



The STI Crisis: Implications for HIV Prevention Research & Implementation

Jeanne MARRAZZO, MD, MPH

University of Alabama at Birmingham

HPTN Annual Meeting, June 2019

Disclosures

Research grants/support: Merck; Cepheid

NIH-funded research on investigational products:
(zolidofloxacin (Entasis); TOL-463 (Toltec))

Advisory panels: Gilead; Biofire; BD

DSMB: Gilead

Discussion

- Quick update on key epidemiologic trends
 - Relationship between increased PrEP uptake and STI crisis?
- Highlight features of particular concern for conducting HIV prevention trials in at-risk populations
 - Biological, behavioral, epidemiologic synergy between STI & HIV: STI as a risk marker for subsequent HIV
 - Operational challenges
 - Asymptomatic nature of most STI; burden of extragenital infection
 - Cost of screening & treatment
 - High index of suspicion for antimicrobial resistance → treatment failure
- What do we need to do differently in HIV prevention trials to embrace these trends?

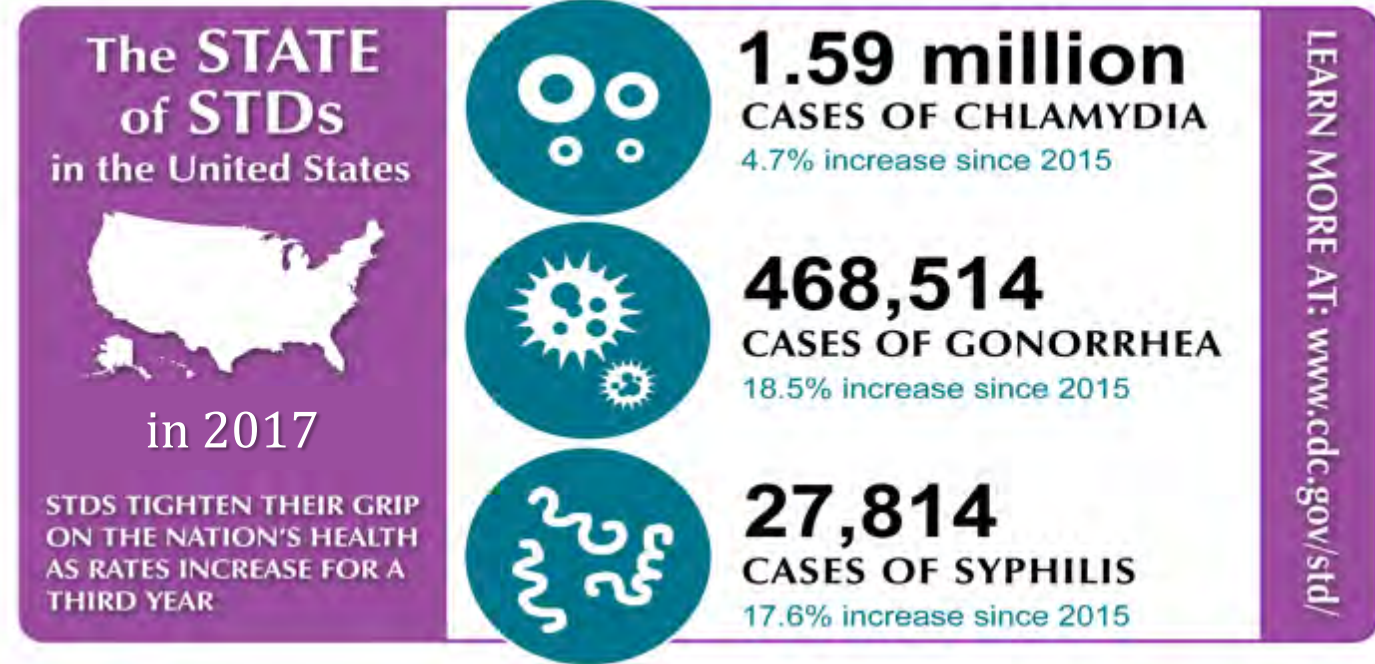
Defining the STI Crisis: WHO & CDC Reports

Dramatic recent increases in bacterial STI incidence in the era of effective HIV treatment & prevention

WHO 2016 Estimates: adults 15 to 49

376 million new cases of curable STI

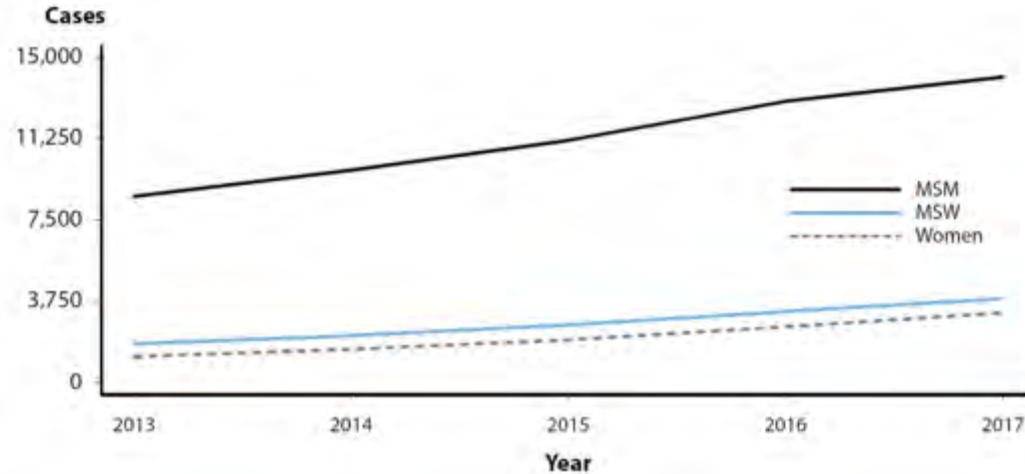
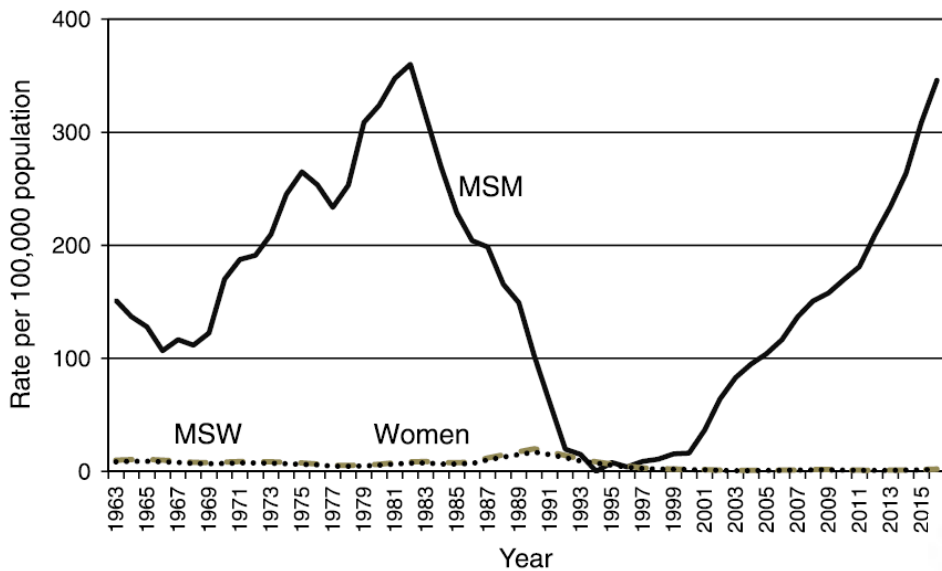
Curable STI (Chlamydia, gonorrhoea, syphilis and trichomoniasis)



- Gonorrhoea: continued antimicrobial resistance; extragenital infection
- Chlamydia: treatment challenges with rectal infections; reappearance of LGV proctitis
- Syphilis: ocular disease; congenital cases

The U.S. Syphilis Epidemic: 2017

Primary / Secondary Syphilis in Men



- 88% of cases
 - 80% in MSM
- 46% in MSM HIV+

Primary/ Secondary & Congenital Syphilis in Women

- Primary / Secondary: 156% increase compared with 2013
- Congenital syphilis: 154% increase



- 918 congenital cases
- In California, >50% of cases without prenatal care
- Strong links to meth, heroin

Source: <http://www.cdc.gov/std>

Bacterial STIs in Young African Women in PrEP Projects: A True STI-HIV Syndemic

	C. trachomatis		N. gonorrhoeae	
	Prevalence	Incidence (per year)	Prevalence	Incidence (per year)
MTN-020/ASPIRE Phase III DPV ring in Malawi, South Africa, Uganda, Zimbabwe; N=2629	12%	27%	4%	11%
HPTN 082 PrEP demo project in South Africa, Zimbabwe; N=416	29%	33%	8%	14%
POWER PrEP implementation study in Kenya, South Africa; N=1600	26%	53%*	9%	20%
VOICE RCT of PrEP in South Africa, Uganda, Zimbabwe; N=5-29	12%	14%	3%	3.5%

* In first 60 women with 6 months follow-up

Baeten R4P 2018
Celum CROI 2018
Morton AIDS 2018
Chirenje STD 2017

Converging epidemics of sexually transmitted infections and bacterial vaginosis in southern African female adolescents at risk of HIV

Key Principle

- Most STI are asymptomatic, or are associated with non-specific symptoms that do not prompt diagnostic testing, **yet...**
- The associated inflammation that increases HIV acquisition risk is still operative

Symptomatic Vaginal Discharge Is a Poor Predictor of Sexually Transmitted Infections and Genital Tract Inflammation in High-Risk Women in South Africa

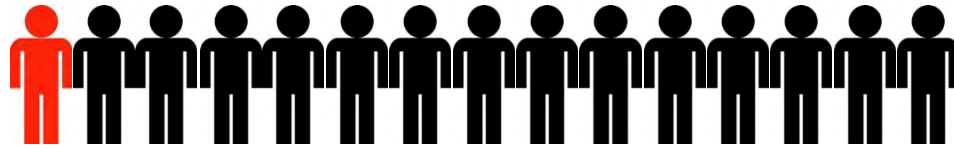
Koleka Mlisana,^{1,2,3} Nivashnee Naicker,¹ Lise Werner,¹ Lindi Roberts,⁴ Francois van Loggerenberg,¹ Cheryl Baxter,¹ Jo-Ann S. Passmore,^{1,4,5} Anneke C. Grobler,¹ A. Willem Sturm,⁶ Carolyn Williamson,^{1,4,5} Katharina Ronacher,⁷ Gerhard Walzl,⁷ and Salim S. Abdool Karim^{1,8}

Inflammatory cytokine biomarkers of asymptomatic sexually transmitted infections and vaginal dysbiosis: a multicentre validation study

Lindi Masson,^{1,2} Shaun Barnabas,^{1,3} Jennifer Deese,^{4,5} Katie Lennard,¹ Smritee Dabee,¹ Hoyam Gamiieldien,¹ Shameem Z Jaumdally,¹ Anna-Lise Williamson,¹ Francesca Little,⁶ Lut Van Damme,⁷ Khatija Ahmed,⁸ Tania Crucitti,⁹ Saïd Abdellati,⁹ Linda-Gail Bekker,^{1,3} Glenda Gray,^{10,11} Janan Dietrich,¹⁰ Heather Jaspan,^{1,12} Jo-Ann S Passmore^{1,2,13}

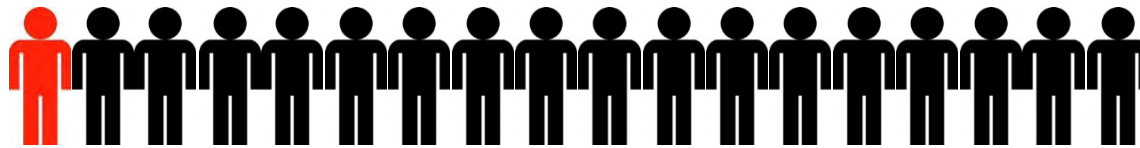
A Vicious Cycle: STDs *predict* future HIV Risk

Rectal GC
or CT



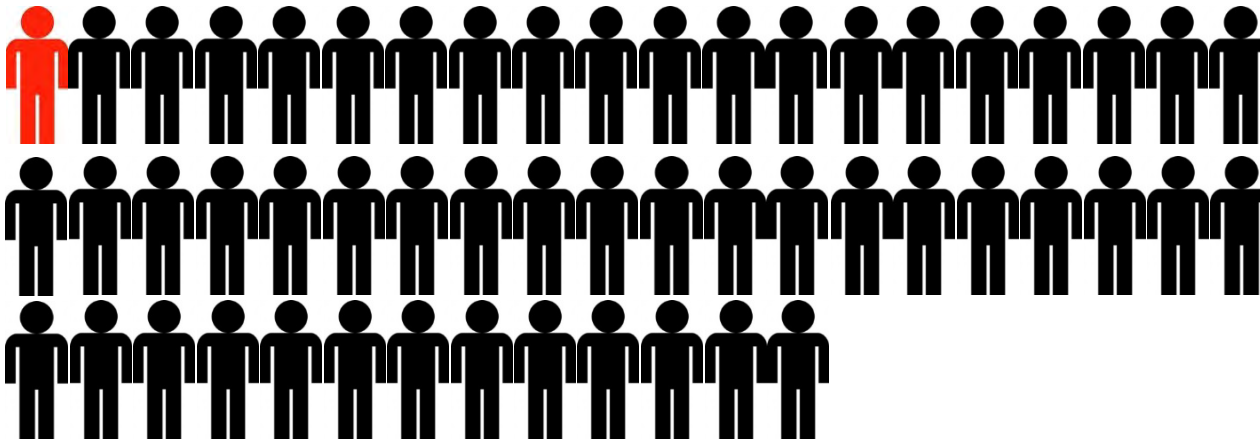
1 in 15 MSM were diagnosed with HIV within 1 year.*

Primary or
Secondary
Syphilis



1 in 18 MSM were diagnosed with HIV within 1 year.**

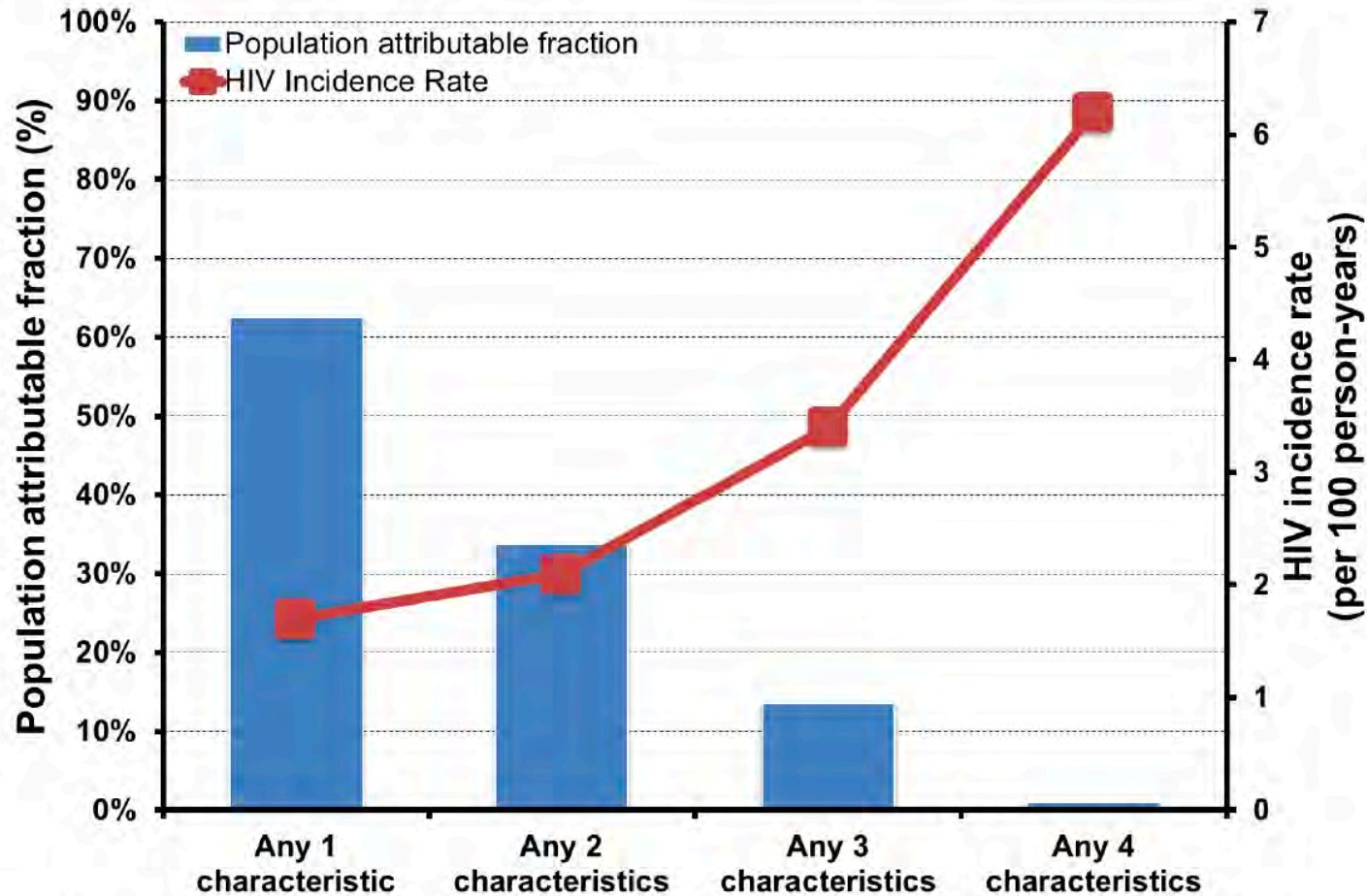
No rectal STD
or syphilis
infection



1 in 53 MSM were diagnosed with HIV within 1 year.*

HIV Incidence and Predictors of Incident HIV among Men Who Have Sex with Men Attending a Sexual Health Clinic in Melbourne, Australia

King T. Cheung^{1,2}, Christopher K. Fairley^{1,3}, Tim R. H. Read^{1,3}, Ian Denham¹, Glenda Fehler¹, Catriona S. Bradshaw^{1,3}, Marcus Y. Chen^{1,3}, Eric P. F. Chow^{1,3*}



Characteristics included: (1) inconsistent condom use during anal sex; (2) injecting drug use; (3) PEP use; and (4) STI diagnosis.

Retrospective cohort study of 5256 MSM attending Melbourne Sexual Health Centre 2007–2013 with at least two HIV tests within 12 months of each other; 81 incident HIV infections

- Inconsistent condom use during anal sex
- IDU
- PEP use
- Any STI diagnosis in last 12 months

Fig 1. The population attributable fraction for HIV and HIV incidence of different risk characteristics. *Cheung 2018*

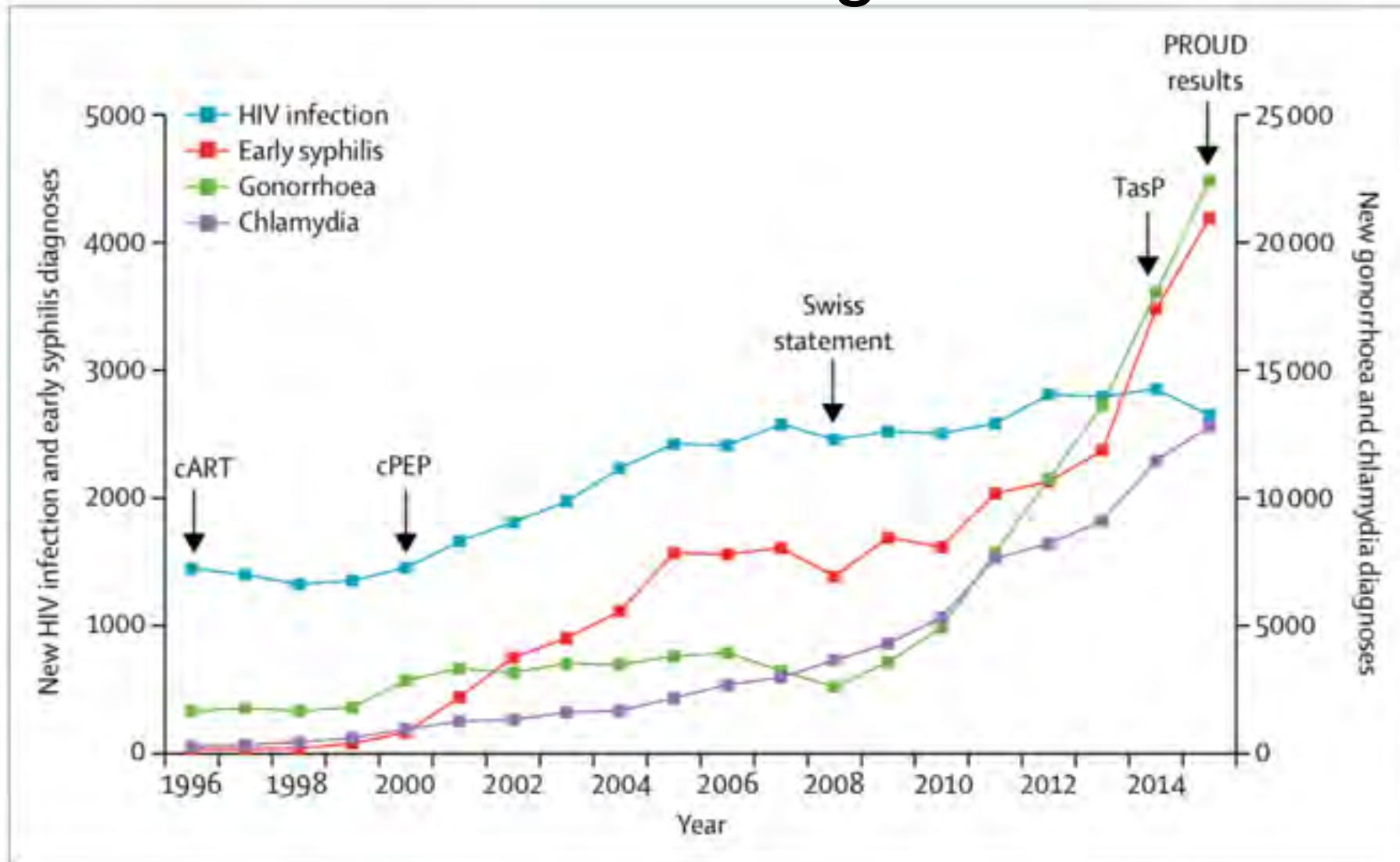
Effect of Relative Risk for HIV Acquisition on HIV Incidence: A Modeling Analysis Among MSM

RR of HIV Acquisition by Anatomic Site		HIV Incidence Rate (per 100 PYAR)*	PAR (%)
Rectal	Urethral		
1.97	1.48	1.96	7.1 (4.6, 9.3)
1	1	1.83	Ref
1	2	1.86	2.0 (-0.7, 4.3)
1	3	1.89	3.2 (0.8, 5.3)
2	1	1.93	5.6 (3.6, 7.8)
2	2	1.98	7.7 (5.9, 9.8)
2	3	2.00	8.6 (6.4, 10.7)
3	1	2.02	9.6 (7.4, 11.9)
3	2	2.07	12.0 (10.0, 13.9)
3	3	2.1	13.8 (11.7, 16)

Approximately 10% of HIV infections among MSM are attributable to gonorrhea/chlamydia infection

PYAR= person-years at risk. HIV transmission RRs held constant at rectal RR = 1.3 and urethral RR = 1.3; see text for CI's

Relationship to Increasing PrEP Use: MSM in England



Association of HIV Preexposure Prophylaxis With Incidence of Sexually Transmitted Infection Among Individuals at High Risk of HIV Infection

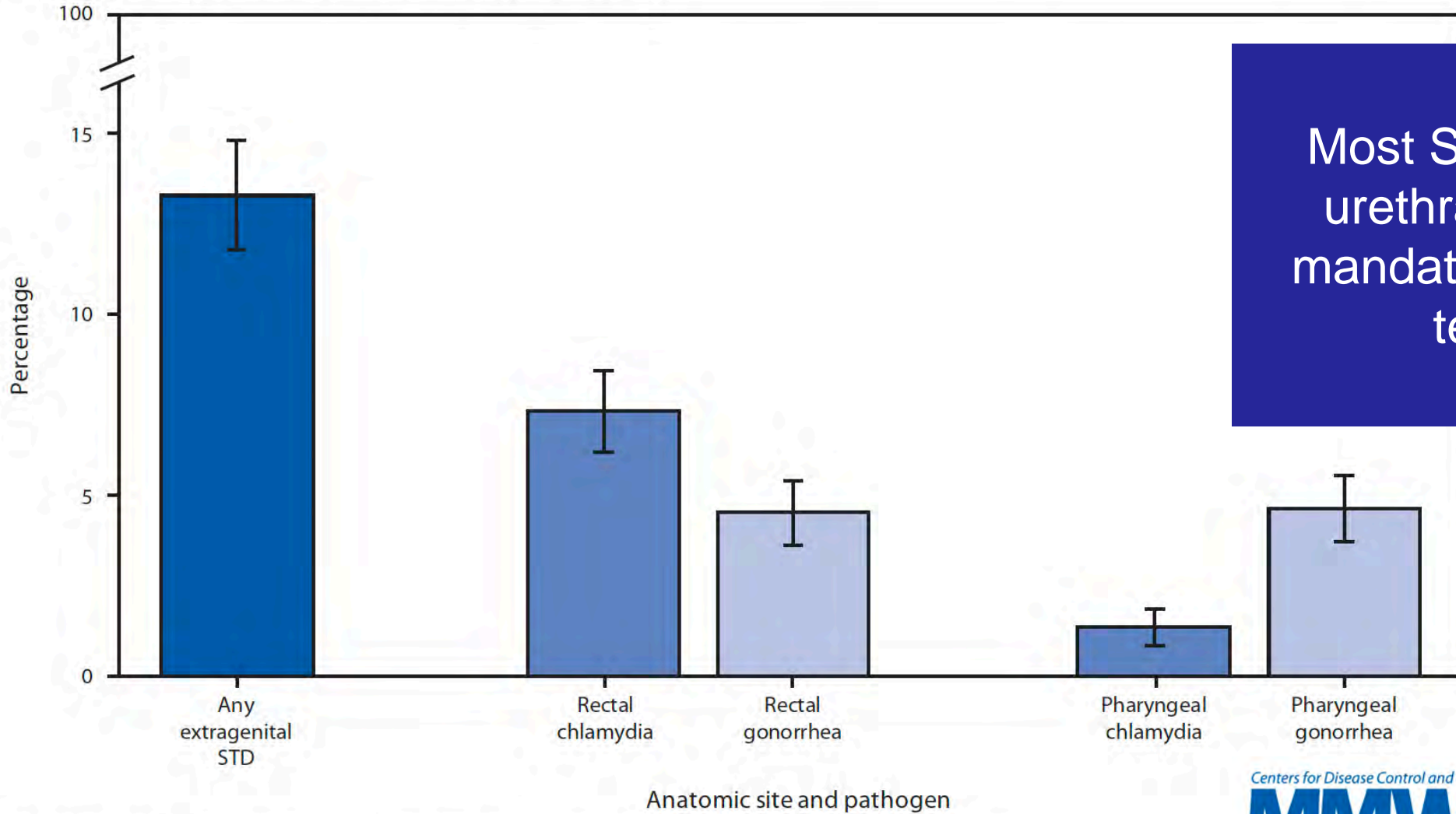
Michael W. Traeger, MSc; Vincent J. Cornelisse, MBBS, PhD; Jason Asselin, BSc; Brian Price, MBA; Norman J. Roth, MBB Ban Kiem Tee, MBBS; Christopher K. Fairley, MBBS, PhD; Christina C. Chang, MBBS, PhD; Jude Armishaw, BNurs; Olga \ Matthew Penn, MBBS; Pauline Cundill, BM; George Forgan-Smith, MBBS; John Gall, MBBS, PhD; Claire Pickett, MBBS; I Anne Mak, BPharm; Tim D. Spelman, MBBS, MSc; Long Nguyen, MCom; Dean A. Murphy, PhD; Kathleen E. Ryan, PhD; I Michael West, BA; Simon Ruth, MSSc; Colin Batrouney, BA; John T. Lockwood, BN; Jennifer F. Hoy, MBBS; Margaret E. I Mark A. Stoové, PhD; Edwina J. Wright, MBBS, PhD; for the PrEPX Study Team

- Compared STI incidence for 1-year pre-enrollment in PrEPX to post-PrEPX rates
- Among 1378 ppts with preenrollment data, STI incidence increased from 69.5 per 100 person-years prior to enrollment to 98.4 per 100 person-years during follow-up (IRR, 1.41 [95%CI, 1.29-1.56]).
- After adjusting for testing frequency, increase in incidence was significant for any STI (adj IRR, 1.12 [95%CI, 1.02-1.23]) & for chlamydia (adj IRR, 1.17 [95%CI, 1.04-1.33]).

Table 2. Incidence of Sexually Transmitted Infections During Follow-up Among Included Participants (N = 2981)

	No. of Infections	Person-Years of Follow-up (n = 3185.0) ^a	Incidence Rate per 100 Person-Years (95% CI)
All STIs	2928		91.9 (88.7-95.3)
Chlamydia	1434		45.0 (42.7-47.4)
Rectal ^b	1091		34.3 (32.3-36.3)
Urethral ^b	381		12.0 (10.8-13.2)
Pharyngeal ^b	127		4.0 (3.3-4.7)
Gonorrhea	1242		39.0 (36.9-41.2)
Rectal ^b	719		22.6 (21.0-24.3)
Urethral ^b	233		7.3 (6.4-8.3)
Pharyngeal ^b	629		19.7 (18.3-21.3)
Syphilis	252	3140.8	8.0 (7.1-9.0)
Site ^b			
Rectal infections	1810		56.8 (53.4-60.4)
Urethral infections	614		19.3 (17.4-21.3)
Pharyngeal infections	756		23.7 (22.0-25.6)
Age group, y ^c			
18-24 (n = 307)	161	186.1	86.5 (74.6-101.5)
25-29 (n = 634)	554	536.3	103.3 (94.9-112.1)
30-34 (n = 620)	733	684.4	107.1 (99.8-115.3)
35-39 (n = 482)	495	593.2	83.4 (76.4-91.2)
40-44 (n = 356)	354	432.2	81.9 (73.8-90.9)
45-49 (n = 437)	486	548.0	88.7 (81.2-97.1)
≥50 (n = 145)	145	204.7	70.8 (60.2-83.4)

FIGURE. Prevalence of extragenital chlamydia and gonorrhea among community venue–attending* men who have sex with men, by anatomic site — National HIV Behavioral Surveillance, five U.S. cities,† 2017



Most STI are non-urethral in MSM, mandating targeted testing

Abbreviations: HIV = human immunodeficiency virus; STD = sexually transmitted disease.

* Community venues include bars, clubs, fitness centers, and other locations frequented by men who have sex with men.

† Houston, Texas; Miami, Florida; New York City, New York; San Francisco, California; Washington, DC.

Centers for Disease Control and Prevention

MMWR

Weekly / Vol. 68 / No. 14

Morbidity and Mortality Weekly Report

April 12, 2019

Extragenital Chlamydia and Gonorrhea Among Community Venue–Attending Men Who Have Sex with Men — Five Cities, United States, 2017

Michelle L. Johnson Jones, MPH¹; Johanna Chapin-Bardsles, PhD²; Destani Bizunc, MPH³; John R. Papp, PhD¹; Christi Phillips¹; Robert D. Kirkcaldy, MD¹; Cyprian Wejnert, PhD²; Kyle T. Bernstein, PhD¹; National HIV Behavioral Surveillance Sexually Transmitted Infection Study Group

FDA NEWS RELEASE

FDA clears first diagnostic tests for extragenital testing for chlamydia and gonorrhea

FDA clears first diagnostic tests for extragenital testing for chlamydia and gonorrhea



For Immediate Release: May 23, 2019

Today, the U.S. Food and Drug Administration cleared for marketing two tests that can detect the presence of the bacteria *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, which cause the sexually-transmitted infections, respectively, chlamydia and gonorrhea, through diagnostic testing of extragenital specimens. The Aptima Combo 2 Assay and the Xpert CT/NG are the first devices cleared for extragenital diagnostic testing of these infections via the throat and rectum. These tests were previously only cleared for testing urine, vaginal and endocervical samples.

FDA
May 23



FDA Clears First Diagnostic Tests for Extragenital Testing for Chlamydia and Gonorrhea

3 min read

Today, the U.S. Food and Drug Administration cleared for marketing two tests that can detect the presence of the bacteria *Chlamydia trachomatis* and *Neisseria gonorrhoeae*, which cause the sexually-transmitted infectio...

Why Bother with STIs in HIV Prevention Research?

- We can achieve U=U in high STI incidence settings
- The more you look, the more you find!
 - Increased screening accounts for observed increase in STI
- STIs are usually asymptomatic & inconvenient at most
- Targeting STIs is regressive & represent a return to stigmatizing sexual behavior
 - U=U → new & welcome era of sexual health for people living with or at risk for HIV



ORIGINAL ARTICLE

Kissing may be an important and neglected risk factor for oropharyngeal gonorrhoea: a cross-sectional study in men who have sex with men

Eric P F Chow,^{1,2} Vincent J Cornelisse,^{1,2} Deborah A Williamson,³ David Priest,² Jane S Hocking,⁴ Catriona S Bradshaw,^{1,2} Tim R H Read,^{1,2} Marcus Y Chen,^{1,2} Benjamin P Howden,³ Christopher K Fairley^{1,2}

Why We SHOULD Bother!

- STI as a risk marker for subsequent HIV can identify appropriate participants for HIV prevention studies
- Opportunity to study STIs in an important population with longitudinal follow-up
 - Imperfect understanding of STI natural history
 - High index of suspicion for antimicrobial resistance → treatment failure
- For women, major reproductive health consequences
 - PID, tubal infertility, ectopic pregnancy, adverse outcomes of pregnancy
 - Stigma highly operative
 - Sexual pleasure / freedom may remain an elusive goal & may not drive PrEP motivation; attitudes toward STI prevention important to assess

Why Discuss STIs in the Era of PrEP and U=U?

“...mantras like “Getting to Zero”...will never be achieved without addressing the potentiating role of STI in the global HIV pandemic, in addition to responding to other drivers of HIV spread, including economic and gender inequality, and other human rights challenges.”

VIEWPOINT

HIV and sexually transmitted infections: responding to the “newest normal”

Kenneth H Mayer^{1,2,3§}  and Henry de Vries^{4,5,6}

Sexually transmitted infections in the era of antiretroviral-based HIV prevention: Priorities for discovery research, implementation science, and community involvement

PLoS One, 2018

Jeanne M. Marrazzo^{1*}, Julia C. Dombrowski², Kenneth H. Mayer^{3,4}

Key Questions for STI Research in the Current Era of HIV Prevention

Overall

- Will high STI incidence undermine success of TASP or PrEP, in certain populations & with new PrEP agents?
- Can we develop PrEP agents that also prevent STI?

Key Questions for STI Research in the Current Era of HIV Prevention

Biology	<ul style="list-style-type: none">• Does hormonal contraception impact the STI-HIV-microbiome relationship? MPT implications• Are adolescents different (encountering STI for the first time)?• Do asymptomatic rectal STI modify mucosal environment's receptivity to HIV infection & increase PrEP threshold for protection?• Could HIV cure strategies that "shock" latent virus release transmissible HIV in the genital tract, with STI potentiating transmission?
Epidemiology & Behavioral Science	<ul style="list-style-type: none">• How much can high STI incidence be attributed to increased screening?• How will intermittent vs. continuous PrEP use impact sexual risk behaviors?
Implementation Science	<ul style="list-style-type: none">• What innovative testing strategies improve STI diagnosis & treatment among people in prevention studies?• What are the economic and workforce implications of increased STI screening?• Can STI clinics routinely integrate PrEP care?
Study Design	<ul style="list-style-type: none">• Can we use factorial design to "layer on" STI interventions in HIV prevention studies?• Can a stepped wedge cluster-randomized trial approach be used more widely to study prevention strategies at the clinic or population level?

Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

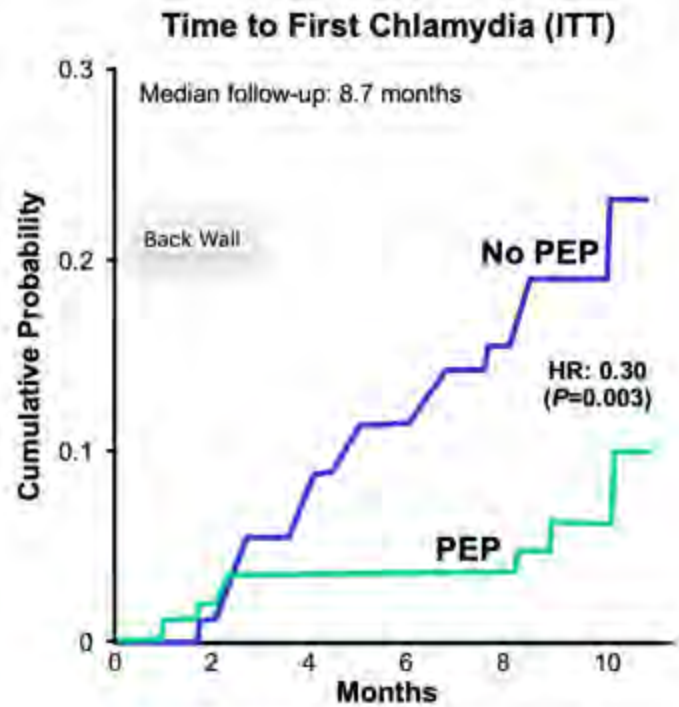
*Jean-Michel Molina, Isabelle Charreau, Christian Chidiac, Gilles Pialoux, Eric Cua, Constance Delaugerre, Catherine Capitant, Daniela Rojas-Castro, Julien Fonsart, Béatrice Bercot, Cécile Bébéar, Laurent Cotte, Olivier Robineau, François Raffi, Pierre Charbonneau, Alexandre Aslan, Julie Chas, Laurence Niedbalski, Bruno Spire, Luis Sagaon-Teyssier, Diane Carette, Soizic Le Mestre, Veronique Doré, Laurence Meyer, for the ANRS IPERGAY Study Group**

On Demand PEP Doxycycline 200 mg (~24 hours after sex, up to 72 hours)

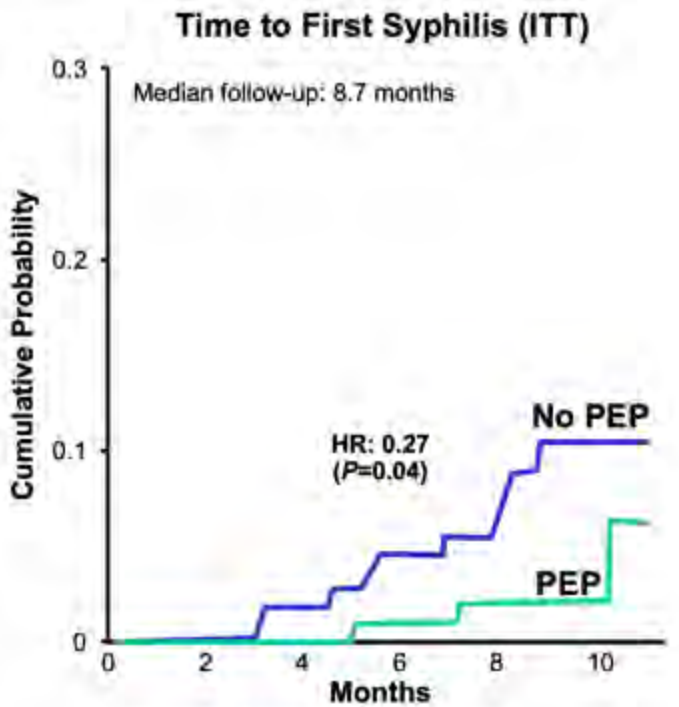
No PEP

Visits: baseline and every 2 months
 Serologic assays for HIV and syphilis
 PCR assays for chlamydia and gonorrhea
 Urine, anal, and throat samples collected

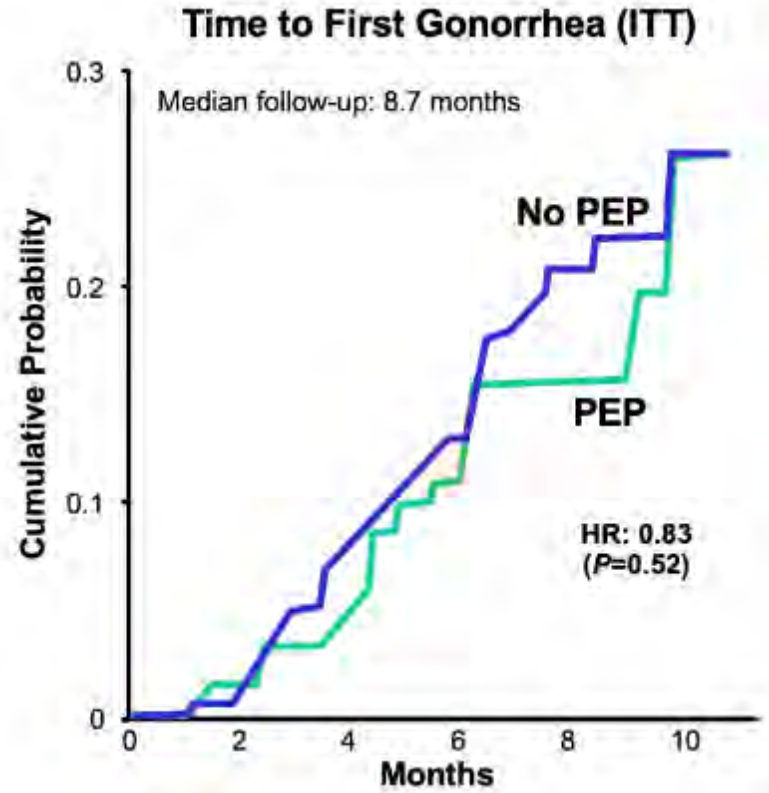
Time to First Chlamydia and Syphilis With On-Demand PEP With Doxycycline for MSM



Incidence of chlamydia (n=28):
 No PEP (n=21): 29/100 person-years.
 PEP (n=7): 9/100 person-years.



Incidence of syphilis (n=13):
 No PEP (n=10): 13/100 person-years.
 PEP (n=3): 4/100 person-years.



Incidence of gonorrhea (n=47):
 No PEP (n=25): 35/100 person-years.
 PEP (n=22): 29/100 person-years.

Doxy-PrEP/PEP for Syphilis & Chlamydia?

Pros

- Effective in early work
- Relatively safe drug
 - Chronic use in acne vulgaris
- Easy to administer
- Few other options for prevention
- Considerable interest among some MSM surveyed, with use already reported (Spinelli 2018)

Cons

- Limited data; duration?
- Costs
- Side effects of doxycycline
 - Esophagitis/ulceration
 - Photosensitivity
- Risk compensation?
- Reproductive concerns (women)?
- Antibiotic resistance?
- Microbiome effects?

Immediate STI Priorities for HIV Prevention Studies

- Deploy rapid, accurate **diagnostic tests** for STI in high HIV incidence settings
 - Reduce use of syndromic management
 - Enable POC tests & detection of antimicrobial resistance
 - Recognize high rates of recurrence at 3-6 months
- Ramp up STI screening in **asymptomatic** people in HIV prevention
 - Ask, screen, intervene! Site-specific testing
- Expand partner management strategies



THANK YOU!!

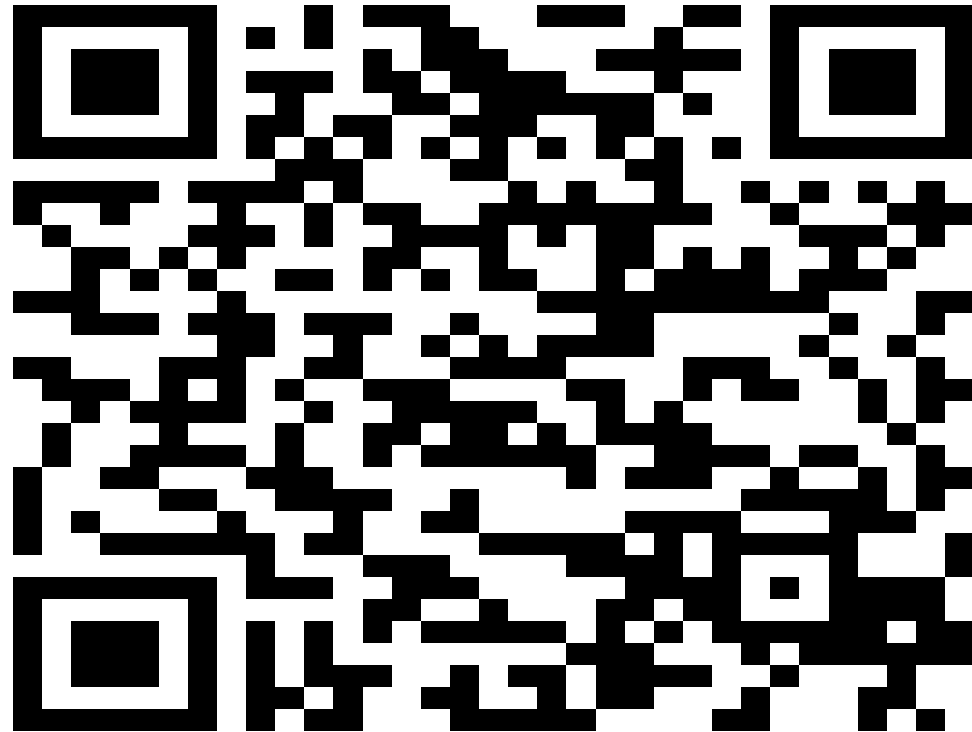


@DrJeanneM
@STD_Journal



Slide courtesy of Ina Park, MD

Download the CDC STD treatment
guidelines app ...





Increases in Pre-exposure Prophylaxis Use and Decreases in Condom Use: Behavioral Patterns Among HIV-Negative San Francisco Men Who have Sex with Men, 2004–2017

Yea-Hung Chen¹ · John Guigayana¹ · Willi McFarland¹ · Jonathan M. Snowden² · Henry F. Raymond^{1,3}

Concurrent Declines in Reported Condom Use

