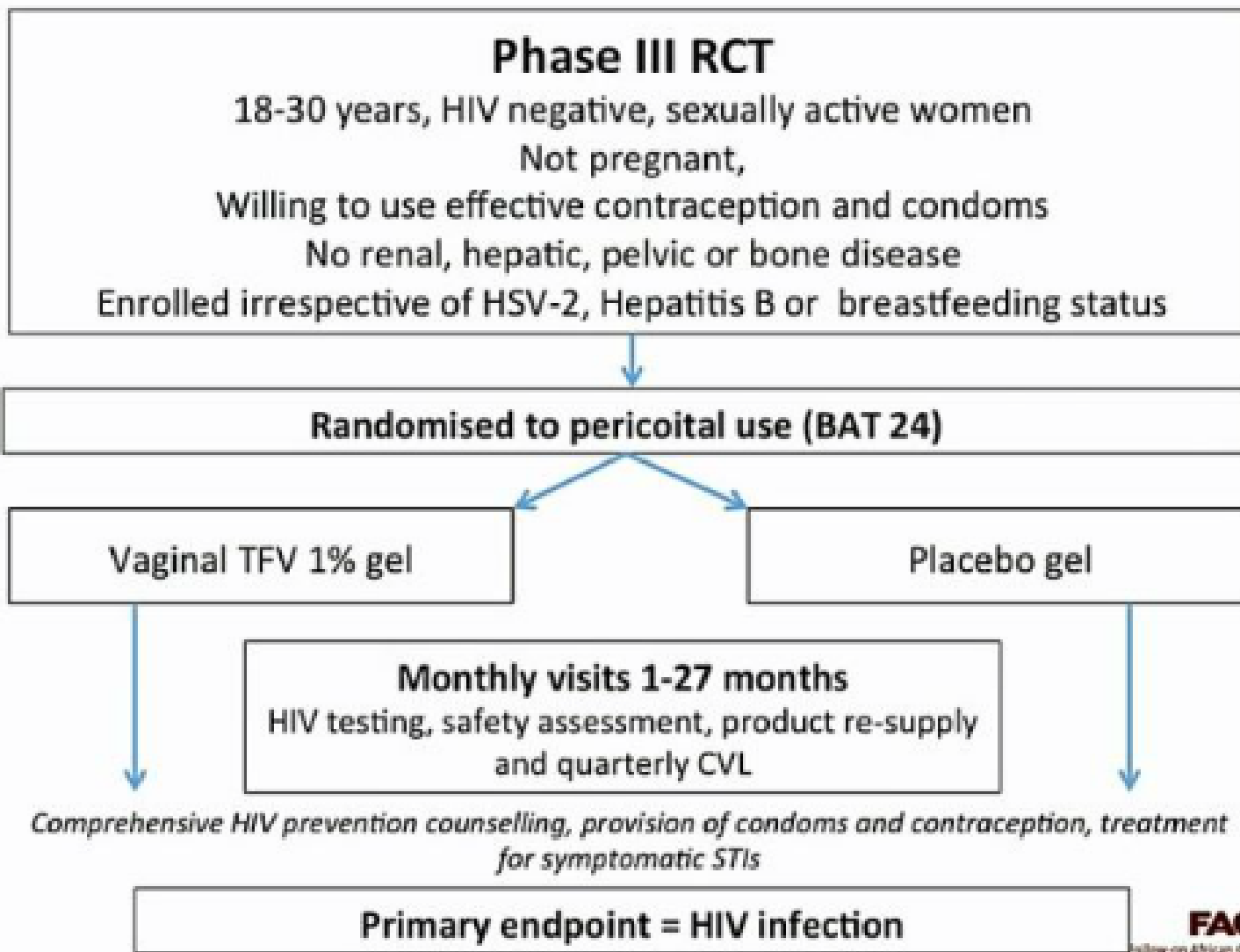
# Partners PrEP + TasP: HIV Incidence



- § Limited PrEP use in the 2 HIV seroconverters.
- Both:
- Started PrEP but reported breaks in use.
  - Undetectable plasma tenofovir concentrations at the time of seroconversion.

The observed HIV incidence is a 96% (95% CI 81-99%)  $P < 0.0001$  reduction compared to the expected incidence rate

# FACTS 001



# Baseline Characteristics

|                                 | TFV gel<br>n= 1015<br>% | Placebo gel<br>N=1014<br>% |
|---------------------------------|-------------------------|----------------------------|
| Mean Age (IQR)                  | 23 (20-25)              | 23 (20-25)                 |
| Single                          | 89%                     | 89%                        |
| Living with parents/siblings    | 61%                     | 63%                        |
| Secondary Educ. Or higher       | 56%                     | 56%                        |
| Anal sex                        | 1%                      | 1%                         |
| Consistent condom use           | 35%                     | 32%                        |
| Perceived HIV risk > than usual | 18%                     | 17%                        |
| Median no. of partners          | 1 (1-1)                 | 1 (1-1)                    |
| HSV-2 seroprevalence            | 43%                     | 40%                        |

# Primary Effectiveness Results (mITT)

|                                   | TFV gel<br>N= 1015<br>% | Placebo gel<br>N=1014<br>% |
|-----------------------------------|-------------------------|----------------------------|
| Person Years                      | 1515                    | 1521                       |
| HIV Infections                    | 61                      | 62                         |
| HIV Incidence per 100 py (95% CI) | 4.0 (3.1-5.2)           | 4.0 (3.1-5.2)              |

**Incident Rate Ratio 1.0 (95% CI 0.7-1.4)**

# Adherence

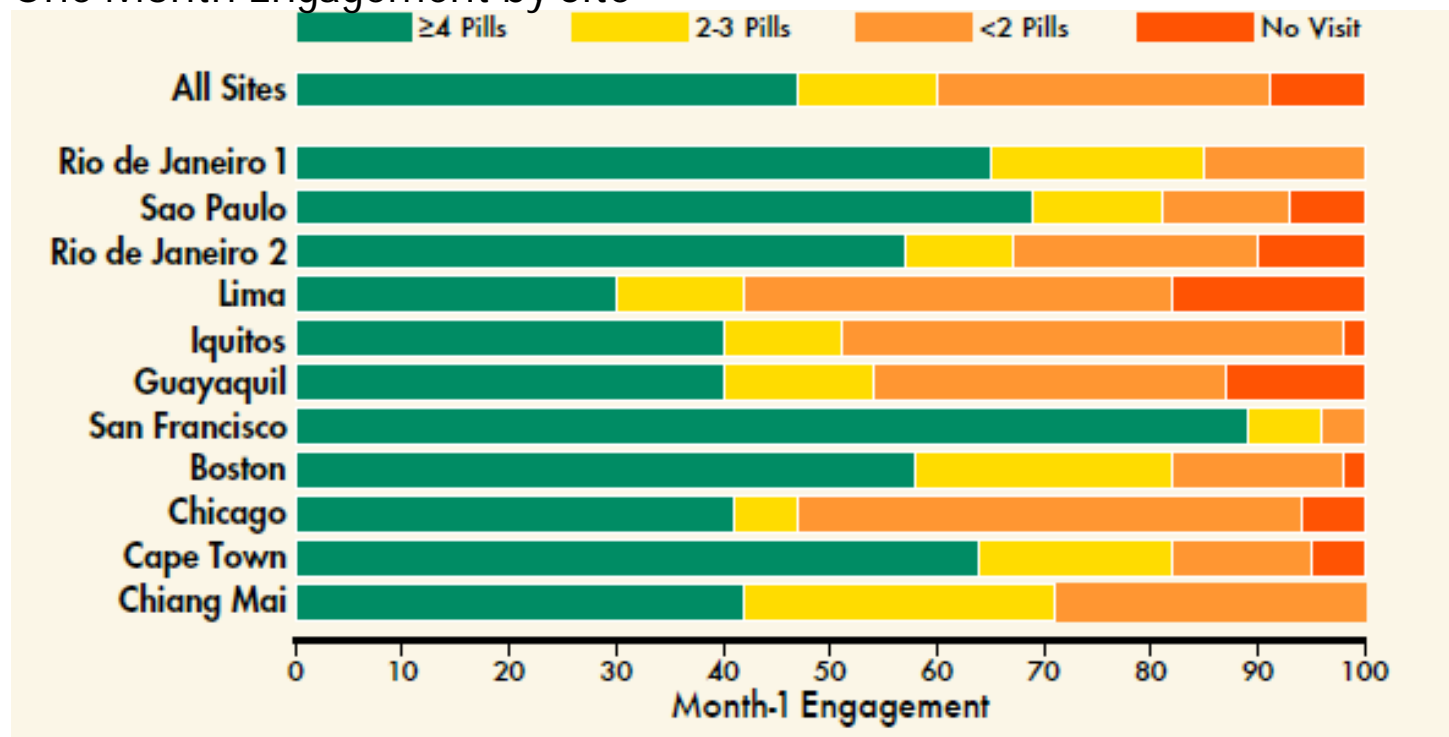
- § Case-cohort of 214 women with 1075 cervical vaginal lavage (CVL) samples
  - 64% of samples with any TFV detected
  
- § Percent of women:
  - 22% TFV detected at all quarterly visits
  - 65% TFV detected at some quarterly visits
  - 13% TFV never detected at quarterly visits

TFV detected in samples from women who reported sex in 10 days preceding CVL

aHR 0.48 (0.23-97) p=0.04

# Variable PrEP Engagement in iPrEx OLE

## One Month Engagement by Site



1603 HIV- participants, 1125 (76%) initiated PrEP

1005 of initiators (84%) attended the 12 month visit

813 had been dispensed PrEP at the last visit,

**354 (29%) of PrEP initiators had TFV-DP levels c/w  $\geq 4$  pills/week**

# PrEP Adverse Events And Resistance

## Adverse Event

|  |   |
|--|---|
| <b>Start-up Syndrome</b>                   | 1-18.5% with nausea, vomiting +/- dizziness   |
| <b>Renal Toxicity</b>                      | 0.2% Grade 2-4 Creatinine elevations among 5469 pts randomized to TDF/FTC                   |
| <b>Bone Mineral Density</b>                | 0.4-1.5% BMD loss.<br>Return toward baseline after d/c.<br>No increased fracture risk.      |
| <b>HIV Resistance among seroconverters</b> | 3.7% (9/243)<br>0.06% of those receiving PrEP after excluding likely transmitted resistance |



# Estimated SF PrEP eligibles and users

| Group   | People        |
|---|---------------|
| HIV negative at substantial risk:                         |               |
| MSM with 2+ ncAI partners <sup>1</sup>                    | 12,589        |
| MSM with 0 ncAI and an STI in the last year <sup>2</sup>  | 2,325         |
| Female partners of HIV+ MSM <sup>3</sup>                  | 653           |
| Trans women <sup>4</sup>                                  | 522           |
| <b>TOTAL estimated PrEP eligibility</b>                   | <b>16,089</b> |
| <b>TOTAL reporting PrEP in past year</b>                  | <b>5,059</b>  |
| <b>Percent of eligible people using PrEP in past year</b> | <b>31%</b>    |

1. SF City Clinic 2014 survey x HIV negative MSM population of 50,000;
2. SF NHBS self report of STI among MSM with 0 ncAI in 2014 x HIV negative MSM population of 50,000;
3. SF NHBS MSM reporting female partners in 2014 x HIV positive MSM population of 14638.
4. IDU and ncRAI in est. 923 HIV negative trans women in SF adapted from Wilson BMCID 2014 14:430.
5. SF NHBS 2014, data on file.

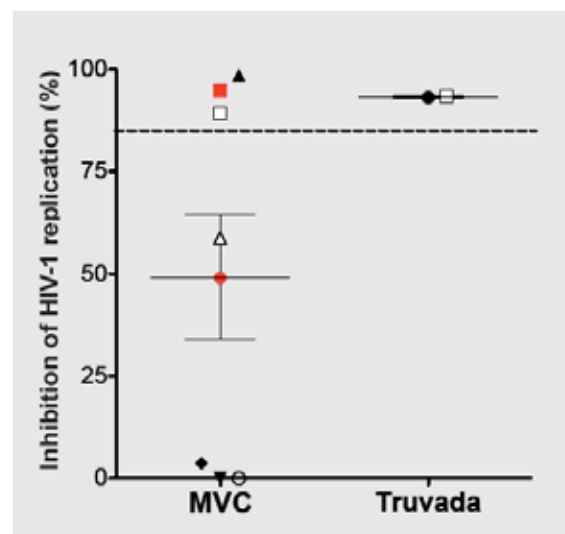
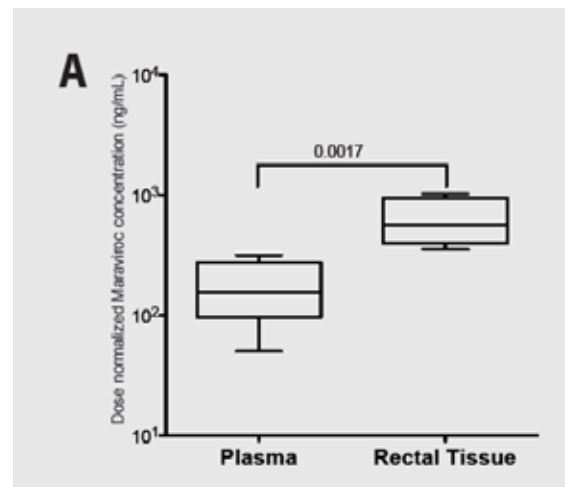


# New PrEP Agents

- § Maraviroc – HPTN 069/ACTG A5305
- § Long Acting Agents
  - Rilpivirine LA – HPTN 076
  - Cabotegravir – HPTN 077/ÉCLAIR
  - Immunotherapies (VRC01) – HVTN / HPTN 081

# Maraviroc

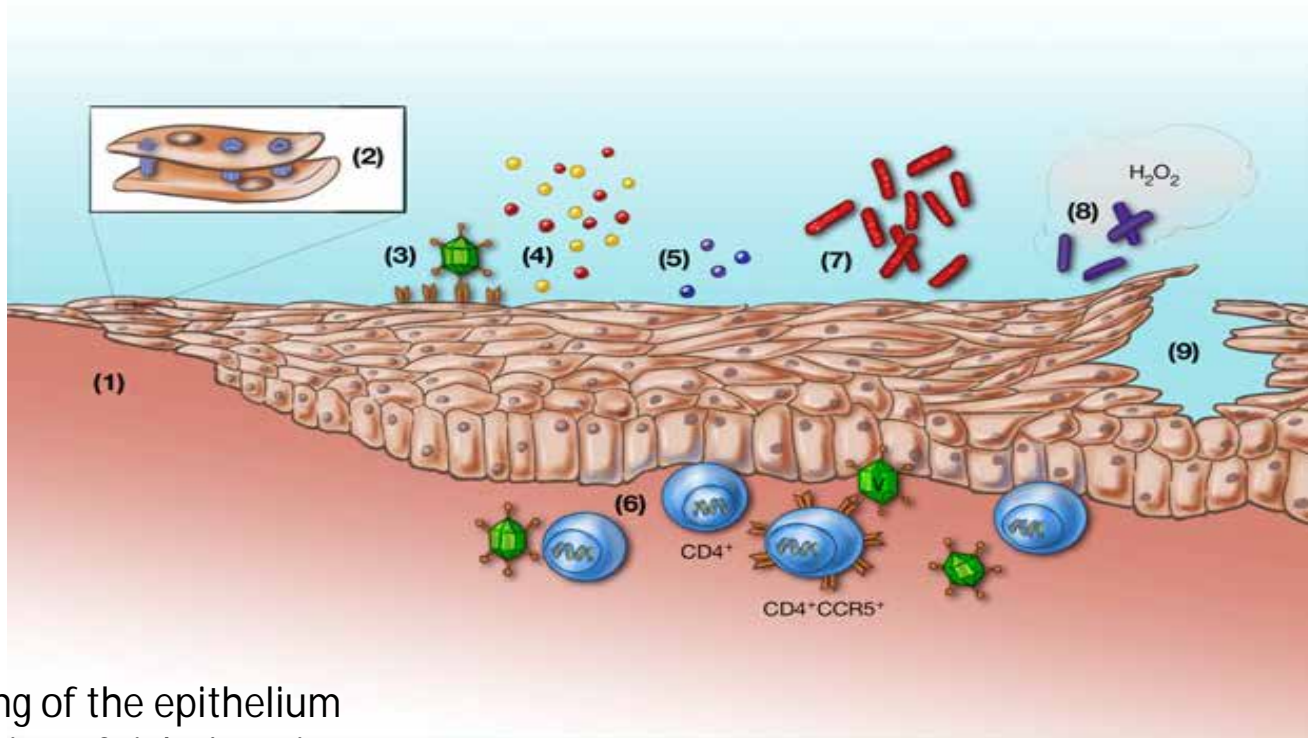
- § Maraviroc does concentrate in rectal tissue compared to plasma.
- § However, single dose of 600mg or 300mg did not prevent ex vivo R5 HIV-1 infection in rectal mucosa 4 hours after dosing.
- § Complete inhibition of infection in those receiving Truvada for 10 days.
- § PK/PD study also showed lack of efficacy in vaginal and rectal ex vivo HIV-1 challenge.
  - Fox Abstract #86LB



# Themed Discussion

- § Recent meta analysis of 18 studies (37, 124 women).
  - aHR compared to no HC:
    - § DMPA - 1.50 (1.25-1.83)
    - § NET-EN - 1.24 (0.84-1.82)
    - § COC - 1.03 (0.88-1.20)
  - Effect estimates reduced for studies at lower risk of bias DMPA 1.22 (0.99-1.5)
  
- § Several mechanisms for biological plausibility including CCR5.

# Hormonal Contraception



1. Thinning of the epithelium
2. Disruption of tight junctions
3. Upregulation of syndecans
- 4/5. Increases in pro-inflammatory or decrease in protective mediators
6. **Increases in CCR5 expressions**
- 7/8. **Changes in microbiome**
9. Increase in HSV or other STIs, ulcerative lesions

# Changes in CCR5 Expression and Vaginal Microbiome

- § Estrogen replacement was associated with lower CCR5+ Expression in postmenopausal women.
  - Meditz Abstract # 859
- § CCR5+ expression in CD4+ and CD8+ T cells from the peripheral blood was higher among women using the levonorgestrel releasing-IUD.
  - Tsibiris Abstract #858
- § Rise in progesterone during luteal phase associated with increased CCR5+ expression.
  - Swaims Abstract #862
- § DMPA led to sustained, and statistically significant declines in vaginal bacterial concentration and cytokine levels.
  - Roxy Abstract #861

# Treatment as Prevention & Epidemiology



# Time with HIV VL >1500 copies/ml

- § Observational cohort of 14,532 HIV patients in care at 6 clinics in US.
- § 4/1/2009- 3/31/2013, followed for at least 12 months.
  - 90.5% prescribed ART
- § Multiple viral loads provides a longitudinal view of VL results.
  - Median #Viral load test: 9 (2-40)



# Time with HIV VL >1500 copies/ml

23.1% of observed time VL exceeded 1,500 copies  
54% of patients had some time above 1,500 copies

| N=14,532                             | % of time VL exceeded 1500 copies | Adjusted rate ratio | 95% CI     | p-value |
|--------------------------------------|-----------------------------------|---------------------|------------|---------|
| <b>Age at initial VL in analysis</b> |                                   |                     |            |         |
| 16-39                                | 32.1                              | 1.38                | 1.30, 1.46 | <0.001  |
| 40-49                                | 22.8                              | 1.18                | 1.12, 1.25 | <0.001  |
| 50-85                                | 16.5                              | ref.                |            |         |
| <b>Race/ethnicity</b>                |                                   |                     |            |         |
| Black                                | 26.1                              | 1.24                | 1.16, 1.32 | <0.001  |
| Hispanic                             | 19.7                              | 0.98                | 0.90, 1.06 | 0.610   |
| Other                                | 12.4                              | 0.72                | 0.55, 0.93 | 0.011   |
| White                                | 16.0                              | ref.                |            |         |
| <b>Gender/orientation</b>            |                                   |                     |            |         |
| MSM                                  | 20.1                              | 0.94                | 0.89, 0.99 | 0.024   |
| Women                                | 25.1                              | 1.01                | 0.97, 1.06 | 0.588   |
| Heterosexual Men                     | 23.6                              | ref.                |            |         |

Higher % time above 1500 copies:

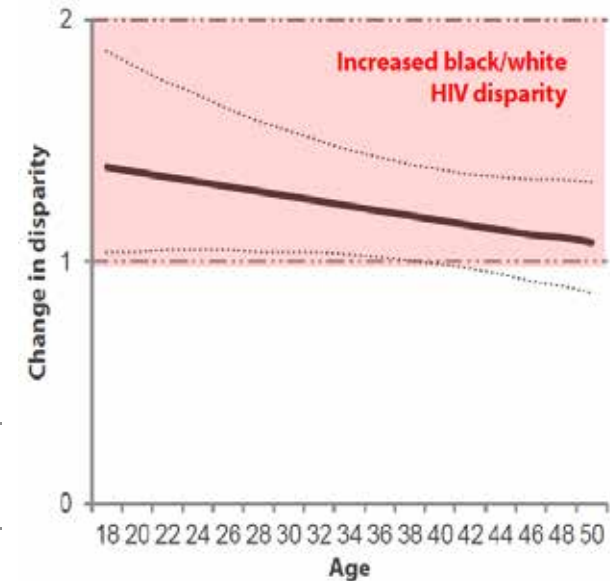
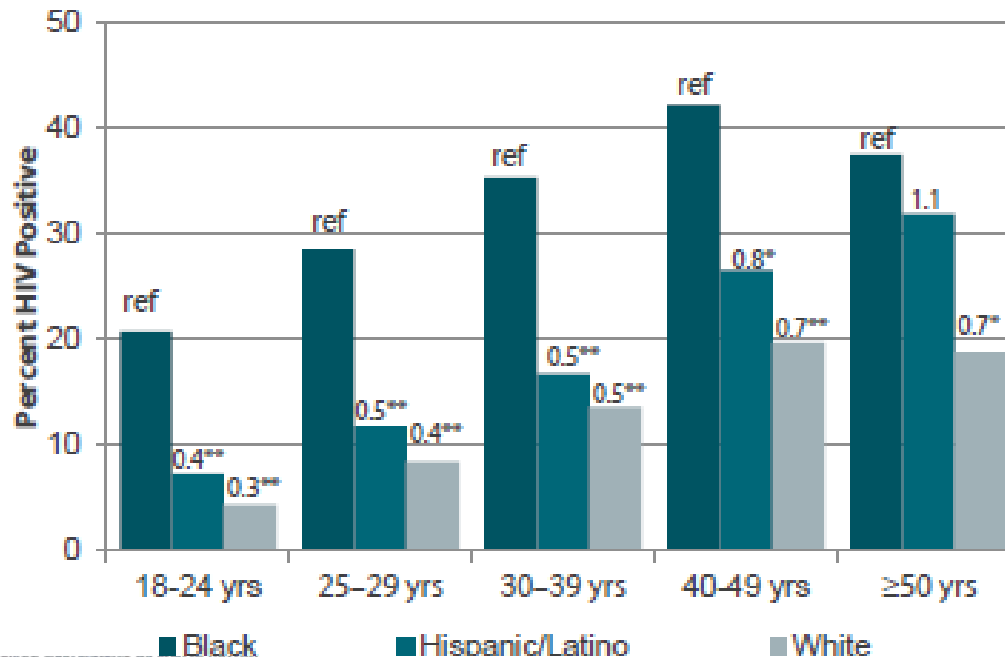
1. Young pts
2. Black pts
3. Pts not on ART
4. Pts with more intervals >6 months between VL measures
5. Medicaid or Ryan White.

**No adherence data or sexual risk behavior data**

# Increasing racial/ethnic HIV disparities among US MSM

- § Used nationally representative CDC Data from 20 US cities – NHBS.
- § Black MSM had higher HIV prevalence, and had lower awareness of HIV infection.

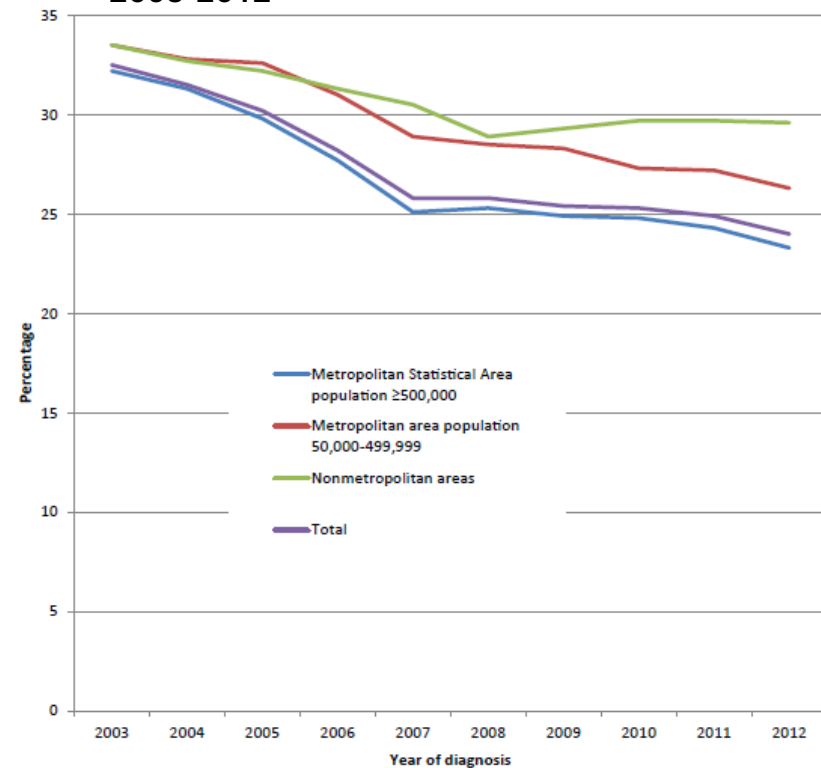
**Figure 1: HIV prevalence among MSM by race and age, 2011**



# Declines in “Late” Diagnoses

- § 24% of HIV diagnoses were “late” in 2012
- § Percentage of late diagnoses decreased overall, but few areas were <20%.
- § Racial/ethnic disparities in late diagnoses:  
Blacks 38/105 MSAs;  
Latinos 68/105 MSAs

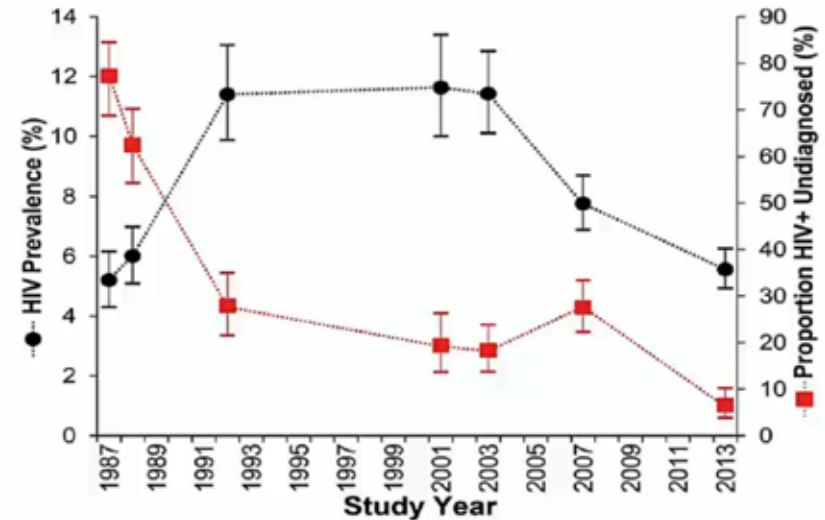
Percentage with AIDS at time of HIV diagnosis.  
2003-2012



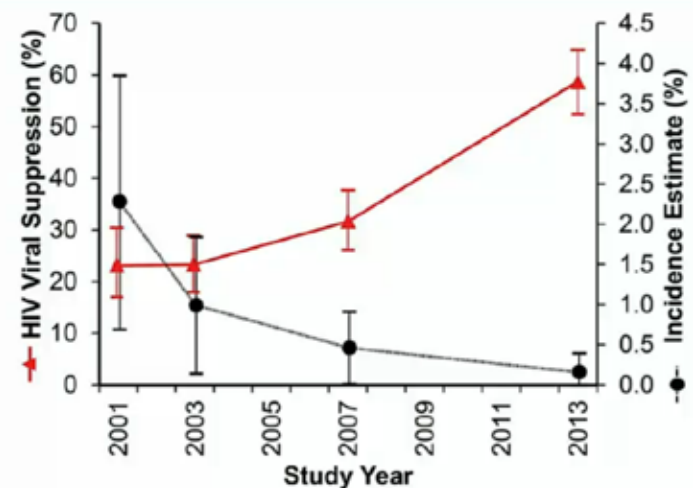
# Increased Awareness of HIV Infection

- § De-identified serosurveys conducted on 18,240 untargeted adult JHH-ED patients between 1987-2013.
- § Trends in HIV prevalence, cross-sectional incidence estimates, viral load and HCV prevalence.
- § JHH ED HIV testing and linkage to care programs were initiated in 2005 and continue to date.

## HIV Prevalence and Proportion of Undiagnosed Infections



## Viral Suppression and HIV Incidence



# Financial Incentives



# HPTN 065

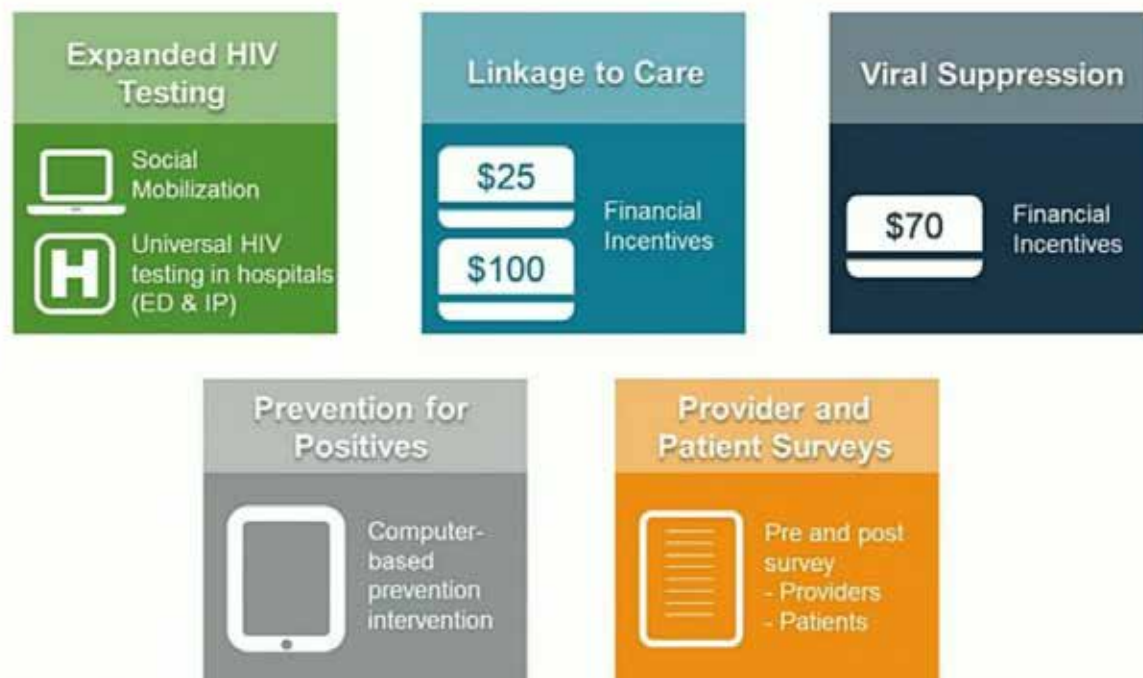
§ Goal to determine feasibility of financial incentives to linkage to care and viral suppression

§ 38 Sites  
– NYC & DC

[Most patients in care at these Sites]



## HPTN 065 Study Components

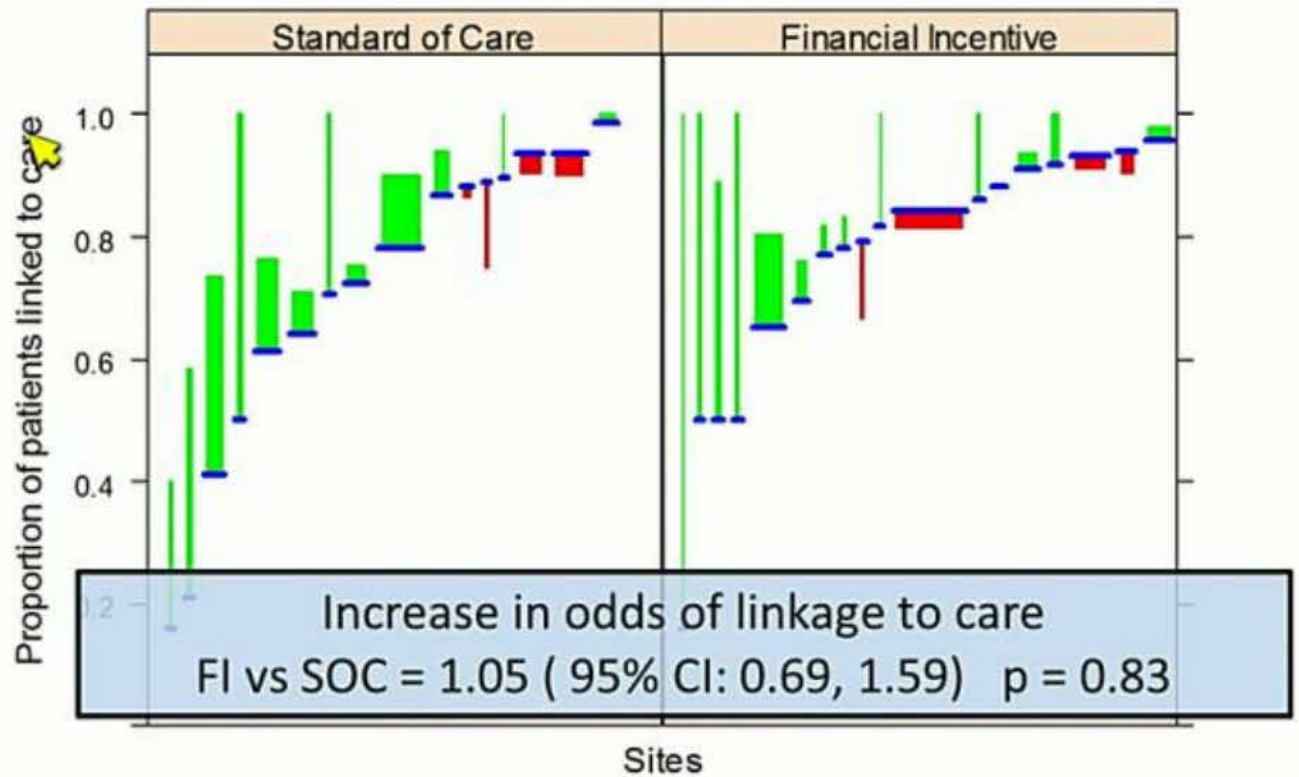




# Linkage to Care

838/1061 Coupons Redeemed

## Change in Linkage to Care, by Test Site



Sites within each arm ordered by baseline L2C

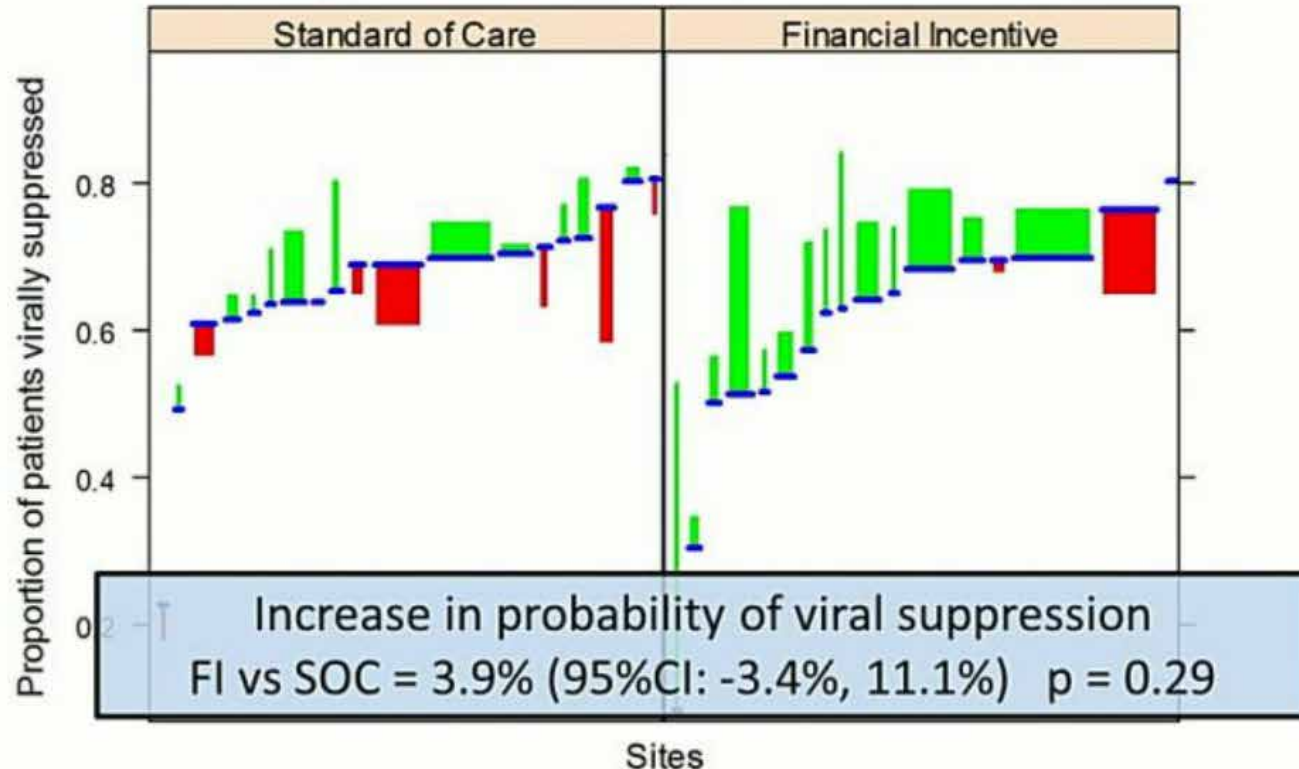
Blue line is baseline L2C

Bar indicates mean change for each site: **green = increase**, **red = decrease**



# Viral Suppression

## Change in Proportion with VS, by Site



39,359 Coupons  
 Dispensed

Sites within each arm ordered by baseline VS

Blue line is baseline VS

Bar indicates mean change for each site: **green = increase**, **red = decrease**

Width of bar is relative to number of patients in care at the site

Mean number of HIV patients in care per site: 438, geometric mean: 243/site





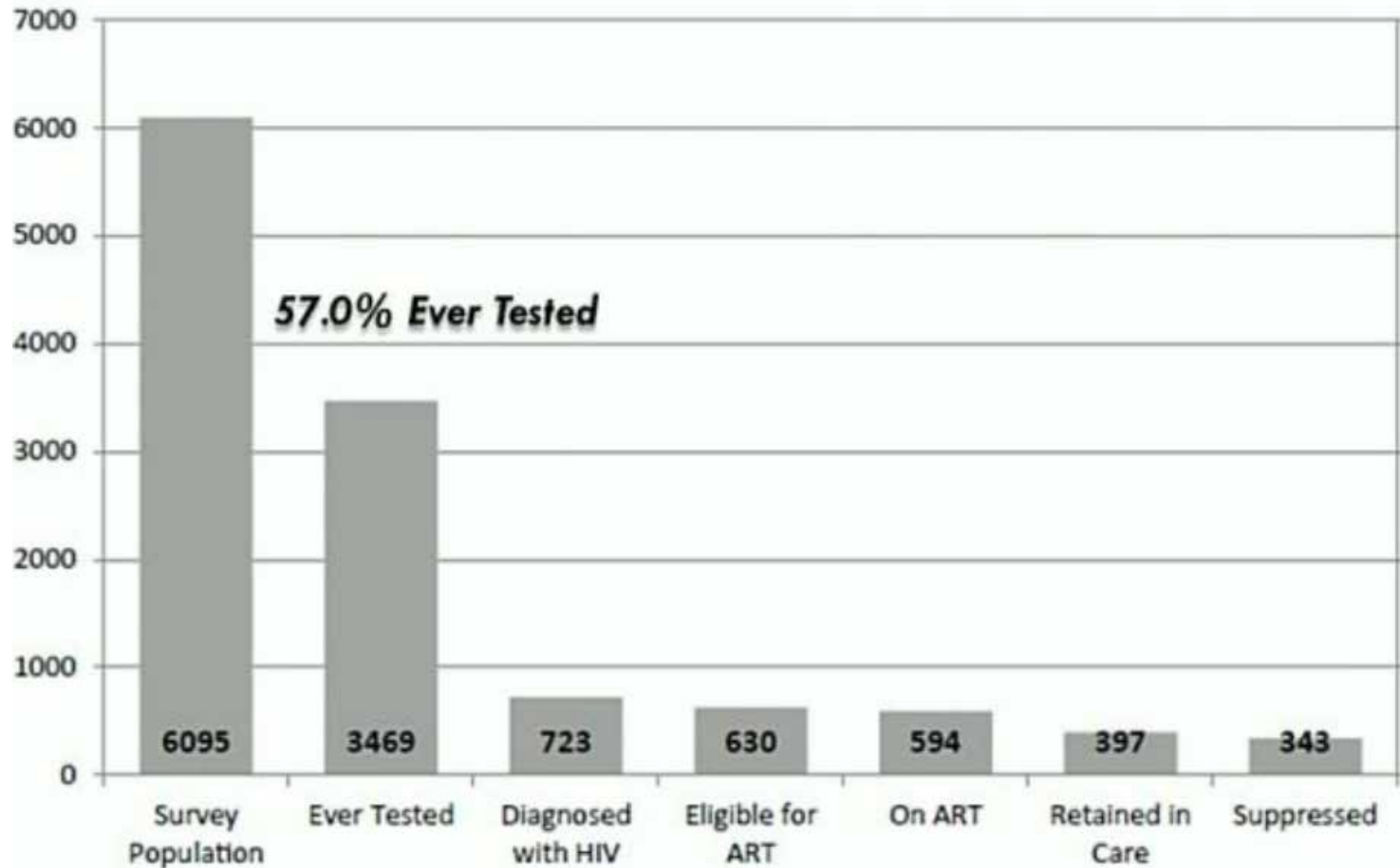
# Other Interesting Abstracts



# Stigma

- § 76% of 4,385 participants in MMP endorsed at least one HIV-related stigma questions.
  - Stigma scores were associated with depression, non-disclosure of HIV status to all sex partners, non-adherence to ART, and lack of viral suppression.
    - § Baughner Abstract #1057
  
- § 89% of women and 81% of men in 18 countries in SSA reported HIV-related stigma.
  - For each 10% increase in ART coverage, there was a 2% (significant) decline in reported HIV-related stigma.
    - § Chan Abstract #1059

# Global Engagement in HIV Continuum Among MSM

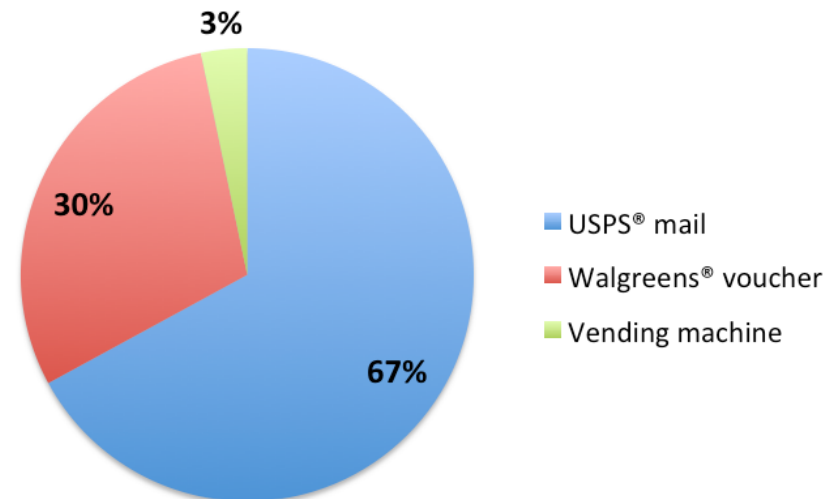


# HOME HIV Testing

- § Used Grindr to advertise free home HIV self-test kits.
- § Over 6 weeks received 12,000 visits to their website and 334 test requests.
  - 28% had tested >12 months prior
  - 11% had never been tested
  - Two new HIV+ Both linked to care.

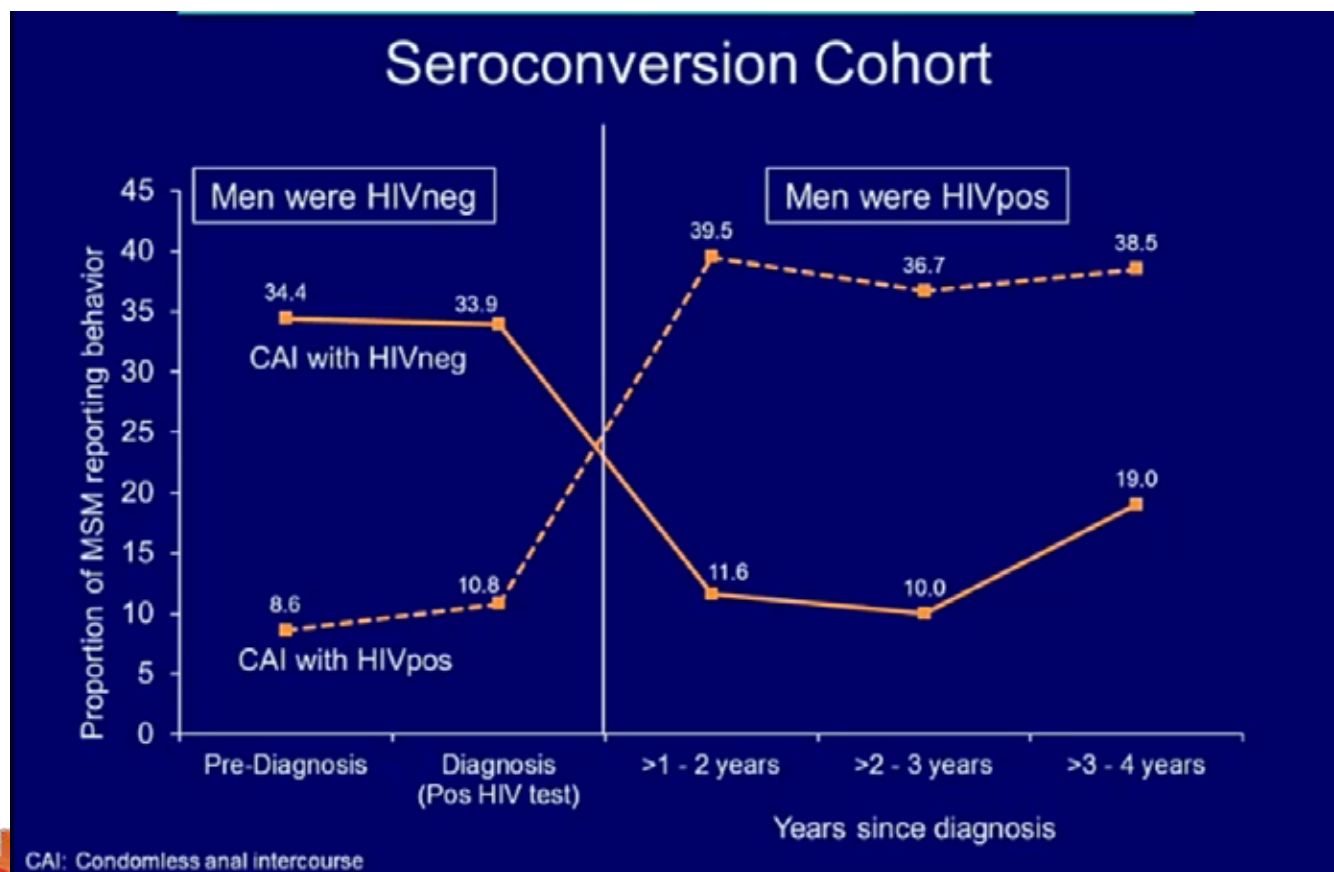


Figure 2: Number of HIV self-test kit requests by delivery method



# Serosorting

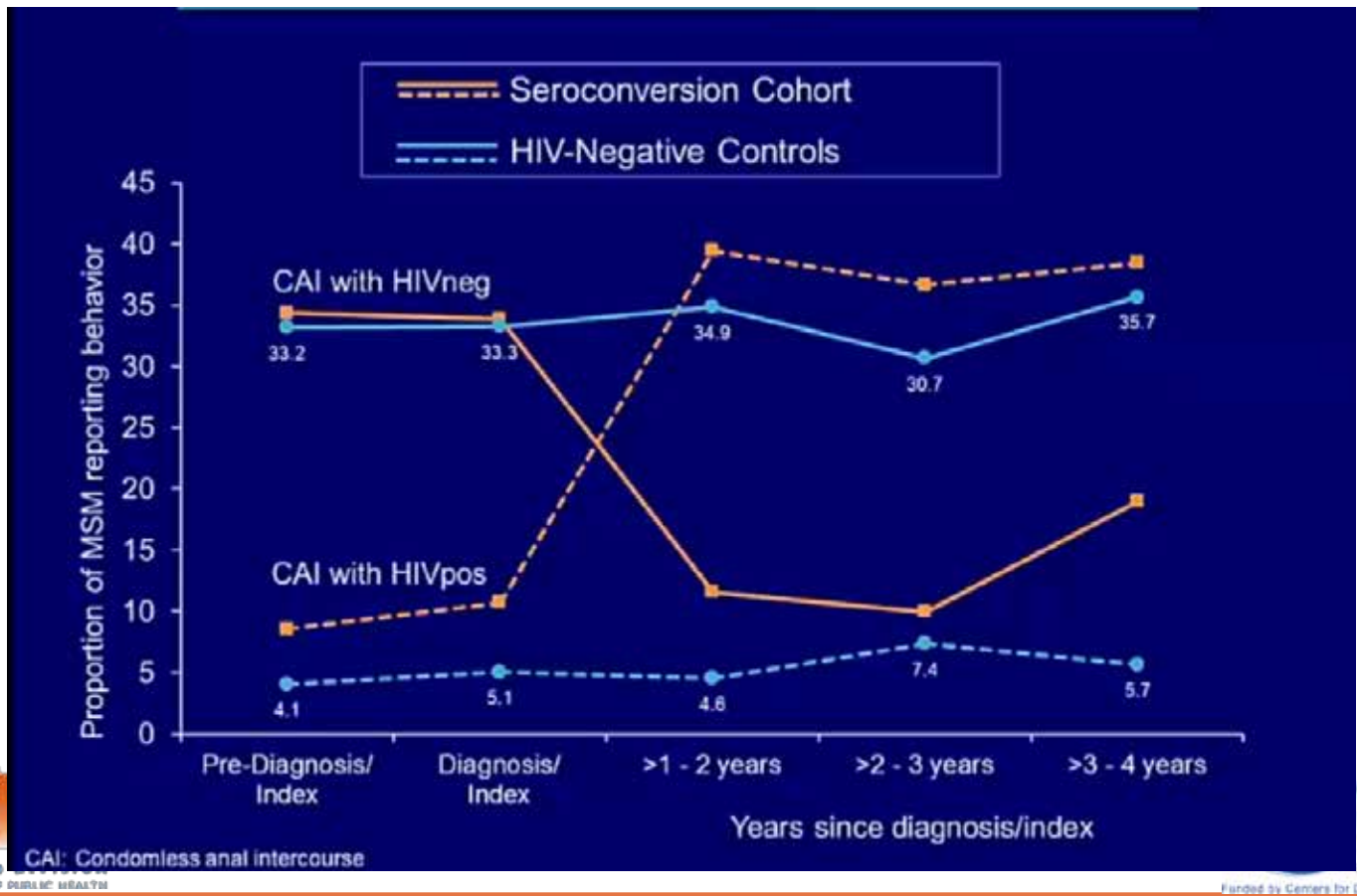
§ Retrospective cohort of 186 MSM newly diagnosed with HIV



CAI: Condomless anal intercourse

# Serosorting

§ Stable serosorting among HIV negative MSM over the same time period.



# Thank you

- § Hyman Scott
- § Albert Liu
- § Harry Lampiris
- § Cait Koss
- § Carina Marquez
- § Brad Hare

*Boston*

Mark Your **2016** Calendar!

**CROI 2016** will be held at the Hynes Convention Center in Boston, Massachusetts, from February 22 to 25, 2016.

