

Revolutionizing Our Approach to STIs in HIV Prevention: The Time is Now!



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University of Alabama at Birmingham
MTN Regional Meeting, September 2019

Discussion

- Key trends in STI epidemiology
 - Long overdue expansion of descriptive STI epidemiology in Africa
 - Consequences for women: congenital syphilis; infertility; vaginal health
 - Increased PrEP use in some populations: related to resurgent STI crisis?
 - Evolving antimicrobial resistance → gonorrhea treatment failure
- Concerns specific to HIV prevention trials
 - Biological, behavioral, epidemiologic synergy between STI & HIV
 - Operational challenges
 - Asymptomatic nature of most STI
 - Lack of point-of-care diagnostic tests
 - Cost of screening & treatment
 - Burden of extragenital infection

**What do we need to do
differently in HIV prevention
trials to confront and manage
STIs?**

NIAID Officials Call for Innovative Research on Sexually Transmitted Infections

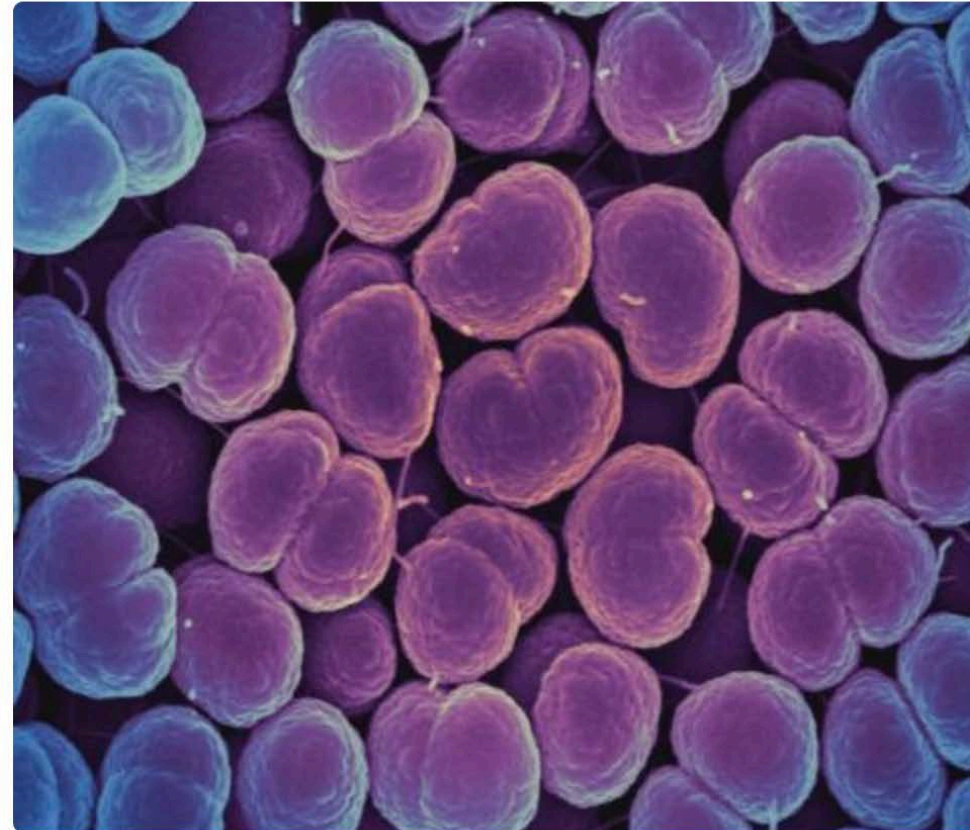


J Infect Dis,
September 9, 2019

September 9, 2019

Sexually transmitted infections, or STIs, pose a significant public health challenge. Globally, more than one million new STI cases are diagnosed each day. In a new article in *The Journal of Infectious Diseases*, experts from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health, suggest that the biomedical research community must refocus its commitment to STI research to surmount this growing global health crisis.

The perspective piece was written by NIAID Director Anthony S. Fauci, M.D., Robert W. Eisinger, Ph.D., special assistant for scientific projects in NIAID's Immediate Office of the Director, and Emily Erbelding, M.D., director of NIAID's Division of Microbiology and Infectious Diseases. The authors note that a variety of STIs are contributing to the public health crisis as cases of gonorrhea, syphilis, and chlamydia are all on the rise. Left untreated, many STIs can cause serious complications. Congenital syphilis can cause stillbirths and health



This scanning electron micrograph shows *Neisseria gonorrhoeae* bacteria, which can cause gonorrhea.

Credit: NIAID

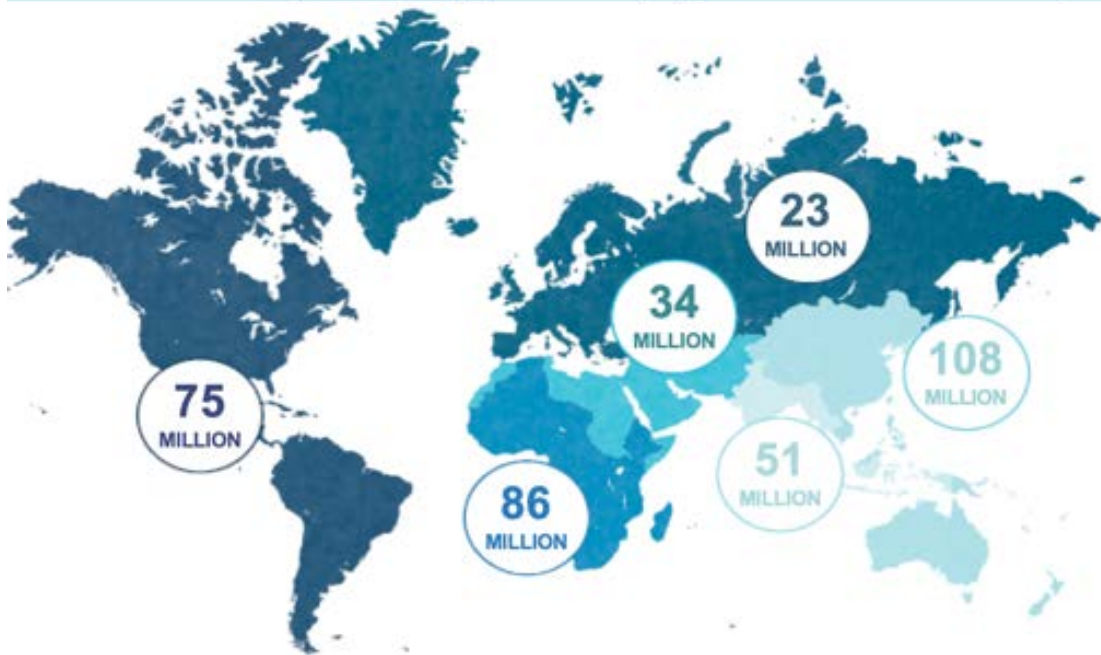
Defining the STI Crisis: WHO & U.S. CDC

- Dramatic recent increases in bacterial STI incidence in era of effective HIV treatment & prevention
- Unaddressed, poorly defined high burden in areas with highest HIV burden

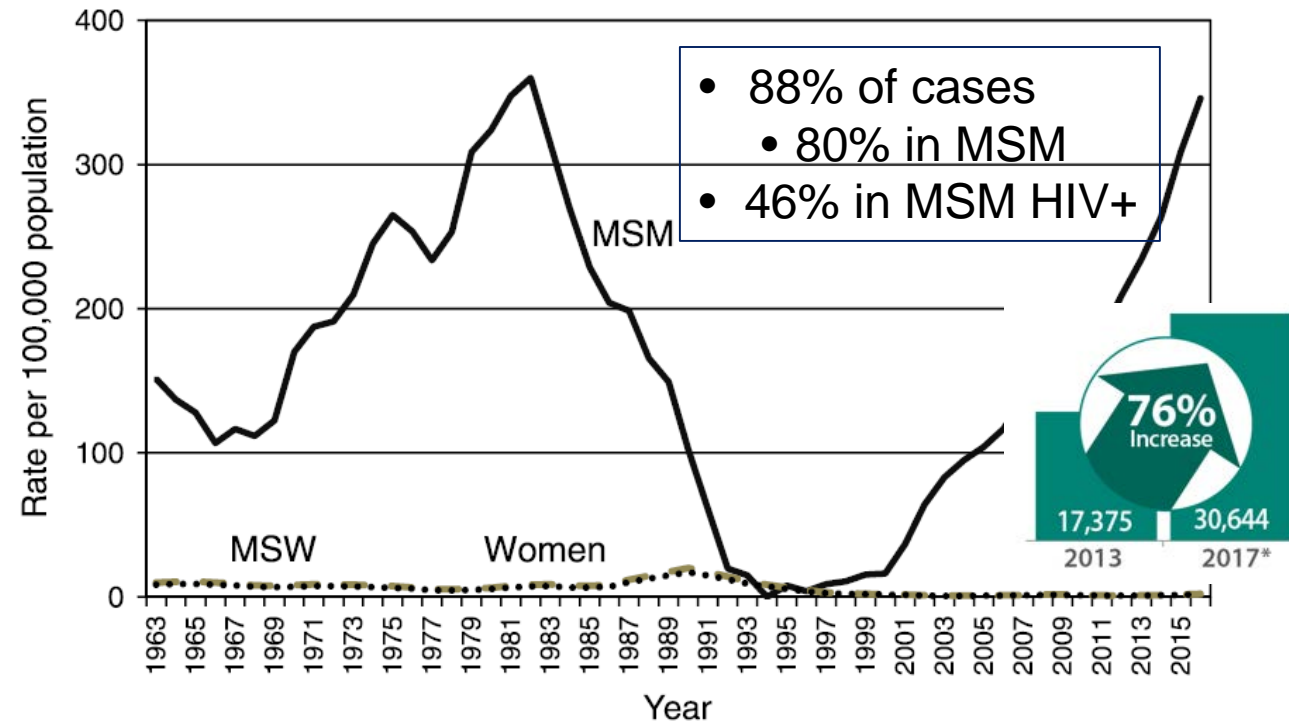
WHO 2016 Estimates: adults 15 to 49

376 million new cases of curable STI

Curable STI (Chlamydia, gonorrhoea, syphilis and trichomoniasis)



Primary / Secondary Syphilis in Men

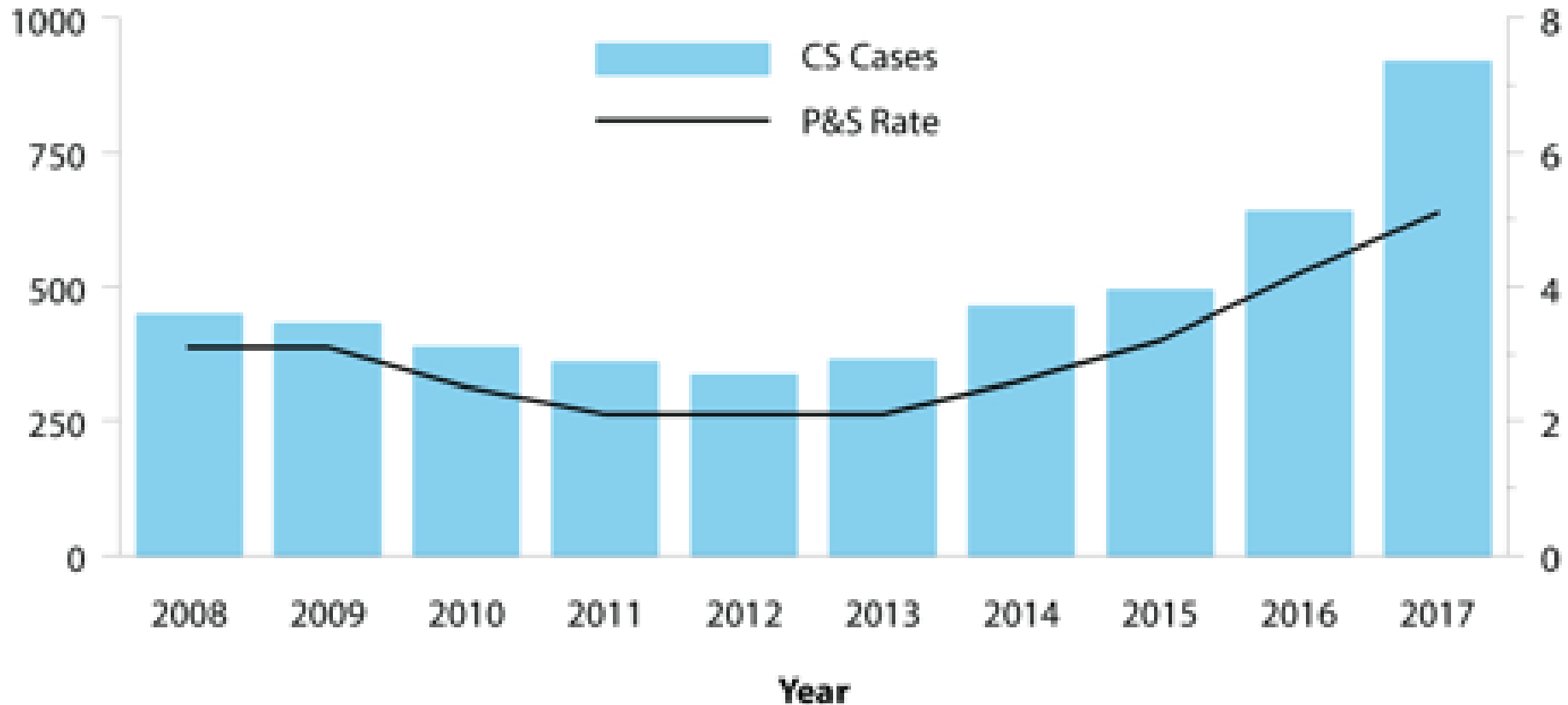


Syphilis in Women: U.S., 2017

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

CS Cases

P&S Rate (per 100,000 women)



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

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%	12%	4.1%	5.7%
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

Kiweewa JIAS 2019
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

Barnabas S et al Intl J STD AIDS 2018

Incident STIs in Young South African Women: HPTN 082

- Most incident STIs were new
 - 79 (66%) of 119 chlamydia
 - 41 (85%) of 48 gonorrhea
 - 23 (79%) of 29 trichomonas
- Not likely due to STI treatment failure or no partner notification
- Few characteristics distinguished women with STI from those without STI during follow-up
 - High prevalence and incidence without strong predictors makes selective screening a challenge

HPTN 082: Evaluation of daily oral PrEP as a primary prevention strategy for young African women



Study Population

Uninfected women
Ages 16-25 yrs

Johannesburg & Cape Town,
South Africa
Harare, Zimbabwe

Target Enrollment

- 400 women who accept PrEP at enrollment
- ≤ 200 women who decline PrEP at enrollment

HPTN Q82
HERS

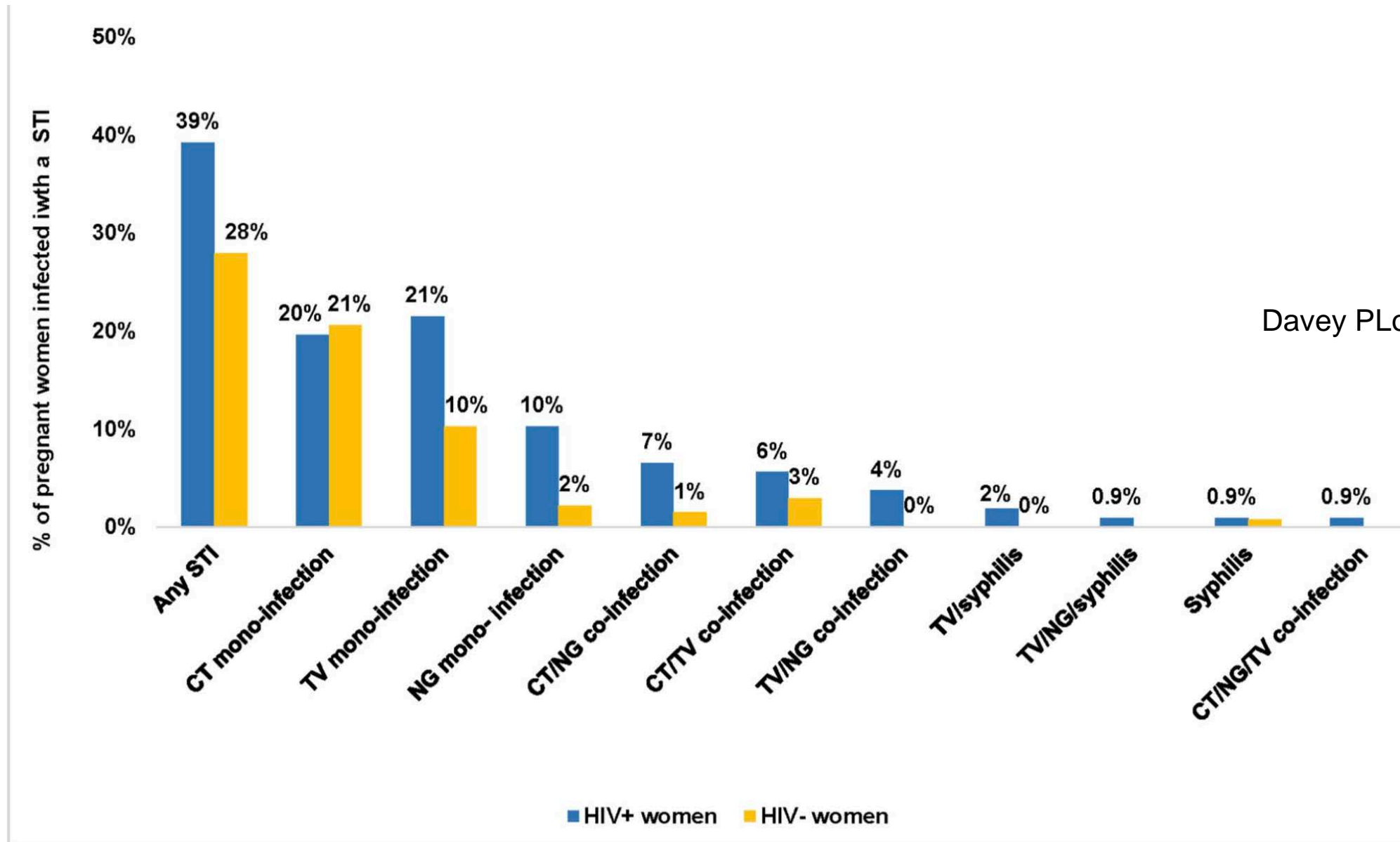


Fig 1. Prevalence of STI by type at first antenatal care visit in pregnant women in Cape Town, South Africa (n = 242). STIs include: *Chlamydia trachomatis* (CT), *Neisseria gonorrhoea* (NG) and *Trichomonas vaginalis* (TV).

ECHO Study: STI prevalence at screening and final visit, by age

	Point Prevalence (95% CI)	
	Screening	Final
≤ 24 Years Old		
<i>N. gonorrhoeae</i>	5.4 (4.8, 6.0)	5.8 (5.2, 6.5)
<i>C. trachomatis</i>	21.5 (20.4, 22.6)	19.6 (18.5, 20.8)
25 + Years Old		
<i>N. gonorrhoeae</i>	3.6 (3.0, 4.3)	3.2 (2.6, 4.0)
<i>C. trachomatis</i>	12.4 (11.3, 13.7)	8.2 (7.2, 9.3)

At both screening and final visit, point prevalence of NG and CT were significantly higher in ≤24y than compared with 25+y

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 present

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}

Molecular-based Testing for Sexually Transmitted Infections Using Samples Previously Collected for Vaginitis Diagnosis

CID 2018

Barbara Van Der Pol,¹ Grace Daniel,¹ Salma Kodsi,² Sonia Paradis,³ and Charles K. Cooper²

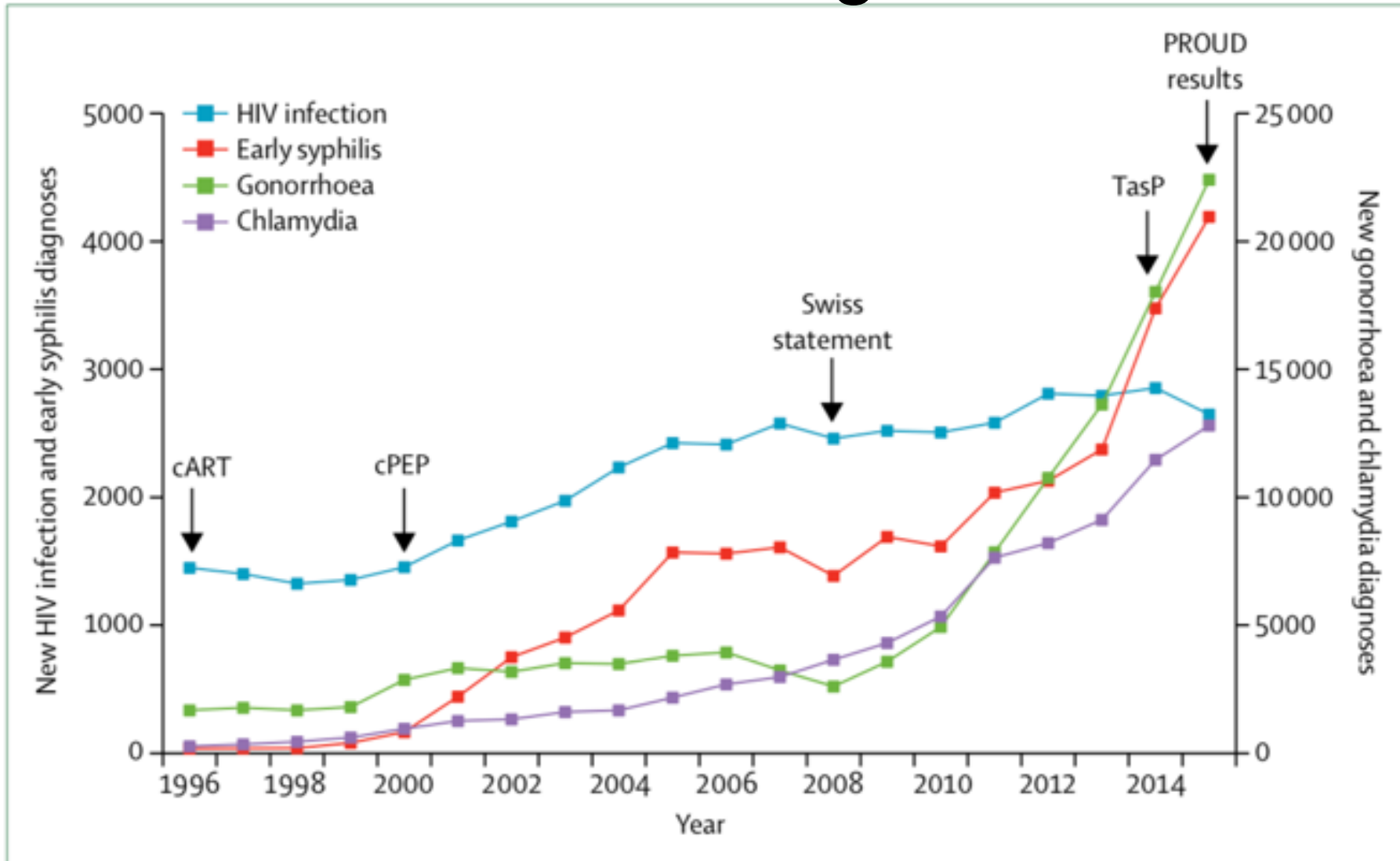
¹Division of Infectious Diseases, School of Medicine, University of Alabama at Birmingham; ²Becton, Dickinson and Company, BD Life Sciences—Diagnostic Systems, Sparks, Maryland; and ³Becton, Dickinson and Company, BD Life Sciences—Diagnostic Systems, Québec City, Québec, Canada

581 samples tested on women enrolled in BD MAX MVP Study

Gaydos *OB GYN* 2017

STI	BV Only	Candida Only	BV + Candida	No Vaginitis	Overall
Chlamydia	6.0%*	6.1%	12.8%*	1.8%	6.2%
Gonorrhea	2.5%	1.5%	1.0%	1.2%	1.7%
Trichomonas	11.4%*	1.6%*	8.6%	8.0%	8.3%
Any STI	17.4%*	9.2%	20.8%*	10.9%	14.9%

Relationship to Increasing PrEP Use: MSM in England




Unemo M Lancet Infect Dis 2017

Do STIs at the Pharynx & Rectum Matter?

TEST YOURSELF
The Visual Guide for a Self-collected Rectal Swab

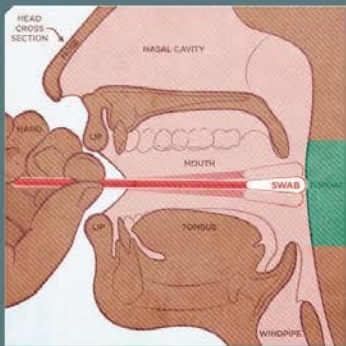


- 1 Wash your hands with soap and water.
- 2 Remove the transport tube and collection swab from packaging.
- 3 Label the transport tube with your Patient label.
- 4 Label the transport tube with the Rectal label.
- 5 Open the package containing the collection swab.
- 6 Hold the collection swab far enough from the tip.
- 7 Insert the collection swab into the rectum. Insert the swab at least 3 times.
- 8 Gently rub the swab tip on your rectum side to side, up and down at least 5 times.
- 9 Unscrew the cap from the transport tube.
- 10 Place the collection swab into the transport tube, snapping it at dashed line.
- 11 Put the cap back on the transport tube and twist it closed to prevent leaks.
- 12 Put the transport tube into the biohazard bag.
- 13 Wash your hands with soap and water.






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TEST YOURSELF
The Visual Guide for a Self-collected Throat Swab

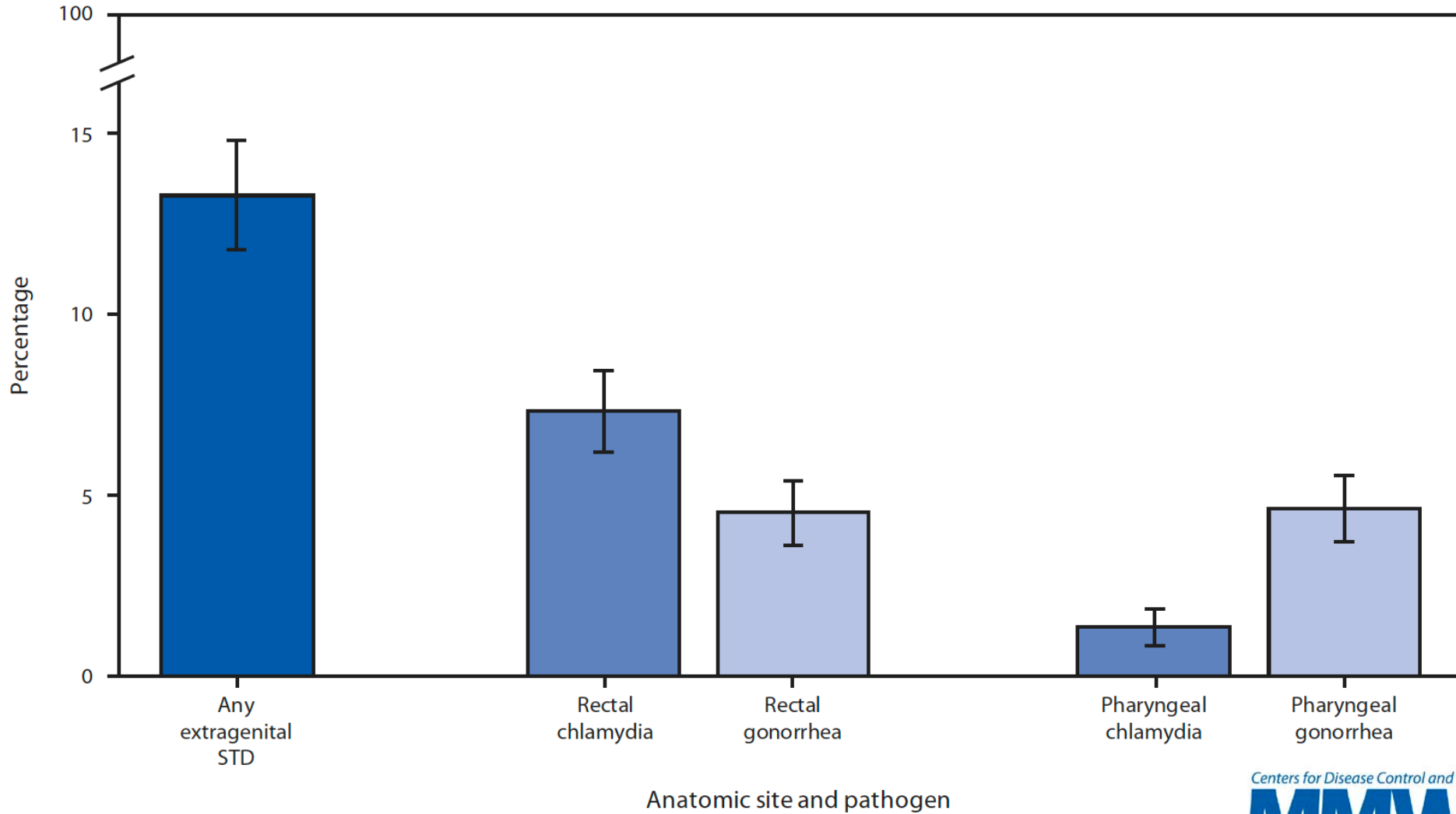


- 1 Wash your hands with soap and water.
- 2 Remove the transport tube and collection swab from packaging.
- 3 Label the transport tube with your Patient label.
- 4 Label the transport tube with the Throat label.
- 5 Open the package containing the collection swab.
- 6 Hold the collection swab far enough from the tip.
- 7 Say AHH... and reach the collection swab into your mouth to gently touch your throat.
- 8 Gently rub the swab tip on your throat side to side, up and down at least 5 times.
- 9 Unscrew the cap from the transport tube.
- 10 Place the collection swab into the transport tube, snapping it at dashed line.
- 11 Put the cap back on the transport tube and twist it closed to prevent leaks.
- 12 Put the transport tube into the biohazard bag.
- 13 Wash your hands with soap and water.

Illustrations and design layout by Cognition Studio, Inc. in Seattle, WA. © 2017, Cognition Studio, Inc. All rights reserved.

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



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-Bardales, PhD²; Destani Bizane, 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

Rectal *Chlamydia trachomatis* and *Neisseria gonorrhoeae* Infections Among Women Reporting Anal Intercourse

Eloisa Llata, MD, MPH, Jim Braxton, Lenore Asbel, MD, Joan Chow, PhD, Lindsay Jenkins, Ryan Murphy, PhD, Preeti Pathela, DrPh, Christina Schumacher, PhD, and Elizabeth Torrone, PhD

- Among more than 50,000 female patient STD visits (SSuN), 7.4% included report of rectal exposure
- ~75% of these women tested for rectal CT and GC
 - 292+ rectal CT and 128+ rectal GC
- Among women tested urogenitally and rectally, 21% of CT and 18% of GC would have been missed with urogenital only testing

Rectal
gonorrhea
Report

Eloisa Lla
Ryan Murp

- Among
rectal
- ~75%
 - 29
- Among
been

Bottom Line:

We don't know if extragenital infections in women confer an independent attributable risk for HIV acquisition. We should.

ort if

ld have

Why Bother with STIs in HIV Prevention Research?

Here are some arguments people make.

- We can achieve U=U in high STI incidence settings
- The more you look, the more you find!
 - Increased testing accounts for observed increase in STI
- STIs are mostly asymptomatic & inconvenient
- 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



Why We SHOULD Bother!

- STI as a risk marker for subsequent HIV can identify appropriate participants for HIV prevention studies
- Public health burden of increasing STIs is considerable—even in well-resourced settings
 - Antibiotic resistance & shortages; syphilis sequelae; partner management challenges; cost of extragenital testing (3 charges instead of 1!)
- For women, major reproductive health consequences
 - PID, tubal infertility, ectopic pregnancy, adverse outcomes of pregnancy
 - Stigma highly operative
 - Sexual pleasure / freedom remains an elusive goal; distinct from situation with PrEP uptake in MSM

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}

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
- Investigate vaccine (& PrEP/PEP?) options



Cochrane Database of Systematic Reviews

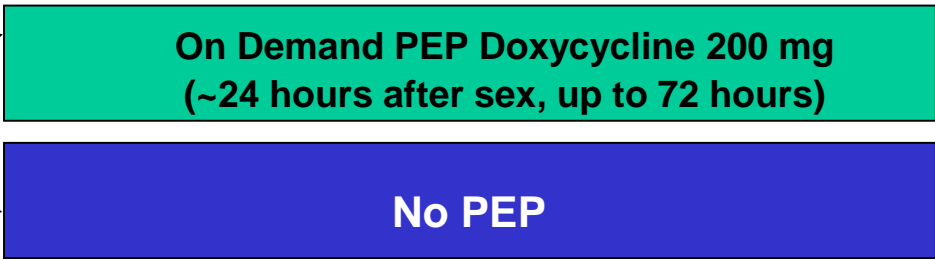
Cochrane Database of Systematic
Reviews 2013, Issue 10. Art. No.
CD002843

Strategies for partner notification for sexually transmitted
infections, including HIV (Review)

Ferreira A, Young T, Mathews C, Zunza M, Low N

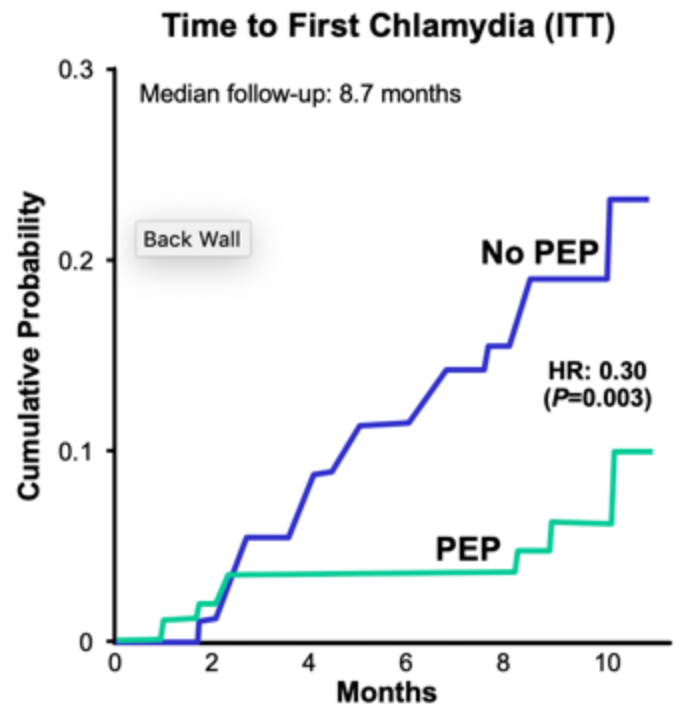
Post-exposure prophylaxis with doxycycline to prevent sexually transmitted infections in men who have sex with men: an open-label randomised substudy of the ANRS IPERGAY trial

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*

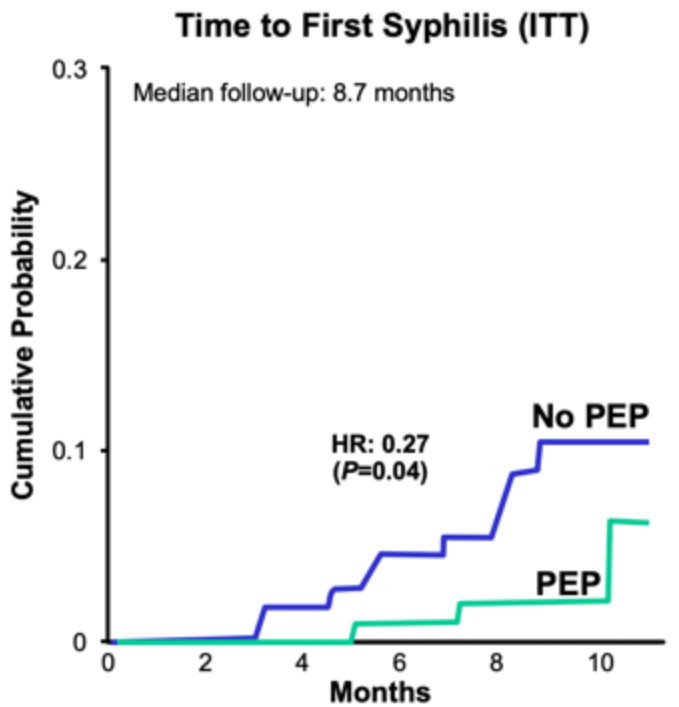


Visits: baseline and every 2 months
 Serologic assays for HIV and syphilis
 PCR assays for chlamydia and gonorrhoea
 Urine, anal, and throat samples collected

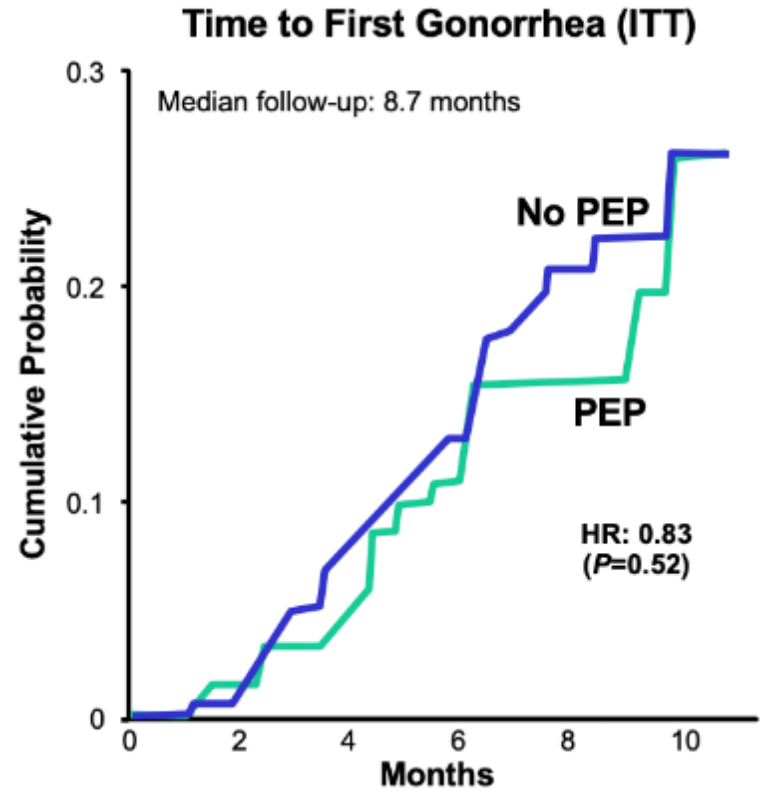
Time to First Chlamydia and Syphilis With On-Demand PEP With Doxycycline for MSM



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 gonorrhoea (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)

Doxycycline Prophylaxis for Bacterial STI. Grant et al, Clin Infect Dis, Sept 1, 2019

Cons

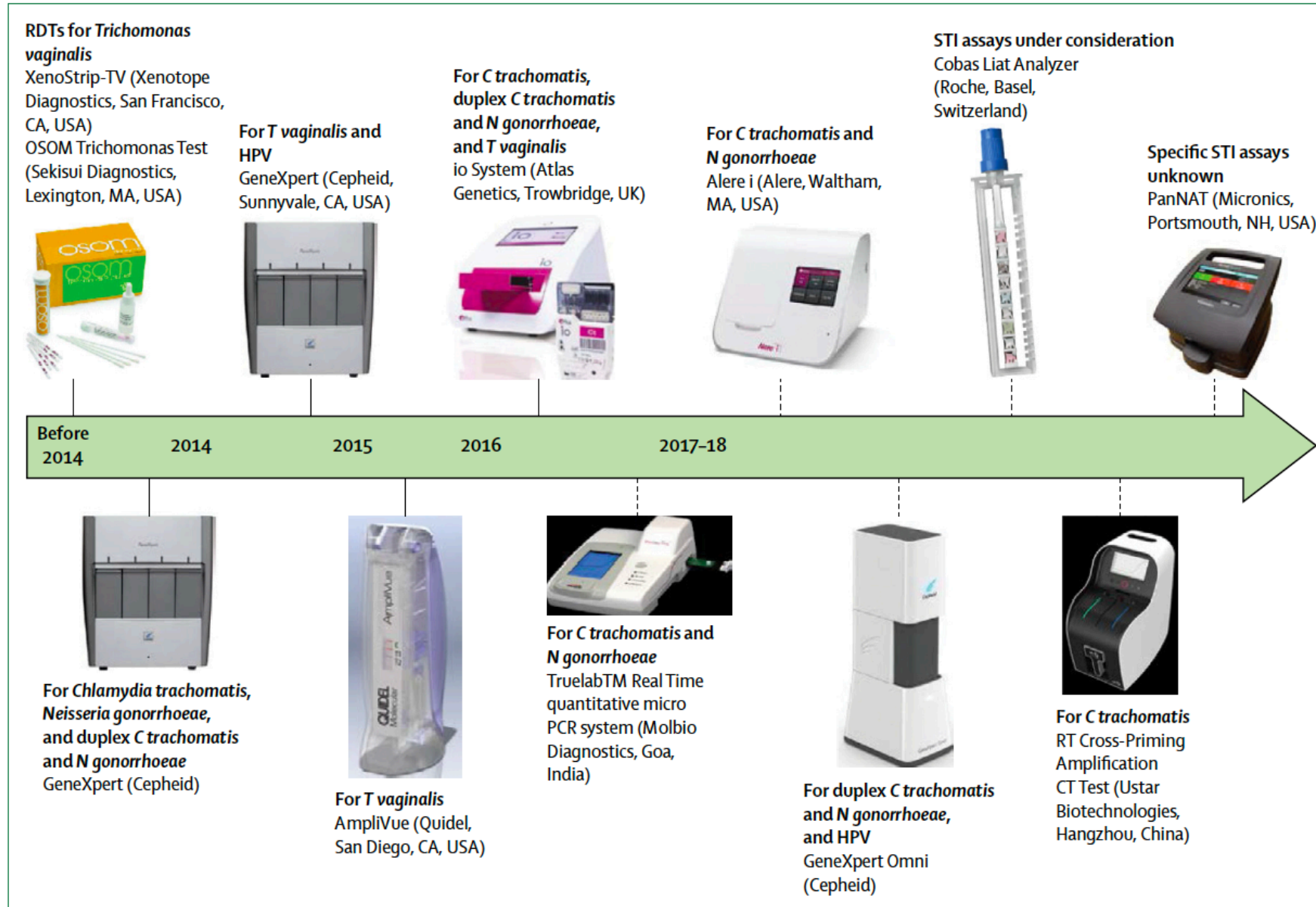
- Limited data; duration?
- Costs
- Side effects of doxycycline
 - Esophagitis/ulceration
 - Photosensitivity
- Risk compensation?
- Reproductive concerns (women)?
- Antibiotic resistance?
- Microbiome effects?

Sexually transmitted infections: challenges ahead



Lancet Infectious Disease
Commission, October 2017

Magnus Unemo*, Catriona S Bradshaw*, Jane S Hocking, Henry J C de Vries, Suzanna C Francis, David Mabey, Jeanne M Marrazzo, Gerard J B Sonder, Jane R Schwebke, Elske Hoornenborg, Rosanna W Peeling, Susan S Philip, Nicola Low†, Christopher K Fairley†



*Point of Care /
Rapid STI
Diagnostics Tests in
the Pipeline, 2017*



[HOW IT WORKS](#)

[FIND MY TEST](#)

[BINX BOXES](#)

[RESOURCES](#) ▼

[ABOUT US](#) ▼

[MY ACCOUNT](#)

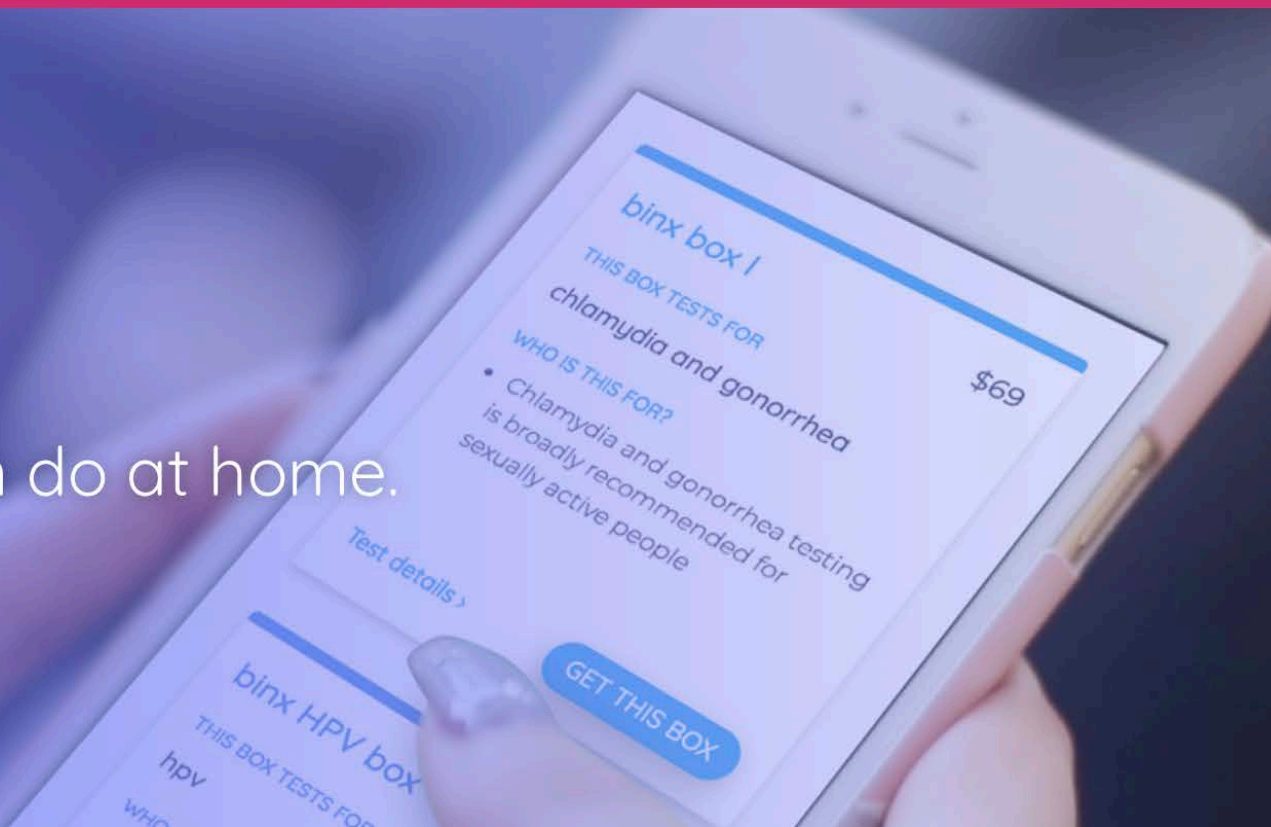
binx health receives FDA 510(k) clearance for the **first ever rapid point-of-care platform** for women's health - [READ MORE](#)

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[FIND MY TEST](#)

Have a test box already? Activate it [here](#).



Does the Group B Meningococcal Vaccine Protect Against Gonorrhoea?

Retrospective case-control study of subjects immunized with NZ MenB OMV vaccine (2004-2014)

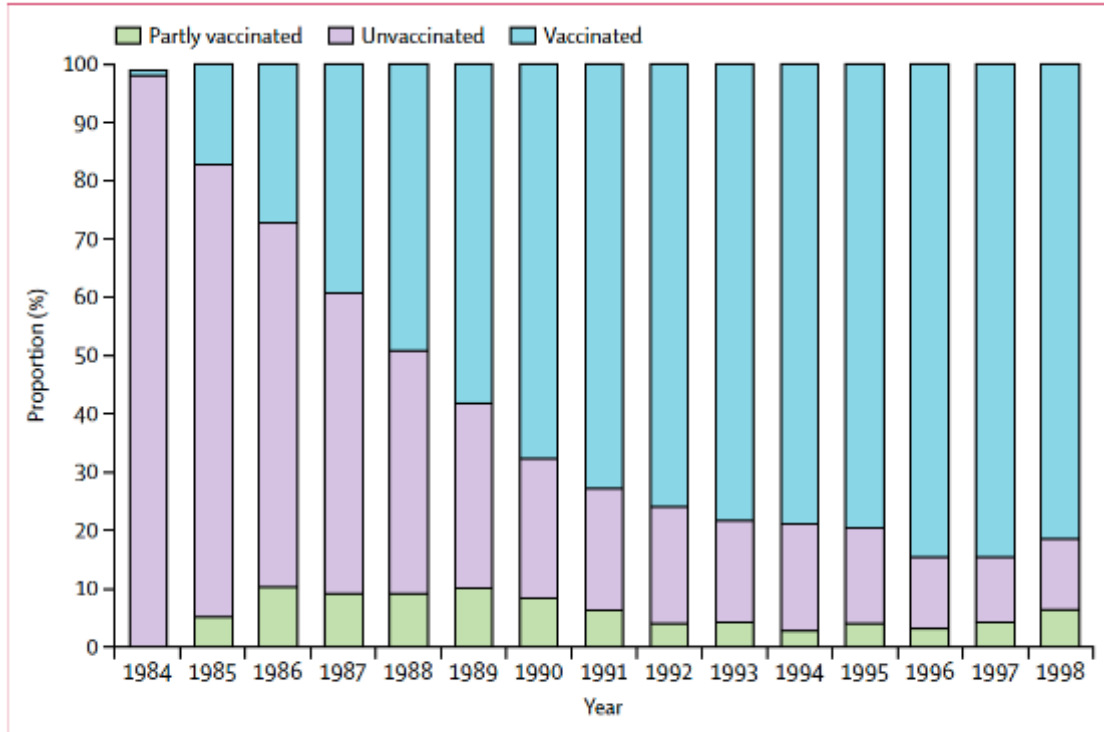


Figure 2: Vaccination status of participants by year of birth

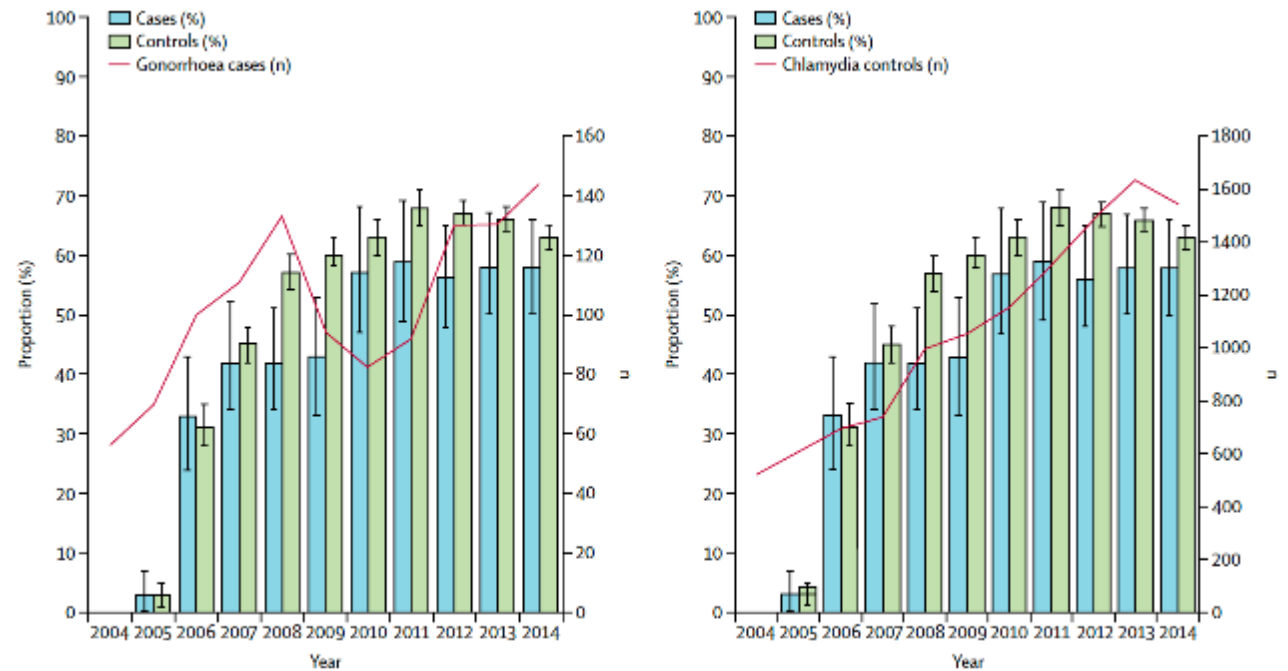


Figure 3: Year-by-year difference in the proportion of cases and controls vaccinated and number of gonorrhoea (A) and chlamydia (B) diagnoses

- 877 diagnoses of gonorrhoea, 772 diagnoses of gonorrhoea/chlamydia co-infection in participants
- Effectiveness of MenB vaccine against gonorrhoea estimated to be 33%
- No reduced risk in individuals with gonorrhoea/chlamydia coinfection

Just funded: NIH STI Clinical Trial (TA2 TO9)

To evaluate efficacy of Bexsero in protection vs. gonorrhoea acquisition in 900 adults in U.S.

Estimated start date: Mid-2020

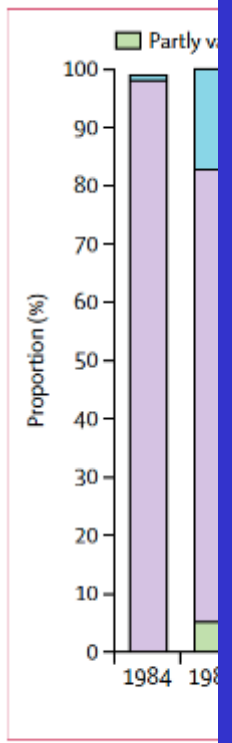
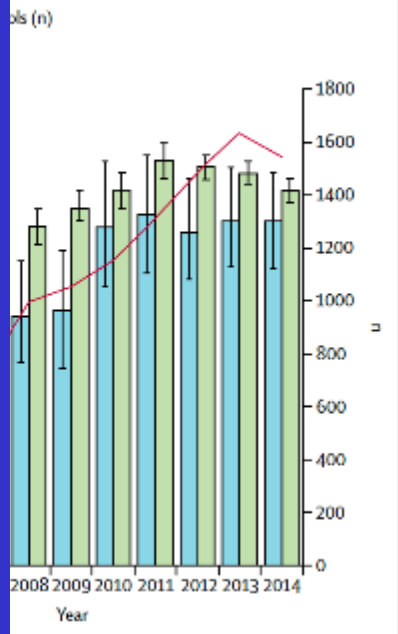


Figure 2: Vaccination

- 877
- Effe
- No reduced risk in individuals with gonorrhoea/chlamydia coinfection

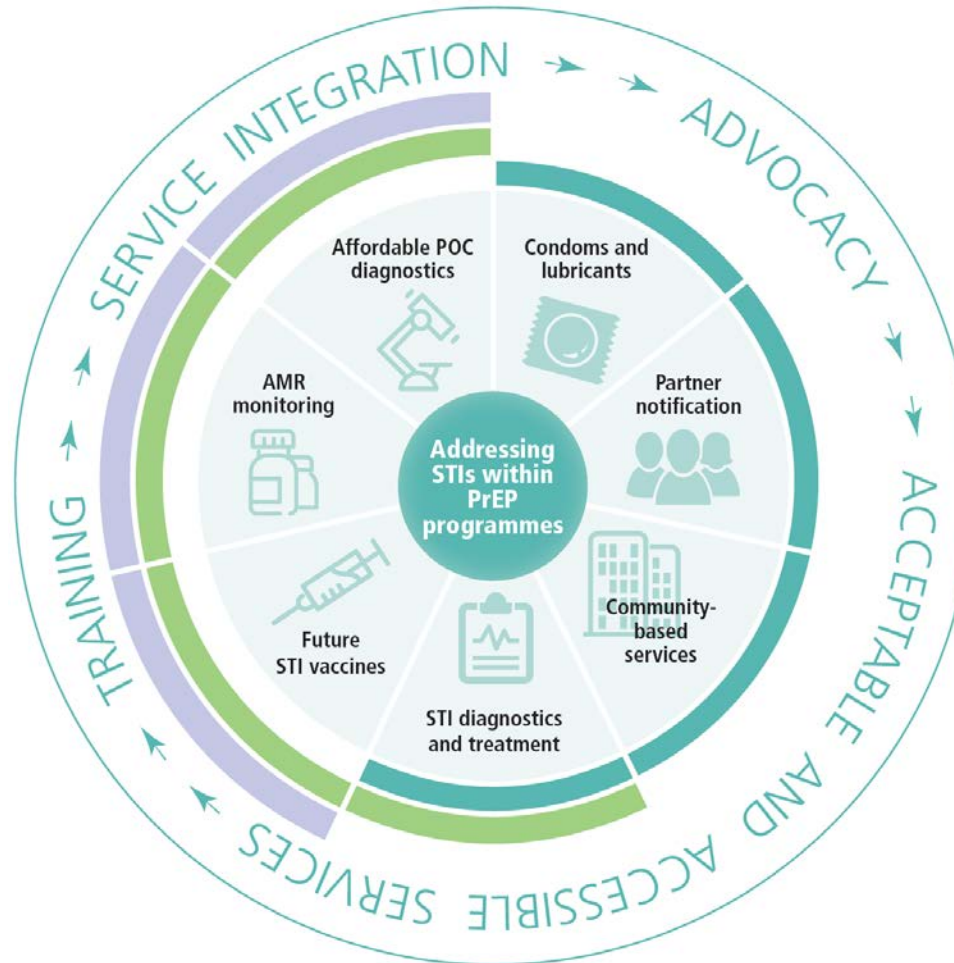


(A) and chlamydia (B) diagnoses

n participants

Addressing STIs in PrEP programs

Figure 1. Existing and future interventions for improving STI prevention and control by leveraging PrEP scale-up



Bobbie Van Der Pol
Connie Celum
Jen Deese



@DrJeanneM
@STD_Journal

Prevalence ratios by arm and visit

	<i>N. gonorrhoeae</i>				<i>C. trachomatis</i>			
	ITT		BAC ^B		ITT		BAC ^C	
	PR*	P value	PR*	P value	PR*	P value	PR*	P value
Copper IUD vs LNG Implant	1.2 (0.9, 1.5)	0.175	1.1 (0.9, 1.5)	0.318	0.9 (0.8, 1.0)	0.178	0.9 (0.8, 1.0)	0.093
DMPA-IM vs Copper IUD	0.7 (0.5, 0.9)	0.002	0.7 (0.5, 0.9)	0.007	0.9 (0.8, 1.0)	0.144	0.9 (0.7, 1.0)	0.062
DMPA -IM vs LNG Implant	0.8 (0.6, 1.0)	0.085	0.8 (0.6, 1.0)	0.064	0.8 (0.7, 0.9)	0.005	0.8 (0.7, 0.9)	0.001

* Comparison group vs reference level

^A Adjusted for Study Site

^B Adjusted for Study Site, HIV status at final visit, and Pelvic Exam Number (total)

^C Adjusted for Study Site, Age group (<=24, >24) and CT status at screening

In both intention to treat (ITT) and best achievable use (BAC) analyses:

- DMPA-IM: 30% lower risk of **NG**, compared with Copper IUD
- DMPA-IM: 20% lower risk of **CT**, compared with LNG implant

STIs in subSaharan Africa: STIMA

- Meta-analysis of 18 HIV prevention studies from 1993-2011, representing >37,000 women
- Higher prevalence for all STIs (other than HSV-2) in 15-24 year old women compared to 25-49 year old
- Chlamydia prevalence: South Africa 15% (95% CI 13-18%); East Africa 10% (95% CI 7-14%)
- GC prevalence: South Africa 5% (95% CI 3-6%); East Africa 2% (95% CI 3-6%)
- Syphilis concentrated in high risk women
- High prevalence of HSV-2 (70-83%) and BV (33-43%)