CROI Report Back

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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.

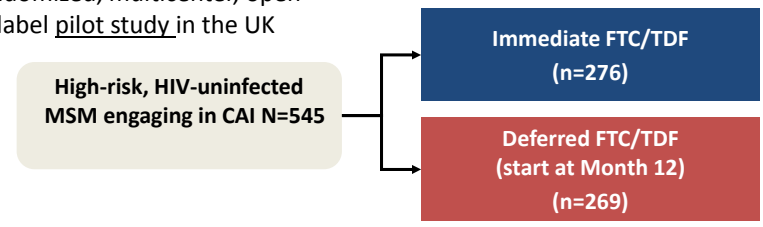
Outline

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

McCormack #22LB

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

CAI: Condomless anal intercourse
All subjects received comprehensive HIV prevention services, including condoms, risk-reduction counseling, testing and treatment for sexually transmitted infections, and HIV pre- and post-test counseling

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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

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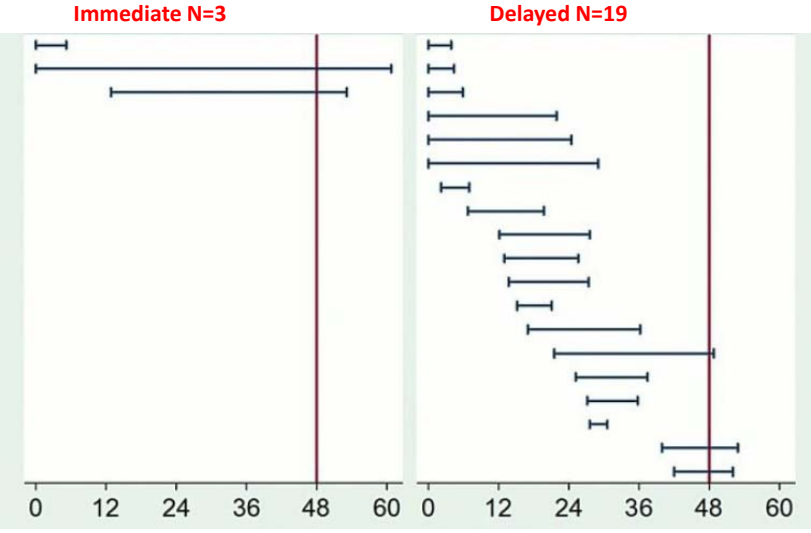
Individual Incident HIV Infections



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PROUD Results

HIV Incidence

Group	Infections, n	Follow-up (PY)	Incidence/100 person-years (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

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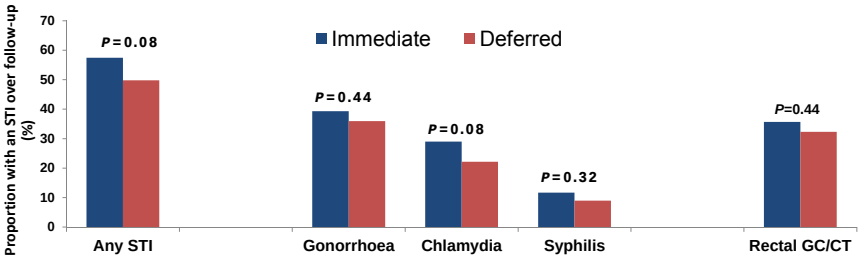
Reported Sexual Risk Behavior and STIs

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

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Ipergay Trial

High-risk, HIV-uninfected MSM
N=400

- Condomless anal sex with ≥2 partners within 6 months
- eGFR > 60 mL/min

Double-blind, randomized

"On-demand" FTC/TDF treatment

All participants received a package of preventative measures:
- counselling
- repeated HIV testing
- screening & treatment for other STIs
- HBV vaccination
- condoms and gel

"On-demand" FTC/TDF placebo

"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**

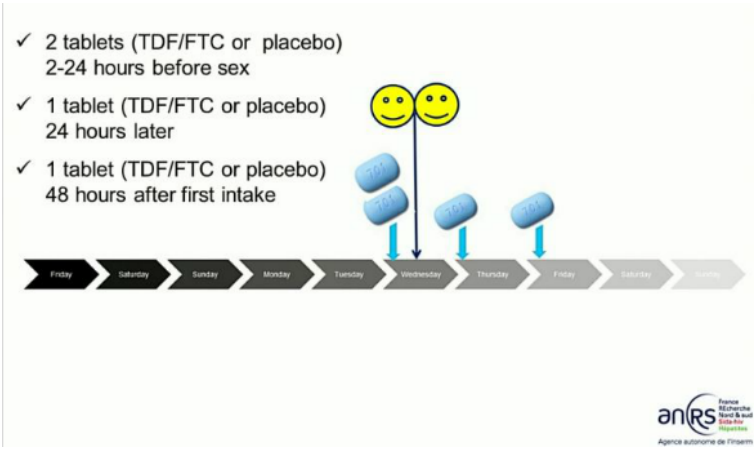
Primary endpoint: HIV seroconversion

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.

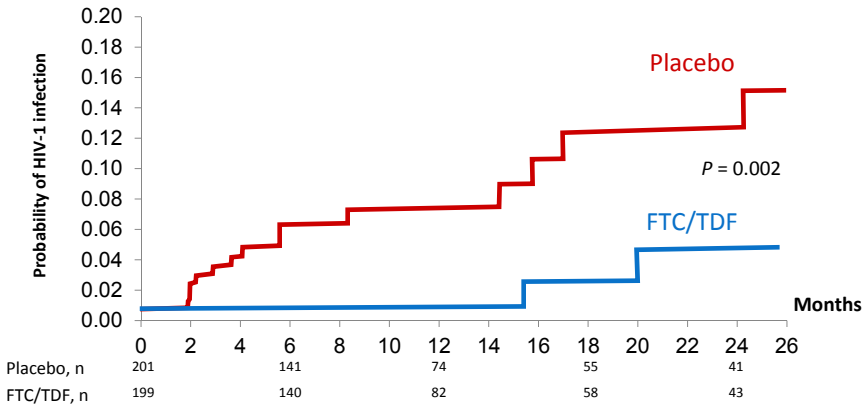
Molina #23LB

Ipergay Event Level PrEP



Molina #23LB

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

Molina #23LB

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.

Molina #23LB

Adherence to PrEP Surrounding Recent Sexual Intercourse – CASI Assessment

PrEP use, % (min-max)	FTC/TDF n=649 sex events	Placebo n=563 sex events	Total % (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

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Sexually Transmitted Infections

	FTC/TDF n=199 N (%)	Placebo n=201 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

Molina #23LB

Adverse Events

	FTC/TDF, n=199 N (%)	Placebo, n=201 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 2º 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 ≥ 2+	10 (5)	9 (5)	0.83
Glycosuria ≥ 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

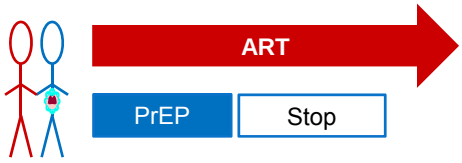
CDC Statement on IPERGAY Trial of Pre-Exposure Prophylaxis (PrEP) for HIV Prevention among Men Who Have Sex with Men

"…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."

Baeten. #29
Mujugira #989

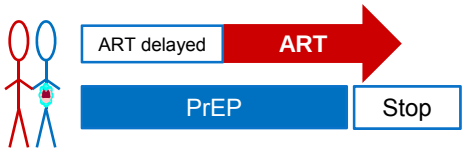
Partners PrEP + TasP for HIV Serodiscordant Couples

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



High uptake of PrEP (>95%) and high adherence

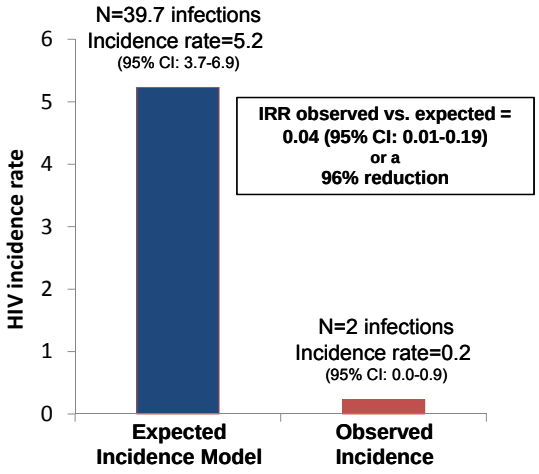
High uptake of ART (80%) and >90% achieved viral suppression



858 Person years of follow-up
- **48% PrEP alone**
- **27% PrEP and ART overlapping**
- **16% ART alone**

Baeten #29
Mujugira #989

Partners PrEP + TasP: HIV Incidence



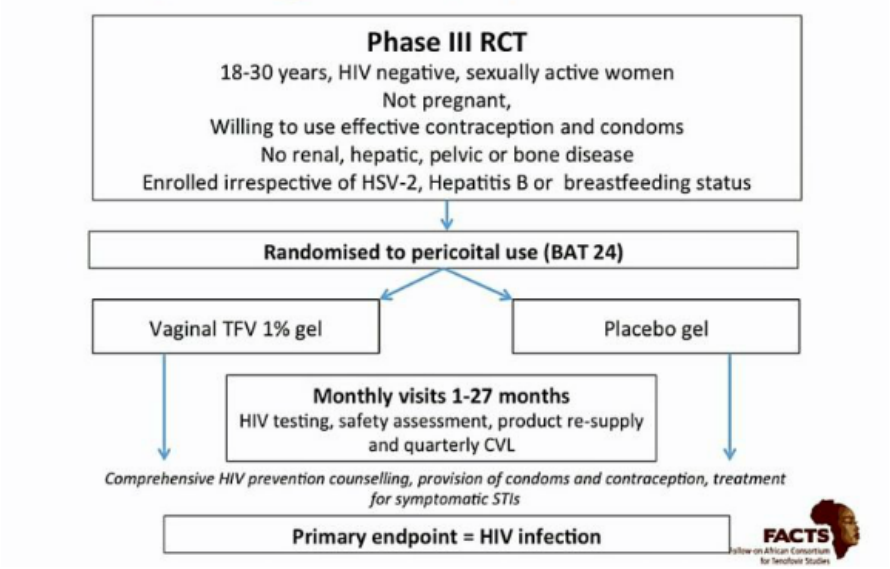
- Limited PrEP use in the 2 HIV seroconverters.

  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

Rees #26LB

FACTS 001



Rees #26LB

Baseline Characteristics

	TFV gel n= 1015 %	Placebo gel N=1014 %
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%

Rees #26LB

Primary Effectiveness Results (mITT)

	TFV gel N= 1015 %	Placebo gel N=1014 %
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)

Rees #26LB

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

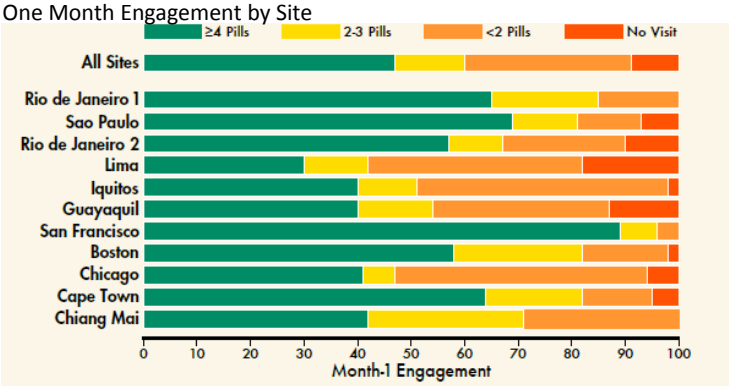
TFV detected in samples from women who reported sex in 10 days preceding CVL

aHR 0.48 (0.23-97) p=0.04

Glidden #970

Variable PrEP Engagement in iPrEx OLE

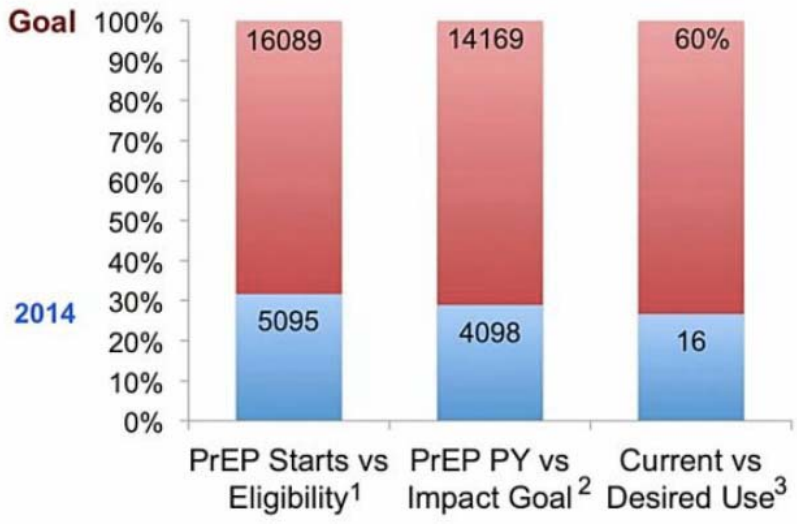
One Month Engagement by Site



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 ≥4 pills/week

Grant Abstract #25

SF: Current PrEP use 1/3 of goal



Landovitz Abstract #20

PrEP Adverse Events And Resistance

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

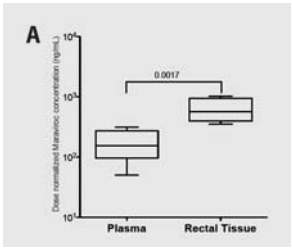
New PrEP Agents

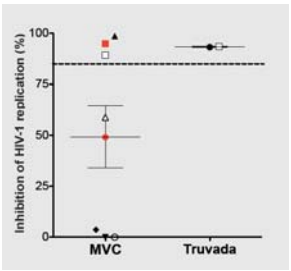
- Maraviroc – HPTN 069/ACTG A5305
- Long Acting Agents
  - Rilpivirine LA – HPTN 076
  - Cabotegravir – HPTN 077/ÉCLAIR
  - Immunotherapies (VRC01) – HVTN / HPTN 081

Coll Abstract #964

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



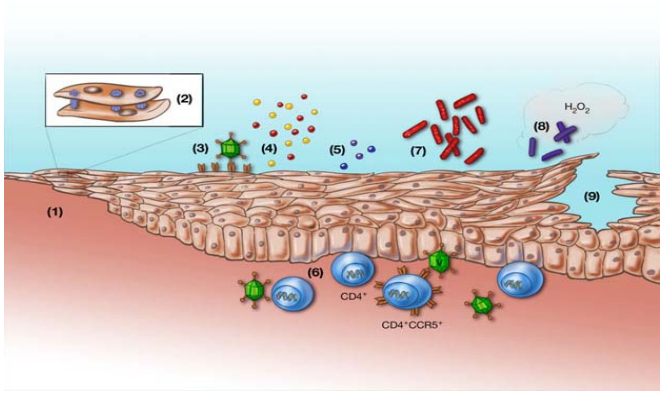


Themed Discussion

- 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.

Morrison et al PLoS Medicine, 2015

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

Murphy et al AJRI 2014

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

Gardner Abstract #101

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)

Gardner CROI 2015 #101

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
Age at initial VL in analysis				
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.		
Race/ethnicity				
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.		
Gender/orientation				
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:

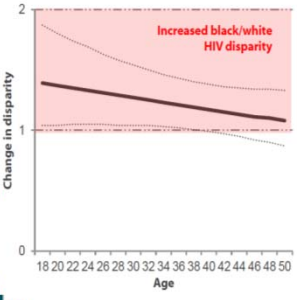
1. Young pts
2. Black pts
3. Pts not on ART
4. Pts with more intervals >6 months between VL measures
5. Medicaid or Ryan White.

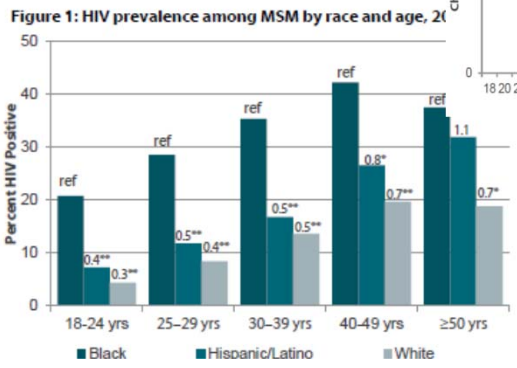
No adherence data or sexual risk behavior data

Wejnart Abstract #1041

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.



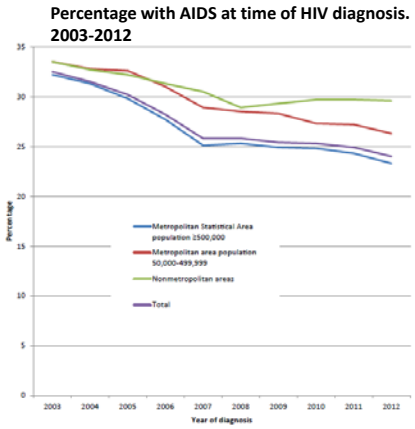


Hall Abstract #999

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:

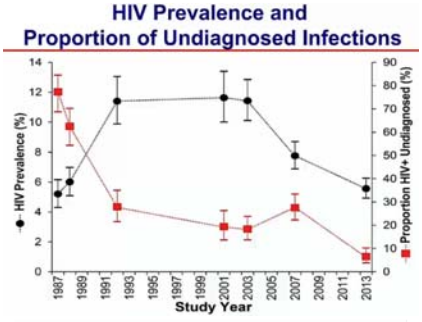
  Blacks 38/105 MSAs;
  Latinos 68/105 MSAs

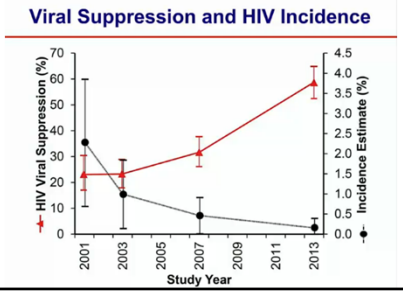


Quinn Abstract #98

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.





Financial Incentives

El-Sadr Abstract #29

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]